Official Title of Study:

A Phase 2 Open-label Randomized Study of Farletuzumab Ecteribulin (MORAb-202), a Folate Receptor Alpha-targeting Antibody-drug Conjugate, versus Investigator's Choice Chemotherapy in Women with Platinum-resistant High-grade Serous (HGS) Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

NCT Number: NCT05613088

Document Date (Date in which document was last revised): 05 Aug 2024

CLINICAL PROTOCOL CA116001/MORAB-202-G000-205

A Phase 2 Open-label Randomized Study of Farletuzumab Ecteribulin (MORAb-202), a Folate Receptor Alpha-targeting Antibody-drug Conjugate, versus Investigator's Choice Chemotherapy in Women with Platinum-resistant High-grade Serous (HGS) Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

Compound: BMS-986445

Brief Title:

A Phase 2 Study of MORAb-202 in Platinum-resistant High-grade Serous Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

Protocol Amendment 03

Medical Monitor Name and Contact Information:

[redacted]
Clinical Trial Physician – Medical Monitor
Bristol-Myers Squibb Company
3401 Princeton Pike
Lawrenceville, NJ 08648
Phone: [redacted]
email: [redacted]

24-hr Emergency Telephone Number
USA: [redacted]
International: [redacted]

Sponsor Name and Legal Registered Address:

Bristol-Myers Squibb Company
Route 206 & Province Line Road
Lawrenceville, NJ 08543

REGULATORY AGENCY IDENTIFIER NUMBER(S)

IND: 157,858
EudraCT/EU Trial Number: 2021-004807-42

DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Protocol Amendment 03	05-Aug-2024	[redacted]
Administrative Letter 01	25-Sep-2023	Change of medical monitor contact information and administrative changes in Table 2-1 and Table 9.4.4-1.
Protocol Amendment 02	07-Apr-2023	[redacted]
Protocol Amendment 01	02-Aug-2022	The main purpose of this Protocol Amendment is to make updates [redacted]. Additionally, further clarification was added to Table 2-4 and Table 7.4.1-2.
Original Protocol	24-Jun-2022	Not applicable.

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

[redacted]

The Protocol Summary has been updated to align with respective changes made in the protocol body and is not summarized in the table below. In addition, this amendment incorporates changes from an approved Administrative Letter 01, which are summarized in the table below.

Minor editorial, formatting, and typographical corrections have been made and therefore have not been summarized.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Schedule of Activities	• Table 2-1: Screening Procedural Outline (CA116001) updated the following: Note section for Clinical Laboratory Assessments updated to include 12-or 24-hour urine collections is required for CrCl measurements. • Table 2-2: On-treatment Procedural Outline for MoRab-202-[redacted] • Table 2-3: On-treatment Procedural Outline for 21-Day Cycle [redacted] Topotecan 1.25mg/m2: • Table 2-4 On-treatment Procedural Outline for a 28-Day Cycle-[redacted] (PLD, Paclitaxel, and Topotecan 4mg/m2): • Table 2-5 (Follow-up Procedural Outline (CA116001)) updated for following: [redacted] ○ Notes section for Survival Status was updated to include survival follow-up visits up to 1 year from the last participant randomized or LPLV (30	[redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	days after the last patient's last treatment visit), whichever is later.	
[redacted]		
Section 5.1: Overall Design	• The section was updated to remove continuous long-term survival follow-up. • The section has been updated to include survival follow-up every 3 months from the safety follow-up visit up to 1 year from the last participant randomized or LPLV (30 days after the last patient's last treatment), whichever is later. • The study design schema was updated to include a survival follow-up of 1 year.	[redacted]
[redacted]		
Section 8.1.1: Post-study Intervention Study Follow-up	Section updated to include survival follow-up every three months from safety follow-up visit up to 1 year from the last participant randomized or LPLV (30 days after last patient last treatment visit); whichever is later.	[redacted]
[redacted]		

TABLE OF CONTENTS

TITLE PAGE 1
DOCUMENT HISTORY 3
OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03: 4
SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03 4
TABLE OF CONTENTS 6
1 PROTOCOL SUMMARY 10
2 SCHEDULE OF ACTIVITIES 20
3 INTRODUCTION 51
3.1 Study Rationale 52
3.1.1 Research Hypothesis 53
3.2 Background 53
3.2.1 Ovarian Cancer Racial and Ethnic Diversity 54
3.2.2 Summary of Key Preclinical Data with MORAb-202 55
3.2.3 MORAb-202 Clinical Data 55
3.2.3.1 Clinical Efficacy 56
3.2.3.2 Clinical Safety 58
3.2.4 MORAb-202 Clinical Pharmacology 61
3.2.4.1 MORAb-202 Clinical Pharmacokinetics 61
3.2.4.2 Exposure-response Efficacy and Safety 62
[redacted] 63
3.2.4.4 Corrected QTc Interval Assessment 63
3.2.4.5 Drug-drug Interaction Potential 63
3.3 Benefit/Risk Assessment 64
3.3.1 Risk Assessment 65
3.3.2 Benefit Assessment 71
3.3.3 Overall Benefit/Risk Conclusion 72
4 OBJECTIVES AND ENDPOINTS 73
5 STUDY DESIGN 75
5.1 Overall Design 75
5.1.1 Data Monitoring Committee and Other Committees 77
5.1.1.1 Safety Committee (SC) 77
5.1.1.2 ILD Expert Review Committee 78
5.2 Number of Participants 78
5.3 End of Study Definition 78
5.4 Scientific Rationale for Study Design 79
5.4.1 Participant Input Into Study Design 80
5.4.2 Rationale for Open-label Design 80
[redacted] 81
5.4.4 Rationale for Choice of Comparators and Dose Justification 81
5.4.4.1 Paclitaxel 82
5.4.4.2 Pegylated Liposomal Doxorubicin 82
5.4.4.3 Topotecan 83
5.4.5 Rationale for Primary Endpoint 84
5.5 Justification for Dose 84

5.6 [redacted] 86
86
87
87
87
5.6.2 Tumor Samples 88
5.6.2.1 Tumor Sample Collection 88
5.6.2.2 Characterization of Tumor Microenvironment 88
5.6.2.3 Tumor Genotyping, Mutational Analysis, and Gene Expression Profiling 89
5.6.2.4 Tumor FRα Expression 89
[redacted] 89
6 STUDY POPULATION 89
6.1 Inclusion Criteria 89
6.2 Exclusion Criteria 91
6.3 Lifestyle Restrictions 96
6.4 Screen Failures 96
6.4.1 Re-testing During Screening 96
7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY 96
7.1 Study Interventions Administered 97
7.1.1 MORAb-202 Administration [redacted] 98
7.1.2 Preparation and Administration of Paclitaxel 100
7.1.3 Preparation and Administration of Pegylated Liposomal Doxorubicin 100
7.1.4 Preparation and Administration of Topotecan 100
7.1.5 Calculation of Dose Based on Body Surface Area 101
7.2 Assignment to Study Intervention 101
7.3 Blinding 102
7.4 Dosage Modification 102
7.4.1 Dose Modification for MORAb-202 102
7.4.1.1 Criteria to Resume MORAb-202 Treatment 109
7.4.2 Dose Modification for Paclitaxel 110
7.4.2.1 Dose Reduction for Paclitaxel 111
7.4.3 Dose Modification for Pegylated Liposomal Doxorubicin (PLD) 112
7.4.3.1 Dose Reduction for Pegylated Liposomal Doxorubicin (PLD) 113
7.4.4 Dose Modification for Topotecan 114
7.4.4.1 Dose Reduction for Topotecan 115
7.5 Preparation/Handling/Storage/Accountability 115
7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability 116
7.6 Study Intervention Compliance 116
7.7 Concomitant Therapy 117
7.7.1 Prohibited and/or Restricted Treatments 117
7.7.2 Supportive Therapies 117
7.7.3 Other Restrictions and Precautions 117
7.7.3.1 Imaging Restrictions and Precautions 117
7.8 Continued Access to Study Intervention After the End of the Study 118
8 DISCONTINUATION CRITERIA 118

8.1 Discontinuation of Study Intervention 118
8.1.1 Post-study Intervention Study Follow-up 119
8.2 Discontinuation From the Study 119
8.2.1 Individual Discontinuation Criteria 120
8.3 Lost to Follow-up 120
9 STUDY ASSESSMENTS AND PROCEDURES 121
9.1 Efficacy Assessments 121
9.1.1 Efficacy Assessment for the Study 121
9.1.2 Imaging Assessment for the Study 122
[redacted] 123
123
124
124
125
9.2 Adverse Events 125
9.2.1 Period and Frequency for Collecting AE and SAE Information 125
9.2.2 Method of Detecting AEs and SAEs 126
9.2.3 Follow-up of AEs and SAEs 126
9.2.4 Regulatory Reporting Requirements for SAEs 127
9.2.5 Pregnancy 127
9.2.6 Laboratory Test Result Abnormalities 127
9.2.7 Potential Drug-induced Liver Injury 128
9.2.8 Other Safety Considerations 128
9.2.9 AEs of Special Interest 128
9.3 Overdose 129
9.4 Safety 129
9.4.1 Physical Examinations 129
9.4.2 Vital Signs 129
9.4.3 Electrocardiograms 129
9.4.4 Clinical Safety Laboratory Assessments 129
9.4.5 ILD/Pneumonitis Assessments 131
9.4.6 Imaging Safety Assessment 132
9.4.7 Echocardiogram (ECHO)/Multigated Acquisition (MUGA) 133
[redacted] 133
134
134
134
135
135
9.9 Health Economics OR Medical Resource Utilization and Health Economics . 135
10 STATISTICAL CONSIDERATIONS 136
[redacted] 136
137
10.3 Analysis Sets 139
10.4 Statistical Analyses 140
10.4.1 General Considerations 140

10.4.2 Primary Endpoint(s) 141
10.4.3 Secondary Endpoints 141
[redacted] 142
10.4.5 Other Safety Analyses 142
[redacted] 143
143
143
144
[redacted] 144
11 REFERENCES 145
12 APPENDICES 152
APPENDIX 1 ABBREVIATIONS 153
APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS 159
APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING 173
APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION 178
APPENDIX 5 AMERICAN JOINT COMMITTEE ON CANCER (AJCC) STAGE AND TNM STAGE GROUPING FOR OVARIAN CANCER (8TH EDITION). 182
APPENDIX 6 ECOG PERFORMANCE STATUS 185
APPENDIX 7 COUNTRY SPECIFIC APPENDIX 186
APPENDIX 8 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS 187
APPENDIX 9 NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION 195
APPENDIX 10 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY 196

1 PROTOCOL SUMMARY

Protocol Title:

A Phase 2 Open-label Randomized Study of Farletuzumab Ecteribulin (MORAb-202), a Folate Receptor Alpha-targeting Antibody-drug Conjugate, versus Investigator's Choice Chemotherapy in Women with Platinum-resistant High-grade Serous (HGS) Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

Brief Title: A Phase 2 Study of MORAb-202 in Platinum-resistant High-grade Serous Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

Rationale:

There is an urgent clinical need for novel therapeutic approaches in platinum-resistant ovarian cancer (PROC). Despite progress in earlier lines of therapy, with the availability of new treatment modalities, patients with PROC still have a poor prognosis.

Debulking surgery and platinum-based chemotherapy form the foundation of care for the treatment of women with advanced ovarian cancer. Although many women with advanced disease may enter remission after surgery and chemotherapy, most patients will eventually relapse. Depending upon the response of the last platinum-based therapy and time for recurrence, most women will receive additional platinum-based regimens on subsequent lines of therapy. With every additional line of platinum-based regimens, the progression-free survival (PFS) decreases. A particular challenge arises when the disease returns less than 6 months after completing the last platinum-based chemotherapy, referred to as PROC. For these patients, additional lines of platinum-based chemotherapy usually provide a small clinical benefit; however, most patients will be only eligible to receive a single-agent non-platinum-based option (eg, pegylated liposomal doxorubicin [PLD], paclitaxel, or topotecan). Although these regimens can provide some clinical benefit, the observed objective response rate (ORR) is low (10% to 15%) with median PFS (mPFS) around 3.5 months. Patients with PROC have a median overall survival of less than 1 year, thus highlighting the unmet medical need.

Folate receptor alpha (FRα)-directed antibody-drug conjugate (ADC) therapy is a potential treatment option for advanced ovarian cancer and is currently under investigation. Various epithelial tumors (eg, ovarian, endometrial, lung, head and neck) have demonstrated abundant FRα messenger ribonucleic acid (mRNA) expression by quantitative polymerase chain reaction and membrane protein expression by immunohistochemistry (IHC). Although FRα expression is limited in normal ovary tissue, 80% to 90% of epithelial ovarian cancer (EOC) tumors express FRα. A recent meta analysis suggests that higher expression of FRα is associated with poor survival of patients with cancer and may serve as a prognostic indicator. Moreover, there is evidence that elevated FRα expression may be a negative prognostic marker for chemotherapeutic response in EOC. In addition to its cell surface localization, FRα can be shed into the bloodstream as a soluble form. Soluble FRα (sFRα) levels correlate with local tumor FRα expression. Higher serum concentrations of sFRα are indicative of the FRα expression status of the tumor and are correlated with clinical stage and poor prognosis. FRα is an attractive target for ADC-based

therapies due to its ability to internalize large molecules, its limited expression in normal tissues, and its overexpression in malignant cells, allowing for effective, targeted drug delivery.

Preliminary efficacy and a manageable safety profile were observed in participants with PROC treated with MORAb-202 in a Phase 1 study, MORAb-202-J081-101 (hereafter referred to as Study 101), and a Phase 1/2 study, MORAb-202-G000-201 (hereafter referred to as Study 201), supporting further clinical development of MORAb-202 in this population. Responses were observed in participants with solid tumors across a range of FRα expression levels, supporting the evaluation in all randomized participants irrespective of their expression levels.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To compare objective response rate (ORR) of MORAb-202 vs IC chemotherapy (in all randomized participants)	• ORR by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per investigator assessment
Main Estimand for the Primary Objective Treatment: MORAb-202, 25 mg/m^2 [redacted], IC chemotherapy [redacted] Population: Platinum-resistant ovarian cancer Variable: Best overall response (BOR), defined as the best response, as determined by the investigator, recorded between the date of randomization and the date of first objectively-documented progression per RECIST v1.1 or the date of subsequent therapy, whichever is earlier. Intercurrent events (strategy): Early discontinuation of study treatment (treatment policy); initiation of subsequent anti-cancer therapy (while on treatment) Population-level summary: Difference in ORR, defined as the number of randomized participants who achieve a BOR of confirmed complete response (CR) or confirmed partial response (PR) based on the investigator assessments (using RECIST v1.1) divided by the number of all randomized participants in each treatment group, with two-sided 95% exact confidence interval (CI) in each treatment group	
• To evaluate the proportion of participants with treatment-related adverse event (TRAEs) leading to discontinuation in each arm within 6 months from first dose of study drug administration in all treated participants	• TRAEs leading to discontinuation
Main Estimand for the Primary Objective Treatment: MORAb-202, 25 mg/m^2 [redacted] IC chemotherapy [redacted] Population: Platinum-resistant ovarian cancer Variable: Occurrence of TRAEs leading to discontinuation observed within 6 months from first dose of study drug administration Intercurrent events (strategy): Early discontinuation of study treatment (while on treatment) Population-level summary: TRAE discontinuation incidence rate	

Objectives	Endpoints
Secondary	
• To assess the safety and tolerability of MORAb-202 and IC chemotherapy in all treated participants	• Incidence and severity of adverse events (AEs)/serious adverse events (SAEs), AEs leading to discontinuation, treatment-related AEs/SAEs leading to discontinuation, AEs of special interest (AESIs), deaths, and laboratory abnormalities
Main Estimand for the Secondary Objective Treatment: MORAb-202, 25 mg/m^2 [redacted], IC chemotherapy [redacted] Population: Platinum-resistant ovarian cancer Variable: Occurrence of the AEs/SAEs, treatment-related AEs/SAEs, AEs leading to discontinuation, AESIs, deaths, and laboratory abnormalities. There are multiple estimands corresponding to each specified safety endpoint. Intercurrent events (strategy): Early discontinuation of study treatment (while on treatment) Population-level summary: AE incidence rate/proportion	
• To evaluate disease control rate (DCR) of MORAb-202 and IC chemotherapy in all randomized participants	• DCR by RECIST v1.1 per investigator assessment
Main Estimand for the Secondary Objective Treatment: MORAb-202, 25 mg/m^2 [redacted] IC chemotherapy [redacted] Population: Platinum-resistant ovarian cancer Variable: Best overall response (BOR), defined as the best response, as determined by the investigator, recorded between the date of randomization and the date of first objectively-documented progression per RECIST v1.1 or the date of subsequent therapy Intercurrent events (strategy): Early discontinuation of study treatment (treatment policy); initiation of subsequent anti-cancer therapy (while on treatment) Population-level summary: Difference in DCR, defined as the number of randomized participants who achieve a BOR of confirmed CR, confirmed PR, or stable disease (SD), based on the investigator assessments (using RECIST v1.1) divided by the number of all randomized participants, with 95% exact CI in each treatment group	
• To evaluate duration of response (DoR) of MORAb-202 and IC chemotherapy in all randomized participants	• DoR by RECIST v1.1 per investigator assessment

Objectives	Endpoints
Main Estimand for the Secondary Objective Treatment: MORAb-202, 25 mg/m^2 [redacted], IC chemotherapy [redacted] Population: Platinum-resistant ovarian cancer participants that achieved a CR or PR as BOR Variable: DoR, defined as the time between the date of first documented response (CR or PR) that is subsequently confirmed, to the date of the first objectively-documented tumor progression as determined by investigator (per RECIST v1.1), or death due to any cause, whichever occurs first Intercurrent events (strategy): Early discontinuation of study treatment (treatment policy); initiation of subsequent anti-cancer therapy (while on treatment) Population-level summary: Kaplan Meier (KM) estimated median response time and landmark response rate of DoR in each treatment group	
• To evaluate progression-free survival (PFS) of MORAb-202 and IC chemotherapy in all randomized participants	• PFS by RECIST v1.1 per investigator assessment
Main Estimand for the Secondary Objective Treatment: MORAb-202, 25 mg/m^2 [redacted], IC chemotherapy [redacted] Population: Platinum-resistant ovarian cancer Variable: PFS, defined as the time between the date of randomization and the first date of documented progression, determined by the investigator assessments (using RECIST v1.1), or death due to any cause, whichever occurs first. Intercurrent events (strategy): Early discontinuation of study treatment (treatment policy); initiation of subsequent anti-cancer therapy prior to PD or death (treatment policy) Population-level summary: KM estimated median survival time and landmark survival rate of PFS in each treatment group	

Abbreviations: AE, adverse event; AESI, adverse event of special interest; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; IC, Investigator's choice; KM, Kaplan Meier; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; SD, stable disease; TRAE, treatment-related adverse event.

Overall Design:

Study CA116001 is a Phase 2, open-label, randomized, multicenter study that will evaluate the safety, efficacy, and tolerability of MORAb-202 in female participants with platinum-resistant high-grade serous (HGS) ovarian, primary peritoneal, or fallopian tube cancer.

All screening assessments to determine participant eligibility must be performed within 28 days prior to randomization. [redacted]

All participants will be treated until disease progression by Response Evaluation Criteria in Solid Tumors version 1.1 ([RECIST v1.1 criteria]; as assessed by the investigator), unacceptable

toxicity, participant withdrawal of consent for receiving study treatment, death, or the end of study, whichever occurs first. Maximum treatment duration will be up to 2 years.

A Safety Follow-up Visit will be conducted 30 days after the last study drug administration. All ongoing treatment-related serious adverse events and interstitial lung disease (ILD)/pneumonitis events will be followed until resolution or stabilization. All participants discontinuing treatment will be followed for tumor assessment until investigator-assessed disease progression by RECIST v1.1, death, or withdrawal of consent for tumor assessment, whichever occurs first. Subsequently, all participants will be followed for information on progression on next line of therapy and survival every 3 months for up to 1 year from last participant randomized or LPLV (30 days after last patient last treatment visit); whichever is later.

[redacted]

Number of Participants:

About 90 participants will be randomized in a [redacted] ratio to 1 of the 2 treatment groups, about [redacted] participants in the MORAb-202 arm [redacted] and [redacted] in the IC chemotherapy arm [redacted] It is estimated that approximately [redacted] participants will be enrolled to achieve approximately 90 randomized participants, assuming a screen failure rate of approximately [redacted]

Study Population:

Main Inclusion Criteria:

- Female participants with histologically-confirmed diagnosis of HGS ovarian, primary peritoneal, or fallopian tube cancer.
- Platinum-resistant disease, defined as:
  - For participants who had only 1 line of platinum-based therapy: progression between > 1 month and ≤ 6 months after the last dose of platinum-based therapy of at least 4 cycles.
  - For participants who had 2 or 3 lines of platinum-based therapy: progression ≤ 6 months after the last dose of platinum-based therapy.
- Participants have received at least 1 but no more than 3 prior lines of systemic therapy and for whom single-agent therapy is appropriate as the next line of therapy. Participants may have been treated with up to 1 line of therapy subsequent to determination of platinumresistance.
- Participants must have received prior treatment with bevacizumab or must be deemed medically inappropriate or ineligible/intolerant to receive bevacizumab, refused to receive bevacizumab, or been unable to receive bevacizumab due to lack of access.

  NOTES:

  Neoadjuvant ± adjuvant chemotherapy will be considered 1 line of therapy.

  Maintenance therapy (eg, bevacizumab, poly [adenosine disphosphate-ribose] polymerase [PARP] inhibitors) will be considered part of the preceding line of therapy.

  Therapy changed in the absence of progression will be considered part of the same line.
- Disease progression per RECIST v1.1 (by investigator assessment) of at least 1 measurable lesion on or after the most recent therapy.
- Either formalin-fixed, paraffin-embedded tissue (up to [redacted] old) or newly-obtained biopsies must be available for FRα assessment prior to randomization. The tumor sample (tissue block [preferred] or a minimum of [redacted] unstained slides) must be evaluable for FRα IHC analysis to meet eligibility criteria. Sample resubmission will be permitted for participants with non-evaluable FRα IHC who are otherwise eligible.
- Eastern Cooperative Oncology Group Performance Status of 0 or 1.
- Participant must be ≥ 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) at the time of signing the informed consent form.

Main Exclusion Criteria:

- Clear cell, mucinous, endometrioid or sarcomatous histology, or mixed tumors containing components of any of these histologies, or low grade or borderline ovarian cancer.
- Primary platinum-refractory ovarian cancer is defined as disease progression within 1 month of the last dose of the first line platinum-containing regimen.
- Pulmonary function test abnormalities: FEV1 < 70% or FVC < 60%, and DLCO < 80%.
- Investigator-assessed current ILD/pneumonitis, or ILD/pneumonitis suspected at screening or history of ILD/pneumonitis of any severity including ILD/pneumonitis from prior anti-cancer therapy.

- Current infectious pneumonia, history of viral pneumonia (including coronavirus disease 2019 [COVID-19]-related infection) with evidence of persistent radiologic abnormalities.
- Significant third-space fluid retention (e.g., ascites or pleural effusion) that requires repeated drainage.
- Clinically significant pericardial effusion requiring drainage.
- Prior pneumonectomy. Prior lobectomy and segmentectomy are allowed >12 months before treatment.
- Recent chest radiotherapy. Participants with chest or chest wall radiation (eg, history of breast cancer) may be permitted if the radiation is documented > 6 months before starting study treatment.
- Any autoimmune, connective tissue, or inflammatory disorders (eg, rheumatoid arthritis, Sjögren's syndrome, sarcoidosis, etc) where there is documented (or suspicion of) pulmonary involvement.
- Spinal cord compression or untreated, symptomatic central nervous system (CNS) metastases. Participants are eligible if CNS metastases are asymptomatic and do not require immediate treatment, or have been treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). In addition, participants have discontinued anticonvulsant therapy and must have been either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to treatment. Imaging performed within 28 days prior to treatment must document radiographic stability of CNS lesions and be performed after completion of any CNS-directed therapy.
- Concurrent malignancy (present during screening) requiring treatment, or history of prior malignancy active within 2 years prior to randomization (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the participant has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.
- Participants with a condition requiring systemic treatment with either corticosteroids > 10 mg daily prednisone equivalents or other immunosuppressive medications within 14 days of study treatment administration, except for steroid adrenal replacement where doses of > 10 mg daily prednisone equivalent, are allowed in the absence of active autoimmune disease.
  - Treatment with a short course (< 5 days) of steroids up to 7 days prior to initiating study treatment is permitted.

Intervention Groups and Duration:

At least 90 evaluable participants will be randomized in a [redacted] ratio to:

- [redacted] (N = [redacted]): MORAb-202 25 mg/m^2 [redacted]
- [redacted] (N = [redacted]): Investigator's choice (IC) single-agent chemotherapy:
  - Paclitaxel 80 mg/m^2 intravenous (IV) on Days 1, 8, 15, and 22 of a 28-day cycle; or
  - Pegylated liposomal doxorubicin (PLD) 40 mg/m^2 IV on Day 1 of a 28-day cycle; or

- Topotecan 4 mg/m^2 IV on Days 1, 8, and 15 of a 28-day cycle or 1.25 mg/m^2 on 5 consecutive days on Days 1 to 5 of a 21-day cycle

Study Intervention:

Study Interventions for CA116001		
Intervention Name	**Unit Dose Strength(s)**	**IMP/Non-IMP/AxMP**
MORAb-202 Lyophilized Powder in a Single Use Vial	[redacted] mg/mL	IMP
Paclitaxel	6 mg/mL	IMP
Pegylated Liposomal Doxorubicin (PLD)	2 mg/mL	IMP
Topotecan	1 mg/mL	IMP

Abbreviations: AxMP, auxiliary medicinal product; IMP, investigational medicinal product; PLD, pegylated liposomal doxorubicin.

Statistical Methods:

[redacted]

Data Monitoring Committee: No

A Data Monitoring Committee (DMC) will not be used in the study.

Given this is an early phase, open-label study, an independent DMC is not commissioned. Nonetheless, the safety of the participants will be closely monitored through a Safety Committee including external members to the Sponsor.

Other Committee: Yes

A Safety Committee will be established to provide oversight of the benefit/risk for the participants enrolled in the CA116001 study and give advice to the Sponsor regarding actions that the committee deems necessary for the continued protection of the participants enrolled. Additionally, an external ILD Expert Review Committee will provide further ILD oversight on the study.

Brief Summary:

CA116001 is a Phase 2 open-label, randomized study assessing the efficacy, safety, and tolerability of MORAb-202. The study research hypothesis is that MORAb-202 will have a favorable benefit risk profile at 25 mg/m^2, compared to IC chemotherapy, as measured by ORR

and safety profile in participants with platinum-resistant HGS ovarian, primary peritoneal, or fallopian tube cancer.

Study Duration: Approximately 4 years

Study Intervention Duration: Until progression, unacceptable toxicity, withdrawal of consent, death, or end of study (whichever occurs first)

Study Visit Frequency:

- [redacted] (MORAb-202 at 25 mg/m^2): [redacted]
- [redacted] (IC Chemotherapy):
  - Paclitaxel: Every 4 weeks. However, paclitaxel will be administered in the clinic on Days 1, 8, 15, and 22 of a 28-day cycle
  - Topotecan 21-day cycle: Every 3 weeks. However, topotecan will be administered in the clinic on Days 1 to 5 of a 21-day cycle
  - Topotecan 28-day cycle: Every 4 weeks. However, topotecan will be administered in the clinic on Days 1, 8, and 15 of a 28-day cycle
  - PLD: Every 4 weeks

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA116001)

Procedure[a]	Screening Visit (Day -28 to Day 1)	Notes[b] All windows are based on calendar days
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed; informed consent must be obtained prior to performing any screening procedures that are not conducted as part of the participant's routine clinical management. Study allows for re-enrollment of a participant who has discontinued the study as a screen failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from Interactive Response Technology (IRT). For participants who may take part remotely, prescreening will be done via a telephone call, and the informed consent will be obtained remotely using a telemedicine module (decentralized clinical trial [DCT] platform) and an electronic consent form, where allowed by applicable local laws and regulations. More details of the consenting process are provided in Appendix 2.
IRT Registration	X	Register in IRT system to obtain participant number at the time informed consent is obtained.
Informed Consent for Optional Sample Collection	X	Consent for optional sample collection can be collected at a later visit if needed.
[redacted]		
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization. See Section 6.1 and Section 6.2.
Demography	X	
Medical History	X	All general medical history, as well as any relevant history to the disease under study, including American Joint Committee on Cancer (AJCC) 8th edition classifications (refer to Appendix 5), histology, breast cancer gene (BRCA) mutation status, smoking history, alcohol use, history of pulmonary-related conditions, and other relevant history. Include any toxicities or allergies to previous treatments. Include findings from physical examination.

Table 2-1: Screening Procedural Outline (CA116001)

Procedure[a]	Screening Visit (Day -28 to Day 1)	Notes[b] All windows are based on calendar days
Prior Cancer Therapies	X	Include details and dates of prior anti-cancer systemic therapy, radiation therapy, and surgery.
Investigator's Choice (IC) of Chemotherapy before Randomization	X	The investigator will select a single-agent chemotherapy regimen to be administered if randomized to [redacted] paclitaxel, PLD, or topotecan (see Section 7.1, Section 7.1.2, Section 7.1.3, and Section 7.1.4). The selection must be determined during screening, prior to randomization, and must be documented and captured in the eCRF. The selection of agent and regimen may not be changed after the participant has been randomized unless discussed with and approved by the Medical Monitor (or designee).
Safety Assessments		
Physical Examination (PE), Vital Signs, and Measurements	X	Includes BP, HR, temperature, height, weight, BMI, respiratory rate, and BSA (see Section 7.1.5 for details on BSA calculations). BP and HR should be measured after the participant has been resting quietly for at least 5 minutes. Must be collected within 14 days prior to randomization. Any findings during the PE will be recorded as medical history in the participant's medical records and on the appropriate CRF.
Pulmonary Function Tests (PFTs)	X	Forced vital capacity (FVC), total lung capacity (TLC), forced expiratory volume during first second of expiration (FEV1), and diffusing capacity of the lungs for carbon monoxide (DLCO; %) must be collected within 14 days prior to randomization.
Pulse Oximetry	X	Oxygen saturation (SpO_2) by pulse oximetry collected at rest and immediately after exercise (eg, walking for at least 6 minutes or equivalent effort) within 14 days prior to randomization.
ECOG Performance Status (PS)	X	Eastern Cooperative Oncology Group (ECOG) PS must be collected within 14 days prior to randomization. Refer to Appendix 6.
Prior/Concomitant Medication Use	X	Within 14 days prior to randomization. Vaccine use within 30 days prior to first study treatment. See Section 7.7.

Table 2-1: Screening Procedural Outline (CA116001)

Procedure[a]	Screening Visit (Day -28 to Day 1)	Notes[b] All windows are based on calendar days
12-lead Electrocardiogram (ECG)	X	ECGs should be recorded after the participant has been supine for at least 5 minutes. Within 28 days prior to randomization.
ECHO/MUGA (PLD only)	X	Only for participants intended to receive PLD as the IC chemotherapy agent. LVEF assessment with documented LVEF by either transthoracic echocardiogram (TTE, preferred test) or MUGA.
Laboratory Tests		See Section 9.4.4.
Clinical Laboratory Assessments	X	Includes blood and urine samples. Note: 12- or 24-hour urine collections is required for CrCl measurments. On-site/local laboratory tests must be performed within 14 days prior to randomization. See Section 9.4.4 for list of laboratory tests to conduct.
Pregnancy Test (WOCBP Only)	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be performed at screening visit and repeated within 24 hours prior to first dose of study treatment. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive. Refer to Appendix 4.
Follicle-stimulating Hormone (FSH)	X	Required to confirm menopause in women < 55 years of age. Refer to Appendix 4.
Serology	X	Includes hepatitis C virus (HCV) indicating presence of active viral replication (detectable HCV ribonucleic acid [RNA]), hepatitis B surface antigen, and human immunodeficiency virus [HIV]-1 and HIV-2 antibody. HIV testing to be performed based on local requirements. Refer to Appendix 7.

