Official Title of Study:

A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Relatlimab Plus Nivolumab in Pediatric and Young Adult Participants with Recurrent or Refractory Classical Hodgkin Lymphoma and Non-Hodgkin Lymphoma

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CLINICAL PROTOCOL CA224069

A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Relatlimab Plus Nivolumab in Pediatric and Young Adult Participants with Recurrent or Refractory Classical Hodgkin Lymphoma and Non-Hodgkin Lymphoma

Brief Title:

Relatlimab + Nivolumab in Pediatric and Young Adult Lymphomas (RELATIVITY-069)

Protocol Amendment 03

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 03	19-Aug-2024	The primary reason for this amendment is [redacted] to modify the inclusion criteria to specify that participants with pathologically confirmed Burkitt's lymphoma, lymphoblastic lymphoma, and natural killer T-cell lymphoma can be included only after nonresponse to or failure of a minimum of 2 prior lines of therapy. Further revisions were made to update the tumor tissue requirements to increase acceptable tumor tissue samples. This change is expected to reduce site and participant burden.
Administrative Letter 05	23-Apr-2024	The purpose of this Administrative Letter is to change the Study Medical Monitor.
Administrative Letter 04	12-Apr-2024	The purpose of this administrative letter is to replace outdated text within the CA224-069 protocol to comply with the European Union Clinical Trials Regulation.
Protocol Amendment 02	27-Feb-2024	[redacted] Incorporated country-specific requirements noted in Appendix 5 to the relevant sections of the protocol. Added a description of the country-specific requirements to consolidate country-specific differences.
Protocol Amendment 01	26-Aug-2022	[redacted] Investigator discretion includes, but is not limited to, continuing relatlimab + nivolumab with a flexible duration of treatment (DOT) to accommodate differences in regional standard of care (SoC) for up to a total of [redacted] maximum study treatment, high-dose chemotherapy (HDCT)/autologous stem cell transplantation (ASCT; eg, classic Hodgkin Lymphoma), CAR-T (eg, certain Non-Hodgkin Lymphoma subtypes) or change to other best available (eg, definitive) treatment, following consultation with the Medical Monitor.
Administrative Letter 01	07-Feb-2022	Change in Study Director and BMS address
Original Protocol	16-Feb-2021	Not applicable

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OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

The primary reason for this amendment is [redacted] to modify the inclusion criteria to specify that participants with pathologically confirmed Burkitt's lymphoma, lymphoblastic lymphoma, and natural killer (NK) T cell lymphoma can be included only after nonresponse to or failure of a minimum of 2 prior lines of therapy.

Further revisions were made to update the tumor tissue requirements to increase acceptable tumor tissue samples. This change is expected to reduce site and participant burden.

Additional revisions, including to sections of the Protocol Summary, have been made to align the protocol with respect to these changes.

This amendment incorporates the changes from the approved Administrative Letters 04 and 05, which are detailed in the Document History but not listed in the Summary of Changes below.

This protocol amendment applies to all participants.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline for Part A and Part B (CA224069)	Updated window for tumor assessment imaging to "to be performed within 31 days prior to first dose."	Clarification.
Section 5.1.1: Screening Phase	Added language regarding the time for the screening period.	Clarification.
Table 2-1: Screening Procedural Outline for Part A and Part B (CA224069) Section 5.1.1: Screening Phase Section 6.1: Inclusion Criteria Section 9.10.1.6: Tumor Samples	Updated tumor tissue requirements to allow enrollment with an archival tissue sample [redacted].	Updated tumor tissue requirements to increase acceptable tumor tissue samples and reduce site and participant burden.
6.1 Inclusion Criteria	Marked Criterion 2) m) as not applicable and added as new Criterion 2) n) with Burkitt's lymphoma, lymphoblastic lymphoma, and NK/T-cell lymphoma removed. Those subtypes were added in a separate line 2) o) to include them after a minimum of 2 prior lines of therapy.	[redacted]

