Official Title of Study:

A Phase 2 Open-label, Two-cohort Study to Evaluate Patient Preference for Nivolumab + Relatlimab Fixed-dose Combination Subcutaneous versus Nivolumab + Relatlimab Fixed-dose Combination Intravenous and Nivolumab Subcutaneous versus Nivolumab Intravenous in Participants with Melanoma

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CLINICAL PROTOCOL CA2241044

A Phase 2 Open-label, Two-cohort Study to Evaluate Patient Preference for nivolumab + relatlimab Fixed-dose Combination Subcutaneous versus nivolumab + relatlimab Fixed-dose Combination Intravenous and nivolumab Subcutaneous versus nivolumab Intravenous in Participants with Melanoma

Compound: BMS-986213, BMS-986298, BMS-936558

Brief Title:

Patient Preference for Route of Administration with Intravenous Infusion Switch to Subcutaneous I-O Regimens in Melanoma

Protocol Amendment 01

Medical Monitor Name and Contact Information:

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

24-hr Emergency Telephone Number
USA: 1-866-470-2267
International: +1-248-844-7390

Sponsor Name and Legal Registered Address:

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

Bristol-Myers Squibb Services Unlimited Company

Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Ireland

REGULATORY AGENCY IDENTIFIER NUMBER(S)

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Protocol Amendment 01	24-May-2024	This amendment incorporates changes to be consistent with study's Pharmacy Manual, clarifying the methods for study drug administration. [redacted] Additionally, administrative changes including clarification regarding AE collection have been made including changes [redacted]
Original Protocol	29-Jun-2023	Not applicable.

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OVERALL RATIONALE FOR PROTOCOL AMENDMENT 01:

This amendment includes updates for alignment with the study Pharmacy Manual and minor language updates for clarity, including consistency with 01 EU amendment.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Regulatory Agency Identifier Number(s) Page	Added the Investigational New Drug (IND) numbers: IND 150904 (nivolumab subcutaneous) and IND 159987 (Nivo/Rela FDC SC). The EU Trial Number was corrected (removal of last 2 digits '00').	To be consistent with BMS standards. Corrections were made based on EU CTR guidance.
Section 2 Schedule of Activities Table 2-1: Screening Procedural Outline (Cohort 1 - Metastatic Melanoma)	Added AE collection to the procedures and in the notes clarified the timeframe of AE/SAE collection. [redacted]	To clarify that both AEs and SAEs are to be assessed and their timeframe of collection.
Section 2 Schedule of Activities Table 2-2: Screening Procedural Outline (Cohort 2 - Resected Melanoma)	In the notes column for AE/SAE Assessment: clarified that all AEs and SAEs will be collected and the timeframe of collection. In the notes column for Clinical Laboratory Assessment, language was added for local laboratory tests and information included on [redacted] and HIV viral testing, [redacted] to align with Cohort 1 Screening Table 2-1.	To clarify that both AEs and SAEs are to be assessed and to clarify the timeframe for collection. To align with Cohort 1 Screening viral Laboratory Assessments.
Section 2 Schedule of Activities Table 2-3: On-treatment Procedural Outline	In the notes column for AE and SAE Assessment: clarified that all AEs and SAEs will be collected and the timeframe of collection.	To clarify that both AEs and SAEs are to be assessed and to clarify the timeframe for collection.

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SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
(Cohort 1 - Metastatic Melanoma)		
Section 2 Schedule of Activities Table 2-4: On-treatment Procedural Outline (Cohort 2 - Resected Melanoma)	Safety assessment [redacted] In the notes column for AE and SAE Assessment: clarified that all AEs and SAEs will be collected and the timeframe of collection.	To align Cohort 2 Schedule of Activities Table 2-4 safety assessments with Cohort 1 Schedule of Activities Table 2-3 safety assessments. To clarify that both AEs and SAEs are to be assessed and to clarify the timeframe for collection.
Section 3.2 Background Section 3.3.1 Cohort 1 (nivolumab + relatlimab)	Deleted the mention of 'unmet medical need' for this study population.	To avoid misinterpretation with the other BMS 127 study.
Section 3.3.1: Cohort 1 (nivolumab + relatlimab)	Add the following text "regardless of PD-L1 expression" to the first paragraph in this section.	[redacted]

[redacted]

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SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 7.1.3 Subcutaneous Administration of nivolumab Combined with relatlimab Administration [redacted]	[redacted]	Instructions regarding administration are provided in the Pharmacy Manual.
Section 9.2.1 Period and Frequency for Collecting AE and SAE Information	This section was revised to clarify that the timeframe of AE and SAE collection (including if associated with confirmed or suspected SARS-CoV-2 infection) begins at the time of signing the informed consent.	To provide clarification of the timeframe for the start of AE/SAE collection.
Section 11 References	Latest versions of the Investigators Brochure's (IB) were added and/or updated, and a new reference for nivolumab (subcutaneous) IB was added.	To reflect latest versions and to align with EU submissions.
Appendix 8 Country Specific Requirements/ Differences	Deleted the mention of "Argentina".	Argentina is no longer a participating country.
Synopsis and throughout the document	Where applicable, the synopsis was updated for consistency in line with the above changes to the main body. In addition, minor formatting and typographical corrections were made to the document.	To improve overall readability, consistency.

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TABLE OF CONTENTS

TITLE PAGE....1
CLINICAL PROTOCOL CA2241044....1
DOCUMENT HISTORY....3
OVERALL RATIONALE FOR PROTOCOL AMENDMENT 01:....4
SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01....4
TABLE OF CONTENTS....7
1 PROTOCOL SUMMARY....11
2 SCHEDULE OF ACTIVITIES....26
3 INTRODUCTION....42
3.1 Study Rationale....43
3.2 Background....43
3.2.1 Relatlimab Mechanism of Action....44
3.2.2 Nivolumab Combined with relatlimab Pre-clinical Activity....45
3.2.3 Nivolumab Combined with relatlimab Clinical Activity....45
3.2.4 Nivolumab Combined with relatlimab Clinical Safety....47
3.2.5 Nivolumab Mechanism of Action....48
3.2.6 Nivolumab Clinical Activity....48
3.2.7 Nivolumab Clinical Safety....48
3.2.8 Recombinant Human Hyaluronidase PH20 Enzyme....49
3.2.9 Nonclinical Toxicity of Recombinant Human Hyaluronidase PH20....49
3.3 Benefit/Risk Assessment....50
3.3.1 Cohort 1 (nivolumab + relatlimab)....50
3.3.2 *Cohort 2 (nivolumab)....51*
3.3.3 General Considerations....51
4 OBJECTIVES AND ENDPOINTS....53
5 STUDY DESIGN....55
5.1 Overall Design....55
5.1.1 Screening Phase....56
5.1.2 Treatment Period....56
5.1.3 Follow-Up Period....56
5.1.4 Data Monitoring Committee and Other Committees....57
5.2 Number of Participants....57
5.3 End of Study Definition....57
5.4 Scientific Rationale for Study Design....58
[redacted]
5.4.2 Cohort 2: Resected Melanoma:....59
5.4.2.1 Rationale for Use of nivolumab....59
[redacted]
5.4.3 Rationale for Patient Preference Endpoints....60
[redacted]
5.5 Justification of Dose....61

Approved v2.0 930207750 2.0

5.5.1 Nivolumab Clinical Pharmacology Summary 61
[redacted] 61
5.5.3 Justification of nivolumab + relatlimab FDC IV Dose 62
[redacted] 62
5.5.5 Justification of nivolumab IV Dose 63
5.5.6 Justification of nivolumab SC Dose 63
6 STUDY POPULATION 65
6.1 Inclusion Criteria 65
6.1.1 Inclusion Criteria for Cohort 1 65
6.1.2 Inclusion Criteria for Cohort 2 67
6.2 Exclusion Criteria 69
6.2.1 Exclusion Criteria for Cohort 1 69
6.2.2 Exclusion Criteria for Cohort 2 72
6.3 Lifestyle Restrictions 75
6.4 Screen Failures 75
6.4.1 Re-testing During Screening 75
7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY 76
7.1 Study Interventions Administered 77
7.1.1 General Considerations 78
7.1.2 Intravenous Administration of nivolumab Combined with relatlimab Administration [redacted] *79*
7.1.3 Subcutaneous Administration of nivolumab Combined with relatlimab Administration [redacted] *79*
7.1.4 Intravenous Administration of nivolumab [redacted] *80*
7.1.5 Subcutaneous Administration of nivolumab with rHuPH20 [redacted] *80*
7.2 Assignment to Study Intervention 81
7.3 Blinding 81
7.4 Dosage Modification 82
7.4.1 Dose Delay Criteria for nivolumab and nivolumab + relatlimab FDC 82
[redacted] *95*
[redacted] *95*
7.4.4 Treatment of Related Infusion- and Injection-reactions 96
[redacted] *96*
7.4.4.2 Management of Local Infusion or Injection Site Reactions 97
7.4.4.3 Management of Needle Stick Injuries 97
7.5 Preparation/Handling/Storage/Accountability 97
7.6 Study Intervention Compliance 98
7.7 Concomitant Therapy 98
[redacted] *98*
7.7.2 Other Restrictions and Precautions 99
7.7.2.1 Imaging Restrictions and Precautions 99
[redacted] *100*
[redacted] *100*
7.7.4 Antiviral Therapy 100
7.8 Continued Access to Study Intervention After the End of the Study 101

Approved v2.0 930207750 2.0

8 DISCONTINUATION CRITERIA 101
8.1 Discontinuation of Study Intervention 101
[redacted] 103
8.3 Discontinuation From the Study 103
8.3.1 Individual Discontinuation Criteria 104
8.4 Lost to Follow-up 104
9 STUDY ASSESSMENTS AND PROCEDURES 105
9.1 Efficacy Surveillance 106
9.1.1 Imaging Assessment for the Study 106
9.1.2 Investigator Assessment of Recurrence/Progression 106
9.1.3 Clinical Outcome Assessments 106
9.1.3.1 Patient Experience Questionnaire (PEQ) and Patient Experience and Preference Questionnaire (PEPQ) 107
[redacted] *107*
9.2 Adverse Events 108
9.2.1 Period and Frequency for Collecting AE and SAE Information 108
9.2.2 Method of Detecting AEs and SAEs 109
9.2.3 Follow-up of AEs and SAEs 109
9.2.4 Regulatory Reporting Requirements for SAEs 110
9.2.5 Pregnancy 110
9.2.6 Laboratory Test Result Abnormalities 111
9.2.7 Potential Drug-induced Liver Injury 111
9.2.8 Other Safety Considerations 111
9.3 Overdose 111
9.4 Safety 112
9.4.1 Physical Examinations 112
9.4.2 Vital Signs 112
[redacted] *112*
9.4.4 Clinical Safety Laboratory Assessments 112
9.4.5 Imaging/Other Safety Assessment 113
9.5 Pharmacokinetics 113
9.6 Immunogenicity Assessments 113
9.7 Biomarkers 113
9.7.1 Germline Genetics 113
9.7.2 Other Biomarkers 113
9.8 Optional Future Research 114
10 STATISTICAL CONSIDERATIONS 114
10.1 Statistical Hypotheses 114
10.2 Sample Size Determination 114
10.3 Analysis Sets 115
10.4 Statistical Analyses 115
10.4.1 General Considerations 116
10.4.2 Primary Endpoint(s) 116
10.4.3 Secondary Endpoint(s) 116
[redacted] *117*
10.4.5 Other Safety Analyses 117

Approved v2.0 930207750 2.0

10.4.6 Other Analyses 117
[redacted] [redacted] 117
11 REFERENCES 118

12 APPENDICES 121
APPENDIX 1 ABBREVIATIONS 122
APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS 124
APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING 135
APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION 139
[redacted] 143
APPENDIX 6 ECOG PERFORMANCE STATUS SCALE AND CONVERSION FORM 153
APPENDIX 7 AJCC MELANOMA STAGING (CANCER STAGING MANUAL 8TH EDITION) 154
APPENDIX 8 COUNTRY SPECIFIC REQUIREMENTS/DIFFERENCES 155
APPENDIX 9 PRODUCT QUALITY ISSUES 156

Approved v2.0 930207750 2.0

1 PROTOCOL SUMMARY

Protocol Title:

A Phase 2, Open-label, Two-cohort Study to Evaluate Patient Preference for nivolumab + relatlimab Fixed-dose Combination Subcutaneous versus nivolumab + relatlimab Fixed-dose Combination Intravenous and nivolumab Subcutaneous versus nivolumab Intravenous in Participants with Melanoma

Brief Title:

Patient Preference for Route of Administration with Intravenous Infusion Switch to Subcutaneous I-O Regimens in Melanoma

Rationale:

With the growing cancer patient population and increasing burden on healthcare resources, there is a need for more efficient treatment options, such as alternative routes of administration. [redacted] CA2241044 will address this important data question by assessing the patient's preference for nivolumab SC or nivolumab + relatlimab FDC SC and provide patient experience data by route of administration. The study will also generate data to further characterize the safety profile of immuno-oncology (IO) therapy in patients switching the route of administration from IV to SC.

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Objectives and Endpoints:

Objectives	Endpoints
Primary Cohort 1: Metastatic melanoma • To evaluate participants' preference for route of administration upon switching from nivolumab + relatlimab FDC IV to nivolumab + relatlimab FDC SC Cohort 2: Resected melanoma • To evaluate participants' preference for route of administration upon switching from nivolumab IV to nivolumab SC	**Primary** Cohort 1: Metastatic melanoma • Proportion of evaluable participants that prefer SC route of administration using the Patient Experience and Preference Questionnaire (Question 7) after Cycle 4 Day 1 dose Cohort 2: Resected melanoma • Proportion of evaluable participants that prefer SC route of administration using the Patient Experience and Preference Questionnaire (Question 7) after Cycle 4 Day 1 dose
Secondary Cohort 1: Metastatic melanoma • To assess the safety and tolerability of nivolumab + relatlimab FDC IV and nivolumab + relatlimab FDC SC Cohort 2: Resected melanoma • To assess the safety and tolerability of nivolumab IV and nivolumab SC	**Secondary** Cohort 1: Metastatic melanoma • AEs, SAEs, treatment-related AEs, AEs leading to discontinuation, IMAEs, OESIs, injection/infusion related AEs, deaths and laboratory abnormalities Cohort 2: Resected melanoma • AEs, SAEs, treatment-related AEs, AEs leading to discontinuation, IMAEs, OESIs, injection/infusion related AEs, deaths and laboratory abnormalities
[redacted]	

Abbreviations: AE, adverse event; FDC, fixed-dose combination; [redacted]; IMAEs, immune-mediated adverse events; IV, intravenous; OESIs, other events of special interest; SAE, serious adverse event; SC, subcutaneous.

Overall Design:

CA2241044 is a Phase 2, open-label, two-cohort study to evaluate patient preference for nivolumab SC or nivolumab + relatlimab FDC SC versus the IV formulations in participants with previously untreated Stage III (unresectable) or Stage IV (metastatic) melanoma (Cohort 1) and those with completely resected Stage IIB/C, III, or IV (Cohort 2).

In Cohort 1, [redacted] adult participants with previously untreated unresectable (Stage III) or metastatic (Stage IV) melanoma will be treated with nivolumab + relatlimab FDC IV for 2 treatment cycles followed by nivolumab + relatlimab FDC SC until disease progression, unacceptable toxicity,

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death, end of study, withdrawal of consent, or a maximum treatment duration of 2 years, whichever comes first.

In Cohort 2, [redacted] adult participants with completely resected Stage IIB/C, III, or IV melanoma will be treated with nivolumab IV for 2 treatment cycles followed by nivolumab SC until disease recurrence, unacceptable toxicity, death, end of study, withdrawal of consent, or a maximum treatment duration of 1 year, whichever comes first.

Number of Participants:

Approximately [redacted] participants will be enrolled in two cohorts of [redacted] treated participants each.

- Cohort 1: [redacted] treated participants with previously untreated Stage III (unresectable) or Stage IV (metastatic) melanoma [redacted]
- Cohort 2: [redacted] treated participants with completely resected Stage IIB/C, III, or Stage IV (≤ 12 weeks post resection) [redacted]

Study Population:

Inclusion Criteria for Cohort 1

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

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1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board /Independent Ethics Committee approved written informed consent form (ICF) in accordance with regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

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

2) Type of Participant and Target Disease Characteristics

a) Participants must have an Eastern Cooperative Oncology Group performance status (ECOG PS) score of ≤ 1.

b) Participants must have histologically confirmed Stage III (unresectable) or Stage IV (metastatic) melanoma, per the American Joint Committee on Cancer (AJCC) staging system (8th edition).

c) Participants must be treatment-naïve (ie, no prior systemic anticancer therapy) for unresectable or metastatic melanoma.

[redacted]

d) Participants are eligible regardless of BRAF status. Participants with known BRAF V600 mutation status, or who consent to BRAF V600 mutation testing per local institutional standards during the Screening Period with the sample collected within 3 months prior to treatment assignment must report BRAF status.

3) Age of Participant

Participants must be ≥ 18 years of age at the time of consent.

4) Reproductive Status

[redacted]

a) Female Participants:

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

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

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ii) WOCBP must have a negative highly sensitive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study intervention. An extension up to 72 hours prior to start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

[redacted]

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

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

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

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, during the intervention period and for the duration of treatment with nivolumab and relatlimab plus 5 half-lives of study treatment for [redacted] post-treatment completion and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

[redacted]

Inclusion Criteria for Cohort 2

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

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board /Independent Ethics Committee approved written informed consent form (ICF) in accordance with regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

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

2) Type of Participant and Target Disease Characteristics

a) Participants must have an (ECOG-PS) score of ≤ 1.

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b) Participants must be eligible for adjuvant therapy for melanoma.
   i) All participants must have completed surgical resection of Stage IIB/C, IIIA (> 1 mm tumor in lymph node)/B/C/D or stage IV (AJCC Cancer Staging, 8th edition) melanoma. All melanomas, except ocular and mucosal melanomas, are allowed regardless of primary site of disease.
   ii) Participants with complete melanoma resection within 12 weeks of treatment assignment. Participants must be surgically rendered free of disease with negative margins on resected specimens. Complete resection must be documented on surgical and pathology report. For central nervous system (CNS) lesion(s), documentation indicating that there has been complete resection of CNS lesion(s) will suffice as confirmation of negative margins.

[redacted]

c) All participants must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to treatment assignment. Imaging studies must include computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, pelvis, and all known sites of resected disease, and brain MRI or CT with contrast (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions).

3) Age of Participant

Participants must be ≥ 18 years of age at the time of consent.

4) Reproductive Status

[redacted]

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

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

   ii) WOCBP must have a negative highly sensitive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study intervention. An extension up to 72 hours prior to start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

[redacted]

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[redacted]

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

- WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).
  i) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:
     (1) Is not a WOCBP

     OR

     (2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, during the intervention period and for the duration of treatment with nivolumab and relatlimab plus 5 half-lives of study treatment for [redacted] post-treatment completion and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

[redacted]

Exclusion Criteria for Cohort 1

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

1) Medical Conditions

a) Participants must not have active brain metastases or leptomeningeal metastases.

[redacted]

b) Participants with brain disease treated with whole brain radiation are not eligible.
c) Participants must not have ocular or mucosal melanoma.
d) Participants must not have an active, known, or suspected autoimmune disease.
e) Participants may enroll with the following conditions:

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i) Type 1 diabetes mellitus.
ii) Hypothyroidism only requiring hormone replacement therapy.
iii) Skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment.
iv) Conditions not expected to recur in the absence of an external trigger.

f) Participants must not have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within [redacted] days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

g) Participants must not have a concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to treatment assignment (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 that have undergone definitive treatment at any time are also eligible.

h) Participants must not have known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome defining opportunistic infection within the last year, or a current CD4 count < 350 cells/uL. 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.
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. (Refer to Appendix 8.)

i) Participants must not have any serious or uncontrolled medical disorder that, in the opinion of the investigator in consultation with the BMS Medical Monitor, may increase the risk associated with study participation or study treatment administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.

j) Participants must not have previous SARS-CoV-2 infection either suspected or confirmed within 4 weeks prior to screening. Acute symptoms must have resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

k) Participant has not recovered adequately from toxicity and/or complications from surgery prior to starting study treatment

l) Participants must not have a history of myocarditis, regardless of etiology.

[redacted]

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[redacted]

2) Reproductive Status

a) Women who are breastfeeding.

b) Women who are pregnant.

3) Prior/Concomitant Therapy

a) Participant must not have had prior treatment with an anti-PD-1 (except if given as adjuvant or neoadjuvant therapy for melanoma), anti- programmed death-ligand 1 (PD-L1), anti-programmed death-ligand 2 (PD-L2), anti-CTLA-4 antibody (except if given as adjuvant or neoadjuvant therapy for melanoma), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways (except for interferon given as adjuvant or neoadjuvant therapy for melanoma) within 6 months prior to start of study treatment

b) Participant must not have had prior treatment with relatlimab or any other lymphocyte activation gene-3 targeted agents.

c) Inability to comply with restrictions and prohibited treatments.

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

e) [redacted]. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study treatment.

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

g) Participants currently in other interventional trials, including those for coronavirus disease 2019 (COVID-19), may not participate in BMS clinical trials until the protocol specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, treatment assignment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the investigator and the Medical Monitor.