Table 2-1: Screening Procedural Outline (CA116001)

Procedure[a]	Screening Visit (Day -28 to Day 1)	Notes[b] All windows are based on calendar days
[redacted]		
Tumor Sample	X	[redacted] Sample resubmission will be required for a result of "not evaluable." If an archival tumor sample is not available or does not meet requirements, a fresh biopsy may be required during the 28-day screening period but prior to randomization. See Section 5.6.2.1 for further guidance on fresh tumor sample collection. A FFPE tumor tissue block (preferred) or [redacted] unstained slides (minimum of [redacted]) of tumor tissue from core biopsy, punch biopsy, excisional biopsy, or surgical specimen obtained during screening or prior to enrollment must be sent to the vendor. If slides are submitted, the unstained slides should be sectioned within [redacted] from the latest FFPE block, which should not be more than [redacted]. Fine needle aspirates, other cytology samples, and bone biopsy samples are not acceptable. The Sponsor's identified vendor must provide IRT with confirmation of receipt of evaluable tumor tissue [redacted] prior to participant randomization. Every effort should be made to obtain tumor tissue at the start of the screening period to account for shipping time and IHC analysis. Please refer to the laboratory manual, Section 5.6.2, [redacted] for additional information.
Baseline Tumor Assessments		
Body Imaging[c]	X	Contrast-enhanced computed tomography (CT) of the chest abdomen, pelvis, and all other known and/or suspected sites of disease within 28 days prior to randomization. See Section 9.1.1 for further details.

Table 2-1: Screening Procedural Outline (CA116001)

Procedure[a]	Screening Visit (Day -28 to Day 1)	Notes[b] All windows are based on calendar days
Brain Imaging[c]	X	Magnetic resonance imaging (MRI) of the brain (without and with contrast) is required for participants with known or suspected brain metastases, unless participant has completed an imaging study of the brain within 28 days of randomization. CT of the brain (without and with contrast) can be performed if MRI is contraindicated. See Section 9.1.1 for further details.
Adverse Event (AE) Reporting		
Assessment of Signs/Symptoms/Clinical Complaints	X	Within 14 days prior to randomization.
Monitor for Serious and Non-serious AEs	X	All AEs and SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection must be collected from the start of the participant's written consent. AEs/SAEs must be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).
[redacted]		

Abbreviations: AE, adverse event; AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; BMI, body mass index; BP, blood pressure; BRCA, breast cancer gene; BSA, body surface area; CRF, case report form; CT, computed tomography; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; DCT, decentralized clinical trial; DLCO, carbon monoxide diffusing capacity; ECG, electrocardiogram; ECHO, echocardiogram;

ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; [redacted] FEV1, forced expiratory volume in the first second of expiration; FFPE, formalin-fixed paraffin-embedded; [redacted]; FSH, follicle-stimulating hormone; FVC, forced vital capacity; HCG, human chorionic gonadotropin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, heart rate; IC, Investigator's choice; IHC, immunohistochemistry; IRT, Interactive Response Technology; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multigated acquisition; NCI, National Cancer Institute; PE, physical examination; PFT, pulmonary function test; PLD, pegylated liposomal doxorubicin; PS, performance status; RNA, ribonucleic acid; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO_2, oxygen saturation; TLC, total lung capacity; TTE, transthoracic echocardiogram; WOCBP, women of child-bearing potential.

[a] Screening safety, laboratory, [redacted] that are performed within 3 days prior to dosing on Cycle 1 Day 1 and prior to randomization do not need to be repeated at the Cycle 1 Day 1 visit.

[b] Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

[c] Images will be submitted to a central imaging vendor for blinded independent central review (BICR). [redacted] See Section 9.1.2.

[redacted]

Table 2-2: On-treatment Procedural Outline for MORAb-202 [redacted]

Procedure [redacted]	Cycle 1[a]			Cycle 2 onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8 ± 3 days	D15 ± 3 days	D1 ± 3 days[c]		
Safety Assessments[d]						
Targeted PE/Vital Signs	X	X	X	X	X	If the screening full PE is performed within 24 hours prior to dosing on Day 1, then a single examination may count as both the screening and predose evaluation. Vital signs include BP, HR, respiratory rate, and temperature. BP and HR should be measured after the participant has been resting quietly for at least 5 minutes. Any findings from the PE will be reported on the AE CRF as appropriate.
Weight/[redacted]	X			X		[redacted].
Pulse Oximetry	X	X	X	X	X	Oxygen saturation (SpO_2) by pulse oximetry collected at rest and immediately after exercise (eg, walking for at least 6 minutes or equivalent effort).
PFTs	As Clinically Indicated					PFTs include FVC, TLC, FEV1, DLCO (%). Perform as clinically indicated for assessment of pulmonary abnormalities.
ILD/Pneumonitis Signs/ Symptoms Assessment	Continuously					To be performed on the day of each scheduled MORAb-202 dose, prior to MORAb-202 administration. See Section 9.4.5 for further information regarding detection & monitoring of ILD/pneumonitis. [redacted] For reporting information see Section 9.2.9. [redacted]

Table 2-2: On-treatment Procedural Outline for MORAb-202 [redacted]

Procedure [redacted]	Cycle 1[a]			Cycle 2 onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8 ± 3 days	D15 ± 3 days	D1 ± 3 days[c]		
						[redacted]
ECOG PS	X	X	X	X	X	Prior to treatment on Day 1 of each cycle. Refer to Appendix 6.
12-lead ECG	As Clinically Indicated				X	To be performed at screening, EOT, and as clinically indicated during treatment. ECGs should be recorded after the participant has been supine for at least 5 minutes.
Laboratory Tests						
Clinical Laboratory Assessments	X[d]			X	X	Includes blood and urine samples. Perform on site/local laboratory testing within 3 days prior to Day 1 dosing of each cycle. For the first treatment visit, labs need not be repeated if they were performed within 3 days and the results are available and have been reviewed for eligibility. See Section 9.4.4 for the list of laboratory tests to be conducted.
Pregnancy Test (WOCBP only)	X	See Notes				For WOCBP only. Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) to be performed within 24 hours prior to first dose of study treatment and then every 4 weeks (± 1 week) regardless of dosing schedule. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such

Table 2-2: On-treatment Procedural Outline for MORAb-202 [redacted]

Procedure [redacted]	Cycle 1[a]			Cycle 2 onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8 ± 3 days	D15 ± 3 days	D1 ± 3 days[c]		
						cases, the participant must be discontinued from study treatment if the serum pregnancy result is positive. Refer to Appendix 4 for further information.
Adverse Event Reporting						
Monitor for Non-serious and Serious AEs	Continuously					Record at each visit. All AEs and SAEs, including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. All AEs/SAEs must be graded using CTCAE v5.0. All AEs and SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
Concomitant Medication Use	Continuously					Record at each visit.
[redacted]						
Efficacy Assessments						
Body Imaging[e]	See Notes					Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 6 weeks (± 1week) starting from randomization for the first 36 weeks, then every 12 weeks

Table 2-2: On-treatment Procedural Outline for MORAb-202

Procedure	Cycle 1[a]			Cycle 2 onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8 ± 3 days	D15 ± 3 days	D1 ± 3 days[c]		
						(± 1 week) until investigator-assessed disease progression per RECIST v1.1 or treatment discontinuation, whichever occurs later. This schedule should be followed even if treatment delay occurs. In the event of unscheduled imaging, efforts should be made to return to the planned schedule for subsequent visits. See Section 9.1.1 for further details.
Brain Imaging[e]	See Notes					Participants with a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) per standard of care (approximately every 12 weeks), or sooner if clinically indicated until investigator-assessed disease progression per RECIST v1.1 or treatment discontinuation, whichever occurs later. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.

Table 2-2: On-treatment Procedural Outline for MORAb-202 [redacted]

Procedure [redacted]	Cycle 1[a]			Cycle 2 onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8 ± 3 days	D15 ± 3 days	D1 ± 3 days[c]		
[redacted]						
Study Treatment						
Randomization	X					Participants must receive the first dose of study treatment within 3 calendar days from treatment allocation, unless previously discussed with Medical Monitor (or designee).
MORAb-202 Premedication	X	See Notes				Premedication will be administered with the first MORAb-202 infusion (30 to 60 minutes prior to infusion). If no infusion reactions are observed, premedications will not be administered with subsequent MORAb-202 infusions (see Section 7.1.1).
MORAb-202 Administration[g]	X			X		MORAb-202 will be administered at a dose of 25 mg/m^2 once [redacted] as an IV infusion [redacted] The first infusion of MORAb-202 will be given over no less than 60 minutes. If no infusion reactions are observed, subsequent infusions can be infused as tolerated, but given over no less than 30 minutes. See Section 7.1.1 for further details on administration. Dose will be recalculated every cycle based on the weight on the day of the dosing. All doses should be rounded to the nearest

Table 2-2: On-treatment Procedural Outline for MORAb-202 [redacted]

Procedure [redacted]	Cycle 1[a]			Cycle 2 onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8 ± 3 days	D15 ± 3 days	D1 ± 3 days[c]		
						milligram. See Section 7.1.5 for details on dose calculations. See Section 7.4.1 for dose modifications for management of AEs.

Abbreviations: AE, adverse event; BICR, blinded independent central review; BP, blood pressure; [redacted] CRF, case report form; CT, computed tomography; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; D, day; DLCO, carbon monoxide diffusing capacity; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; [redacted] FEV1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; HCG, human chorionic gonadotropin; HR, heart rate; ILD, interstitial lung disease; IV, intravenous; MRI, magnetic resonance imaging; PE, physical examination; PFT, pulmonary function test; [redacted] PS, performance status; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO_2, oxygen saturation; TLC, total lung capacity; WOCBP, women of child-bearing potential.

[a] If study treatment dosing is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when the time point's dosing actually occurs, with the exception of tumor assessments and AE-related safety procedures/assessments.

[b] EOT is defined as the date at which the decision is made to discontinue the participant from study treatment. Participants must be followed for at least 30 days after the last dose of study treatment or the date of discontinuation, whichever occurs later. The safety follow-up visit should occur 30 days (+ 7 days) from EOT visit; if EOT occurs ≥ 30 days from last dose administration, then a single visit for EOT and safety follow-up is allowed.

[c] Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

[d] Screening safety, laboratory, [redacted] that are performed within 3 days prior to dosing on Cycle 1 Day 1 and prior to randomization do not need to be repeated at the Cycle 1 Day 1 visit.

[e] Images will be submitted to a central imaging vendor for blinded independent central review (BICR). [redacted] See Section 9.1.2.

[redacted]

[g] The minimum time interval between 2 consecutive MORAb-202 doses cannot be < 18 days.

Table 2-3: On-treatment Procedural Outline for a 21-Day Cycle [redacted] Topotecan 1.25 mg/m^2

Procedure (1 Cycle = 21 Days)	Cycle 1[a]			Cycle 2 onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8 ± 3 days	D15 ± 3 days	D1 ± 3 days[c]		
Safety Assessments[d]						
Targeted PE/Vital Signs	X			X	X	If the screening full PE is performed within 24 hours prior to dosing on Day 1, then a single examination may count as both the screening and predose evaluation. Vital signs include BP, HR, respiratory rate, and temperature. BP and HR should be measured after the participant has been resting quietly for at least 5 minutes. Any findings from the PE will be reported on the AE CRF as appropriate.
Weight/[redacted]	X			X		[redacted]
ECOG PS	X			X	X	Prior to treatment on Day 1 of each cycle. Refer to Appendix 6.
12-lead ECG	As Clinically Indicated				X	To be performed at screening, EOT, and as clinically indicated during treatment. ECGs should be recorded after the participant has been supine for at least 5 minutes.
Laboratory Tests						
Clinical Laboratory Assessments	X[d]			X	X	Includes blood and urine samples. Perform on site/local laboratory testing within 3 days prior to Day 1 dosing of each cycle. For the first treatment visit, labs need not be repeated if they were performed within 3 days and the results are available and have been reviewed for eligibility. See Section 9.4.4 for the list of laboratory tests to be conducted.

Table 2-3: On-treatment Procedural Outline for a 21-Day Cycle [redacted] Topotecan 1.25 mg/m^2

Procedure (1 Cycle = 21 Days)	Cycle 1[a]			Cycle 2 onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8 ± 3 days	D15 ± 3 days	D1 ± 3 days[c]		
Pregnancy Test (WOCBP only)	X	See Notes				For WOCBP only. Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) to be performed within 24 hours prior to first dose of study treatment and then every 4 weeks (± 1 week) regardless of dosing schedule. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be discontinued from study treatment if the serum pregnancy result is positive. Refer to Appendix 4 for further information.
Adverse Event Reporting						
Monitor for Non-serious and Serious AEs	Continuously					Record at each visit. All AEs and SAEs, including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. All AEs/SAEs must be graded using CTCAE v5.0. All AEs and SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
Concomitant Medication Use	Continuously					Record at each visit.
[redacted]						

Table 2-3: On-treatment Procedural Outline for a 21-Day Cycle [redacted] Topotecan 1.25 mg/m^2

Procedure (1 Cycle = 21 Days)	Cycle 1[a]			Cycle 2 onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8 ± 3 days	D15 ± 3 days	D1 ± 3 days[c]		
Efficacy Assessments						
Body Imaging[e]	See Notes					Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 6 weeks (± 1 week) starting from randomization for the first 36 weeks, then every 12 weeks (± 1 week) until investigator-assessed disease progression per RECIST v1.1 or treatment discontinuation, whichever occurs later. This schedule should be followed even if treatment delay occurs. In the event of unscheduled imaging, efforts should be made to return to the planned schedule for subsequent visits. See Section 9.1.1 for further details.
Brain Imaging[e]	See Notes					Participants with a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) per standard of care (approximately every 12 weeks), or sooner if clinically indicated until investigator-assessed disease progression per RECIST v1.1or treatment discontinuation, whichever occurs later. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.
[redacted]						

Table 2-3: On-treatment Procedural Outline for a 21-Day Cycle [redacted] Topotecan 1.25 mg/m^2

Procedure (1 Cycle = 21 Days)	Cycle 1[a]			Cycle 2 onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8 ± 3 days	D15 ± 3 days	D1 ± 3 days[c]		
[redacted]						
Study Treatment						
Randomization	X					Participants must receive the first dose of study treatment within 3 calendar days from treatment allocation, unless previously discussed with Medical Monitor (or designee).
Topotecan Administration	See Notes					For a 21-day cycle, topotecan will be administered at a dose of 1.25 mg/m^2 by IV infusion over 30 minutes on Days 1 to 5 of a 21-day cycle. Other study-related assessments and procedures are not required for Days 2 to 5. See Section 7.1.4 for further details on administration. Refer to the approved local Product Label for complete information. Dose calculations will be performed using BSA and body weight assessed within 3 days prior to start of study dose administration on Cycle 1 Day 1. Dose will be recalculated every cycle based on the weight on the day of the dosing. All doses should be rounded to the nearest milligram. See Section 7.1.5 for details on dose calculations. See Section 7.4.4 for dose modifications for management of AEs.

Abbreviations: AE, adverse event; BICR, blinded independent central review; BP, blood pressure; BSA, body surface area; CRF, case report form; CT, computed tomography; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; [redacted]

[redacted]HCG, human chorionic gonadotropin; HR, heart rate; IU, international unit; IV, intravenous; MRI, magnetic resonance imaging; PE, physical examination; PS, performance status; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of child-bearing potential.

[a] If study treatment dosing is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when the time point's dosing actually occurs, with the exception of tumor assessments and AE-related safety procedures/assessments.

[b] EOT is defined as the date at which the decision is made to discontinue the participant from study treatment. Participants must be followed for at least 30 days after the last dose of study treatment or the date of discontinuation, whichever occurs later. The safety follow-up visit should occur 30 days (+ 7 days) from EOT visit; if EOT occurs ≥ 30 days from last dose administration, then a single visit for EOT and safety follow-up is allowed.

[c] Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

[redacted]

[e] Images will be submitted to a central imaging vendor for blinded independent central review (BICR). [redacted] See Section 9.1.2.

[redacted]

Table 2-4: On-treatment Procedural Outline for a 28-Day Cycle - [redacted] (PLD, Paclitaxel, and Topotecan 4 mg/m^2)

Procedure (1 Cycle = 28 Days)	Cycle 1[a]				Cycle 2, onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8	D15	D22	D1 ± 3 days[c]		
Safety Assessments[d]							
Targeted PE/Vital Signs	X				X	X	If the screening full PE is performed within 24 hours prior to dosing on Day 1, then a single examination may count as both the screening and predose evaluation. Vital signs include BP, HR, respiratory rate, and temperature. BP and HR should be measured after the participant has been resting quietly for at least 5 minutes.
Weight/[redacted]	X				X		[redacted]
ECOG PS	X				X	X	Prior to treatment on Day 1 of each cycle. Refer to Appendix 6.
12 Lead ECG	As Clinically Indicated					X	To be performed at screening, EOT, and as clinically indicated during treatment. ECGs should be recorded after the participant has been supine for at least 5 minutes. ECGs will be performed locally.
ECHO/MUGA (PLD only)	See Notes					X	To be performed at screening and every 4 cycles from screening assessment or as medically indicated. Performed locally with the same assessment of LVEF used at screening.

Table 2-4: On-treatment Procedural Outline for a 28-Day Cycle - [redacted] (PLD, Paclitaxel, and Topotecan 4 mg/m^2)

Procedure (1 Cycle = 28 Days)	Cycle 1[a]				Cycle 2, onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8	D15	D22	D1 ± 3 days[c]		
Laboratory Tests							
Clinical Laboratory Assessments	X[d]	X[e]	X[e]	X[e]	X	X	Includes blood and urine samples. Perform on site/local laboratory testing within 3 days prior to Day 1 dosing of each cycle. Hematologic and chemistry laboratory assessments to be performed at every treatment visit for paclitaxel or topotecan 4mg/m^2. All other clinical laboratory assessments (see Table 9.4.4-1) will be performed at the start of each cycle. For participants receiving PLD, all clinical laboratory assessments to be performed at every cycle. For the first treatment visit, labs need not be repeated if they were performed within 3 days and the results are available and have been reviewed for eligibility. See Section 9.4.4 for the list of laboratory tests to be conducted.
Pregnancy Test (WOCBP)	X	See Notes				X	For WOCBP only. Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) to be performed within 24 hours prior to first dose of study treatment and then every 4 weeks (± 1 week) regardless of dosing schedule. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be discontinued from study treatment if the serum pregnancy result is positive. Refer to Appendix 4.

Table 2-4: On-treatment Procedural Outline for a 28-Day Cycle - [redacted] (PLD, Paclitaxel, and Topotecan 4 mg/m^2)

Procedure (1 Cycle = 28 Days)	Cycle 1[a]				Cycle 2, onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8	D15	D22	D1 ± 3 days[c]		
Adverse Event Reporting							
Monitor for Non-serious and Serious AEs	Continuously						Record at each visit. All AEs and SAEs, including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. All AEs/SAEs must be graded using CTCAE v5.0. All AEs and SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
Concomitant Medication Use	Continuously						Record at each visit.
[redacted]							

Table 2-4: On-treatment Procedural Outline for a 28-Day Cycle - [redacted] (PLD, Paclitaxel, and Topotecan 4 mg/m^2)

Procedure (1 Cycle = 28 Days)	Cycle 1[a]				Cycle 2, onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8	D15	D22	D1 ± 3 days[c]		
Efficacy Assessment							
Body Imaging[f]	See Notes						Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 6 weeks (± 1 week) starting from randomization for the first 36 weeks, then every 12 weeks (± 1 week) until investigator-assessed disease progression per RECIST v1.1 or treatment discontinuation, whichever occurs later. This schedule should be followed even if treatment delay occurs. In the event of unscheduled imaging, efforts should be made to return to the planned schedule for subsequent visits. See Section 9.1.1 for further details.
Brain Imaging[f]	See Notes						Participants with a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) per standard of care (approximately every 12 weeks), or sooner if clinically indicated until investigator-assessed disease progression per RECIST v1.1 or treatment discontinuation, whichever occurs later. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.
[redacted]							

Table 2-4: On-treatment Procedural Outline for a 28-Day Cycle - [redacted] (PLD, Paclitaxel, and Topotecan 4 mg/m^2)

Procedure (1 Cycle = 28 Days)	Cycle 1[a]				Cycle 2, onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8	D15	D22	D1 ± 3 days[c]		
[redacted]							
Study Treatment							
Randomization	X						Participants must receive the first dose of study treatment within 3 calendar days from treatment allocation, unless previously discussed with Medical Monitor (or designee).
Paclitaxel Premedication	See Notes						[redacted] participants receiving paclitaxel should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions, per the approved local Product Label. Such premedication may consist of dexamethasone 20 mg PO 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.
Paclitaxel Administration	See Notes						Paclitaxel will be administered at a dose of 80 mg/m^2 by IV infusion over 60 minutes on Days 1, 8, 15, and 22 of a 28-day cycle. Use BSA for dosing calculations using height measured at screening, and weight measured on Day 1 of each cycle (or up to 3 days prior to Day 1). See Section 7.4.2 for dose modifications for management of AEs. See Section 7.1.2 for further details on administration. Refer to the approved local Product Label for complete information. Dose calculations will be performed using BSA and body weight assessed within 3 days prior to start of study dose administration on Cycle 1 Day 1. Dose will be recalculated every cycle based on the weight on the day of the dosing. All doses should be rounded to the nearest milligram. See Section 7.1.5 for details on dose calculations.

Table 2-4: On-treatment Procedural Outline for a 28-Day Cycle - [redacted] (PLD, Paclitaxel, and Topotecan 4 mg/m^2)

Procedure (1 Cycle = 28 Days)	Cycle 1[a]				Cycle 2, onwards[a]	EOT[b]	Notes
	D1 ± 3 days[c,d]	D8	D15	D22	D1 ± 3 days[c]		
Topotecan Administration	See Notes						For a 28-day cycle, topotecan will be administered at dose of 4 mg/m^2 by IV infusion over 30 minutes on Days 1, 8, and 15 of a 28-day cycle. Use BSA for dosing calculations using height measured at screening, and weight measured on Day 1 of each cycle (or up to 3 days prior to Day 1). See Section 7.4.4 for dose modifications for management of AEs. See Section 7.1.4 for further details on administration. Refer to the approved local Product Label for complete information. Dose calculations will be performed using BSA and body weight assessed within 3 days prior to start of study dose administration on Cycle 1 Day 1. Dose will be recalculated every cycle based on the weight on the day of the dosing. All doses should be rounded to the nearest milligram. See Section 7.1.5 for details on dose calculations.
PLD Administration[h]	X				X		PLD will be administered at a dose of 40 mg/m^2 by a 1 mg/min IV infusion on Day 1 (± 3 days) of a 28-day cycle. After Cycle 1, if tolerated, PLD can be administered as a 60-minute infusion. Use BSA for dosing calculations using height measured at screening, and weight measured on Day 1 of each cycle (or up to 3 days prior to Day 1). See Section 7.4.3 for dose modifications for management of AEs. See Section 7.1.3 for further details on administration. Refer to the approved local Product Label for complete information. Dose calculations will be performed using BSA and body weight assessed within 3 days prior to start of study dose administration on Cycle 1 Day 1. Dose will be recalculated every cycle based on the weight on the day of the dosing. All doses should be rounded to the nearest milligram. See Section 7.1.5 for details on dose calculations.

Abbreviations: AE, adverse event; BICR, blinded independent central review; BP, blood pressure; BSA, body surface area; CRF, case report form; CT, computed tomography; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; D, day; ECG, electrocardiogram; ECHO, echocardiogram; ECOG,

Eastern Cooperative Oncology Group; [redacted] HCG, human chorionic gonadotropin; HR, heart rate; IU, international unit; IV, intravenous; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multigated acquisition; PE, physical examination; PLD, pegylated liposomal doxorubicin; PO, per os (oral route of administration); PS, performance status; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of child-bearing potential.

[a] If study treatment dosing is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when the time point's dosing actually occurs, with the exception of tumor assessments and AE-related safety procedures/assessments.

[b] EOT is defined as the date at which the decision is made to discontinue the participant from study treatment. Participants must be followed for at least 30 days after the last dose of study treatment or the date of discontinuation, whichever occurs later. The safety follow-up visit should occur 30 days (+ 7 days) from EOT visit; if EOT occurs ≥ 30 days from last dose administration, then a single visit for EOT and safety follow-up is allowed.

[c] Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

[redacted]

[e] Hematologic and chemistry laboratory assessments only for participants receiving paclitaxel or topotecan.

[f] Images will be submitted to a central imaging vendor for blinded independent central review (BICR). [redacted] See Section 9.1.2.

[redacted].

[h] The minimum time interval between 2 consecutive PLD doses cannot be < 24 days.

Table 2-5: Follow-up Procedural Outline (CA116001)

Procedure	Safety Follow-up Visit[a,]	Survival Follow-up[b,c]	Notes
Safety Assessments			
Targeted PE/Vital Signs	X		Includes BP, HR, respiratory rate, and temperature. BP and HR should be measured after the participant has been resting quietly for at least 5 minutes. Any findings from the PE will be reported on the AE CRF as appropriate.
ECOG PS	X		Refer to Appendix 6.
Pulse Oximetry (MORAb-202 only)	X		Oxygen saturation (SpO_2) by pulse oximetry collected at rest and immediately after exercise (eg, walking for at least 6 minutes or equivalent effort).
ILD/Pneumonitis Signs/Symptoms Assessment (MORAb-202 only)	X		See Table 7.4.1-2, Section 9.2.9, and Section 9.4.5 for further information.
AE and SAE Assessment	X		Collect continuously throughout the treatment period and for a minimum of 30 days following treatment discontinuation. Participants will be followed for all SAEs, non-serious AEs of special interest, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution; the condition stabilizes; the event is otherwise explained; the event is deemed irreversible; the participant is lost to follow-up; or, for suspected cases, until SARS-CoV-2 infection is ruled-out. [redacted]
Concomitant Medication Use	X		Review/document all concomitant medications.
Laboratory Tests			
Pregnancy Test (WOCBP only)	X		Serum or urine pregnancy test. See Section 9.4.4.

Table 2-5: Follow-up Procedural Outline (CA116001)

Procedure	Safety Follow-up Visit[a,]	Survival Follow-up[b,c]	Notes
Clinical Laboratory Assessments	X		Includes blood and urine samples. On site/local laboratory testing. See Section 9.4.5 for the list of laboratory tests.
Efficacy Assessments			
Body Imaging[d]	See Notes		Only for participants who discontinue study treatment prior to documented radiographic progression per RECIST v1.1 (refer to Appendix 8). Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 6 weeks (± 7 days) starting from randomization for the first 36 weeks, then every 12 weeks (± 7 days) until investigator-assessed disease progression per RECIST v1.1. See Section 9.1.1 for further details. [redacted]
Brain Imaging[d]	See Notes		Only for participants who discontinue study treatment prior to documented radiographic progression per RECIST v1.1 (refer to Appendix 8). Participants with a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) per standard of care (approximately every 12 weeks), or sooner if clinically indicated, until investigator-assessed disease progression per RECIST v1.1. CT of the brain with and without contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.

Table 2-5: Follow-up Procedural Outline (CA116001)

Procedure	Safety Follow-up Visit[a,]	Survival Follow-up[b,c]	Notes
[redacted]			
Participant Status			
Subsequent Anti-cancer Therapy	X	X	Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therapy) and response to the regimen and date of progression.
Survival Status	X	X	Participant survival status will be assessed by a documented clinic visit, email, or telephone contact every 3 months (+/- 14 days) from safety follow-up visit up to 1 year from the last participant randomized or LPLV (30 days after last patient last treatment visit); whichever is later.

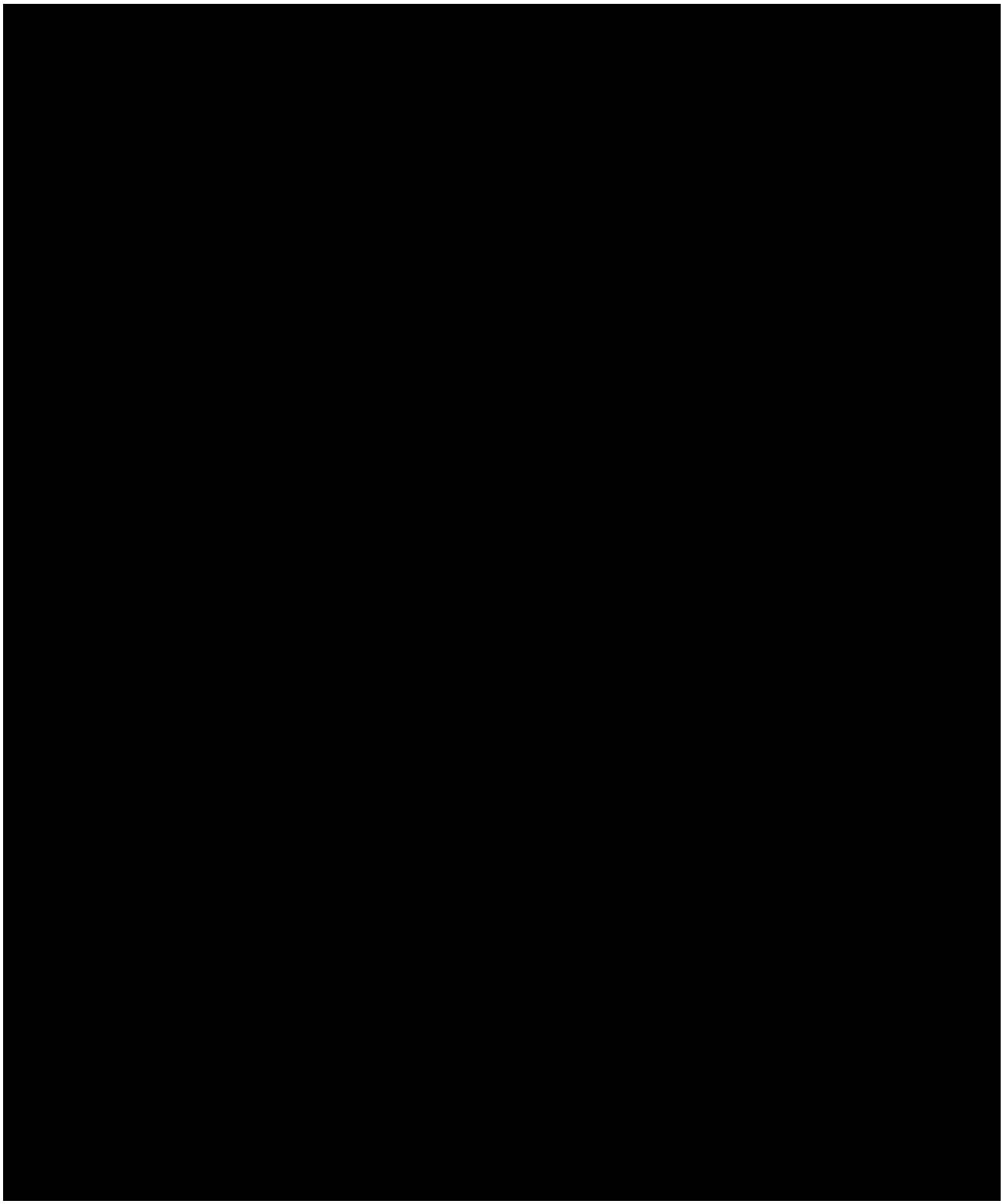
Abbreviations: AE, adverse event; BICR, blinded independent central review; BP, blood pressure; CRF, case report form; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; [redacted] HR, heart rate; ILD, interstitial lung disease; MRI, magnetic resonance imaging; PE, physical examination; SpO_2, oxygen saturation; [redacted] PS, performance status; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of child-bearing potential.

[a] Participants must be followed for at least 30 days after the last dose of study treatment or the date of discontinuation, whichever occurs later. The safety follow-up visit should occur 30 days (+ 7 days) from EOT visit; if EOT occurs ≥ 30 days from last dose administration, then a single visit for EOT and safety follow-up is allowed.

[b] Survival follow-up visits may be conducted in clinic or by telephone or via digital technology (including email and participant portal). The Sponsor may request that survival data be collected on all treated participants outside of the 3-month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

[c] Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulation.

[d] Images will be submitted to a central imaging vendor blinded independent central review (BICR). [redacted] See Section 9.1.2.



3 INTRODUCTION

Study CA116001 is a Phase 2, open-label, randomized, multicenter, study assessing the safety, tolerability, and efficacy of farletuzumab ecteribulin MORAb-202 (BMS-986445), a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC) in female participants with platinum-resistant high-grade serous (HGS) ovarian, primary peritoneal, or fallopian tube cancer.

Folate functions as a coenzyme to transfer one-carbon units that are necessary for deoxythymidylate synthesis, purine synthesis, and various methylation reactions, thus contributing to growth and development.[1] FRα, also known as FOLR1 or folate-binding protein, is a glycosylphosphatidylinositol-anchored membrane protein and is one of the cell surface receptors that internalizes folate. Interestingly, normal adult tissues mainly employ folate receptor β, reduced folate carrier and proton-coupled folate transporter for folate uptake, and FRα distribution is restricted to low level expression in the apical surfaces of some organs such as the kidney, lung, and choroid plexus. Importantly, in all normal tissues except the kidneys, the receptor is out of direct contact with folate and any folate receptor-targeting agents in the circulation. Up regulation of FRα occurs in epithelial cancer, and it has been demonstrated that in this setting FRα may function not only as a folate transporter but may also confer signaling and growth advantages on malignant cells.[2,3,4,5,6]

MORAb-202 is a novel ADC consisting of farletuzumab, a humanized monoclonal antibody that binds to FRα paired with eribulin (E7389) mesylate, a microtubule dynamics inhibitor, via a cathepsin B-cleavage linker (1:4 antibody-payload ratio).[7] Upon binding to FRα-expressing cancer cells, MORAb-202 is internalized into the lysosomal compartment where the novel serum-stable cathepsin B linker is enzymatically cleaved and releases the active payload, free eribulin, within the lysosomal compartment of target cells.

