Official Title of Study:

A Phase 2, Open-label, Randomized Study of MORAb-202 (Farletuzumab Ecteribulin), a Folate Receptor Alpha-targeting Antibody-Drug Conjugate, in Participants with Metastatic Non-Small Cell Lung Cancer (NSCLC) Adenocarcinoma (AC) After Progression on Prior Therapies

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CLINICAL PROTOCOL CA116003/MORAB-202-G000-203

A Phase 2, Open-label, Randomized Study of MORAb-202 (Farletuzumab Ecteribulin), a Folate Receptor Alpha-targeting Antibody-Drug Conjugate, in Participants with Metastatic Non-Small Cell Lung Cancer (NSCLC) Adenocarcinoma (AC) After Progression on Prior Therapies

Brief Title: Phase 2 Study of MORAb-202 in Previously Treated Metastatic NSCLC AC

Protocol Amendment 03

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IND: 160574
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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 03	07-Apr-2023	The overall rationale for Protocol Amendment 03 is to [redacted]
Protocol Amendment 02	06-Feb-2023	The main purpose of this Protocol Amendment is to make updates based on [redacted], investigator feedback, and updates to Sponsor guidelines.
Protocol Amendment 01	27-Jul-2022	The main purpose of this Protocol Amendment is to make updates based on a [redacted].
Original Protocol	06-Jun-2022	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

The main purpose of this Protocol Amendment is [redacted]

[redacted] Protocol Amendment 03 [redacted] but continues [redacted] (MORAb-202, 25 mg/m^2). As of 31-Mar-2023, [redacted] Following reconsent, treatment may continue at the reduced dose of 25 mg/m^2.

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 03

Section Number & Title	Description of Change	Brief Rationale
Table 2-1: Screening Procedural Outline (CA116003) Table 2-2: On Treatment Procedural Outline (CA116003) Section 6.1: Inclusion Criteria Section 6.2: Exclusion Criteria Section 6.4: Screen Failures Section 6.4.1: Retesting During Screening or Lead-in Period Table 7.1.1-1: Administration of MORAb-202 Section 9: Study Assessments and Procedures [redacted]	All instances of [redacted] were replaced with [redacted] or "assigned to treatment".	[redacted]
Table 2-1: Screening Procedural Outline (CA116003) Table 2-2: On Treatment Procedural Outline (CA116003) Table 2-3: Follow-up Procedural Outline (CA116003)	For Body Imaging and Brain Imaging, [redacted] was replaced with [redacted].	[redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.1.2: Imaging Assessments Section 9.4.5: ILD/Pneumonitis Assessments		[redacted]
Table 2-2: On Treatment Procedural Outline (CA116003) Section 9.1.2: Imaging Assessments Section 9.4.5: ILD/Pneumonitis Assessments	For Body Imaging added that [redacted] should be assessed by local team for [redacted]	[redacted]
Section 3: Introduction Section 5.4: Scientific Rationale for Study Design Section 7.3: Blinding	Removed [redacted].	[redacted]
Section 3.1: Study Rationale [redacted] Section 3.3: Benefit/Risk Assessment	Clarified the MORAb-202 dosing. Added dose confirmation data updates.	[redacted] Recent data update.
Section 3.1: Study Rationale Section 3.2.5: MORAb-202 Clinical Data Section 3.3: Benefit/Risk Assessment	Added that [redacted] participants received MORAb-202 after data cutoff date.	Updated experience with MORAb-202 following the data cutoff date.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.2.6.3: Key Differences Between Study 101 and Study 201 Section 5.4: Scientific Rationale for Study Design Section 5.5: Justification for Dose	Removed dose equivalency information [redacted].	[redacted], this information is no longer applicable.
Section 3.2.9: Summary of Data from Subjects who Resumed Treatment After ILD Events	Updated the text that MORAb-202 treatment can be resumed at a reduced dose after [redacted] Updated the [redacted] saying that MORAb-202 [redacted]	Updates based on [redacted]
Section 3.2.10.2: Exposure-response Analysis of Efficacy (ORR) and Safety (ILD)	Updated the text based on emerging data from Study 201.	Updates based on emerging [redacted].
Table 4-1: Objectives, Endpoints and Estimands	Removed the [redacted]. [redacted] as a timepoint was [redacted]	Updates based on emerging [redacted]. Objectives, endpoints, and estimands using date of [redacted] as the study is [redacted].
Section 5.1: Overall Design	[redacted] dose and updated the number of participants receiving the 25 mg/m^2 dose.	Updates based on emerging [redacted]
Figure 5.1-1: Study Design Schema	Schema was updated.	[redacted] from the schema.
Section 5.1.1.1: Safety Committee	Clarified that the Safety Committee review occurred [redacted].	Language updated due to the [redacted].
Section 5.2: Number of Participants	Updated the number of participants receiving a dose of 25 mg/m^2 [redacted]	[redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03

Section Number & Title	Description of Change	Brief Rationale
Section 5.3: End of Study Definition	Updated [redacted] participants to [redacted] participants.	[redacted]
Section 5.4: Scientific Rationale for Study Design	Added that [redacted]	[redacted]
Section 5.5: Justification for Dose	[redacted]	[redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 6.1: Inclusion Criteria Section 6.2: Exclusion Criteria	The criteria that were no longer applicable as per Protocol Amendment 02 were deleted.	Correction of typo, it was an error to leave the non-applicable criteria once they were updated.
Table 7.1-1: Study Interventions	Study intervention details for [redacted] were removed.	[redacted]
Section 7.1.1: MORAb-202 Administration ([redacted]	Removed [redacted] from the text.	[redacted]
Table 7.1.1-1: Administration of MORAb-202 Table 7.4.2-1: MORAb-202 Dose Levels	Removed information [redacted] dose.	[redacted]
Section 7.2: Method of Study Intervention Assignment	Removed mention of [redacted] with MORAb-202.	[redacted]
Section 7.4.1: Dosage Modifications for MORAb-202 [redacted] Section 9.4.5: ILD/Pneumonitis Assessments [redacted] Section 10.1: Sample Size Determination	Removed the mention of the [redacted].	[redacted]
Table 7.4.1-1: Recommended Dose Modifications and Management for MORAb-202 Treatment-related Adverse Events	[redacted]	
Table 9.4.4-1: Clinical Laboratory Assessments	Clarified that urine creatinine clearance was to be done.	Clarification based on eligibility criteria requirement; it was not clear in the table that creatinine clearance was to be tested based on urine collection.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.1: Sample Size Determination	Sample size was updated to reflect only [redacted] (25 mg/m^2 dose)	[redacted]
[redacted]	Added posterior probability of [redacted] adverse events leading to discontinuation.	Posterior probability was adjusted to reflect the [redacted].
Section 10.2: Analysis Sets	Removed [redacted] and replaced [redacted] for the [redacted] set	[redacted] Measurements will be based on those who received treatment to exclude participants who are screen failures.
Section 10.3.1: General Considerations	Removed language that data will be summarized by [redacted] and added that the data for the [redacted]	[redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
		[redacted]
Section 10.3.2: Efficacy Analyses	Clarified that the analyses were from first dose [redacted] in participants who were treated. Removed mention of [redacted]	[redacted]
Section 10.3.3: Safety Analyses	Removed mention of [redacted]	

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title:

A Phase 2, Open-label, Randomized Study of MORAb-202 (Farletuzumab Ecteribulin), a Folate Receptor Alpha-targeting Antibody-Drug Conjugate, in Participants with Metastatic Non-Small Cell Lung Cancer (NSCLC) Adenocarcinoma (AC) After Progression on Prior Therapies

Brief Title: Phase 2 Study of MORAb-202 in Previously Treated Metastatic NSCLC AC

Rationale:

Patients with non-small cell lung cancer (NSCLC) adenocarcinoma (AC) who have experienced disease progression after prior approved therapies with platinum-doublet chemotherapy and immune checkpoint inhibitors, or targeted therapies for actionable mutations, face a high unmet medical need. Effective treatment options after progression on standard-of-care therapies are urgently needed in this population.

MORAb-202 (BMS-986445, farletuzumab ecteribulin) is a novel folate receptor alpha (FRα) targeting antibody-drug conjugate (ADC) comprising a humanized monoclonal antibody, farletuzumab, which binds to FRα-expressing tumor cells, conjugated to eribulin (E7389) mesylate via a cathepsin β-cleavable linker. The eribulin payload of MORAb-202 is a microtubule dynamics inhibitor that exerts its primary pharmacologic effects by preventing normal mitotic spindle formation, leading to irreversible mitotic blockage and subsequent cell death by apoptosis. FRα is highly expressed in NSCLC AC, whereas limited expression is seen in normal tissue.

The CA116003 study aims to further characterize the safety and efficacy of MORAb-202 in previously treated, metastatic NSCLC AC with the goal of selecting an optimal dose of MORAb-202 that can provide better outcomes compared with available treatment options in this study population.

Objectives and Endpoints:

Objectives	Endpoints
Primary	**Primary**
• To assess safety and tolerability of MORAb-202 in participants with previously treated, metastatic non-small cell lung cancer (NSCLC) adenocarcinoma (AC)	• Incidence of treatment-related adverse events (TRAEs) leading to study treatment discontinuation
• To assess tumor response of MORAb-202 in participants with previously treated, metastatic NSCLC AC	• Objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 per investigator assessment
Secondary	**Secondary**
• To assess safety and tolerability of MORAb-202 in participants with previously treated, metastatic non-small cell lung cancer (NSCLC) adenocarcinoma (AC)	• Incidence and severity of adverse events (AEs)/serious AEs (SAEs), treatment related AEs/SAEs, AEs of special interest (AESI), deaths and laboratory abnormalities.
• To evaluate progression-free survival (PFS) of MORAb-202 in participants with previously treated, metastatic NSCLC AC	• PFS by RECIST 1.1 per investigator assessment
• To evaluate disease control rate (DCR) of MORAb-202 in participants with previously treated, metastatic NSCLC AC	• DCR by RECIST 1.1 per investigator assessment
• To evaluate duration of response (DoR) of MORAb-202 in participants with previously treated, metastatic NSCLC AC who achieved a complete response (CR) or partial response (PR)	• DoR by RECIST 1.1 per investigator assessment

Overall Design:

CA116003 is a Phase 2 open-label, randomized, multicenter study assessing the safety, efficacy, and tolerability of MORAb-202 in participants with previously treated, metastatic NSCLC AC.

Participants will receive MORAb-202 at a dose of 25 mg/m^2 [redacted] every 3 weeks. [redacted] (see details below).

- Participants must have received prior treatment, including platinum-based chemotherapy, and
  - If without actionable genetic alterations or unknown genetic alterations status, treatment with anti-PD-1/PD-L1

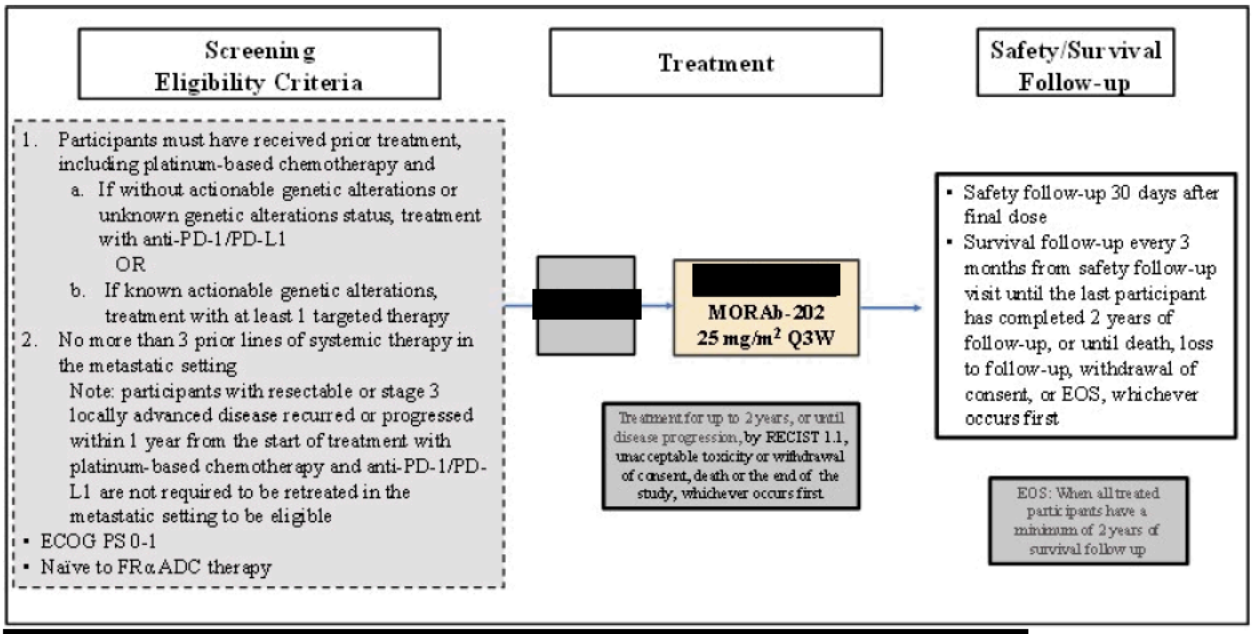
    OR

  - If with known actionable genetic alterations, treatment with at least 1 targeted therapy
- No more than 3 prior lines of systemic therapy in the metastatic setting

  Note: Participants with resectable or stage 3 locally advanced disease that has recurred or progressed within 1 year from the start of treatment with platinum-based chemotherapy and anti-PD-1/PD-L1 are not required to be retreated in the metastatic setting to be eligible.

See the study design figure below.

Study Design Schema:



[redacted]

A Safety Committee (SC) will be established to provide oversight of risk/benefits of participants enrolled in the CA116003 study and give advice to the Sponsor regarding actions the SC deems necessary for the continued protection of participants enrolled. [redacted] 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.

[redacted] Adjudicated ILD/pneumonitis events will be submitted to the SC routinely, and when required, sent to Health Authorities for review.

A Study Steering Committee (SSC), consisting of investigators and members representing the Sponsor of the study, will be established to provide scientific guidance for the protocol and conduct of the study.

Number of Participants:

- Approximately [redacted] participants will be treated in [redacted] (25 mg/m^2 Q3W). It is estimated that approximately [redacted] participants will be enrolled to achieve approximately [redacted] participants, assuming a screen failure rate of [redacted] Additional participants will

be enrolled and treated to account for participants who discontinue before receiving their first dose of MORAb-202.

- The size of the treatment population is calculated to assess preliminary safety and efficacy objectives based on a targeted [redacted] added from historical data.

Study Population:

The study population will consist of participants with previously treated, metastatic NSCLC AC.

Eligible participants must have received prior treatment, including platinum-based chemotherapy and: if without actionable genetic alterations or unknown genetic alterations status, treatment with anti-PD-1/PD-L1; OR, if with known actionable genetic alterations, treatment with at least 1 targeted therapy. Participants must have received no more than 3 prior lines of systemic therapy in the metastatic setting. Participants with resectable or stage 3 locally advanced disease that has recurred or progressed within 1 year from the start of treatment with platinum-based chemotherapy and anti-PD-1/PD-L1 are not required to be retreated in the metastatic setting to be eligible. Eligible participants will have measurable disease, an ECOG PS 0 to 1, be naïve to FRα ADC therapy, and have no current infectious pneumonia (including coronavirus 2019-related infection), or a history of viral pneumonia with evidence of persistent radiologic abnormalities.

Intervention Groups and Duration:

Participants will be treated on Day 1 (± 3 days) to receive MORAb-202 at a dose of 25 mg/m^2 in [redacted] every 3 weeks, for up to 2 years, or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. However, continuous safety and tumor assessment evaluation will guide the Sponsor's decision for a participant to be treated with additional cycles of study therapy beyond 2 years, if the participant has confirmed clinical benefit.

Doses of MORAb-202 may be reduced, interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment, as specified in the protocol.

Safety follow-up visits will be conducted 30 days after the last study drug administration. All ongoing treatment-related serious AEs and ILD events will be followed until resolution or stabilization. Survival follow-up visits will occur every 3 months (± 14 days) from safety follow-up, for up to 2 years, or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever occurs first. All participants discontinuing treatment for reasons other than disease progression will be followed for continued tumor assessments until investigator-assessed disease progression per Response Evaluation Criteria in Solid Tumors 1.1, death, or withdrawal of consent for tumor assessment, whichever occurs first.

End of study is defined as all treated participants who complete their last visit or scheduled procedure. Study completion is defined as the final date on which data for the endpoint of overall

survival were or are expected to be collected if this is not the same. A participant is considered to have completed the study if he/she has completed all survival follow-up visits.

Study Intervention:

Name	[redacted]
Intervention Name/ Unit Dose Strength(s)	MORAb-202 (BMS-986445)/ [redacted] mg/ml]
Type	Drug
Dose Formulation	Lyophilized powder in a single use vial
Dosage Level(s)	25 mg/m^2 Q3W
Route of Administration	IV infusion
Use	Experimental
IMP and NIMP/AxMP	IMP
Sourcing	Provided centrally by the Sponsor

Abbreviations: AxMP, auxiliary medicinal product; IMP, investigational medicinal product; IV, intravenous; NIMP, non-investigational medicinal product; Q3W, every 3 weeks.

Statistical Methods:

The primary endpoints are being assessed based on a targeted [redacted] The primary analysis will be performed when all participants in each arm have been followed up for a minimum of 6 months or discontinued earlier from treatment.

Data Monitoring Committee: No

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

Other Committee: Yes

A SC, [redacted], and SSC will be used in this study.

Brief Summary:

The purpose of CA116003 study is to assess the safety and efficacy of MORAb-202 in previously treated, metastatic NSCLC AC. The study hypothesis is that the study intervention will demonstrate anti-tumor activity, as measured by ORR, and a manageable safety profile.

Study visits will occur on Day 1, Day 8 and Day 15 of Cycle 1 and Day 1 of each [redacted] cycle thereafter.

The study intervention duration is up to 2 years of treatment or until disease progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

The duration of the study is up to 2 years of treatment and until the last participant has completed 2 years of survival follow-up.

2 SCHEDULE OF ACTIVITIES

The following schedule of activities are provided:

Table 2-1: Screening Procedural Outline (CA116003).

Table 2-2: On Treatment Procedural Outline (CA116003).

Table 2-3: Follow-up Procedural Outline (CA116003).