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TABLE OF CONTENTS

TITLE PAGE 1
DOCUMENT HISTORY 3
OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03: 4
SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03 4
TABLE OF CONTENTS 5
1 PROTOCOL SUMMARY 9
2 SCHEDULE OF ACTIVITIES 23
3 INTRODUCTION 37
3.1 Study Rationale 37
3.1.1 LAG-3 Expression in Pediatric Tumors 38
3.1.2 Overview of Select Pediatric Hematologic Malignancies 39
3.1.2.1 Classical Hodgkin Lymphoma 39
3.1.2.2 Non-Hodgkin Lymphoma 40
3.2 Background 41
[redacted] 46
3.2.2 Nivolumab Mechanism of Action 46
3.2.3 Relatlimab Combined with Nivolumab Preclinical Activity 46
3.2.4 Relatlimab Combined with Nivolumab Clinical Activity 47
[redacted] 48
3.2.6 Nivolumab Clinical Activity 48
3.2.7 Relatlimab Combined with Nivolumab Clinical Safety 49
3.3 Benefit/Risk Assessment 52
3.3.1 Risk Assessment 52
3.3.2 Benefit Assessment 53
3.3.3 Overall Benefit/Risk Conclusion 54
4 OBJECTIVES AND ENDPOINTS 57
5 STUDY DESIGN 59
5.1 Overall Design 59
5.1.1 Screening Phase 64
5.1.2 Treatment Phase 65
5.1.3 Follow-up Phase 67
5.1.4 Data Monitoring Committee and Other Committees 68
5.2 Number of Participants 68
5.3 End of Study Definition 68
[redacted] 69
69
70
70
5.5 Justification for Dose 70
5.5.1 Justification for the 30 Minute Infusion Duration 73
5.6 Clinical Pharmacology Summary 73
5.6.1 Nivolumab Clinical Pharmacology Summary 73
[redacted] 75
6 STUDY POPULATION 75

Approved v4.0 930165609 4.0

6.1 Inclusion Criteria 75
6.2 Exclusion Criteria 79
6.3 Lifestyle Restrictions 84
6.4 Screen Failures 84
6.4.1 Retesting During Screening or Lead-in Period 84
7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY 84
7.1 Study Interventions Administered 85
7.1.1 Relatlimab Combined with Nivolumab Administration 86
7.2 Method of Study Intervention Assignment 87
[redacted] 87
7.4 Dosage Modification 88
7.4.1 Dose Modification Criteria for Relatlimab and Nivolumab 88
7.4.2 Criteria to Resume Treatment 95
7.4.3 Management Algorithms for Relatlimab and Nivolumab 95
7.4.4 Treatment of Related Infusion Reactions 95
7.4.5 Dose-Limiting Toxicities 96
7.4.5.1 Rationale for [redacted] DLT Period 97
7.4.5.2 Definitions of DLTs 98
7.5 Preparation/Handling/Storage/Accountability 100
7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability 101
7.6 Treatment Compliance 101
7.7 Concomitant Therapy 101
7.7.1 Prohibited and/or Restricted Treatments 101
7.7.2 Other Restrictions and Precautions 102
7.7.2.1 Imaging Restriction and Precautions 102
7.8 Continued Access to Study Intervention After the End of the Study 102
8 DISCONTINUATION CRITERIA 103
8.1 Discontinuation From Study Intervention 103
8.1.1 Treatment Beyond Disease Progression 104
8.1.2 Post-study Treatment Study Follow-up 105
8.2 Discontinuation From the Study 105
8.2.1 Individual Discontinuation Criteria 106
8.3 Lost to Follow-up 106
9 STUDY ASSESSMENTS AND PROCEDURES 107
9.1 Efficacy Assessments 108
9.1.1 Efficacy Assessment for the Study 108
9.1.2 Imaging Assessment for the Study 108
9.2 Adverse Events 109
9.2.1 Time Period and Frequency for Collecting AE and SAE Information 109
9.2.2 Method of Detecting AEs and SAEs 110
9.2.3 Follow-up of AEs and SAEs 111
9.2.4 Regulatory Reporting Requirements for SAEs 111
9.2.5 Pregnancy 111
9.2.6 Adverse Events of Special Interest 112
9.2.6.1 Definition of Immune-mediated Adverse Events 112
9.2.7 Laboratory Test Result Abnormalities 113

Approved v4.0 930165609 4.0

9.2.8 Potential Drug-induced Liver Injury 113
9.2.9 Other Safety Considerations 114
9.3 Overdose 114
9.4 Safety 114
9.4.1 Physical Examinations 114
9.4.2 Vital Signs 114
9.4.3 Electrocardiograms 115
9.4.4 Echocardiogram 115
9.4.5 Pregnancy Tests 115
9.4.6 Clinical Safety Laboratory Assessments 115
9.4.7 Imaging/Other Safety Assessment 116
9.5 Pharmacokinetics 116
[redacted] 120
120
120
120
9.10 121
[redacted]
9.10.1.6 Tumor Samples 123
[redacted] 124
124
124
124
9.11 Additional Research 124
9.12 Health Economics OR Medical Resource Utilization and Health Economics 126
10 STATISTICAL CONSIDERATIONS 126
10.1 Statistical Hypotheses 126
10.2 Sample Size Determination 126
10.3 Analysis Sets 128
10.4 Statistical Analyses 129
10.4.1 General Considerations 129
10.4.2 Primary Endpoints 132
10.4.2.1 Safety Analyses 132
10.4.2.2 Pharmacokinetic Analysis 132
10.4.2.3 Primary Efficacy Analysis 132
10.4.3 Secondary Endpoint(s) 133
[redacted] 133
..... 134