Once internalized, MORAb-202 elicits its anti-tumor activity through apoptosis mediated by free eribulin-inhibition of microtubule elongation and mitotic spindle formation. Moreover, MORAb-202 exhibits bystander antiproliferative activity against surrounding tumor cells in the tumor microenvironment (TME) by the release of free eribulin from apoptotic cancer cells. The payload, eribulin, also exerts anti-tumor activity within the TME and tumor phenotype by mechanisms independent of its antimitotic effects, such as i) tumor vasculature remodeling whereby inner tumor cores become better perfused and less hypoxic; and ii) promotion of cellular differentiation processes resulting in shifts to less aggressive phenotypes, either via reversal of the epithelial-mesenchymal transition (EMT) in carcinomas or tissue-specific differentiation of sarcomas.[8,9,10] Thus, MORAb-202 is expected to exhibit a bystander effect on the surrounding tumor microenvironment by eribulin leaching from apoptotic tumors, in addition to showing direct cytotoxicity against the targeted tumor.[11]

MORAb-202 has shown encouraging clinical activity in various solid tumor types that express FRα [redacted][11]

3.1 Study Rationale

There is an urgent clinical need for novel therapeutic approaches in platinum-resistant ovarian cancer (PROC). Despite progress in earlier lines of therapy, with the availability of new treatment modalities, patients with PROC still have a poor prognosis.

Debulking surgery and platinum-based chemotherapy form the foundation of care for the treatment of women with advanced ovarian cancer. Although many women with advanced disease may enter remission after surgery and chemotherapy, most patients will eventually relapse.[12,13] Depending upon the response of the last platinum-based therapy and time for recurrence, most women will receive additional platinum-based regimens on subsequent lines of therapy. With every additional line of platinum-based regimens, the progression-free survival (PFS) decreases.[14] A particular challenge arises when the disease returns less than 6 months after completing the last platinum-based chemotherapy, referred to as PROC. For these patients, additional lines of platinum-based chemotherapy usually provide a small clinical benefit; however, most patients will be only eligible to receive a single-agent non-platinum-based option (eg, pegylated liposomal doxorubicin [PLD], paclitaxel, or topotecan). Although these regimens can provide some clinical benefit, the observed objective response rate (ORR) is low (10% to 15%) with median PFS (mPFS) around 3.5 months. Patients with PROC have a median overall survival (mOS) of less than 1 year, thus highlighting the unmet medical need.[15,16,17,18]

FRα-directed ADC therapy is a potential treatment option for advanced ovarian cancer and is currently under investigation. Various epithelial tumors (eg, ovarian, endometrial, lung, head and neck) have demonstrated abundant FRα messenger ribonucleic acid (mRNA) expression by quantitative polymerase chain reaction and membrane protein expression by immunohistochemistry (IHC).[19] Although FRα expression is limited in normal ovary tissue, 80% to 90% of EOC tumors express FRα.[20,21] A recent meta-analysis suggests that higher expression of FRα is associated with poor survival of patients with cancer and may serve as a prognostic indicator.[22] Moreover, there is evidence that elevated FRα expression may be a negative prognostic marker for chemotherapeutic response in EOC.[23] In addition to its cell surface localization, FRα can be shed into the bloodstream as a soluble form. Soluble FRα (sFRα) levels correlate with local tumor FRα expression.[24] Higher serum concentrations of sFRα are indicative of the FRα expression status of the tumor and are correlated with clinical stage and poor prognosis.[25] FRα is an attractive target for ADC-based therapies due to its ability to internalize large molecules, its limited expression in normal tissues, and its overexpression in malignant cells, allowing for effective, targeted drug delivery.[20]

Preliminary efficacy and a manageable safety profile were observed in participants with PROC treated with MORAb-202 in a Phase 1 study, MORAb-202-J081-101 (hereafter referred to as Study 101), and a Phase 1/2 study, MORAb-202-G000-201 (hereafter referred to as Study 201), supporting further clinical development of MORAb-202 in this population.[11] Responses were observed in participants with solid tumors across a range of FRα expression levels, supporting the

evaluation in all randomized participants irrespective of their expression levels. See Section 3.2.3 for additional details on clinical efficacy and safety.

3.1.1 Research Hypothesis

MORAb-202 monotherapy will demonstrate a favorable overall benefit/risk profile compared to Investigator's choice (IC) chemotherapy in participants with HGS platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube cancer.

3.2 Background

Ovarian cancer is the second most common cause of gynecologic cancer death in women worldwide.[26] In the United States (US), ovarian cancer is the leading cause of death from gynecological cancer and the country's fifth most common cause of cancer mortality in women. Ovarian cancer remains a major cause of death, with an estimated 313,959 new cases in 2020 worldwide and a 5-year survival of 30.3% for patients with advanced stage disease. For 2022, the American Cancer Society estimates 19,880 new cases and 12,810 deaths from ovarian cancer in the US, while 26,500 deaths are predicted by the World Health Organization and Eurostats in the European Union (EU) countries.[27,28]

Several types of malignancies arise from the ovary; however, EOCs comprise 90% of ovarian cancers. Epithelial cancers of ovarian, fallopian tube, and peritoneal origin exhibit similar clinical characteristics and, as such, are grouped together. Subtypes of EOC include high-grade serous, low-grade serous, endometrioid, clear cell, mucinous, and mixed subtypes. HGS ovarian carcinoma is the most common type of ovarian cancer and accounts for approximately 70% to 80% of all malignant ovarian neoplasms.[29] Most HGS ovarian carcinomas are diagnosed at an advanced stage (Stage III or IV) and have a poor overall prognosis. HGS carcinomas that are confined to the ovary at diagnosis are rare (< 10%).[30]

The initial treatment of advanced ovarian cancer involves a combination of cytoreductive surgery (either at the time of diagnosis or interval debulking) and chemotherapeutic agents. Platinum- and taxane-based chemotherapy is the global standard of care. However, despite cytoreductive (debulking) surgery and platinum-based chemotherapy, most patients will experience disease recurrence, requiring further treatment.[12]

The addition of bevacizumab as maintenance therapy after first line chemotherapy demonstrated an increase in PFS of up to 4 months. With the approval of bevacizumab-based chemotherapy in the front line and maintenance setting, outcomes have improved in ovarian cancer, and a large proportion of patients are expected to receive bevacizumab in the earlier lines of therapy and will no longer be eligible to receive bevacizumab in the PROC setting. Nevertheless, if not used in earlier lines, its use can be considered for patients with PROC in addition to single-agent chemotherapy, where it showed benefit in ORR (27.3%) and PFS (6.7 months) when compared to single-agent chemotherapy, but without survival benefit.[31]

Molecular analysis of HGS ovarian carcinomas by The Cancer Genome Atlas has shown that around half have aberrations in homologous recombination repair, a critical deoxyribonucleic

acid (DNA) damage response pathway.[32] Repair of DNA damage following platinum-based therapy has long been considered an important determinant of tumor chemosensitivity. Several genetic lesions causing homologous recombination deficiency (HRD) include germline and somatic breast cancer gene 1 (*BRCA1*) and *BRCA2* mutations as well as mutations of genes such as *ATM*, *CHEK2*, *RAD51,* and *MRE11A*, and epigenetic silencing of homologous recombination repair genes has also been described in HGS ovarian carcinomas.[13]

Furthermore, exploitation of HRD by inhibiting poly (adenosine diphosphate-ribose) polymerase (PARP), a DNA repair enzyme involved in base-excision repair, produces further disruption of DNA damage repair and has formed the basis of a new molecularly-targeted therapeutic strategy to treat ovarian cancer.[33] Recently, PARP inhibitor (PARPi) maintenance therapy has emerged as a strategy to prolong the period between platinum responses and disease relapse in the first-line and relapsed settings in both HRD and non-HRD tumors. However, as with platinum chemotherapy, many patients will eventually acquire resistance to PARPi treatment.

Antibody–drug conjugates (ADCs) are a novel approach that show promise as emerging therapy in ovarian cancer. ADC are composed of a monoclonal antibody (mAb) conjugated to a cytotoxic payload via a chemical linker and are tailored to highly specific target antigens expressed on cancer cell surfaces. ADCs are capable of delivering highly potent drugs to tumor cells while sparing normal cells, thus attenuating the clinical obstacles of traditional chemotherapy. Ovarian tumors differentially express a large number of tumor antigens such as FRα that are ideal candidates for this novel approach. Presently, there are several ADC undergoing clinical evaluation in ovarian cancer.[34]

Due to the overall high disease burden and likelihood of recurrence despite standard-of-care treatments, there remains an urgent unmet need for novel treatment approaches in advanced ovarian cancer. This study will investigate MORAb-202, a novel FRα-directed ADC, as a potential treatment option in this population.

3.2.1 Ovarian Cancer Racial and Ethnic Diversity

Data from the Surveillance, Epidemiology, and End Results (SEER) database project that in the US, ovarian cancer incidence rates are highest in Non-hispanic White (NHW) women, followed by Hispanic, Asian/Pacific Islander, and African American (AA) women (12.2, 10.6, 9.5, and 9.4 cases per 100,000 women, respectively).[35]Among NHW and AA women, the distribution of ovarian cancer is similar across the age groups, while Hispanic and Asian women are comparatively younger at the time of diagnosis than NHW or AA women.[36]

Although the incidence of epithelial ovarian cancer (EOC) is approximately 30% higher among NHW women than AA women,[37] AA women have a 5-year lower survival than NHW women (39% vs 48%, respectively).[38,39] The difference in relative survival between AA and NHW women is greatest for distant disease (18% vs 27%) respectively. This lower survival among AA women persists across both serous and non-serous (clear cell, endometrioid, mucinous) carcinoma. Hispanic and Asian women demonstrate similar or improved survival compared with NHW women.[36] A study evaluating the differences in survival between NHW and Asian women in

SEER from 1988 to 2009 reported that the 5-year disease-specific survival for Asian women was considerably higher than NHW women, 59.1% and 47.3%, respectively. This improved outcome persisted after adjustment for age, year of diagnosis, surgery, stage, and grade.[40]

This study plans to enroll and evaluate MORAb-202 in a diverse and representative patient population with PROC to explore any clinically meaningful differences [redacted] to inform safe and effective dosing regimens across the intended patient population.

3.2.2 Summary of Key Preclinical Data with MORAb-202

Preclinical data support clinical exploration of MORAb-202 in HGS platinum-resistant ovarian, primary peritoneal, and fallopian tube cancer, as proposed in this study. MORAb-202 is selectively cytotoxic to FRα-positive cells, with low levels of off-target killing. It demonstrates a clear in vitro bystander effect in mixed tumor cell populations of FRα-positive and FRα-negative cells. The total balance of the physicochemical properties of MORAb-202 could account for this clear in vitro bystander effect. Consistent with these in vitro profiles, MORAb-202 was highly efficacious against FRα-expression positive ovarian cancer (OC) tumor cell line-derived and patient-derived xenograft (PDX) models of human cancer with a single administration at 5 and 12.5 mg/kg.[41,7] MORAb-202 resulted in tumor regression against FRα-positive tumors. [redacted]

Please refer to the current MORAb-202 Global Investigator's Brochure (IB) for additional details.[11]

These results suggest that MORAb-202 may have antitumor [redacted] and warrants clinical investigation.

3.2.3 MORAb-202 Clinical Data

MORAb-202 clinical trial data are presented as of the cut-off date of 31-Aug-2021, unless otherwise specified. Please refer to the MORAb-202 IB for complete information on MORAb-202 clinical trials. See Section 3.3 for further information on overall benefit/risk.

MORAb-202 has been clinically evaluated in 2 clinical trials: Study 101 and Study 201. Across both trials, a total of 107 participants have been treated with MORAb-202. Study 101 is a first-in-human, open-label, dose-escalation and expansion study with a primary objective to

evaluate the safety, tolerability, and PK of MORAb-202 as a single agent administered by intravenous (IV) injection every 3 weeks (Q3W) in participants with solid tumors (Part 1: Dose Escalation part) or PROC [redacted] (Part 2: Dose Expansion part) in the Japan population. Preliminary efficacy of MORAb-202 was also evaluated in Study 101. Study 201 is an open-label study with a two-dose level escalation part, evaluating the safety, tolerability, and efficacy of MORAb-202 in participants with select tumor types [redacted] in the US population.

In Study 101, 82 participants have been exposed to MORAb-202 across 5 dose levels during the dose escalation and dose expansion parts. In the dose escalation part of Study 101, a total of 22 participants with solid tumors were enrolled across the following 5 MORAb-202 dose cohorts: 0.3 mg/kg Q3W; 0.45 mg/kg Q3W; 0.68 mg/kg Q3W; 0.9 mg/kg Q3W; and 1.2 mg/kg Q3W. Based on the observed safety and preliminary efficacy profile of MORAb-202 in the dose escalation part of Study 101, the dose expansion part of Study 101 (N = 60) evaluated 45 participants with PROC in 2 expansion cohorts at 0.9 mg/kg (n = 24) and 1.2 mg/kg (n = 21) and 15 participants [redacted] in one expansion cohort at 1.2 mg/kg. Across both parts of Study 101, 2 participants with ovarian cancer were treated with MORAb-202 at the 0.68 mg/kg Q3W dose, 28 participants with MORAb-202 at the 0.9 mg/kg Q3W dose, and 24 participants at the 1.2 mg/kg Q3W dose.[42]

In the dose escalation part of Study 201, 25 participants have been exposed to MORAb-202 at dose levels of 0.9 mg/kg Q3W and 1.2 mg/kg Q3W. Of the 25 participants exposed to MORAb-202 in Study 201, 10 OC and 3 non-OC participants were enrolled in the 0.9 mg/kg dose cohort, and 10 OC and 2 non-OC participants were enrolled in the 1.2 mg/kg dose cohort.[43]

[redacted]

3.2.3.1 Clinical Efficacy

In both Study 101 and Study 201, durable responses were observed in participants [redacted] across a range of tumor FRα expression levels.[20] Anti-tumor activity was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 for all participants in Studies 101 and 201.

Study 101:

In the dose escalation part of Study 101, the investigator-assessed objective response rate (ORR) was 45% (10/22 participants) across cohorts. Responses included 1 CR (OC at 0.9 mg/kg) and 9 PRs in 1 participant [redacted] at 0.3 mg/kg, 4 participants [redacted] 1 OC, and [redacted] at 0.68 mg/kg, 2 participants (OC) at 0.9 mg/kg, and 2 participants (OC) at 1.2 mg/kg.

Across both OC expansion cohorts, 39/45 participants had HGS OC: 19 HGS OC participants were enrolled in the 0.9 mg/kg MORAb-202 dose cohort, and 20 HGS OC participants were enrolled in the 1.2 mg/kg MORAb-202 dose cohort. In ovarian cohorts, 50% and 66.7% of the participants had 3 or more previous lines of therapy at the 0.9 and 1.2 mg/kg dose levels, respectively. Clinical

efficacy data for participants with HGS and overall PROC in Study 101 are presented in Table 3.2.3.1-1.

Table 3.2.3.1-1: Study 101 Dose Expansion Clinical Efficacy in HGS/Overall PROC Participants

	HGS		Total PROC	
MORAb-202 Treatment	**0.9 mg/kg Q3W (n=19)**	**1.2 mg/kg Q3W (n=20)**	**0.9 mg/kg Q3W (n=24)**	**1.2 mg/kg Q3W (n=21)**
Best Overall Response (BOR)[a]				
Complete Response (CR), n (%)	1 (5.3)	0	1 (4.2)	0
Partial Response (PR), n (%)	5 (26.3)	10 (50.0)	5 (20.8)	11 (52.4)
Stable Disease (SD), n (%)	6 (31.6)	9 (45.0)	10 (41.7)	9 (42.9)
Progressive Disease (PD), n (%)	7 (36.8)	1 (5.0)	8 (33.3)	1 (4.8)
Objective Response Rate (CR + PR), n (%)	6 (31.6)	10 (50.0)	6 (25.0)	11 (52.4)
Duration of Response (months)				
Median	10.6	8.0	10.6	7.6
Progression-free Survival (months)				
Median	6.7	7.2	6.7	8.2

Abbreviations: BOR, best overall response; CR, complete response; HGS, high-grade serous; n, number of participants; PD, progressive disease; PR, partial response; PROC, platinum-resistant ovarian cancer; Q3W, every 3 weeks; SD, stable disease.

[a] Confirmed responses are used in this analysis. Data cut-off: 31-Aug-2021.

Study 201:

A total of 20 PROC participants were treated with MORAb-202 in the dose escalation part of Study 201, 10 each at 0.9 and 1.2 mg/kg. Clinical efficacy data for PROC participants at each MORAb-202 dose cohort in Study 201 are presented in Table 3.2.3.1-2.

Table 3.2.3.1-2: Study 201 Dose Escalation Clinical Efficacy in PROC Participants

MORAb-202 Dose Cohort	**MORAb-202 0.9 mg/kg PROC (n=10) n (%)**	**MORAb-202 1.2 mg/kg PROC (n=10) n (%)**
Best Overall Response, n (%)[a]		
Complete Response (CR)	0 (0.0)	0 (0.0)
Partial Response (PR)	1 (10.0)	1 (10.0)
Stable Disease (SD)	6 (60.0)	5 (50.0)

Table 3.2.3.1-2: Study 201 Dose Escalation Clinical Efficacy in PROC Participants

MORAb-202 Dose Cohort	MORAb-202 0.9 mg/kg PROC (n=10) n (%)	MORAb-202 1.2 mg/kg PROC (n=10) n (%)
Progressive Disease (PD)	2 (20.0)	4 (40.0)
Objective Response Rate (CR + PR), n (%)	1 (10.0)	1 (10.0)
Duration of Objective Response (months)		
Median	4.7	NE
Progression-free Survival (months)		
Median	3.4	2.5

Abbreviations: BOR, best overall response; CR, complete response; n, number of participants; NE, not estimable; PD, progressive disease; PR, partial response; PROC, platinum-resistant ovarian cancer; SD, stable disease.

[a] Data cut-off: 31-Aug-2021. Confirmed responses are used in this analysis.

Participants in the Study 201 were more heavily pretreated, had more extensive disease burden upon study entry, and had disease characteristics related to a poorer prognosis, as compared with Study 101 participants. However, despite an overall compromised baseline disease status in Study 201 PROC participants, stable disease was observed, justifying further exploration with MORAb-202 treatment in this population.

In summary, encouraging efficacy with MORAb-202 was observed in both studies across tumor types, including in participants with HGS PROC.

3.2.3.2 Clinical Safety

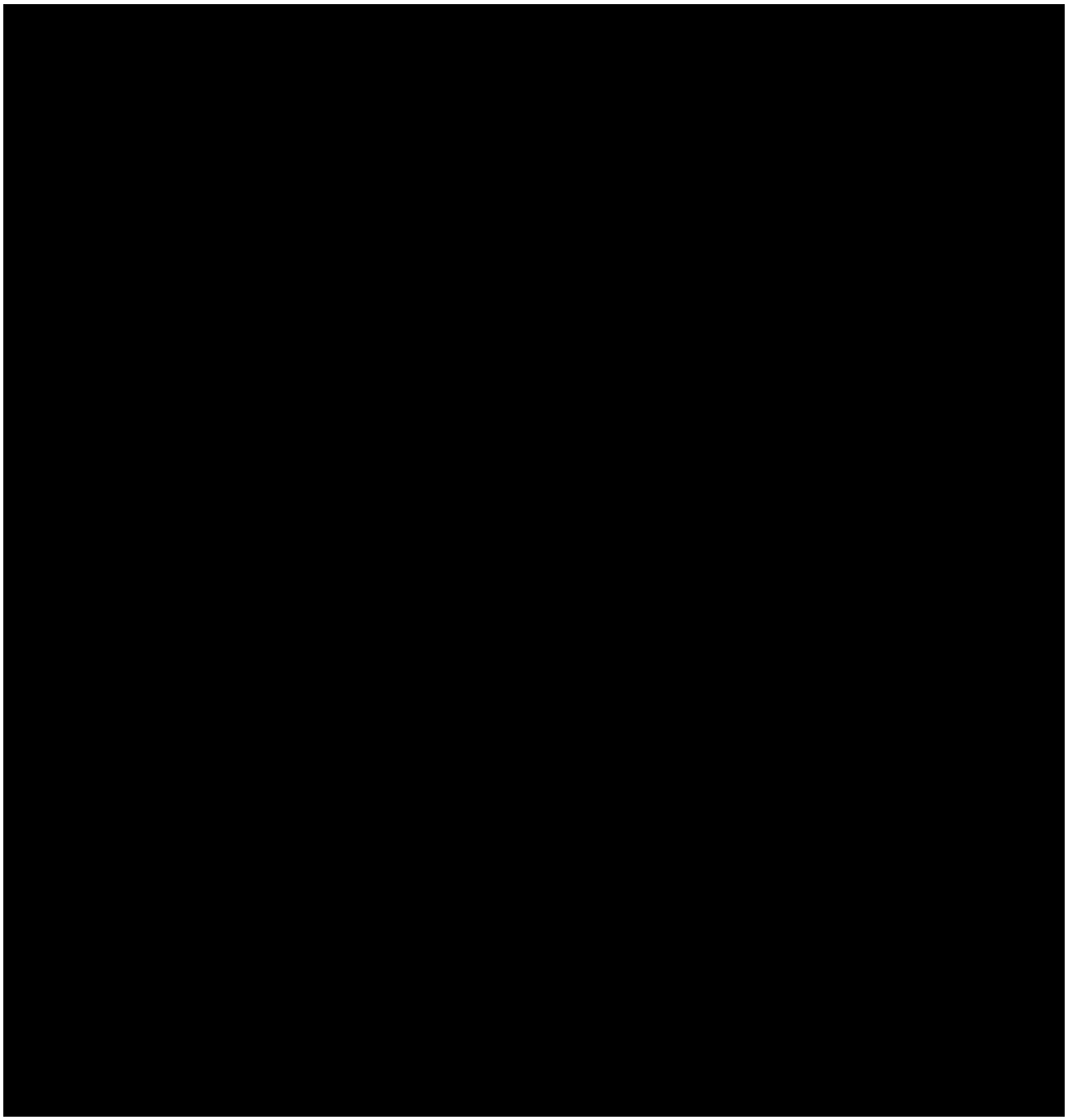
Study 101:

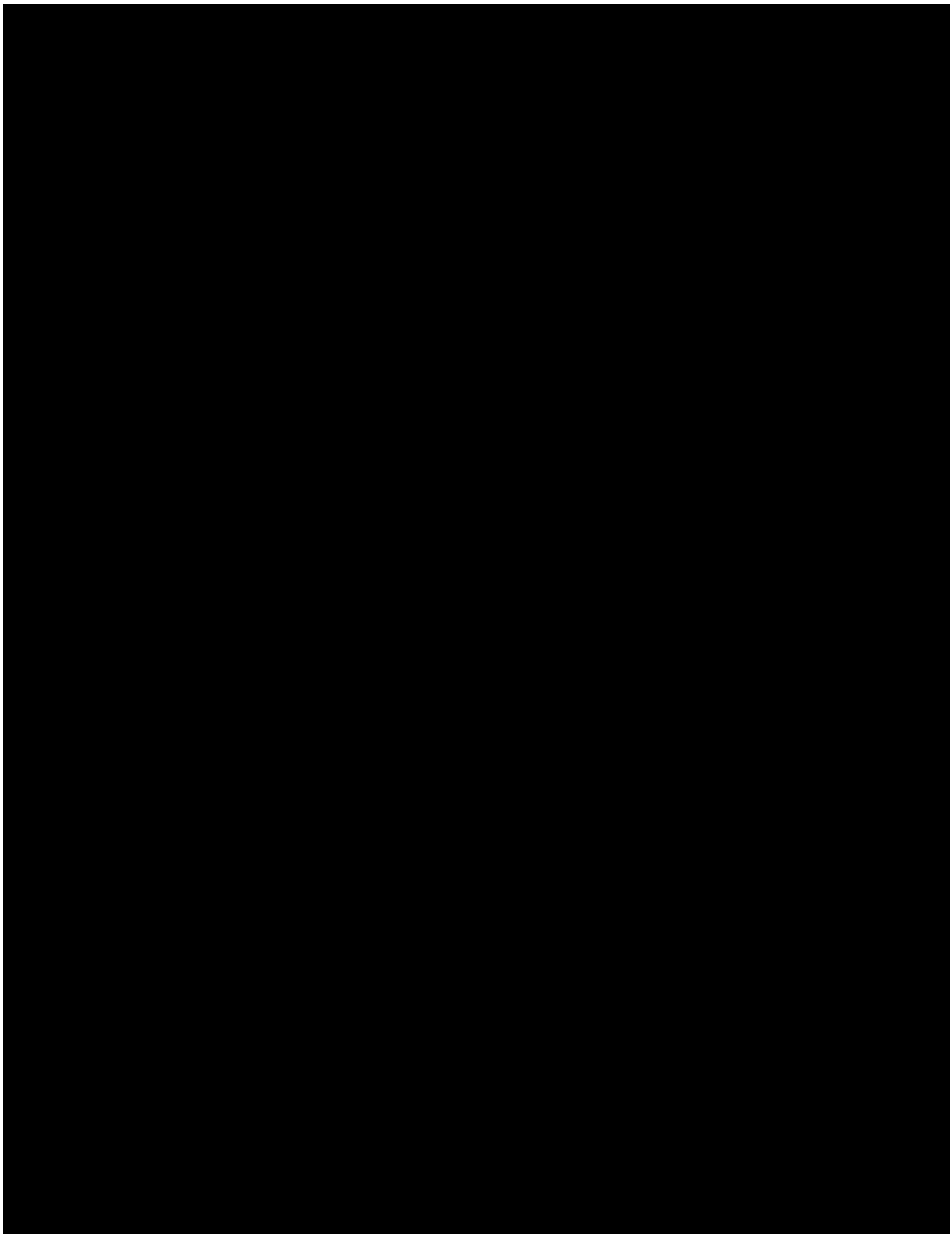
Across both parts of Study 101, 79/82 (96.3%) of participants treated with single-agent MORAb-202 experienced at least 1 treatment-emergent adverse event (TEAE), and the most frequently (> 20%) reported TEAEs were interstitial lung disease (ILD)/pneumonitis (26.8%), alanine aminotransferase (ALT) increased (26.8%), aspartate aminotransferase (AST) increased (23.2%), nausea (23.2%), and pyrexia (23.2%). The maximum tolerated dose (MTD) was not reached in Study 101.

In the dose escalation part of Study 101, Grade ≥ 3 TEAEs were reported in 2/22 (9.1%) of participants. Serious TEAEs were reported in 2/22 (9.1%) of participants, of which 1/22 (4.5%) were related. There were no reported treatment-related deaths.

In the dose expansion part of Study 101, Grade ≥ 3 TEAEs were reported in 15/60 (25.0%) participants. Serious TEAEs were reported in 12/60 (20.0%) participants, of which 7/60 (11.7%) participants had treatment-related events. In the dose expansion ovarian cancer cohorts (0.9 mg/kg, n = 24; 1.2 mg/kg, n = 21) of Study 101, Grade ≥ 3 TEAEs were reported in 8/24 (33.3%) and 5/21 (23.8%) of participants, respectively. Serious TEAEs were reported in

5/24 (20.8%) and 5/21 (23.8%) of participants, of which 2/24 (8.3%) and 3/21 (14.3%) were related, respectively. There were no reported treatment-related deaths at the time of data cut-off. ILD/pneumonitis events were reported in 9/24 (37.5%) and 14/21 (66.7%) of participants, respectively. As of the cut-off date, all events of ILD/pneumonitis were reported as Grade 1 or Grade 2. However, after the data cut-off date, one Grade 1 event in the 1.2 mg/kg ovarian cancer expansion cohort was retrospectively reclassified as Grade 3 by the investigator, and a Grade 5 respiratory-related event was reported in a 0.9 mg/kg ovarian cancer expansion cohort.[42]





[redacted]

3.2.4 MORAb-202 Clinical Pharmacology

MORAb-202 is an immunoglobulin G1 (IgG1) antibody (farletuzumab) conjugated to the microtubule inhibitor eribulin via a cathepsin cleavable linker [redacted] Eribulin mesylate, marketed as Halaven®, is approved in the US and European Union (EU) for the treatment of metastatic breast cancer and for unresectable or metastatic liposarcoma.[44]

3.2.4.1 MORAb-202 Clinical Pharmacokinetics

MORAb-202 PK was evaluated after IV administration at doses of 0.3 mg/kg (n = 3), 0.45 mg/kg (n = 3), 0.68 mg/kg(n = 6), 0.9 mg/kg (n = 7), and 1.2 mg/kg Q3W (n = 3) in Part 1 (dose escalation) and at doses of 0.9 mg/kg (n = 39) and 1.2 mg/kg Q3W (n = 21) in Part 2 (dose expansion) in Study 101 (Japanese population). PK was also evaluated at doses of 0.9 mg/kg (n = 9) and 1.2 mg/kg (n = 6) Q3W in Study 201 (global, non-Japanese population). MORAb-202, total antibody (antibodies that are both unconjugated and conjugated to at least 1 payload molecule) and released eribulin PK have been previously described over the escalation dose range 0.3 to 1.2 mg/kg Q3W in Study 101.[44] From noncompartmental analysis (NCA), MORAb-202 PK was near dose-proportional from 0.3 to 1.2 mg/kg Q3W with a half-life of 4 to 6 days and no accumulation using Q3W dosing with steady state concentrations achieved after Cycle 1. Concentration vs time profiles were similar for MORAb-202 and total antibody levels with low levels of released eribulin near the assay limit of quantitation, indicating MORAb-202 is stable in the systemic circulation. Released eribulin levels detected in plasma from MORAb-202 ranged from 0.5 to 2 ng/mL and were significantly lower than the maximum concentration of eribulin in plasma (approximately 300 ng/mL) when dosed at the United States Prescribing Information (USPI) approved dose of 1.4 mg/m^2 IV on Days 1 and 8 of a 21-day cycle.[44,45,46] [redacted] Based on human metabolism studies conducted with ^{14}C-eribulin as described in the Halaven® USPI, released eribulin is expected to be eliminated primarily in the feces (82% of dose) with no major circulating metabolites in plasma (< 0.6% of parent compound). Furthermore, released eribulin is expected to have a mean half-life of approximately 40 hours, the same as single-agent eribulin mesylate dosed at the USPI-recommended dose.

PK was also characterized using a population PK approach to include those participants with both intense and sparse PK sampling. The analysis included 1299 MORAb-202 PK observations across 97 participants (Study 101 N=82; [redacted]). PK was linear and described by a two-compartment model with significant effects of baseline body weight (BW) on clearance (CL) and volume distribution of the central compartment (V) and baseline albumin levels on CL. This

results in participants with higher baseline BW having higher CL and V and participants with low albumin having higher CL and is consistent with that observed for other monoclonal antibodies.[47]

3.2.4.2 Exposure-response Efficacy and Safety

There was an apparent dose and exposure-response (E-R) relationship observed for ORR in Study 101 over the dose range 0.68 to 1.2 mg/kg Q3W in PROC, which was the tumor type with the largest number of patients enrolled (N=58). There was also a dose and E-R relationship observed for ILD combining data across tumor types from Studies 101 and 201 (N = 96 total; n = 81 [Study 101] [redacted]). The highest tested dose at 1.2 mg/kg Q3W in Study 101 (including both escalation and expansion) had the highest ORR 54.2% (13/24) in PROC and highest ILD rate 58.3% (14/24) across tumor types. The next lower dose level, 0.9 mg/kg Q3W, led to a lower ORR 32.1% (9/28) and ILD rate 37.0 % (17/46) in Study 101. At the next lower dose 0.68 mg/kg Q3W, a 50% ORR (1/2) in PROC and ILD rate 16.7% (1/6) in Study 101 were observed.