Table 2-1: Screening Procedural Outline (CA116003)

Procedure[a]	Screening[b] (Day-28 to 1)	Notes All windows are based on calendar days
Eligibility Assessments		
Informed Consent (IC)[c]	X	A participant is considered enrolled only when a protocol-specific IC is signed. IC 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 pre-treatment failure. If re-enrolled, the participant must be reconsented and assigned a new participant number from Interactive Response Technology (IRT).
IRT Registration	X	Register in IRT system to obtain participant number after the IC is obtained.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to treatment assignment (within IRT). See Section 6.1 and Section 6.2.
Medical History	X	All general medical history, as well as any relevant history of the disease under study, including American Joint Committee on Cancer (AJCC) stage (per 8th edition), histology, all prior therapy, and other relevant history.
Safety Assessments		
Physical Examination (PE) and Measurements	X	Includes height and weight. Must be collected within 14 days prior to treatment assignment. If the screening PE is performed within 24 hours prior to dosing on Day 1 then a single exam may count as both the screening and predose evaluation.
Performance Status (PS)	X	Eastern Cooperative Oncology Group (ECOG) PS within 14 days prior to treatment assignment (see Appendix 5).
Vital Signs	X	Includes body temperature, respiratory rate, seated blood pressure (BP), and heart rate (HR). 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 treatment assignment.
Concomitant Medication Use	X	Within 14 days prior to treatment assignment. NOTE: Treatment with any live/attenuated vaccine use within 30 days prior to first study treatment is prohibited.

Table 2-1: Screening Procedural Outline (CA116003)

Procedure[a]	Screening[b] (Day-28 to 1)	Notes All windows are based on calendar days
Pulmonary Function Tests (PFTs)	X	PFTs include forced vital capacity (FVC), total lung capacity (TLC), forced expiratory volume during first second of forced breath (FEV1), diffusing capacity of the lungs for carbon monoxide (DLCO; %) within 28 days prior to treatment assignment. May be repeated during the screening period if necessary (Section 6.4.1).
Pulse Oximetry	X	Oxygen saturation 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 treatment assignment.
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 treatment assignment.
Adverse Event Reporting		
Assessment of Signs/Symptoms/Clinical Complaints	X	Within 14 days of treatment assignment.
Monitor for Serious Adverse Events (SAEs)	X	All 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 adverse events (AEs; SAEs or non-serious AEs) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection must be collected from the start of the participant's written consent. AEs/SAEs must be graded by using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5 (CTCAE v5.0).
Laboratory Tests		See Section 9.4.4.
Clinical Laboratory Assessments	X	Includes blood and urine samples. On-site/local laboratory testing must be performed within 14 days prior to treatment assignment.
Pregnancy Test (For Women of childbearing Potential [WOCBP] only)	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]). If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. To be conducted at screening visit and repeated within 24 hours prior to first dose of study treatment. See Appendix 4.
Follicle-stimulating Hormone	X	Required to confirm menopause in women < 55 years of age. See Appendix 4.

Table 2-1: Screening Procedural Outline (CA116003)

Procedure[a]	Screening[b] (Day-28 to 1)	Notes All windows are based on calendar days
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 (see Section 6.2). Must be performed within 28 days of treatment assignment.
[redacted]		
Baseline Tumor Assessments		
Body Imaging	X	Contrast enhanced [redacted], abdomen, pelvis, and all other known and/or suspected sites of disease within 28 days prior to first dose. See Section 9.1.1 for further details.
Brain Imaging	X	Magnetic resonance imaging (MRI) of the brain (without and with contrast) is required for ALL participants during screening, within 28 days prior to first dose. CT of the brain (without and with contrast) can be performed if MRI is medically contraindicated. See Section 9.1.1 for further details and exceptions.
Study Intervention		
Contact IRT for Treatment and Vial Assignment	X	Participant must receive the first dose of study medication within 3 calendar days from treatment assignment and vial allocation in IRT.

[a] Some of the assessments referred to in this section may not be captured as data in the case report form (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.

[b] Screening safety, laboratory, and clinical outcomes assessments that are performed within 3 days prior to dosing on Cycle 1 Day 1 and prior to treatment assignment, unless otherwise specified above, do not need to be repeated at the Cycle 1 Day 1 visit

[c] For participants who may take part remotely, prescreening will be done remotely via a telephone call, and the informed consent will be obtained remotely using 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 will be provided in a separate document.

Table 2-2: On Treatment Procedural Outline (CA116003)

Procedure[a]	Cycle 1 ([redacted])			Cycle 2 onwards	End of treatment (EOT)[b]	Notes[c]
	Day 1 - 3 days	Day 8 ± 3 days	Day 15 ± 3 days	Day 1 ± 3 days		
Eligibility Assessments						
Inclusion/Exclusion Criteria	X					
Safety Assessments						
Targeted Physical Examination (PE)	X	X	X	X	X	If the screening full PE is performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and predose evaluation.
Vital Signs and Performance Status	X	X	X	X	X	Includes blood pressure (BP), heart rate (HR), temperature, and performance status. BP and HR should be measured after the participant has been resting quietly for at least 5 minutes.
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).
12-Lead Electrocardiogram (ECGs)	As clinically indicated				X	ECGs should be recorded after the participant has been supine for at least 5 minutes. Refer to Section 9.4.3 for more details on frequency of ECG measurements.
Concomitant Medication Use	Continuously					Review/document all concomitant medications.

Table 2-2: On Treatment Procedural Outline (CA116003)

Procedure[a]	Cycle 1 [redacted]			Cycle 2 onwards	End of treatment (EOT)[b]	Notes[c]
	Day 1 - 3 days	Day 8 ± 3 days	Day 15 ± 3 days	Day 1 ± 3 days		
Adverse Event Reporting						
Monitor for Serious and Non-Serious Adverse Events (AEs)	Continuously					All serious AEs (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. See Section 9.2.1 and Appendix 3. Record at each visit all AEs (SAEs or non-serious AEs), including those associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. All AEs/SAEs must be graded using Common Terminology Criteria for Adverse Events version 5 (CTCAE v5.0).
Interstitial Lung Disease (ILD)/Pneumonitis Signs/Symptoms Assessment	Continuously					[redacted]
Laboratory Tests						See Section 9.4.4.
Clinical Laboratory Assessments	X			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 of Cycle 1 Day 1 and the results are available and have been reviewed for eligibility. Refer to Section 9.4.4 for the list of laboratory tests to be conducted.

Table 2-2: On Treatment Procedural Outline (CA116003)

Procedure[a]	Cycle 1 [redacted]			Cycle 2 onwards	End of treatment (EOT)[b]	Notes[c]
	Day 1 - 3 days	Day 8 ± 3 days	Day 15 ± 3 days	Day 1 ± 3 days		
Pregnancy Test (Women of Childbearing Potential [WOCBP] only)	X	See Notes		X		Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of human chorionic gonadotropin [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. Refer to Appendix 4 for further information.
[redacted]						

Table 2-2: On Treatment Procedural Outline (CA116003)

Procedure[a]	Cycle 1 [redacted]			Cycle 2 onwards	End of treatment (EOT)[b]	Notes[c]
	Day 1 - 3 days	Day 8 ± 3 days	Day 15 ± 3 days	Day 1 ± 3 days		
Efficacy Assessments						
Body Imaging	See Notes					Contrast enhanced CT of the [redacted], abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 6 weeks (± 7 days) starting from first dose for the first 36 weeks, then every 12 weeks (± 7 days) until investigator-assessed disease progression and 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 and exceptions. [redacted]
Brain Imaging	See Notes					Participants with a history of brain metastasis or symptoms should have a surveillance magnetic resonance imaging (MRI; without and with contrast) per standard of care (approximately every 12 weeks), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.
[redacted]						
[redacted]						

Table 2-2: On Treatment Procedural Outline (CA116003)

Procedure[a]	Cycle 1 [redacted]			Cycle 2 onwards	End of treatment (EOT)[b]	Notes[c]
	Day 1 - 3 days	Day 8 ± 3 days	Day 15 ± 3 days	Day 1 ± 3 days		
[redacted]						
Study Intervention						
Contact Interactive Response Technology (IRT) for Treatment and Vial Assignment/Dispense/ Administer/Deliver Study Intervention	X			X		Participants must receive the first dose of study treatment (MORAb-202) within 3 calendar days from treatment assignment in IRT, unless previously discussed with Medical Monitor (or designee). See Section 7.1.1 for details on administration.
Contact IRT					X	Register EOT visit.

[a] Some of the assessments referred to in this section may not be captured as data in the case report form. 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.

[b] EOT is defined as the date at which the decision is made to discontinue the participant from study treatment. The EOT visit should be performed ≤ 7 days from the treatment discontinuation decision. Evaluations will be performed prior to study discharge or for participants who are prematurely discontinued. 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] Screening safety, laboratory, and clinical outcomes assessments that are performed within 3 days prior to dosing on Cycle 1 Day 1 and prior to treatment assignment, unless otherwise specified, do not need to be repeated at the Cycle 1 Day 1 visit.

[redacted]

Table 2-3: Follow-up Procedural Outline (CA116003)

Procedure	Safety Follow-up Visit[a]	Survival Follow-up	Notes
Safety Assessments			
Targeted Physical Examination	X		
Vital Signs and Performance Status	X		Includes blood pressure (BP), heart rate (HR), temperature, and performance status. BP and HR should be measured after the participant has been resting quietly for at least 5 minutes.
Pulse Oximetry	X		Oxygen saturation (SpO2) by pulse oximetry collected at rest and immediately after exercise (eg, walking for at least 6 minutes or equivalent effort).
Concomitant Medication Use	X		Review/document all concomitant medications.
Adverse Event Reporting			
Serious and Non-Serious Adverse Events (AEs) Assessment	X	See Notes	Collect continuously for a minimum of 30 days following treatment discontinuation (see Section 9.2.3). Participants will be followed for all serious AEs (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.
Interstitial Lung Disease (ILD)/Pneumonitis	X	See Notes	[redacted]
Laboratory Tests			See Section 9.4.4.
Clinical Laboratory Assessments	X		Includes blood and urine samples. Refer to Section 9.4.4 for the list of laboratory tests.
Pregnancy Test (Women of Childbearing Potential [WOCBP] only)	X	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) to be performed every 4 weeks (± 1 week) through the contraceptive period of 7 months after the last dose of study treatment. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required.

Table 2-3: Follow-up Procedural Outline (CA116003)

Procedure	Safety Follow-up Visit[a]	Survival Follow-up	Notes
[redacted]			
Efficacy Assessments			
Body Imaging	See Notes		Only for participants who discontinue study treatment prior to documented radiographic progression per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (see Appendix 6). Contrast enhanced computed tomography (CT) of the [redacted] abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 6 weeks (± 7 days) starting from first dose for the first 36 weeks, then every 12 weeks (± 7 days) until investigator assessed disease progression. See Section 9.1.1 for further details.
Brain Imaging	See Notes		Only for participants who discontinue study treatment prior to documented radiographic progression per RECIST 1.1 (see Appendix 6). Participants with a history of brain metastasis or symptoms should have a surveillance magnetic resonance imaging (MRI; without and with contrast) per standard of care (approximately every 12 weeks), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.

Table 2-3: Follow-up Procedural Outline (CA116003)

Procedure	Safety Follow-up Visit[a]	Survival Follow-up	Notes
Survival Follow-up			
Survival Status[b]	X	X	Participant disease and survival status, and subsequent cancer therapy will be assessed by a documented clinic visit, email, or telephone contact every 3 months (± 14 days) from the safety follow-up visit until the last participant has completed 2 years of survival follow-up, or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever occurs first. Include response to subsequent anticancer therapy and any details relevant to the participant's disease status.
[redacted]			

[redacted]

[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 the last dose or can be performed on the date of discontinuation if that date is greater than 30 days after last dose.

[b] Survival follow-up visits may be conducted in clinic or by telephone or via digital technology (including email and participant portal). BMS 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.

[redacted]

3 INTRODUCTION

CA116003 is a Phase 2 open-label, multicenter study assessing the safety, tolerability, and efficacy of MORAb-202 (BMS-986445, farletuzumab ecteribulin), a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC) in participants with previously treated, metastatic non-small cell lung cancer (NSCLC) adenocarcinoma (AC). The goal of the study is to optimize dose and appropriate study population and potentially provide better outcomes compared with available treatment options.

Worldwide, lung cancer is the second most diagnosed cancer but is the leading cause of cancer-related deaths in both men and women, claiming approximately 1.8 million deaths in the year 2020, due to a high fatality rate. NSCLC accounts for about 85% of all primary lung cancers diagnosed, with AC the major subtype.[1]

Lung AC mostly originates in the peripheral lung tissue from the mucous producing epithelial, alveolar type 2 cells.[2] and strongly correlates with prior smoking history. The majority of patients present with Stage IV disease at initial diagnosis and have a very poor prognosis.[3,4,5] The most common clinical symptoms at presentation are cough, dyspnea, hemoptysis, pain, or other symptoms associated with spread to most common metastatic sites: lung, brain, bone, adrenal glands, and liver.[5]

With the approval of immune checkpoint inhibitors as single agents or in combination with chemotherapy in the first line setting and as second line monotherapy for metastatic NSCLC AC after platinum doublet chemotherapy, the treatment paradigm has changed significantly with improved 5-year overall survival (OS) rates reaching to about 20% in these patients. In patients with molecular alterations as well, approved targeted therapies have increased long term survival rates.[6] Despite these advances, once patients progress on these therapies, treatment options remain very limited and prognosis very poor.[7,8,9]

3.1 Study Rationale

Patients with NSCLC who have experienced disease progression after prior approved therapies with platinum-doublet chemotherapy, anti-programmed cell death protein 1 (PD-1)/ programmed death-ligand 1 (PD-L1) inhibitors or target therapies face a high unmet medical need, with median OS of 9.4 to 11.3 months despite treatment with the current option of single-agent chemotherapy.[7,8,9] Effective treatment options after progression on standard of care therapies are urgently needed. This phase 2 study aims to investigate a novel therapeutic approach, MORAb-202, for these patients with previously treated, metastatic NSCLC. A randomized, parallel dose-ranging study design was initially selected using a [redacted] approach for MORAb-202. The [redacted] approach has the advantage of scaling the dose/exposures more evenly across [redacted] ranges. [redacted] maintains exposures in the lower [redacted] quartiles, similar to that of [redacted], while reducing exposure in the highest [redacted] quartiles. Dose selection for MORAb-202 was based on a detailed assessment of pharmacokinetics (PK) and exposure-response (E-R) safety (interstitial lung disease [ILD]/pneumonitis) across multiple tumor types [redacted]

see Section 5.5.

Farletuzumab ecteribulin (also known as MORAb-202, BMS-986445) is an ADC that has 3 components, a humanized monoclonal antibody, farletuzumab, the mitotic inhibitor payload, eribulin, and a cathepsin β-cleavable linker that binds them. MORAb-202 has high affinity to FRα expressed on the membrane of tumor cells and leverages the FRα transport mechanism to enter the cells. Once internalized, the cathepsin β-cleavable linker of the ADC is cleaved inside the lysosomal compartment and free eribulin is released which elicits cytotoxic effects directly to the tumor cells. The eribulin payload of MORAb-202 is a first-in-class halichondrin B-based microtubule dynamics inhibitor that exerts its primary pharmacologic effects by preventing normal mitotic spindle formation, leading to irreversible mitotic blockage and subsequent cell death by apoptosis.[10,11,12] Eribulin mesylate binds with high affinity to the plus ends of microtubules, where it suppresses the growth phase of microtubules without affecting the corresponding shortening phase.[13,14] In addition, eribulin mesylate induces formation of nonproductive tubulin aggregates, lowering concentrations of free tubulin available for polymerization and thus further inhibiting microtubule growth.

Preclinical data show the pleiotropic effects of MORAb-202 are also evident from the bystander antiproliferative activity on surrounding tumor cells and remodeling of tumor microenvironment (TME) by unconjugated eribulin released into the TME after cancer cell death.[15] In in vitro cell culture studies, MORAb-202 exhibited anticancer effects on FRα-negative cells, when co-cultured with FRα-positive cells.[15]

Of note, the mechanisms of eribulin-mediated changes to the TME and tumor are not linked to its antimitotic effects. These additional effects of eribulin include: (i) tumor vasculature remodeling whereby inner tumor cores become better perfused and less hypoxic, and (ii) promotion of cellular differentiation processes resulting in shifts from more aggressive to less aggressive phenotypes, either via reversal of the epithelial-mesenchymal transition (EMT) in carcinomas or tissue-specific differentiation of sarcomas. These data indicate that eribulin mesylate induces beneficial changes in tumor biology or tumor-host interactions that are over and above those which can be attributed to direct antiproliferative activities of eribulin mesylate against tumor cells alone.[16,17,18]

FRα is a glycosylphosphatidylinositol-linked protein, highly expressed in a variety of cancers, such as [redacted] as well as lung cancer. Although FRα expression is limited in normal lung tissue, approximately 74% of NSCLC ACs express FRα.[19] The differential distribution of FRα expression, coupled with its ability to internalize large molecules, allows for effective drug delivery. Thus, FRα is ideally suited for MORAb-202-based therapeutic approach.[20] Although clinical activity was observed with MORAb-202 across FRα expression levels in MORAb-202-J081-101 (hereafter referred to as Study 101), [redacted].[15] Thus, the role of FRα expression levels in NSCLC AC and its association with MORAb-202 activity require further investigation in order to understand which patients may derive greater benefit from treatment with MORAb-202.

MORAb-202 is being clinically evaluated in 2 clinical studies: Study 101, a study being conducted in Japan, and MORAb-202-G000-201 (hereafter referred to as Study 201) being conducted under Eisai IND 132,199 (EudraCT Number: 2019-003600-12) across several primary solid tumors that express FRα (eg, [redacted]). As of the cutoff date of 31-Aug-2021, 107 participants have been treated with MORAb-202 across both trials, including 20 participants with [redacted]. [redacted] have received MORAb-202 in Study 201 after the data cutoff date of 31-Aug-2021.

Study 101 is a first-in-human, open-label, dose-escalation, and expansion study. The primary objective is to evaluate the safety, tolerability, and pharmacokinetics of MORAb-202 as a single agent administered by intravenous (IV) injection every 3 weeks (Q3W) in Japanese participants with solid tumors (Part 1: Dose Escalation part) or platinum-resistant ovarian carcinoma (PROC) [redacted] (Part 2: Dose Expansion part). Of the 82 participants, 4 participants [redacted] were enrolled in the 0.68 mg/kg (n = 3), or 0.9 mg/kg (n = 1) dose escalation cohort and 15 participants [redacted] were enrolled in the 0.9 mg/kg dose expansion cohort. Overall, the investigator-assessed objective response rate (ORR) was 45% (10/22 participants) for the dose escalation cohort and 30.0% (8/60 participants) for the dose expansion cohort. Across both parts of Study 101, 79/82 (96.3%) participants treated with single-agent MORAb-202 experienced at least 1 treatment-emergent adverse event (TEAE), and the most frequently (> 25%) reported TEAEs were ILD/pneumonitis, and alanine aminotransferase (ALT) increased. In all participants in the dose expansion part of Study 101, 28/60 events of ILD/pneumonitis were reported by investigators and an additional 7 events identified by the ILD expert committee only. The maximum tolerated dose (MTD) was not reached in Study 101.