Approved v4.0 930165609 4.0

[redacted] 134
135
11 REFERENCES 136
12 APPENDICES 144
APPENDIX 1 ABBREVIATIONS AND TRADEMARKS 145
APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS 151
APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING 162
APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION 166
APPENDIX 5 COUNTRY-SPECIFIC REQUIREMENTS 170
[redacted] 172
APPENDIX 7 LUGANO 2014 RESPONSE CRITERIA 173
[redacted] 176
APPENDIX 9 SECOND-LINE THERAPY AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX SCALE* 185
APPENDIX 10 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY 186

Approved v4.0 930165609 4.0

1 PROTOCOL SUMMARY

Protocol Title:

A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Relatlimab Plus Nivolumab in Pediatric and Young Adult Participants with Recurrent or Refractory Classical Hodgkin Lymphoma and Non-Hodgkin Lymphoma

Brief Title:

Relatlimab + Nivolumab in Pediatric and Young Adult Lymphomas (RELATIVITY-069)

Rationale:

Immune checkpoint blockade has recently demonstrated clinical efficacy in several types of cancer types. Pediatric hematologic malignancies including classical Hodgkin lymphoma (cHL) and select subtypes of pediatric non-Hodgkin lymphoma (NHL) may modulate and evade the host immune response through a number of mechanisms, including immune checkpoints.

Hodgkin lymphoma (HL) has a bimodal age distribution, with peak incidence at 15-34 years of age and again at 50-60 years. A significant proportion of cases occur in the pediatric age group, the majority of which present in adolescents, and a minority of the cases in patients younger than 10 years of age. The most predictive prognostic factors in pediatric patients with relapsed or refractory cHL include primary progression or early relapse, chemotherapy-resistant disease at relapse, and the presence of disease prior to autologous stem cell transplant (ASCT). Disease status following salvage therapy is the most important prognostic factor for long-term outcome. As response to salvage therapy is an important determinant on long-term event-free survival post-ASCT, it is important to develop well-tolerated regimens that increase complete metabolic response (CMR) pre-ASCT. There is currently no consensus or identified best salvage regimen in pediatric and adolescent patients with recurrent/relapsed or refractory (R/R) HL.

Classical Hodgkin lymphoma is characterized by rare, malignant Reed Sternberg cells surrounded by an extensive but ineffective inflammatory immune cell infiltrate. Genetic alterations commonly found in cHL, for example on chromosome 9p24.1/CD274(programmed death-ligand 1[PD-L1])/PDCD1LG2(PD-L2) leading to an upregulation of the programmed death-1 (PD-1) ligand and abberations in the JAK2-STAT signalling pathway, indicate that PD-1 blockade is a reasonable target in this disease. [redacted] Additionally, tumor samples from Children's Oncology Group clinical trial AHOD0031 with matched patient outcome data analyzed by immunohistochemistry for expression of LAG-3 and PD-L1 demonstrated [redacted] LAG-3 expression positive, [redacted].