E-R Efficacy (ORR) Analysis

An E-R efficacy (ORR) analysis was conducted with PROC participants from Study 101 (N = 58) across the dose range 0.3 to 1.2 mg/kg Q3W. Twenty-one participants had a partial response (PR), and 2 participants had a CR in PROC with an ORR of 39.7 % (23/58) across the dose range. Exposure (area under the concentration-time curve [AUC]) was the only significant predictor of the probability of an objective response (OR) in a multivariate logistic regression analysis [redacted] Age, weight, non-HGS (versus HGS OC), and Eastern Cooperative Oncology Group (ECOG) performance status (PS) (1 vs 0) were not significant predictors of an OR. Based on the results of the E-R analysis, clinically meaningful efficacy is expected across the dose range of 0.68 to 1.2 mg/kg. However, as described below, an overlapping AUC dependent ILD is observed, indicating doses < 1.2 mg/kg may provide the optimal balance of benefit/risk and requires further dose optimization. [redacted]

E-R Safety (ILD) Analysis

An E-R analysis of ILD by expert review was conducted including participants from Study 101 across the dose range of 0.3 to 1.2 mg/kg Q3W and from Study 201 across the dose range of 0.9 to 1.2 mg/kg Q3W (N = 96 participants in total). Forty-eight participants had ILD identified by expert review for an ILD rate of 50% (48/96) across the studies and dose range. AUC and age were significant predictors in multivariate analysis with both higher AUC and higher age predicting a higher probability of ILD.[47] [redacted]

[redacted]

3.2.4.4 Corrected QTc Interval Assessment

[redacted] While single-agent eribulin mesylate at the prescribed dose of 1.4 mg/m^2 prolonged QTc with a maximum mean QTcF change from baseline (95% upper confidence interval [CI]) of 11.4 ms (19.5) in 26 patients with solid tumors, there was no concentration effect identified.[48] The total dose of eribulin (free form) at the highest MORAb-202 dose evaluated (1.2 mg/kg Q3W) is 0.85 mg/m^2, which is 1.6-fold lower than the approved eribulin single-agent dose of 1.4 mg/m^2. This combined with plasma levels of released eribulin from MORAb-202 that are approximately 300-fold lower than with single-agent eribulin indicates a low risk of MORAb-202 QTc prolongation. Therefore, for [redacted] participants, electrocardiograms (ECGs) will only be required at screening and end of treatment (EOT). During study treatment and safety follow-up, ECGs should be performed as clinically indicated.

3.2.4.5 Drug-drug Interaction Potential

There are no drug-drug interactions expected for MORAb-202 and released eribulin.

There have been no in vitro or in vivo drug-drug interactions studies conducted for MORAb-202. The antibody portion of MORAb-202 (farletuzumab) is not expected to impact cytochrome P450 (CYP)-mediated metabolism since its mechanism of action does not involve increases in proinflammatory cytokines that have historically been linked to antibody-based modulation of P450s. As described in the Halaven® (eribulin mesylate) USPI, drug-drug interaction studies have been conducted for eribulin and there were no clinically meaningful differences in exposure (AUC) observed in patients with advanced solid tumors when eribulin was administered with or without ketoconazole (a strong inhibitor of CYP3A and a P-gp inhibitor) and when eribulin was administered with or without rifampin (a CYP3A inducer). In vitro, eribulin did not inhibit CY1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A enzymes or induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4 enzymes at relevant clinical concentrations. Since eribulin did

not induce or inhibit the CYP3A enzyme, pharmacokinetic interactions with corticosteroids, including dexamethasone, which is metabolized by CYP3A, are not expected. Investigators should refer to the prescribing information for the selected corticosteroids.

3.3 Benefit/Risk Assessment

Overall, the observed safety profile of MORAb-202 has been manageable and generally consistent across clinical trials with no MTD reached at dose levels up to 1.2 mg/kg. [redacted] As described in Section 3.2.3.1, clinical activity with MORAb-202 was observed across multiple FRα-expressing tumor types. Clinical responses were observed in participants [redacted] across a range of MORAb-202 dose levels; however, lower rates of all-grade ILD were observed with lower doses, while a trend for higher grade ILD was observed in participants with higher body weights. [redacted]

Furthermore, based on clinical trial experience to date, ILD/pneumonitis associated with MORAb-202 appears to be responsive to systemic corticosteroids. For several participants who experienced ILD/pneumonitis, corticosteroid treatment along with dose delays and reductions allowed for MORAb-202 treatment and maintenance of disease control. AEs due to corticosteroid use in Study 101 were generally not reported, which aligns with current clinical experience with corticosteroid use as a treatment for AEs in cancer patients.[49,50] [redacted]

Lastly, the recommendations for monitoring and management of ILD/pneumonitis included in this protocol have been revised from the initial recommendations implemented in Studies 101 and 201, based upon thorough analyses of clinical data from participants who experienced events of MORAb-202-related ILD/pneumonitis (see Section 7.4.1 for ILD management guidelines) and advisement from expert medical oncologists, pulmonologists, and radiologists experienced with management of drug-induced ILD/pneumonitis. [redacted]

[redacted] See Section 3.2.3.2 for further details on overall safety profile observed in MORAb-202 clinical trials.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of MORAb-202 may be found in the IB. Please refer to the approved local Product Label for the IC chemotherapy agents for a summary of the known benefits and risks of treatment in approved indications.

With respect to the benefit/risk of receiving coronavirus disease 2019 (COVID-19) vaccinations during treatment with MORAb-202, non-live COVID-19 vaccination is considered a concomitant medication within the study. The efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving MORAb-202 is unknown.

The assessed benefit/risk profile of MORAb-202 in participants with PROC is described further in the following sections.

3.3.1 Risk Assessment

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: MORAb-202 ([redacted])		
ILD/pneumonitis	MORAb-202 IB	I/E criteria, consistent safety monitoring (eg, [redacted], pulse oximetry, signs/symptoms, 6-minute walk test), close weekly monitoring visits [redacted] and via phone calls during [redacted] investigator/site training on ILD detection and management, participant alert card, SC, and ILD Expert Review Committee. [redacted]

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infusion-related reactions	MORAb-202 IB	Premedications for first MORAb-202 infusion, I/E criteria, close monitoring for hypersensitivity/allergic reactions during MORAb-202 infusions, and secondary prophylaxis. Guidelines for management and dose modification are included in protocol Section 7.4.1.
AST/ALT elevations	MORAb-202 IB	I/E criteria and safety monitoring with predose liver enzymes at each cycle. Guidelines for management and dose modification are included in protocol Section 7.4.1.
Nausea	MORAb-202 IB	Monitoring at each cycle. Guidelines for dose modification are included in protocol Section 7.4.1. Management per institutional protocol/investigator discretion.
Pyrexia	MORAb-202 IB	Monitoring at each cycle. Guidelines for dose modification and recommended management algorithm is included in protocol Section 7.4.1. Management or as per institutional protocol/investigator discretion.
Potential reproductive toxicity	MORAb-202 IB	I/E criteria, pregnancy testing, and contraception requirements per protocol Section 6.1, Section 6.2, Section 9.2.5, and Appendix 4.
Study Intervention: Paclitaxel [redacted]		
Bone marrow suppression (eg, neutropenia, thrombocytopenia, anemia, infections)	USPI and SmPC for paclitaxel	I/E criteria and safety monitoring with predose CBCs at every treatment visit. Recommended dose reductions and discontinuations included in protocol Section 7.4.2 or per approved Product Label or as per institutional protocol/investigator discretion.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypersensitivity reactions	USPI and SmPC for paclitaxel	I/E criteria, premedication, and close monitoring for hypersensitivity/allergic reactions during paclitaxel infusions. Recommended dose reductions and discontinuations included in protocol Section 7.4.2 or per approved Product Label or as per institutional protocol/investigator discretion.
Peripheral neuropathy	USPI and SmPC for paclitaxel	I/E criteria and monitoring at every cycle. Recommended dose reductions and discontinuations included in protocol Section 7.4.2 or per approved Product Label or institutional protocol/investigator discretion.
Mucositis	USPI and SmPC for paclitaxel	I/E criteria and monitoring at every cycle. Recommended dose reductions and discontinuations included in protocol Section 7.4.2 or per approved Product Label or institutional protocol/investigator discretion.
Potential reproductive toxicity	USPI and SmPC for paclitaxel	I/E criteria, pregnancy testing, and contraception requirements per protocol Section 6.1,Section 6.2, Section 9.2.5 and Appendix 4.
Study Intervention: PLD [redacted]		
Palmar-Plantar erythrodyesthesia/hand-foot syndrome (HFS)	USPI and SmPC for PLD	Monitoring at every cycle. Recommended dose reductions and discontinuations included in protocol Section 7.4.3 or per approved Product Label or institutional protocol/investigator discretion.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infusion-related reactions	USPI and SmPC for PLD	I/E criteria and close monitoring for hypersensitivity/allergic reactions during PLD infusions. Recommended dose reductions and discontinuations included in protocol Section 7.4.3 or per approved Product Label or institutional protocol/investigator discretion.
Bone marrow suppression (eg, anemia, leukopenia, thrombocytopenia, neutropenia), febrile neutropenia, superinfection, and hemorrhage	USPI and SmPC for PLD	I/E criteria and safety monitoring with predose CBCs at every cycle. Recommended dose reductions and discontinuations included in protocol Section 7.4.3 or per approved Product Label or institutional protocol/investigator discretion.
Secondary hematological malignancies	USPI and SmPC for PLD	I/E criteria and safety monitoring with hematology clinical laboratory assessments at every cycle. Recommended dose reductions and discontinuations included in protocol Section 7.4.3 or per approved Product Label or institutional protocol/investigator discretion.
Secondary oral neoplasms	USPI and SmPC for PLD	Monitoring at every cycle. Recommended dose reductions and discontinuations included in protocol Section 7.4.3 or per approved Product Label or institutional protocol/investigator discretion.
Extravasation	USPI and SmPC for PLD	Close monitoring for symptoms of extravasation (eg, stinging, erythema) during PLD infusion. Recommended dose reductions and discontinuations included in protocol Section 7.4.3 or per approved Product Label or institutional protocol/investigator discretion.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cardiac toxicity (eg, reduced LVEF)	USPI and SmPC for PLD	I/E criteria and safety monitoring of LVEF with ECHO/MUGA every 4 cycles. Recommended dose reductions and discontinuations included in protocol Section 7.4.3 or per approved Product Label or institutional protocol/investigator discretion.
Mucositis	USPI and SmPC for PLD	Monitoring at every cycle. Recommended dose reductions and discontinuations included in protocol Section 7.4.3 or per approved Product Label or institutional protocol/investigator discretion.
Gastrointestinal toxicity (eg, nausea, vomiting)	USPI and SmPC for PLD	Monitoring at every cycle. Recommended dose reductions and discontinuations included in protocol Section 7.4.3 or per approved Product Label or institutional protocol/investigator discretion.
Potential reproductive toxicity	USPI and SmPC for PLD	I/E criteria, pregnancy testing, and contraception requirements per protocol Section 6.1, Section 6.2, Section 9.2.5, and Appendix 4.
Study Intervention: Topotecan [redacted]		
Bone marrow suppression (eg, neutropenia, thrombocytopenia, anemia), febrile neutropenia, and neutropenic enterocolitis; infection	USPI and SmPC for topotecan	I/E criteria and safety monitoring with predose CBCs at every treatment visit. Recommended dose reductions and discontinuations included in protocol Section 7.4.4 or per approved Product Label or institutional protocol/investigator discretion.
Gastrointestinal toxicity (eg, severe nausea, vomiting, and/or diarrhea, constipation, abdominal pain, mucositis)	USPI and SmPC for topotecan	Monitoring at every cycle. Recommended dose reductions and discontinuations included in protocol Section 7.4.4 or per approved Product Label or institutional protocol/investigator discretion.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Interstitial lung disease (ILD)	USPI and SmPC for topotecan	I/E criteria and consistent safety monitoring (eg, [redacted], pulse oximetry, signs/symptoms). Recommended dose reductions and discontinuations included in protocol Section 7.4.4 or per approved Product Label or institutional protocol/investigator discretion.
Pyrexia, asthenia, and fatigue	USPI and SmPC for topotecan	Monitoring at every cycle. Recommended dose reductions and discontinuations included in protocol Section 7.4.4 or per approved Product Label or institutional protocol/investigator discretion.
Potential reproductive toxicity	USPI and SmPC for topotecan	I/E criteria, pregnancy testing, and contraception requirements per protocol Section 6.1, Section 6.2, Section 9.2.5, and Appendix 4.
Infertility	USPI and SmPC for topotecan	Informed consent.
Study Procedures		
Tumor biopsy (eg, pain, infection) for participants without archival tissue	--	Allow submission of archival tumor sample of sufficient quality and quantity. If tumor biopsy performed, management will be per institutional protocol/investigator discretion.
Blood draws/use of IV catheter for laboratory assessments (eg, pain, bruising, bleeding, infection, fainting)	--	Per institutional protocol/investigator discretion.
CT scan/MRI radiation exposure	--	Per institutional protocol/investigator discretion.
Allergy to contrast agent for CT scan/MRI (eg, allergic reaction, anaphylaxis)	Contrast USPI and SmPC	Prophylaxis and/or treatment per institutional protocol/investigator discretion.
Other (if applicable)		
SARS-CoV-2 infection	Policy and Guidance for the conduct of BMS-sponsored clinical research in light of SARS-CoV-2	See exclusion criteria (Section 6.2), re-screening criteria (Section 6.4.1), and dose modifications (Section 7.4) sections for SARS-CoV-2 Safety Surveillance Plan.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Dosing delay due to SARS-CoV-2 lockdowns	BMS SARS-CoV-2 Clinical Research Project Management Office	Specific measures have been considered to ensure the trial can continue should the hospital be subject to increased demands/restrictions due to the pandemic (travel restrictions, remote access / monitoring, preventative measures, etc).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMS, Bristol-Myers Squibb; [redacted] CBC, complete blood count; CT, computed tomography; ECHO, echocardiogram; HFS, hand-foot syndrome; IB, Investigator's Brochure; I/E, inclusion/exclusion criteria; ILD, interstitial lung disease; IV, intravenous; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multigated acquisition; PLD, pegylated liposomal doxorubicin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SC, Safety Committee; SmPC, Summary of Product Characteristics; USPI, United States Prescribing Information.

3.3.2 Benefit Assessment

Effective treatment of patients with PROC remains a substantial unmet need (see Section 3.1 and Section 3.2). Patients with platinum-resistant disease who relapse typically receive single-agent chemotherapy alone (eg, liposomal doxorubicin, topotecan, or paclitaxel) or in combination with bevacizumab.[17] Randomized Phase 3 studies for these agents in this patient population demonstrated response rates of 10% to 15%, mPFS of 3 to 4 months, and poor median overall survival (OS) of approximately 12 months.[31] Furthermore, these treatments are associated with significant toxicities such as myelosuppression, hypersensitivity reactions, palmar plantar erythrodysesthesia, mucositis, and neuropathy.[46] Because PROC remains a significant unmet medical need, the National Comprehensive Cancer Network (NCCN) guidelines and the European Society for Medical Oncology (ESMO) guidelines recommend that patients with PROC consider participation in clinical trials.[8,51]

MORAb-202 may address the high unmet need in a large subset of PROC patients, given its unique, tumor-specific mechanism (ie, FRα-directed ADC), the high prevalence of FRα-expression in ovarian cancer, and the clinical activity seen to date in this population (see Section 3.2.3). HGS carcinoma is the most common histologic subtype of OC, accounting for approximately 70% of epithelial cell OC and is responsible for the majority of deaths in OC.[52]

The additional medical surveillance provided by a clinical trial translates into close monitoring of the participants for toxicities and promotes prompt identification and adequate treatment of adverse events.

3.3.3 Overall Benefit/Risk Conclusion

MORAb-202 has the potential to provide an overall favorable benefit/risk balance based on clinical responses observed at various doses, in combination with measures to minimize overexposure to participants.

In addition to the eligibility criteria, safety assessments, AE management/dose modification guidelines, [redacted] incorporated in the study protocol, to ensure safety of participants, the Sponsor and SC will continuously assess safety throughout the course of the study (see Section 5.1.1 and Section 5.1.1.1). [redacted] Additionally, the Sponsor will evaluate the benefit/risk profile of the study intervention on an ongoing basis. This evaluation will be based on all available data, with particular attention to: i) AEs, including ILD/pneumonitis, or other safety trends in this or any other clinical study of MORAb-202 whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury, and ii) new nonclinical data suggesting unreasonable and significant risk of illness or injury.

If such evaluation suggests that the benefit/risk profile of the study intervention has become unfavorable to participants, the Sponsor will pause enrollment and/or treatment until further evaluation of data and communication with the appropriate Health Authority(ies) on potential actions. Such actions may include, but are not limited to, study continuation, substantial amendment, or termination of the study.

[redacted]

- Enrollment will continue in [redacted] (MORAb-202 25 mg/m^2) and [redacted] (IC Chemotherapy)

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To compare objective response rate (ORR) of MORAb-202 vs IC chemotherapy (in all randomized participants)	• ORR by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per investigator assessment
Main Estimand for the Primary Objective Treatment: MORAb-202, 25 mg/m^2 [redacted], IC chemotherapy [redacted] Population: Platinum-resistant ovarian cancer Variable: Best overall response (BOR), defined as the best response, as determined by the investigator, recorded between the date of randomization and the date of first objectively-documented progression per RECIST v1.1 or the date of subsequent therapy, whichever is earlier. Intercurrent events (strategy): Early discontinuation of study treatment (treatment policy); initiation of subsequent anti-cancer therapy (while on treatment) Population-level summary: Difference in ORR, defined as the number of randomized participants who achieve a BOR of confirmed complete response (CR) or confirmed partial response (PR) based on the investigator assessments (using RECIST v1.1) divided by the number of all randomized participants in each treatment group, with two-sided 95% exact confidence interval (CI) in each treatment group	
• To evaluate the proportion of participants with treatment-related adverse event (TRAEs) leading to discontinuation in each arm within 6 months from first dose of study drug administration in all treated participants	• TRAEs leading to discontinuation
Main Estimand for the Primary Objective Treatment: MORAb-202, 25 mg/m^2 [redacted] IC chemotherapy [redacted] Population: Platinum-resistant ovarian cancer Variable: Occurrence of TRAEs leading to discontinuation observed within 6 months from first dose of study drug administration Intercurrent events (strategy): Early discontinuation of study treatment (while on treatment) Population-level summary: TRAE discontinuation incidence rate	
Secondary	
• To assess the safety and tolerability of MORAb-202 and IC chemotherapy in all treated participants	• Incidence and severity of adverse events (AEs)/serious adverse events (SAEs), AEs leading to discontinuation, treatment-related AEs/SAEs leading to discontinuation, AEs of special interest (AESIs), deaths, and laboratory abnormalities

Table 4-1: Objectives, Endpoints, and Estimands

Objectives	Endpoints
Main Estimand for the Secondary Objective Treatment: MORAb-202, 25 mg/m^2 [redacted], IC chemotherapy [redacted] Population: Platinum-resistant ovarian cancer Variable: Occurrence of the AEs/SAEs, treatment-related AEs/SAEs, AEs leading to discontinuation, AESIs, deaths, and laboratory abnormalities. There are multiple estimands corresponding to each specified safety endpoint. Intercurrent events (strategy): Early discontinuation of study treatment (while on treatment) Population-level summary: AE incidence rate/proportion	
• To evaluate disease control rate (DCR) of MORAb-202 and IC chemotherapy in all randomized participants	• DCR by RECIST v1.1 per investigator assessment
Main Estimand for the Secondary Objective Treatment: MORAb-202, 25 mg/m^2 [redacted], IC chemotherapy [redacted] Population: Platinum-resistant ovarian cancer Variable: Best overall response (BOR), defined as the best response, as determined by the investigator, recorded between the date of randomization and the date of first objectively-documented progression per RECIST v1.1 or the date of subsequent therapy Intercurrent events (strategy): Early discontinuation of study treatment (treatment policy); initiation of subsequent anti-cancer therapy (while on treatment) Population-level summary: Difference in DCR, defined as the number of randomized participants who achieve a BOR of confirmed CR, confirmed PR, or stable disease (SD), based on the investigator assessments (using RECIST v1.1) divided by the number of all randomized participants, with 95% exact CI in each treatment group	
• To evaluate duration of response (DoR) of MORAb-202 and IC chemotherapy in all randomized participants	• DoR by RECIST v1.1 per investigator assessment
Main Estimand for the Secondary Objective Treatment: MORAb-202, 25 mg/m^2 [redacted], IC chemotherapy [redacted] Population: Platinum-resistant ovarian cancer participants that achieved a CR or PR as BOR Variable: DoR, defined as the time between the date of first documented response (CR or PR) that is subsequently confirmed, to the date of the first objectively-documented tumor progression as determined by investigator (per RECIST v1.1), or death due to any cause, whichever occurs first Intercurrent events (strategy): Early discontinuation of study treatment (treatment policy); initiation of subsequent anti-cancer therapy (while on treatment) Population-level summary: Kaplan Meier (KM) estimated median response time and landmark response rate of DoR in each treatment group	
• To evaluate progression-free survival (PFS) of MORAb-202 and IC chemotherapy in all randomized participants	• PFS by RECIST v1.1 per investigator assessment

Table 4-1: Objectives, Endpoints, and Estimands

Objectives	Endpoints
Main Estimand for the Secondary Objective Treatment: MORAb-202, 25 mg/m^2 [redacted] IC chemotherapy [redacted] Population: Platinum-resistant ovarian cancer Variable: PFS, defined as the time between the date of randomization and the first date of documented progression, determined by the investigator assessments (using RECIST v1.1), or death due to any cause, whichever occurs first. Intercurrent events (strategy): Early discontinuation of study treatment (treatment policy); initiation of subsequent anti-cancer therapy prior to PD or death (treatment policy) Population-level summary: KM estimated median survival time and landmark survival rate of PFS in each treatment group	

[redacted]

Abbreviations: [redacted]; AE, adverse event; AESI, adverse event of special interest; BOR, best overall response; CI, confidence interval; CR, complete response; [redacted]; DCR, disease control rate; DoR, duration of response; [redacted] IC, Investigator's choice; [redacted]; KM, Kaplan Meier; ORR, objective response rate; [redacted]; PD, progressive disease; PFS, progression-free survival; [redacted] PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; SD, stable disease; TRAE, treatment-related adverse event; [redacted].

5 STUDY DESIGN

5.1 Overall Design

[redacted]

Study CA116001 is a Phase 2, open-label, randomized, multicenter study that will evaluate the safety, efficacy, and tolerability of MORAb-202 in female participants with platinum-resistant HGS ovarian, primary peritoneal, or fallopian tube cancer.

At least 90 evaluable participants will be randomized in a [redacted] ratio to:

- [redacted] (N = [redacted]): MORAb-202 25 mg/m^2 [redacted]
- [redacted] (N = [redacted]): IC single-agent chemotherapy:
  - Paclitaxel 80 mg/m^2 IV on Days 1, 8, 15, and 22 of a 28-day cycle; or
  - Pegylated liposomal doxorubicin (PLD) 40 mg/m^2 IV on Day 1 of a 28-day cycle; or
  - Topotecan 4 mg/m^2 IV on Days 1, 8, and 15 of a 28-day cycle or 1.25 mg/m^2 on 5 consecutive days on Days 1 to 5 of a 21-day cycle

All screening assessments to determine participant eligibility must be performed within 28 days prior to randomization (see Table 2-1). [redacted]

[redacted]

All participants will be treated until disease progression by RECIST v1.1 criteria (as assessed by the investigator), unacceptable toxicity, participant withdrawal of consent for receiving study treatment, death, or the end of study, whichever occurs first. Maximum treatment duration will be up to 2 years. .

A Safety Follow-up Visit will be conducted 30 days after the last study drug administration (see Table 2-5). All ongoing treatment-related SAEs and ILD/pneumonitis events will be followed until resolution or stabilization. All participants discontinuing treatment will be followed for tumor assessment until investigator-assessed disease progression by RECIST v1.1, death, or withdrawal of consent for tumor assessment, whichever occurs first. Subsequently, all participants will be

followed for information on progression on next line of therapy and survival every 3 months from safety follow-up visit up to 1 year from the last participant randomized or LPLV (30 days after last patient last treatment); whichever is later.

5.1.1 Data Monitoring Committee and Other Committees

Given this is an early phase, open-label study, an independent Data Monitoring Committee (DMC) is not commissioned. Nonetheless, the safety of the participants will be closely monitored through a Safety Committee (SC) including external members to the Sponsor. Additionally, an external ILD Expert Review Committee will provide further ILD oversight on the study (see Section 5.1.1.1 and Section 5.1.1.2).

5.1.1.1 Safety Committee (SC)

An SC will be established to provide oversight of the benefit/risk for the participants enrolled in the CA116001 study and give advice to the Sponsor regarding actions that the committee deems necessary for the continued protection of the participants enrolled.

The SC will hold regularly-scheduled and ad-hoc meetings to evaluate the ongoing benefit/risk for the participants included in the study in the context of internal and external data. The SC will perform its first safety review after approximately

or earlier if otherwise warranted.

[redacted] Following each meeting, the SC will recommend continuation, modification, or discontinuation of the dose based on observed benefit/risk profile of each arm. Information reviewed at each time point may include disposition, demographics, AEs, SAEs, treatment-related AEs (TRAEs), TRAEs leading to discontinuation, exposure, death data, and any other data deemed relevant (laboratory, pathology, autopsy reports, physical descriptions, and investigator-assessed clinical response). The minutes of these meetings will be documented and stored in the Trial Master File. Decisions on safety, toxicity, and benefit/risk regarding the dose level will be solely the responsibility of BMS and will take account of the totality of the data available. The Oncology Research and Development unit of BMS (or BMS study team) has primary responsibility for the design and conduct of the study, including managing the communication of study data. The Sponsor will be responsible for promptly reviewing the SC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required. Periodic safety reviews for all arms will continue at a frequency determined and specified in the charter.

Procedures related to the committee membership, responsibilities, and procedures will be described in the SC Charter.

5.1.1.2 ILD Expert Review Committee

An external independent ILD Expert Review Committee will be established for this study. This committee is comprised of independent central ILD expert reviewers who will assess [redacted] for potential ILD/pneumonitis diagnosis from all participants receiving MORAb-202 following submission [redacted] and will communicate findings to the site and the Sponsor. Adjudicated ILD/pneumonitis events will be submitted to the SC routinely, and when required, sent to Health Authorities for review. Details of the ILD Committee membership, responsibilities, and procedures will be described in the Committee Charter.

5.2 Number of Participants

Approximately 90 participants will be randomized in a [redacted] ratio to 1 of 2 treatment groups, about [redacted] participants in the MORAb-202 arm ([redacted] and [redacted] participants in the IC chemotherapy arm ([redacted] It is estimated that approximately [redacted] participants will be enrolled to achieve approximately 90 randomized participants, assuming a screen failure rate of approximately [redacted]

5.3 End of Study Definition

The start of the study is defined as the first participant's first visit.

The primary completion date is defined as the date on which the last data point is collected for the study's primary endpoint. If the study has multiple primary endpoints, the primary completion date is the date on which the last data point is collected for the last primary endpoint.

End of study is defined as the last participant's last visit.

A participant is considered to have completed the study if he/she has completed all periods of the study including the safety and all survival follow-up visits or the last procedure shown in the Schedule of Activities.

5.4 Scientific Rationale for Study Design

Study CA116001 is a Phase 2, open-label, randomized, multicenter study to evaluate the safety, tolerability, and efficacy of MORAb-202, a FRα-targeting ADC in female participants with platinum-resistant HGS ovarian, primary peritoneal, or fallopian tube cancer.

Previous studies have demonstrated that 81.7% of recurrent serous ovarian tumors have detectable expression of FRα by IHC, which can be targeted by MORAb-202.[53] Upon binding to FRα, MORAb-202 is internalized into the tumor cell by endocytosis and is transported into the lysosome, where the cathepsin β-cleavable linker is enzymatically cleaved to release the payload, eribulin. Unconjugated eribulin has demonstrated significant cytotoxic effects on tumor cells as well as to the surrounding TME in cell culture and in tumor xenograft models. These preclinical data and the clinical activity of MORAb-202 from early dose exploration and expansion Phase 1/2 Study 101 and Study 201, support the current study design and further dose exploration. The study will evaluate the clinically-active [redacted] MORAb-202; 25 mg/m^2 [redacted]

The study randomly assigns participants to 1 of 2 cohorts (MORAb-202 25 mg/m^2 or Investigator's choice chemotherapy) in a [redacted] ratio, in an effort to balance any variables that may impact study outcomes and mitigate potential selection bias. [redacted] The safety profile of the agents in the control arm is well defined. Furthermore, this design allows for adequate characterization of the benefit/risk profile of each dose cohort and selection of a dose that maximizes tolerability, safety, and efficacy in patients with platinum-resistant HGS ovarian, primary peritoneal, or fallopian tube cancer, in line with the Food and Drug Administration's (FDA's) current initiative of oncology drug dose optimization.[54,55] To ensure the safety of all participants, the study will be closely monitored by an SC and includes prospectively established stopping rules to mitigate higher incidence of severe ILD events. Additionally, an external ILD Expert Review Committee will provide further ILD oversight on the study (see Section 5.1.1.1 and Section 5.1.1.2).

Emerging data from the dose-confirmation part of Study 201 prompted an ad-hoc SC meeting. The Sponsor proposed [redacted] and this was supported by the SC members. The

safety and preliminary efficacy in the 25 mg/m^2 cohort support continued investigation of this dose level.

5.4.1 Participant Input Into Study Design

BMS approached advocacy groups to discuss key details of the study. Feedback was positive as the trial serves a population with a high unmet medical need. This population has a high level of burden given the advanced stage of their disease, but may be more familiar with managing treatment side effects. Efforts for reducing patient burden have been implemented into the study design and will continue to be assessed via Patient Voice interactions. Specific suggestions from patient advocates are aligned with the study design as follows:

[redacted]

- Patient advocates further noted that the inclusion of patients with brain metastasis is a positive feature of the study. To address their concern to limit the number of scans as possible, the study will only require baseline brain magnetic resonance imaging (MRI) imaging for participants with a history or symptoms of brain metastasis, and not for all participants. An additional request was to provide clarity in the eligibility criteria on prior lines of treatment; detailed guidance is now provided in the inclusion criteria on this topic.
- There was also a recommendation to reduce waiting times in the study design, as longer timelines may cause more anxiety, and it is less likely that participants will stay in the study. Operational logistics have been streamlined and will require short turnaround times for [redacted]
- Another suggestion was to administer questionnaires separate from the study visit. Taking this into consideration and to help minimize the potential burden of participation, this study implements decentralized aspects (refer to Appendix 2), such as telemedicine visits when appropriate, [redacted] In addition, telehealth visits may be implemented on this study. [redacted] eConsent will be an option. The eConsent platform will minimize in-person clinic visits and allow for less burdensome participation.

5.4.2 Rationale for Open-label Design

This trial will follow an open-label design. Key differences in adverse event profiles, administration schedules, dose modifications, and safety management of MORAb-202 and the IC chemotherapy agents make blinding impractical. The complexity of including multiple visits for placebo infusions are burdensome for this participant population. An open-label design will help to ensure that the adverse events typically seen with MORAb-202 or IC chemotherapy are promptly identified and managed appropriately.

5.4.4 Rationale for Choice of Comparators and Dose Justification

In the platinum-resistant setting, OC patients are typically treated with a non-platinum agent used as monotherapy, such as paclitaxel, pegylated liposomal doxorubicin, or topotecan. None of these agents stand out as superior to others, with similar efficacy but different patterns of side effects. The choice among these agents is primarily based on prior therapies, the side effect profile, and the clinician's experience.

For participants who are randomized [redacted], the investigator will select a single-agent chemotherapy regimen based on individual eligibility criteria to be administered: paclitaxel, PLD, or topotecan (see Table 2-1).

5.4.4.1 Paclitaxel

Paclitaxel is a taxoid antineoplastic agent that interferes with the normal function of microtubule growth. Paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.[67]

Paclitaxel is a highly active agent used in front-line treatment of ovarian cancer in combination with a platinum-based drug. Paclitaxel has been used at several doses and schedules; however, the optimal dose for PROC has not been defined. A dose-dense approach of weekly paclitaxel may be associated with greater antitumor potency than Q3W dosing through increased exposure of proliferating tumor cells to the drug. The lower doses used with weekly dosing should also minimize bone marrow suppression and other toxicities associated with standard paclitaxel 3-weekly administration.[68] In PROC, weekly administration of paclitaxel has shown better tolerance compared to the approved 3-weekly schedule and is recommended by the NCCN and ESMO guidelines.[8,69] A Phase 2 trial reported response rates of 21% in 48 women with both platinum- and paclitaxel-resistant ovarian cancer receiving weekly paclitaxel (80 mg/m^2/week). SAEs were relatively uncommon, with 21% and 4% of patients experiencing Grade 2 and Grade 3 neuropathy, respectively.[70] The weekly versus every-3-weeks paclitaxel schedule for treatment of advanced ovarian cancer was furthered studied in a randomized Phase 3 trial in women with recurrent EOC. Results showed comparable efficacy in platinum resistant patients with ORRs of 19% in the weekly group and 26% in the every 3 weeks group. However, the toxicity profile favored a weekly administration with less neuropathy, arthralgia/myalgia, alopecia, and neutropenia observed compared to the 3-weekly group.[71]

These considerations support the dose selection of paclitaxel at 80 mg/m^2 weekly as an option for participants who are randomized to the IC chemotherapy arm.