[redacted]

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[redacted]

5) Allergies and Adverse Drug Reactions

a) Participants must not have a history of allergy or hypersensitivity to study intervention components.

6) Other Exclusion Criteria

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

Exclusion Criteria for Cohort 2

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

1) Medical Conditions

a) Participants must not have active brain metastases or leptomeningeal metastases. [redacted]

b) Participants with brain disease treated with whole brain radiation are not eligible.

c) Participants must not have ocular or mucosal melanoma.

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d) Participants must not have an active, known, or suspected autoimmune disease.

e) Participants may enroll with the following conditions:
   i) Type 1 diabetes mellitus.
   ii) Hypothyroidism only requiring hormone replacement therapy.
   iii) Skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment.
   iv) Conditions not expected to recur in the absence of an external trigger.

f) Participants must not have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within [redacted] days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

g) Participants must not have a concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to treatment assignment (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 that have undergone definitive treatment at any time are also eligible.

h) Participants must not have known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome defining opportunistic infection within the last year, or a current CD4 count < 350 cells/uL. 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.
   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. (Refer to Appendix 8.)

i) Participants must not have any serious or uncontrolled medical disorder that, in the opinion of the investigator in consultation with the BMS Medical Monitor, may increase the risk associated with study participation or study treatment administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.

j) Participants must not have previous SARS-CoV-2 infection either suspected or confirmed within 4 weeks prior to screening. Acute symptoms must have resolved and based on

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investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

2) Reproductive Status

a) Women who are breastfeeding.

b) Women who are pregnant.

3) Prior/Concomitant Therapy

a) Participant must not have had prior treatment with an anti-PD-1 (except if given as adjuvant or neoadjuvant therapy for melanoma), anti-programmed death-ligand 1 (PD-L1), anti-programmed death-ligand 2 (PD-L2), anti-CTLA-4 antibody (except if given as adjuvant or neoadjuvant therapy for melanoma), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways (except for interferon given as adjuvant or neoadjuvant therapy for melanoma)

b) Participant must not have had prior treatment with relatlimab or any other lymphocyte activation gene-3 targeted agents.

c) Inability to comply with restriction and prohibited treatments.

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

e) [redacted]. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study treatment.

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

g) Participants currently in other interventional trials, including those for coronavirus disease 2019 (COVID-19), may not participate in BMS clinical trials until the protocol specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, treatment assignment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the investigator and the Medical Monitor.

[redacted]

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[redacted]

5) Allergies and Adverse Drug Reactions

Participants must not have a history of allergy or hypersensitivity to study intervention components.

6) Participants must not have active brain metastases or leptomeningeal metastases.

7) Prior immunotherapy treatments for any prior malignancies are not permitted (such as, but not limited to anti-PD-1, anti-PD-L1, PD-L2, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways).

8) Other Exclusion Criteria

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

Intervention Groups and Duration:

Approximately [redacted] participants will be enrolled in two cohorts of [redacted] treated participants each.

Cohort 1: [redacted] treated participants in Cohort 1 (metastatic melanoma) [redacted];

Participants will receive two cycles of treatment with nivolumab (480 mg) and relatlimab (160mg) FDC (nivolumab + relatlimab FDC IV). Starting with Cycle 3, participants will receive nivolumab (960 mg) and relatlimab (320 mg) FDC and rHuPH20 SC (nivolumab + relatlimab FDC SC). Participants will continue to receive study treatment until investigator-determined disease progression, unacceptable toxicity, withdrawal of consent, lost to follow-up, completion of up to 2 years (104 weeks) of treatment, death, or the end of study, whichever occurs first.

Participants will be permitted to continue study treatment beyond disease progression, as determined by investigator, provided that the treating investigator considers that the participant may experience clinical benefit with continued treatment, and the participant is tolerating study treatment with a stable or improved performance and clinical status [redacted]

Cohort 2: [redacted] treated participants in Cohort 2 (resected melanoma) [redacted]

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Participants will receive two cycles of treatment with nivolumab (480 mg) (nivolumab IV). Starting with Cycle 3, participants will receive nivolumab (1200 mg) and rHuPH20 SC (nivolumab SC). Participants will continue to receive study treatment until investigator-determined disease recurrence, unacceptable toxicity, withdrawal of consent, lost to follow-up, completion of up to 1 year (52 weeks) of treatment, death, or the end of study, whichever occurs first.

Study Intervention:

Study Intervention for CA2241044		
Intervention Name	**Unit Dose Strength(s)**	**IP/IMP/Non IP/ Non IMP/AxMP**
nivolumab + relatlimab FDC IV	[redacted]	IMP
nivolumab + relatlimab FDC SC		IMP
nivolumab IV	nivolumab (10 mg/mL)	IMP
nivolumab SC	[redacted]	IMP

Abbreviations: AxMP, Auxiliary Medicinal Product; FDC, Fixed-dose combination; IMP, Investigational Medicinal Product; IP, Investigational Product; IV, Intravenous; Non-IMP, Non-investigational Medicinal Product; Non-IP, Non-investigational Product; SC, Subcutaneous.

Statistical Methods:

All analyses will be descriptive in nature. Descriptive statistics including n (the corresponding sample size), means, medians, standard deviations, minimum, and maximum will be calculated for continuous variables, and categorical data will be summarized using frequency counts and percentages. [redacted]

Data Monitoring Committee: No

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

Brief Summary:

With the advancement in I-O therapies, cancer patients are surviving longer while receiving long-term maintenance therapy. Currently, immunotherapies are administered by IV infusion. The option of treatment administered by subcutaneous injection presents multiple potential benefits, including shorter administration times (less than 5 minutes) as compared with IV infusion (30 to 60 minutes), improved patient quality of life as well as efficiencies in healthcare resource utilization.

Immunotherapy has become the standard of care for the treatment of melanoma.

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The pivotal Phase 2/3 CA224047 study demonstrated clinical benefit with nivolumab 480 mg + relatlimab 160 mg IV FDC Q4W in participants with previously untreated metastatic or unresectable melanoma and has received FDA approval for the treatment of these patients.

Similarly, in Stage III/IV completely resected melanoma, adjuvant nivolumab is an established standard of care that is recognized in guidelines globally. In CA209238, adjuvant nivolumab demonstrated clinical benefit with an acceptable safety profile in patients with resected Stage IIIB/C or Stage IV melanoma (AJCC 7th edition). Recently, the Phase 3 CA20976K study demonstrated statistically significant and clinically meaningful RFS benefit with adjuvant nivolumab versus placebo in patients with completely resected Stage IIB or IIC melanoma.

The current study, CA2241044, is a Phase 2, open-label study, to evaluate patient preference of IV vs SC immunotherapy in adult participants with previously untreated metastatic or unresectable melanoma (Cohort 1) or resectable melanoma (Cohort 2).

Participants in Cohort 1 will receive nivolumab + relatlimab FDC IV for 2 treatment cycles followed by nivolumab + relatlimab FDC SC until investigator-assessed disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent for study treatment, lost to follow-up, death, study termination by the Sponsor, or up to a maximum of 26 cycles or 2 years, whichever comes first. For this cohort, consideration may be given to optional retreatment post progression after discussion between the Investigator and Sponsor.

Participants in Cohort 2 will receive nivolumab IV for 2 treatment cycles followed by nivolumab SC until investigator-assessed disease recurrence per RECIST v1.1, unacceptable toxicity, withdrawal of consent for study treatment, lost to follow-up, death, study termination by the Sponsor, or up to a maximum of 13 cycles or 1 year, whichever comes first.

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2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (Cohort 1 – Metastatic Melanoma)

Procedure	Screening (Day -28 to Day -1)	Notes[a] All windows are based on calendar days
Eligibility Assessments		See Section 6
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed; IRB/IEC-approved informed consent must be obtained prior to performing any screening procedures. The study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from Interactive Response Technology (IRT).
Enroll in IRT	X	Register in IRT system to obtain participant number.
Inclusion/Exclusion Criteria	X	Assessed at screening and must be confirmed prior to treatment assignment
Demography and Participant Characteristics	X	For US only. See Appendix 8 for further information.
Medical History	X	All medical history relevant to disease under study. Include findings from physical examination.
Baseline Tumor Assessments		
Body Imaging	X	[redacted]
Brain Imaging	X	

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Table 2-1: Screening Procedural Outline (Cohort 1 – Metastatic Melanoma)

Procedure	Screening (Day -28 to Day -1)	Notes[a] All windows are based on calendar days
Safety Assessments		See Section 9.4
Physical Examination, Measurements, Vital signs, and ECOG PS	X	Complete physical exam including height, weight, body mass index, ECOG PS, respiratory rate, seated blood pressure and heart rate, and body temperature. Must be collected within [redacted] days prior to treatment assignment. If the screening physical examination is within [redacted] hours prior to Cycle 1 Day 1, then a single exam may count as both the screening and predose evaluation. Any findings during the Physical Examination will be recorded as medical history in the participant's medical records and on the appropriate CRF.
Assessment of Signs and Symptoms	X	Within [redacted] days prior to treatment assignment.
Prior Medications	X	Prior medications will include medications taken within [redacted] days prior to treatment assignment. Document live/attenuated vaccine use if within 30 days prior to first study treatment. (Use of live/attenuated vaccine within 30 days prior to first study visit is prohibited.) See Section 7.7.
AE/SAE Assessment	X	AEs/SAEs will be graded according to the NCI-CTCAE version 5.0. All AEs and SAEs must be collected from the time of signing the informed consent. Record at each visit. Collect continuously throughout the treatment period and for a minimum of [redacted] days following discontinuation of study treatment. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection must be collected from the time of signing the informed consent. For AE/SAE monitoring on-study during the treatment period, please refer to Table 2-3. For participants assigned to treatment and never treated with study drug, collect SAEs for 30 days from the date of treatment assignment.
[redacted]		

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Table 2-1: Screening Procedural Outline (Cohort 1 – Metastatic Melanoma)

Procedure	Screening (Day -28 to Day -1)	Notes[a] All windows are based on calendar days
[redacted]		
Laboratory Tests		See Section 9.4.4.
Clinical Laboratory Assessments	X	On-site/local laboratory tests must be performed within [redacted] days prior to treatment assignment. [redacted] See Section 9.4.4 for list of laboratory tests to conduct.
[redacted]		
Pregnancy Test (WOCBP Only)	X	Negative highly sensitive serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) to be done at screening visit and repeated within 24 hours prior to first dose of study treatment. Results of the test should be reported by the study site to the sponsor in a timely manner.

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Table 2-1: Screening Procedural Outline (Cohort 1 – Metastatic Melanoma)

Procedure	Screening (Day -28 to Day -1)	Notes[a] All windows are based on calendar days
FSH	X	Females under the age of 55 years must have a serum FSH level > 40 mIU/mL to confirm menopause. If not confirmed, protocol pregnancy testing requirements must be followed. See Appendix 4.

Abbreviations: AE, adverse event; [redacted]; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; FSH, follicle-stimulating hormone; HIV, human immunodeficiency virus; IEC, Independent Ethics Committee; IRB, Institutional Review Board; [redacted]; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SAE, serious adverse event; [redacted]; WOCBP, women of childbearing potential.

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

Approved v2.0 930207750 2.0

Table 2-2: Screening Procedural Outline (Cohort 2 – Resected Melanoma)

Procedure	Screening	Notes[a] **All windows are based on calendar days.**
Eligibility Assessments		See Section 6
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed; IRB/IEC-approved informed consent must be obtained prior to performing any screening procedures. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Enroll in IRT	X	Register in IRT system to obtain participant number.
Inclusion/Exclusion Criteria	X	Assessed at screening and must be confirmed prior to treatment assignment
Demography and Participant Characteristics	X	For US only. See Appendix 8 for further information.
Medical History	X	All medical history relevant to the disease under study. Include findings from physical examination.
Baseline Tumor Assessments		
Review of Pathology Report	X	Confirm negative margins prior to treatment assignment and file as source document by site.
Body Imaging	X	[redacted]
Brain Imaging	X	
Safety Assessments		See Section 9.4
Complete Physical Examination, Measurements, Vital signs, Performance Status,	X	Complete physical exam including height, weight, body mass index, ECOG PS, respiratory rate, seated blood pressure and heart rate, and body temperature. Must be collected within [redacted] days prior to treatment assignment.

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Table 2-2: Screening Procedural Outline (Cohort 2 – Resected Melanoma)

Procedure	Screening	Notes[a] **All windows are based on calendar days.**
		If the screening physical examination is within [redacted] hours prior to Cycle 1 Day 1, then a single exam may count as both the screening and predose evaluation. Any findings during the Physical Examination will be recorded as medical history in the participant's medical records and on the appropriate CRF.
Assessment of Signs and Symptoms		Within [redacted] days prior to treatment assignment
Prior Medications	X	Prior medications will include medication taken within [redacted] days prior to treatment assignment. Document live/attenuated vaccine use if within 30 days prior to first study treatment. (Use of live/attenuated vaccine within 30 days prior to the first study treatment is prohibited) See Section 7.7
[redacted]		
AE/SAE Assessment	X	AEs/SAEs will be graded according to the NCI-CTCAE version 5.0. All AEs and SAEs must be collected from the time of signing the informed consent. Record at each visit. Collect continuously throughout the treatment period and for a minimum of [redacted] days following discontinuation of study treatment. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection must be collected from the time of signing the informed consent. For AE/SAE monitoring on-study during the treatment period, please refer to Table 2-4. For participants assigned to treatment and never treated with study drug, collect SAEs for 30 days from the date of treatment assignment.
Laboratory Tests		
Clinical Laboratory Assessments	X	On-site/local laboratory tests must be performed within [redacted] days prior to treatment assignment. [redacted]

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Table 2-2: Screening Procedural Outline (Cohort 2 – Resected Melanoma)

Procedure	Screening	Notes[a] **All windows are based on calendar days.**
		[redacted] - [redacted]. For HIV: testing at sites where locally mandated. [redacted] See Section 9.4.4 for list of laboratory tests to conduct.
Pregnancy Test (WOCBP)	X	Negative highly sensitive serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG) to be done at screening visit and repeated within 24 hours prior to first dose of study treatment. Results of the test should be reported by the study site to the sponsor in a timely manner.
FSH	X	Females under the age of 55 years must have a serum FSH level > 40 mIU/mL to confirm menopause. If not confirmed, protocol pregnancy testing requirements must be followed. See Appendix 4.

Abbreviations: AE, adverse event; [redacted]; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; IEC, Independent Ethics Committee; IRB, Institutional Review Board; [redacted]; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of child-bearing potential.

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

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Table 2-3: On-treatment Procedural Outline (Cohort 1 – Metastatic Melanoma)

Procedure	Intravenous Treatment	Subcutaneous Treatment	Notes[a,b] **Cycle Duration = 4 weeks/28 days** **All windows based on calendar day**
Study Treatment			See Section 7.1
Dispense Study Treatment	X	X	First drug to be administered within 3 calendar days following treatment assignment, subsequent doses can be administered within 3 days before or after scheduled date if necessary (every 28 days ± 3 days). Route of administration will switch from IV to SC starting at **Cycle 3, Day 1**. Treatment will continue until progression, unacceptable toxicity, withdrawal of consent, lost to follow-up, death, study termination by the Sponsor, or after a maximum treatment duration of up to 2 years (26 cycles) from first dose. See treatment details in Section 7
Safety Assessments			See Section 9.4
[redacted]			
Targeted Physical Examination, Measurements, and Vital Signs[c]	X*	X	Weight, seated blood pressure, respiratory rate, heart rate, and body temperature within 3 days prior to each dosing *Targeted physical exam not required on Cycle 1 Day 1 if a full physical exam was completed within 3 days of first dose.
Performance Status[c]	X	X	ECOG PS, See Appendix 6.
AE and SAE Assessment	Continuous		AEs/SAEs will be graded according to the NCI-CTCAE version 5.0. AEs/SAEs will be graded according to the NCI-CTCAE version 5.0.

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Table 2-3: On-treatment Procedural Outline (Cohort 1 – Metastatic Melanoma)

Procedure	Intravenous Treatment	Subcutaneous Treatment	Notes[a,b] **Cycle Duration = 4 weeks/28 days** **All windows based on calendar day**
			All AEs and SAEs must be collected from the time of signing the informed consent. Record at each visit. Collect continuously throughout the treatment period and for a minimum of [redacted] days following discontinuation of study treatment. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection must be collected from the time of signing the informed consent. For AE/SAE monitoring on-study during the treatment period, please refer to Table 2-3. For participants assigned to treatment and never treated with study drug, collect SAEs for 30 days from the date of treatment assignment.
Concomitant Medications	Continuous		Concomitant medications will include medications taken from treatment assignment and throughout treatment phase. Record at each visit. See Section 7.7.
Report of Product Complaints	Continuously		By site
Laboratory Tests			See Section 9.4.4
Pregnancy Test (WOCBP)	X*	X^	Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG); a negative pregnancy test should be documented within 1 day prior to administration of first dose of study treatment. For Norway, see Appendix 8 for specific requirements. *Pregnancy test not required to be repeated on Cycle 1 Day 1 if completed within 24 hours of first dose (during screening). ^For subsequent cycles, a negative pregnancy test should be documented within 3 days prior to dosing.
Clinical Laboratory Assessments[c]	X	X	Laboratory testing should be performed within 3 days prior to each dose. For the first treatment visit, labs need not be repeated if they were performed within 3 days and the results are available and have been reviewed for eligibility. Refer to Section 9.4.4 for the list of laboratory tests to be conducted.

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Table 2-3: On-treatment Procedural Outline (Cohort 1 – Metastatic Melanoma)

Procedure	Intravenous Treatment	Subcutaneous Treatment	Notes[b] Cycle Duration = 4 weeks/28 days All windows based on calendar day
Efficacy Surveillance			See Section 9.1
Imaging Assessments	X	X	
Assessment of Progression	X	X	assess and report disease progression per local guidelines. The timepoint of disease progression should be reported on the eCRF based on the investigator's assessment using RECIST v1.1 criteria to document any disease progression. Documentation of progression should be provided for source verification
Clinical Outcomes Assessments			
PEQ	X		
PEPQ		X	To be completed immediately after treatment administration on **Cycle 4 Day 1** (no greater than 24 hours post dose). See Section 9.1.3.1

Abbreviations: AE, adverse event; ; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; hCG, human chorionic gonadotropin; ; IMAE, immune-mediated adverse event; IV, intravenous; ; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PEPQ, Patient Experience and Preference Questionnaire; PEQ, Patient Experience Questionnaire; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SC, subcutaneous; WOCBP, women of child-bearing potential.

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

[c] Screening assessments performed within 3 days of first dose are not required to be repeated at Cycle 1 Day 1.

Approved v2.0 930207750 2.0

Table 2-4: On-treatment Procedural Outline (Cohort 2 – Resected Melanoma)

Procedure	Intravenous Treatment	Subcutaneous Treatment	Notes[a,b] Cycle duration = 4 weeks
Study Treatment			See Section 7.1
Dispense Study Treatment	X	X	First drug to be administered within 3 calendar days following treatment assignment, subsequent doses can be administered within 3 days before or after scheduled date if necessary (every 28 days ± 3 days). Route of administration will switch from IV to SC starting at Cycle 3, Day 1. Treatment will continue until recurrence, unacceptable toxicity, withdrawal of consent, lost to follow-up, death, study termination by the Sponsor, or after a maximum duration of 1 year from first dose (maximum of 13 doses), whichever occurs first. See treatment details in Section 7
Safety Assessment			

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Table 2-4: On-treatment Procedural Outline (Cohort 2 – Resected Melanoma)

Procedure	Intravenous Treatment	Subcutaneous Treatment	Notes[a,b]
Targeted Physical Examination, Measurements, and Vital Signs[c]	X*	X	Weight, seated blood pressure, respiratory rate, heart rate, and body temperature within 3 days prior to each dosing. *Targeted physical exam not required on Cycle 1 Day 1 if a full physical exam was completed within 3 days of first dose.
Performance Status[c]	X	X	ECOG PS (≥ 18 years old) See Appendix 6.
AE and SAE Assessment	Continuously		All AEs and SAEs must be collected from the time of signing the informed consent. Record at each visit. Collect continuously throughout the treatment period and for a minimum of [redacted] days following discontinuation of study treatment. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection must be collected from the time of signing the informed consent. For AE/SAE monitoring on-study during the treatment period, please refer to Table 2-4. For participants assigned to treatment and never treated with study drug, collect SAEs for 30 days from the date of treatment assignment.
Concomitant Medications	Continuously		Concomitant medications will include medications taken from treatment assignment and throughout treatment phase. Record at each visit. See Section 7.7.

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Table 2-4: On-treatment Procedural Outline (Cohort 2 – Resected Melanoma)

Procedure	Intravenous Treatment [redacted]	Subcutaneous Treatment [redacted]	Notes[redacted],b [redacted]
Laboratory Tests			
Pregnancy Test (WOCBP)	X*	X^	Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG); a negative pregnancy test should be documented within 1 day prior to administration of first dose of study treatment. *Pregnancy test not required to be repeated on Cycle 1 Day 1 if completed within 24 hours of first dose (during screening). ^For subsequent cycles, a negative pregnancy test should be documented within 3 days prior to dosing.
Clinical Laboratory Assessments[c]	X	X	Laboratory testing should be performed within 3 days prior to each dose. For the first treatment visit, labs need not be repeated if they were performed within 3 days and the results are available and have been reviewed for eligibility. Refer to Section 9.4.4 for the list of laboratory tests to be conducted.
Efficacy Surveillance			
Imaging Assessment	See Notes		[redacted]
Assessment of Recurrence	See Notes		[redacted] assess and report disease recurrence per local guidelines. Documentation of recurrence should be provided for source verification.