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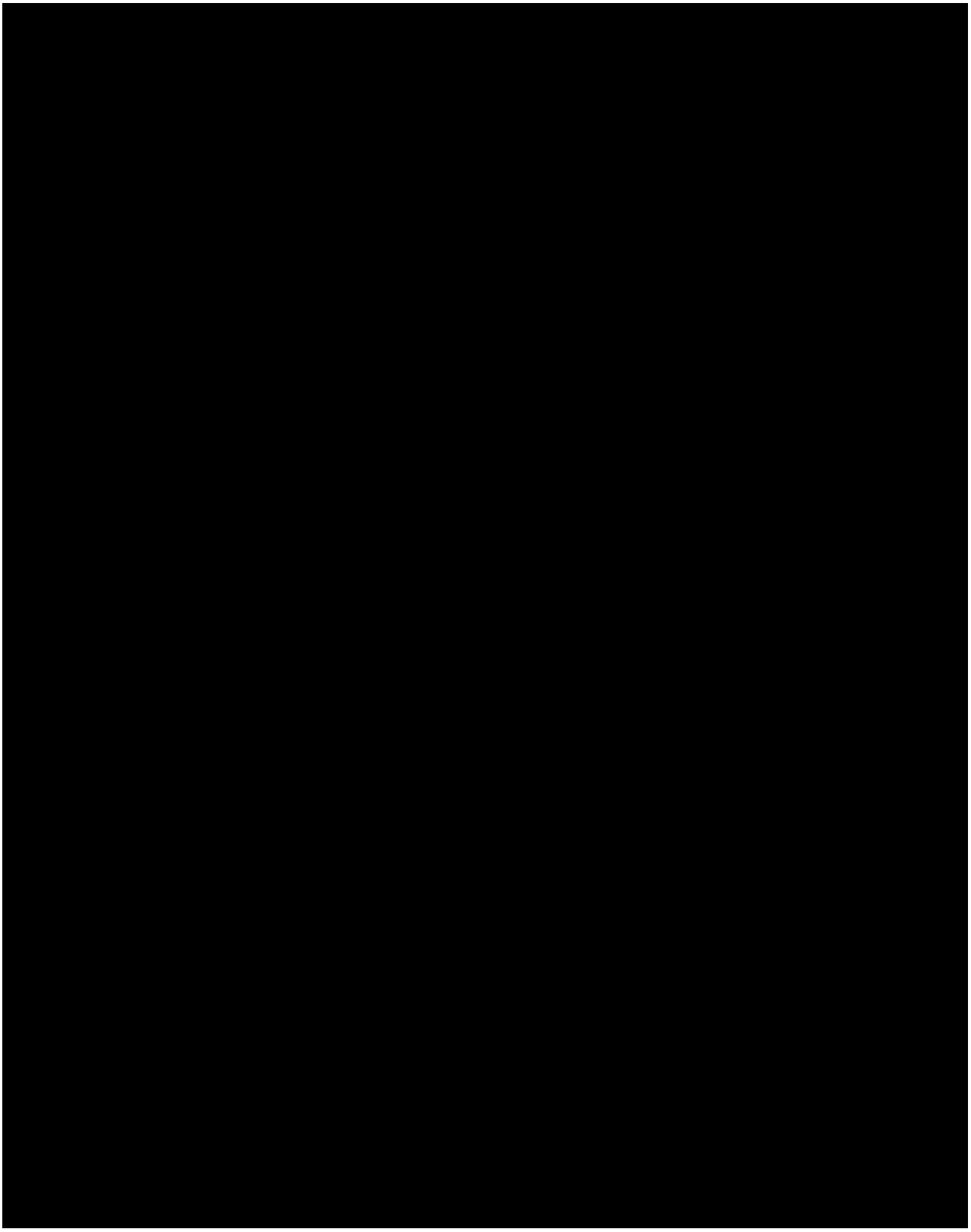
Non-Hodgkin lymphomas rank third in the list of most common childhood malignancies, constituting 10% to 12% of cancers in children. Although the outcome for NHL at diagnosis is favorable using treatment strategies that are tailored to the specific patient and disease subtype, those with recurrent or refractory disease do poorly. There is little consistency in therapeutic approaches, and there is no formal recommendation on the best approach for this poor prognostic subgroup; new treatment options are needed. In the ADVL1412 (Children's Oncology Group Developmental Therapeutic Committee) study, a complete metabolic response was observed in a participant who received nivolumab alone. [redacted]

Collectively, these findings support the combination of LAG-3 and PD-1 inhibitors, relatlimab and nivolumab, to effectively target exhausted T cell populations in pediatric HL and NHL.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• **Part A:** To characterize the safety, tolerability, and define the MTD or RP2D for the combination of relatlimab + nivolumab in pediatric participants less than 18 years of age with R/R cHL and NHL.	• DLTs, MTD/RP2D, and incidences of AEs, SAEs, AEs leading to discontinuation, deaths and laboratory abnormalities
• **Part A:** To characterize the PK of relatlimab for the combination of relatlimab + nivolumab in pediatric participants less than 18 years of age with R/R cHL and NHL.	• Cmax, Ctrough, Tmax, and AUC(TAU) for relatlimab
• **Part B:** To assess the preliminary efficacy of relatlimab + nivolumab based on the RP2D from Part A in participants less than or equal to 30 years old with cHL (Cohort 1).	• CMR rate – The CMR rate is defined as the proportion of all response-evaluable participants who achieve the best response of CMR using Lugano 2014 criteria.
Secondary	
• **Part B:** To assess the safety of relatlimab + nivolumab in R/R cHL (Cohort 1) and NHL (Cohort 2)	• Incidence of AEs, SAEs, AEs leading to discontinuation, deaths and laboratory abnormalities
• **Part B:** To evaluate the ORR of relatlimab + nivolumab in participants ≤ 30 years of age with cHL (Cohort 1)	• ORR – ORR is defined as the proportion of all response-evaluable participants who achieve a best response of CMR or PMR using the Lugano 2014 classification.
[redacted]	