5.4.4.2 Pegylated Liposomal Doxorubicin

Pegylated liposomal doxorubicin is a nucleic acid synthesis inhibitor (intercalating agent) packaged in a liposome (phospholipid bilayer) surrounded by a polyethylene glycol layer. The active ingredient of PLD is doxorubicin hydrochloride. The mechanism of action of doxorubicin hydrochloride is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. The polyethylene glycol hydrophilic polymer protects the doxorubicin liposome from being degraded by the reticuloendothelial system in a process called pegylation. This allows for a longer circulation time by decreasing uptake in the liver, lowering peak plasma levels of free drug, and allowing greater tumor concentration of PLD. PLD represents a novel chemotherapy delivery system that improves the therapeutic index of doxorubicin for patients with ovarian cancer.

PLD 40 mg/m^2 IV every 4 weeks (Q4W) has been selected as an option for participants who are randomized to the IC chemotherapy arm. PLD is an active agent indicated for the treatment of patients with ovarian cancer that has progressed or recurred after platinum-based chemotherapy, approved at a dose of 50 mg/m^2 every 28 days. Clinical studies in this setting have shown that,

compared with other standard chemotherapy regimens, PLD possesses a non-inferior survival rate and is well tolerated, exhibiting reduced alopecia and neurotoxicity.[72] The distinguishing toxicity of PLD is palmar-plantar erythrodysesthesia (PPE) or hand–foot syndrome (HFS). A Phase 3 trial of PLD at a 50 mg/m^2 dose in PROC showed an ORR of 12.3%, with 23% of participants developing Grade 3 to 4 PPE. Reducing the PLD dose from 50 to 40 mg/m^2 every 28 days decreases the incidence of PPE from 23% to 8% without affecting therapeutic efficacy.[73] A recently updated meta-analysis showed that PLD was well-tolerated at the 40 mg/m^2 regimen, which did not adversely affect survival compared with other single regimens, and confirmed PLD 40 mg/m^2 as a good choice for women in whom monotherapy was a treatment. PLD is widely recognized to be administered in clinical practice at an initial dose of 40 mg/m^2 rather than at the higher approved dose. To emphasize this point, a recent retrospective review at a tertiary cancer center revealed that 96% of 321 patients with gynecologic cancer treated with single-agent PLD received their initial dose at 40 mg/m^2, compared to only 4% of patients treated at 50 mg/m^2. These considerations support the use of PLD at a dose of 40 mg/m^2 in this trial.[74]

5.4.4.3 Topotecan

Topotecan, a topoisomerase I inhibitor, is a commonly used agent in recurrent ovarian cancer. Topoisomerase I relieves torsional strain in DNA by inducing reversible single-strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of these single strand breaks. The cytotoxicity of topotecan is thought to be due to double-strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA.[75]

Topotecan either at a dose of 1.25 mg/m^2 IV on consecutive Days 1 to 5 of a 21-day cycle, or at a dose of 4.0 mg/m^2 IV on Days 1, 8, and 15 of a 28-day cycle has been selected as an option for participants who are randomized to the IC chemotherapy arm. The approved topotecan dosing for relapsed ovarian cancer is 1.5 mg/m^2 as a once-daily infusion for 5 days of a 28-day cycle. However, a reduced dose of 1.25 mg/m^2/day is associated with decreased toxicity and similar outcomes and is now widely used in routine clinical practice.[76]

Topotecan is commonly used on a weekly schedule. A randomized trial in 194 women with platinum-resistant disease from the North Eastern German Society of Gynecologic Oncology showed there was no difference in survival outcomes between topotecan 5-day treatment (1.25 mg/m^2/day on 5 consecutive days on Days 1 through 5 of a 21-day cycle) or weekly topotecan (4 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle). Compared to the conventional 5-day therapy, the weekly dosing significantly reduced the incidence of Grade 3 and 4 hematotoxicity with relative risk reduction for major adverse events ranging from 62% (neutropenia) to 77% (thrombocytopenia). The results from this study showed that use of topotecan 4.0 mg/m^2 on a weekly schedule is associated with a better toxicity profile and tolerability compared with the conventional 5-day regimen.[77]

These considerations support the use of topotecan either at a dose of 1.25 mg/m^2 IV on consecutive Days 1 to 5 of a 21-day cycle, or at a weekly dose of 4.0 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle in this trial.

5.4.5 Rationale for Primary Endpoint

ORR is an accepted Phase 2 efficacy endpoint in PROC studies that allows data to be assessed earlier and in a smaller study population compared with survival-based endpoints. ORR allows the effect to be attributed to a single regimen, removed from subsequent therapies.[78] Furthermore, clinical data for MORAb-202 has shown significant cytotoxicity and tumor reduction. The mechanism of action of the drug indicates direct activity on the tumor; hence, ORR is an appropriate measure of activity in this dose-finding study. In this study, ORR will be assessed by the investigator using RECIST v1.1 to avoid delays in implementation of subsequent intervention in this advanced cancer setting. The tumor response will be further described by the durability of responses.

Preliminary data has shown a dose-response relationship in PROC, with a higher ORR, but also elevated rates of ILD at higher doses of MORAb-202.[11] ORR as a primary endpoint, with safety and tolerability as co-primary endpoints, will allow the selection of the dose with the optimal benefit/risk profile.

5.5 Justification for Dose

A MORAb-202 dose of 25 mg/m^2 [redacted] was selected for evaluation in CA116001. The dose selection was based on a detailed assessment of PK, exposure-response (E-R) efficacy (ORR), and E-R safety (ILD) (see Section 3.2.4.2).

In Study 101 dose escalation phase, multiple doses of MORAb-202 (0.3, 0.45, 0.68, 0.9, and 1.2 mg/kg Q3W) were assessed and MTD was not reached. In Study 101 dose expansion phase [redacted] doses were further explored. [redacted] The next lower dose,0.45 mg/kg evaluated in Study 101 dose escalation, has potential to be efficacious and safe based on E-R efficacy and safety analyses. Since the prediction of efficacy for the 0.45 mg/kg dose is based on a model prediction of efficacy (albeit lower than 0.68 mg/kg) and none of the N = 3 PROC participants dosed at 0.45 mg/kg in Study 101 escalation had a tumor response, the 0.45 mg/kg dose will be reserved for dose reduction to manage ILD. [redacted]

[redacted]

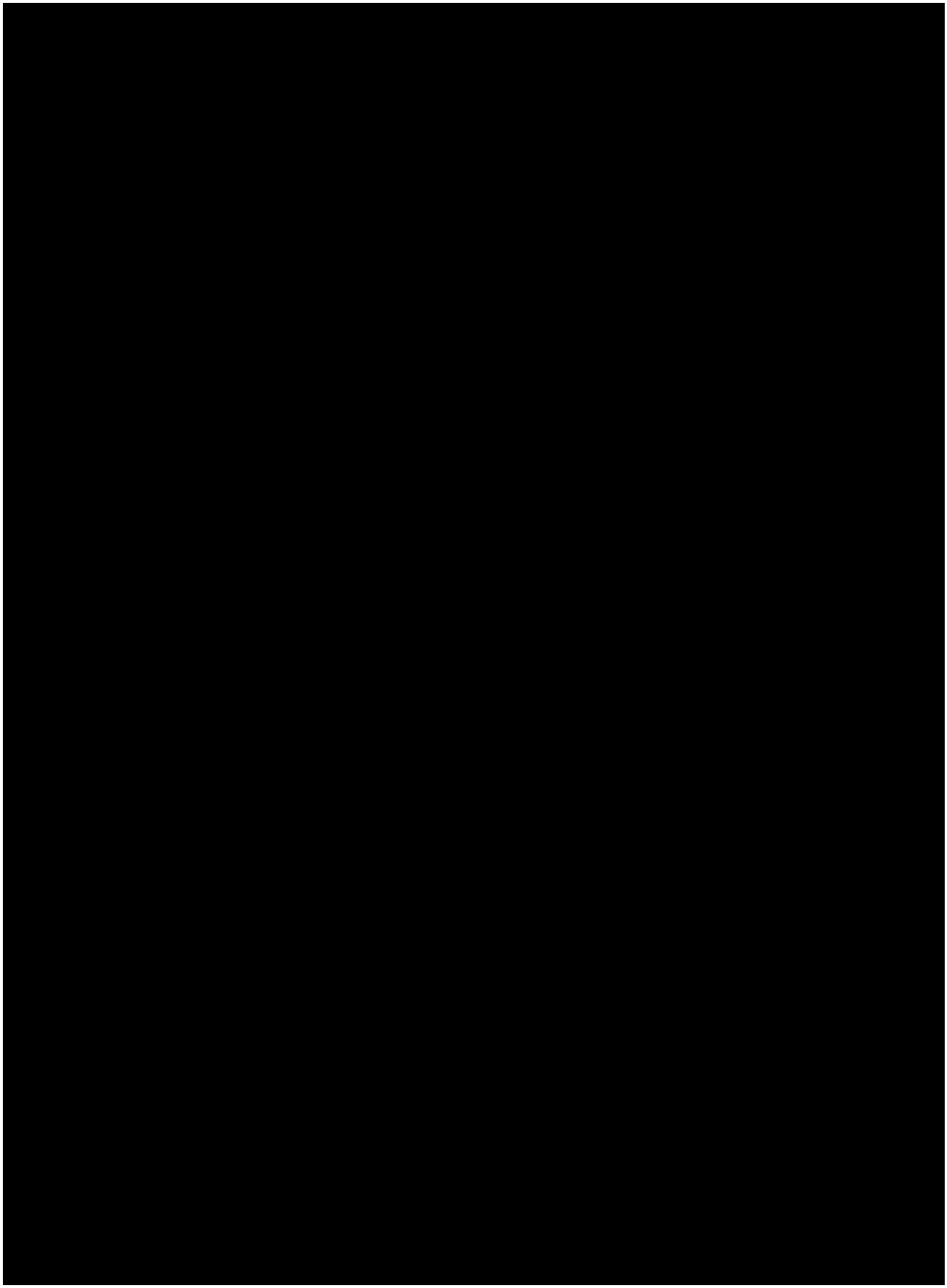
Several different doses and dosing scenarios were simulated using height, weight, and serum albumin levels obtained from a previous farletuzumab Phase 3 study in OC.[79] Stochastic simulations (N=1000) were conducted using the MORAb-202 population PK model to predict exposures (AUC) for different dosing scenarios and then AUCs were used to predict ORR and ILD rate [redacted][44][redacted]

[redacted]

[redacted]

5.6 [redacted]

[redacted]



[redacted]

5.6.2 Tumor Samples

Tumor biopsy specimens (archival and/or fresh samples) will be obtained from consenting participants prior to treatment to characterize the tumor microenvironment and assess gene expression and tumor genomics. [redacted]

A formalin-fixed, paraffin-embedded (FFPE) tumor tissue block (preferred) or [redacted] unstained slides (minimum of [redacted]) of tumor tissue from core biopsy, punch biopsy, excisional biopsy, or surgical specimen obtained during screening or prior to enrollment must be sent to the vendor. If slides are submitted, the unstained slides should be sectioned within [redacted] from latest FFPE block, which should not be more than [redacted] old.

Fine needle aspirates, other cytology samples, and bone biopsy samples are not acceptable.

An optional biopsy while on treatment may be scheduled within 7 days prior to Cycle 2 Day 1. Submission of on-treatment biopsy samples is strongly encouraged unless a biopsy is not clinically feasible and provided that the participant's disease is easily accessible and the tumor biopsies can be performed with minimal risk and discomfort. An additional optional biopsy will be performed to obtain a tumor sample at time of progression or recurrence (+ 21 days) unless not clinically feasible and provided the participant's disease is easily accessible and the tumor biopsies can be performed with minimal risk and discomfort.

5.6.2.1 Tumor Sample Collection

The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen; however, if a surgical procedure is performed for a clinical indication, excess tumor tissue should be submitted with the consent of the participant. Detailed instructions of the obtaining, processing, labeling, handling, storing, and shipping of specimens will be provided in a separate laboratory manual.

5.6.2.2 Characterization of Tumor Microenvironment

IHC or other technologies may be used to assess tumor markers and the tumor microenvironment within FFPE tumor tissue before, during, and/or after exposure to therapy. These IHC analyses may include, but are not limited to, natural killer cell markers, macrophage markers, and EMT markers.

5.6.2.3 Tumor Genotyping, Mutational Analysis, and Gene Expression Profiling

DNA and/or RNA isolated from the tumor tissue collected at baseline and on treatment may be analyzed using next generation sequencing or other appropriate techniques to interrogate association of various genomic correlates [redacted] with treatment efficacy or safety. Tumor mutational burden may be examined in this study.

[redacted]

5.6.2.4 Tumor FRα Expression

[redacted] The estimated prevalence of EOC with FRα expression ≥ 75% is approximately 35%.[80] [redacted]

[redacted]

6 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1) Signed Written Informed Consent

a) Participants or their legally acceptable representative (LAR; refer to Appendix 2) must have signed and dated an Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written informed consent form (ICF) in accordance with

regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.

2) Type of Participant and Target Disease Characteristics

a) Female participants with histologically-confirmed diagnosis of HGS ovarian, primary peritoneal, or fallopian tube cancer.

b) Platinum-resistant disease, defined as:

i) For participants who had only 1 line of platinum-based therapy: progression between > 1 month and ≤ 6 months after the last dose of platinum-based therapy of at least 4 cycles.

ii) For participants who had 2 or 3 lines of platinum-based therapy: progression ≤ 6 months after the last dose of platinum-based therapy.

c) Participants have received at least 1 but no more than 3 prior lines of systemic therapy and for whom single-agent therapy is appropriate as the next line of therapy. Participants may have been treated with up to 1 line of therapy subsequent to determination of platinum-resistance.

i) Participants must have received prior treatment with bevacizumab or must be deemed medically inappropriate or ineligible/intolerant to receive bevacizumab, refused to receive bevacizumab, or been unable to receive bevacizumab due to lack of access.

NOTES:

Neoadjuvant ± adjuvant chemotherapy will be considered 1 line of therapy.

Maintenance therapy (eg, bevacizumab, PARP inhibitors) will be considered part of the preceding line of therapy.

Therapy changed in the absence of progression will be considered part of the same line.

d) Disease progression per RECIST v1.1 (by investigator assessment) of at least 1 measurable lesion on or after the most recent therapy.

e) Either FFPE tissue (up to [redacted] old) or newly-obtained biopsies must be available for FRα assessment prior to randomization. The tumor sample (tissue block [preferred] or a minimum of [redacted] unstained slides) must be evaluable for FRα IHC analysis to meet eligibility criteria. Sample resubmission will be permitted for participants with non-evaluable FRα IHC who are otherwise eligible. See Section 5.6.2 for tumor tissue requirements.

f) Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

3) Age of Participant

a) Participant must be ≥ 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) at the time of signing the ICF.

4) Reproductive Status

- Investigators shall counsel women of childbearing potential (WOCBP, as defined in Appendix 4) participants on the importance of pregnancy prevention and the implications of an unexpected pregnancy.
- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants:

i) Female participants must have documented proof that they are not of childbearing potential.

(1) Women who are not of childbearing potential (as defined in Appendix 4) are exempt from contraceptive requirements.

ii) WOCBP must have a negative highly sensitive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are in Section 2: Schedule of Activities.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to potentially decrease the risk for inclusion of a woman with an undetected pregnancy.

iii) WOCBP must agree to follow instructions for method(s) of contraception as described below and included in the ICF.

- WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).

iv) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with user independent methods, as described in Appendix 4, during the intervention period and for at least 28 days before dosing and throughout the study and for 90 days after MORAb-202 discontinuation and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same period. For [redacted] participants, WOCBP are required to use a highly effective contraceptive method during the intervention period and for at least 28 days before dosing and throughout the study and for 6 months after IC chemotherapy discontinuation and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same period.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1) Medical Conditions

a) Clear cell, mucinous, endometrioid or sarcomatous histology, or mixed tumors containing components of any of these histologies, or low grade or borderline ovarian cancer.

b) Primary platinum-refractory ovarian cancer defined as disease progression within 1 month of the last dose of the first line platinum-containing regimen.

c) Pulmonary function test (PFT) abnormalities: FEV1 < 70% or FVC < 60%, and DLCO < 80%.

d) Investigator-assessed current ILD/pneumonitis, or ILD/pneumonitis suspected at screening or history of ILD/pneumonitis of any severity including ILD/pneumonitis from prior anti-cancer therapy.

e) Current infectious pneumonia, history of viral pneumonia (including COVID-19-related infection) with evidence of persistent radiologic abnormalities.

f) Significant third-space fluid retention (eg, ascites or pleural effusion) that requires repeated drainage.

g) Clinically significant pericardial effusion requiring drainage.

h) Prior pneumonectomy. Prior lobectomy and segmentectomy are allowed >12 months before treatment.

i) Recent chest radiotherapy. Participants with chest or chest wall radiation (eg, history of breast cancer) may be permitted if the radiation is documented > 6 months before starting study treatment.

j) Any autoimmune, connective tissue, or inflammatory disorders (eg, rheumatoid arthritis, Sjögren's syndrome, sarcoidosis, etc) where there is documented (or suspicion of) pulmonary involvement.

k) Spinal cord compression or untreated, symptomatic central nervous system (CNS) metastases. Participants are eligible if CNS metastases are asymptomatic and do not require immediate treatment, or have been treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). In addition, participants have discontinued anticonvulsant therapy and must have been either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to treatment. Imaging performed within 28 days prior to treatment must document radiographic stability of CNS lesions and be performed after completion of any CNS-directed therapy.

l) Concurrent malignancy (present during screening) requiring treatment, or history of prior malignancy active within 2 years prior to randomization (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the participant has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.

m) Participants with a condition requiring systemic treatment with either corticosteroids > 10 mg daily prednisone equivalents or other immunosuppressive medications within 14 days of study treatment administration, except for steroid adrenal replacement where doses of > 10 mg daily prednisone equivalent, are allowed in the absence of active autoimmune disease.

    i) Treatment with a short course (< 5 days) of steroids up to 7 days prior to initiating study treatment is permitted.

n) Evidence of active infection including tuberculosis and uncontrolled infection requiring systemic antibacterial, antiviral, or antifungal therapy ≤ 14 days prior to treatment.

o) Previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, either suspected or confirmed within 4 weeks prior to screening. Additionally, acute symptoms must have completely resolved and based on the investigator assessment in consultation with the BMS Medical Monitor (or designee), there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.
   i) Note: COVID-19 polymerase chain reaction (PCR) viral testing may be required prior to randomization based on specific country/regional guidelines, and the result of this testing may impact study participation. Testing results should be discussed with the BMS Medical Monitor (or designee) to confirm eligibility.

p) Evidence of active bleeding or bleeding susceptibility; or medically significant hemorrhage within 3 months prior to enrollment.

q) Known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome (AIDS) defining opportunistic infection within the last year, or a current CD4 count < 350 cells/μL. Participants with HIV are eligible if:
   i) They have received antiretroviral therapy (ART) for at least 4 weeks prior to randomization as clinically indicated while enrolled on study.
   ii) They continue on ART as clinically indicated while enrolled on study.
   iii) CD4 counts and viral load are monitored per standard of care by a local health care provider.

   NOTE: Testing for HIV must be performed at sites where mandated locally. HIV positive participants must be excluded where mandated locally.

r) Has a known history of active TB (bacillus tuberculosis).

s) History of active chronic hepatitis as evidenced by the following:
   i) Any positive test result for hepatitis B virus (HBV) indicating presence of virus, eg, hepatitis B surface antigen (HBsAg, Australia antigen) positive.
   ii) Any positive test result for hepatitis C virus (HCV) indicating presence of active viral replication (detectable HCV-ribonucleic acid [RNA]). Note: Participants with positive HCV antibody and an undetectable HCV RNA are eligible to enroll.
   iii) Additional testing or substitute testing per institutional guidelines to rule out infection is permitted.

t) Uncontrolled or significant cardiovascular conditions within 6 months prior to enrollment, including, but not limited, to any of the following:
   i) Cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery bypass graft surgery, symptomatic peripheral vascular disease, class III or IV congestive heart failure (as defined by the New York Heart Association; refer to Appendix 9), pericarditis, or myocarditis.
   ii) Ongoing symptomatic cardiac dysrhythmias, history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes).

u) History of deep vein thrombosis (DVT) within 6 weeks prior to enrollment. Participants who completed at least 1 month of anticoagulation prior to starting study treatment and continue while on study are eligible.

i) Participants at risk for DVT secondary to central venous catheters or with past medical history of DVT or clinical symptoms suggestive of DVT must have venous Doppler ultrasonography to rule out DVT during the screening period and prior to initiation of study treatment.

v) Any condition requiring folate supplementation (eg, folate deficiency).

w) Uncontrolled medical disorders that, in the opinion of the investigator or Sponsor, may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.

x) For [redacted] participants intended to receive Investigator's choice of PLD: Left ventricular ejection fraction (LVEF) below institutional lower limit of normal or below 50%, whichever is lower.

2) Prior/Concomitant Therapy

a) Time from the end of prior anticancer therapy to the first administration of the study drug:

i) Radiation therapy (other than bone or chest): ≤ 4 weeks.

ii) Bone radiation therapy: ≤ 2 weeks.

iii) Chemotherapy, endocrine therapy, or small-molecule targeted therapy: < 2 weeks or 5 half-lives, whichever is shorter.

iv) Immunotherapy, antibody, and other biologic therapeutic agents: < 4 weeks or 5 half-lives, whichever is shorter.

v) Investigational product(s) (IPs) < 4 weeks or 5 half-lives, whichever is shorter.

b) Any major surgery within 4 weeks of the first dose of study treatment. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

c) Resolution of anticancer therapy-related or radiation-related toxicities to Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 [NCI CTCAE v5.0) severity or lower prior to start of study treatment, except for stable sensory neuropathy (Grade ≤ 2), anemia (hemoglobin ≥ 9.0 g/dL), and alopecia (any grade).

d) Treatment with any live/attenuated vaccine within 30 days of first study treatment.

e) Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to first study treatment. Such medications are permitted if they are used as supportive care. See Section 7.7.1 for prohibited therapies.

f) Prior treatment with an investigational FRα-targeting agent and FRα-targeting ADC.

3) Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically-significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population.

i) Inadequate renal function as evidenced by calculated creatinine clearance (CrCl) < 50 mL/minute according to a 12- or 24-hour urine collection.

ii) Inadequate bone marrow function, as evidenced by:

(1) Absolute neutrophil count (ANC) < 1.0×10^9/L

(2) Hemoglobin < 9.0 g/dL

(3) Platelet count < 100×10^9/L

NOTE: Supportive therapies such as blood/platelet transfusion, hematopoietic stimulating agent including granulocyte colony-stimulating factor (G-CSF) formulation needed to achieve the above values are allowed, as per institutional practice, if given ≥ 1 week before study treatment.

iii) Inadequate liver function, as evidenced by:

(1) Total bilirubin > 1.5× upper limit of normal (ULN) except for unconjugated hyperbilirubinemia (eg, Gilbert's syndrome, who must have a total bilirubin < 3× ULN).

(2) Alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) > 3× ULN (in the case of liver metastases > 5× ULN) unless there are bone metastases. Participants with alkaline phosphatase (ALP) > 3× ULN, unless they and are known to have bone metastases in which case higher ALP values will also be allowed. In case ALP is > 3× ULN (in absence of liver metastases) or > 5× ULN (in presence of liver metastases) and participant is also known to have bone metastases, the liver-specific ALP must be separated from the total and used to assess the liver function instead of the total ALP.

iv) Serum albumin < 3.0 g/dL.

b) Clinically significant ECG abnormality, including marked prolonged baseline QTcF (repeated demonstration of a QTcF interval > 480 msec). A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QTcF.

4) Allergies and Adverse Drug Reactions

a) Has any prior severe hypersensitivity (≥ Grade 3) to monoclonal antibodies or eribulin or contraindication to the receipt of corticosteroids or any of the excipients (investigators should refer to the prescribing information for the selected corticosteroid).

b) History of allergy or contraindication to IC chemotherapy agent selected if randomized [redacted].

5) Other Exclusion Criteria

a) Male participants.

b) Participants are unable to follow contraception guidelines as specified in the protocol.

c) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and Sponsor approval is required.)

d) Participants who are compulsorily detained for treatment of either a psychiatric or physical illness (eg, infectious disease).

e) Participants currently in other interventional trials, including those for COVID-19, may not participate in BMS clinical trials until the protocol specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product (IP) designed to treat or prevent COVID-19 prior to screening,

enrollment must be delayed until the biologic impact of the vaccine or IP is stabilized, as determined by documented discussion between the investigator and the Medical Monitor (or designee).

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs) that occurred following consent.

6.4.1 Re-testing During Screening

This study permits the re-enrollment of a participant who has discontinued the study as a screen failure (ie, participant has not been randomized/has not been treated). If re-enrolled, the participant must be re-consented and all other screening activities must be met within the designated screening window.

Re-testing of laboratory parameters and/or other assessments within any single screening or lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to randomization is the value by which study inclusion will be assessed because it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline, may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, procedure(s), or medical device intended to be administered to a study participant according to the study protocol.

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational/Auxiliary [Medicinal] Product (Non-IP/Non-IMP/AxMP) as indicated in Table 7.1-1.

An IP, also known as an IMP in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently

from the authorized form, used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis may be considered Non-IMPs/AxMPs.

7.1 Study Interventions Administered

Table 7.1-1: Study Intervention(s) Administered

Type/ Intervention Name/ Dose Formulation	Unit Dose Strength(s)	IMP/Non-IMP/AxMP Blinded or Open-label Use	Sourcing	Packaging and Labeling	Current/ Former Name(s) or Alias(es)
MORAb-202 Lyophilized Powder in a Single Use Vial	[redacted] mg/mL	IMP	Provided centrally by the Sponsor	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.	--
Paclitaxel	6 mg/mL	IMP	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement	Paclitaxel Bendalis
Pegylated Liposomal Doxorubicin (PLD)	2 mg/mL	IMP	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement	Caelyx Pegylated Liposomal Doxorubicin

Table 7.1-1: Study Intervention(s) Administered

Type/ Intervention Name/ Dose Formulation	Unit Dose Strength(s)	IMP/Non-IMP/AxMP Blinded or Open-label Use	Sourcing	Packaging and Labeling	Current/ Former Name(s) or Alias(es)
Topotecan	1 mg/mL	IMP	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement	Hycamtin

Abbreviations: AxMP, auxiliary medicinal product; IMP, investigational medicinal product; PLD, pegylated liposomal doxorubicin.

Table 7.1-2: Study Arm(s)

Arm Title/ Arm Type	Intervention Description/ Dosage Levels	Route of Administration
[redacted]	MORAb-202 25 mg/m^2 [redacted]	IV infusion
[redacted][a]	Paclitaxel 80 mg/m^2 on Days 1, 8, 15, and 22 of a 28-day cycle	IV infusion
	PLD 40 mg/m^2 on Day 1 (±3 days) of a 28-day cycle	IV infusion
	Topotecan 1.25 mg/m^2 on 5 consecutive days on Days 1 to 5 of a 21-day cycle	IV infusion
	Topotecan 4.0 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle	IV infusion

Abbreviation: IV, intravenous, PLD, pegylated liposomal doxorubicin.

[a] The investigator will select paclitaxel, topotecan, or PLD as the single-agent chemotherapy prior to participant randomization.

7.1.1 MORAb-202 Administration [redacted]

Participants will receive MORAb-202 at a dose 25 mg/m^2 [redacted], for a maximum treatment duration of 2 years, or until disease progression, unacceptable toxicity, death, withdrawal of consent, or the study ends, whichever occurs first.

Table 7.1.1-1: Administration of MORAb-202

Study Intervention	Cycle 1 Day 1, onwards	Notes
[redacted] Premedication Acetaminophen/paracetamol 400 to 600 mg orally or clinical equivalent per clinic routine	X	Premedication will be administered 30 to 60 minutes prior to the first infusion of MORAb-202. If no infusion reactions are observed, premedications will not be administered with subsequent MORAb-202 infusions. Monitor participants carefully for infusion reactions during each MORAb-202 administration. If an acute infusion reaction is noted, manage participants according to Table 7.4.1-2.
[redacted] MORAb-202 25 mg/m^2 [redacted]	X	Participants must receive the first dose of study treatment within 3 calendar days from randomization, unless previously discussed with Medical Monitor (or designee). MORAb-202 will be administered as an intravenous (IV) infusion [redacted] for a maximum treatment duration of 2 years, until disease progression, unacceptable toxicity, withdrawal of consent, death, or the study ends, whichever occurs first. Participants may be dosed no less than 18 days from the previous dose. [redacted] Doses of MORAb-202 may be reduced, interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment (see Section 7.4.1 for dose modifications for management of TRAEs). Dosing visits are not skipped, only delayed. The first infusion of MORAb-202 will be given over no less than 60 minutes. If no infusion reactions are observed, subsequent infusions can be infused as tolerated, but given over no less than 30 minutes. Flush the intravenous line with an appropriate amount of diluent (eg, 0.9% sodium chloride) to ensure that the complete dose is administered.

Abbreviations: [redacted] IV, intravenous; TRAE, treatment-related adverse event.

Please refer to the current Investigator's Brochure and/or Pharmacy Manual for further details regarding storage, preparation, and handling of MORAb-202.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

7.1.2 Preparation and Administration of Paclitaxel

Paclitaxel will be prepared according to institutional standards or the approved local Product Label. Paclitaxel will be administered at a dose of 80 mg/m^2 by IV infusion over 60 minutes on Days 1, 8, 15, and 22 of a 28-day cycle.

Participants should be premedicated prior to paclitaxel administration to prevent severe hypersensitivity reactions, per the approved local Product Label. Such premedication may consist of dexamethasone 20 mg by mouth (per os [PO]) 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.

Use BSA for dosing calculations using height measured at screening, and weight measured on Day 1 of each cycle (or up to 3 days prior to Day 1). Round all doses to the nearest milligram per institutional standard.

Doses of paclitaxel may be reduced, interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment (see Section 7.4.2 for dose modifications for management of TRAEs). Dosing visits are not skipped, only delayed.

Please refer to the approved local Product Label for complete details regarding storage, preparation, and handling of paclitaxel.

7.1.3 Preparation and Administration of Pegylated Liposomal Doxorubicin

PLD will be prepared according to institutional standards or the approved local Product Label. PLD will be administered at dose of 40 mg/m^2 by IV infusion at an initial rate of 1 mg/min on Day 1 (± 3 days) of a 28-day cycle. After Cycle 1, if tolerated, PLD can be administered as a 60-minute infusion. Use BSA for dosing calculations using height measured at screening, and weight measured on Day 1 of each cycle (or up to 3 days prior to Day 1). Round all doses to the nearest milligram per institutional standard.

Doses of PLD may be reduced, interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment (see Section 7.4.3 for dose modifications for management of TRAEs). Dosing visits are not skipped, only delayed.

The minimum time interval between 2 consecutive PLD doses cannot be < 24 days.

Please refer to the approved local Product Label for complete details regarding storage, preparation, and handling of PLD.

7.1.4 Preparation and Administration of Topotecan

Topotecan will be prepared according to institutional standards or the approved local Product Label. Topotecan will be administered as a 21-day cycle regimen or a 28-day cycle regimen. For

a 21-day cycle, topotecan will be administered at a dose of 1.25 mg/m^2 by IV infusion over 30 minutes on Days 1 to 5 of a 21-day cycle. For a 28-day cycle, topotecan will be administered at dose of 4 mg/m^2 by IV infusion over 30 minutes on Days 1, 8, and 15 of a 28-day cycle. Use BSA for dosing calculations using height measured at screening, and weight measured on Day 1 of each cycle (or up to 3 days prior to Day 1). Round all doses to the nearest milligram per institutional standard.

Doses of topotecan may be reduced, interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment (see Section 7.4.4 for dose modifications for management of TRAEs). Dosing visits are not skipped, only delayed.

Please refer to the approved local Product Label for complete details regarding storage, preparation, and handling of topotecan.