Study 201 is an open-label study with a two-dose level escalation part followed by a dose confirmation part, evaluating the safety, tolerability, and efficacy of MORAb-202 in participants with select tumor types ([redacted]) in the United States (US) population. In the dose escalation part, 25 participants have been exposed to MORAb-202 at dose levels of 0.9 and 1.2 mg/kg. Of the 25 participants exposed, 1 participant with [redacted] was enrolled in the 0.9 mg/kg dose cohort. The investigator-assessed [redacted] participants.

The dose confirmation part of Study 201 includes sequential [redacted] of MORAb-202 at 25 mg/m^2 [redacted] A total of [redacted] participants have been enrolled and treated with MORAb-202 in the dose confirmation part, with [redacted]

[redacted] weeks or longer.

In the [redacted]

Based on the emerging data for MORAb-202 at the [redacted] in Study 201, notably a [redacted] continue in [redacted] patients in Study 201. Please refer to Section [redacted] for additional details.

See Section 3.2.7 Summary of Clinical Safety and the current MORAb-202 Global Investigator's Brochure (IB)[15] for additional details on safety.

[redacted]

MORAb-202 has shown clinical activity in participants with [redacted], including notable disease control in heavily pretreated participants, warranting further clinical exploration. [redacted] this study implements multiple risk mitigation measures as outlined in Section 3.3 and Table 3.3.1-1.

The CA116003 study aims to further characterize the safety and efficacy of MORAb-202 in previously treated, metastatic NSCLC AC with the goal of selecting an optimal dose of MORAb-202 that can provide better outcomes compared with available treatment options in this study population. [redacted].

3.1.1 Research Hypothesis

MORAb-202 (farletuzumab ecteribulin) will demonstrate anti-tumor activity (as measured by ORR) with a manageable safety profile in participants with previously treated, metastatic NSCLC AC who have progressed during or after treatment with standard-of-care therapies.

3.2 Background

3.2.1 Metastatic Non-Small Cell Lung Cancer

NSCLC remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths.[21] There are 3 major histological subtypes of NSCLC: AC, squamous cell carcinoma, and large cell carcinoma, with AC being the most common histologic subtype accounting for over 60% of NSCLC cases.[22,23] Most NSCLC ACs are diagnosed at an advanced stage (stage III or IV) with a poor overall prognosis. The standard approach to treatment of advanced NSCLC AC includes platinum-based chemotherapy, immune checkpoint inhibitors, targeted therapy for tumors with driver mutations, and combination therapy. However, most patients with advanced disease experience disease progression within 12 to 24 months from the initial diagnosis of metastatic NSCLC, requiring further treatment. Per the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for NSCLC, the current standard of care in patients progressing on standard first- and second-line approved therapies is salvage chemotherapy, such as docetaxel. Outcomes with docetaxel are poor, with response rates of 6.8% to 14%, median progression-free survival (PFS) of 3.0 to 4.2 months, and median OS of 9.4 to 11.3 months.[8,9]

Identification of targetable alterations (ie, epidermal growth factor receptor [EGFR], ALK, PI3K/AKT/mTOR, RAS-MAPK, RET, MET, BRAF, and NTRK/ROS1) in patients with advanced NSCLC has evolved its treatment paradigm.[24] In lung AC, actionable driver mutations are present in approximately 30% to 35% of the patients. These mutations confer sensitivity to small-molecule tyrosine kinase inhibitors, resulting in high response rates (ranging from 60% to 80%), longer PFS (8 to 13 months),[25,26] significant improvements in OS, and more favorable toxicity profiles compared with chemotherapy. Nevertheless, while targeted therapy in NSCLC has significantly improved disease control in patients with actionable mutations, the tumors inevitably develop drug resistance and progress, indicating the need for identifying effective therapies to continue improving lung cancer treatment.[27]

[redacted]

3.2.3 MORAb-202 Mechanism of Action

MORAb-202 is a novel ADC consisting of farletuzumab, a humanized monoclonal antibody that binds to FRα-expressing tumor cells, conjugated to eribulin (E7389) mesylate, a microtubule dynamics inhibitor, via a cathepsin β-cleavable linker. When MORAb-202 binds to the FRα-expressing tumor cell, the ADC is internalized, which results in lysosomal cleavage of the cathepsin β-cleavable linker and intracellular release of eribulin.

Unconjugated eribulin elicits its antitumor activity by inhibiting the growth of microtubules, which cause irreversible mitotic arrest and cell death. In addition, unconjugated eribulin exhibits a bystander effect through non-mitotic effects, which include (i) the inhibition of cell migration, (ii) the induction of tumor vasculature remodeling whereby inner tumor cores become better perfused and less hypoxic, and (iii) the promotion of cellular differentiation processes resulting in shifts from more aggressive to less aggressive phenotypes via reversal of the EMT.[39,40,41] The release of unconjugated eribulin from cells undergoing cell death also potentially has effects on adjacent tumor and stromal cells in the TME, which may allow MORAb-202 to effectively target tumors with heterogenous FRα expression and modify the TME.[15] Thus, it is postulated that eribulin may induce beneficial changes in tumor biology or tumor-host interactions in addition to direct cytotoxic effects.

3.2.4 Summary of Key Preclinical Data with MORAb-202

Preclinical data support clinical exploration of MORAb-202 in NSCLC AC, 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 NSCLC tumor cell line-derived and patient-derived xenograft (PDX)[19] models of human cancer with a single administration at 5 mg/kg.[42]

[redacted]

[redacted]

Please refer to the current MORAb-202 Global IB for additional details.[15]

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

3.2.5 MORAb-202 Clinical Data

Across both Study 101 and Study 201 (data cutoff of 31-Aug-2021), a total of 107 participants [redacted] have been treated with MORAb-202.[15] [redacted] have received MORAb-202 in Study 201 after the data cutoff date of 31-Aug-2021. Study 101 is a first-in-human, open-label, dose-escalation and expansion study with a primary objective of evaluating the safety, tolerability, and PK of MORAb-202 as a single agent administered by IV injection Q3W in participants with solid tumors (Part 1: Dose escalation) or PROC [redacted] (Part 2: Dose expansion), with no requirement for FRα expression in the Japanese population. Preliminary efficacy of MORAb-202 was also evaluated in Study 201, an open-label study with a 2-dose level escalation part, followed by a dose confirmation part, which evaluated the safety, tolerability, and efficacy of MORAb-202 in participants with select tumor types ([redacted]), with no minimum requirement for FRα expression in the US population.

In Study 101, 82 participants have been exposed to MORAb-202 across 5 dose levels in the dose escalation and dose expansion parts. Twenty-two participants with solid tumors were enrolled in the dose escalation part across 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, including 4 participants [redacted] (n = 3 at 0.68 mg/kg; n = 1 at 0.9 mg/kg). Sixty participants were enrolled in the dose expansion part, including 15 participants [redacted] in the 0.9 mg/kg dose cohort and 45 participants with OC in the 0.9 mg/kg and 1.2 mg/kg dose cohorts.

In the dose escalation part of Study 201, 25 participants have been exposed to MORAb-202 at dose levels of 0.9 mg/kg and 1.2 mg/kg. Of the 25 participants exposed to MORAb-202 in Study 201, 1 participant [redacted] was enrolled in the 0.9 mg/kg dose cohort.

The dose confirmation part of Study 201 includes [redacted] and the study has opened recruitment globally. A total of [redacted] participants have been enrolled and treated with MORAb-202 in the dose confirmation part, with [redacted] participants [redacted] in the [redacted] and [redacted] participants [redacted]. However, based on the emerging data for MORAb-202 at the [redacted] in Study 201, notably [redacted] in the study at the

[redacted]. Enrollment at the [redacted] dose level will continue in [redacted] patients in Study 201. Please refer to Section [redacted] for additional details.

3.2.6 Summary of Clinical Efficacy

Clinical efficacy data is presented as of the cutoff date of 31-Aug-2021, unless otherwise specified. Please refer to the current MORAb-202 Global IB[15] for complete information on clinical efficacy.

In both Study 101 and Study 201, [redacted] Anti-tumor activity was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for all participants in Studies 101 and 201.

3.2.6.1 Study 101

Across Study 101 dose escalation cohorts, the investigator-assessed ORR was 45% (10/22 participants). Responses included 1 CR ([redacted] at 0.9 mg/kg) and 9 partial responses (PRs); 1 participant ([redacted]) at 0.3 mg/kg, 4 participants ([redacted]) at 0.68 mg/kg, 2 participants ([redacted]) at 0.9 mg/kg, and 2 participants ([redacted]) at 1.2 mg/kg. The disease control rate (DCR) was 82% (18/22 participants). Of note, the 2 PRs reported for participants [redacted] at 0.6 mg/kg were not confirmed on subsequent scans and both were later declared as SD.

[redacted]

3.2.6.2 Study 201

Across Study 201 dose-escalation cohorts, the investigator-assessed [redacted]

3.2.6.3 Key Differences Between Study 101 and Study 201

Encouraging efficacy was observed in participants with non-high-grade serous (HGS) PROC in both the dose-escalation and expansion parts of Study 101 (0.9 mg/kg dose: ORR of 31.5%, duration of response [DoR] of 10.6 months; 1.2 mg/kg dose: ORR of 50%, DoR of 8.0 months). However, [redacted] was observed in the PROC cohorts in Study 201 (0.9 mg/kg dose: ORR of [redacted]. Evaluation of differences in participant populations enrolled across the 2 studies [redacted].

Number of prior lines of therapy and baseline tumor burden are well established prognostic factors associated with response in PROC.[43] In Study 201, [redacted] of participants of PROC received > 3

prior lines of therapy (as permitted by the eligibility criteria). In contrast, only [redacted] of [redacted] participants in Study 101 had > 3 prior lines of treatment.

At the [redacted] dose level in Study 201, mean sum of diameters of target lesions at baseline was [redacted] mm (range, [redacted] mm), whereas in Study 101 (at the same dose level), participants had relatively lower disease burden at baseline with a mean sum of diameters of target lesions of [redacted] mm (range, [redacted] mm). At the [redacted] dose level, the mean sum of diameters of target lesions were similar between Study 201 and 101 ([redacted] mm [redacted] mm] [redacted] mm [redacted] mm], [redacted].

The high neutrophil-to-lymphocyte ratio (NLR), which is also associated with poorer outcomes, was also different between the 2 study populations.[44] [redacted]. Finally, baseline [redacted] g/dL) [redacted] g/dL). Low albumin levels are associated with [redacted] and are also considered to be an independent predictor of worse prognosis.[15,45]

Taken together, these observations indicate that participants in Study 201 had [redacted] with participants in Study 101. These factors could account for [redacted] with MORAb-202.

In summary, encouraging efficacy with MORAb-202 was observed in both studies across tumor types, including notable [redacted] in participants with [redacted] is a significant predictor of survival outcomes[46] indicating that further dose optimization is warranted in this population.

3.2.7 Summary of Clinical Safety

Clinical safety data are presented as of the cutoff date of 31-Aug-2021, unless otherwise specified. Please refer to the current MORAb-202 Global IB for complete information on clinical safety.[15]

3.2.7.1 Study 101

Across both parts of Study 101, 79/82 (96.3%) participants treated with single-agent MORAb-202 experienced at least 1 TEAE, and the most frequently (> 20%) reported TEAEs were ILD/pneumonitis (26.8%), increased ALT (26.8%), increased aspartate aminotransferase (AST; 23.2%), nausea (23.2%), and pyrexia (23.2%). The 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%) participants. Serious TEAEs were reported in 2/22 (9.1%) participants, of which 1/22 (4.5%) participant had a treatment-related event. There were no reported treatment-related deaths at the time of data cutoff. Five (5/22; 22.7%) events of ILD/pneumonitis/pneumonia/traumatic lung injury were reported, including 1 in 0.68 mg/kg, 3 in 0.9 mg/kg, and 1 in 1.2 mg/kg cohorts (3

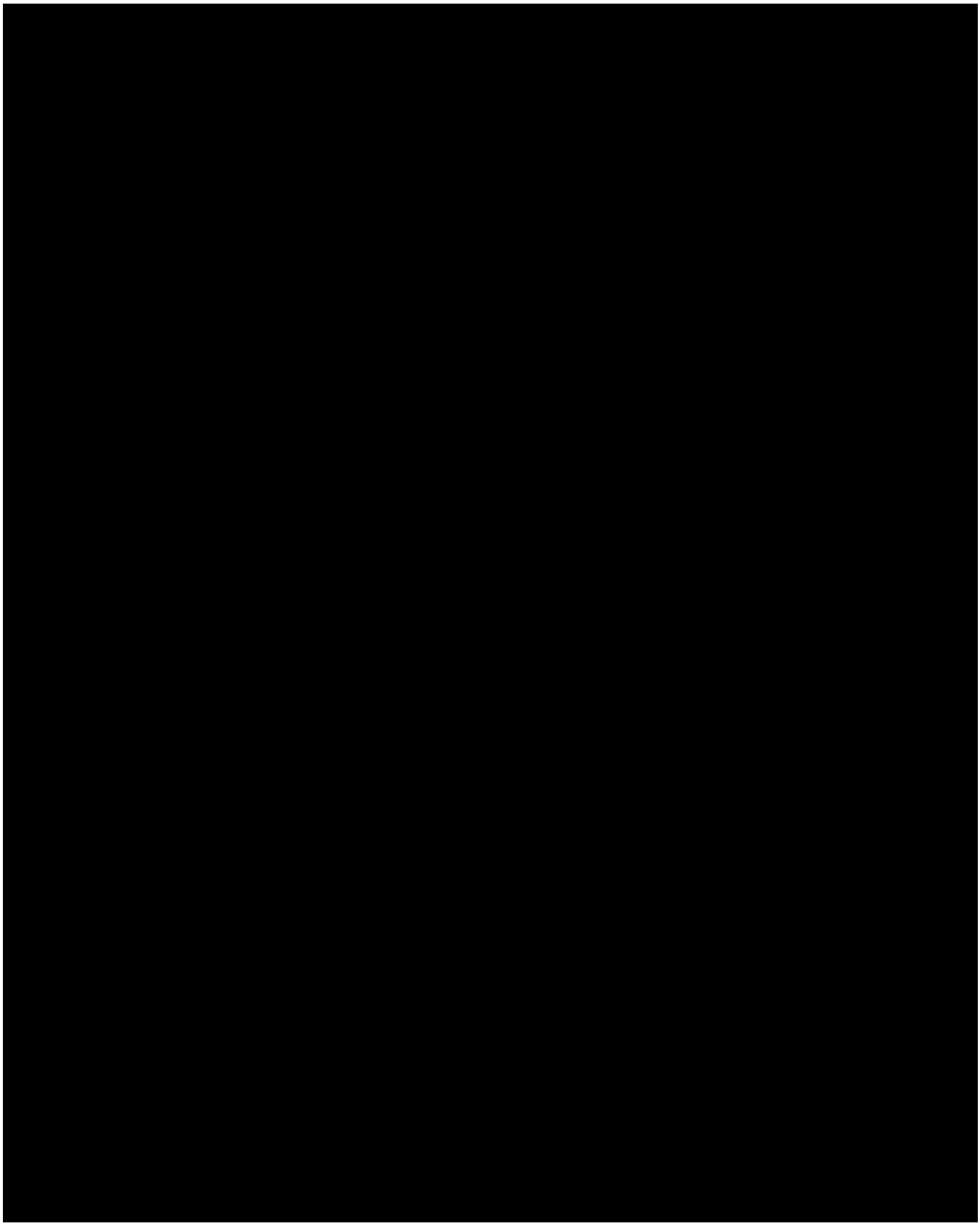
Grade 1 and 2 Grade 2 events), which were identified by the investigators and confirmed by the ILD expert committee.

In the dose expansion part of Study 101, Grade ≥ 3 TEAEs were reported in 15/60 (25%) participants. Serious TEAEs were reported in 12/60 (20.0%) participants, of which 7/60 (11.7%) participants had treatment-related events. The most frequent treatment-related SAEs were pneumonitis and ILD. In the [redacted] 0.9 mg/kg expansion cohort, serious TEAEs (Grade 3) were reported in 2/15 (13.3%) participants, and both were pneumonitis.

In all participants (n = 60) in the Study 101 dose expansion, 28 (46.7%) events of ILD/pneumonitis were reported by the investigators and an additional 7 events identified by the ILD expert committee only (total of 35 events; 58.3%). In participants [redacted] in Study 101 dose expansion, ILD/pneumonitis events were reported for 8 (53.3%) participants, including 5 participants diagnosed by the investigators (4 Grade 1 and 1 Grade 2 events), and 3 additional participants identified by the ILD expert committee (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events version 5 [CTCAE v5.0] grade not assigned). There were no confirmed high-grade (Grade ≥ 3) ILD events in participants [redacted].

Serious Adverse Events:

Of the 82 participants exposed in Study 101 (cutoff date, 31-Aug-2021), 14 participants (17.1%) experienced at least 1 treatment-emergent SAE. Of the 14 SAEs reported in participants who received MORAb-202, 8 were assessed by the investigator as related to study treatment and 6 were assessed as unrelated to study treatment. The most frequent treatment-related SAEs were pneumonitis and ILD.



[redacted]

3.2.8 Summary of Clinical Safety in [redacted]

As of cutoff date 31-Aug-2021, in Study 101, [redacted] participants with metastatic [redacted] were treated with Q3W MORAb-202 across both the dose escalation part ([redacted] at 0.9 mg/kg and [redacted] at 0.68 mg/kg dose) and expansion part ([redacted] at 0.9 mg/kg dose). In Study 201, [redacted] with [redacted] was treated at the 0.9 mg/kg dose.

In the dose expansion cohort of Study 101 [redacted] participants with [redacted] were treated with MORAb-202 at 0.9 mg/kg Q3W. Any [redacted] were reported in [redacted] participants, respectively. Overall, [redacted] were reported and there were [redacted] participants [redacted] as assessed by investigator; [redacted] additional [redacted] based on the clinical information and [redacted]. Among the [redacted] participants with [redacted], the time to onset from first dose of MORAb-202 ranged from [redacted]. As of the cutoff date, the reported [redacted] Based on the totality of the data, the clinical safety profile of MORAb-202 in participants with NSCLC appear to be consistent with that observed in other tumors in both studies.