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Table 2-4: On-treatment Procedural Outline (Cohort 2 – Resected Melanoma)

Procedure	Intravenous Treatment	Subcutaneous Treatment	Notes[a,b]
Health Outcomes Assessments			
PEQ	X		
PEPQ		X	To be completed immediately after **Cycle 4 Day 1** (no greater than 24 hours post dose). See Section 9.1.3.1

Abbreviations: AE, adverse event; ; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; hCG, human chorionic gonadotropin; ; IMAE, immune-mediated adverse event; IV, intravenous; ; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PEPQ, Patient Experience and Preference Questionnaire; PEQ, Patient Experience Questionnaire; SAE, serious adverse event; SARSCoV-2, severe acute respiratory syndrome coronavirus 2; SC, subcutaneous; WOCBP, women of child-bearing potential.

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

[c] Screening assessments performed within 3 days of first dose are not required to be repeated at Cycle 1 Day 1 .

Approved v2.0 930207750 2.0

Table 2-5: Long-term Follow-up Procedural Outline (Cohort 1a and Cohort 2b)

Procedure	Follow-up Visits 1 & 2 [redacted]	Notes[c] All windows are based on calendar days
Safety Assessments		See Section 9.4
Targeted Physical Examination, Measurements, Vital signs, and ECOG PS	X	Include weight, seated blood pressure, respiratory rate, heart rate, body temperature, and ECOG PS
AE and SAE Assessment	See Notes	AEs/SAEs will be graded according to the NCI-CTCAE version 5.0. Record at each visit. Collect continuously from date of signed informed consent and for a minimum of [redacted] following discontinuation of study treatment. Beyond [redacted] from the last dose of study treatment, participants will be followed for drug-related AEs/SAEs until resolution, returns to baseline, or is deemed irreversible, or until the participant is lost to follow-up or withdraws study consent. All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the time of the participant's signing the informed consent until [redacted] days for Cohort 1 and [redacted] days for Cohort 2 following discontinuation of study treatment.
Concomitant Medications	X	Record at each visit. All medications with a start date occurring between 14 days prior to treatment administration and within [redacted] of the last dose date of study intervention are considered concomitant. See Section 7.7.

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Table 2-5: Long-term Follow-up Procedural Outline (Cohort 1a and Cohort 2b)

Procedure	Follow-up Visits 1 & 2 [redacted]	Notes[c] All windows are based on calendar days
Laboratory Tests		See Section 9.4.4.
Clinical Laboratory Assessments	X	To be performed at Follow-up Visit 1, repeat at Follow-up Visit 2 if study treatment-related toxicity persists. Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the follow-up phase, based on results from on-site/local labs, until all study intervention related toxicities resolve, return to baseline, or are deemed irreversible.
Pregnancy Test (WOCBP Only)	X	Serum or urine. Results of the test should be reported to the study site as well as the sponsor in a timely manner.
Efficacy Surveillance Assessments		
Imaging Assessment	X	[redacted]

Abbreviations: AE, adverse event; [redacted]; ECOG, Eastern Cooperative Oncology Group; [redacted]; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SAE, serious adverse event; WOCBP, women of childbearing potential.

[redacted]

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

In the event that multiple procedures are required at a single time point, the following is the order in which the procedures should be performed, from highest to lowest priority:

- Safety [redacted]
- Safety (clinical laboratory tests)

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3 INTRODUCTION

[redacted]

For many patients with cancer, intravenous (IV) administration of anticancer therapies can be associated with significant burdens including more time spent in clinic (treatment preparation and IV administration time), challenges with implantable venous access ports, and complex scheduling placing a strain on medical centers. Some patients also describe negative psychological impact factors due to stress and anxiety associated with IV administration. As the cancer patient population continues to grow, the impact of these burdens is poised to increase accordingly.

[redacted]

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Throughout the protocol, the co-formulation of nivolumab 960 mg + relatlimab 320 mg FDC (BMS-986213; [redacted] nivolumab and relatlimab) and rHuPH20 [redacted] administered SC will be referred to as nivolumab + relatlimab FDC SC, and the IV formulation of nivolumab 480 mg + relatlimab 160 mg FDC (BMS-986213; [redacted] of nivolumab and relatlimab) will be referred to as nivolumab + relatlimab FDC IV.

The coformulation of nivolumab 1200 mg (BMS-986298) and rHuPH20 [redacted] administered SC will be referred to as nivolumab SC, and the IV formulation of nivolumab 480 mg (BMS-936558) will be referred to as nivolumab IV.

3.1 Study Rationale

Repeated IV infusion appointments require considerable time and resources from both patients and the healthcare system. With the growing cancer patient population and increasing burden on healthcare resources, there is a need for more efficient treatment options, such as alternative routes of administration. [redacted]

CA2241044 will address this important data question by assessing the patient's preference for nivolumab SC or nivolumab + relatlimab FDC SC and provide patient experience data by route of administration. Two cohorts of patients will be enrolled in this study. In addition to addressing patient preferences, this study will also generate safety data which will further characterize the safety profile of patients switching the route of administration from IV to SC.

- Cohort 1 will include participants with previously untreated Stage III (unresectable) or Stage IV (metastatic) melanoma.
- Cohort 2 will include participants with completely resected melanoma Stage IIB/C, III, or Stage IV.

3.2 Background

Melanoma, the most serious form of skin cancer, is the 5th most common cause of cancer in the United States (US)[1] and accounts for approximately 1% to 2% of all cancer deaths and approximately 5% of all new cases of cancer in the US with a historical 5-year survival rate of

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18% for late-stage disease.[2] While rare in the pediatric population, melanoma is the second leading cause of cancer in adolescents and young adults over the age of 15, with an incidence of over 10 per million in 15- to 19-year-olds.[3] In the era of immuno-oncology (IO) therapy, the expected 5-year survival rate for metastatic melanoma has a lower bound of approximately 35% and could be as high as 50% for the nivolumab+ ipilimumab combination among patients who would meet criteria for clinical trials.[4]

Prior to 2011, approved therapies for the treatment of metastatic melanoma were limited and included chemotherapy (dacarbazine) and immunotherapy (interleukin 2). Since then, 3 new therapeutic classes have been added to the treatment armamentarium and include 7 new drugs administered as monotherapy or in combination. These drugs include 1) ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4)-blocking antibody, 2) drugs targeting the tyrosine kinase pathways including BRAF and MEK, which include vemurafenib, dabrafenib, trametinib, and cobimetinib, and 3) mAbs that bind to the programmed death-1 (PD-1) receptor, which include nivolumab and pembrolizumab. Though many of these therapies have demonstrated an overall survival (OS) benefit in Phase 3 studies, there are still areas of high unmet medical need for this population. Many patients relapse within months of initiating treatment[5,6,7] or are not eligible for treatment due to tumor mutation status requirements (eg, BRAF V600 mutation is present in approximately 50% of melanoma tumors).[6,7] [redacted] Disease course for melanoma has fundamentally changed with the introduction of immunotherapies targeting the cytotoxic T-lymphocyte-associated antigen 4 and PD-1 checkpoints as well as BRAF and MEK inhibitors. Such agents have dramatically improved outcome for patients with metastatic melanoma; however, their role in the adjuvant setting continues to be evaluated.

3.2.1 Relatlimab Mechanism of Action

Relatlimab is a fully human antibody specific for human lymphocyte activation gene-3 (LAG-3) that was isolated from immunized transgenic mice expressing human Ig genes.[8] It is expressed as an IgG4 isotype antibody that includes a stabilizing hinge mutation [redacted] for attenuated Fc receptor binding to reduce or eliminate the possibility of antibody- or complement-mediated target cell killing. relatlimab binds to a defined epitope on LAG-3 with high affinity (dissociation constant, 0.25 to 0.5 nM) and specificity and potently blocks the interaction of LAG-3 with its known ligands, major histocompatibility complex (MHC) Class II (half maximal inhibitory concentration [IC50], 0.7 nM) and fibrinogen-like protein 1 (FGL1). [redacted]

Approved v2.0 930207750 2.0

3.2.2 Nivolumab Combined with relatlimab Pre-clinical Activity

LAG-3 is expressed on tumor-infiltrating lymphocytes (TILs) of several tumor types, including melanoma; hepatocellular carcinoma (HCC); and breast, ovarian, and lung cancers, often in connection with increased PD-1+ T cells.[9] Preclinical data presented in recent years illustrate a clear synergy between the inhibitory receptors LAG-3 and PD-1 in controlling immune homeostasis, preventing autoimmunity, and enforcing tumor-induced tolerance.[6,8,9] Importantly, combined treatment of mice with blocking antibodies against both receptors resulted in more robust immune responses than either single-treated group in these studies and analyses of *Lag3*$^{-/-}$*Pdcd1*$^{-/-}$ double knockout mice revealed a cooperative requirement for LAG-3 and PD-1 in maintaining immune homeostasis.

The single-agent anti-tumor activity of anti-LAG-3 antibody (19C7) was evaluated in the immunogenic Sa1N fibrosarcoma tumor model.[10] Compared with the isotype control group, all doses between 1 mg/kg and 30 mg/kg of anti-LAG-3 clone 19C7 demonstrated anti-tumor efficacy leading to between 30% and 60% of the mice being rendered tumor-free at the end of study.

Combined anti-PD-1 and anti-LAG-3 activity were also assessed in the Sa1N model. In 2 different studies, an anti-LAG-3 antibody, C9B7W, inhibited the growth of Sa1N tumors in mice when administered as monotherapy and when combined with anti-PD-1 antibody, 4H2.[11,12] The combination of these 2 antibodies resulted in 80% to 90% tumor-free mice and reductions in median tumor volumes superior to that of anti-PD-1 or anti-LAG-3 antibody monotherapy alone.[8]

Similarly, a greater anti-tumor effect was also demonstrated for combined anti-PD-1 and anti-LAG-3 in the MC38 colon adenocarcinoma models than with either agent alone.[8]

3.2.3 Nivolumab Combined with relatlimab Clinical Activity

Clinical efficacy of relatlimab as monotherapy and in combination with nivolumab has been studied in CA224020 and CA224022 at different doses and schedules. As monotherapy, relatlimab demonstrated activity in hematologic malignancies in the Phase 1/2a study CA224022. Objective responses were observed in participants with relapsed or refractory marginal zone lymphoma, Hodgkin lymphoma, and mantle cell lymphoma.[8]

The Phase 1/2a study CA224020 is investigating the safety, tolerability, and effectiveness of relatlimab, with and without nivolumab, to treat various solid tumors. [redacted] As of the cutoff date of 25-Feb-2021 for Part C of study CA224020, objective responses in the range of 5.3% to 47% were achieved with nivolumab + relatlimab combination therapy in participants with IO-refractory and 1L advanced melanoma, IO-naive bladder cancer, IO-refractory/relapsed and 1L NSCLC, IO-naive RCC, IO-naive gastric cancer (GC), IO-naive HCC, and IO-naive squamous cell carcinoma of the head and neck.[8]

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As of the cutoff date of 25-Feb-2021, objective responses were achieved in participants with IO-refractory melanoma treated with nivolumab + relatlimab. Part D1 included heavily pretreated participants with advanced melanoma (with a high proportion of participants treated with 2 or more prior lines of therapy including anti-CTLA-4 and/or anti-PD-1) and with many additional poor prognostic factors such as primary resistance to prior anti-PD-1, Stage IV disease with liver metastasis, and high lactate dehydrogenase who experienced disease progression. In part D1, 189 patients received nivolumab and [redacted] The overall response rate (ORR) by blinded independent central review (BICR) was 12.0% (95% confidence interval [CI], 8.8 to 15.8) in D1 pooled and 9.2% (95% CI, 5.2 to 14.7) in D2.13

As of the same cutoff date (25-Feb-2021), the advanced melanoma participants with progression on prior I-O therapies in Part E treated with nivolumab [redacted] the ORR by BICR was 11.7%. With a minimum follow-up of 11.3 months, the median duration of response was not reached (NR; 95% CI: 3.06, nonestimable).[8] Refer to the [redacted] for further information.

CA224047, a global, double-blind, randomized, Phase 2/3 study comparing an FDC formulation of nivolumab 480 mg + relatlimab 160 mg FDC Q4W to nivolumab 480 mg Q4W in participants with previously untreated advanced melanoma demonstrated a statistically significant and clinically meaningful benefit by dual inhibition of the LAG-3 and PD-1 pathways. The study achieved its primary endpoint, demonstrating statistically significant improvement in progression-free survival (PFS) by BICR with nivolumab + relatlimab FDC [redacted] compared to nivolumab monotherapy in all randomized participants (N = 714) (PFS hazard ratio [HR] = 0.75 [95% CI: 0.62, 0.92], P-value = 0.0055). With a median follow-up of 19.3 months, the median PFS according to BICR in the nivolumab + relatlimab FDC [redacted] group was 10.2 months (95% CI, 6.5–14.8) compared to 4.6 months (95% CI, 3.5–6.4) in the nivolumab monotherapy arm. PFS rates at 12 months were 48.0% (95% CI, 42.5–53.4) and 36.9% (95% CI, 31.7–42.1) for nivolumab + relatlimab FDC [redacted] and nivolumab monotherapy, respectively. The PFS benefit of nivolumab + relatlimab FDC [redacted] was consistent across key prespecified subgroups.[12,15] The secondary endpoint of OS showed clinically meaningful improvement with nivolumab + relatlimab FDC over nivolumab monotherapy (median OS nonestimable (95% CI 34.20, NR) versus 34.1 months (95% CI 25.23, NR); HR = 0.80 [0.64-1.01]); p = 0.0593) in all randomized participants but was not statistically significant.[12,15]

Due to the statistical non-significance of the secondary endpoint of OS, ORR was not formally tested per the statistical testing hierarchy; however, clinically meaningful numerical differences were observed with the nivolumab + relatlimab FDC arm over nivolumab monotherapy (43.1% versus 32.6%).[24]

Approved v2.0 930207750 2.0

3.2.4 Nivolumab Combined with relatlimab Clinical Safety

The Phase 1/2a study CA224020 enrolled the highest number of participants treated with the combination therapy of nivolumab + relatlimab in dose-escalation (Part B) and expansion cohorts in Parts C, D, and E tested in Q2W [redacted] dosing intervals. Refer to [redacted] for details of the dose levels tested across a range of solid tumor cohorts in Part B and dose-limiting toxicities observed.[8] The safety profile was acceptable at all dose levels tested up to [redacted] relatlimab in combination with nivolumab [redacted], with the MTD not reached at this dose level. Part C included expansion cohorts with multiple tumor types and Parts D and E included advanced melanoma participants (1L and progressed on prior-PD-1 therapy). Refer to [redacted] for the details of the number of participants tested with the dose combinations.[8]

[redacted], 1457 participants in study CA224020 have been treated with nivolumab + relatlimab across Parts B, C, D, and E demonstrating that the combination was well tolerated across multiple tumor types.[8] Based on an analysis of adverse events (AEs) in the all-combination group, 1422 (97.6%) participants experienced at least 1 event and 1422 (97.6%) participants experienced at least 1 event occurring in ≥ 5% of participants (refer to [redacted] for details). Across Parts B, C, D, and E, drug-related AEs were reported in 1003 (68.8%) participants, with the most commonly reported (≥ 5% of participants) being fatigue (17.4%), pruritus (13.0%), rash (10.0%), diarrhea (9.1%), hypothyroidism (8.6%), arthralgia (7.9%), increased lipase and nausea (7.3% each), asthenia (7.1%), and dry mouth (5.9%). Most drug-related AEs were Grades 1 to 2. Grade 3- 4 drug-related AEs were reported in 251 (17.2%) participants and the most frequently reported included lipase increased (3.7%), and 3 (0.2%) participants reported Grade 5 events (dyspnea, pulmonary fibrosis, and pneumopathy).

Refer to the [redacted] for details of drug-related AEs analyzed separately for Part D1, which included 82 heavily pretreated participants with advanced melanoma, with poor prognostic factors treated with [redacted]

Drug-related serious AEs (SAEs) were reported in 196 of the 1457 (13.5%) participants with Grade 3-4 drug-related SAEs occurring in 145 (10.0%) participants and Grade 5 events occurring in 3 (0.2%) participants (dyspnea, pulmonary fibrosis, and immune-mediated lung disease). More information can be found in [redacted]

The safety profile of the combination of nivolumab [redacted] was confirmed in the pivotal Phase 2/3 global, multicenter study CA224047 (n = 355), in previously untreated advanced melanoma participants (clinical data cutoff 09-Mar-2021). The study findings demonstrated a well-tolerated regimen with a manageable safety profile and without unexpected safety signals. The incidence of Grade 3 to 4 drug-related AEs was 24.5% in the nivolumab + relatlimab FDC group. There were 4 treatment-related deaths with nivolumab + relatlimab FDC. Drug-related AEs (any grade) led to treatment discontinuation in 20.6% of participants in the nivolumab + relatlimab FDC group.[25] [redacted] for safety analysis based on the clinical data cutoff date of 12-Sep-2022.[15]

Approved v2.0 930207750 2.0

3.2.5 Nivolumab Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-[redacted]) that targets the PD-1 cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands programmed death ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. nivolumab is expressed in Chinese hamster ovary cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

3.2.6 Nivolumab Clinical Activity

Nivolumab has been approved for the treatment of unresectable or metastatic melanoma, adjuvant treatment of melanoma, neoadjuvant treatment of resectable NSCLC, metastatic NSCLC, malignant pleural mesothelioma, advanced renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer, hepatocellular carcinoma, esophageal cancer, gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in patients with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or recurrent or metastatic squamous cell carcinoma of head and neck (SCCHN). Details of the clinical activity in these various malignancies are provided in the US Package Insert and Summary of Product Characteristics (SmPC).

For resected melanoma, nivolumab is an established standard of care that is recognized in guidelines globally with positive recommendation ratings. In CA209238, nivolumab demonstrated clinical benefit with an acceptable safety profile in the patient populations (Stage IIIA with > 1 mm tumor in lymph node was not included) that are being evaluated in this study. For resected stage IIB or IIC melanoma, the CA20976K study demonstrated statistically significant and clinically meaningful RFS benefits with adjuvant nivolumab versus placebo in patients with completely resected stage IIB or IIC melanoma. At the interim analysis with a minimum follow-up of 8 months, the endpoint was met, demonstrating improved RFS with nivolumab versus placebo (stratified HR 0.42 [95% CI: 0.30, 0.59] $p<0.0001$. The landmark 12-month RFS rate for nivolumab was 89% and 79% for the placebo arm.

3.2.7 Nivolumab Clinical Safety

The overall safety experience with IV nivolumab (BMS-936558), as a monotherapy or in combination with other therapeutics, is based on experience in approximately 29,349 subjects treated to date. For monotherapy, the IV nivolumab safety profile is similar across tumor types. In

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Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines.

Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care. Based on data from a completed Phase 1b study and a Phase 1/2 study, single doses of either [redacted] mg nivolumab did not result in unexpected safety findings for participants with sepsis or septic shock. In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. Nivolumab as monotherapy and nivolumab in combination with other agents are approved in subjects with melanoma, RCC, microsatellite instability-high or mismatch repair deficient colorectal cancer (CRC), HCC, non-small cell lung cancer (NSCLC), cHL, SCCHN, UC, esophageal cancer (EC) gastric cancer (GC), and malignant pleural mesothelioma MPM.

Study CA2098KX is ongoing and clinical safety regarding the use of SC nivolumab (BMS-986298)[16] is collected on ongoing basis. Overall, the safety profile of SC nivolumab monotherapy in subjects with advanced/metastatic cancer is manageable and consistent with the AE profile observed with nivolumab when administered via IV route. There was no pattern in the incidence, severity, or causality of AEs across all doses studied of nivolumab (600, 720, 960 and 1,200 mg) with or without rHuPH20. Most AEs were low-grade (Grade 1-2) with relatively few drug-related (Grade 3-4) AEs. The majority of treatment-related AEs regardless of grade were manageable based on established management guidelines.

3.2.8 Recombinant Human Hyaluronidase PH20 Enzyme

rHuPH20 is a glycosylated 447-amino acid single-chain recombinant human polypeptide that depolymerizes hyaluronan in the SC space locally at the site of injection. Hyaluronan is an anionic, nonsulfated glycosaminoglycan that consists of a polymer of N-acetyl-glucosamine and glucuronic acid subunits. It contributes to the soluble gel-like component of the extracellular matrix of the skin. Depolymerization of hyaluronan by rHuPH20 results in a transient reduction in the viscosity of the gel-like phase of the extracellular matrix and increased hydraulic conductance that facilitates the dispersion and absorption of injected drugs (see rHuPH20 IB). Use of rHuPH20 enables the delivery of large volumes of liquid into the SC space (approximately 2 to 20 mL), decreasing dose administration times.