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[redacted]

Abbreviations: AE = adverse event; AUC(TAU) = area under the curve within a dosing interval; cHL = classical Hodgkin Lymphoma; [redacted] Cmax = maximum observed serum concentration; Ctrough = trough observed concentration; CMR = complete metabolic response; DLT = dose-limiting toxicity; [redacted] MTD = maximum tolerated dose; NHL = non-Hodgkin Lymphoma; ORR = overall response rate; [redacted] PK = pharmacokinetics; PMR = partial metabolic response; R/R = recurrent/relapsed or refractory; RP2D = recommended Phase 2 dose; SAE = serious adverse event; [redacted] Tmax = time to maximum concentration.

Overall Design:

CA224069 is an open-label, Phase 1/2 clinical trial of relatlimab + nivolumab in children, adolescents, and young adults with R/R cHL and NHL. Part A will encompass safety and dose determination of relatlimab + nivolumab. Part B will be composed of an expansion cohort of cHL (Cohort 1) and [redacted] in NHL (Cohort 2). A schematic of the study design showing the relationship between dose finding (Part A) and cohort expansion (Part B) is shown in Figure 1.

***Part A*:** Pediatric participants with R/R cHL or R/R NHL less than 18 years of age will be recruited.

The proposed dosing regimen for the starting dose of relatlimab + nivolumab is based upon all available clinical safety/efficacy data. Because pediatric participants vary in age and weight, the proposed starting doses of relatlimab + nivolumab will be determined separately based on age and/or weight. Participants less than 12 years of age and/or weighing less than 40 kg will be given a weight-based dose of relatlimab + nivolumab (Figure 3), and participants aged ≥ 12 to < 18 years and weighing at least 40 kg will be given a flat dose of relatlimab + nivolumab (Figure 2).

Part A: [redacted] participants per age/weight group

Flat-dosing (AF) cohort will include the following: participants ≥ 12 years old who weigh ≥ 40 kg:

- D = Relatlimab 160 mg + nivolumab 480 mg intravenous (IV) every 4 weeks (Q4W) (A1F); if the starting dose is found to be not tolerated, the relatlimab dose will be decreased as follows:
- D-1 = Relatlimab 80 mg + nivolumab 480 mg IV Q4W (A2F)

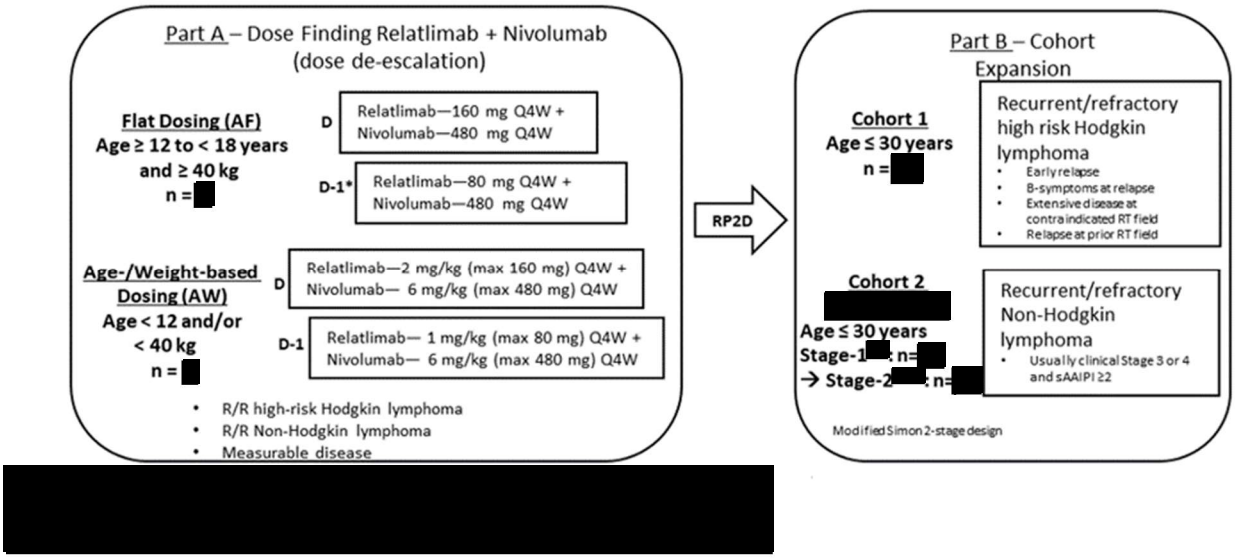
Age/weight-based dosing (AW) cohort will include the following: participants ≥ 12 years old who weigh < 40 kg and/or participants < 12 years old irrespective of weight:

- D = Relatlimab 2 mg/kg (max 160 mg) + nivolumab 6 mg/kg (max 480 mg) Q4W (A1W); if the starting dose is found to be not tolerated, then the relatlimab dose will be decreased as follows:

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- D-1 = Relatlimab 1 mg/kg (max 80 mg) with nivolumab 6 mg/kg (max 480) Q4W (A2W)

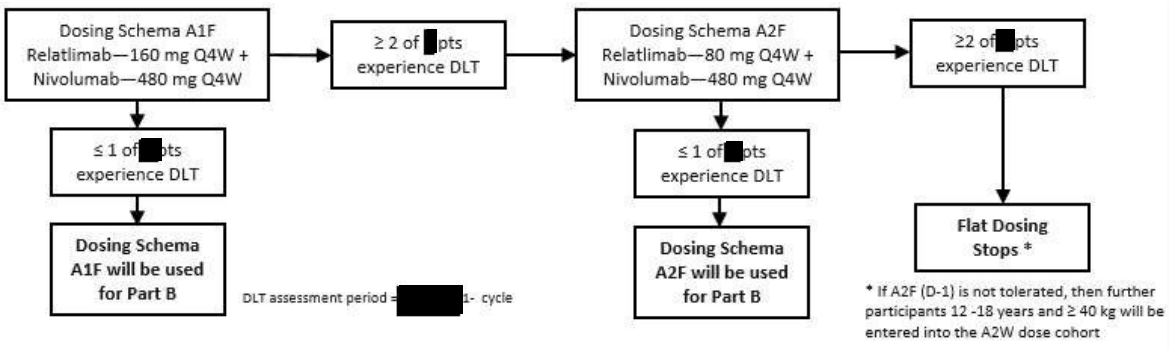
Figure 1: Study Design for Dose Finding (Part A) and Cohort Expansion (Part B)



Participants will continue treatment until PMD, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, for a maximum of [redacted] of study treatment, the participant is lost to follow-up, or study termination by the Sponsor.

Abbreviations: AF = flat dosing; AW = age/weight-based dosing; [redacted] PMD = progressive metabolic disease; Q4W = every 4 weeks; RP2D = recommended Phase 2 dosing; R/R = recurrent/relapsed or refractory; RT = radiotherapy; sAAIPI = second-line therapy age-adjusted International Prognostic Index (score).

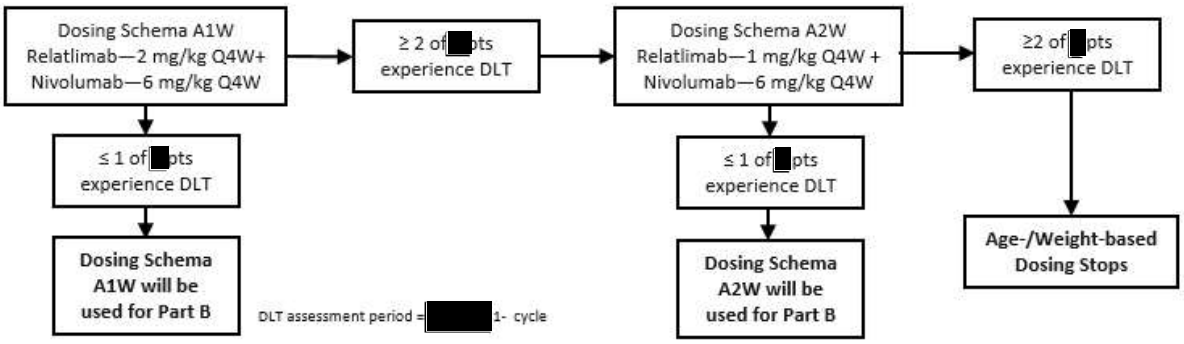
Figure 2: -finding Dose Study Design for Flat Dosing (AF) in Part A



Abbreviations: DLT = dose limiting toxicity; pts = participants; Q4W = every 4 weeks.