3.2.9 Summary of Data from Subjects who Resumed Treatment After [redacted]

Clinical experience with MORAb-202 suggest that resuming treatment [redacted]

Pooled analysis of [redacted] events from Study 101 and Study 201 show that [redacted]

In Study 101, [redacted],

In the Study 201 dose-confirmation part, [redacted] participant treated in the MORAb-202 [redacted] cohort with [redacted] (MORAb-202 at [redacted]), [redacted]

In CA116003, treatment with MORAb-202 is held for [redacted] and prompt treatment with [redacted] is recommended. Treatment with MORAb-202 at a dose level -1 can be resumed only if [redacted] improves or resolves.

See Section 7.4 for recommendations on management of ILD/pneumonitis events.

Please refer to the current MORAb-202 Global IB for complete information on clinical safety.

3.2.10 Clinical Pharmacology

MORAb-202 is an immunoglobulin G1 (IgG1) antibody (farletuzumab) conjugated to the microtubule inhibitor eribulin via a cathepsin β-cleavable linker [redacted]. Eribulin mesylate, marketed as Halaven®, is approved in the US and European Union for the treatment of metastatic breast cancer and for unresectable or metastatic liposarcoma.[47]

3.2.10.1 Pharmacokinetics

The PK of MORAb-202 was evaluated after IV administration at Q3W 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 (n = 3) in Part 1 (dose escalation), and at Q3W doses of 0.9 mg/kg (n = 39) and 1.2 mg/kg (n = 21) in Part 2 (dose expansion) in Study 101 (Japanese population). PK was also evaluated at Q3W doses of 0.9 mg/kg (n = 9) and 1.2 mg/kg (n = 6) in Study 201 (non-Japanese population). The PK of MORAb-202, total antibody and released eribulin have been previously described over the escalation dose range of 0.3 to 1.2 mg/kg Q3W in Study 101.[48] From noncompartmental analysis (NCA), the PK of MORAb-202 was near dose-proportional from 0.3 mg/kg 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 the Cycle 1 dose. Concentration versus time profiles were similar for MORAb-202 and total antibody levels, with low levels of released eribulin near the assay limit of quantitation, indicating that 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 US Prescribing Information (USPI) approved dose of 1.4 mg/m^2 IV on Days 1 and 8 of a 21-day cycle.[47,48] [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, consistent with 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 BW on clearance (CL) and volume of 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, which is consistent with that observed for other monoclonal antibodies.[49]

3.2.10.2 Exposure-response Analysis of Efficacy (ORR) and Safety (ILD)

There was a dose and E-R relationship observed for ORR in Study 101 over the dose range 0.68 to 1.2 mg/kg Q3W in participants with 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 when data were combined across tumor types from Studies 101 and 201 (N = 96 total; n = 81, Study 101 and [redacted]). The highest tested dose of 1.2 mg/kg Q3W in Study 101 (including both escalation and expansion) had the highest ORR of 54.2% (13/24) in PROC and highest ILD rate of 58.3% (14/24) across tumor types. The next lower dose level, 0.9 mg/kg Q3W, led to a lower ORR of 32.1% (9/28) and ILD rate of 37.0% (17/46) in Study 101.

An E-R efficacy (ORR) analysis was conducted with participants with PROC from Study 101 (n = 58). Across the dose range of 0.3 to 1.2 mg/kg Q3W, 21 participants had a PR, and 2 participants had a CR with an ORR of 39.7% (23/58). 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.[50] Age, weight, non-HGS (vs HGS OC), and Eastern Cooperative Oncology Group performance status (ECOG PS; 1 vs 0) were not significant predictors of an OR. Higher doses above 1.2 mg/kg Q3W would be expected to result in a higher probability of an OR, given linear PK and lack of saturation of OR across the current dose range. 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. [redacted]

An E-R analysis of all grade 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. In a multivariate analysis, AUC and age were significant predictors of ILD, with both higher AUC and

higher age predicting a higher probability of ILD.[50] [redacted]

3.2.10.4 Corrected QT Interval Assessment

[redacted] msec. 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) of 11.4 msec (19.5) in 26 patients with solid tumors, there was no concentration effect identified.[51] The total dose of eribulin (unconjugated) 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. These data combined with plasma levels of released eribulin from MORAb-202 that are approximately 300-fold lower than with single-agent eribulin, indicate a low risk of QTc prolongation for MORAb-202. Therefore, for all treated participants, electrocardiograms (ECGs) will only be required at baseline and at end of treatment (EOT). During study treatment and safety follow-up, ECGs should be performed as clinically indicated.

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] (see Section 3.2.6). As described in Section 3.2.6, clinical activity with MORAb-202 treatment was observed across multiple FRα-expressing tumor types. Across Studies 101 and 201, 107 participants were exposed to MORAb-202 as of the cutoff date of 31-Aug-2021, including 20 participants with [redacted] participants [redacted] have received MORAb-202 in Study 201 in the dose confirmation part, after the data cutoff date of 31-Aug-2021. Clinical responses were observed in participants with [redacted], and [redacted] tumors across FRα-expression levels at different MORAb-202 dose range levels; however, lower rates of all grade ILD have been observed with lower doses while a trend was observed for higher grade ILD in participants with higher BW. In order to reduce the overall rate of ILD and high-grade ILD, [redacted]

[redacted] for Study CA116003 to be evaluated in parallel. The extensive PK analyses performed for MORAb-202 (see Section 3.2.10.1 and Section 5.5) [redacted] dosing in this advanced NSCLC AC setting where outcomes remain poor.

As described in Section [redacted] emerging data for MORAb-202 [redacted]

[redacted]

Based on clinical study experience to date, ILD/pneumonitis associated with MORAb-202 appears to be responsive to treatment with corticosteroids.[52] For some participants who experienced [redacted]. AEs due to steroid use in Study 101 were generally not reported, which is in line with current clinical experience with steroid use as a treatment for AEs in cancer patients.[53,54] [redacted].

Lastly, the recommendations for monitoring and management of ILD/pneumonitis included in this study have been revised since 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 (refer to Section 7.4.1 for ILD/pneumonitis management recommendations). [redacted]

[redacted] See Section 3.2.8 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 current MORAb-202 Global IB.[15]

The global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical study participants in general and may particularly affect individuals with underlying chronic diseases on immunomodulatory therapies. In general, participants with lung cancer are at an increased risk for respiratory compromise. As described in the Global IB and informed consent form (ICF), MORAb-202 is an immunomodulatory Investigational Medicinal Product (IMP) with the potential for immunosuppressive effects. Based on the mechanism of action, infections are a potential risk. It is not known whether taking MORAb-202 increases the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, or the duration or severity of COVID-19 disease. The inclusion criteria (Section 6.1) have been designed to exclude people with current and recent infections. Testing to exclude asymptomatic SARS-CoV-2 prior to enrollment should follow local standard practice. The study has been designed with study visits that allow for close monitoring of participants' safety throughout the clinical study (Section 2), and participants are encouraged to contact the investigator if an intercurrent illness develops between study visits. Testing for COVID-19 to inform decisions about clinical care during the study should follow local standard practice. In addition, the Sponsor has also developed guidance for investigators on how to manage a participant with a clinical suspicion of, or a diagnosis of, COVID-19. This includes criteria for temporarily interrupting or permanently discontinuing IMP (Section 8.1), and criteria for reinitiating IMP on resolution of a COVID-19 infection (Section 8.1). In order to facilitate enhanced reporting of COVID-19 events that occur during the study, all AEs and SAEs reported after the time of consent that are related to SARS-CoV-2 or COVID-19 infection must be reported (Section 9.2). Individual benefit-risk considerations remain the responsibility of the investigator. Investigators should apply clinical judgment and these risks should be considered when enrolling a participant. With respect to the benefit/risk of receiving COVID-19 vaccinations during treatment with MORAb-202, non-live COVID-19 vaccination is considered a concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving MORAb-202 is unknown.

Refer to the risk assessment Section 3.3.1 for identified risks and mitigation strategy.

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(s)		
Interstitial Lung Disease (ILD)/pneumonitis.	MORAb-202 Global Investigator's Brochure (IB)	Eligibility criteria, consistent monitoring (eg, [redacted], pulse oximetry, signs/symptoms), [redacted] dosing of MORAb-202 to limit exposure variance in participants with higher body weight, investigator/site training on ILD/pneumonitis detection and management, participant alert card, Safety Committee continuous safety monitoring, ILD Expert Review Committee. [redacted]. These mitigation measures, together with the use of [redacted] is expected to improve toxicity profile of MORAb-202 and its benefit/risk ratio.
Infusion-related reactions	MORAb-202 Global IB	Premedications for first MORAb-202 infusion, eligibility criteria; close monitoring for hypersensitivity/allergic reactions during MORAb-202 infusions, secondary prophylaxis. Guidelines for management and dose modification are included in Section 7.4.
Aspartate aminotransferase (AST) / alanine aminotransferase (ALT) elevations	MORAb-202 Global IB	Eligibility criteria, monitoring with predose evaluation of liver enzymes at each cycle. Guidelines for management and dose modification are included in Section 7.4.
Nausea	MORAb-202 Global IB	Monitoring at each cycle. Guidelines for dose modification are included in Section 7.4. Management per institutional protocol/investigator discretion.
Pyrexia	MORAb-202 Global IB	Monitoring at each cycle. Guidelines for dose modification and recommended management algorithm is included in Section 7.4. Management or as per institutional protocol/investigator discretion.
Potential reproductive toxicity	MORAb-202 Global IB	Eligibility criteria, pregnancy testing, contraception per Sections 6.1 and 9.2.5, and Appendix 4.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Study Procedures		
[redacted]		
Blood draws/use of intravenous catheter for laboratory assessments (eg, pain, bruising, bleeding, infection, fainting)		Per institutional protocol/investigator discretion.
CT scan/ magnetic resonance imaging (MRI) radiation exposure		Per institutional protocol/investigator discretion.
Allergy to contrast agent for CT scan/MRI (eg, allergic reaction, anaphylaxis)	Contrast United States Prescribing Information and Summary of Product Characteristics	Prophylaxis and/or treatment per institutional protocol/investigator discretion.
Other (if applicable)		
Severe acute respiratory syndrome coronavirus 2 (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), rescreening criteria (Section 6.4.1) and dose modifications (Section 7.4.1) sections for SARS-CoV-2 Safety Surveillance Plan.
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 study can continue should the hospital be subject to increased demands/restrictions due to the pandemic (travel restrictions, remote access / monitoring, preventative measures, etc).

3.3.2 Benefit Assessment

There is currently an unmet medical need for safe and effective therapy for patients with advanced NSCLC who have progressed on currently approved therapies. Existing data suggest promising clinical activity with MORAb-202 in participants with FRα-expressing advanced cancers. Safety and efficacy are primary endpoints of this study. Safety will be monitored on an ongoing basis by the clinical study team, the pharmacovigilance team and various oversight committees.

MORAb-202 may address this high unmet need for patients with NSCLC AC, given its unique, tumor-specific mechanism (ie, FRα-directed ADC), the high prevalence of FRα overexpression in lung cancer, and the preclinical and clinical activity seen to date (see Section 5.4.1). See Section 5.4.2 for further details on clinical efficacy in MORAb-202 studies.

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 AEs.

3.3.3 Overall Benefit/Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with MORAb-202 ILD/pneumonitis are justified by the anticipated benefits that may be afforded to participants with previously treated, metastatic NSCLC AC.

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 where character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury; (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 communicate 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.

In conclusion, the overall benefit/risk of MORAb-202 in participants with previously treated, metastatic NSCLC AC is assessed to be acceptable and is described further in the following sections.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives, Endpoints and Estimands

Objectives	Endpoints
Primary	**Primary**
• To assess safety and tolerability of MORAb-202 in participants with previously treated, metastatic non-small cell lung cancer (NSCLC) adenocarcinoma (AC)	• Incidence of treatment-related adverse events (TRAEs) leading to study treatment discontinuation
Main Estimand for the Primary Objective[a] • Treatment: MORAb-202, 25 mg/m^2 [redacted] • Population: Participants with previously treated, metastatic NSCLC AC • Variable: Occurrence of TRAEs leading to study treatment discontinuation • Intercurrent events: Early discontinuation of study treatment due to reasons other than TRAE leading to treatment discontinuation – Strategy to handle intercurrent events: While on treatment (early discontinuation of treatment due to reasons other than TRAEs would not be counted towards population-level summary) • Population-level summary: Adverse event (AE) incidence rate; [redacted]	
• To assess tumor response of MORAb-202 in participants with previously treated, metastatic NSCLC AC	• Objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 per investigator assessment
Main Estimand for the Primary Objective[a] • Treatment: MORAb-202, 25 mg/m^2 [redacted] • Population: Participants with previously treated, metastatic NSCLC AC with evaluable baseline tumor assessment • Variable: Best overall response (BOR), defined as the best response, as determined by investigator, recorded between the date of first dose and the date of first objectively documented progression per RECIST 1.1 • Intercurrent events: Early discontinuation of study treatment – Strategy to handle intercurrent events: Treatment policy (all post-baseline tumor assessment regardless of on-treatment status will contribute to BOR determination) • Intercurrent events: Initiation of subsequent anticancer therapy (excluding allowed palliative radiotherapy/surgery to non-target/non-thoracic sites) – Strategy to handle intercurrent events: Treatment policy (all post-baseline tumor assessment regardless of initiation of subsequent anticancer therapy will contribute to BOR determination)	

Table 4-1: Objectives, Endpoints and Estimands

Objectives	Endpoints
• Population-level summary: ORR, defined as the number of participants who achieve a BOR of confirmed complete response (CR) or confirmed partial response (PR) based on investigator assessments (using RECIST 1.1) divided by the number of all response-evaluable participants, with two-sided 95% exact confidence interval (CI); [redacted].	
Secondary	**Secondary**
• To assess safety and tolerability of MORAb-202 in participants with previously treated, metastatic NSCLC adenocarcinoma (AC)	• Incidence and severity of AEs/serious AEs (SAEs), TRAEs/SAEs, AEs of special interest (AESI), deaths and laboratory abnormalities
Main Estimand for the Secondary Objective[a] • Treatment: MORAb-202, 25 mg/m^2 [redacted] • Population: Participants with previously treated, metastatic NSCLC AC • Variable: Occurrence of the AEs/SAEs, TRAEs/SAEs, AESI, deaths and laboratory abnormalities • Intercurrent events: Early discontinuation of study treatment – Strategy to handle intercurrent events: while on treatment (only treatment-emergent AEs between first study dose date and 30 days from last study dose will be counted) • Population-level summary: AE incidence rate	
• To evaluate progression-free survival (PFS) of MORAb-202 in participants with previously treated, metastatic NSCLC AC	• PFS by RECIST 1.1 per investigator assessment
Main Estimand for the Secondary Objective[a] • Treatment: MORAb-202, 25 mg/m^2 [redacted] • Population: Participants with previously treated, metastatic NSCLC AC • Variable: PFS, defined as the time between the date of first dose and the first date of documented progression, determined by investigator assessments (using RECIST 1.1), or death due to any cause, whichever occurs first • Intercurrent events: Early discontinuation of study treatment – Strategy to handle intercurrent events: treatment policy (consider time of first PD or death as PFS event regardless of treatment discontinuation) • Intercurrent events: Initiation of subsequent anticancer therapy (excluding allowed palliative radiotherapy/surgery to non-target/non-thoracic sites) – Strategy to handle intercurrent events: treatment policy (consider time of first PD or death as PFS event regardless of initiation of subsequent anticancer therapy) • Population-level summary: Kaplan Meier (KM) estimated median survival time and landmark survival rate of PFS	

Table 4-1: Objectives, Endpoints and Estimands

Objectives	Endpoints
• To evaluate DCR of MORAb-202 in participants with previously treated, metastatic NSCLC AC	• DCR by RECIST 1.1 per investigator assessment
Main Estimand for the Secondary Objective[a] • Treatment: MORAb-202, 25 mg/m^2 [redacted] • Population: Participants with previously treated, metastatic NSCLC AC with evaluable baseline tumor assessment • Variable: BOR, defined as the best response, as determined by investigator, recorded between the date of first dose and the date of first objectively documented progression per RECIST 1.1 • Intercurrent events: Early discontinuation of study treatment – Strategy to handle intercurrent events: treatment policy (all post-baseline tumor assessment regardless of on-treatment status will contribute to BOR determination) • Intercurrent events: Initiation of subsequent anticancer therapy (excluding allowed palliative radiotherapy/surgery to non-target/non-thoracic sites) – Strategy to handle intercurrent events: treatment policy (all post-baseline tumor assessment regardless of initiation of subsequent anticancer therapy will contribute to BOR determination) • Population-level summary: DCR, defined as the number of participants who achieve a BOR of confirmed CR, confirmed PR, or stable disease (SD), based on investigator assessments (using RECIST 1.1) divided by the number of all response evaluable participants, with two-sided 95% exact CI	
• To evaluate duration of response (DoR) of MORAb-202 in participants with previously treated, metastatic NSCLC AC who achieved a CR or PR	• DoR by RECIST 1.1 per investigator assessment
Main Estimand for the Secondary Objective[a] • Treatment: MORAb-202, 25 mg/m^2 [redacted] • Population: Participants with previously treated, metastatic NSCLC AC with a best overall response as PR or CR • 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 1.1), or death due to any cause, whichever occurs first. DoR will be evaluated for responders (confirmed CR or PR) only • Intercurrent events: Early discontinuation of study treatment – Strategy to handle intercurrent events: Treatment policy (consider time of first PD or death as DoR event regardless of treatment discontinuation) • Intercurrent events: Initiation of subsequent anticancer therapy (excluding allowed palliative radiotherapy/surgery to non-target/non-thoracic sites) – Strategy to handle intercurrent events: Treatment policy (consider time of first PD or death as DoR event regardless of initiation of subsequent anticancer therapy)	

Table 4-1: Objectives, Endpoints and Estimands

Objectives	Endpoints
• Population-level summary: KM estimated median response time and landmark response rate of DoR	

[redacted]

Table 4-1: Objectives, Endpoints and Estimands

Objectives	Endpoints
[redacted]	

[a] Sensitivity estimators of the main estimand and supplemental estimands will be defined in the Statistical Analysis Plan, where applicable.

5 STUDY DESIGN

5.1 Overall Design

CA116003 is a Phase 2 open-label, multicenter study assessing the safety, efficacy, and tolerability of MORAb-202 in participants with previously treated, metastatic NSCLC AC. Participants will receive MORAb-202 at a dose of 25 mg/m^2 [redacted] every 3 weeks. The [redacted]

- Eligible participants must have received prior treatment, including platinum-based chemotherapy and:
  - If without actionable genetic alterations or unknown genetic alterations status, treatment with anti-PD-1/PD-L1

    OR
  - If with known actionable genetic alterations, treatment with at least 1 targeted therapy
- Participants must have received no more than 3 prior lines of systemic therapy in the metastatic setting

  NOTE: Participants with resectable or stage 3 locally advanced disease that has recurred or progressed within 1 year from the start of treatment with platinum-based chemotherapy and anti-PD-1/PD-L1 are not required to be retreated in the metastatic setting to be eligible.