3.2.9 Nonclinical Toxicity of Recombinant Human Hyaluronidase PH20

General toxicity studies were performed in cynomolgus monkeys, and a developmental and reproductive toxicity program was performed in mice (see rHuPH20 IB[17]). [redacted] In mice, at very high doses (≥ 9 mg/kg/day SC) of rHuPH20, embryo-fetal toxicity consisted of reduced fetal weights and a trend for late resorption; however, these high dose levels did not result in prenatal or postnatal developmental effects. Rabbit studies

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were also conducted to evaluate the potential effects of anti-rHuPH20 antibody exposure on reproduction and development. These studies showed no adverse effects on general toxicity endpoints, male or female fertility, or embryo-fetal development. In a pivotal Good Laboratory Practice compliant lifetime repeat-dose toxicity study conducted in juvenile mice, there were no rHuPH20-related effects on any of the parameters tested, except for minimal-to-moderate, nonadverse microscopic findings at the injection site noted in male and female mice in the subset treated through postnatal Day 241. There were no adverse effects of rHuPH20 at 1 mg/kg/dose or anti-rHuPH20 antibodies on neurobehavioral assessments, reproductive capacity, fetal evaluations, or any other toxicity endpoints evaluated in juvenile mice through adulthood. Genotoxicity and carcinogenicity studies have not been conducted.

See the rHuPH20 IB for detailed descriptions of the nonclinical pharmacology, clinical safety, PK, and toxicity studies of rHuPH20 and results.[17]

3.3 Benefit/Risk Assessment

BMS is evaluating novel ways of administering nivolumab, as well as nivolumab + relatlimab FDC as a SC injection to provide patients with an alternate route of administration as compared with IV infusion. Study CA2241044 has been designed to assess patient preferences for the SC route of administration versus IV infusions. An SC injection is less invasive and has a substantially shorter administration period as compared with a conventional IV infusion, which for other SC biologics has translated to improved patient quality of life, as well as efficiencies in medical resource utilization.[18,19,20] Both patients and prescribers have reported a preference for SC to IV administration for other drug products.[21,22]

3.3.1 Cohort 1 (nivolumab + relatlimab)

CA224047, a pivotal Phase 2/3 study in participants with unresectable or metastatic melanoma, demonstrated that nivolumab 480 mg + relatlimab 160 mg FDC IV Q4W has clinical benefit, regardless of PD-L1 expression, with a statistically significant and clinically relevant PFS benefit [redacted] compared to nivolumab [redacted].[23,24] The combination was confirmed to be well tolerated with a manageable safety profile in the 355 participants treated and there were no unexpected safety signals from this combination.[24]

[redacted]

Approved v2.0 930207750 2.0

[redacted]

3.3.2 *Cohort 2 (nivolumab)*

Despite the availability of nivolumab IV, there is a need to improve patient quality of life in cancer care. In addition to the benefits of nivolumab to potentially improve RFS and overall OS in resected melanoma patients, participants would also benefit from the use of the SC route of administration of nivolumab co-formulated with rHuPH20.

3.3.3 General Considerations

Preliminary safety data for relatlimab SC from the Phase 1 CA224087 study have been consistent with safety data seen across studies for nivolumab + relatlimab FDC IV. Further details can be found in the relatlimab IB.

Overall, the safety profile of SC nivolumab monotherapy in subjects with advanced/metastatic cancer is manageable and consistent with the AE profile observed with IV nivolumab. Further details can be found in the [redacted].

The risks anticipated for CA2241044 and proposed mitigations are summarized in Table 3.3-1. Key to mitigating these risks, investigators and the Sponsor will utilize continuous safety assessments to determine whether additional safety measures or termination from the study are required at any time. In addition, AEs and SAEs will be reviewed on an ongoing basis by the Sponsor's Medical Monitor and Worldwide Patient Safety representatives to monitor for any safety signals or trends.

Table 3.3-1: Potential Risk Assessment and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk[8,16, 26]	Mitigation Strategy
Study Intervention: nivolumab + relatlimab		
IMAEs (eg, colitis diarrhea/colitis, pneumonitis, [redacted], nephritis, endocrinopathy, rash, neurologic)	Relatlimab IV and SC IBs nivolumab IV and SC IBs BMS-986213 IB	Recommended IMAE management algorithms are included in [redacted] or as per institutional protocol/investigator discretion.
Potential infusion-related reaction, Potential injection-site reaction, and cytokine release syndrome	Relatlimab IV and SC IBs nivolumab IV and SC IBs BMS-986213 IB	Please refer to Section 7.4.4 of protocol.

Approved v2.0 930207750 2.0

Table 3.3-1: Potential Risk Assessment and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk[8, 16, 26]	Mitigation Strategy
Cardiovascular AEs (ie, myocarditis, [redacted])	Relatlimab IV and SC IBs nivolumab IV and SC IBs BMS-986213 IB	relatlimab management of myocarditis per AE Management Algorithm in [redacted] or as per institutional protocol/investigator discretion. [redacted]
Study Intervention: nivolumab		
IMAEs (eg, colitis diarrhea/colitis, pneumonitis, [redacted] nephritis, endocrinopathy, rash, neurologic)	nivolumab SC and IV IBs	Recommended IMAE management algorithms are included in [redacted] or as per institutional protocol/investigator discretion.
Potential infusion-related reaction, potential injection site reaction	nivolumab IV IB nivolumab SC IB	Please refer to Section 7.4.4 of protocol.
Cardiovascular AEs (ie, myocarditis, [redacted])	Nivolumab IV and SC IBs	Management of myocarditis per AE Management Algorithm in [redacted] or as per institutional protocol/investigator discretion.
Study Procedures (Both Cohorts)		
SC Injection	Please refer to Section 3.3 (Benefit/Risk Assessment).	Per IFU.
MRI	Not applicable	Per institutional protocol/investigator discretion.
CT	Not applicable	Per institutional protocol/investigator discretion.
Allergy to Contrast Agent (eg, reaction to anaphylaxis)	Not applicable	Prophylaxis and/or treatment per institutional protocol/investigator discretion.
Other (if applicable)		
Non-Clinical Safety (animal studies)	BMS-986213 IB	Not applicable.

Approved v2.0 930207750 2.0

Abbreviations: AE, adverse event; CT, computed tomography; IB, Investigator's Brochure; IFU, instructions for use; IMAE, immune-mediated adverse event; IV, intravenous; MRI, magnetic resonance imaging; SC, subcutaneous.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary Cohort 1: Metastatic melanoma • To evaluate participants' preference for route of administration upon switching from nivolumab + relatlimab FDC IV to nivolumab + relatlimab FDC SC Cohort 2: Resected melanoma • To evaluate participants' preference for route of administration upon switching from nivolumab IV to nivolumab SC	**Primary** Cohort 1: Metastatic melanoma • Proportion of evaluable participants that prefer SC route of administration using the Patient Experience and Preference Questionnaire (Question 7) after Cycle 4 Day 1 dose Cohort 2: Resected melanoma • Proportion of evaluable participants that prefer SC route of administration using the Patient Experience and Preference Questionnaire (Question 7) after Cycle 4 Day 1 dose
Secondary Cohort 1: Metastatic melanoma • To assess the safety and tolerability of nivolumab + relatlimab FDC IV and nivolumab + relatlimab FDC SC Cohort 2: Resected melanoma • To assess the safety and tolerability of nivolumab SC and nivolumab IV	**Secondary** Cohort 1: Metastatic melanoma • AEs, SAEs, treatment-related AEs, AEs leading to discontinuation, IMAEs, OESIs, injection/infusion related AEs, deaths and laboratory abnormalities Cohort 2: Resected melanoma • AEs, SAEs, treatment-related AEs, AEs leading to discontinuation, IMAEs, OESIs, injection/infusion related AEs, deaths and laboratory abnormalities
[redacted]	

Abbreviations: AE, adverse event; FDC, fixed dose combination; IMAE, immune-mediated adverse event; IV, intravenous; [redacted]; OESI, other events of special interest ; SAE, serious adverse event.

Approved v2.0 930207750 2.0

Table 4-2: Main Estimands for the Primary and Key Secondary Endpoints

Endpoint (Variable)	Description	Analysis Population	Timeframe	Summary Statistics
Primary	Cohort 1: Metastatic melanoma • Proportion of evaluable participants that prefer SC route of administration using the Patient Experience and Preference Questionnaire (Question 7) after Cycle 4 Day 1 dose • Cohort 2: Resected melanoma • Proportion of evaluable participants that prefer SC route of administration using the Patient Experience and Preference Questionnaire (Question 7) after Cycle 4 Day 1 dose	Proportion of evaluable participants that prefer SC route of administration using the Patient Experience and Preference Questionnaire (Question 7) after Cycle 4 Day 1 dose	After Cycle 4 Day 1 dose	Estimated proportion and exact 95% CI
Secondary	• Cohort 1: Metastatic melanoma • AEs, SAEs, treatment-related AEs, AEs leading to discontinuation, IMAEs, OESIs, deaths and laboratory abnormalities • Cohort 2: Resected melanoma • AEs, SAEs, treatment-related AEs, AEs leading to discontinuation, IMAEs, OESIs, deaths and laboratory abnormalities	All treated population	Throughout the treatment period	Descriptive proportion of participants

Abbreviations: AE, adverse event; IMAE, immune-mediated adverse event; OESI, other events of special interest; SAE, serious adverse event; SC, subcutaneous.

Approved v2.0 930207750 2.0

For the primary and secondary endpoints, the treatment policy strategy will be used to address all intercurrent events. The occurrence of the intercurrent event is considered irrelevant, information after intercurrent event is used.

5 STUDY DESIGN

5.1 Overall Design

CA2241044 is a Phase 2, open-label, 2-cohort study to evaluate patient preference for nivolumab SC or nivolumab + relatlimab FDC SC vs the IV formulations in participants with previously untreated Stage III (unresectable) or Stage IV (metastatic) melanoma (Cohort 1) and those with completely resected Stage IIB/C, III, or IV melanoma (Cohort 2).

In Cohort 1, [redacted] treated adult participants with previously untreated metastatic or unresectable melanoma will receive nivolumab + relatlimab FDC IV for 2 treatment cycles followed by nivolumab + relatlimab FDC SC until withdrawal of consent, disease progression, unacceptable toxicity, lost to follow-up, death, study termination by the Sponsor, or a maximum treatment duration of 26 cycles or 2 years whichever comes first.

In Cohort 2, [redacted] treated adult participants with completely resected Stage IIB/C, III, or IV melanoma will receive nivolumab IV for 2 treatment cycles followed by nivolumab SC until disease recurrence, unacceptable toxicity, withdrawal of consent for study treatment, lost to follow-up, death, study termination by the Sponsor, or a maximum treatment duration of 13 cycles or 1 year, whichever comes first.

[redacted]

Approved v2.0 930207750 2.0

5.1.1 Screening Phase

Screening will occur between Day -28 and Day -1. Participants will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the participants' standard care. After signing the informed consent form (ICF), participants will be evaluated based on the assessments outlined in the Schedule of Activities (SoA-Section 2) and inclusion and exclusion criteria within [redacted] (unless otherwise specified) prior to treatment assignment. [redacted] Re-enrollment after screen failure is allowed and requires reconsenting and a new participant number assignment. Participants who complete the Screening Period and meet the criteria for inclusion/exclusion will begin with the Treatment Period.

5.1.2 Treatment Period

The Treatment Period begins at the time of treatment assignment (first day of treatment) and will end at the beginning of the Follow-up Period. Cycle length is 28 days. Treatment cycles will be counted from Cycle 1 Day 1 (C1D1) continuously regardless of dose interruptions or missed doses for both treatment arms. Participants will undergo safety and efficacy surveillance as defined in the SoA Section 2.

Cohort 1 (SoA Table 2-3)

Participants will receive 2 cycles of treatment with nivolumab + relatlimab FDC IV. Starting with Cycle 3, participants will receive nivolumab + relatlimab FDC SC. Participants will continue to receive study treatment until investigator-determined disease progression, unacceptable toxicity, withdrawal of consent, lost to follow-up, death, study termination by the Sponsor, or completion of up to 2 years (104 weeks) of treatment, whichever occurs first.

[redacted]

Cohort 2 (SoA Table 2-4)

Participants will receive 2 cycles of treatment with nivolumab IV. Starting with Cycle 3, participants will receive nivolumab SC. Participants will continue to receive study treatment until investigator-determined disease recurrence, unacceptable toxicity, withdrawal of consent, lost to follow-up, death, study termination by the Sponsor, or completion of up to 1 year (52 weeks) of treatment, whichever occurs first.

5.1.3 Follow-Up Period

Follow-up assessments are to be performed as described in the SoA (Table 2-5).

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Safety Follow-up Period

Safety Follow-up will begin the day after the Treatment Period when the participant has completed their course of treatment or the decision to discontinue a participant from study treatment is made (ie, participants have discontinued study treatment). The Safety Follow-up Period consists of 2 Follow-up Visits: [redacted] should be collected continuously using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5 during the Safety Follow-up.

For Cohort 1 - participants must be followed [redacted] after last dose of study treatment. Follow-up Visit 1 should occur [redacted] or can be performed on the date of discontinuation if that date is greater than [redacted] last dose. Follow-up Visit 2 occurs [redacted] from last dose of study treatment. Both follow-up visits should be conducted in person.

For Cohort 2 - participants must be followed for at least [redacted] after last dose of study treatment. Follow-up Visit 1 should occur [redacted] from the last dose [redacted] or can be performed on the date of discontinuation if that date is greater than [redacted] after last dose. Follow-up Visit 2 occurs approximately [redacted] from last dose of study treatment. Both follow-up visits should be conducted in person.

5.1.4 Data Monitoring Committee and Other Committees

A Data Monitoring Committee or other review committee will not be used in the study.

5.2 Number of Participants

Approximately [redacted] participants will be enrolled in two cohorts of [redacted] treated participants each; [redacted] treated participants will be enrolled in Cohort 1 (metastatic melanoma) [redacted] treated participants will be enrolled in Cohort 2 (resected melanoma) [redacted]. No replacement of discontinued participants will be performed.

5.3 End of Study Definition

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

The primary completion date is defined as the date on which the last data point is collected for the study's primary endpoint (outcome). For this study, the last primary outcome for the primary endpoint is defined as the completion of the Patient Experience and Preference Questionnaire (PEPQ).

End of study is defined as the last participant's last visit, which will occur [redacted] from last treatment dose for Cohort 1 (nivolumab + relatlimab) and [redacted] from the last treatment dose for Cohort 2 (nivolumab).

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A participant is considered to have completed the study if he/she has completed the last visit or the last procedure shown in the Schedule of Activities (Section 2), whichever occurs later.

5.4 Scientific Rationale for Study Design

The pivotal Phase 2/3 CA224047 study demonstrated clinical benefit with nivolumab 480 mg + relatlimab 160 mg IV FDC Q4W in participants with previously untreated metastatic or unresectable melanoma and has received FDA approval for the treatment of these patients. In Stage III/IV completely resected melanoma, adjuvant nivolumab is an established standard of care that is recognized in guidelines globally. In CA209238, adjuvant nivolumab demonstrated clinical benefit with an acceptable safety profile in patients with resected Stage IIIB/C or Stage IV melanoma (American Joint Committee on Cancer AJCC 7th edition). Recently, the Phase 3 CA20976K study demonstrated statistically significant and clinically meaningful RFS benefit with adjuvant nivolumab versus placebo in patients with completely resected Stage IIB or IIC melanoma. With advancement in I-O therapies, cancer patients are surviving longer and hence enduring the burden of being on treatment for longer. Therefore, strategies to lessen this burden have the potential to improve the quality of life for patients and their caregivers. A faster SC injection as compared with IV infusion may allow for improved patient quality of life as well as efficiencies in healthcare resource utilization.

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[redacted]

5.4.2 Cohort 2: Resected Melanoma:

5.4.2.1 Rationale for Use of nivolumab

In the adjuvant Stage III/IV resected melanoma setting, nivolumab is an established standard of care that is recognized in guidelines globally with positive recommendation ratings. In CA209238, nivolumab demonstrated clinical benefit with an acceptable safety profile in the patient populations (Stage IIIA with > 1 mm tumor in lymph node was not included) that are being evaluated in this study.

CA209238 randomly assigned patients with resected Stage IIIB, IIIC, or IV disease to receive nivolumab versus ipilimumab. Patients' diseases were categorized by the AJCC v7, and all patients underwent resection and lymph node dissection. The 12-month RFS was 70.5% in the nivolumab group versus 60.8% in the ipilimumab group. At 24 months, RFS was 62.6% in the nivolumab group versus 50.2% in the ipilimumab arm. This benefit was found regardless of stage, PD-L1 status, or BRAF status. Treatment was better tolerated in the nivolumab group, with 14.4% of patients experiencing Grade 3 or 4 toxicity compared with 45.9% in the ipilimumab group. On the basis of the results of CA209238, the use of ipilimumab is no longer recommended in the adjuvant setting given the superiority of nivolumab coupled with less toxicity.

For resected Stage IIB or IIC melanoma, the CA20976K study demonstrated statistically significant and clinically meaningful RFS benefit with adjuvant nivolumab versus placebo in patients with completely resected Stage IIB or IIC melanoma. CA20976K is a Phase 3 study in treatment-naive patients ≥ 12 years of age with completely resected Stage IIB/C melanoma with standard wide local excision and negative sentinel lymph node biopsy. Patients were randomized 2:1 [redacted]. At the interim analysis with a minimum follow-up of 8 months, the primary endpoint was met, demonstrating improved RFS with nivolumab versus placebo (stratified HR 0.42 [95% CI: 0.30, 0.59] p<0.0001). The landmark 12-month RFS rate for nivolumab was 89% and 79% for the placebo arm. The RFS benefit with nivolumab was observed across prespecified subgroups, including age, sex, location of primary melanoma, T-category, disease stage, and melanoma subtype. The safety profile of nivolumab was consistent with previous reports. The results of CA20976K support nivolumab as an effective adjuvant treatment option in resected Stage IIB/C melanoma.

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[redacted]

5.4.3 Rationale for Patient Preference Endpoints

Participants will be asked to complete the Patient Experience Questionnaire (PEQ) at the site immediately after Cycle 2 Day 1 following IV treatment administration, to assess patient experience of IV treatment, and the PEPQ at the site immediately after Cycle 4 Day 1 following SC treatment administration to assess experience of SC administration and preference between SC and IV treatment administration.[30] (See Section 2 SoA). [redacted]. Patient preference has been shown to have an impact on adherence to treatment in many chronic conditions. Within oncology, patient preference has been associated with improved clinical outcomes and adherence to treatment.[27] Additionally, a recent study identified that in a metastatic melanoma patient population, considerations for patient preference of treatment can help patients get the full benefit of treatment.[28]

In this study, patient preference using the PEPQ will be evaluated immediately after Cycle 4 Day 1.

[redacted]

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5.5 Justification of Dose

5.5.1 Nivolumab Clinical Pharmacology Summary

The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab as a 60-minute IV infusion every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 24.5% (47.6%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CLss is not considered clinically relevant. nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady state. The geometric mean volume of distribution at steady state (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was 3.7-fold. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W. The predicted exposure (C_{avg} and C_{max}) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

[redacted]

[redacted]

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[redacted]

5.5.3 Justification of nivolumab + relatlimab FDC IV Dose

The proposed dose of the FDC product is nivolumab 480 mg + relatlimab 160 mg Q4W. The dose and dosing regimen for this study were primarily based on the observed benefit/risk profile observed in metastatic melanoma participants from Study CA224047 and CA224020 PK, PD, and extensive nivolumab monotherapy clinical experience.

Clinical efficacy and safety data from the pivotal Study CA224047 confirmed the positive benefit/risk profile of the proposed dose in adult melanoma participants. The benefit/risk of nivolumab 480 mg + relatlimab 160 mg Q4W regimen is supported by exposure-response (E-R) efficacy and E-R safety analyses performed using data from 1L and prior-I-O melanoma participants.

[redacted]

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[redacted]

5.5.5 Justification of nivolumab IV Dose

The IV flat dose of nivolumab 480 mg was selected based on comprehensive PPK analyses and E-R data using Cavgd28 as the primary driver of efficacy across multiple tumor types. The IV nivolumab 480 mg Q4W regimen presents a comparable benefit-risk profile as the IV nivolumab 3 mg/kg Q2W dosing regimen across multiple tumor types.

5.5.6 Justification of nivolumab SC Dose

PK data from participants enrolled in Study CA2098KX, where nivolumab [redacted] was administered SC with or without rHuPH20, and historical IV nivolumab data across several tumor types (data from approximately 3,000 patients) were used to characterize the absorption profile of nivolumab when given SC. PPK analysis estimated the typical value (90% CI) bioavailability to be 70% (66% to 74%) and first-order rate of absorption to be 0.250 (90% CI: 0.225 to 0.274).[16] All other PK parameters and effects of covariates on these parameters were consistent with those estimated previously with the IV nivolumab PPK model.

[redacted]

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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 the following criteria apply:

6.1.1 Inclusion Criteria for Cohort 1

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

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board /Independent Ethics Committee approved written informed consent form (ICF) in accordance with regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

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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) Participants must have an Eastern Cooperative Oncology Group performance status (ECOG PS) score of ≤ 1.

b) Participants must have histologically confirmed Stage III (unresectable) or Stage IV (metastatic) melanoma, per the American Joint Committee on Cancer (AJCC) staging system (8th edition).

c) Participants must be treatment-naïve (ie, no prior systemic anticancer therapy) for unresectable or metastatic melanoma.