7.1.5 Calculation of Dose Based on Body Surface Area

Before dose administration, the amount of study treatment needed for each participant will be calculated in the following manner:

Dose (mg) = scheduled dose (mg/m^2) × body surface area (BSA) (m^2)

BSA will be calculated using any accepted method customarily used by the clinical site, such as the Haycock, Du Bois and Du Bois or the Mosteller formula:

- BSA (m^2) = 0.024265 × Height (cm)^0.3964 × Weight (kg)^0.5378 (Haycock)[81]
- BSA (m^2) = 0.007184 × Height (cm)^0.725 × Weight (kg)^0.425 (Du Bois and Du Bois)[82]
- BSA (m^2) = ([Height (cm) × Weight (kg)]/3600)½ (Mosteller)[83]

[redacted]

7.2 Assignment to Study Intervention

All participants will be centrally randomized [redacted] using Interactive Response Technology (IRT). Before the study is initiated, each user will receive log-in information and directions on how to access the IRT.

Study intervention will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

After the participant's informed consent has been obtained and initial eligibility is established, the participant must be enrolled into the study by using IRT to obtain the participant number. Every participant who signs the ICF must be assigned a participant number in IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by the Sponsor.

After enrollment in the IRT, participants who have met all eligibility criteria will be randomized through the IRT.

The IC chemotherapy must be identified prior to randomization and captured in both IRT and eCRFs. The selection of agent and regimen may not be changed after the participant has been randomized and prior to the first dose unless discussed with and approved by the Medical Monitor (or designee).

7.3 Blinding

Not applicable as this is a randomized open-label study; it has been determined that blinding is not required to meet study objectives and access to treatment assignment information is unrestricted. Aggregate data by arm will be provided only for Safety Committee review. The specific treatment to be taken by a participant will be assigned using IRT. The site will contact the Interactive Response System prior to the start of study intervention administration for each participant. The site will record the treatment assignment on the case report form (CRF).

The bioanalytical laboratory will receive treatment assignments in order to minimize unnecessary analysis of samples.

7.4 Dosage Modification

Recommendations for dose reduction, delay, interruption, or discontinuation of individual study drugs in the management of study drug-related adverse reactions are summarized below. For additional information, please refer to individual drug labels. Clinical judgment of the treating physician should guide the management plan of each participant based on individual benefit/risk assessment. However, for events requiring a discontinuation, treatment must be discontinued. Any changes to the dose must be recorded on the appropriate electronic case report form (eCRF).

7.4.1 Dose Modification for MORAb-202

For participants who experience toxicity but meet criteria for dose modification, the next administration of MORAb-202 should be reduced 1 dose level lower (see Table 7.4.1-1). Once a dose is decreased, it cannot be increased again.

Table 7.4.1-1: MORAb-202 Dose Levels

Dose level	**MORAb-202**
	[redacted]
Starting dose	25 mg/m^2
First dose reduction (Dose level -1)	[redacted]

Only 1 dose level reduction is allowed. If more than 1 dose level reduction is required, study treatment must be discontinued.

Table 7.4.1-2: Recommended Dose Modifications and Management for MORAb-202 Treatment-related Adverse Events

Drug-related Adverse Event per CTCAE v5.0	Severity	Action Taken
Infusion-related reaction		
Infusion-related reaction	Grade 1	• Supervise at bedside and continue the infusion of MORAb-202, or manage the infusion per institutional standard (eg, suspending infusion). • If necessary, give 400 to 600 mg orally (PO) acetaminophen/paracetamol, either alone or in combination with diphenhydramine 30 to 50 mg PO or intravenous (IV). Equivalent premedications may be used, as per local standard of care. • If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve. If no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study medication will be administered at that visit. • Subsequent prophylaxis: – Administer acetaminophen 1000 mg PO + diphenhydramine 30 to 50 mg PO ± ranitidine 50 mg IV or famotidine 20 mg IV; equivalent medications may be used, as per local standard of care. – Administer 30 to 60 minutes prior to MORAb-202 infusion.
	Grade 2	• Suspend the infusion of MORAb-202. • Give 400 to 600 mg acetaminophen/paracetamol PO, either alone or in combination with diphenhydramine 30 to 50 mg PO or IV. • Restart the infusion at 50% of the original infusion rate when symptoms resolve. If no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study medication will be administered at that visit. • Subsequent prophylaxis: – Administer acetaminophen 1000 mg PO + diphenhydramine 30 to 50 mg PO ± ranitidine 50 mg IV or famotidine 20 mg IV ± dexamethasone 20 mg IV; equivalent medications may be used, as per local standard of care. – Administer 30 to 60 minutes prior to MORAb-202 infusion. • Note: No MORAb-202 dose reduction by 1 dose level is needed if symptoms are resolved at next cycle. See Table 7.4.1-1.

Table 7.4.1-2: Recommended Dose Modifications and Management for MORAb-202 Treatment-related Adverse Events

Drug-related Adverse Event per CTCAE v5.0	Severity	Action Taken
		• If Grade 2 infusion reactions occur despite subsequent prophylaxis, MORAb-202 must be permanently discontinued.
	Grade 3 or 4	• Permanently discontinue.
Pulmonary		
Interstitial Lung Disease (ILD)/Pneumonitis	[redacted]	

Table 7.4.1-2: Recommended Dose Modifications and Management for MORAb-202 Treatment-related Adverse Events

Drug-related Adverse Event per CTCAE v5.0	Severity	Action Taken
[redacted]	[redacted]	[redacted]
	[redacted]	

Table 7.4.1-2: Recommended Dose Modifications and Management for MORAb-202 Treatment-related Adverse Events

Drug-related Adverse Event per CTCAE v5.0	Severity	Action Taken
		[redacted]

Table 7.4.1-2: Recommended Dose Modifications and Management for MORAb-202 Treatment-related Adverse Events

Drug-related Adverse Event per CTCAE v5.0	Severity	Action Taken
	[redacted]	
Hematological		
Neutrophil count decreased	Grade ≥ 3	Hold MORAb until absolute neutrophil count (ANC) is ≥ 1000/µL
	Grade 4	Dose reduce 1 level (Table 7.4.1-1) if lasting > 7 days
Febrile neutropenia	Grade ≥ 3	Hold MORAb-202 until < 38°C (100.4°F) + ANC ≥ 1000/µL Dose reduce 1 level (Table 7.4.1-1) if Grade ≥ 3 febrile neutropenia (fever > 38°C [100.4°F] + ANC < 1000/µL)
Platelet count decreased	Grade ≥ 2	Hold MORAb-202 until platelet count is ≥ 75,000/µL Dose reduce 1 level (Table 7.4.1-1) if: • Thrombocytopenia Grade 4 on 2 separate days, or requiring a platelet transfusion on 2 separate days, within a 7-day period. • Thrombocytopenia Grade ≥ 3 complicated by bleeding and/or requiring platelet or blood transfusion.

Table 7.4.1-2: Recommended Dose Modifications and Management for MORAb-202 Treatment-related Adverse Events

Drug-related Adverse Event per CTCAE v5.0	Severity	Action Taken
Other		
All other laboratory abnormalities (both symptomatic and asymptomatic)	Grade ≥ 3	• Hold MORAb-202 until resolution to Grade ≤ 1 or baseline. • Dose reduce 1 level (Table 7.4.1-1). • Do not dose reduce for Grade 3 labs without clinical significance, such as hypophosphatemia, hypocalcemia, or hypomagnesemia responsive to oral supplementation, which resolve to baseline or Grade 1 within 48 hours.
All other non-hematologic toxicities:	Grade ≥ 3	Hold MORAb-202 until resolution to Grade ≤ 1 or baseline. Dose reduce 1 level after AE resolves, except: • Grade 3 fatigue for < 5 days. • Diarrhea, nausea, and vomiting, unless lasting > 3 days despite optimal supportive care

Abbreviations: AE, adverse event; [redacted] ; ANC, absolute neutrophil count; [redacted]; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; ILD, interstitial lung disease; IV, intravenous; PO, per os (oral route of administration); [redacted]

7.4.1.1 Criteria to Resume MORAb-202 Treatment

Starting Next Cycle:

To start the next cycle of MORAb-202 administration, participants must meet the following minimum requirements plus be appropriate for additional cycles per investigator judgment:

- ANC ≥ 1000/μL
- Platelet count ≥ 75,000/μL
- All non-hematologic toxicity has resolved to Grade ≤ 1 or baseline.
- Participants with Grade ≥ 2 peripheral neuropathy should not be retreated until neuropathy is Grade < 2, except for stable sensory neuropathy that was present at baseline, which can be Grade ≤ 2, as per exclusion criterion 2) c).
- All Grade ≥ 3 laboratory abnormalities even if asymptomatic must be corrected to Grade ≤ 1 or baseline.
- Meet the requirements for dosing (see Table 7.4.1-2).

Dose Reduction for the Next Cycle:

For participants who experience toxicity and meet criteria for dose modification, the next administration of MORAb-202 should be reduced 1 dose level lower (see Table 7.4.1-1 for dose levels). Once a dose is decreased, it cannot be increased again. Only one dose level reduction is allowed.

Postponement of Next Cycle:

MORAb-202 administration in subsequent cycles may be postponed [redacted] to recover from any toxicities. Treatment delay [redacted] may be allowed in participants with ILD/pneumonitis to allow for recovery, which requires consultation with and approval from the Sponsor's Medical Monitor.

7.4.2 Dose Modification for Paclitaxel

Table 7.4.2-1: Dose Modification for Paclitaxel

Drug-related AE per CTCAE v5.0	Severity	Action Taken
Hematologic Toxicities	Grade 1	Investigator judgement to continue or interrupt paclitaxel treatment.
	Grade 2 or 3	Hold paclitaxel until ANC and platelet levels meet the following criteria: • Day 1: – ANC ≥ 1.5×10^9/L (1,500/μL), and – Platelets ≥ 100×10^9/L (100,000/μL) • Day 8, 15, and 22: – ANC ≥ 1.0×10^9/L (1,000/μL), and – Platelets ≥ 100×10^9/L (100,000/μL) Retreat at same dose level.
	Grade 4	Hold paclitaxel until ANC and platelet levels meet the following criteria: • Day 1: – ANC ≥ 1.5×10^9/L (1,500/μL), and – Platelets ≥ 100×10^9/L (100,000/μL) • Day 8, 15, and 22: – ANC ≥ 1.0×10^9/L (1,000/μL), and – Platelets ≥ 100×10^9/L (100,000/μL) Dose reduce by 1 level.
For febrile neutropenia and/or severe bleeding, permanently discontinue paclitaxel.		
Non-hematologic Toxicities	Grade 1	Investigator judgement to continue or interrupt paclitaxel treatment.
	Grade 2	• Investigator judgement to continue or interrupt paclitaxel treatment. • For participants experiencing neuropathy, dose reduce by 1 level. • Dose delay if: – Total bilirubin > 1× ULN or if AST and/or ALT > 1.5× ULN occurs concomitant with ALP > 2.5× ULN.

Table 7.4.2-1: Dose Modification for Paclitaxel

Drug-related AE per CTCAE v5.0	Severity	Action Taken
	Grade 3 or 4	• Hold paclitaxel until the event resolves or improves to Grade 1. Dose reduce by 1 level. • Grade 3 lymphopenia does not require a dose delay. • Grade ≥ 3 neuropathy lasting > 7 days permanently discontinue paclitaxel

Abbreviations: AE, adverse events; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; ULN, upper limit of normal.

Subsequent dose reductions may be required, per Section 7.4.2.1.

A dose given more than 3 days after the intended dose date will be considered a dose delay. Longer delays may be allowed following discussion with the Medical Monitor (or designee).

7.4.2.1 Dose Reduction for Paclitaxel

The full dose of paclitaxel is 80 mg/m^2. This dose may be reduced by 1 dose level to 70 mg/m^2 and subsequently by 1 more dose level to 60 mg/m^2. In the case of any toxicity requiring more than 2 dose reductions, paclitaxel must be discontinued, unless the participant is benefitting from therapy.

7.4.3 Dose Modification for Pegylated Liposomal Doxorubicin (PLD)

Table 7.4.3-1: Dose Modification for Pegylated Liposomal Doxorubicin (PLD)

Drug-related AE per CTCAE v5.0	Severity	Action Taken
Hematologic Toxicities	Grade 1 ANC: LLN-1.5 × 10^9/L (< LLN-1,500/µL) Platelets: < LLN-75.0 × 10^9/L (< LLN-75,000/uL)	Resume treatment; no dose reduction.
	Grade 2 ANC: < 1.5-1.0 × 10^9/L (< 1,500-1000/µL) Platelets: < 75.0-50.0 × 10^9/L (< 75,000-50,000/uL)	Hold PLD until ANC and platelet levels meet the following criteria: • ANC ≥ 1.5 × 10^9/L (1,500/µL), and • Platelets ≥ 75.0 × 10^9/L (75,000/µL) Retreat at same dose level.
	Grade 3 ANC: < 1.0-0.5 ×10^9/L (< 1,000-500/µL) Platelets: < 50.0-25.0 × 10^9/L (< 50,000-25,000/µL)	Hold PLD until ANC and platelet levels meet the following criteria: • ANC ≥ 1.5 × 10^9/L (1,500/µL), and • Platelets ≥ 75.0 × 10^9/L (75,000/µL) Retreat at same dose level.
	Grade 4 ANC: < 0.5 × 10^9/L (< 500/µL) Platelets: < 25.0 × 10^9/L (< 25,000/µL)	Hold PLD until ANC and platelet levels meet the following criteria: • ANC ≥ 1.5 × 10^9/L (1,500/µL), and • Platelets ≥ 75.0 × 10^9/L (75,000/µL) Dose reduce by 25% dose level or continue previous dose with cytokine support.

Table 7.4.3-1: Dose Modification for Pegylated Liposomal Doxorubicin (PLD)

Drug-related AE per CTCAE v5.0	Severity	Action Taken
Non-hematologic Toxicities (HFS and Mucositis)	Grade 1 HFS: mild erythema, swelling or desquamation not interfering with daily activities Mucositis: painful ulcers, erythema, or mild soreness	Continue PLD unless previous Grade 3 or 4 HFS. In case of previous Grade 3 or 4 HFS delay up to 2 weeks and decrease dose by 25%.
	Grade 2 HFS: Erythema, desquamation, or swelling interfering with but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter Mucositis: painful erythema, edema, ulcers, but can eat	Hold PLD until resolved to Grade 1 or baseline. If after 2 weeks there is no resolution, PLD should be discontinued. If no prior Grade 3 or 4 HFS resume at the dose prior to the event. If previous Grade 3 or 4 toxicity, decrease dose by 25%.
	Grade 3 HFS: Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing Mucositis: painful erythema, edema, or ulcers; cannot eat	• Hold PLD until the event resolves or improves to Grade 1 or baseline. • Dose reduce by 25% dose level. If after 2 weeks there is no resolution, PLD should be discontinued.
	Grade 4 HFS: diffuse or local process causing infectious complications, a bed ridden state or hospitalization Mucositis: requires parenteral or enteral support	• Hold PLD until the event resolves or improves to Grade 1 or baseline. • Dose reduce by 25% dose level. If after 2 weeks there is no resolution, PLD should be discontinued.

Abbreviations: AE, adverse event; ANC, absolute neutrophil count; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; HFS, hand-foot syndrome; LLN, lower limit of normal; PLD, pegylated liposomal doxorubicin.

7.4.3.1 Dose Reduction for Pegylated Liposomal Doxorubicin (PLD)

The full dose of PLD is 40 mg/m^2. This dose may be reduced by 1 dose level to 30 mg/m^2 and subsequently by 1 more dose level to 20 mg/m^2. In the case of any toxicity requiring more than 2 dose reductions, PLD must be discontinued, unless the participant is benefitting from therapy.

If a participant's LVEF drops below normal or by at least 15% from baseline value, treatment with PLD should be interrupted and event should be discussed with the Medical Monitor before restarting treatment.

7.4.4 Dose Modification for Topotecan

Table 7.4.4-1: Dose Modification for Topotecan

Drug-related AE per CTCAE v5.0	Severity	Action Taken
Hematologic Toxicities	Grade 1	Investigator judgement to continue or interrupt topotecan treatment.
	Grade 2 or 3	Hold topotecan until ANC and platelet levels meet the following criteria: Day 1: • ANC ≥ 1.5×10^9/L (1,500/μL), and • Platelets ≥ 100×10^9/L (100,000/μL) Days 8 and 15: • ANC ≥ 1.0×10^9/L (1,000/μL), and • Platelets ≥ 100×10^9/L (100,000/μL) Re-treat at same dose level.
	Grade 4 or any grade neutropenia complications (fever, infection)	Hold topotecan until ANC and platelet levels meet the following criteria: Day 1: • ANC ≥ 1.5×10^9/L (1,500/μL) and • Platelets ≥ 100×10^9/L (100,000/μL) Days 8 and 15: • ANC ≥ 1.0×10^9/L (1,000/μL) and • Platelets ≥ 100×10^9/L (100,000/μL) Dose reduce by 1 level.
Non-hematologic Toxicities	Grade 1	Investigator judgement to continue or interrupt topotecan treatment.

Table 7.4.4-1: Dose Modification for Topotecan		
Drug-related AE per CTCAE v5.0	**Severity**	**Action Taken**
	Grade 2	Investigator judgement to continue or interrupt topotecan treatment.
	Grade 3 or 4	Hold topotecan until the event resolves or improves to Grade 1. Dose reduce by 1 level.

Abbreviations: AE, adverse event; ANC, absolute neutrophil count; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0.

7.4.4.1 Dose Reduction for Topotecan

The full dose of topotecan is 4 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle or 1.25 mg/m^2 on 5 consecutive days of a 21-day cycle. These doses may be reduced by 1 dose level to 3.5 mg/m^2 and to 1 mg/m^2, respectively, and subsequently by 1 more dose level to 3 mg/m^2 and 0.75 mg/m^2. In the case of any toxicity requiring more than 2 dose reductions, topotecan must be discontinued, unless the participant is benefitting from therapy.

7.5 Preparation/Handling/Storage/Accountability

The IP/IMP/Non-IMP/AxMP must be stored in a secure area according to local regulations. It is the responsibility of the investigator, or designee where permitted, to ensure that IP/IMP/Non-IMP/AxMP is only dispensed to study participants. The IP/IMP/Non-IMP/AxMP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study intervention is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Sponsor. If concerns regarding the quality or appearance of the study intervention arise, the study intervention should not be dispensed, and the Sponsor should be contacted immediately.

Study intervention not supplied by the Sponsor will be stored in accordance with the package insert.

IP/IMP/Non-IMP/AxMP documentation (whether supplied by the Sponsor or not) must be maintained and must include all processes required to ensure the drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage

temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition of records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual and Appendix 2.

Please refer to the current IB and/or Pharmacy Manual for further details regarding storage, preparation, and handling.

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

At the time of receipt of the IP by the investigator or designee, the Sponsor will specify the appropriate number of containers or units to select for retention, the conditions of sample storage, required duration of sample retention, and provisions for returning or disposing of the IP. When samples are selected, containers or units should be placed in packaging with a tamper-evident seal provided by the Sponsor or sourced by the site. Package labeling should clearly identify the contents as retention samples and state that the IP should be stored in the restricted area with limited access.

Additional details regarding the retention process will be provided in a Pharmacy Manual or other written documentation.

7.6 Study Intervention Compliance

Study intervention compliance will be periodically monitored by drug accountability. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and electronic case report form (eCRF). This will be source data verified by the BMS Unblinded Site Monitor through regularly scheduled monitoring visits.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study

intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

The following medications and treatments are prohibited during the study (unless utilized to treat a drug-related AE):

- Any folate supplementation prescribed for folate deficiency.
- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.
- Any concurrent anti-neoplastic therapy (eg, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents for treatment of malignancy). However, the continued use of drugs for bone diseases (such as bisphosphonates and anti-receptor activator of nuclear factor kappa-B ligand monoclonal antibody) that were already being used by the participant prior to the initial study treatment is permitted. These uses of such agents can be discussed with the Sponsor Medical Monitor as needed.
- Any live, attenuated vaccine within 30 days prior to the first dose of study drug, during study treatment, and 30 days post last dose. Inactivated vaccines (such as hepatitis A or polio vaccines) are permitted during the study. Seasonal influenza and COVID-19 vaccines that do not contain live virus are permitted.

7.7.2 Supportive Therapies

Supportive therapies as blood/platelet transfusion, hematopoietic stimulating agent, including granulocyte colony stimulating factor (G-CSF) formulation, are allowed at the discretion of the investigators, in accordance with institutional and/or current American Society of Clinical Oncology guidelines within 1 week prior to initiating/resuming study treatment.

7.7.3 Other Restrictions and Precautions

Participants are prohibited from enrolling in another clinical trial while participating in this study.

7.7.3.1 Imaging Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether they should receive contrast and if so, which contrast agent and dose are appropriate. Specific to magnetic resonance imaging (MRI), participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis; therefore, MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. These restrictions will be outlined in the Imaging Manual.

Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant enrolled in this study rests with the site radiologist, the investigator, and standards set by the local Ethics Committee.

7.8 Continued Access to Study Intervention After the End of the Study

At the end of the study, the Sponsor will not continue to provide Sponsor-supplied study intervention to participants or investigators unless the Sponsor chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study. The Sponsor reserves the right to terminate access to Sponsor-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of MORAb-202 is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives; or c) the participant can obtain medication from a government-sponsored or other health program. In all cases, the Sponsor will follow local regulations.

8 DISCONTINUATION CRITERIA

Discontinuation of specific sites or of the study as a whole is detailed in Appendix 2.

8.1 Discontinuation of Study Intervention

Participants MUST discontinue IP/IMP (and Non-IMP/AxMP at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study intervention. Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.
- Any clinical AE, laboratory test result abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by the Sponsor.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness (eg, infectious disease). (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and Sponsor approval is required).
- Pregnancy (see Section 9.2.5).
- Documented disease progression per RECIST v1.1, as assessed by the investigator.
- Clinical deterioration while receiving active study therapy, that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant. Significant noncompliance with protocol (eg, procedures, assessments, medications, etc). The investigator should discuss such issues with the Medical Monitor.
- Per criteria for permanent discontinuation in Section 7.4 and in accordance with the local Product Label for IC chemotherapy agents.

- Any dosing delay lasting > [redacted] with the following exception:
  - Treatment delay [redacted] may be allowed in participants with ILD/pneumonitis to allow for recovery, which requires consultation with and approval from the Sponsor's Medical Monitor.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 12 weeks, the Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

Refer to the Section 2: Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

All participants who discontinue study intervention should comply with protocol-specified follow-up procedures as outlined in Section 2: Schedule of Activities. The only exception to this requirement is when a participant withdraws consent for all study procedures, including post-treatment study follow-up, or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study intervention is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records per local regulatory requirements in each region/country and entered on the appropriate CRF page.

8.1.1 Post-study Intervention Study Follow-up

In this study, PFS is a key secondary endpoint [redacted] of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study intervention must continue to be followed for data collection of outcome, disease response (until investigator-assessed disease progression by RECIST 1.1), and/or survival follow-up every 3 months from safety follow-up visit up to 1 year from the last participant randomized or LPLV (30 days after last patient last treatment visit); whichever is later as required and in line with Section 5 until death or the conclusion of the study.

8.2 Discontinuation From the Study

Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified safety follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up.
- The withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is from further treatment with study intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.

- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Activities. See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from both the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **3** documented phone calls, faxes, or emails, as well as lack of response by participant to **1** registered mail letter. All attempts should be documented in the participant's medical records.
- If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data, such as public health registries and databases, necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (see Section 2).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Perform additional measures, including non-study required laboratory tests, as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug-induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.
- Evaluate the participant immediately to rule out pulmonary toxicity if the participant shows pulmonary-related signs (eg, [redacted] hypoxemia) or symptoms (eg, shortness of breath, dyspnea, non-productive cough, fever). See Section 9.4.5 for further details and Section 7.4.1 for ILD/pneumonitis management guidelines.
- Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

9.1.1 Efficacy Assessment for the Study

Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). [redacted]

Every attempt should be made to image each participant using an identical acquisition protocol on

the same scanner for all imaging timepoints. Tumor measurements should be made by the same investigator or radiologist for each assessment, whenever possible.

If a participant has a contraindication for CT intravenous contrast, then a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for both MRI and CT intravenous contrasts, then a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for MRI (eg, incompatible pacemaker) in addition to contraindication to CT intravenous contrast, then a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

Use of CT component of a positron emission tomography-computed tomography (PET-CT) scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomically-based RECIST v1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST v1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

For this study, a rise in CA-125 alone is not sufficient to declare progression, and progression events should be determined by radiographic evidence of progression per RECIST v1.1 criteria.

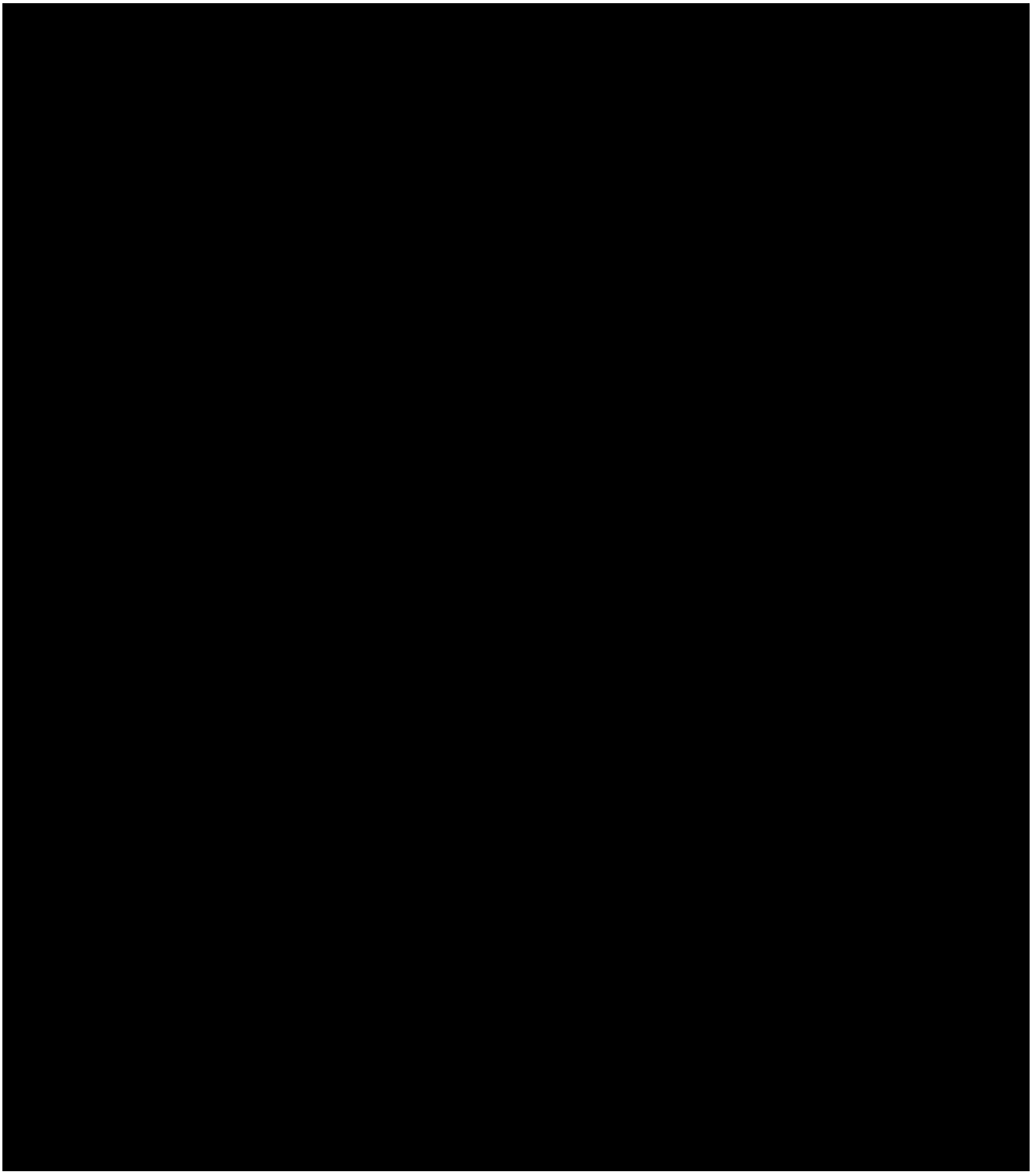
9.1.2 Imaging Assessment for the Study

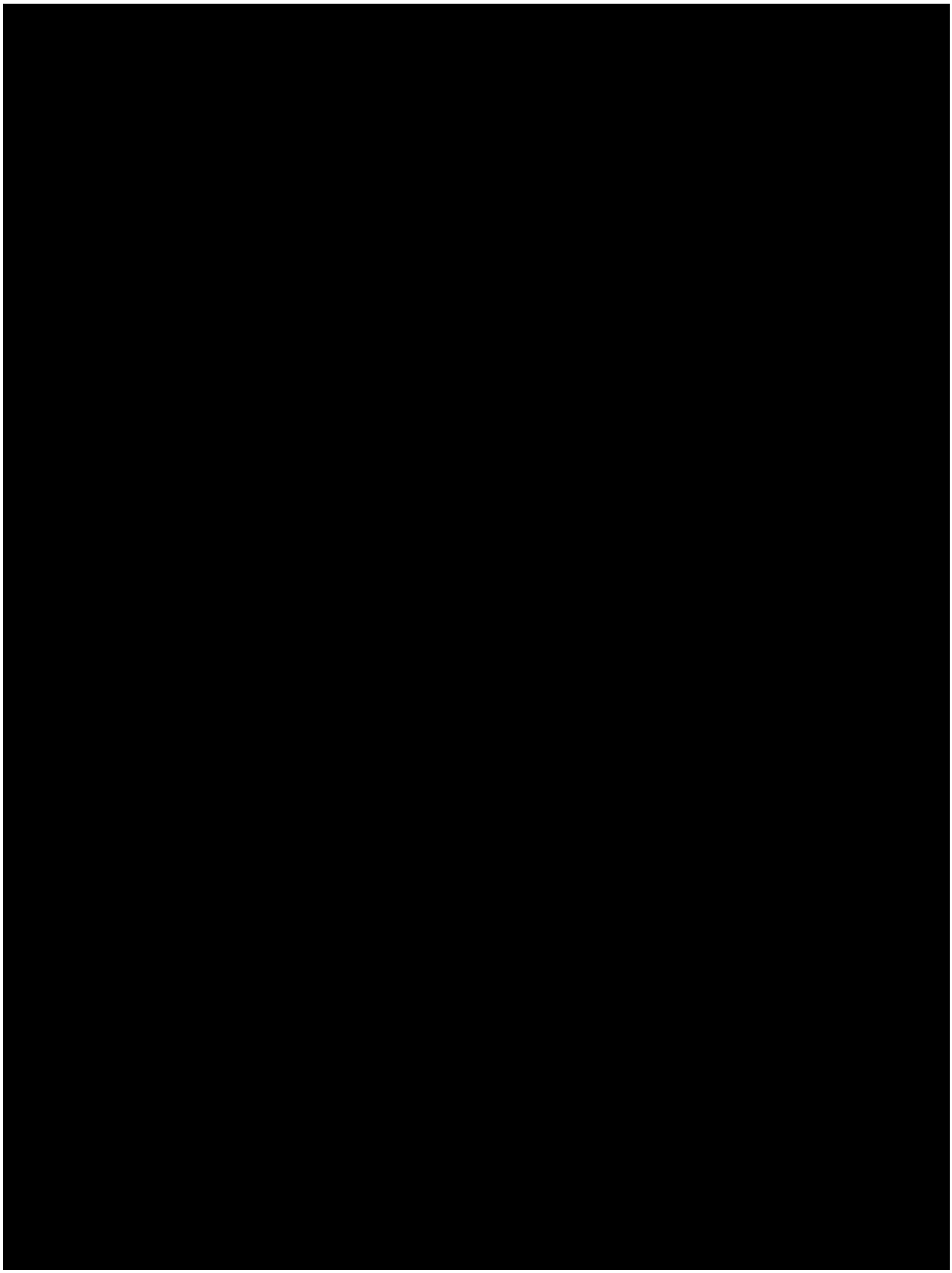
Images will be submitted to a central imaging vendor for blinded independent central review (BICR). Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the Imaging Manual provided by the central imaging vendor.

Tumor assessments [redacted] should continue on the protocol-defined imaging schedule regardless of dosing delays or discontinuation. Collect any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) for RECIST v1.1 tumor assessment and submit to the central imaging vendor as soon as possible. X-rays and/or bone scans that clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, they do not need to be submitted centrally.

Changes in tumor measurements and tumor responses will be assessed by the same investigator or designee using RECIST v1.1 criteria. Investigators will report the number and size of new lesions

that appear while on study. The timepoint of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST v1.1 criteria (refer to Appendix 8 for specifics of RECIST v1.1 criteria to be used in this study). Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. A best overall response (BOR) of stable disease (SD) requires a minimum of 35 days on study from randomization to the date of the first imaging assessment.





9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, a surrogate, or the participant's legally acceptable representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue before completing the study.

Refer to Appendix 3 for SAE reporting.