The full eligibility criteria are described in Section 6.

Approximately [redacted] participants will receive treatment in [redacted] (25 mg/m^2 Q3W). Protocol Amendment 03 [redacted]) but continues [redacted]. Participants already treated in [redacted] and may choose to continue MORAb-202 treatment at a dose of 25 mg/m^2 [redacted] Please refer to Section 3.3 for a description of the rationale to [redacted].

Participants will enroll through IRT (see Section 7.2) and will be assigned to treatment [redacted] at 25 mg/m^2.

All screening assessments to determine participant eligibility must be performed within 28 days prior to treatment assignment (see Section 2). [redacted] FRα expression levels will be analyzed by immunohistochemistry (IHC) on an ongoing basis. There is no minimum requirement for FRα expression (%). A tumor sample of sufficient quality and quantity is highly recommended. An archival sample resubmission beyond the screening period for participants without tumor sample of sufficient quality and quantity who

are otherwise eligible for the study is highly recommended [redacted] Additional details on tumor sample quality and quantity metrics and logistics will be provided in the laboratory manual.

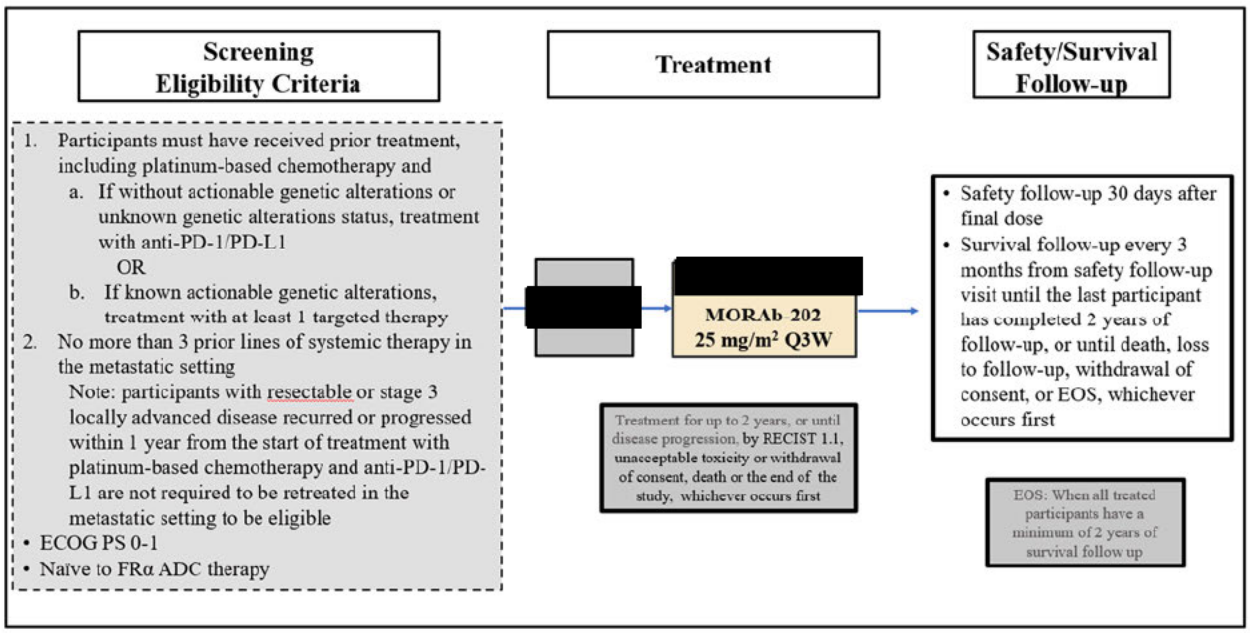
All participants will be treated until disease progression per RECIST 1.1 criteria as assessed by the investigator, unacceptable toxicity, participant withdrawal of consent for receiving study treatment, death, or the end of study, whichever occurs first. Maximum treatment duration will be up to 2 years; however, continuous safety and tumor assessment evaluation will guide the Sponsor's decision for a participant to be treated with additional cycles of study therapy beyond 2 years, if the participant has confirmed clinical benefit (see Section 7.8).

[redacted] All relevant data (safety, efficacy, PK, and pharmacodynamics) will inform the Sponsor's decision on subsequent clinical development, including enrollment of additional participants into an expansion cohort to assess the relationship with FRα expression through a protocol amendment or continuing development in a separate study (see Section 10.1).

The primary analysis will be performed when all participants have been followed up for a minimum of 6 months or discontinued earlier from treatment. One dose level of MORAb-202 will be selected at the primary analysis to continue further evaluation. The dose selection will be based on the totality of efficacy and safety data and as described in Section 10.1. Safety follow-up visits will be conducted 30 days after the last study drug administration. All ongoing treatment-related SAEs and ILD/pneumonitis events will be followed until resolution or stabilization. All participants discontinuing treatment for reasons other than disease progression will be followed for continued tumor imaging assessments until investigator-assessed disease progression per RECIST 1.1, death, or withdrawal of consent for tumor assessment, whichever occurs first. All participants will be followed for survival every 3 months until the last participant has completed 2 years of survival follow-up.

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schema



Physical examinations, vital sign measurements, and clinical laboratory evaluations will be performed at selected times throughout the treatment period. Participants will be closely monitored for AEs throughout the study. Blood samples will be collected for PK analysis. See Section 2 for more detail.

5.1.1 Data Monitoring Committee and Other Committees

Given this is an early phase open-label, MORAb-202 dose optimization study, where the Sponsor has the most extensive knowledge and experience of the medicinal product, a Data Monitoring Committee will not be used in this study. Nonetheless, a Safety Committee (including external members to the Sponsor) and an external ILD Expert Review Committee will provide oversight of this study (see Section 5.1.1.1 and Section 5.1.1.2) and assist with objective decision making.

5.1.1.1 Safety Committee

A Safety Committee (SC) will be established to provide oversight of risk/benefits of participants enrolled in the CA116003 study and give advice to the Sponsor regarding actions the SC deems necessary for the continued protection of participants enrolled. [redacted]. 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 [redacted] or earlier if otherwise warranted. [redacted]

[redacted]. The SC will re-evaluate the benefit/risk profile of the drug and the totality of the data and assess whether termination or resumption of the cohort/study is appropriate. Following each meeting, the SC will recommend continuation, modification, or discontinuation of a dose based on observed benefit/risk profile. Information reviewed at each time point may include disposition, demographics, AEs, SAEs, treatment-related AEs (TRAEs), TRAEs leading to discontinuation, AESIs, 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 each 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 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 Committee Charter.

5.1.1.2 ILD Expert Review Committee

An external independent ILD Expert Review Committee will be established for this study. [redacted]

5.1.1.3 Study Steering Committee

A Study Steering Committee (SSC), consisting of investigators and members representing the Sponsor of the study, will be established to provide scientific guidance for the protocol and conduct of the study. Details of the SSC responsibilities and procedures will be specified in the SSC charter.

5.2 Number of Participants

Approximately [redacted] participants will receive treatment with MORAb-202 at a dose of 25 mg/m^2 [redacted] Q3W. It is estimated that approximately [redacted] participants will be enrolled to achieve approximately [redacted] treated participants in [redacted] assuming a screen failure rate of [redacted]

5.3 End of Study Definition

The start of the study is defined as the first participant first visit. End of study is defined as all treated participants who complete their last visit or scheduled procedure shown in the Schedule of Activities (including survival follow-up). Study completion is defined as the final date on which data for the endpoint of OS were or are expected to be collected if this is not the same.

A participant is considered to have completed the study if he/she has completed all survival follow-up visits.

5.4 Scientific Rationale for Study Design

This study is a multicenter, open-label, Phase 2 study, evaluating safety, tolerability, and efficacy of MORAb-202 in participants with NSCLC AC who progressed after receiving up to 3 prior lines of therapy, including platinum-based chemotherapy and checkpoint inhibitors, or up to 3 prior lines of therapy, including targeted therapy in those with actionable mutations. The treatment option for these patients listed in the NCCN and ESMO treatment guidelines is salvage therapy, such as docetaxel, which has very poor outcomes.

NSCLC AC tumors have high expression of FRα that can be targeted by the ADC, MORAb-202. Upon binding to FRα, the ADC is internalized into the tumor cell by endocytosis and is transported into the lysosome, where the cathepsin β-cleavable linker in the ADC is enzymatically cleaved to release the payload eribulin. [redacted] The study will evaluate the [redacted] of MORAb-202 at 25 mg/m^2 Q3W [redacted] which corresponds to 0.68 mg/kg, a dose that has shown clinical activity. The MORAb-202 dose of [redacted] has been [redacted]. Refer to Section 3.3 for further details on the [redacted].

The study design allows for adequate characterization of the benefit/risk profile of MORAb-202 and selection of a dose that maximizes tolerability, safety and efficacy in patients with NSCLC AC, in line with Food and Drug Administration's (FDA's) current initiative of oncology drug dose optimization.[55,56] To ensure safety of all participants, the study will be closely monitored by a Safety Committee and is designed with prospectively established stopping rules for higher incidence of severe ILD cases.

5.4.1 Rationale for Choice of Endpoints

ORR is an accepted Phase 2 endpoint in NSCLC 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.[57] 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 1.1 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. Safety and tolerability are a co-primary endpoint to allow selection of the dose with the optimal benefit/risk profile.

5.4.2 Participant Considerations and Input Into Study Design

5.4.2.1 Racial and Ethnic Disparity in Lung Cancer Diagnosis, Treatment and Outcomes

There are differences in the incidence and mortality rates of lung cancer between racial and ethnic groups globally, which may be associated with socioeconomic status.[58] In the United States, black men and women are more likely to develop and die from lung cancer than persons of any other racial or ethnic group. For example, black Americans with lung cancer are 18% less likely to be diagnosed early, 23% less likely to receive surgical treatment, 9% more likely to receive no treatment and 21% less likely to survive 5 years compared with white Americans.[59] Similar differences are also observed for Latino patients with lung cancer, who are 16% less likely to be diagnosed early, 26% more likely to receive no treatment and 16% less likely to survive 5 years compared with white Americans. Given the racial and ethnic disparities in lung cancer diagnosis, treatment, and outcomes, this study plans to enroll and evaluate MORAb-202 in a diverse and representative patient population with lung cancer.

5.4.2.2 Patient Voice Interviews

Input into the study design was obtained from Patient Voice interviews (a process within BMS, with a goal of improving patient experience and engagement). Patients living with advanced NSCLC are uniquely positioned to help in the drug development process. Patients who participated in Patient Voice opted-in to being interviewed to provide BMS with their patient and treatment journey, as well as their perspectives on clinical trials. BMS learned that patients with advanced NSCLC generally viewed clinical trials favorably, and their participation helps to advance the development of novel treatments for the broader population of patients with NSCLC in the future. Patients are open to considering treatment options that provide a better quality of life over those with debilitating side effects. Patients noted that the provision of clear information regarding the side-effect profile and management is important to assess their interest in participating in a trial.

Patients generally considered the CA116003 study design to be realistic for advanced NSCLC. Specific input from patients that aligned with protocol are listed below:

- Some patients thought that weekly clinic visits for the first 9 weeks could be a deterrent to participation for those patients with a long distance commute to a study site. In response to this feedback and after careful reassessment of scheduled visits, the requirement for weekly clinic visits was reduced from the first 9 weeks to the first 3 weeks. Safety of the patients will continue to be monitored during this time through weekly phone calls to patients during Cycle 2. Patients will have site contact information and a participant alert card.
- The 2-year treatment period was considered reasonable when the patients were provided with the option for continued access to study medication at the conclusion of the trial by Patient Voice. If participants are clinically benefiting from treatment after the 2-year treatment period,

consideration will be given on an individual basis to allow continuation of study treatment (see Section 7.8).

- To help minimize the potential burden of participation, Patient Voice recommended strategies to include the use of decentralized capabilities, such as telemedicine visits when appropriate, flexible methods to complete questionnaires, and expense re-imbursement. As such, telehealth visits may be implemented on this study. Clinical outcome assessments will be completed electronically and eConsent will be an option. The eConsent platform will minimize in-person clinic visits and allow for less burdensome participation.

5.5 Justification for Dose

A MORAb-202 dose of 25 mg/m^2 Q3W (0.68 mg/kg equivalent) was selected for this study. The dose was based on a detailed assessment of PK and E-R safety (ILD/pneumonitis) across multiple tumor types [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 legally acceptable representatives (LAR, see Appendix 2; where acceptable per local guidelines) must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written 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) Histologically or cytologically documented metastatic NSCLC AC (as defined by the 8th International Association for the Study of Lung Cancer Classification).[60]

b) **Not applicable per Protocol Amendment 02**

c) **Not applicable per Protocol Amendment 02**

d) Investigator-assessed radiologically documented disease progression during or after last treatment

e) Measurable target disease assessed by the investigator according to RECIST 1.1.

f) Lesions that have had external beam radiotherapy (EBRT) or loco-regional therapies such as radiofrequency (RF) ablation must show evidence of disease progression based on RECIST 1.1 to be deemed a target lesion.

g) ECOG PS of 0 or 1

h) Resolution of toxicities from prior anticancer therapies to Grade 1 (NCI CTCAE v5.0) severity or lower before administration of study drug except for stable sensory neuropathy (Grade $\leq$ 2), anemia (hemoglobin [Hgb] $\geq$ 9.0 g/dL), and long-lasting sequelae (such as alopecia, fatigue) that are not expected to interfere with study treatment.

i) **Not applicable per Protocol Amendment 02**

j) Participants must have received prior treatment, including platinum-based chemotherapy and:

i) If without actionable genetic alterations or unknown genetic alterations status, treatment with anti-PD-1/PD-L1

OR

ii) If with known actionable genetic alterations, treatment with at least 1 targeted therapy

k) Participants must have received no more than 3 prior lines of systemic therapy in the metastatic setting

NOTE: Participants with resectable or stage 3 locally advanced disease that has recurred or progressed within 1 year from the start of treatment with platinum-based chemotherapy and anti-PD-1/PD-L1 are not required to be retreated in the metastatic setting to be eligible.

l) [redacted]

3) Age of Participant

Participants (male or female) must be 18 years or older at the time of signing the informed consent.

4) Reproductive Status

- Investigators shall counsel women of childbearing potential (WOCBP), and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study intervention, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

- 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 who are not of childbearing potential must have documented proof in their medical documents.

ii) Women who are not of childbearing potential are exempt from contraceptive requirements.

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

(1) 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.

(2) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Activities.

(3) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

iv) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4, described below and included in the ICF.

- WOCBP are permitted to use hormonal contraception methods.

v) 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) **Not applicable per Protocol Amendment 02**

(3) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, as described in Appendix 4 during the intervention period and for at least 28 days before dosing and throughout the study and for 7 months after MORAb-202 discontinuation and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

b) Male Participants:

Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception as defined in Appendix 4 and as described below.

i) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

ii) **Not applicable per Protocol Amendment 02**

iii) **Not applicable per Protocol Amendment 02**

iv) **Not applicable per Protocol Amendment 02**

v) **Not applicable per Protocol Amendment 02**

vi) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

vii) Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom during the intervention period and for at least 28 days before dosing and throughout the study and 4 months after MORAb-202 discontinuation.

viii) Female partners of males participating in the study should be advised to use highly effective methods of contraception during the intervention period and for at least 4 months after the last dose of study intervention in the male participant.

ix) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral), even if the participants have undergone a successful vasectomy, during the intervention period and for at least 4 months after the last dose of study intervention.

x) Male participants must refrain from donating sperm during the intervention period and for at least 4 months after the last dose of study intervention.

6.2 Exclusion Criteria

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

1) Medical Conditions

a) NSCLC histologies other than AC (ie, squamous cell carcinoma, large cell carcinoma).

b) **Not applicable per Protocol Amendment 02**

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

d) Clinically significant pericardial effusion requiring drainage.

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

f) Recent chest radiotherapy. Participants with chest or chest wall radiation may be permitted if chest radiation is documented > 6 months before starting study treatment.

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

i) Previous SARS-CoV-2 infection, either suspected or confirmed, within 4 weeks prior to treatment assignment. Additionally, acute symptoms must have completely resolved and based on 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.

ii) Participants currently in interventional trials for coronavirus disease 2019 (COVID-19), may not participate in BMS clinical studies until the specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other 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).

NOTE: COVID-19 polymerase chain reaction (PCR) viral testing[61] may be required prior to treatment assignment 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.

h) Investigator assessed current ILD/pneumonitis, or ILD/pneumonitis is suspected at screening or history of ILD/pneumonitis of any severity including ILD/pneumonitis from prior anticancer therapy.

i) Spinal cord compression or untreated, symptomatic central nervous system (CNS) metastases (brain or leptomeningeal). Participants are eligible if CNS metastases are asymptomatic and do not require immediate treatment or if these have been treated and there is no magnetic resonance imaging (MRI) or CT evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study treatment and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). In addition, participants must have discontinued anticonvulsant therapy and must have discontinued corticosteroids, or be 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.

j) 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 (< 5 days) course of steroids up to 7 days prior to initiating study treatment is permitted.

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

l) 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 8), pericarditis, or myocarditis.

ii) Ongoing symptomatic cardiac dysrhythmias, history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes).

m) Clinically significant ECG abnormality, including marked prolonged baseline QTcF (repeated demonstration of a QTcF interval > 500 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.

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

o) **Not applicable per Protocol Amendment 02**

p) Any autoimmune, connective tissue, or inflammatory disorders (eg, rheumatoid arthritis, Sjögren's syndrome, sarcoidosis, etc) where there is documented (or suspicion of) pulmonary involvement. Participants with an active, known, or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

q) Concurrent malignancy (present during screening) requiring treatment, or history of prior malignancy active within 2 years prior to treatment assignment, except for the NSCLC under study (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before treatment assignment 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 (ie, superficial bladder cancer, carcinoma in situ of the prostate, cervix, or breast) that have undergone definitive treatment at any time are also eligible.

r) Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the investigator, would preclude the participant from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.

s) Pulmonary function test (PFT) abnormalities: Forced expiratory volume during first second of forced breath (FEV1) < 70%, or forced vital capacity (FVC) < 60%, and diffusing capacity of the lung for carbon monoxide (DLCO) < 70%.

t) History of deep vein thrombosis (DVT) within 6 weeks prior to enrollment. Participants who completed at least 2 weeks 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.

2) Prior/Concomitant Therapy

a) Participants who have received prior investigational treatment with FRα-targeting agent, or FRα-targeting ADCs including MORAb-202.