[redacted]

d) Participants are eligible regardless of BRAF status. Participants with known BRAF V600 mutation status, or who consent to BRAF V600 mutation testing per local institutional standards during the Screening Period with the sample collected within 3 months prior to treatment assignment must report BRAF status.

3) Age of Participant

Participants must be ≥ 18 years of age at the time of consent.

4) Reproductive Status

[redacted]

a) Female Participants:

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

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

ii) WOCBP must have a negative highly sensitive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study intervention. An extension up to 72 hours prior to start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

Approved v2.0 930207750 2.0

[redacted]

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

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

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

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, during the intervention period and for the duration of treatment with nivolumab and relatlimab plus 5 half-lives of study treatment for a [redacted] post-treatment completion and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

[redacted]

6.1.2 Inclusion Criteria for Cohort 2

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

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board /Independent Ethics Committee approved written informed consent form (ICF) in accordance with regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

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

2) Type of Participant and Target Disease Characteristics

a) Participants must have an (ECOG-PS) score of ≤ 1.

b) Participants must be eligible for adjuvant therapy for melanoma.

i) All participants must have completed surgical resection of Stage IIB/C, IIIA (> 1 mm tumor in lymph node)/B/C/D or stage IV (AJCC Cancer Staging, 8th edition)

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melanoma. All melanomas, except ocular and mucosal melanomas, are allowed regardless of primary site of disease.

ii) Participants with complete melanoma resection within 12 weeks of treatment assignment. Participants must be surgically rendered free of disease with negative margins on resected specimens. Complete resection must be documented on surgical and pathology report. For central nervous system (CNS) lesion(s), documentation indicating that there has been complete resection of CNS lesion(s) will suffice as confirmation of negative margins.

[redacted]

c) All participants must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to treatment assignment. Imaging studies must include computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, pelvis, and all known sites of resected disease, and brain MRI or CT (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions).

3) Age of Participant

Participants must be ≥ 18 years of age at the time of consent.

4) Reproductive Status

[redacted]

a) Female Participants:

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

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

ii) WOCBP must have a negative highly sensitive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study intervention. An extension up to 72 hours prior to start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

[redacted]

Approved v2.0 930207750 2.0

[redacted]

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

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

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

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, during the intervention period and for the duration of treatment with nivolumab and relatlimab plus 5 half-lives of study treatment for a [redacted] post-treatment completion and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

[redacted]

6.2 Exclusion Criteria

6.2.1 Exclusion Criteria for Cohort 1

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

1) Medical Conditions

a) Participants must not have active brain metastases or leptomeningeal metastases.

[redacted]

b) Participants with brain disease treated with whole brain radiation are not eligible.
c) Participants must not have ocular or mucosal melanoma.
d) Participants must not have an active, known, or suspected autoimmune disease.
e) Participants may enroll with the following conditions:

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i) Type 1 diabetes mellitus.
ii) Hypothyroidism only requiring hormone replacement therapy.
iii) Skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment.
iv) Conditions not expected to recur in the absence of an external trigger.

f) Participants must not have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within [redacted] days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
g) Participants must not have a concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to treatment assignment (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 that have undergone definitive treatment at any time are also eligible.
h) Participants must not have known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome defining opportunistic infection within the last year, or a current CD4 count < 350 cells/uL. 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.
   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. (Refer to Appendix 8.)

i) Participants must not have any serious or uncontrolled medical disorder that, in the opinion of the investigator in consultation with the BMS Medical Monitor, may increase the risk associated with study participation or study treatment administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.
j) Participants must not have previous SARS-CoV-2 infection either suspected or confirmed within 4 weeks prior to screening. Acute symptoms must have resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.
k) Participant has not recovered adequately from toxicity and/or complications from surgery prior to starting study treatment
l) Participants must not have a history of myocarditis, regardless of etiology.

[redacted]

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[redacted]

2) Reproductive Status

a) Women who are breastfeeding.

b) Women who are pregnant.

3) Prior/Concomitant Therapy

a) Participant must not have had prior treatment with an anti-PD-1 (except if given as adjuvant or neoadjuvant therapy for melanoma), anti- programmed death-ligand 1 (PD-L1), anti-programmed death-ligand 2 (PD-L2), anti-CTLA-4 antibody (except if given as adjuvant or neoadjuvant therapy for melanoma), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways (except for interferon given as adjuvant or neoadjuvant therapy for melanoma) within 6 months prior to start of study treatment

b) Participant must not have had prior treatment with relatlimab or any other lymphocyte activation gene-3 targeted agents.

c) Inability to comply with restriction and prohibited treatments.

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

e) [redacted]. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study treatment.

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

g) Participants currently in other interventional trials, including those for coronavirus disease 2019 (COVID-19), may not participate in BMS clinical trials until the protocol specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, treatment assignment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the investigator and the Medical Monitor.

[redacted]

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[redacted]

5) Allergies and Adverse Drug Reactions

a) Participants must not have a history of allergy or hypersensitivity to study intervention components.

6) Other Exclusion Criteria

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

6.2.2 Exclusion Criteria for Cohort 2

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

1) Medical Conditions

a) Participants must not have active brain metastases or leptomeningeal metastases. [redacted]

b) Participants with brain disease treated with whole brain radiation are not eligible.

c) Participants must not have ocular or mucosal melanoma.

d) Participants must not have an active, known, or suspected autoimmune disease.

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e) Participants may enroll with the following conditions:
   i) Type 1 diabetes mellitus.
   ii) Hypothyroidism only requiring hormone replacement therapy.
   iii) Skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment.
   iv) Conditions not expected to recur in the absence of an external trigger.

f) Participants must not have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within [redacted] days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

g) Participants must not have a concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to treatment assignment (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 that have undergone definitive treatment at any time are also eligible.

h) Participants must not have known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome defining opportunistic infection within the last year, or a current CD4 count < 350 cells/uL. 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.
   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. (Refer to Appendix 8.)

i) Participants must not have any serious or uncontrolled medical disorder that, in the opinion of the investigator in consultation with the BMS Medical Monitor, may increase the risk associated with study participation or study treatment administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.

j) Participants must not have previous SARS-CoV-2 infection either suspected or confirmed within 4 weeks prior to screening. Acute symptoms must have resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

2) Reproductive Status

a) Women who are breastfeeding.

b) Women who are pregnant.

3) Prior/Concomitant Therapy

a) Participant must not have had prior treatment with an anti-PD-1 (except if given as adjuvant or neoadjuvant therapy for melanoma), anti- programmed death-ligand 1 (PD-L1), anti-programmed death-ligand 2 (PD-L2), anti-CTLA-4 antibody (except if given as

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adjuvant or neoadjuvant therapy for melanoma), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways (except for interferon given as adjuvant or neoadjuvant therapy for melanoma)

b) Participant must not have had prior treatment with relatlimab or any other lymphocyte activation gene-3 targeted agents.

c) Inability to comply with restriction and prohibited treatments.

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

e) [redacted]. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study treatment.

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

g) Participants currently in other interventional trials, including those for coronavirus disease 2019 (COVID-19), may not participate in BMS clinical trials until the protocol specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, treatment assignment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the investigator and the Medical Monitor.

[redacted]

Approved v2.0 930207750 2.0

5) Allergies and Adverse Drug Reactions

Participants must not have a history of allergy or hypersensitivity to study intervention components.

6) Participants must not have active brain metastases or leptomeningeal metastases.

7) Prior immunotherapy treatments for any prior malignancies are not permitted (such as, but not limited to anti-PD-1, anti-PD-L1, PD-L2, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways).

8) Other Exclusion Criteria

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

6.3 Lifestyle Restrictions

Not applicable.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently enrolled 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 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 SAEs that occurred following consent.

6.4.1 Re-testing During Screening

This study permits the re-enrollment of a participant who has discontinued the study as a screen failure (ie, participant has not been treated). If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.

Re-testing of laboratory parameters and/or other assessments within any single screening or leading- period 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 and Table 2-2, 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.

Approved v2.0 930207750 2.0

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 IP as indicated in Table 7.1-1.

An IP, also known as an Investigational Medicinal Product (IMP) in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently from the authorized form, used for an unauthorized indication, or when used to gain further information about the authorized form.

In this protocol, the IPs are the following:

Cohort 1:

- nivolumab 480 mg + relatlimab 160 mg FDC IV
- nivolumab 960 mg + relatlimab 320 mg FDC + [redacted] rHuPH20 SC

Cohort 2:

- nivolumab 480 mg IV
- nivolumab 1200 mg + [redacted] rHuPH20 SC

[redacted]

There are no non-IPs used in this study.

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

Approved v2.0 930207750 2.0

7.1 Study Interventions Administered

Table 7.1-1: Study Intervention(s) Administered

Type/ Intervention Name/ Dose Formulation	Unit Dose Strength(s)	IMP/Non-IMP/ AxMP Blinded or Open-label	Sourcing[a]	Packaging and Labeling	Current/ Former Name(s) or Alias(es)
Cohort 1 Metastatic Melanoma					
Drug/BMS-986213/ relatlimab/nivolumab/ solution for infusion	[redacted]	IMP/ Open-label	Provided centrally by the Sponsor	Study intervention will be provided vials. Each vial will be labeled as required per country requirement.	BMS-986213; nivolumab + relatlimab FDC IV; Opdualag
Drug/ nivolumab, relatlimab, rHuPH20/ (solution for injection)	[redacted]	IMP/ Open-label	Provided centrally by the Sponsor	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.	BMS-986213; nivolumab + relatlimab + rHuPH20; FDC SC
Cohort 2 – Resected Melanoma					
Drug/ nivolumab (solution for infusion)	nivolumab (10 mg/mL)	IMP/ Open-label	Provided centrally by the Sponsor	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.	BMS-936558/ nivolumab IV
Drug/nivolumab and rHuPH20/ (solution for injection)	nivolumab [redacted]	IMP/ Open-label	Provided centrally by the Sponsor	Study intervention provided in vials. Each vial will be labeled as required per country requirement.	BMS-986298 nivolumab SC

Abbreviations: AxMP, Auxiliary Medicinal Product; IMP, Investigational Medicinal Product; IV, intravenous; SC, subcutaneous; Non_IMP, Non-investigational Medicinal Product; SmPC, summary of product characteristics.

[a] These products may be obtained by investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or SmPC

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Table 7.1-2: Study Cohorts

Cohort Title/ Cohort Type	Intervention Description/ Dosage Levels	Route of Administration/ Administration Time
Cohort 1 Metastatic Melanoma/ Open Label	Participants will receive nivolumab 480 mg + relatlimab 160 mg on Day 1 for first 2 cycles (28-day cycle).	IV Infusion over 30 minutes
	Participants will receive nivolumab 960 mg + relatlimab 320 mg rHuPH20 [redacted] beginning on Day 1 of Cycle 3 for up to 2 years (28-day cycle).	SC injection [redacted]
Cohort 2 Resected Melanoma/ Open Label	participants will receive nivolumab 480 mg on Day 1 for first 2 cycles (28-day cycle).	IV Infusion over 30 minutes
	Participants will receive nivolumab 1200 mg + rHuPH20 [redacted] beginning on Day 1 of Cycle 3 for up to 1 year (28-day cycle).	SC injection [redacted]

7.1.1 General Considerations

Study treatment will be dispensed at the study visits as listed in Section 2 (Schedule of Activities). The selection and timing of dose for each participant is provided in Table 7.1-2. The selection, timing, and other parameters regarding dose administration for participants are further described as follows:

Treatment cycles are 28 days in length (Q4W).

Cohort 1 will receive nivolumab + relatlimab FDC IV on Day 1 of Cycle 1 and Cycle 2 (± 3 days).

Starting on Cycle 3 Day 1, nivolumab + relatlimab FDC will be administered SC Q4W ± 3 days on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of treatment, lost to follow-up, death, or the end of study, whichever occurs first, up to 2 years.

Cohort 2 will receive nivolumab IV on Day 1 of Cycle 1 and Cycle 2 (± 3 days).

Starting on Cycle 3 Day 1, nivolumab will be administered SC Q4W ± 3 days on Day 1 of each treatment cycle until disease recurrence, unacceptable toxicity, withdrawal of consent, lost to follow-up, completion of treatment, death, or the end of study, whichever occurs first, up to 1 year.

Participants should begin study treatment within 3 calendar days of treatment assignment.

- There will be no dose escalations or reductions of immunotherapy allowed.
- Premedications are not recommended for the first dose of immunotherapy.
- Participants should be carefully monitored for infusion/local site reactions during immunotherapy administration.

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- If an acute infusion/site reaction is noted, participants should be managed according to Section 7.4
- Participants should receive study therapy until disease progression (Cohort 1) or recurrence (Cohort 2), unacceptable toxicity, lost to follow-up, death, withdrawal of consent, completion of treatment, or study termination by the sponsor, whichever comes first.
- Doses of study therapy may be interrupted (for IV administration only), delayed, or discontinued depending on how well the participant tolerates the treatment according to Section 7.4.1.
- Dosing visits must not be skipped, only delayed. See Section 7.4 and Section 8.1.

[redacted]

7.1.2 *Intravenous Administration of nivolumab Combined with relatlimab Administration* [redacted]

On Day 1 of Treatment Cycle [redacted] participants in Cohort 1 will receive an IV infusion of nivolumab and relatlimab FDC [redacted]

[redacted]

7.1.3 *Subcutaneous Administration of nivolumab Combined with relatlimab Administration* [redacted]

[redacted], participants will be administered nivolumab + relatlimab SC Q4W ±3 days on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of treatment, death, or the end of study, whichever occurs first (as shown in SoA Table 2-3) up to 2 years.

[redacted]

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[redacted]

7.1.4 Intravenous Administration of nivolumab [redacted]

Participants in Cohort 2 will initially receive nivolumab 480 mg administered [redacted], Q4W ± 3 days on Day 1 [redacted]

[redacted]

7.1.5 Subcutaneous Administration of nivolumab with rHuPH20 [redacted]

[redacted], participants will be administered nivolumab SC Q4W ± 3 days on Day 1 of each treatment cycle until recurrence, unacceptable toxicity, withdrawal of consent, completion of treatment, death, or the end of study, whichever occurs first (as shown in SoA Table 2-4) up to 1 year.

[redacted]

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[redacted]

7.2 Assignment to Study Intervention

Each site user will receive login information and/or directions on how to access IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document.

During the screening visit, 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 5-digit participant number which will be unique across all sites. Every participant who signs the informed consent form must be assigned a participant number in IRT. The investigator or designee will register the participant for treatment assignment by following the treatment assignment procedures established by BMS. The following information is required for treatment assignment:

- Confirmation of informed consent
- Year of birth
- Gender at birth

All enrolled participants will be assigned sequential participant numbers starting with [redacted] (eg, [redacted]). [redacted]. For example, the first participant screened (ie, enrolled) at site number 1 will have a PID of [redacted].

Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will login to the IRT to enroll the participant.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

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7.4 Dosage Modification

No dose modifications for either treatment are permitted.

7.4.1 Dose Delay Criteria for nivolumab and nivolumab + relatlimab FDC

Dose delay criteria apply for all drug-related AEs graded using NCI-CTCAE v5.0 (regardless of whether the event is attributed to nivolumab, relatlimab, or rHuPH20).

Delay administration of nivolumab IV or nivolumab + relatlimab FDC IV or nivolumab SC or nivolumab + relatlimab FDC SC if any of the delay criteria in Table 7.4.1-1 and Table 7.4.1-2 are met.

Delay nivolumab IV or nivolumab + relatlimab FDC IV or nivolumab or nivolumab SC + relatlimab FDC SC dosing for any AE, laboratory abnormality, or intercurrent illness that in the judgment of the investigator, warrants delaying the dose of study medication.

[redacted]

No dose escalations or reductions are permitted in the study.

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Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation nivolumab + relatlimab FDC

Drug-Related Adverse Event (AE) per CTCAE V5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or Diarrhea	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 4	Permanently discontinue	
[redacted]			
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 4	Permanently discontinue	
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1.
	Grade 3 or 4	Permanently discontinue	

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Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation nivolumab + relatlimab FDC

Drug-Related Adverse Event (AE) per CTCAE V5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Hepatic			
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T. Bili) increased	AST or ALT > 3× and ≤5× upper limit of normal (ULN) or T. Bili >1.5× and ≤3× ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5× ULN or T. Bili > 3× ULN, regardless of baseline value	Delay dose or permanently discontinue	In most cases of AST or ALT > 5 × ULN, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/designee must occur and approval from Medical Monitor prior to resuming therapy.
	Concurrent AST or ALT > 3 × ULN and T. Bili > 2 × ULN, regardless of baseline value	Permanently discontinue	
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study intervention.
	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤1 or baseline value, or is adequately controlled with glucose-controlling agents.

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Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation nivolumab + relatlimab FDC

Drug-Related Adverse Event (AE) per CTCAE V5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Hyperglycemia	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study intervention.
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study intervention.
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study intervention.
Skin			
	Grade 2 rash covering >30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤10% body surface area

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Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation nivolumab + relatlimab FDC

Drug-Related Adverse Event (AE) per CTCAE V5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Rash	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤10% body surface area
	Grade 4 rash or confirmed SJS, TEN, or DRESS	Permanently discontinue	
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if encephalitis is not drug-related, then dosing may resume when AE resolves
	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if myelitis is not drug-related, then dosing may resume when AE resolves
	Any Grade drug-related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3 or 4	Permanently discontinue	

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Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation nivolumab + relatlimab FDC

Drug-Related Adverse Event (AE) per CTCAE V5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated.	Permanently discontinue	
[redacted]			

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Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation nivolumab + relatlimab FDC

Drug-Related Adverse Event (AE) per CTCAE V5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Clinical AE			
Pancreatitis: Amylase or Lipase increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when patient becomes asymptomatic.
	Grade 4	Permanently discontinue	
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If patient requires oral steroids for uveitis, then permanently discontinue study intervention.
	Grade 3 or 4 uveitis	Permanently discontinue	
Other Drug-Related AE (not listed above)	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	

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Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation nivolumab + relatlimab FDC

Drug-Related Adverse Event (AE) per CTCAE V5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Lab abnormalities			
Other Drug-Related lab abnormality (not listed above)	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding.
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study intervention: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset
Injection Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions.)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	[redacted]

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; DRESS, drug reaction with eosinophilia and systemic symptoms; FDC, fixed-dose combination; GBS, Guillain-Barre syndrome; MG, myasthenia gravis; SJS, Stevens-Johnson syndrome; T. Bili, total bilirubin; TEN, toxic epidermal necrolysis; ULN, upper limit of normal.

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Table 7.4.1-2: Adverse Event Criteria for Delay, Resumption, and Discontinuation of nivolumab

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3	Nivolumab monotherapy: Delay dose	Dosing may resume when AE resolves to baseline
			Nivolumab monotherapy may be resumed when AE resolves to baseline. If Grade 3 diarrhea or colitis recurs while on nivolumab monotherapy, permanently discontinue
	Grade 4	Permanently discontinue	
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 4	Permanently discontinue	
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1.
	Grade 3 or 4	Permanently discontinue	
Hepatic			
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T.bili) increased	AST or ALT > 3x and ≤5x upper limit of normal (ULN) or T.Bili >1.5x and ≤3x ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5 x ULN or T. bili > 3 x ULN, regardless of baseline value	Delay dose or Permanently discontinue	In most cases of AST or ALT > 5 x ULN, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/ designee must occur and approval from Medical Monitor prior to resuming therapy.

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Table 7.4.1-2: Adverse Event Criteria for Delay, Resumption, and Discontinuation of nivolumab

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value	Permanently discontinue	
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤1 or baseline value, or is adequately controlled with glucose-controlling agents.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug.
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management.