Use CTCAE v5.0 definitions and grading for safety reporting of all AE and SAEs on the CRF.

9.2.1 Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and until 30 days following discontinuation of dosing.

The investigator must report any SAE that occurs after these periods and that is believed to be related to a study intervention or protocol-specified procedure (eg, a follow-up biopsy).

- All SAEs will be recorded and reported to the Sponsor or designee, promptly and not to exceed 24 hours of awareness of the event, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant

has been discharged from the study, and he/she considers the event reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

All SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection, must be collected from the date of the participant's written consent until 30 days following discontinuation of dosing.

For participants assigned to treatment and never treated with study drug, collect SAEs for 30 days from the date of treatment assignment.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study intervention and for those present at the end of study intervention as appropriate.
- All identified non-serious AEs must be recorded and described on the non-serious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory test result abnormalities that are reported/identified during the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2.9), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3), or, for suspected cases, until SARS-CoV-2 infection is ruled out.

In addition, any serious/nonserious ILD/pneumonitis event (AEs of special interest, as defined in Section 9.2) must be followed [redacted] approximately every 3 weeks until resolution or stabilization [redacted], until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3). [redacted]

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A suspected, unexpected serious adverse reaction (SUSAR) is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

This section is not applicable for women not of childbearing potential (WNOCBP).

If, following initiation of the study intervention, it is discovered that a participant is pregnant or may have been pregnant at the time of study intervention exposure, including at least 90 days after MORAb-202 administration or 6 months after IC chemotherapy administration, the investigator must immediately notify the Sponsor Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the Sponsor designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

In all cases, the study intervention will be discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety).

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form. Protocol-required procedures for study discontinuation and follow-up must be performed.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the Adverse Events – Non-serious and Serious Events CRF page. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that requires the participant to have study intervention discontinued or interrupted
- Any laboratory test result abnormality that requires the participant to receive specific corrective therapy

It is expected that, wherever possible, the clinical rather than the laboratory term will be used by the reporting investigator (eg, anemia vs low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory test result abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

A potential DILI is defined as follows:

- Aminotransferase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) elevation > 3× upper limit of normal (ULN)

  AND

- Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

  AND

- No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

9.2.8 Other Safety Considerations

Any significant worsening of conditions noted during interim or final physical examinations, ECG, radiographic imaging, or any other potential safety assessment required or not required by the protocol should also be recorded as a non-serious AE or SAE, as appropriate, and reported accordingly.

9.2.9 AEs of Special Interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

Below events are considered as AESIs for MORAb-202:

[redacted]

Any ILD/pneumonitis events, and for Grade ≥ 3 infusion-related reactions, sites must report the event in the database immediately (ie, within 24 hours of diagnosis by the investigator).

AESIs that are Grade ≥ 3 in severity are considered important medical events and will be immediately reported by a completed SAE form using the procedures detailed in Appendix 3.

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses that meet the regulatory definition of an SAE will be reported as SAEs (see Appendix 3).

In the event of an overdose with MORAb-202, the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AEs/SAEs and laboratory test result abnormalities until MORAb-202 can no longer be detected systemically (at least 30 days).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

In the event of an overdose for IC chemotherapy agents, refer to USPI/SmPC.[67,75,89]

9.4 Safety

Planned time points for all safety assessments are listed in Section 2: Schedule of Activities.

9.4.1 Physical Examinations

See Section 2: Schedule of Activities.

9.4.2 Vital Signs

See Section 2: Schedule of Activities.

9.4.3 Electrocardiograms

See Section 2: Schedule of Activities.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- Laboratory assessments are listed in Table 9.4.4-1.
- All clinical safety laboratory assessments will be performed locally per the Schedule of Activities (Section 2).

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology
Hemoglobin
Hematocrit
Total leukocyte count, including differential
RBC Count
Platelet count
PT/INR, aPTT

Table 9.4.4-1: Clinical Laboratory Assessments

Chemistry	
AST ALT T. bili Direct bilirubin (reflex)[a] GGT (reflex)[b] ALP LDH Creatinine BUN or serum urea Uric acid Glucose Total protein C-reactive protein	Albumin Sodium Potassium Chloride Calcium CO_2 Phosphorus Magnesium Folate Creatinine clearance (CrCl) by 12- or 24-hour urine collection - screening only
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick	
Serology	
Hepatitis B/C (HBsAg, HCV Ab or HCV RNA) - screening only. HIV-1 and -2 Ab - screening only (as mandated by local requirement [refer to Appendix 7])	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG).	
FSH (screening only for confirmation of menopause in women age < 55 years; refer to Appendix 4).	

Abbreviations: Ab, antibody; ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CO2, carbon dioxide; CrCl, creatinine clearence; FSH, follicle-stimulating hormone; GGT, gamma-glutamyl transferase; HBsAg, hepatitis B surface antigen; HCG, human chorionic gonadotropin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; RBC, red blood cell; RNA, ribonucleic acid; T. bili, total bilirubin; WOCBP, women of childbearing potential.

[a] Reflex testing to be performed only if T.bili test is abnormal.

[b] Reflex testing to be performed only if liver function test is abnormal.

9.4.5 ILD/Pneumonitis Assessments

ILD/pneumonitis is a known TRAE associated with MORAb-202 (see Section 3.2.3.2). All [redacted] participants must be assessed and monitored regularly for any new onset of signs and symptoms potentially consistent with ILD/pneumonitis. To monitor for onset of ILD/pneumonitis, investigators should routinely ask participants about any new onset of pulmonary symptoms, and [redacted] and pulse oximetry results should be reviewed for potential abnormal findings. [redacted]

[redacted]

The clinical symptoms of ILD/pneumonitis are generally nonspecific, and patients may be asymptomatic [redacted] Signs/symptoms potentially consistent with ILD/pneumonitis may include but are not limited to the following:

- Shortness of breath (at rest and/or with ordinary physical activity)
- Dyspnea
- Non-productive cough
- Malaise
- Fever (low-grade)
- Oxygen saturation (SpO2) of < 92% at rest or immediately after exercise (eg, walking for at least 6 minutes or equivalent effort)

[redacted]

[redacted]

9.4.6 Imaging Safety Assessment

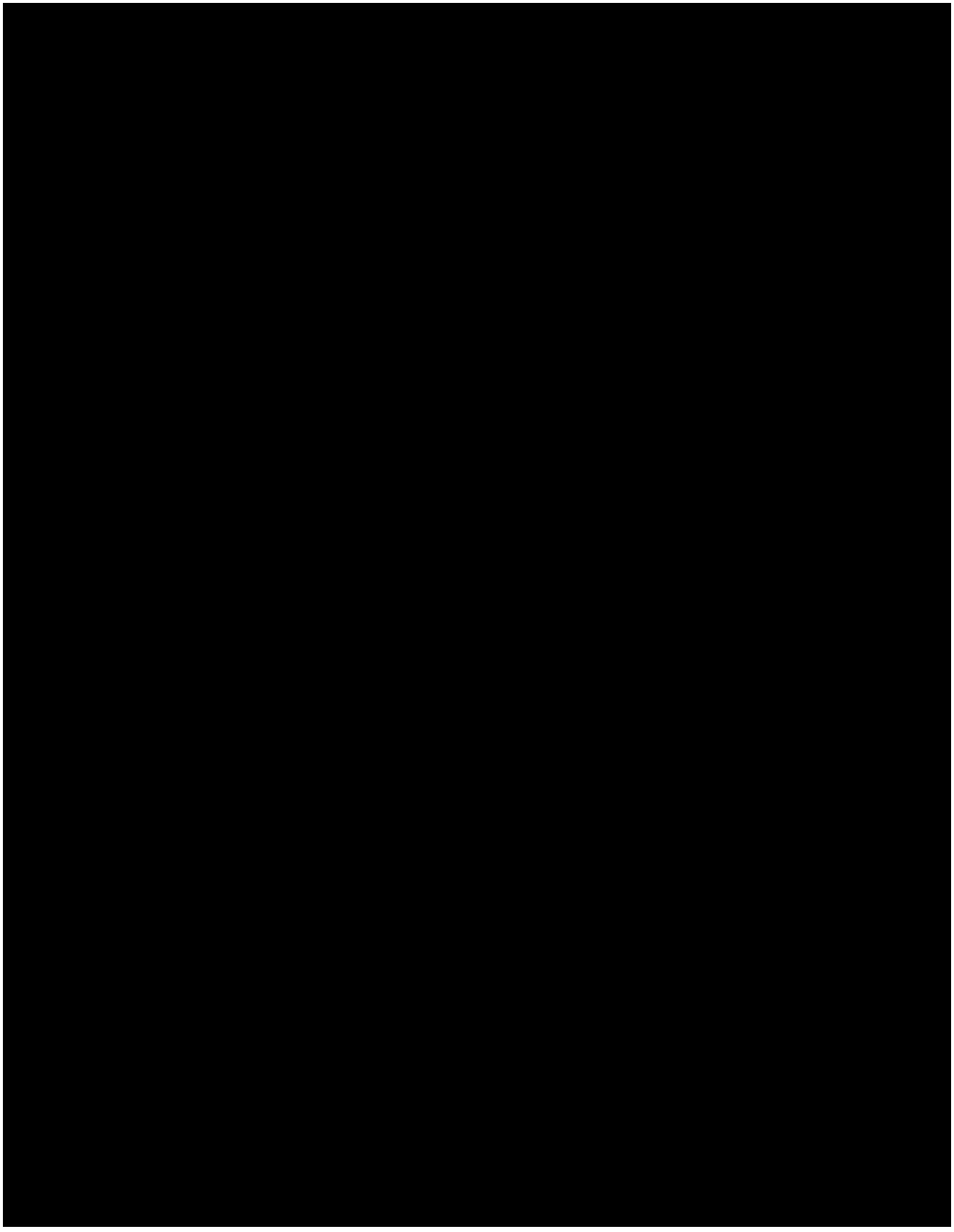
Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator per standard medical/clinical judgment.

[redacted]

9.4.7 Echocardiogram (ECHO)/Multigated Acquisition (MUGA)

Electrocardiogram (ECHO)/multigated acquisition (MUGA) assessments are only required for [redacted] participants receiving treatment with PLD. See the Schedule of Activities (Section 2).

[redacted]



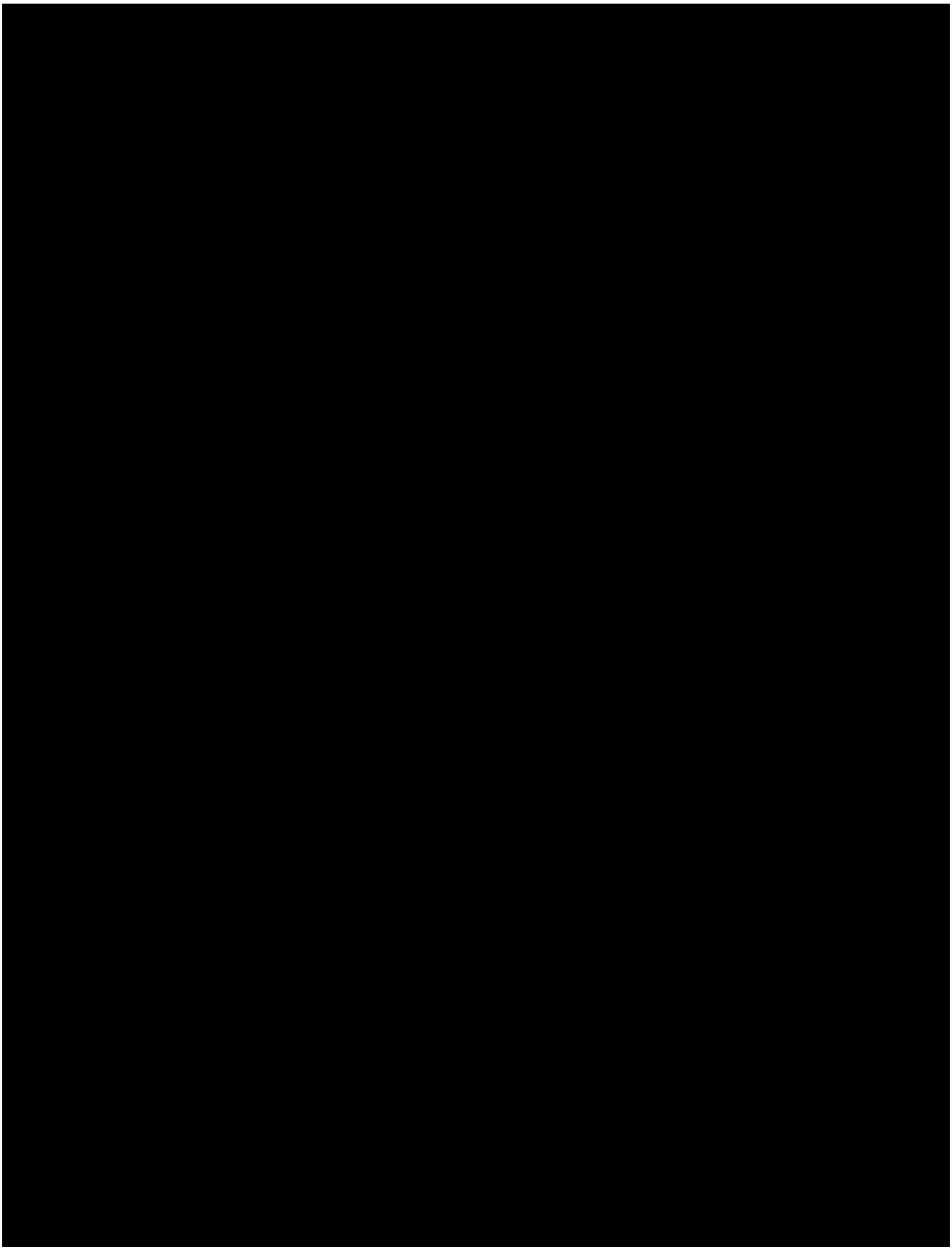
[redacted]

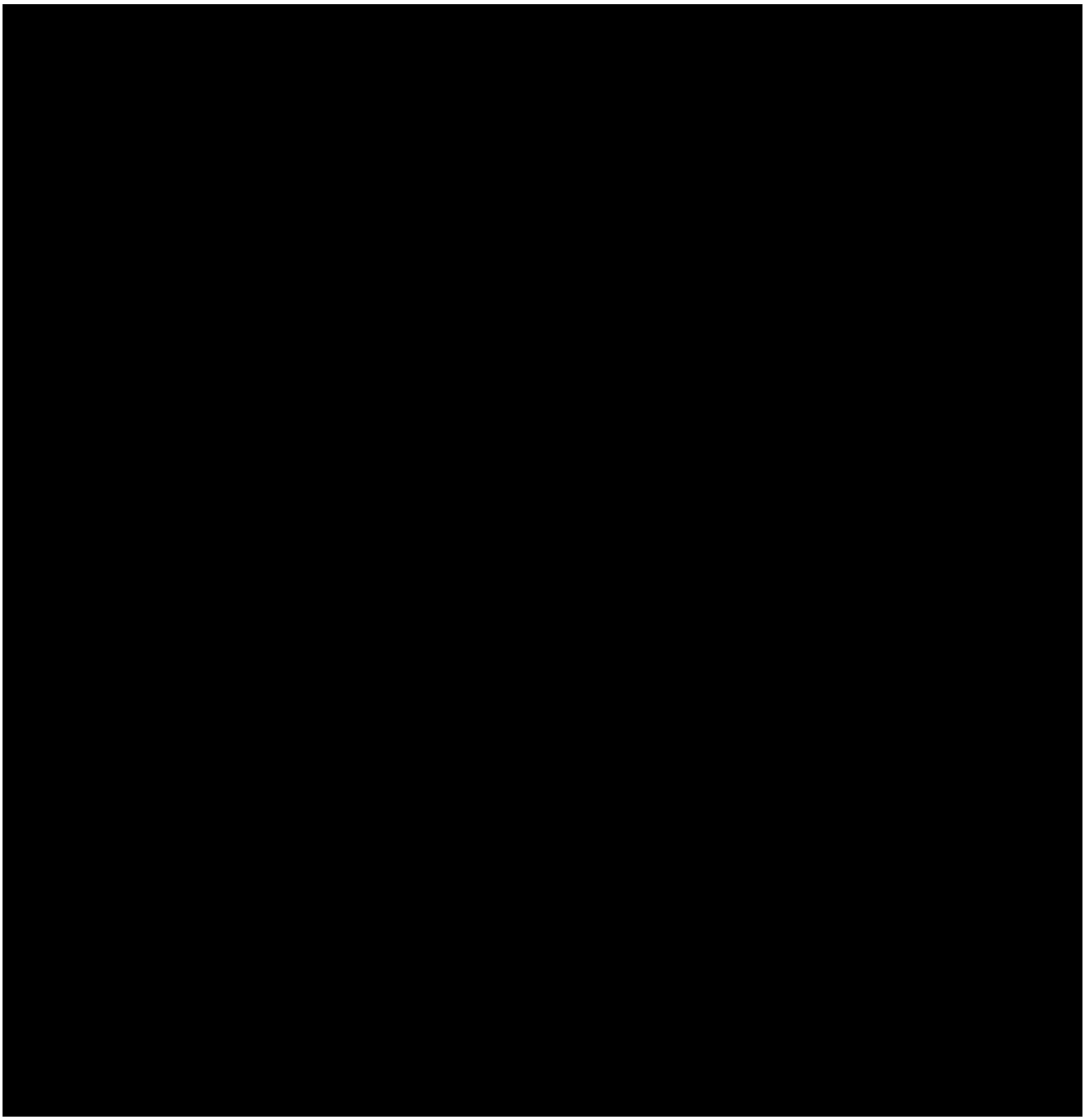
9.9 Health Economics OR Medical Resource Utilization and Health Economics

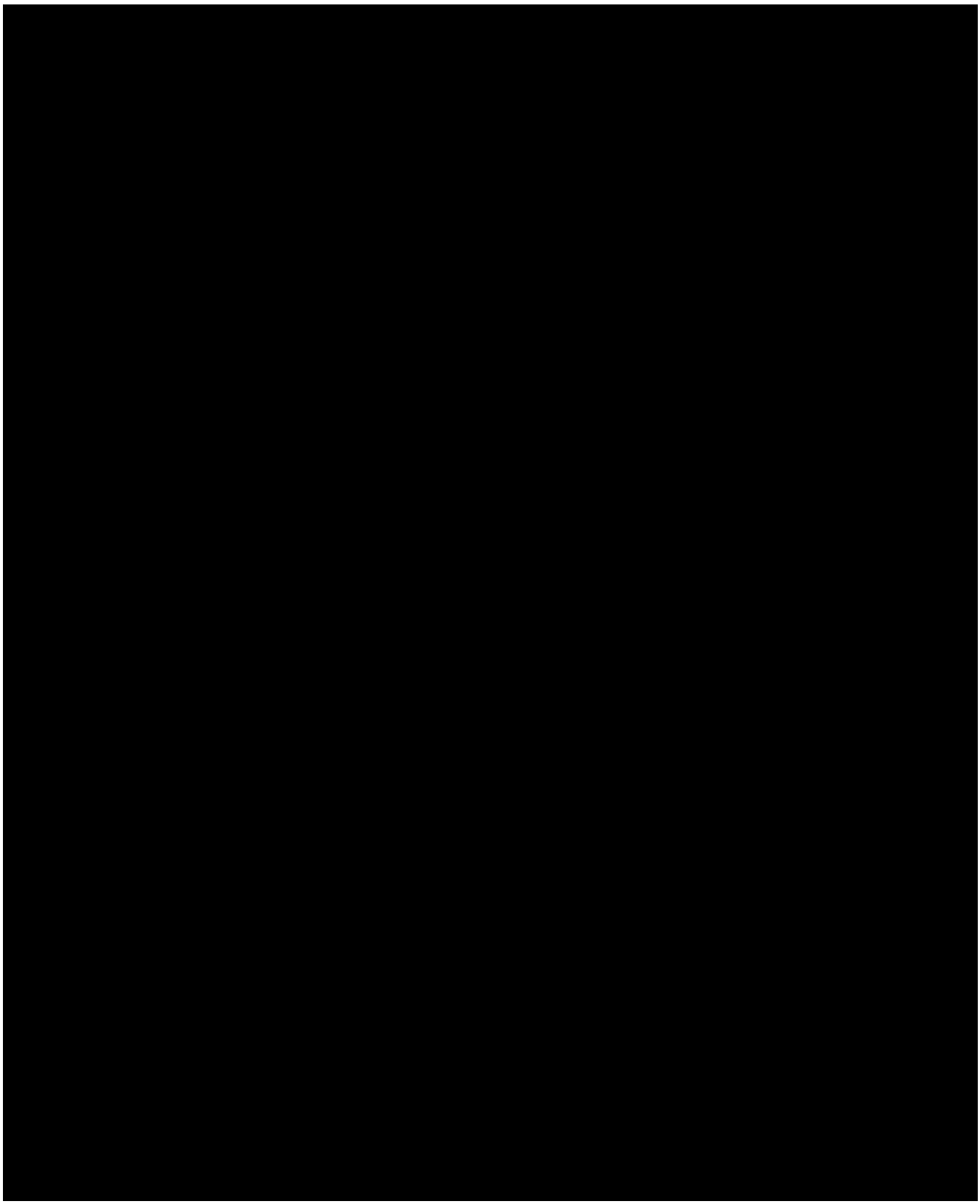
Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

[redacted]







10.3 Analysis Sets

For the purposes of analysis, the following populations are defined:

Analysis Sets	Description
Enrolled	All participants have agreed to participate in the clinical study following completion of the informed consent process, unless otherwise specified by the protocol.
All Randomized	All participants who were randomized using IRT.
All Treated	All randomized participants who received at least 1 dose of study intervention.
All Response Evaluable	All randomized participants with baseline tumor assessment.

[redacted]

Abbreviations: [redacted] IRT, interactive response technology; [redacted]

10.4 Statistical Analyses

10.4.1 General Considerations

In general, continuous data will be summarized by descriptive statistics, including number of participants, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage of participants. Unless otherwise specified, data will be summarized by treatment arm.

The posterior probabilities corresponding to the decision guidelines at the interim and final analysis are reported as follows:

- Successful efficacy benefit assessment criteria
- Explore alternative strategies

The posterior probability will be compared to a pre-defined threshold.

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses and procedures for accounting for missing, unused, and spurious data.

Participant characteristics and/or demographic data may be pooled across studies for future analysis.

10.4.2 Primary Endpoint(s)

Table 10.4.2-1: Primary Endpoints

Endpoint	Statistical Analysis Methods
Primary Analyses	
ORR by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per Investigator Assessment	Objective Response Rate (ORR) is defined as the number of randomized participants who achieve a best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR), based on investigator assessments (using RECIST v1.1), divided by the number of all randomized participants. BOR is defined as the best response, as determined by the investigator, recorded between the date of randomization and the date of first objectively-documented progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. The number and percentage of participants in each category of BOR per investigator (CR, PR, stable disease [SD], progressive disease [PD], or unable to determine [UTD]) will be presented, by treatment group. Estimates of difference in response rates, along with its exact two-sided 95% CI by Clopper and Pearson[93] will be presented, by treatment group. The treatment effect is summarized using the estimated difference in ORR. A similar supportive/sensitivity analysis would be conducted based on BICR assessment.
TRAEs Leading to Discontinuation	TRAE discontinuation incidence rate is computed using the proportion of participants with TRAEs leading to discontinuation in each arm within 6 months from first dose of study drug administration in all treated participants. The number and percentage of participants per arm will be described in a frequency table. [redacted]

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; [redacted]; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; TRAE, treatment-related adverse event; UTD, unable to determine.

10.4.3 Secondary Endpoints

Table 10.4.3-1: Summary of Secondary Endpoint Analysis

Endpoint	Statistical Analysis Methods
Secondary Analyses	
AEs, SAEs, Treatment-related AEs/SAEs, AEs Leading to Discontinuation, AESIs, Deaths, Laboratory Abnormalities	To assess the safety and tolerability of the investigational product in the target population, incidence and severity of the following safety events will be evaluated: adverse events (AEs)/serious adverse events (SAEs), AEs leading to discontinuation, TRAEs leading to discontinuation, AEs of special interest (AESIs), deaths, and laboratory abnormalities. AE, SAE, and TRAE discontinuation incidence rate is computed using the proportion of participants with AEs, SAEs, and TRAEs leading to discontinuation in each arm within 6 months from first dose of study drug administration in all treated participants. AE, SAE, and TRAE incidence rate is computed using the proportion of participants with AEs, SAEs, and TRAEs occurring at least once in each arm within 6 months from first dose of study drug administration in all treated participants. The number and percentage of participants per arm will be described in a frequency table.

Table 10.4.3-1: Summary of Secondary Endpoint Analysis

Endpoint	Statistical Analysis Methods
PFS by RECIST v1.1 per Investigator Assessment	PFS is defined as the time between the date of randomization and the first date of documented progression, per investigator assessments (using RECIST v1.1), or death due to any cause, whichever occurs first. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments and did not die will be censored on their date of randomization. The PFS function for each treatment group will be estimated using the Kaplan Meier (KM) product limit method and will be displayed graphically. The hazard ratio is the measure of the difference in PFS. A two-sided 95% CI for median PFS in each treatment group will be computed via the log-log transformation method. PFS rates at fixed time points (eg, 3, 6 months, depending on the minimum follow-up) will be presented along with their associated 95% CIs. These estimates will be derived from the KM estimate and corresponding CIs will be derived based on Greenwood's formula[94] for variance derivation and the log-log transformation applied on the survivor function.[95] A similar supportive/sensitivity analysis would be conducted based on BICR assessment.
DCR by RECIST v1.1 per Investigator Assessment	Disease control rate (DCR) is defined as the number of randomized participants who achieve a BOR of confirmed CR, confirmed PR, or stable disease (SD), based on investigator assessments (using RECIST v1.1) divided by the number of all randomized participants. Estimates of DCR, along with its exact two-sided 95% CI by Clopper and Pearson, will be presented by treatment group. The treatment effect is summarized using the estimated difference in DCR. A similar supportive/sensitivity analysis would be conducted based on BICR assessment.
DoR by RECIST v1.1 per Investigator Assessment among Responders	Duration of Response (DoR) is defined as the time between the date of first documented response (CR or PR) that is subsequently confirmed, to the date of the first objectively-documented tumor progression as determined by investigator (per RECIST v1.1), or death due to any cause, whichever occurs first. Participants who die without a reported prior progression will be considered to have an event on the date of their death. Participants who neither progress nor die will be censored on the date of their last evaluable tumor assessment. DoR will be evaluated for responders (confirmed CR or PR) only. DoR will be analyzed using similar method as PFS. A similar supportive/sensitivity analysis would be conducted based on BICR assessment.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; KM, Kaplan Meier; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse events; SD, stable disease; TRAE, treatment-related adverse event.

[redacted]

10.4.5 Other Safety Analyses

All safety analyses will be performed on the All Treated set.

Table 10.4.5-1: Summary of Safety Analysis

Summary of Safety Analysis	Statistical Analysis Methods
Primary Analyses	
Safety	Incidence and severity of AEs/SAEs, treatment-related AEs/SAEs, AEs leading to discontinuation, adverse events of special interest (AESI), deaths, and laboratory abnormalities. Safety analysis will be performed in all treated participants. Descriptive statistics of safety will be presented using NCI CTCAE v5.0 by treatment group. All on-study AEs, drug-related AEs, SAEs, and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v5.0 by system organ class and preferred term. On-study laboratory parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade per NCI CTCAE v5.0.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; NCI, National Cancer Institute; SAE, serious adverse event.

11 REFERENCES

1 Ebara S. Nutritional role of folate. Congenit Anom 2017;57:138-41.

2 Cheung A, Bax HJ, Josephs DH, et al. Targeting folate receptor alpha for cancer treatment. Oncotarget 2016;7:52553-74.

3 Weitman SD, Weinberg AG, Coney LR, et al. Cellular localization of the folate receptor: potential role in drug toxicity and folate homeostasis. Cancer Res 1992;52:6708-11.

4 Mantovani LT, Miotti S, Menard S, et al. Folate binding protein distribution in normal tissues and biological fluids from ovarian carcinoma patients as detected by the monoclonal antibodies MOv18 and MOv19. Eur J Cancer 1994;30A:363-9.

5 Elnakat H, Ratnam M. Distribution, functionality and gene regulation of folate receptor isoforms: implications in targeted therapy. Adv Drug Deliv Rev 2004;56:1067-84.

6 Kelemen LE. The role of folate receptor alpha in cancer development, progression and treatment: cause, consequence or innocent bystander? Int J Cancer 2006;119:243-50.

7 Cheng X, Li J, Tanaka K, et al. MORAb-202, an antibody-drug conjugate utilizing humanized anti-human FRα farletuzumab and the microtubule-targeting agent eribulin, has potent antitumor activity. Mol Cancer Ther 2018;17:2665-75.

8 Yoshida T, Ozawa Y, Kimura T, et al. Eribulin mesilate suppresses experimental metastasis of breast cancer cells by reversing phenotype from epithelial-mesenchymal transition (EMT) to mesenchymal-epithelial transition (MET) states. Br J Cancer 2014;110:1497-505.

9 Funahashi Y, Okamoto K, Adachi Y, et al. Eribulin mesylate reduces tumor microenvironment abnormality by vascular remodeling in preclinical human breast cancer models. Cancer Sci 2014;105:1334-42.

10 Kawano S, Asano M, Adachi Y, et al. Antimitotic and Non-mitotic Effects of Eribulin Mesilate in Soft Tissue Sarcoma. Anticancer Res 2016;36:1553-61.

11 MORAb-202 Global Investigator's Brochure (GIB) Ed 5, Release Date 07-Dec-2021.

12 Ledermann JA, Kristeleit RS. Optimal treatment for relapsing ovarian cancer. Ann Oncol 2010;21(Suppl 7):218–22.

13 Ledermann JA, Drew Y, Kristeleit RS. Homologous recombination deficiency and ovarian cancer. Eur J Cancer 2016;60:49-58.

14 Markman M, Markman J, Webster K, et al. Duration of response to second-line, platinum-based chemotherapy for ovarian cancer: implications for patient management and clinical trial design. J Clin Oncol 2004;22:3120-5.

15 Ethier J, Wang L, Oza AM, et al. Survival outcomes in patients with platinum-resistant (PL-R) ovarian cancer (OC): The Princess Margaret Cancer Centre (PM) experience [abstract]. J Clin Oncol 2017;35(Suppl):17049.

[16] Naumann RW, Coleman RL. Management strategies for recurrent platinum-resistant ovarian cancer. Drugs 2011;71:1397-412.

[17] National Comprehensive Cancer Network. Ovarian Cancer (Version 3.2021). Available from: URL: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.

[18] Keener AB. Innovative therapies to tackle platinum-resistant ovarian cancer. Nature 2021;600(Suppl):45-7.

[19] Nawaz FZ, Kipreos ET. Emerging roles for folate receptor FOLR1 in signaling and cancer. Trends Endocrinol Metab 2022;33:159-74.

[20] Scaranti M, Cojocaru E, Banerjee S, et al. Exploiting the folate receptor α in oncology. Nat Rev Clin Oncol 2020;17:349-59.

[21] Hough CD, Cho KR, Zonderman AB, et al. Coordinately up-regulated genes in ovarian cancer. Cancer Research 2001;61:3869-76.

[22] Liu Y, Lian T, Yao Y. A systematic review and meta-analysis of higher expression of folate receptor alpha (FOLR1) predicts poor cancer prognosis. Biomarkers 2020;25:367-74.

[23] Chen YL, Chang MC, Huang CY, et al. Serous ovarian carcinoma patients with high alpha-folate receptor had reducing survival and cytotoxic chemo-response. Mol Oncol 2012;6:360-9.

[24] Kurosaki A, Hasegawa K, Kato T, et al. Serum folate receptor alpha as a biomarker for ovarian cancer: Implications for diagnosis, prognosis and predicting its local tumor expression. Int J Cancer 2016;138:1994-2002.

[25] Chan JK, Brady MF, Penson RT, et al. Weekly vs every-3-week paclitaxel and carboplatin for ovarian cancer. N Engl J Med 2016;374:738-48.

[26] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87.

[27] Dalmartello M, La Vecchia C, Bertuccio P, et al. European cancer mortality predictions for the year 2022 with focus on ovarian cancer. Ann Oncol 2022;33:330-9.

[28] National Cancer Institute. Cancer stat facts: ovarian cancer. Available from: URL: https://seer.cancer.gov/statfacts/html/ovary.html.

[29] Köbel M, Kalloger SE, Huntsman DG, et al. Differences in tumor type in low-stage versus high-stage ovarian carcinomas. Int J Gynecol Pathol 2010;29:203-11.

[30] Kurman RJ. Origin and molecular pathogenesis of ovarian high-grade serous carcinoma. Ann Oncol 2013;24(Suppl 10):16-21.