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

c) Participants with known intolerance to components of the study drug.

d) Currently enrolled in another clinical study or used any investigational drug or device, which in the opinion of the Sponsor may interfere with the study treatment, within the past 28 days or 5 times the half-life of the investigational drug (whichever is longer) prior to the start of the study treatment.

e) 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.

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

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) Hgb < 9.0 g/dL

(3) Platelet count < 75×10^9/L

NOTE: Supportive therapies 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) ALT and aspartate aminotransferase (AST) > 3× ULN (in the case of liver metastases > 5× ULN).

iv) Participants with alkaline phosphatase (ALP) > 3× ULN, unless they are known to have bone metastases in which case higher ALP values will also be allowed.

v) Serum albumin < 3.0 g/dL.

b) Known human immunodeficiency virus (HIV) positive with an 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 treatment assignment 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.

c) Active viral hepatitis B or C 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.

4) Allergies and Adverse Drug Reaction

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).

5) Other Exclusion Criteria

a) 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 BMS approval is required.)

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

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

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 assigned to treatment 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 AEs.

6.4.1 Retesting During Screening or Lead-in Period

Participant re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment failure (ie, participant has not been assigned to treatment/has not been treated). If re-enrolled, the participant must be reconsented and will be issued a new patient identification number.

Retesting of laboratory parameters, PFTs and/or other assessments within any single screening visit will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to treatment assignment 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 IMP in some regions, is defined 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, or 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 as IPs/AxMPs.

7.1 Study Interventions Administered

Table 7.1-1: Study Interventions

Name	[redacted]
Intervention Name/ Unit Dose Strength(s)	MORAb-202/[redacted] mg/ml
Type	Drug
Dose Formulation	Lyophilized powder in a Single Use Vial
Dosage Level(s)	25 mg/m^2 Q3W
Route of Administration	IV infusion
Use	Experimental
IMP and NIMP/AxMP	IMP
Sourcing	Provided centrally by the Sponsor

7.1.1 MORAb-202 Administration [redacted]

Participants will receive MORAb-202 at a dose of 25 mg/m^2 in [redacted] Q3W (± 3 days), for a maximum treatment duration of 2 years or, as described in Section 7.8, until disease progression, unacceptable toxicity, 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 onward	Notes
[redacted] Premedication Acetaminophen/paracetamol 400 mg 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 7.4.1-1.
[redacted] MORAb-202 Administration 25 mg/m^2 Q3W (+3 days)	X	Participants must receive the first dose of study treatment within 3 calendar days from treatment assignment, unless previously discussed with Medical Monitor (or designee). MORAb-202 will be administered as an intravenous (IV) infusion on Day 1 of each [redacted] cycle. Participants may be dosed no less than 18 days from the previous dose. [redacted] See Section 7.4 for dose modifications and management of adverse events (AEs). The first infusion of MORAb-202 will be given over no less than 60 minutes. Participants should be observed for at least 60 minutes following the first infusion. If no infusion reactions are observed, subsequent infusions can be infused as tolerated, but given over no less than 30 minutes, with an observation period of at least 30 minutes following each infusion. If an infusion reaction occurred during a previous cycle, participants should continue to be observed for at least 60 minutes for the subsequent infusion. If there is no subsequent reaction, then at least a 30-minute observation period should be used. Flush the intravenous line with an appropriate amount of diluent (eg, 0.9% sodium chloride) to ensure that the complete dose is administered.

Doses of MORAb-202 may be reduced, interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment (see Table 7.4.1-1 for dose modifications for management of TRAEs). Dosing visits are not skipped, only delayed.

Please refer to the current MORAb-202 Global IB 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.

[redacted]

7.2 Method of Study Intervention Assignment

All participants will be centrally assigned to treatment with MORAb-202 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).

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted] Sequential numbering may restart at [redacted] for each participating site because the distinct patient identification number will ultimately comprise the site number and participant number [redacted] Those enrolled participants meeting inclusion and exclusion criteria will be eligible to receive treatment with MORAb-202.

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 BMS.

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

7.3 Blinding

Not applicable as this is an open-label study; it has been determined that blinding is not required to meet study objectives and access to treatment assignment information is unrestricted. The specific treatment to be taken by a participant will be assigned using IRT. The site will contact the IRT 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. 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 CRF (eCRF).

Participants will be evaluated for AEs at each visit with the CTCAE v5.0 as a guide for the grading of severity.

7.4.1 Dosage Modifications for MORAb-202

Dosage modifications for MORAb-202 and recommended management of TEAEs are shown in Table 7.4.1-1.

Table 7.4.1-1: 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 Section 7.4.2.

Table 7.4.1-1: 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]	[redacted]

Table 7.4.1-1: 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 7.4.1-1: 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 7.4.1-1: Recommended Dose Modifications and Management for MORAb-202 Treatment-related Adverse Events

Drug-Related Adverse Event per CTCAE v5.0	Severity	Action Taken
[redacted]		
Hematologic		
Neutrophil count decreased	Grade ≥ 3	Hold MORAb until absolute neutrophil count (ANC) is ≥ 1000/µL.
	Grade 4	Dose reduce 1 level (Table 7.4.2-1) if lasting > 7 days.

Table 7.4.1-1: Recommended Dose Modifications and Management for MORAb-202 Treatment-related Adverse Events

Drug-Related Adverse Event per CTCAE v5.0	Severity	Action Taken
Febrile neutropenia	Grade ≥ 3	Hold MORAb-202 until < 38°C (100.4°F) + ANC ≥ 1000/µL. Dose reduce 1 level (Table 7.4.2-1) 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 7.4.2-1) 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.
Non-hematologic		
All other lab abnormalities (both symptomatic and asymptomatic)	Grade ≥ 3	• Hold MORAb-202 until resolution to Grade ≤ 1 or baseline. • Dose reduce 1 level (Table 7.4.2-1). • 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.

7.4.2 Dosage Modifications 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 7.4.2-1). Consultation with the study Medical Monitor is required prior to dose reduction. Once a dose is decreased, it cannot be increased again.

Table 7.4.2-1: MORAb-202 Dose Level

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.

7.4.3 Criteria to Resume Treatment

To start the next cycle of MORAb-202 administration, participants must meet the minimum requirements below and 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.
- All Grade ≥ 3 laboratory abnormalities even if asymptomatic must be corrected to Grade ≤ 1 or baseline
- Meet the requirements for dosing as per management of infusion reactions and ILD/pneumonitis events (Table 7.4.1-1).

7.4.4 Dose Delays

MORAb-202 administration in subsequent cycles may be postponed for up to [redacted] from the subsequent scheduled dose to recover from any toxicities. Treatment delays of [redacted] are allowed in participants with ILD/pneumonitis to permit recovery. Disease assessment should continue as per the protocol-mandated schedule (see Table 2-2). Study treatment should not be reinitiated in participants with disease progression.

If the treatment has been held and the next cycle is delayed, Day 1 of the next cycle will be defined as the first day that study treatment is resumed. Cycles will not be skipped; treatment will resume at the next planned cycle.

7.5 Preparation/Handling/Storage/Accountability

The IP/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/AxMP is only dispensed to study

participants. The IP/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 BMS. If concerns regarding the quality or appearance of the study intervention arise, the study intervention should not be dispensed, and BMS should be contacted immediately.

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

IP/AxMP documentation (whether supplied by BMS or not) must be maintained that includes 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 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.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition 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 MORAb-202 Global 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, BMS 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 BMS 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 Treatment Compliance

Study intervention compliance will be periodically monitored by drug accountability.

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF. This will be source data verified by the BMS 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, 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 Palliative Local Therapy

Palliative local therapy, including palliative radiation therapy and palliative surgical resection, to symptomatic non-target lung lesions (ie, causing hemoptysis or obstruction), bone lesions, skin lesions, or CNS lesions is permitted prior to discontinuation of study treatment for participants who do not have evidence of overall clinical or radiographic progression, per RECIST 1.1. Any palliative radiation therapy where the radiation field involves the lung (ie, chest wall, thoracic spine, mediastinum, esophagus, lung, etc), should first be discussed with and approved by the Medical Monitor/designee.

Participants requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy. If progression, per RECIST 1.1 by investigator assessment, is identified on any tumor assessments prior to the initiation of palliative local therapy, then participants must discontinue study drug treatment.

The potential for overlapping toxicities with radiotherapy and MORAb-202 currently is not known. As concurrent radiotherapy and MORAb-202 have not been evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then it is recommended that MORAb-202 dosing is held prior to initiation of radiation therapy. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade $\leq$ 1 prior to resuming study drug.

7.7.2 Supportive Therapies and COVID-19 Vaccines

- Supportive therapies as blood/platelet transfusion, hematopoietic stimulating agent including 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 7 days prior to initiating/resuming study treatment.
- COVID-19 vaccines that are NOT live are allowed and should be handled in the same manner as other vaccines. Administration may occur during the study, including during the administration of the BMS study treatment and after the last administration of the BMS study treatment.

7.7.3 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 studies on drug-drug interactions conducted for MORAb-202. Farletuzumab, the antibody portion of MORAb-202, is not expected to impact cytochrome P450 (CYP)-mediated metabolism since its mechanism of action does not involve

increases in proinflammatory cytokines that historically have been linked to antibody-based modulation of CYPs. As described in the Halaven® USPI, drug-drug interaction studies have been conducted for eribulin; 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 CYP1A2, 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.

7.7.4 Prohibited and/or Restricted Treatments

The following medications and treatments are prohibited during the study (unless utilized to treat a treatment-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 systemic anti-neoplastic therapy (eg, systemic chemotherapy, hormonal therapy, immunotherapy, non-palliative radiotherapy, tumor debulking surgery or standard or investigational agents for treatment of malignancy). Medical Monitor approval in writing for any localized use of systemic anticancer. However, the continued use of drugs for bone diseases (such as bisphosphonates and anti-receptor activator of nuclear factor kappa-B ligand [RANKL] monoclonal antibody) that were already being used by the participant prior to the initial study treatment is permitted. The use of such agents can be discussed with the Sponsor Medical Monitor as needed.
- Any non-palliative radiation therapy. Radiation therapy administered with palliative intent as described in Section 7.7.1.
- 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.

7.7.5 Other Restrictions and Precautions

Participants are prohibited from joining another clinical study while they are participating in this study.

7.7.5.1 Imaging Restriction 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 or not they should receive contrast and if so, which contrast agent and dose is appropriate. Specific to 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. This 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 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 conclusion of the study, if the study intervention is not available as an approved treatment in the local country, participants who continue to demonstrate clinical benefit may be eligible to receive BMS-supplied study intervention, as specified in Section 7.1. If the study treatment is not available as an approved and available treatment, study intervention may be provided via an extension of the study, a rollover study requiring approval by the responsible Health Authority and ethics committee, or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS-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; c) the participant can obtain medication from a government-sponsored or other health program. In all cases, BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Intervention

Participants MUST discontinue IP (and Non-IP/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 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 BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (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 BMS approval is required.)
- Pregnancy (refer to Section 9.2.5)

- Documented disease progression per RECIST 1.1, as assessed by the investigator
- Clinical deterioration while receiving 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 8.
- Any dosing delays lasting [redacted] from the subsequent scheduled dose with the following exception:
  - Treatment delays of [redacted] are allowed in participants with ILD/pneumonitis to permit recovery

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 Schedule of Activities (Section 2) 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. 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 and [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 (in this study or a rollover study) for collection of outcome, disease response (until investigator assessed disease progression by RECIST 1.1), and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

8.1.2 Long-term Survival Follow-up

Survival follow-up visits will occur every 3 months (± 14 days) from the safety follow-up visit, until the last participant has completed 2 years of survival follow-up, or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever occurs first. The survival visit may be conducted in the clinic, by telephone, or via digital technology (including email and participant portal).

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 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 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, or compliance. 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 Section 2 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 both from the study intervention and from 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 **three (3)** documented phone calls, faxes, or emails, as well as lack of response by participant to one (1) registered mail letter. All attempts should be 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.
- If the investigator's use of 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 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, in order 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.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in Section 2.
- 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 treatment assignment. 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).
- Evaluate the participant immediately to rule out pulmonary toxicity if the participant shows pulmonary-related signs (eg, abnormalities on [redacted] hypoxia) 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

Images will be submitted to a central imaging vendor and may undergo blinded independent central review (BICR) at any time during the study (Refer to Section 9.4.5 [redacted]

[redacted]. 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.

Screening and on-study images should be acquired as outlined in Section 2 Schedule of Activities. 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 1.1 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.

9.1.1 Efficacy Assessment

Contrast-enhanced CT of the [redacted], abdomen, pelvis, and all 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). As [redacted] imaging will also be [redacted], sites are encouraged to obtain [redacted] with a minimal slice thickness of 2 mm (Refer to Section 9.4.5 for [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 IV contrast, then a non-contrast CT of the [redacted] 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 IV contrasts, then a non-contrast CT of the [redacted] 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 IV contrast, then a non-contrast CT of the [redacted], abdomen, pelvis, and other known/suspected sites of disease is acceptable.

Use of CT component of a positron emission 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 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 1.1 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 1.1 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.

9.1.2 Imaging Assessments

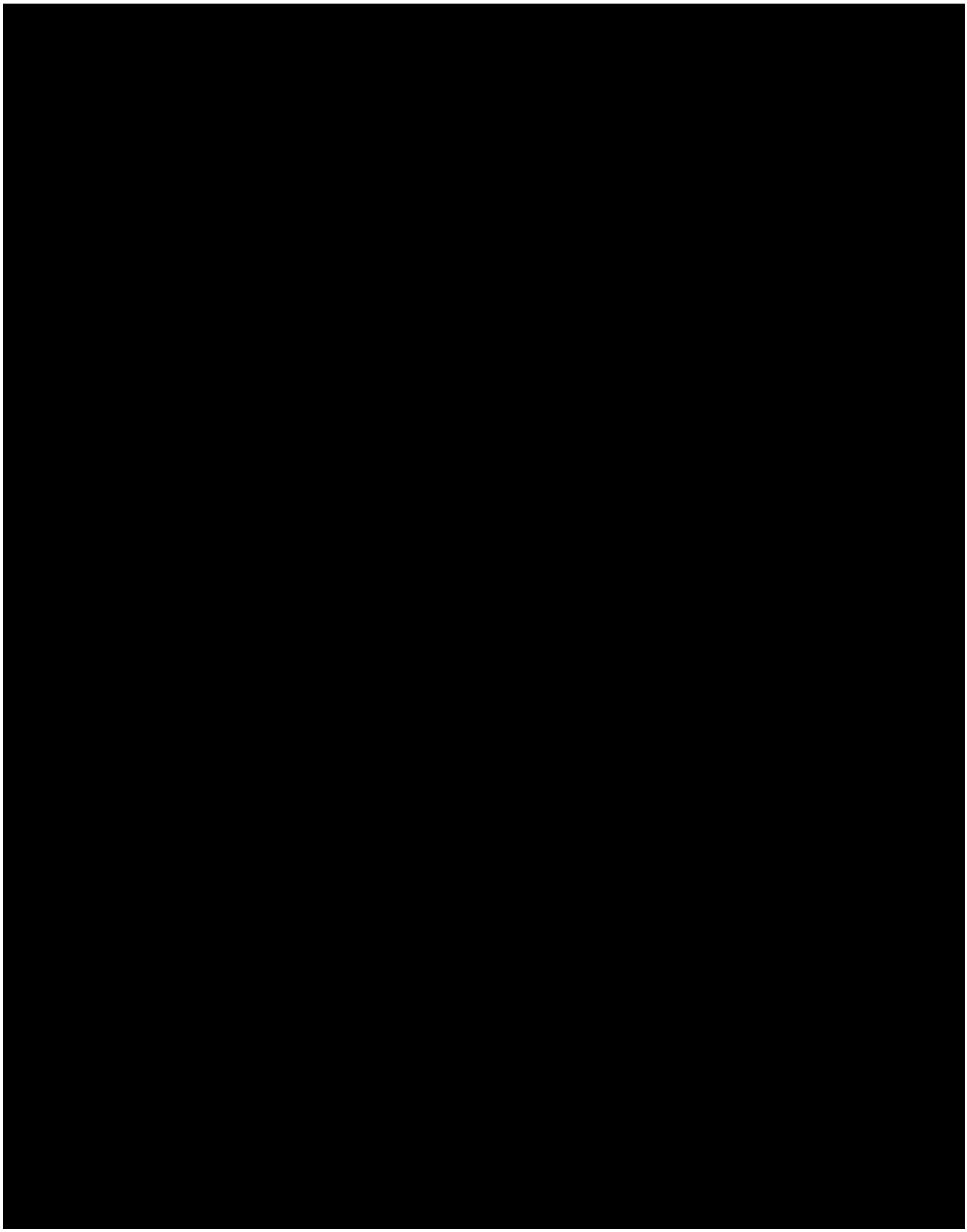
Screening and on study images should be acquired as outlined in Section 2 Schedule of Activities.

On-treatment images should be assessed by the local team for [redacted]

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 1.1 tumor assessment and submit to the imaging vendor. Tumor assessments should continue on the protocol-defined imaging schedule, regardless of whether dosing is delayed or discontinued, until investigator-assessed disease progression by RECIST 1.1. Changes in tumor measurements and tumor responses will be assessed by the same investigator or designee using RECIST 1.1 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 1.1 criteria (see Appendix 6 for specifics of RECIST 1.1 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 BOR of SD requires a minimum of 35 days on study from first dose to the date of the first imaging assessment.

Refer to Section 9.4.5 for details of [redacted].

[redacted]



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, or a surrogate).

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.

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

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

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

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

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, 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.

Collect all nonserious AEs (not only those deemed to be treatment related) continuously during the treatment period and for a minimum of 30 days following discontinuation of study treatment.

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 judgement in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious 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 nonserious AEs that cause interruption, delays or discontinuation of study intervention and for those present at the end of study intervention as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AESIs; as defined in Section 9.2) 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). Any serious/nonserious ILD/pneumonitis event (AESIs, as defined in Section 9.2.6) must be followed with [redacted] approximately Q3W 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).

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.

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 current MORAb-202 Global IB 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 SUSAR (suspected, unexpected serious adverse reaction) 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

If, following initiation of the study intervention, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for 7 months after study product administration (for MORAb-202), the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

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 on the participant.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor or designee. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

If any sexual activity involving penile intercourse (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom during and at least for 90 days after study product administration, the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy.

9.2.6 Adverse Events of Special Interest - Infusion-related Reactions and ILD/Pneumonitis

Administration of MORAb-202 could be associated with immune-mediated responses. These immune-mediated AEs may occur shortly after administration of the first dose or might have a

delayed presentation. Signs and symptoms associated with these reactions are listed in Table 9.2.6-1 and, if they occur after administration of MORAb-202, should be classified as AESIs.