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Table 7.4.1-2: Adverse Event Criteria for Delay, Resumption, and Discontinuation of nivolumab

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug.
Skin			
Rash	Grade 2 rash covering >30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤10% body surface area
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤10% body surface area
	Grade 4 rash or confirmed SJS,TEN, or DRESS	Permanently discontinue	
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis (i.e. infection, tumor-related), if encephalitis is not drug-related, then dosing may resume when AE resolves
	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis (i.e. infection, tumor-related), if myelitis is not drug-related, then dosing may resume when AE resolves
	Any Grade drug-related myelitis	Permanently discontinue	

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Table 7.4.1-2: Adverse Event Criteria for Delay, Resumption, and Discontinuation of nivolumab

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3 or 4	Permanently discontinue	
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated.	Permanently discontinue	
Other Clinical AE			
Pancreatitis: Amylase or Lipase increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when patient becomes asymptomatic.
	Grade 4	Permanently discontinue	
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If patient requires oral steroids for uveitis, then permanently discontinue study drug.
	Grade 3 or 4 uveitis	Permanently discontinue	
Other Drug-Related AE **(not listed above)**	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE- First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	

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Table 7.4.1-2: Adverse Event Criteria for Delay, Resumption, and Discontinuation of nivolumab

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	
Other Lab abnormalities			
Other Drug-Related lab abnormality **(not listed above)**	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding.
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset
AEs, which in the judgement of the investigator, require delaying dose	**N/A**	**Delay dose**	
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions.)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	[redacted]

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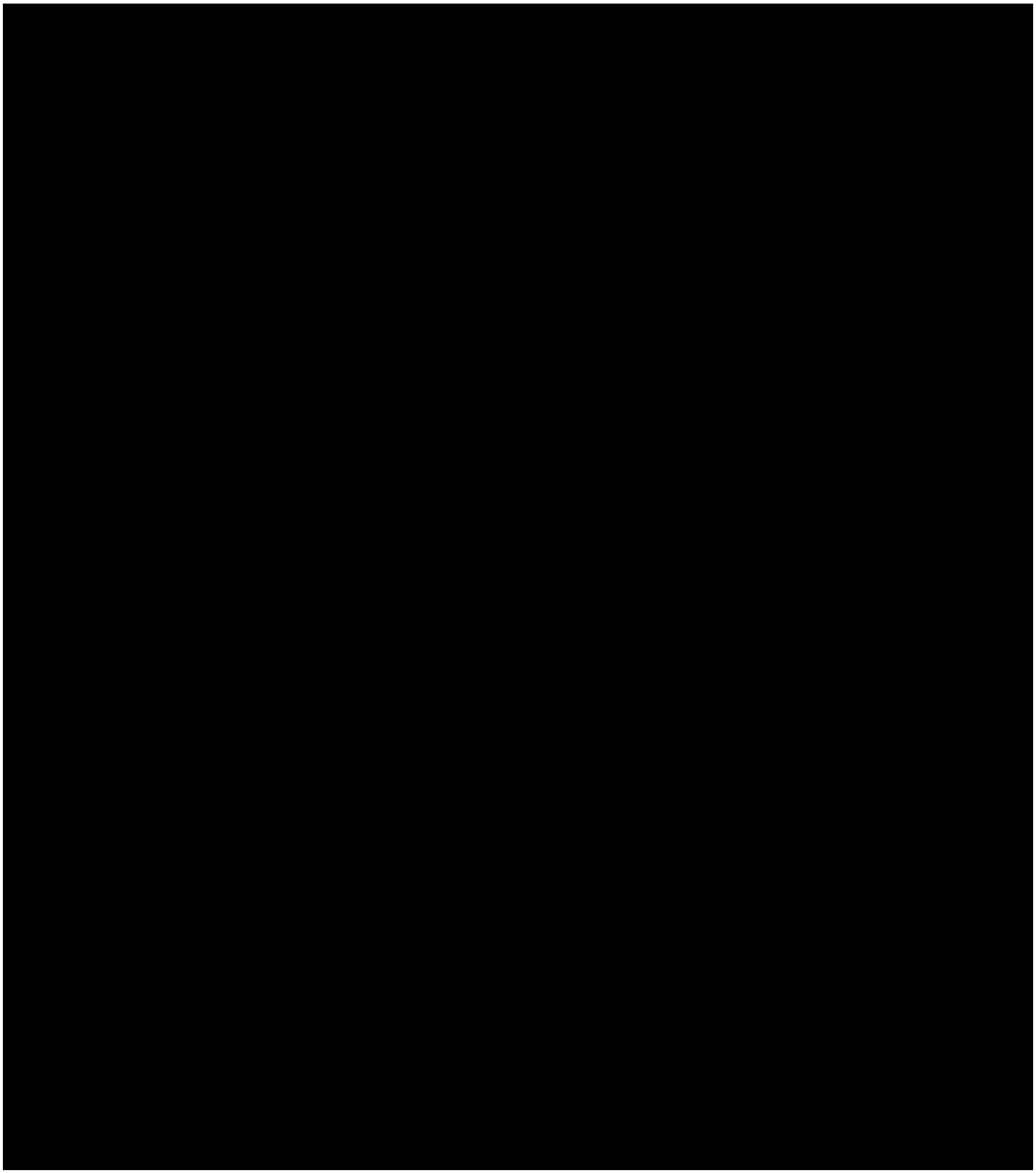

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7.4.4 Treatment of Related Infusion- and Injection-reactions

[redacted]

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[redacted]

7.4.4.2 Management of Local Infusion or Injection Site Reactions

In the clinical experience with nivolumab IV, no tissue necrosis has been observed after accidental extravasations of nivolumab IV. The use of oral medications (eg, antihistamines, acetaminophen/paracetamol) and topically applied therapies such as cold packs and steroid or antihistamine creams or gels is allowed for the treatment of local injection reactions due to nivolumab SC (eg, swelling, erythema, pain, induration, local pruritus) and infusion local site reactions (local inflammation, necrosis due to drug extravasation) including those related to procedures (eg, hematoma). Local/institutional guidelines, if available, can be followed.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

These management strategies are applicable to both cohorts.

7.4.4.3 Management of Needle Stick Injuries

In case of participant needle stick injuries, sites should follow recommended institutional guidelines.

Initial measures should include the following:

- Wash the exposed area right away with water and soap or using a skin disinfectant (antiseptic) such as rubbing alcohol or a hand sanitizer.
- Seek immediate medical attention.
- Notify the site staff.

7.5 Preparation/Handling/Storage/Accountability

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

The product storage manager should ensure that the study intervention is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Sponsor. If

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concerns regarding the quality or appearance of the study intervention arise, the study intervention should not be dispensed, and the Sponsor should be contacted immediately.

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

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

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

7.6 Study Intervention Compliance

Study intervention compliance will be monitored by drug accountability as well as the participant's medical record and eCRF. Drug accountability should be reviewed by the study site staff at each visit to confirm treatment compliance. The source data will be verified by the Site Monitor through regularly scheduled monitoring visits.

7.7 Concomitant Therapy

Concomitant medications are recorded at treatment assignment and throughout the treatment phase of the study in the appropriate section of the eCRF. All medications (prescriptions and over-the-counter medications) continued at the start of the study or started during the study and different from the study treatment must be documented in the concomitant therapy section of the eCRF. Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving BMS-986213 is unknown.

[redacted]

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[redacted]

7.7.2 Other Restrictions and Precautions

Participants are prohibited from joining another interventional clinical trial that includes systemic treatment with another investigational agent (IMP) while they are participating in this study.

7.7.2.1 Imaging Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether they should receive contrast and if so, which contrast agent and dose are appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate

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< 30 mL/min/1.73 m2) 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. Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant enrolled in this study rests with the site radiologist, the investigator, and standards set by the local Ethics Committee.

[redacted]

7.7.4 Antiviral Therapy

Participants on antiviral therapy [redacted] should continue antiviral therapy during the study. Changing of dosage and regimens of antiviral therapy will be at the discretion of the investigator. [redacted]. Adherence to current antiviral therapy should be assessed, and resistance testing performed according to local practices. [redacted]

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If a participant has documented virologic breakthrough due to antiviral resistance, then this should be managed based on standardized regional guidelines and treatment with study drug temporarily withheld.

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

At the end of the study/period, the Sponsor will not continue to provide Sponsor-supplied study intervention to participants/investigators unless the Sponsor chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

The Sponsor reserves the right to terminate access to Sponsor-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of nivolumab or nivolumab + relatlimab FDC is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives; or c) the participant can obtain medication from a government-sponsored or other health program. In all cases, the Sponsor will follow local regulations.

8 DISCONTINUATION CRITERIA

[redacted]

8.1 Discontinuation of Study Intervention

Participants MUST discontinue IP/IMP at the discretion of the investigator for any of the following reasons:

- Participant's request to stop study intervention. Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.
- Any clinical AE, laboratory test result abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by the Sponsor.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness (eg, infectious disease). (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)
- In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the Sponsor Medical Monitor or designee of this event. In most cases,

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the study treatment will be permanently discontinued in an appropriate manner. (refer to Section 9.2.5).

- Disease progression in the absence of clinical benefit as determined by the investigator.
- Noncompliance of the participant with protocol-mandated procedures based on the judgment and agreement of both the investigator and Sponsor.
- [redacted]

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

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

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

Discontinuation of nivolumab or nivolumab + relatlimab FDC SC and nivolumab or nivolumab + relatlimab FDC IV treatment must be permanently discontinued per criteria in Table 7.4.1-1 and Table 7.4.1-2 in Section 7.4.

[redacted]

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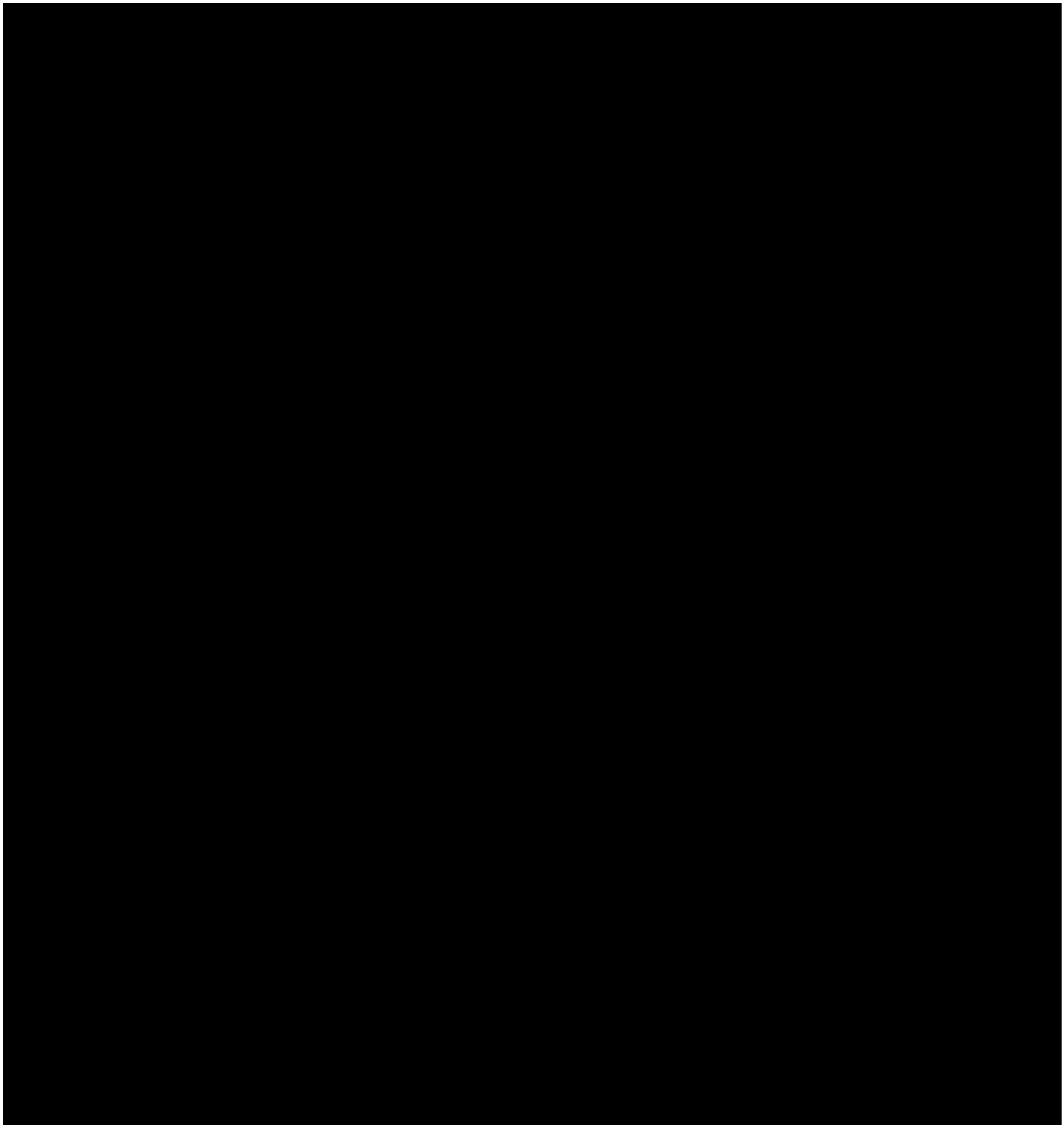

8.3 Discontinuation From the Study

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 the participant to provide this information.

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- 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 eCRF 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.
- Participants will be discontinued if new information regarding the efficacy or safety of SC treatments indicates a detrimental benefit/risk association compared to IV treatment.

8.3.1 Individual Discontinuation Criteria

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

8.4 Lost to Follow-up

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

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of 3 documented phone calls, faxes, or emails, as well as lack of response by participant to 1 registered mail letter. All attempts should be documented in the participant's medical records.
- If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's

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contact information or other public vital status data, such as public health registries and databases, necessary to complete the follow-up portion of the study.

- The site staff and representative will consult publicly available sources, such as public health registries and databases, to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine whether 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, complete 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 time frame defined in the Schedule of Activities (Section 2).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Perform additional measures, including non-study required laboratory tests, as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug-induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study intervention-related toxicities resolve, return to baseline, or are deemed irreversible.
- Evaluate participant immediately to rule out cardiac or pulmonary toxicity if participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate, or changes from baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations).
- Some of the assessments referred to in this section may not be captured as data in the eCRF. 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.

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9.1 Efficacy Surveillance

9.1.1 Imaging Assessment for the Study

Study evaluations will take place outlined in Section 2 Schedule of Activities.

Baseline or screening imaging assessment must be performed during the [redacted] Screening Period utilizing CT or MRI of the chest, abdomen, pelvis and brain MRI or CT (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions) and other clinically indicated sites as determined by the study investigator.

Subsequent imaging assessment should be performed following local guidelines or as needed at the discretion of the investigator.

[redacted]

9.1.2 Investigator Assessment of Recurrence/Progression

For metastatic melanoma:

Tumor assessments should continue per local standards or guidelines irrespective of whether the dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator or designee investigators must report once disease progression has been determined. The timepoint of disease progression should be reported on the eCRF based on the investigator's assessment using RECIST v1.1 criteria to document any disease progression.

For resected melanoma:

Disease recurrence is defined as the appearance of one or more new tumor lesions which can be local, regional, or distant in location from the primary resected site. Specific criteria and definitions for diagnosing recurrence is based on local standards and guidelines. The date of recurrence is the first date when recurrence was observed regardless the method of assessment and should be documented in the eCRF.

9.1.3 Clinical Outcome Assessments

The evaluation of clinical outcomes assessments, specifically patient-reported outcomes is an increasingly important aspect of clinical efficacy and patient experience in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into patient experience that may not be captured through physician reporting.

[redacted] and the PEPQ at the site immediately following treatment administration at Cycle 4 Day 1 [redacted]

The PEQ and PEPQ will be provided in the participant's preferred language, if available, and will be administered via paper. This data will be recorded in the eCRF by the site. If exceptional circumstances preclude the continued administration of measures using planned modalities, then

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alternate administration methods may be required, after consultation with the Sponsor or the Sponsor's representative.

9.1.3.1 Patient Experience Questionnaire (PEQ) and Patient Experience and Preference Questionnaire (PEPQ)

[redacted]. Participants will then complete the PEPQ following treatment administration at Cycle 4 Day 1 to assess patient experience with SC treatment administration and preference between IV and SC treatment administration.[30]

The PEQ and the PEPQ are identical questionnaires, with the exception of the single item to assess preference between route of treatment administration in the PEPQ, and not the PEQ. The PEPQ questionnaire was developed following discussions with clinicians and health economics and outcomes research specialists, regarding the concepts most important when considering patient preference with route of treatment administration. It is a patient self-complete questionnaire containing seven items, assessing patient perceptions regarding:

[redacted]

The PEPQ has been implemented in clinical trials (CA209-8KX and CA209-76U). Patient qualitative interviews were embedded into both those clinical trials, where evidence of the content validity of the PEPQ was generated, indicating that the wording of items and response options is comprehensive and relevant to patients receiving SC treatment administration.

[redacted]

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[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.

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.

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

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.

Refer to Appendix 3 for SAE reporting.

9.2.1 Period and Frequency for Collecting AE and SAE Information

For participants assigned to treatment and never treated with study intervention, collect SAEs [redacted] from the date of treatment assignment.

All AEs and SAEs must be collected from the time of signing informed consent, including those thought to be associated with protocol-specified procedures, and must continue [redacted] following the last treatment administration. All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the time of the participant's signing the informed

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consent until [redacted] for Cohort 1 and [redacted] for Cohort 2 following discontinuation of study treatment.

The investigator must report any SAE that occurs after these periods and that is believed to be related to a study intervention or protocol-specified procedure (eg, imaging assessment, clinical blood draw).

- All SAEs will be recorded and reported to the Sponsor or designee, without undue delay, but no later than within 24 hours of becoming aware of the events, 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.

9.2.2 Method of Detecting AEs and SAEs

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

Every AE must be assessed by the investigator to verify whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs (as defined in Section 9.2: Adverse Events), 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 8.4: Lost to Follow-up).

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

Additionally, all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.4) or for suspected cases, until SARS-CoV-2 infection is ruled-out.

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 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 suspected, unexpected serious adverse reaction (SUSAR) is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

This section is not applicable for women not of child-bearing potential.

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

In all cases, the study intervention will be discontinued in an appropriate manner.

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.

After a pregnancy is confirmed, study treatment must be discontinued, and the participant followed. If, for whatever reason, the pregnancy has ended, as confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant, sponsor, and IRB/EC, as applicable.

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9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug-induced Liver Injury

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

A potential DILI is defined as follows:

- Aminotransferase (alanine aminotransferase or aspartate aminotransferase) 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 aminotransferase elevation and hyperbilirubinemia, including, but not limited to, [redacted], pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

9.2.8 Other Safety Considerations

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

9.3 Overdose

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

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In the event of an overdose, the investigator/treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AEs/SAEs and laboratory test result abnormalities
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions 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 Section 2: Schedule of Activities.

9.4.1 Physical Examinations

Refer to Section 2: Schedule of Activities.

9.4.2 Vital Signs

Refer to Section 2: Schedule of Activities.

[redacted]

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- All clinical safety laboratory assessments will be performed locally per the Schedule of Activities.

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Alkaline phosphatase Gamma-glutamyl transferase only when alkaline phosphatase is ≥ Grade 2 Lactate dehydrogenase Creatinine Blood urea nitrogen or serum urea Uric acid Glucose	Albumin Sodium Potassium Chloride Calcium Phosphorus Thyroid-stimulating hormone (TSH), free T3 and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment Creatine phosphokinase – at screening only and for Cohort 1 only Creatinine clearance (CrCl) – if used, at screening only

[redacted]

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Table 9.4.4-1: Clinical Laboratory Assessments

[redacted]

Urinalysis
Protein
Glucose
Blood
Leukocyte esterase
Specific gravity
pH
Serology

[redacted]

On Treatment : Participants with positive HBsAg (hepatitis B surface antigen) or positive anti-HBc (hepatitis B core antibody) - test HBV DNA up to 3 days before every dose. If Hepatitis B Reactivation> 1 log IU/mL increase in HBV DNA from screening baseline refer to Table 7.4.1-1 HIV-1 and -2 antibodies (screening only; testing for HIV must be performed at sites where mandated by local requirements [see Appendix 8]). SARS-CoV-2 viral test (if clinically indicated)
Other Analyses
Pregnancy test (WOCBP only: screening, during treatment, and follow-up).
Follicle stimulating hormone (screening only for women only, if needed to document post-menopausal status)

Abbreviations: HIV, human immunodeficiency virus; WOCBP, women of childbearing potential.

9.4.5 Imaging/Other Safety Assessment

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

9.5 Pharmacokinetics

Not applicable.

9.6 Immunogenicity Assessments

Not applicable.

9.7 Biomarkers

9.7.1 Germline Genetics

Not applicable.

9.7.2 Other Biomarkers

Not applicable.

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9.8 Optional Future Research

This protocol will not include sample collection and/or residual sample storage for optional future research.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

This is a descriptive study. No formal hypothesis testing will be performed.

10.2 Sample Size Determination

Cohort 1 Metastatic melanoma: The primary objective of this cohort is to evaluate patient preference (Question 7 of the PEPQ) for route of administration upon switching from IV to SC. The primary endpoint is the proportion of participants who prefer the SC route of administration as assessed by PEPQ Question 7 after Cycle 4 Day 1. [redacted] participants are planned to be treated in Cohort 1, of which approximately participants are expected to be evaluable for the primary endpoint. [redacted] The PEPQ Evaluable population is defined as all enrolled participants who have received two doses of nivolumab + relatlimab FDC IV, two doses of nivolumab + relatlimab FDC SC and have answered Question 7 of the PEPQ.

Cohort 2 Resected melanoma: The primary objective of this cohort is to evaluate patient preference (Question 7 of the PEPQ) for route of administration upon switching from IV to SC. The primary endpoint is the proportion of participants who prefer the SC route of administration as assessed by PEPQ Question 7 after Cycle 4 Day 1. [redacted] participants are planned to be treated in Cohort 2, of which approximately participants are expected to be evaluable for the primary endpoint. [redacted] The PEPQ Evaluable population is defined as all enrolled participants who have received two doses of both nivolumab IV, nivolumab SC and have answered Question 7 of the PEPQ.