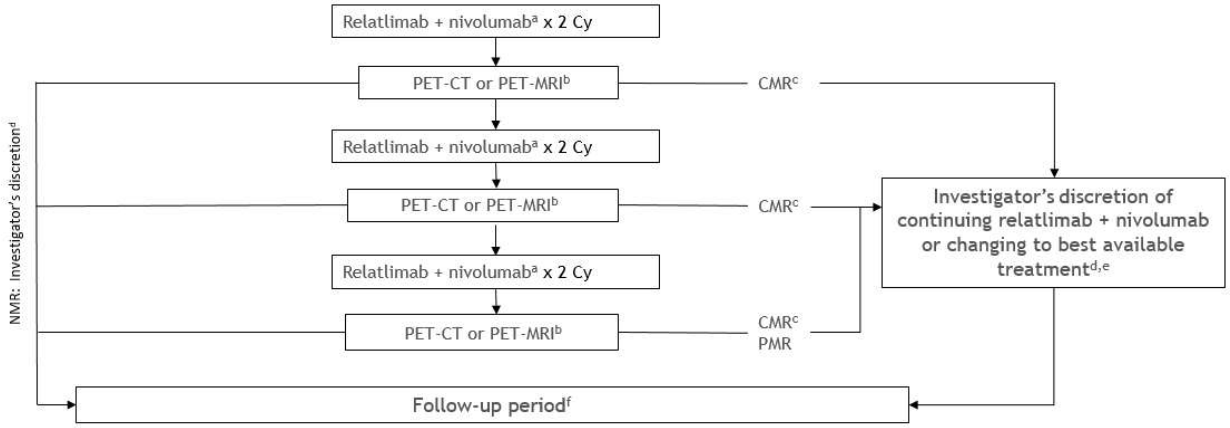
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Figure 3: Dose-finding Study Design for Age- and Weight-based Dosing (AW) in Part A



Abbreviations: DLT = dose limiting toxicity; pts = participants; Q4W = every 4 weeks.

Figure 4: Schematic of Cohort Expansion (Part B) Individual Participant Duration of Treatment Decision Tree



Abbreviations: ASCT = autologous stem cell transplantation; CAR-T = chimeric antigen receptor T-cells; cHL = classic Hodgkin lymphoma; CMR = complete metabolic response; Cy = (4W) cycle (s); DOT = duration of treatment; EOT = end of treatment; HDCT = high-dose chemotherapy; FDG-PET-CT = [^{18}F]fluorodeoxyglucose-positron emission tomography (PET) – computed tomography (CT) combination; FDG-PET-MRI = [^{18}F]fluorodeoxyglucose-positron emission tomography (PET) – magnetic resonance imaging (MRI); MM = Medical Monitor; MRI = magnetic resonance imaging; NHL = non-Hodgkin lymphoma; NMR = no metabolic response; PMD = progressive metabolic disease; PMR = partial metabolic response; QxW = every x weeks; RP2D = recommended Phase 2 dose; SoC = standard of care; W = week.

[a] RP2D (Part A).

[b] FDG-PET-CT or FDG-PET-MRI at Days 49, 105 and 161 (± 7 days), respectively, then Q12W until CMR, PMD, or treatment discontinuation, whichever occurs later, participant withdrawal, or death.

[c] Per Lugano 2014 criteria (see Appendix 7) where CMR includes Deauville 1–3 or qPET < 1.3.

[d] Investigator's discretion including but not limited to continuing relatlimab + nivolumab with a flexible DOT to accommodate differences in regional SoC for up to a total of [redacted] maximum study treatment, HDCT/ASCT (ie, cHL), CAR-T (ie, NHL) or other best available (eg, definitive) treatment, following consultation with BMS MM. Participants are to be followed with diagnostic quality CT or MRI scans every 12 weeks (± 7 days) from the last

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on-treatment scan date until PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death.

[e] PMR participants at the end of 6 cycles proceeding to receive Investigator's choice of continuing relatlimab + nivolumab will be followed up by FDG-PET-CT or FDG-PET-MRI imaging every 12 weeks (± 7 days) from the last on-treatment scan date until CMR, PMD, or treatment discontinuation, whichever occurs later, participant withdrawal, or death.

[f] After EOT (Follow-Up), CT or MRI every then Q12W until suspected progression, after which PMD must be confirmed by FDG-PET-CT or FDG-PET-MRI.