Table 9.2.6-1: Adverse Events of Special Interest

Category	Adverse Events
Infusion Reactions[a]	Allergic reaction Anaphylaxis Cytokine release syndrome Angioedema Chills/Rigors Sweating/diaphoresis Urticaria Pruritus/itching Bronchospasm/wheezing Bronchial edema
Interstitial Lung Disease (ILD)/Pneumonitis events[b]	Pneumonitis ILD Pulmonary fibrosis

[a] When single/multiple signs or symptoms concomitantly occur; each sign/symptom should be reported on the eCRF and the investigator should also record whether they correspond to "infusion reaction" on the eCRF. In case of each sign/symptom judged as an "infusion reaction," their onset/outcome date and time should be recorded on the adverse event eCRF.

[b] ILD/pneumonitis events of Grade 3 or above should be immediately reported as an important medical event by a completed serious adverse event form.

AESIs that are Grade ≥ 3 in severity will be immediately reported by a completed SAE form. The AESIs will be clarified on AE form in eCRF.

Any ILD/pneumonitis events of Grade ≥ 3 should always be considered as serious important medical events, entered in the Adverse Event eCRF, and reported using the procedures detailed in Section 9.2.3 and Appendix 3.

9.2.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE eCRF, as appropriate. 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 required the participant to have study intervention discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

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

9.2.8 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory 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 9.2.8 and Appendix 3 for reporting details).

Potential DILI is defined as:

- Aminotransferase (AT; ALT or AST) elevation > 3× ULN
- AND
- Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- AND
- No other immediately apparent possible causes of AT 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.

9.2.9 Other Safety Considerations

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

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 SAE will be reported as an SAE (see Appendix 3).

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately
- Closely monitor the participant for AEs/SAEs and laboratory 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

Decisions regarding dose interruptions, delays or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4 Safety

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

9.4.1 Physical Examinations

Refer to Schedule of Activities (Section 2).

9.4.2 Vital signs

Includes pulse oximetry and ECOG PS. Refer to Schedule of Activities (Section 2).

9.4.3 Electrocardiograms

Refer to Schedule of Activities (Section 2).

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).

A local laboratory will perform the analyses and will provide reference ranges for these tests.

Results of clinical laboratory tests must be available prior to study intervention administration.

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Red blood cell (RBC) count	
Platelet count	
Chemistry	
Amylase and/or lipase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin (T.bili) Direct bilirubin (reflex)[a] Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Blood urea nitrogen or urea per local guidance Uric acid Glucose	Total protein Albumin Sodium Potassium Chloride Calcium CO_2 Phosphorus Magnesium Folate Creatine kinase (Urine) Creatinine clearance (CrCL) - 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 (screening only)	

Table 9.4.4-1: Clinical Laboratory Assessments

Hepatitis B/C (Hepatitis B surface antigen [HBsAG], hepatitis C virus (HCV) indicating presence of active viral replication (detectable HCV ribonucleic acid [RNA]) - screening only. Human immunodeficiency virus (HIV)-1 and HIV-2 antibody - screening only (as mandated by local requirement)
Other Analyses
Pregnancy test (minimum sensitivity equivalent units 25 IU/L; women of childbearing potential only: screening, predose, discharge).
Follicle stimulating hormone (screening only for confirmation of menopause in women age < 55 years)

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

9.4.5 ILD/Pneumonitis Assessments

ILD/pneumonitis is a known TRAE associated with MORAb-202 (see Section 3.2.8. All 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 all 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 participants may be asymptomatic [redacted] Signs/symptoms potentially consistent with ILD/pneumonitis may include but are not limited to the following:

- Dyspnea (at rest and/or with ordinary physical activity)
- Non-productive cough
- Malaise
- Fever (low-grade)
- Oxygen saturation (SpO_2) of < 92% at rest or immediately after exercise (eg, walking for at least 6 minutes or equivalent effort)

[redacted]

All [redacted] for all participants [redacted]

[redacted] See Table 7.4.1-1 for [redacted]

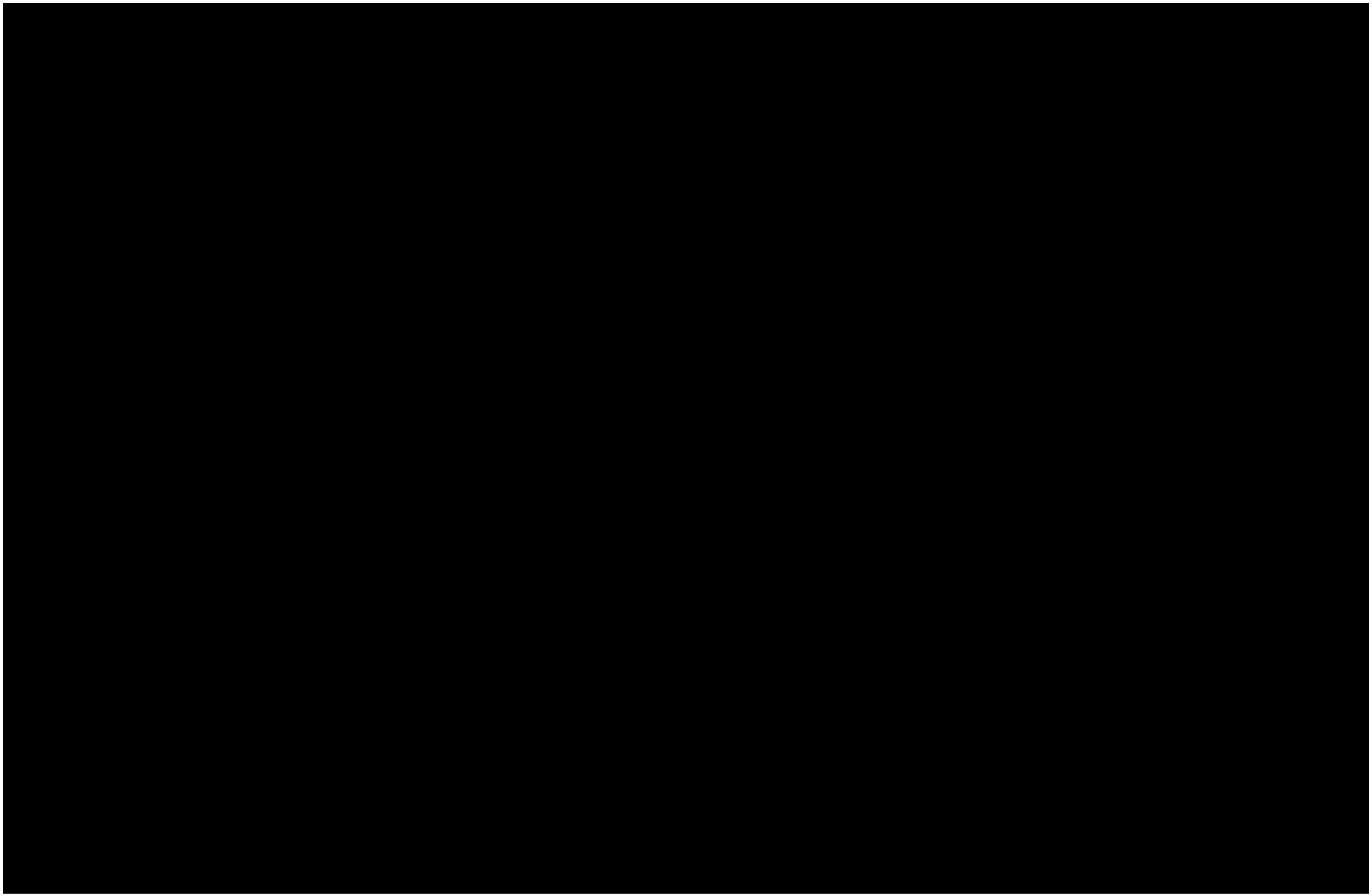
[redacted]

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 as per standard medical/clinical judgment.

[redacted]

[redacted]



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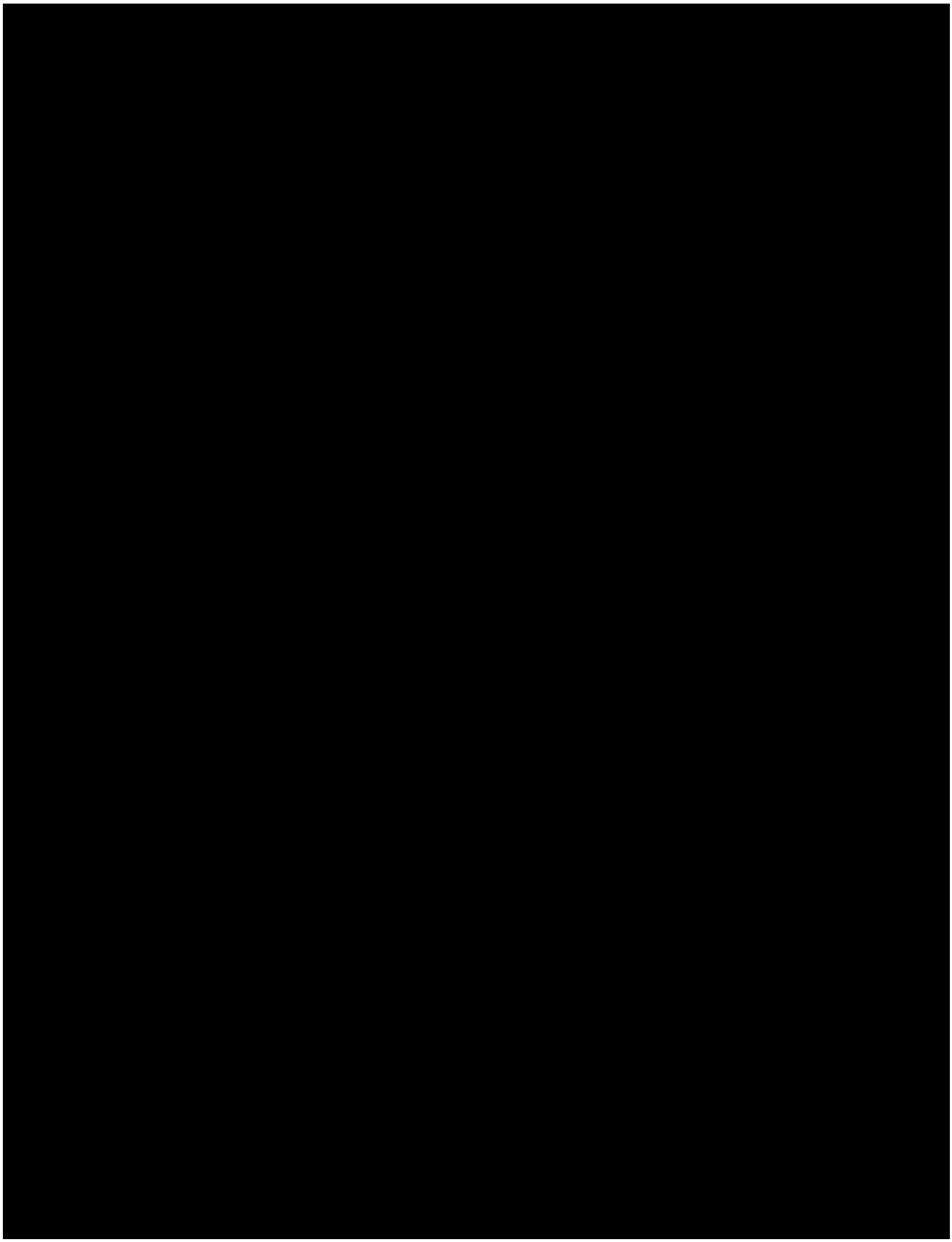

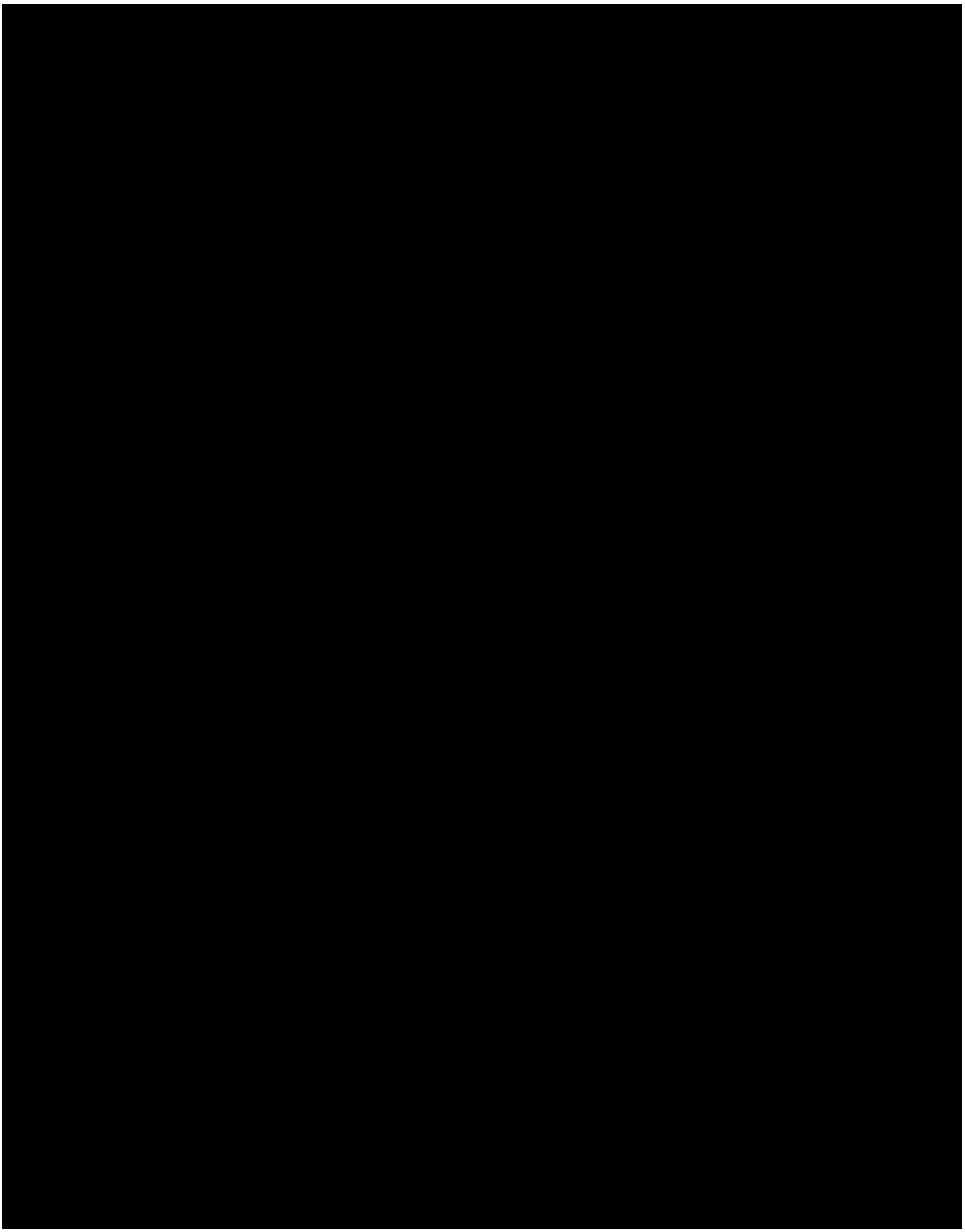

9.9 Additional Research

This protocol will include residual sample storage for additional research.

For All Sites:

Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, prohibited by local laws or regulations, or academic/institutional requirements. Where 1 or more of these exceptions occurs, participation in the additional research should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and/or collection.

[redacted]

Sample Collection and Storage

[redacted]

Samples kept for future research will be stored at the [redacted], or an independent, BMS-approved storage vendor.

[redacted]

Transfers of samples by research Sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual.

Table 9.9-1: Residual Sample Retention for Additional Research Schedule

[redacted]	Timepoints for which residual samples will be retained
	All
	All
	All
	All
	All
	All

9.10 Other Assessments

Not applicable.

9.11 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

10.1 Sample Size Determination

Approximately [redacted] participants will be assigned to receive MORAb-202 at a dose of 25 mg/m^2 every 3 weeks [redacted]

The sample size of [redacted] is calculated to assess preliminary safety and efficacy objectives [redacted]

[redacted]

[redacted]

All relevant data (eg, safety, efficacy, [redacted]) will guide subsequent development. [redacted]

[redacted]

[redacted]

A final analysis will be performed [redacted] Details of other analyses will be included in study statistical analysis plan (SAP) and will be finalized prior to database lock.

10.2 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 Treated	All participants who received at least 1 dose of study intervention. This will be the primary analysis set for safety objectives.
All Response Evaluable	All treated participants with baseline tumor assessment. This will be the primary analysis set for efficacy objectives.

[redacted]

10.3 Statistical Analyses

10.3.1 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.

[redacted]

The 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.

10.3.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary Analyses	
ORR by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 per investigator assessment	Objective Response Rate (ORR) is defined as the number of participants who achieve a best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR), based on investigator assessments (using RECIST 1.1), divided by the number of all response-evaluable participants. BOR is defined as the best response, as determined by the investigator, recorded between the date of first dose and the date of first objectively documented progression per RECIST 1.1. 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 (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or unable to determine [UTD]) will be presented. Estimates of response rate, along with its exact two-sided 95% confidence interval (CI) by Clopper and Pearson[70] will be presented.
Secondary/[redacted] Analyses	
PFS by RECIST 1.1 per investigator assessment	PFS is defined as the time between the date of first dose and the first date of documented progression, per investigator assessments (using RECIST 1.1), 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 first dose. The PFS function will be estimated using the KM product limit method and will be displayed graphically. A two-sided 95% CI for median PFS 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 Kaplan Meier estimate and corresponding CIs will be derived based on Greenwood's[71] formula for variance derivation and the log-log transformation applied on the survivor function[72].
DCR by RECIST 1.1 per investigator assessment	Disease Control Rate (DCR) is defined as the number of participants who achieve a BOR of confirmed CR, confirmed PR, or stable disease (SD), based on investigator assessments (using RECIST 1.1) divided by the number of all response-evaluable participants. Estimates of DCR, along with its exact two-sided 95% CI by Clopper and Pearson.
DoR by RECIST 1.1 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 1.1), 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.

[redacted]

10.3.3 Safety Analyses

Endpoint	Statistical Analysis Methods
Primary Analyses	
Safety	Incidence of AEs leading to study treatment discontinuation. Safety analysis will be performed in all treated participants. Descriptive statistics of AE incidence rate will be presented.
Secondary 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. All on-study AEs, drug-related AEs, SAEs, and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v5.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v5.0 criteria.

[redacted]

10.4 Interim Analyses

Not applicable.