[redacted]

Approved v2.0 930207750 2.0

[redacted]

10.3 Analysis Sets

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

Population	Description
All Screened Participants	All participants who signed an ICF and registered into the study. This is the primary dataset for disposition.
All Enrolled Participants	All screened participants who meet study eligibility criteria and enroll in the study. This is the primary dataset for analyses of demography, protocol deviations, and baseline characteristics.
All Treated Participants	All enrolled participants who receive at least one dose of study intervention (on-study). This is the primary dataset for dosing and safety analyses.
PEPQ Evaluable	All treated participants who have received 2 doses of both IV and SC study treatments and have answered Question 7 of the PEPQ.
[redacted]	

Abbreviations: ICF, informed consent form; IV, Intravenous; PEPQ, Patient Experience and Preference Questionnaire; [redacted].

10.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed, and it will include a more technical and detailed description of the statistical analyses described in this section, eg, the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

[redacted]

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10.4.1 General Considerations

All analyses will be descriptive in nature. Descriptive statistics including n (the corresponding sample size), means, medians, standard deviations, minimum, and maximum will be calculated for continuous variables, and categorical data will be summarized using frequency counts and percentages. [redacted]

10.4.2 Primary Endpoint(s)

Metastatic melanoma Cohort 1

The primary endpoint is the proportion of evaluable participants that prefer nivolumab + relatlimab FDC SC using PEPQ (Question 7). Participants' preference will be assessed using the single item in the PEPQ (Question 7) which asks participants to report their preferred route of treatment administration based on the PEPQ Evaluable population.

Resected melanoma Cohort 2

The primary endpoint is the proportion of evaluable participants that prefer nivolumab SC using PEPQ (Question 7). Participants' preference will be assessed using the single item in the PEPQ (Question 7) which asks participants to report their preferred route of treatment administration based on the PEPQ Evaluable population.

For both cohorts, the analyses will be descriptive, and the number and percentage of participants who report a preference for 'IV infusion', 'SC injection', or 'no preference' will be presented. [redacted]. Participants who do not complete Question 7 of the PEPQ will be excluded from the PEPQ evaluable population.

10.4.3 Secondary Endpoint(s)

For both cohorts, safety and tolerability will be measured by incidence of all AEs/SAEs, treatment-related AEs including IMAEs, Other events of special interest (OESIs), AEs leading to discontinuation or death, laboratory abnormalities and injection/infusion-related AEs. All treated participant population will be used for safety and tolerability analyses.

AEs will be coded using the Medical Dictionary for Regulatory Activities, and the most recent version of the dictionary at the time of the database lock will be used. AEs and laboratory values will be graded for severity according to the NCI-CTCAE version 5.0.

Frequency distribution of treated participants with AE using the worst CTCAE grade will be presented. Participants will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the "total participant" row at their worst CTCAE grade, regardless of SOC or PT.

The secondary endpoints for this study will be reported for each cohort and summarized by:

overall treatment duration
treatment switch period (Cycle 1-4)

Approved v2.0 930207750 2.0

route of administration

[redacted]

10.4.5 Other Safety Analyses

Not applicable.

10.4.6 Other Analyses

Not applicable.

[redacted]

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[redacted]

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12 APPENDICES

Approved v2.0 930207750 2.0

APPENDIX 1 ABBREVIATIONS

Term	Definition
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
BICR	blinded independent central review
BMS	Bristol-Myers Squibb Company
CI	confidence interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRF	Case Report Form, paper or electronic
CSR	Clinical Study Report
CT	computed tomography
DNA	deoxyribonucleic acid
[redacted]	
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EU	European Union
FDA	US Food and Drug Administration
FDC	fixed-dose combination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
[redacted]	
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMAE	Immune mediate adverse event
IMP	Investigational Medicinal Product
IRB	Institutional Review Board

Approved v2.0 930207750 2.0

Term	Definition
IRT	Interactive Response Technology
IU	international unit
IUS	intrauterine system
IV	intravenous(ly)
LAG-3	lymphocyte activation gene-3
[redacted]	
mAb	monoclonal antibody
MRI	magnetic resonance imaging
[redacted]	
OESI	Other events of special interest
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PEQ	Patient Experience Questionnaire
PEPQ	Patient Experience and Preference Questionnaire
PFS	progression-free survival
[redacted]	
RECIST	Response Evaluation Criteria in Solid Tumours
[redacted]	
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOP	Standard Operating Procedure
[redacted]	
ULN	Upper limit of normal
US	United States
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential

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APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

FINANCIAL DISCLOSURE

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

RECRUITMENT AND INFORMED CONSENT PROCEDURES

Potential participants may be identified by the recruiting investigational team (called “site”) within the affiliated clinic/hospital, and/or group practice, through their own chart/database review, using

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the inclusion/exclusion criteria defined by the protocol. Potential participants may also be referred to the site by medical doctors from surrounding hospitals/practices or directly contact one of the investigative 'sites' following study and site identification through a public registry, such as clinicaltrials.gov or euclinicaltrials.eu. The investigator has access to the participant's medical file, so, the medical data will remain confidential without the sponsor having access to them. Recruitment material will also be utilized as an additional tool to recruit participants per local regulations and requirements.
The principal investigator or sub-investigator, or a qualified designee of the investigator's research team will approach potential participants to discuss the option of participating in the clinical trial and the consent process. Informed consent will be obtained by the principal investigator or a qualified delegate on the principal investigator's research team from each participant prior to enrolment into the study. The participant will be provided the opportunity to read the information sheet and consent form and have all their questions and concerns addressed before giving consent in writing.

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 the participant that his/her participation is voluntary. The participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for the participant to inquire about the details of the study.
- Obtain an ICF signed and personally dated by the participant and by the person who conducted the informed consent discussion.
- Include a statement in the participant's medical record that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent the participant to the most current version of the ICF(s) during his/her participation.

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- 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.

If informed consent is initially given by a participant's 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.

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

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

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

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

SOURCE DOCUMENTS

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

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

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

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures.

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Such systems may include, but are not limited to, electronic medical records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

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

STUDY INTERVENTION RECORDS

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

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

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

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents, or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory test result abnormalities that are reported or identified during the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to serious adverse events (SAEs) and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the Sponsor or designee.

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. For eCRFs, review and approval/signature are completed electronically through the BMS EDC tool. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

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

MONITORING

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

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

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Certain CRF electronic files may serve as source documents.

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY INTERVENTION

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

If	Then
Study interventions supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study intervention containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxic or biologic agents). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. However, unused Investigational Medicinal Product must be reconciled by the site monitor/clinical research associate prior to destruction. If study interventions will be returned, the return will be arranged by the responsible study monitor.

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If	Then
Study interventions sourced by site, not supplied by BMS (or its vendors; eg, study interventions sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

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

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

STUDY AND SITE CLOSURE

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

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

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

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For study termination:

- Discontinuation of further study intervention development

For site termination:

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

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

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

In the European Union (EU, the summary of results and summary for laypersons will be submitted within 1 year of the end of trial in the EU/European Economic Area and third countries.

CLINICAL STUDY REPORT

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

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

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

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to the Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements

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set forth in the Clinical Trial Agreement (CTAg) governing [study site or investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to the Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the period set forth in the CTAg.

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

Authorship of publications at the Sponsor is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). Authorship selection is based on significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

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

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

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

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

Approved v2.0 930207750 2.0

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

ADVERSE EVENTS

Adverse Event Definition:

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

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory test result), symptom, or disease temporally associated with the study intervention 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 sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal laboratory test results or other safety assessment findings should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though the condition may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the iinvestigator), 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).

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DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

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

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

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

EVALUATING AES AND SAES

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

Assessment of Intensity
The investigator will make an assessment of grade for each AE and SAE according to the NCI-CTCAE version 5.0.

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.)

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

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

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: worldwide.safety@BMS.com

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

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

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APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

DEFINITIONS

Women of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

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

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

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

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End of Relevant Systemic Exposure

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

METHODS OF CONTRACEPTION

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

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

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- Vasectomized partner.

Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence.

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2 of the protocol.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participant chooses to forego complete abstinence.
- Periodic abstinence (including, but not limited to, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactation amenorrhea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the Investigational Medicinal Product and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria [redacted]

[c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria and [redacted]

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.

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• Cervical cap with spermicide. • Vaginal sponge with spermicide. • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action. (This method of contraception cannot be used by WOCBP participants in studies in which hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • LAM.

COLLECTION OF PREGNANCY INFORMATION

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

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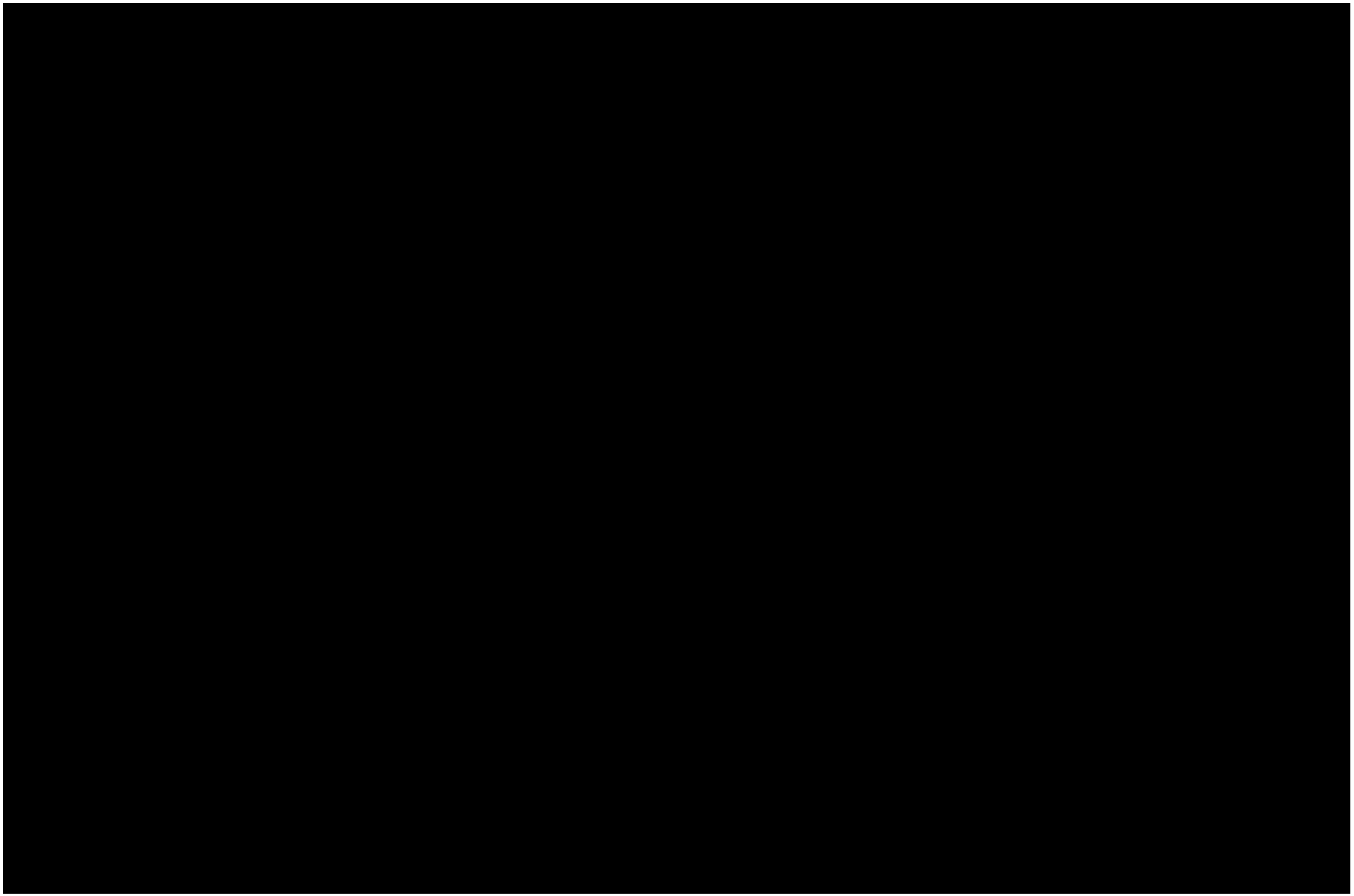

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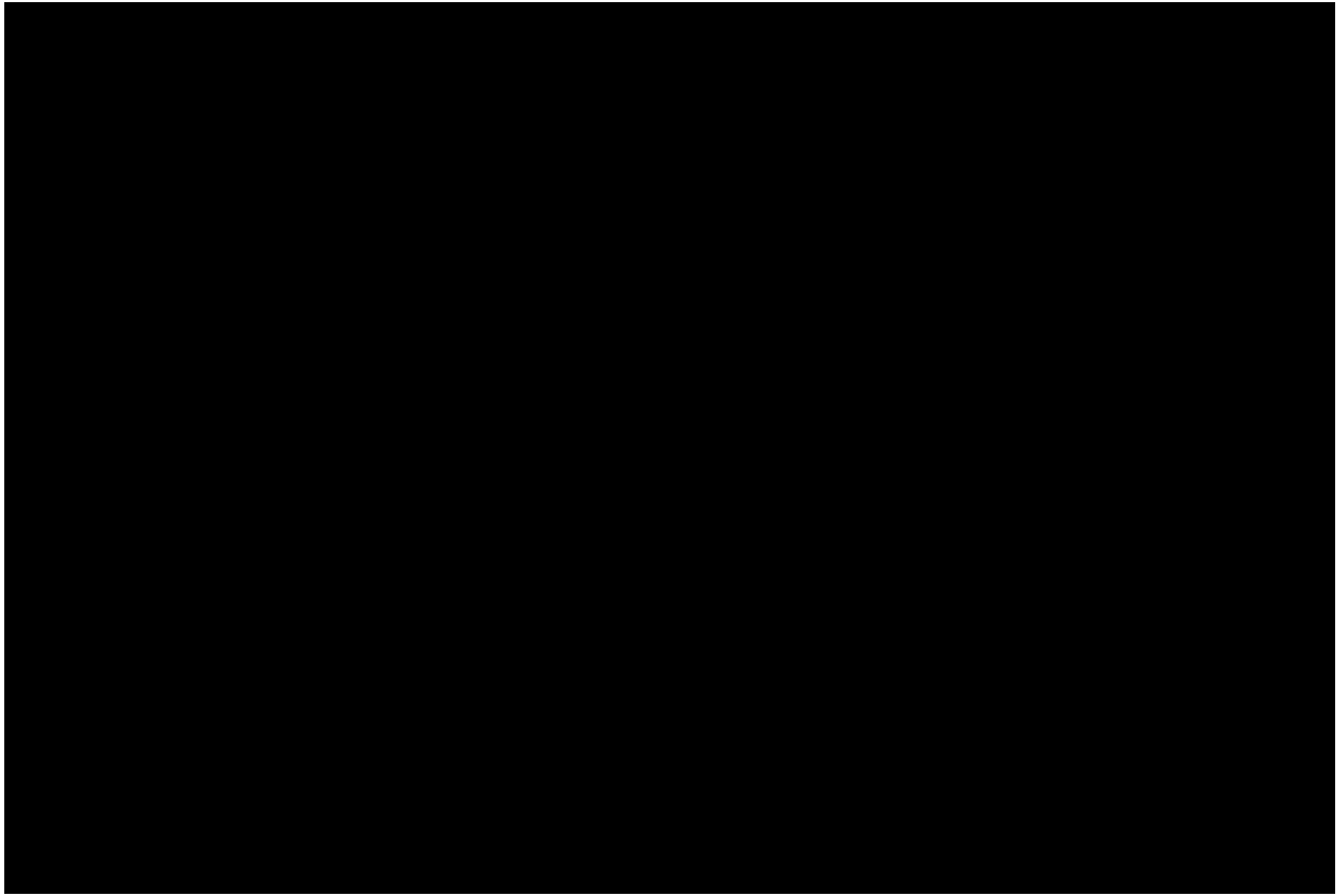

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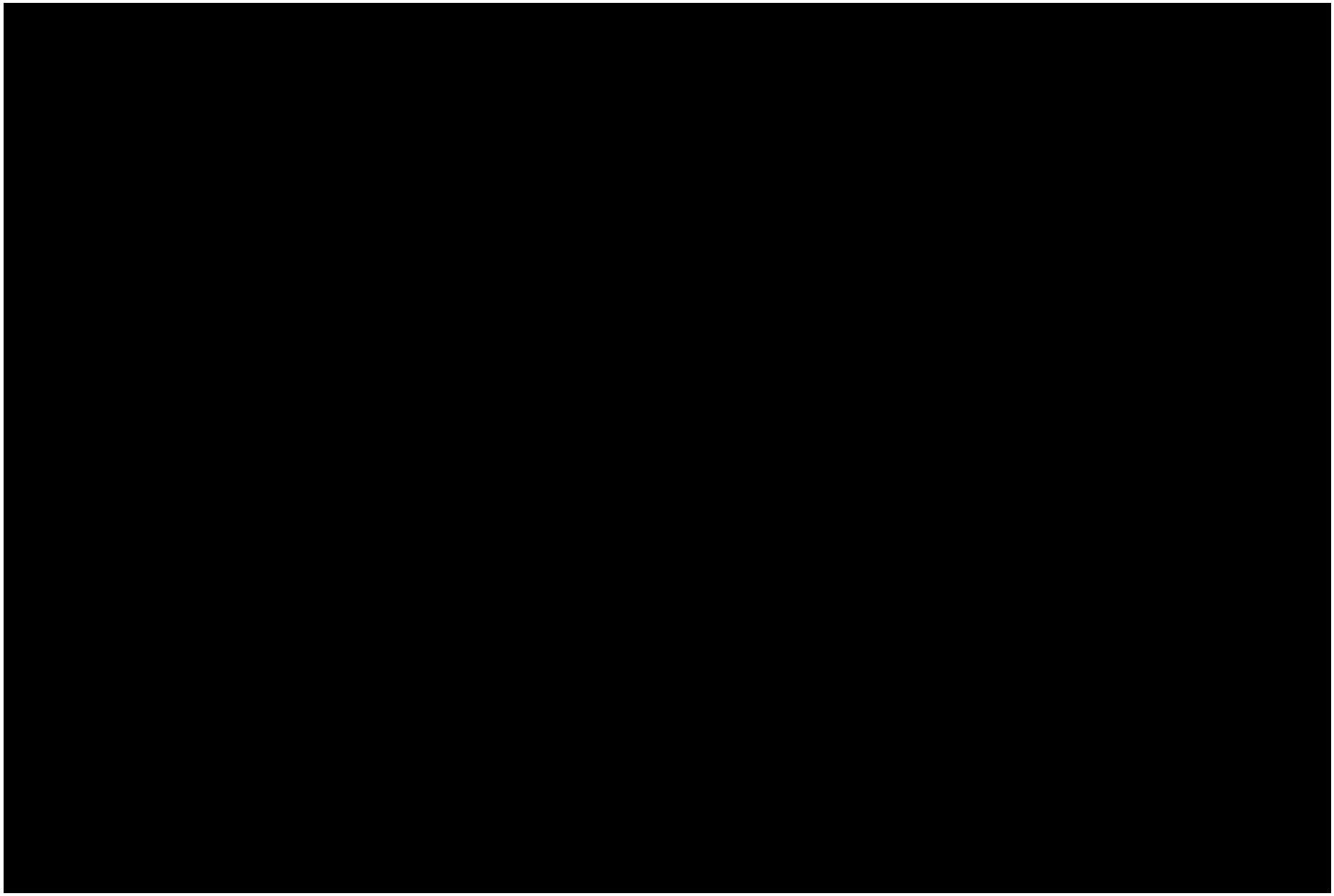