[31] Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized Phase III trial. J Clin Oncol 2014;32:1302-08.

[32] Helleday T, Petermann E, Lundin C, et al. DNA repair pathways as targets for cancer therapy. Nat Rev Cancer 2008;8:193-204.

[33] Schreiber V, Dantzer F, Ame J, et al. Poly(ADP-ribose): novel functions for an old molecule. Nat Rev Mol Cell Biol 2006;7:517-28.

[34] Leung SOA, Konstantinopoulos PA. Advances in the treatment of platinum resistant epithelial ovarian cancer: an update on standard and experimental therapies. Expert Opin Investig Drugs 2021;30:695-707.

[35] Peres LC, Risch H, Terry KL, et al. Racial/ethnic differences in the epidemiology of ovarian cancer: a pooled analysis of 12 case-control studies. Int J Epidemiol 2018;47:460-72.

[36] Park HK, Ruterbusch JJ, Cote ML. Recent Trends in ovarian cancer incidence and relative survival in the United States by race/ethnicity and histologic subtypes. Cancer Epidemiol Biomarkers Prev 2017;26:1511-8.

[37] Torre LA, Trabert B, DeSantis CE, et al. Ovarian cancer statistics, 2018. CA Cancer J Clin 2018;68:284-96.

[38] Peres LC, Bethea TN, Camacho TF, et al. Racial differences in population attributable risk for epithelial ovarian cancer in the OCWAA Consortium. J Natl Cancer Inst 2021;113:710-8.

[39] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.

[40] Fuh KC, Shin JY, Kapp DS, et al. Survival differences of Asian and Caucasian epithelial ovarian cancer patients in the United States. Gynecol Oncol 2015;136:491-7.

[41] O'Shannessy DJ, Yu G, Smale R, et al. Folate receptor alpha expression in lung cancer: diagnostic and prognostic significance. Oncotarget 2012;3:414-25.

[42] Nishio S, Yunokawa M, Matsumoto K, et al. Safety and efficacy of MORAb-202 in patients (pts) with platinum-resistant ovarian cancer (PROC): results from the expansion part of a Phase 1 trial. American Society of Clinical Oncology; 2022 Jun 3-7; Chicago, IL. J Clin Oncol 40; 2022

[43] Luvero D, Milani A, Ledermann J.A. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. Ther Adv Med Oncol 2014;6:229-39.

[44] Halaven® (eribulin mesylate). United States Prescribing Information. Eisai Inc; 2021

[45] Shimizu T, Fujiwara Y, Yonemori K, et al. First-in-human Phase 1 study of MORAb-202, an antibody-drug conjugate comprising farletuzumab linked to eribulin mesylate, in patients with folate receptor-α-positive advanced solid tumors. Clin Cancer Res 2021;27:3905-15.

[46] Majid O, Gupta A, Reyderman L, et al. Population pharmacometric analyses of eribulin in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. J Clin Pharmacol 2014;54:1134-43.

[47] Bajaj G, Suryawanshi S, Roy A, et al. Evaluation of covariate effects on pharmacokinetics of monoclonal antibodies in oncology. Br J Clin Pharmacol 2019;85:2045-58.

[48] Lesimple T, Edeline J, Carrothers TJ, et al. A Phase I, open-label, single-arm study for QT assessment of eribulin mesylate in patients with advanced solid tumors. Invest New Drugs. 2013;31:900-9.

[49] Twycross R. The risks and benefits of corticosteroids in advanced cancer. Drug Saf 1994;11:163-78.

[50] Wooldridge JE, Anderson CM, Perry MC. Corticosteroids in advanced cancer. Oncology (Williston Park) 2001;15:225-34;dis.234-6.

[51] Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Ann Oncol 2019;30:672-705.

[52] Lisio MA, Fu L, Goyeneche A, et al. High-grade serous ovarian cancer: basic sciences, clinical and therapeutic standpoints. Int J Mol Sci 2019;20:952.

[53] Kalli K, Oberg AL, Keeney GL, et al. Folate receptor alpha as a tumor target in epithelial ovarian cancer. Gynecol Oncol 2008;108:619-26.

[54] Shah M, Rahman A, Theoret MR, et al. The drug-dosing conundrum in oncology - when less is more. N Engl J Med 2021;385:1445-7.

[55] FDA Oncology "Beyond Breakthrough" Project Takes Shape: Review of Decade-Old Program To Result In "Menu" Of Benefits, Process For Rescinding Designation. May 24, 2021. Available from: URL: https://www.previsionpolicy.com/fda-oncology-beyond-breakthrough-project-takes-shapereview-of-decade-old-program-to-result-in-menu-of-benefits-process-for-rescinding-designation.

[redacted]

67 Taxol. US Prescribing Information. Bristol-Myers Squibb Company; 2011.

68 Thomas H, Rosenberg P. Role of weekly paclitaxel in the treatment of advanced ovarian cancer. Crit Rev Oncol Hematol 2002;44(Suppl):43-51.

69 Baird RD, Tan DS, Kaye SB. Weekly paclitaxel in the treatment of recurrent ovarian cancer. Nat Rev Clin Oncol 2010;7:575-82.

70 Markman M, Blessing J, Rubin SC, et al. Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. Gynecol Oncol 2006;101:436-40.

71 Rosenberg P, Andersson H, Boman K, et al. Randomized trial of single agent paclitaxel given weekly versus every three weeks and with peroral versus intravenous steroid premedication to patients with ovarian cancer previously treated with platinum. Acta Oncol 2002;41:418-24.

72 Cannon TL, Lai DW, Hirsch D, et al. Squamous cell carcinoma of the oral cavity in nonsmoking women: A new and unusual complication of chemotherapy for recurrent ovarian cancer? Oncologist 2012;17:1541-6.

73 Rose PG. Pegylated liposomal doxorubicin: optimizing the dosing schedule in ovarian cancer. Oncologist 2005;10:205-14.

74 Li XR, Zhu Y, Zhang GN, et al. The impact of pegylated liposomal doxorubicin in recurrent ovarian cancer: an updated meta-analysis of randomized clinical trials. J Ovarian Res 2021;14:42.

75 Hycamtin. Highlights of US Prescribing Information. Novartis Pharmaceuticals Corporation; 2018.

76 Sehouli J, Oskay-Ozcelik G. Current role and future aspects of topotecan in relapsed ovarian cancer. Curr Med Res Opin 2009;25:639-51.

77 Sehouli J, Stengel D, Harter P, et al. Topotecan weekly versus conventional 5-day schedule in patients with platinum-resistant ovarian cancer: a randomized multicenter phase II trial of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. J Clin Oncol 2011;29:242-8.

78 Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). 2007.

79 Vergote I, Armstrong D, Scambia G, et al. A randomized, double-blind, placebo-controlled, phase III study to assess efficacy and safety of weekly farletuzumab in combination with carboplatin and taxane in patients with ovarian cancer in first platinum-sensitive relapse. J Clin Oncol 2016;34:2271-8.

80 Moore K, Oza A, Oaknin A, et al. FORWARD I (GOG 3011): A Phase III study of mirvetuximab soravtansine, a folate receptor alpha (FRa)-targeting antibody-drug conjugate (ADC), versus chemotherapy in patients (pts) with platinum-resistant ovarian cancer (PROC). Ann Oncol 2019;30:v403-34

81 Haycock GB, Schwartz GJ, Wisolsky D. Geometric method for measuring body surface area: A height-weight formula validated in infants, children, and adults. J Pediatr 1978;93:62-6.

82 Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916;17:863-71.

83 Mosteller RD. Simplified calculation of body surface area. N Engl J Med 1987;317:1098.

[redacted]

89 Doxil. Highlights of Prescribing Information. Baxter Healthcare Corporation; 2019.

[redacted]

[redacted]

93 Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-13.

94 Greenwood M. The errors of sampling of the survivorship tables. Reports on Public Health and Statistical Subjects. Vol 33. London: HMSO; 1926. Appendix 1.

95 Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. 2nd ed. New York: John Wiley & Sons; 2002. (Available upon request).

12 APPENDICES

APPENDIX 1 ABBREVIATIONS

Term	Definition
AA	African American
[redacted]	
ADC	antibody-drug conjugate
[redacted]	
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AxMP	Auxiliary Medicinal Product
BICR	blinded independent central review
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BRCA1/BRCA2	breast cancer gene 1/2
BSA	body surface area
BUN	blood urea nitrogen
BW	body weight
C	cycle
CBC	complete blood count
[redacted]	
CI	confidence interval
CL	clearance
[redacted]	

Term	Definition
CNS	central nervous system
CO_2	carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CrCl	creatinine clearance
CRF	case report form, paper or electronic
CT	computed tomography
CTCAE v5.0	Common Terminology Criteria for Adverse Events version 5.0
[redacted]	
CYP	cytochrome P450
D	day
DCR	disease control rate
DCT	decentralized clinical trial
DILI	drug-induced liver injury
DLCO	carbon monoxide diffusing capacity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DoR	duration of response
DVT	deep vein thrombosis
[redacted]	
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EMT	epithelial-mesenchymal transition
EOC	epithelial ovarian cancer
[redacted]	
EOS	end of study

Term	Definition
EOT	end of treatment
[redacted]	
ESMO	European Society for Medical Oncology
EU	European Union
E-R	exposure-response
[redacted]	
FEV1	forced expiratory volume in the first second of expiration
FFPE	formalin-fixed, paraffin-embedded
FRα	folate receptor alpha
FSH	follicle-stimulating hormone
FVC	forced vital capacity
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HFS	hand-foot syndrome
HGS	high-grade serous
HIV	human immunodeficiency virus
HR	heart rate
HRD	homologous recombination deficiency
IB	Investigator's Brochure
IC	Investigator's choice
ICF	informed consent form
I/E	inclusion/exclusion
IEC	Independent Ethics Committee
[redacted]	
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
INR	international normalized ratio

Term	Definition
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	international unit
IV	intravenous
K_D	dissociation constant
KM	Kaplan Meier
LAR	legally acceptable representative
LDH	lactate dehydrogenase
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
min	minute
mOS	median overall survival
mPFS	median progression-free survival
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MUGA	multigated acquisition
N/n	number of participants
NCA	noncompartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHW	Non-hispanic White
[redacted]	
OC	ovarian cancer
OS	overall survival
OR	objective response
ORR	objective response rate
PARP	poly (adenosine disphosphate-ribose) polymerase
PARPi	poly (adenosine disphosphate-ribose) polymerase inhibitor
PCR	polymerase chain reaction
PD	progressive disease
PDX	patient-derived xenograft

Term	Definition
PE	physical examination
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PFT	pulmonary function test
[redacted]	
PK	pharmacokinetic
PLD	pegylated liposomal doxorubicin
PO	per os (oral route of administration)
PPE	palmar-plantar erythrodysesthesia
PPK	population pharmacokinetics
PR	partial response
[redacted]	
PROC	platinum-resistant ovarian cancer
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
Q3W	every 3 weeks
Q4W	every 4 weeks
[redacted]	
QTc	corrected QT interval
QTcF	Fridericia corrected QTc
RBC	red blood cell
[redacted]	
RBC	red blood cell
RECIST v.1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	safety committee
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
sFRα	soluble folate receptor alpha

Term	Definition
SmPC	Summary of Product Characteristics
SpO_2	oxygen saturation
SUSAR	suspected, unexpected serious adverse reaction
TB	bacillus tuberculosis
T. bili	total bilirubin
TEAE	treatment-emergent adverse event
TLC	total lung capacity
TME	tumor microenvironment
[redacted]	
TRAE	treatment-related adverse event
TTE	transthoracic echocardiogram
[redacted]	
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
V	volume distribution of the central compartment
[redacted]	
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws, regulations, and requirements

The study will be conducted in compliance with the protocol. The protocol, any revisions/amendments, and the participant informed consent form (ICF) will receive approval/favorable opinion by the Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a quality issue (eg, protocol deviation) that is likely to affect, to a significant degree, 1 or more of the following: (1) the rights, physical safety, or mental integrity of 1 or more participants; (2) the scientific value of the clinical trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP regulation(s) or trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, administrative letters) annually, or more frequently, in accordance with regulatory requirements or institution procedures.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines
- United States (US) Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union (EU) Directive 2001/20/EC
- European Regulation 536/2014 for clinical studies (if applicable)
- European Medical Device Regulation 2017/745 for clinical device research (if applicable)
- the IRB/IEC
- all other applicable local regulations

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and, if applicable, by the local Health Authority), except where necessary to eliminate an immediate hazard(s) to study participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to the following:

- IRB/IEC
- Regulatory authority(ies), if applicable according to local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and, if applicable, by the local Health Authority must be sent to Bristol-Myers Squibb Company (BMS).

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the ICF must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with regulations, to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

The Sponsor or designee will provide the investigator with an appropriate sample ICF, which will include all elements required by the ICH GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant or his/her legally acceptable representative and answer all questions regarding the study.
- Inform the participant that his/her participation is voluntary. The participant or his/her legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for the participant or his/her legally acceptable representative to inquire about the details of the study.
- Obtain an ICF signed and personally dated by the participant or his/her legally acceptable representative and by the person who conducted the informed consent discussion.
- Include a statement in the participant's medical record that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent the participant to the most current version of the ICF(s) during his/her participation.
- Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or his/her legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF, and, in the US, the participant's signed HIPAA authorization.

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

In situations where consent cannot be given by participants, their legally acceptable representatives (per country regulation) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel
2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the source data location list/map or equivalent document.

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

When paper records from such systems are used in place of an electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY INTERVENTION RECORDS

Records for study intervention (whether supplied by BMS, its vendors, or the site) must substantiate study intervention integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors)	Records or logs must comply with applicable regulations and guidelines and should include the following: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • non-study disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include Investigational Product sourced from the site's stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study intervention integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

BMS or its designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents, or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance

understanding of product safety. CRFs may be requested for AEs and/or laboratory test result abnormalities that are reported or identified during the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to serious adverse events (SAEs) and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

Each individual electronically signing eCRFs must meet Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by the Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by the Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to the Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or its designee, whichever is longer.

The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or its designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed-upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or its designee.

RETURN OF STUDY INTERVENTION

For this study, study interventions (those supplied by BMS or a vendor or sourced by the investigator), such as partially used study intervention containers, vials, and syringes, may be destroyed on site.

If	Then
Study interventions supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study intervention containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxic or biologic agents). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. However, unused Investigational Medicinal Product must be reconciled by the site monitor/clinical research associate prior to destruction. If study interventions will be returned, the return will be arranged by the responsible study monitor.
Study interventions sourced by site, not supplied by BMS (or its vendors; eg, study interventions sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal of study interventions, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.

- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study interventions provided by BMS (or its vendors). Destruction of non-study interventions sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

STUDY AND SITE CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable

regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

To benefit potential study participants, patients, health care providers, and researchers and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public per regulatory and BMS requirements. BMS will post study information on local, national, or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

For each CSR related to this protocol, the following criteria will be used to select the Signatory Investigator:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to the Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the Clinical Trial Agreement (CTAg) governing [study site or investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to the Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the period set forth in the CTAg.

Scientific publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any Principal Investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at the Sponsor is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). Authorship selection is based on

significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights, and conclusion)
2) Drafting the work or revising it critically for important intellectual content
3) Final approval of the version to be published
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Those who make the most significant contributions, as defined above, will be considered by the Sponsor for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

DECENTRALIZED CLINICAL TRIAL (DCT)

A Decentralized Clinical Trial (DCT) gives patients and site staff the flexibility to take trials home with them. The DCT platform used (Medable, Inc. platform) is a HIPAA, 21 CFR part 11 compliant and easy to use. With TeleVisit, patients can bring the in-office experience home, maintaining the same level of rapport and face-to-face interactions. Additionally, TeleVisits may be paired with eConsent [redacted] to improve patient access, increase patient engagement and reduce both site and patient burden. For example, within the DCT platform TeleVisit, [redacted] eConsents may be viewed in real-time, enabling discussions between the patient and the healthcare provider. For compliance and regulatory reasons, the platform automatically creates a log of the time, date stamp and duration of activities completed in the DCT platform for the Tele Visit, in order to augment the visit recording. TeleVisit is a 21CFR Part 11, HIPAA compliant solution that is fully integrated with the clinical studies' clinical workflows.

Elements of this study may be conducted remotely, ie, the participant will remain in their own home and complete study assessments via technology. The design of the study requires each participant to interact with study personnel. Where allowed by applicable laws and regulations, remote assessments may be done in parallel to, but separate from, other sites in other countries that will conduct study visits in the traditional manner, ie, with all assessments performed at the study center (ie, with the original site personnel performing survival follow-up).

Data collected from participants via remote assessments will be collected electronically within purpose-built technology (Medable platform or EDC) and will be monitored remotely by the Sponsor or designee representatives, where allowed by applicable country law and regulation. Serious adverse events (reporting, assessing and follow-ups) will be handled similarly to a traditional model, with the participant contacting study personnel or engaging local care for emergencies.

Televisit

This study may deploy TeleVisits as part of the eConsent [redacted] described in the study schedule of events. This means that some study visits (see Table 2-3 in the protocol Schedule of Activities) may be conducted using a telehealth video remote visit platform. The TeleVisit module will provide a remote environment for the clinical research team and clinical trial patient to remain closely connected throughout the life of the study. The study has opted to convert some nontreatment study visits to a TeleVisit to help ease the study burden for participants and hence minimize participant drop-out.

For participants who may take part in the study remotely, pre-screening will be done remotely via a telephone call, and the informed consent will be obtained remotely. TeleVisit and an electronic consent form will be used where allowed by applicable local laws and regulations.

In accordance with country and local regulations, participants who have completed study treatment and safety follow-up visits, quarterly survival follow-up visits may be conducted at the investigative site, through telephone contact or conducted remotely with TeleVisit. Data will be collected digitally, if regulations permit (see Schedule of Activities).

The survival follow-up portion of the study that may be conducted remotely is not complex. Allowing the participants to take part in the study remotely will not increase complexity or increase difficulty in adhering to the protocol. As the aim of the long-term follow-up study does not include participants currently under treatment, there is no increased risk to participants by conducting the survival status assessments remotely. No impact on the data in support of endpoints is expected.

eConsent

eConsent is a platform designed to present IRB/EC-approved informed consent information to a potential participant within a secure system. The platform is designed to enhance participant comprehension and facilitate a better informed consent discussion that is the cornerstone to any informed consent process. This consent discussion will either be conducted within an on-site visit in a face-to-face (F2F) environment, or remotely via an on-TeleVisit platform that enables virtual F2F communication between participant and site staff over a video connection. Consent to participation within the clinical trial, if this is the participant's decision, is then captured within the eConsent platform via a 21CFR part 11 compliant eSignatures (equivalent to an Advanced eSignature under electronic IDentification, Authentication and trust Services [eIDAS] guidelines) from both participant and site staff as well as any other witnesses, legally authorized representatives, or caregivers necessary.

For participants who may take part remotely, pre-screening will be done remotely via a telephone call, and the informed consent will be obtained remotely using telemedicine and an electronic consent form, where allowed by applicable local laws and regulations.

In order to facilitate the management of the study, and the remote monitoring of the consenting process by Clinical Research Associates (CRAs), there are 2 standard reports held within the Study Manager portal. The first of these, the Signed Document Report, contains no Personal Identifiable Information (PII) and only reports the patient ID number, consent template signed, and the date stamp of the eSignature. The second report, the CRA Signed Document Report, provides an additional URL link to the PDF of the signed eConsent form. Access to this report is limited to the 'Study Monitor' role (see User Roles below) and so only CRAs, and those permitted to view PII data, would be granted this role. The URL link provided to the signed consent form has a number of additional security features, and will expire after a set period of time (15 min as standard) to prevent inadvertent access.

User Roles

The platform utilizes a role-based access management system for the creation and managing of specific roles and users. All access design and assignment is controlled by the client. Clients first create or use pre-templated roles for the study, then assign access rights to each role group. Once access by role is complete, users can be assigned to a specific role.

The role assigned to a user determines the level of permissions, options, and features available within the web application.

In order to facilitate the management of the study, and the remote monitoring of the data collection process, CRAs are given the Site Monitor role and access to the Study Manager portal. The CRA can review data, raise manual queries and view participant status, missed ePRO, and Query Reports.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition occurring in a clinical investigation participant after signing of informed consent, whether or not considered related to the study intervention.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory test result), symptom, or disease temporally associated with the study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal laboratory test results or other safety assessment findings should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though the condition may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per the definition above, then it cannot be an SAE, even if serious conditions are met.

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below). NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • A visit to the emergency department or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery that was planned prior to signing consent. • Admissions per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to enrollment in the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.
Is an important medical event (defined as a medical event[s] that may not be immediately life threatening or results in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency department or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important

medical event. (See Section 9.2.7: Potential Drug-induced Liver Injury of the protocol for the definition of a potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as those used for SAEs. (See Section 9.2.5: Pregnancy of the protocol for reporting pregnancies.)

EVALUATING AES AND SAES

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship that cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or product information for marketed products, in his/her assessment. • For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Assessment of Intensity
For the reporting of all AEs, including intensity or severity, on case report forms, please follow the definitions in National Cancer Institute Common Terminology Criteria for Adverse Events version 5 (NCI CTCAE v5).
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term[s] initially reported.).

If an ongoing SAE changes in its intensity or relationship to study intervention or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or the designee) using the same procedure used for transmitting the initial SAE report.

All AEs/SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study intervention, and pregnancies must be reported to BMS (or the designee) promptly and not to exceed 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the electronic Case Report Form (eCRF).
  - The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or the designee).
    - In this case, the paper form is transmitted via email or confirmed fax transmission.
    - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed fax transmission.

SAE Email Address: [redacted]

SAE Fax Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Women of Childbearing Potential (WOCBP) and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1: Inclusion Criteria of the protocol. Only the contraception methods as described in Section 6.1: Inclusion Criteria of the protocol are acceptable for this study.

DEFINITIONS

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Pre-menopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Post-menopausal female
  - A post-menopausal state is defined as 12 months of amenorrhea in a woman over the age of 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. Investigators should use their judgment in checking serum FSH levels.

- 1-week minimum for vaginal hormonal products (rings, creams, gels)
- 4-week minimum for transdermal products
- 8-week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

End of relevant systemic exposure is the time point at which the study intervention (Investigational Medicinal Product [IP/IMP] and other study interventions ie, Non-IMP/AxMP required for study) or any active major metabolites have decreased to a concentration that is no longer considered relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the study intervention to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b] – Oral – Injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device.

• Intrauterine system (IUS). (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b,c] • Bilateral tubal occlusion.
• Vasectomized partner. Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence. *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • Continuous abstinence must begin at least 30 days prior to initiation of study therapy. • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2 of the protocol. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participant chooses to forego complete abstinence. • Periodic abstinence (including, but not limited to, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactation amenorrhea method (LAM) are not acceptable methods of contraception for this study.
NOTES: [a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the Investigational Medicinal Product and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria and Section 7.7.1: Prohibited and/or Restricted Treatments of the protocol. [c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria and Section 7.7.1: Prohibited and/or Restricted Treatments of the protocol.

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of > 1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously. • Diaphragm with spermicide. • Cervical cap with spermicide. • Vaginal sponge with spermicide. • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action. (This method of contraception cannot be used by WOCBP participants in studies in which hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • LAM.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5: Pregnancy of the protocol and Appendix 3.

APPENDIX 5 AMERICAN JOINT COMMITTEE ON CANCER (AJCC) STAGE AND TNM STAGE GROUPING FOR OVARIAN CANCER (8TH EDITION)

1 DEFINITIONS OF AJCC TNM

1.1 Definition of Primary Tumor (T)

T Category	*T criteria*
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to ovaries (one or both) or fallopian tube(s)
T1a	Tumor limited to one ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1b	Tumor limited to both ovaries (capsule intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1c	Tumor limited to one or both ovaries or fallopian tubes, with any of the following: • Surgical spill • Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface • Malignant cells in ascites or peritoneal washings
T2	Tumor involves one or both ovaries or fallopian tubes with pelvic extension below pelvic brim or primary peritoneal cancer
T2a	Extension and/or implants on the uterus and/or fallopian tube(s) and/or ovaries
T2b	Extension to and/or implants on other pelvic tissues
T3	Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to the retroperitoneal (pelvic and/or para-aortic) lymph nodes
T3a	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
T3b	Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension with or without metastasis to the retroperitoneal lymph nodes

T Category	*T criteria*
T3c	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)

1.2 Definition of Regional Lymph Node (N)

N Category	*N criteria*
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N0(i+)	Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	Positive retroperitoneal lymph nodes only (histologically confirmed)
N1a	Metastasis up to and including 10 mm in greatest dimension
N1b	Metastasis more than 10 mm in greatest dimension

1.3 Definition of Distant Metastases

M Category	*M criteria*
M0	No distant metastases
M1	Distant metastases, including pleural effusion with positive cytology; liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); and transmural involvement of intestine
M1a	Pleural effusion with positive cytology
M1b	Liver or splenic parenchymal metastases; metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); and transmural involvement of intestine, microscopically confirmed

2 AJCC PROGNOSTIC STAGE GROUPS

When T is...	*And N is...*	*And M is...*	*Then the stage group is...*
T1	N0	M0	I
T1a	N0	M0	IA
T1b	N0	M0	IB

When T is...	*And N is...*	*And M is...*	*Then the stage group is...*
T1c	N0	M0	IC
T2	N0	M0	II
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T1/T2	N1	M0	IIIA1
T3a	NX, N0, N1	M0	IIIA2
T3b	NX, N0, N1	M0	IIIB
T3c	NX, N0, N1	M0	IIIC
Any T	Any N	M1	IV
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB

3 HISTOLOGIC GRADE (G)

G	*G Definition*
GX	Grade cannot be defined
GB	Borderline tumor
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated or undifferentiated

4 LYMPHOVASCULAR INVASION (LVI)

Component of LVI Coding	*Description*
0	LVI not present (absent)/not identified
1	LVI present/identified, NOS
2	Lymphatic and small vessel invasion only (L)
3	Venous (large vessel) invasion only (V)
4	BOTH lymphatic and small vessel AND venous (large vessel) invasion
9	Presence of LVI unknown/indeterminate

APPENDIX 6 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS	
0	Fully active, able to carry on all pre-disease 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 housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Reference: Oken MM, Creech RH, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 7 COUNTRY SPECIFIC APPENDIX

Criteria for exclusion of HIV-positive subjects in Any Countries Where Exclusion of HIV Positive Participants Is Locally Mandated.

Section 6.2 Exclusion Criteria Exclusion criterion 1) q)	"Known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within the last year, or a current CD4 count < 350 cells/µL. Participants with HIV are eligible if: i) They have received antiretroviral therapy (ART) for at least 4 weeks prior to randomization as clinically indicated while enrolled on study. ii) They continue on ART as clinically indicated while enrolled on study. iii) CD4 counts and viral load are monitored per standard of care by a local health care provider. NOTE: Testing for HIV must be performed at sites where mandated locally. HIV positive participants must be excluded where mandated locally." To be replaced with: "Positive test for HIV".
Section 2 Flow Chart/Time and Events Schedule, Table 2- 1: Screening Assessments- Laboratory Tests	Add "HIV" to the list of laboratory tests

APPENDIX 8 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) guideline with BMS modifications.[1]

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.1 Measurable

Tumor 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:

- 10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥ 2x slice thickness if greater than 5 mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures that 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/MRI 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 two 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. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. 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.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone lesions

- Bone scan, PET scan and plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two 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 two organ sites involved a maximum of two and four lesions respectively will be recorded).

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

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) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 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. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group 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. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

2.2.1 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

2.2.1.1 When the Patient Also Has Measurable Disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions, and ascites will not be followed as a target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the Patient Has Only Non-measurable Disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the

patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response

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

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, inevaluable.

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR, complete response; PD, progressive disease; NE, unevaluable.

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on the increase in the size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, inevaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

REFERENCES

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

APPENDIX 9 NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Heart failure is usually classified according to the severity of the patient's symptoms. The table below describes the most commonly used classification system, the New York Heart Association (NYHA) functional classification. It places patients in 1 of 4 categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

APPENDIX 10 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 02: 07-Apr-2023

The main purpose of Protocol Amendment 02 is [redacted] in the ongoing Phase 1/2 Study, MORAb-202-G000-201, [redacted] As of March 31 2023, [redacted] MORAb-202, 25 mg/m^2. Enrollment of eligible participants will continue in [redacted] (MORAb-202, 25 mg/m^2) and [redacted] (Investigator's Choice Chemotherapy).

Additional revisions, including to sections of the Protocol Summary, have been made to align the protocol with respect to these changes.

Minor editorial, formatting, and typographical corrections have been made and therefore have not been summarized.

This protocol amendment applies to all participants.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2, On-treatment Procedural Outline for MORAb-202 [redacted]	Table headers and footnotes updated to remove reference [redacted]	[redacted]
Table 2-2, On-treatment Procedural Outline for MORAb-202 [redacted] Section 3.2.4.4, Corrected QTc Interval Assessment Section 3.3, Benefit/Risk Assessment Section 3.3.1, Risk Assessment Section 4, Objectives and Endpoints Section 5, Study Design Section 5.1.1.1, Safety Committee (SC) Section 5.2, Number of Participants	All references [redacted] have been removed throughout the study.	[redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.4, Scientific Rationale for Study Design Section 5.5, Justification for Dose Section 7.1.1, MORAb-202 Administration [redacted] Table 7.1.1-1, Administration of MORAb-202 Table 7.4.1-1, MORAb-202 Dose Levels Section 9.4.5, ILD/Pneumonitis Assessments [redacted] Table 10.4.2-1, Primary Endpoints [redacted]		
Section 3.2.3, MORAb-202 Clinical Data	Added updated data from Study 201.	[redacted]
Section 3.2.3.2, Clinical Safety	Added updated data from Study 201.	
[redacted]		
Section 3.2.4.2, Exposure-response Efficacy and Safety	Modified wording from exposure-response paragraph based on updated data.	Wording modified due to emerging safety data from Study 201.
Section 3.3.3, Overall Benefit/Risk Conclusion	Update to the benefit risk conclusion based on data from Study 201.	[redacted]
[redacted]		

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 5.1, Overall Design	The study design schema has been updated.	
Section 5.5, Justification for Dose	Revisions to the justification for dose section have been made based on the changes in Protocol Amendment 02.	
Section 5.6.2.4, Tumor FRα Expression	Moved from 5.6.2.2 to 5.6.2.4, but content is the same	Administrative move.
Table 7.1-2, Study Arm	[redacted] study intervention information was removed.	[redacted]
[redacted]		
[redacted]		

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		

Overall Rationale for Protocol Amendment 01:02-Aug-2022

The main purpose of this Protocol Amendment is to make updates [redacted]. Additionally, further clarification was added to Table 2-4 and Table 7.4.1-2.

Summary of Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Removed local addresses for Belgium and Japan.	Addresses removed as any differences in the local sponsor information will be submitted in local applications.
Table 2-4: On-treatment Procedural Outline for a 28-Day Cycle - [redacted] (PLD, Paclitaxel, and Topotecan 4 mg/m^2) Table 3.3.1-1: Risk Assessment	Added Clinical Laboratory Assessments to be conducted before each treatment visit. Updated the notes and added a footnote for these additional assessments to clarify that only hematologic and chemistry assessments were to be conducted for participants receiving paclitaxel or topotecan. Also updated the notes to clarify that participants receiving pegylated liposomal doxorubicin will have all clinical laboratory assessments performed at every cycle. Updated predose complete blood cell count assessments to be conducted at every treatment visit, instead of every cycle, for both paclitaxel and topotecan treatments [redacted]	To ensure appropriate safety monitoring in accordance with standard of care in participants [redacted]
Section 6.1: Inclusion Criteria	Under inclusion criterion 4) a): • Updated numbering for "WOCBP must agree to follow instructions for	Corrected errors in the numbering of the inclusion criteria.

Summary of Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	method(s) of contraception as described below and included in the ICF." from i) to iii). • Updated numbering for "A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:" from i) to iv).	
Section 6.2 Exclusion Criteria	Updated exclusion criterion 3) a) iii) (2) to clarify the eligibility requirements for the assessment of alkaline phosphatase (ALP).	To further clarify a population with elevated ALP values and known bone and liver metastases.
	Updated the repeated demonstration of a QTcF interval from > 500 msec to > 480 msec in exclusion criterion 3) b).	Updated the QTcF cutoff to a more stringent value of > 480 msec.
[redacted]		
Section 7.4.1.1: Criteria to Resume MORAb-202 Treatment	Clarified that the next cycle of MORAb-202 could be resumed when participants return to their baseline stable sensory neuropathy Grade ≤ 2, as per exclusion criterion 2) c).	Clarified MORAb-202 dose resumption to align with exclusion criterion 2) c).