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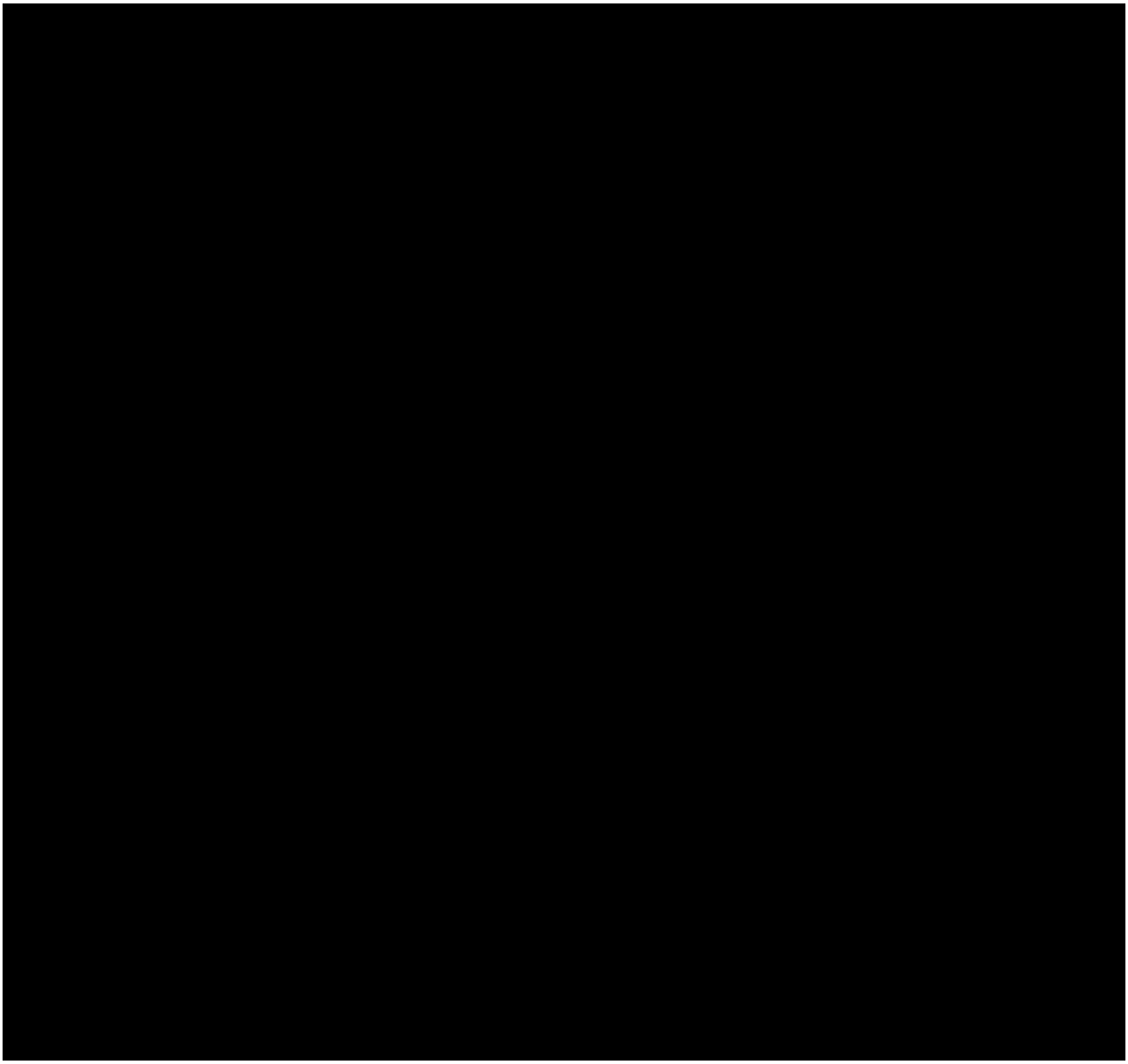

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS

Abbreviation	Term
AC	adenocarcinoma
[redacted]	[redacted]
ADC	Antibody-drug conjugate
AE	adverse event
AESI	adverse events of special interest
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
AT	Aminotransferase
AUC	area under the concentration-time curve
AxMP	Auxiliary Medicinal Product
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
[redacted]	[redacted]
BW	body weight
[redacted]	[redacted]
CI	confidence interval
CL	clearance
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRA	Clinical Research Associate
CrCL	creatinine clearance

Abbreviation	Term
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTAg	Clinical Trial Agreement
CTCAE v5.0	Common Terminology Criteria for Adverse Events version 5
[redacted]	
CYP	cytochrome P450
DCR	disease control rate
DCT	Decentralized Clinical Trial
DILI	drug-induced liver injury
DLCO	diffusing capacity of the lungs for carbon monoxide
DoR	duration of response
DVT	deep vein thrombosis
EBRT	external beam radiotherapy
[redacted]	[redacted]
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCOA	electronic Clinical Outcomes Assessments
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMT	epithelial-mesenchymal transition
[redacted]	[redacted]
EOS	end of study
EOT	end of treatment
[redacted]	[redacted]
E-R	exposure-response
ESMO	European Society for Medical Oncology
F2F	face-to-face

Abbreviation	Term
[redacted]	[redacted]
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FEV1	forced expiratory volume during first second of forced breath
[redacted]	[redacted]
FRα	a folate receptor alpha
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
Hgb	hemoglobin
HGS	high-grade serous
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
[redacted]	[redacted]
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC	Informed consent
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	Investigational Medicinal Product

Abbreviation	Term
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
KM	Kaplan Meier
LAM	lactational amenorrhea method
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCA	noncompartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NLR	neutrophil-to-lymphocyte ratio
NSCLC	non-small cell lung cancer
[redacted]	[redacted]
[redacted]	[redacted]
OR	objective response
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PDX	patient-derived xenograft
PE	physical examination
PET	positron emission tomography
PFS	progression-free survival
PFT	pulmonary function test
[redacted]	[redacted]
PK	pharmacokinetic
PO	per os (by mouth route of administration)
PR	partial response

Abbreviation	Term
[redacted]	[redacted]
PROC	platinum resistant ovarian cancer
PS	performance status
Q3W	every 3 weeks
QTc	corrected QT interval
QTcF	Fridericia corrected QTc
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RF	radiofrequency
RNA	ribonucleic acid
SAEs	serious adverse events
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	Safety Committee
SD	stable disease
SSC	Study Steering Committee
TEAE	treatment-emergent adverse event
TLC	total lung capacity
[redacted]	[redacted]
TME	tumor microenvironment
[redacted]	[redacted]
TRAE	treatment-related adverse event
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
V	volume of distribution of the central compartment
[redacted]	[redacted]
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 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, one or more of the following: (1) the rights, physical safety or mental integrity of one 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 Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union Directive 2001/20/EC; or
- European Regulation 536/2014 for clinical studies (if applicable),
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC
- and 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, also 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:

- IRB/IEC
- Regulatory authority(ies), if applicable by 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, also by the local Health Authority, must be sent to Bristol-Myers Squibb (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 course of 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 and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR 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 participant to inquire about the details of the study.

Obtain an ICF signed and personally dated by participant and by the person who conducted the informed consent discussion.

- Include a statement in participant's medical record that written informed consent was obtained before 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 participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

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 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 (as 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 CRF (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.
- Definitions of what constitutes source data can be found in systems that may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event (AE) tracking/reporting, protocol required assessments, and/or drug accountability records.
- 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 MORAb-202 (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: • 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 • nonstudy 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, as per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment 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 abnormalities that are reported or identified during the course of 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 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 noncompliance 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 TREATMENT

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

If	Then
Study treatments 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 treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors; eg, study treatments 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 treatments provided by BMS (or its vendors). Destruction of non-study treatments 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:

- 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 recruitment of participants by the investigator
- Discontinuation of further study intervention development

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 assure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare 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 as 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 their 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 time 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 BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon 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); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
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 BMS 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)

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 or electronic Clinical Outcomes Assessments (eCOA) to improve patient access, increase patient engagement and reduce both site and patient burden. For example, within the DCT platform TeleVisit, eCOAs and 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 and eCOAs 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 non-treatment 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 Table 2-3 in the protocol 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.

eCOA

This trial will deploy eCOA using provisions that allow participants to complete eCOAs at the research site or at home. This flexible, customizable, and easy to use system, helps to simplify instrument and survey completion for participants.

Preprogrammed completion windows, along with built-in reminders (with flexibility in the options, such as push notifications, SMS, email) ensure that eCOAs are completed at the right time in line with the protocol requirements, whilst also enabling some flexibility for participants to personalize alarm times within that window to suit their lifestyle.

Alerts to sites will be deployed based on incoming symptom data to ensure that potential safety concerns are flagged in a timely manner, prior to the next scheduled study visit. Alerts to sites have been configured based on specific study parameters to notify sites when participants have a drop in compliance with eCOA and enable follow-up with the participant to remedy any problems.

Data collected from participants via remote assessments will be collected electronically within purpose-built technology and will be monitored remotely by the Sponsor or designee representatives, where allowed by applicable country law and regulation. Survival follow-up visits using TeleVisits will be handled similarly to a traditional model, with the participant contacting study personnel.

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 in a clinical investigation participant administered study treatment that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

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 signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments 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 it 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 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 which 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 Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as 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 entry into 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 result 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 room 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 for the definition of potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 9.2.5 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 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 one 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 v5.0).

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 predefined 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 treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 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 designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile 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 facsimile transmission.

SAE Email Address: worldwide.safety@BMS.com

SAE Facsimile 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 Woman of Childbearing Potential 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 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman 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
- Premenopausal 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.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 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 in order 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 judgement 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 timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have decreased to a concentration that is no longer considered to be 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 IMP 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 where 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 where 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 where hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device.

• Intrauterine hormone-releasing system (IUS). (This method of contraception can only be used by WOCBP participants in studies where 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. Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.
• 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 treatment. 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. • 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, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational 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 treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP 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 .Sections 6.1 INCLUSION CRITERIA and 7.7.4 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 .Sections 6.1 INCLUSION CRITERIA and 7.7.4 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 where hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation 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 and Appendix 3.

APPENDIX 5 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 6 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 1.1) 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 5mm.

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 which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT/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 which 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 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 fluorodeoxyglucose (FDG)- positron emission tomography (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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = not evaluable

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

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = not evaluable.		

[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 [redacted].

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 increase in 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
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR

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**
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
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.		

[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 7 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.

APPENDIX 8 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 02, 06-Feb-2023

The main purpose of this Protocol Amendment is to make updates based on [redacted], investigator feedback, and updates to Sponsor guidelines.

Summary of Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Protocol Summary Protocol Summary Study Design Schema Section 5.1: Overall Design Figure 5.1-1: Study Design Schema Section 6.1: Inclusion Criteria	Updated the prior therapy requirements. Inclusion criteria 2)b) and 2)c) were noted as not applicable per Protocol Amendment 02 and new criteria 2)j) and 2)k) were added.	Expanded inclusion of prior therapy to include neoadjuvant and adjuvant therapy, and allow 1 additional line of systemic therapy to better reflect the actual patient population
Protocol Summary Section 5.2: Number of Participants	Updated: "Randomized participants who discontinue before receiving their first dose of MORAb-202 will be replaced" to "Additional participants will be randomized to account for participants who are randomized but discontinue before receiving their first dose of MORAb-202."	Updated for clarity.
Table 2-1: Screening Procedural Outline (CA116003) Section 6.4.1: Retesting During Screening or Lead-in Period	Updated pulmonary function tests (PFTs) to be conducted within 28 days prior to randomization and may be repeated during the screening period if necessary. Clarified that PFTs could be retested during the screening period.	Expanded time to perform PFTs from 14 to 28 days. Clarified that PFTs could be retested during the screening period if initially not within eligible parameters.
Table 2-1: Screening Procedural Outline (CA116003) Section 5.1: Overall Design	[redacted]	

Summary of Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA116003) [redacted]	Removed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing at screening.	Removed SARS-CoV-2 [redacted] optional sample collection in alignment with updated Sponsor guidance
Table 2-3: Follow-up Procedural Outline (CA116003)	Added the following text for pregnancy testing: "Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) to be performed every 4 weeks (± 1 week) through the contraceptive period of 7 months after the last dose of study treatment." Updated to include a pregnancy test at the survival follow-up visit.	Extended pregnancy testing to the end of the contraception period.
Section 3.1: Study Rationale	Updated "MORAb-202 has high affinity to FRα located on apical surfaces of epithelial cells" to "MORAb-202 has high affinity to FRα expressed on the membrane of tumor cells."	Corrected the text.
Table 4-1: Objectives, Endpoints and Estimands	Updated the estimands for the primary and key secondary objectives to clarify the evaluation criteria of the intercurrent events and the corresponding analysis strategy.	Aligned with the ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials from the guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017).
Section 5.1: Study Design [redacted] Section 10.1: Sample Size Determination	[redacted]	

Summary of Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1: Overall Design Section 5.4.3.2: Patient Voice Interviews Section 7.1.1: MORAb-202 Administration [redacted] Section 7.8: Continued Access to Study Intervention After the End of the Study Section 9.2.5: Pregnancy	Added text to refer to Section 7.8 wherever it was indicated that participants may have the potential to be treated with additional cycles of study therapy beyond 2 years, if the participant has confirmed clinical benefit. In Section 7.8, replaced the following text: "Since this is a dose-optimizing study, at the end of the study, BMS will not continue to provide BMS supplied study intervention to participants or investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study." with: "At the conclusion of the study, if the study intervention is not available as an approved treatment in the local country, participants who continue to demonstrate clinical benefit may be eligible to receive BMS-supplied study intervention, as specified in Section 7.1. If the study treatment is not available as an approved and available treatment, study intervention may be provided via an extension of the study, a rollover study requiring approval by the responsible Health Authority and ethics committee, or through another mechanism at the discretion of BMS."	Clarified treatment duration.
Section 6.1: Inclusion Criteria	[redacted] Noted inclusion criterion 2)i) as not applicable per Protocol Amendment 02 and added new criterion 2)n).	[redacted] is not an eligibility criterion.
Section 6.1: Inclusion Criteria Section 9.2.5: Pregnancy	Updated the timing for contraception use after discontinuation of study drug from 90 days to 7 months for women of childbearing potential, and from 90 days to 4 months for male participants: Noted inclusion criterion 4)a)v)(2) as not applicable per Protocol Amendment 02 and added new criterion 4)a)v)(3). Noted inclusion criterion 4)b)ii) as not applicable per Protocol Amendment 02 and added new criterion 4)b)vii). Noted inclusion criterion 4)b)iii) as not applicable per Protocol Amendment 02 and added new criterion 4)b)viii). Noted inclusion criterion 4)b)iv) as not applicable per Protocol Amendment 02 and added new criterion 4)b)ix). Noted inclusion criterion 4)b)v) as not applicable per Protocol Amendment 02 and added new criterion 4)b)x).	Extended the contraceptive period to the end of relative exposure of MORAb-202 (ie, 5 times the human half-life) plus 6 months for women of childbearing potential and plus 3 months for male participants, in line with Clinical Trial Facilitation Group and Safety Working Party recommendations.

Summary of Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2: Exclusion Criteria	Updated exclusion criterion for diffusing capacity of the lung for carbon monoxide (DLCO) from < 80% to < 70%. Noted exclusion criterion 1)b) as not applicable per Protocol Amendment 02 and added new criterion 1)r).	Provided flexibility in DLCO criteria, in alignment with forced expiratory volume during first second of forced breath and forced vital capacity criteria, to allow participants with mild impairment in DLCO at baseline to be included in the study.
	Updated the eligibility criteria for participants with a history of deep vein thrombosis (DVT) from having to have completed at least 4 weeks of anticoagulation prior to starting study treatment to having to have completed at least 2 weeks of anticoagulation: Noted exclusion criterion 1)o) as not applicable per Protocol Amendment 02 and added new criterion 1)s).	Increased the flexibility for participants with history of DVT.
	Removed "unless there are bone metastases" from the liver function exclusion criterion 3)a)iii)(2).	Corrected an error.
	Removed "unless there are bone metastases Removed alkaline phosphatase (ALP) from liver function exclusion criterion 3)a)iii)(2) and created separate criterion 3)a)iv.	Separated ALP criteria from liver function criteria for clarity.
Table 7.4.1-1: Recommended Dose Modifications and Management for MORAb-202 Treatment-related Adverse Events	Clarified that equivalent premedications to acetaminophen with/without diphenhydramine, as per local standard of care, could be used for infusion-related reactions of Grade 1 severity.	To align with global standards of care.
Section 8.2.1: Individual Discontinuation Criteria	Removed "administrative reasons" as a basis for an investigator to withdraw a participant from the study.	Clarified discontinuation criteria do not include administrative reasons by investigator.
Table 9.4.4-1: Clinical Laboratory Assessments	Added "or urea per local guidance" to the blood urea nitrogen assessment.	Updated to account for regional- or country-specific differences in assessment.
[redacted]	Added: [redacted]	Clarified the requirements for [redacted]

Summary of Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]	Removed "every 8 cycles" from the footnote (d) for [redacted] Day 1.	The timing of sample collection is every 4 cycles, which is stated in the within the table.
All	Minor formatting and editorial updates.	These changes are minor and, therefore, have not been summarized.

Overall Rationale for Protocol Amendment 01, 27-Jun-2022

The main purpose of this Protocol Amendment is to make updates based on a [redacted].

Summary of Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated contact number for the Medical Monitor.	A new contact number was provided.
	Added the European Union Drug Regulating Authorities Clinical Trials (EudraCT) number.	EudraCT number became available after finalization of the original protocol.
Section 5.1.1.1: Safety Committee	Included any death attributed to MORAb-202, as assessed by the Sponsor, as an event that would result in an enrollment hold of the related treatment arm. Added that the applicable Health Authority would be notified of any enrollment hold. Clarified that at the ad hoc Safety Committee meeting convened after an enrollment hold, the benefit/risk profile of the drug and the totality of the data would be re-evaluated by the Safety Committee to assess whether termination or resumption of the cohort/study is appropriate.	[redacted]
Table 7.1.1-1: Administration of MORAb-202	Added that participants should be observed for at least 60 minutes following the first infusion of MORAb-202. Added that for subsequent infusions, the observation period should be at least 30 minutes following each infusion, unless a reaction occurred during a previous cycle, in which case participants should continue to be observed for at least 60 minutes following the subsequent infusion. If there is no subsequent	Clarified the required observation period of MORAb-202 after the initial and subsequent administration of the drug given the possibility of infusion-related reactions, as requested by [redacted]

Summary of Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	reaction, then at least a 30-minute observation period should be used.	
Table 7.4.1-1: Recommended Dose Modifications and Management for MORAb-202 Treatment-related Adverse Events	[redacted]	[redacted]
All	Minor formatting and editorial updates.	These changes are minor and, therefore, have not been summarized.