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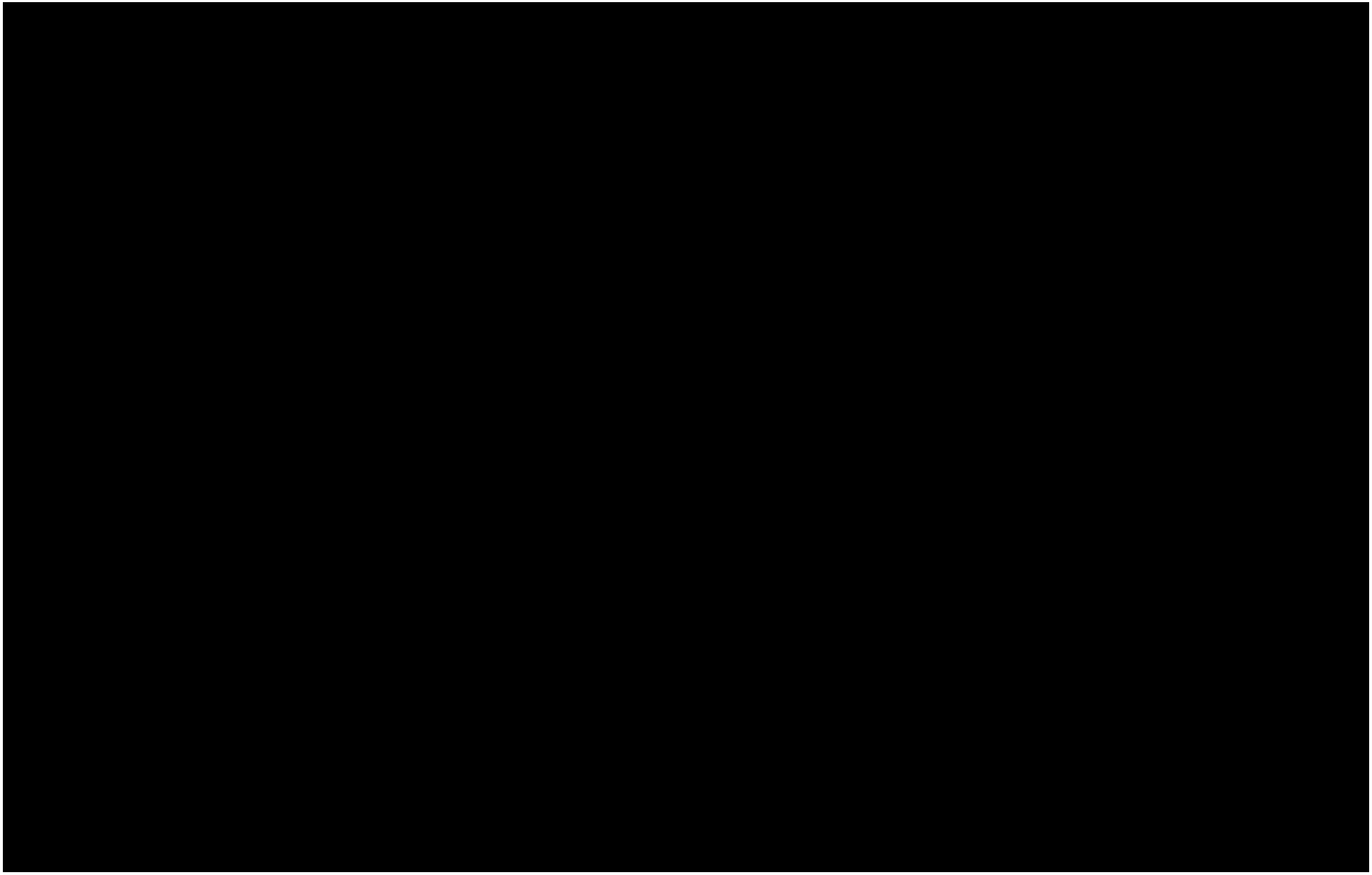

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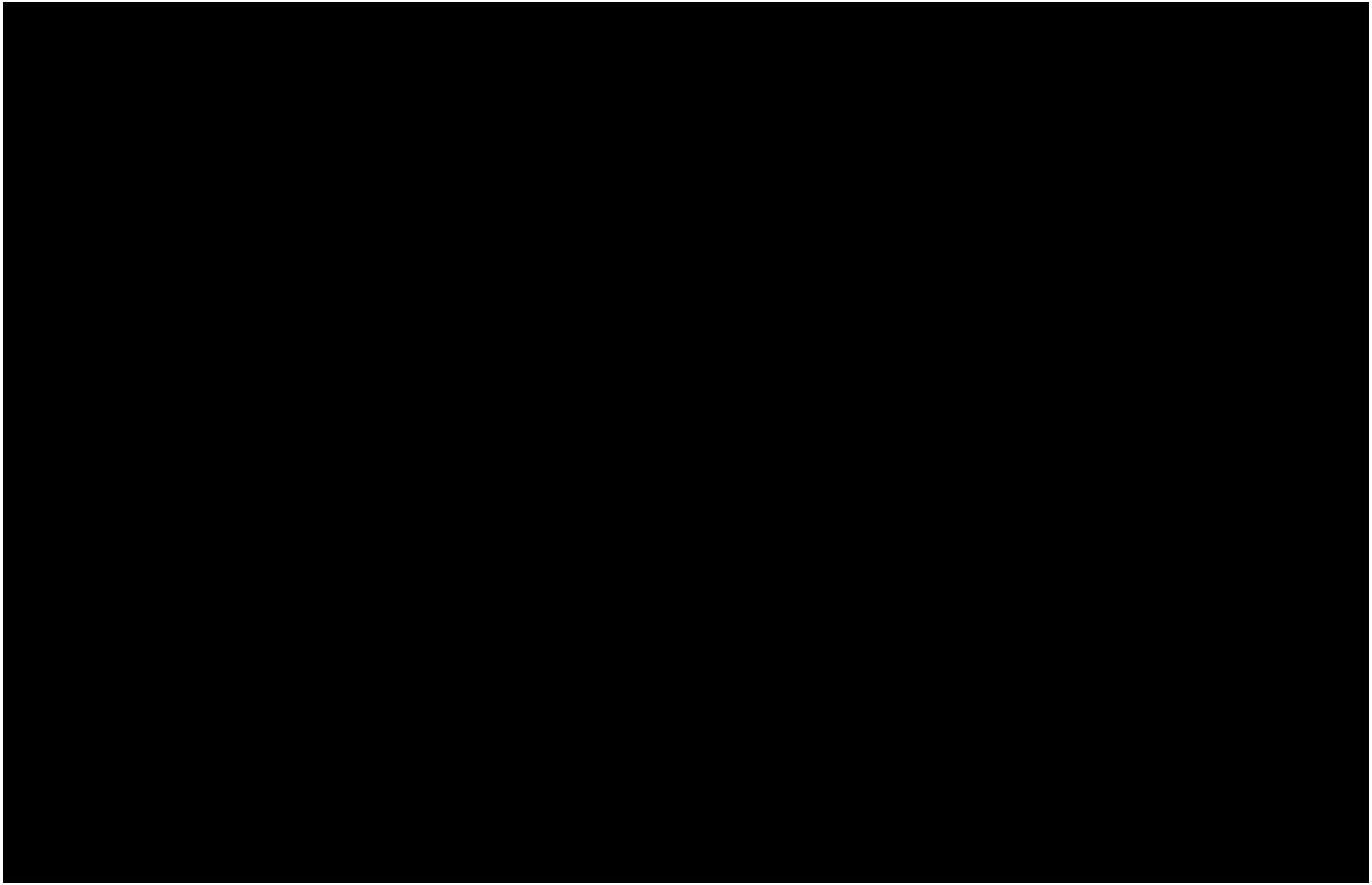

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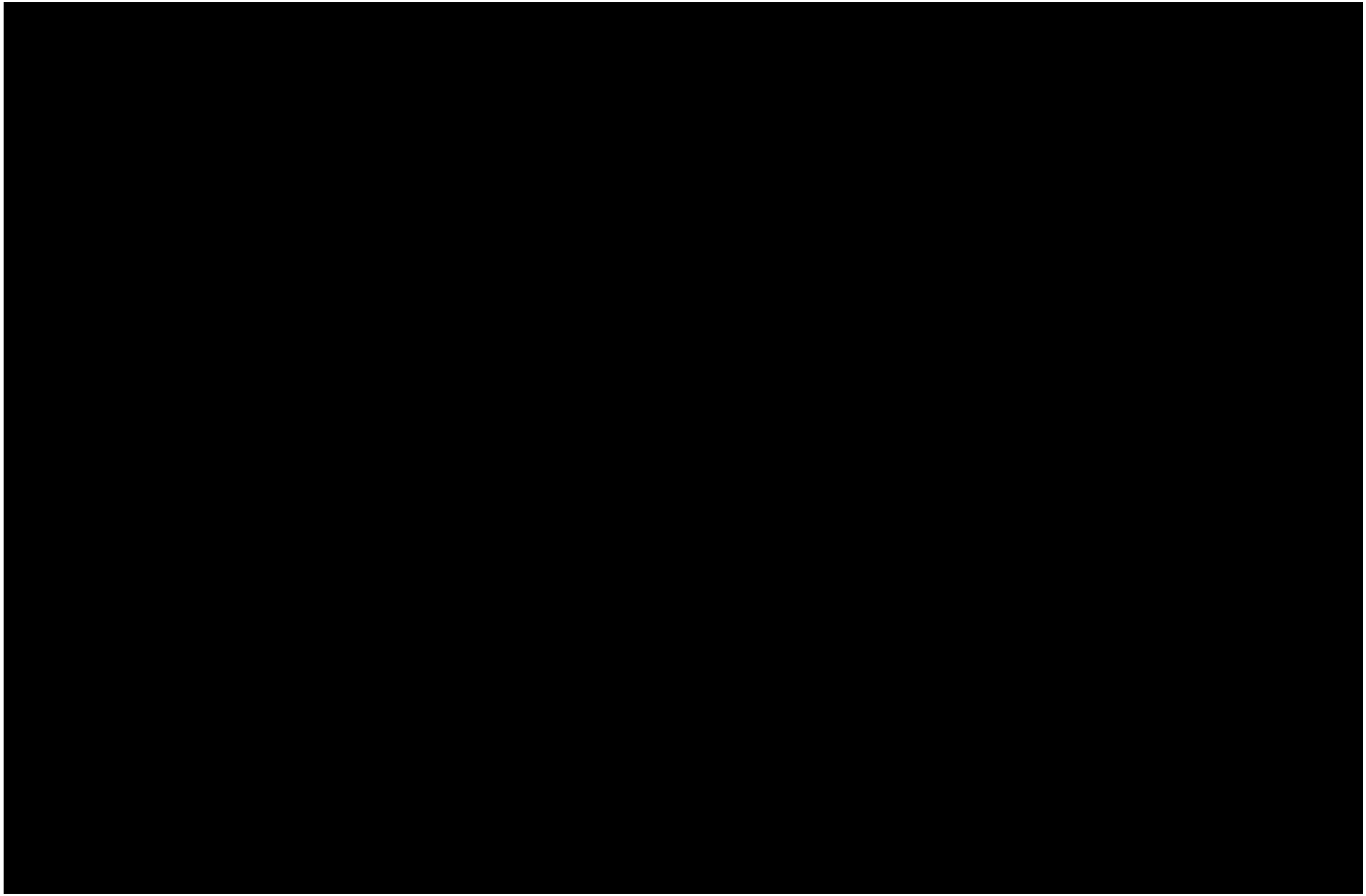

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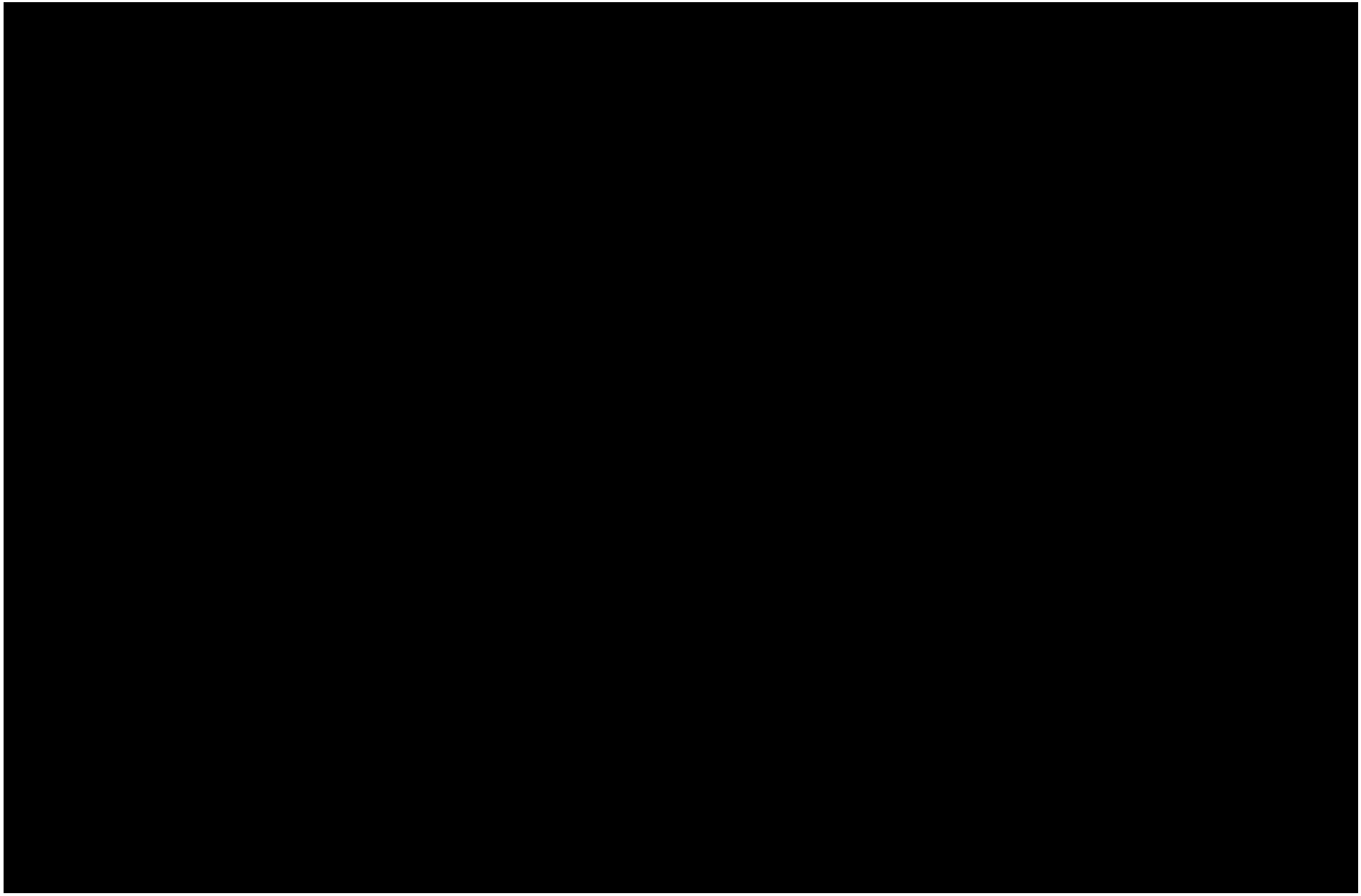

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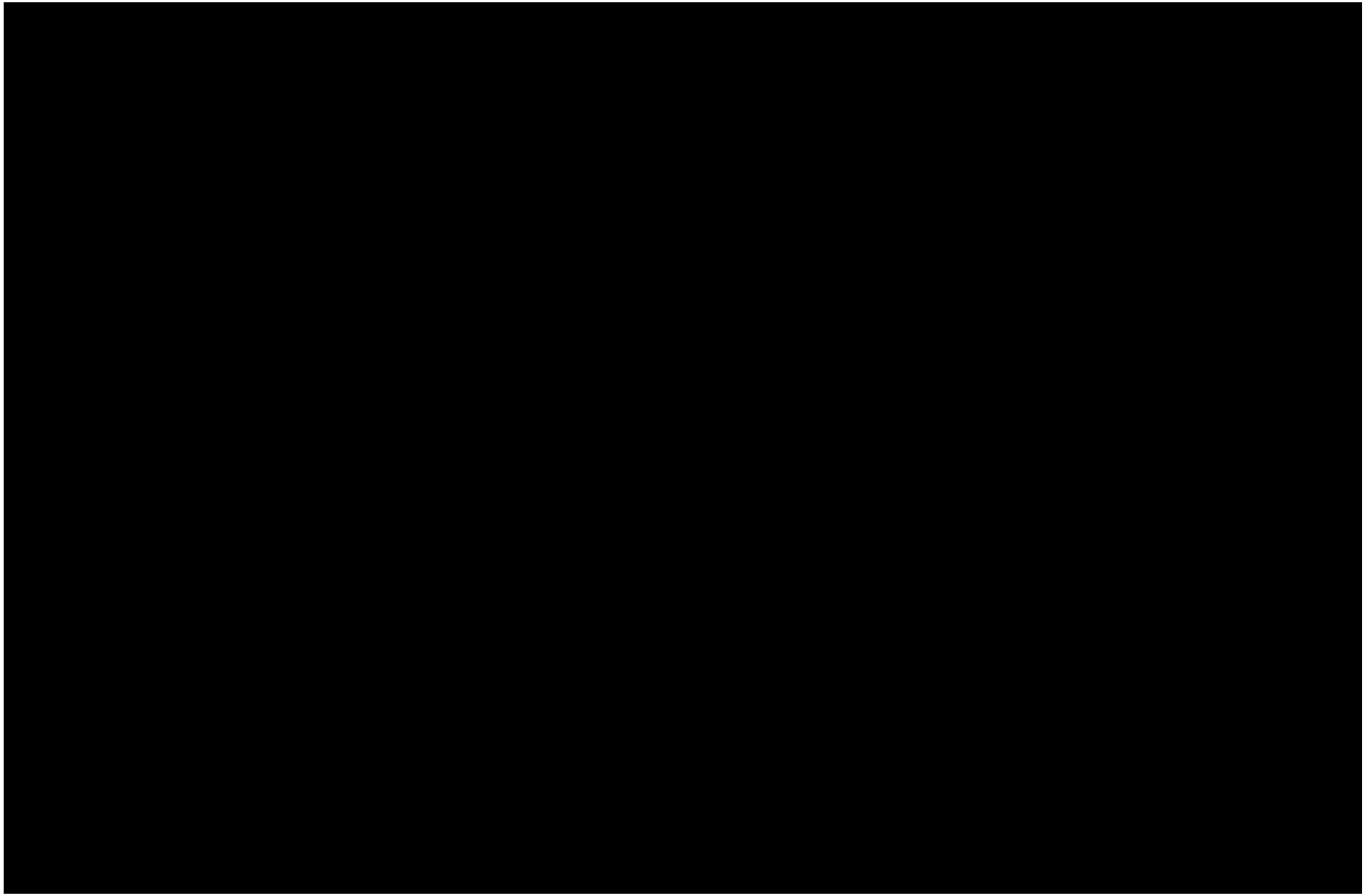

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APPENDIX 6 ECOG PERFORMANCE STATUS SCALE AND CONVERSION FORM

ECOG [a]	
Score	**Description**
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

[a] Reference: Oken MM, Creech RH, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649655.

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APPENDIX 7 AJCC MELANOMA STAGING (CANCER STAGING MANUAL 8TH EDITION)

[From AJCC Cancer Staging Manual, 8th Edition. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. editors. Springer International Publishing. 2017 (pages 577 & 578)]

Definition of Primary Tumor (T)

T Category	Thickness	Ulceration Status
TX: primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable	Not applicable
T0: no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 0.8-1.0 mm	With ulceration With or without ulceration
T2	>1.0-2.0 mm	Unknown or unspecified
T2a	>1.0-2.0 mm	Without ulceration
T2b	>1.0-2.0 mm	With ulceration
T3	>2.0-4.0 mm	Unknown or unspecified
T3a	>2.0-4.0 mm	Without ulceration
T3b	>2.0-4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

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APPENDIX 8 COUNTRY SPECIFIC REQUIREMENTS/DIFFERENCES

Cohort 1:

Original Language	Country-specific Language or Differences
Criteria for exclusion of HIV-positive participants in **any country** where exclusion of HIV-positive participants is locally mandated. Section 6.2 Exclusion Criteria, criterion 1) h)	"Participants must not have known human immunodeficiency virus (HIV) positive with an AIDS defining opportunistic infection within the last year, or a current CD4 count <350 cells/uL. Participants with HIV are eligible if: • they have received antiretroviral therapy (ART) for at least 4 weeks prior to randomization as clinically indicated while enrolled on study. • they continue on ART as clinically indicated while enrolled on study. • 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 (Refer to Appendix 9.)"** to be replaced with **"Positive test for HIV."**
Section 2 Flow Chart/Time and Events Schedule, Tables 2-1 and 2-2: Screening Assessments - Laboratory Tests	Add "HIV" to the list of laboratory tests.
USA Section 2-1 Screening Procedural Outline None.	Added a row, Demography and Participant Characteristics.
[redacted]	[redacted]
None.	[redacted]
Section 10.4 Statistical Analyses None.	Added the following text: "A description of the participant population will be included in the CSR, including subgroups of age, gender, gender identity, race, and other study-specific populations and demographic characteristics. A description of participant disposition will also be included in the CSR."

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APPENDIX 9 PRODUCT QUALITY ISSUES

DEFINITIONS: STUDY INTERVENTION DEFECTS Study intervention defects may be related to component, product, or packaging and labeling issues prior to or during use. The list below includes, but is not limited to, descriptions of product complaints in these 3 categories that should be reported as a defect:

- Component Issue: Defect in container or dosing mechanism of the investigational product (IP). The component defect may be damaged, missing, or broken.

Product Issue (related to drug appearance, solution): Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallization, discoloration, turbidity, insufficient volume, or anything that is not consistent to the product description in the IFU.

- Packaging/Labeling Issue: Defect in the packaging or labeling of the study drug. The packaging (carton or tamper-evident seal) or labeling defects may be damaged or unreadable, or the label may be missing.

REPORTING PRODUCT QUALITY ISSUES

Issues that call into question study intervention defects or study intervention device malfunctions (eg, IMP safety, purity, potency, quality, and identity [eg, evidence of suspected tampering of product]), device failed to activate, labelling issues) **must be reported to the Sponsor using the following [redacted] within one business day and no longer than three calendar days (upon clinical site's identification or time of receipt from study participants receiving treatment at home)**.

This includes suspected quality issues of components co-packaged with the drug, labelling, IMP device/drug combination products, and medical devices.
In the event of a suspected product quality issue, the immediate action to be taken by the site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (eg, cytotoxic, risk of injury from broken glass or sharps). When reporting, provide as much product information as possible. Suspected IMP quality issues will be investigated, and a response will be provided back to the investigational site.

Site staff will be asked to send back malfunctioning devices to the depot or local sponsor company according to local guidance/regulations.

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