Enrollment in the two dosing cohorts (A1F and A1W) will be initiated in parallel. Up to [redacted] participants for each age/weight group will be assessed for safety and pharmacokinetics (PK). The observation period for dose-limiting toxicities (DLTs; DLT-evaluation period) will be one cycle, defined as [redacted]. Participants will be monitored for safety using Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 criteria. If dose limiting toxicity with CTCAE v5.0 criteria of Grade 3 or higher severity (as defined further in the protocol and based on the known safety profiles of relatlimab and nivolumab) is observed in [redacted] or more participants, the dose will be de-escalated to D-1 (A2F and A2W) and an additional [redacted] participants will be evaluated for toxicity and exposure, for another ≥ 2 DLTs. If no DLTs are observed, a minimum of [redacted] participants will be enrolled in A1F and A1W, respectively.

- If, in Part A, a safe dose in pediatric participants cannot be identified, Part B may not be initiated in some age/weight subsets.
- If the AF cohort is not tolerated at A1F and A2F dose levels, accrual into this cohort will be terminated. Additional participants aged 12 and above and at least 40 kg will be enrolled onto dose level -1 (A2W) in the age/weight-based dosing schema, and if found to be tolerated, A2W will be declared as the recommended Phase 2 dose (RP2D) for this age/weight group. The participants aged < 12 years and/or weighing < 40 kg would continue to be enrolled and evaluated in parallel.
- Participants will continue treatment until disease progression, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, for a maximum of [redacted] of study treatment, the participant is lost to follow up, or study termination by the Sponsor.

Part B: Expansion cohort in Hodgkin lymphoma (Cohort 1) and [redacted] in Non-Hodgkin lymphoma (Cohort 2)

The doses of relatlimab + nivolumab are the RP2D or maximum tolerated dose (MTD) from Part A. Male and female participants with R/R cHL (Cohort 1) or NHL (Cohort 2) less than or equal to 30 years of age will be recruited.

The goal of Part B is to evaluate the preliminary efficacy of relatlimab + nivolumab at its RP2D from Part A in pediatric participants with high-risk R/R cHL (Cohort 1) and in a cohort of R/R NHL (Cohort 2). Participants in Part A will be counted towards the accrual goals of Part B if they are treated at the same dose selected for Part B. Details of the analyses will be specified in the statistical analysis plan (SAP). Due to the heterogeneity of NHL tumors resulting in differences in

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treatment and outcome, analysis as a single cohort with cHL is not optimal. As such, the expansion portion of the trial (Part B) will enroll approximately [redacted] NHL participants will be enrolled in Stage 1 and Stage 2, respectively, at the RP2D or MTD as defined above.

The primary objective of Part B is to evaluate preliminary efficacy in cHL (cohort 1) [redacted]. Preliminary efficacy in cHL (Cohort 1) will be evaluated using the estimated CMR rate and exact 2-sided 90% confidence interval (CI) in the [redacted] response-evaluable participants. [redacted]

[redacted]

Participants who have an initial increase in target lesions but eventually show a response according to the Lugano 2014 lymphoma metabolic response criteria will be considered responders for defining response. Parameters for response and progression will be calculated relative to baseline or nadir measurements according to the applicable response criteria. All participants will undergo baseline tumor assessments by [^{18}F] fluorodeoxyglucose-positron emission tomography computed tomography (FDG-PET-CT) or by [^{18}F] fluorodeoxyglucose-positron emission tomography magnetic resonance imaging (FDG-PET-MRI) per protocol requirements. If central nervous system involvement is suspected, in addition to lumbar puncture for cerebrospinal fluid (CSF) evaluation that may be performed as part of standard-of-care (SoC) practice, brain magnetic resonance imaging (MRI) without and with Gadolinium contrast will be performed to exclude participants with brain involvement. In addition, contrast-enhanced computed tomography (CT) or MRI may be performed as part of SoC practice per Investigator discretion. During the treatment period for Part A, FDG-PET-CT or FDG-PET-MRI whole-body should occur at Day 49 (± 7 days), Day 105 (± 7 days) and Day 161 (± 7 days) starting from the date of first dose and corresponding with Day 21 (± 7 days) of Cycles 2, 4 and 6, then every 12 weeks (± 7 days) after Cycle 6 assessment until progressive metabolic disease (PMD) or treatment discontinuation (EOT), whichever occurs later, participant withdrawal, or death. During the treatment period for Part B, tumor assessments by FDG-PET-CT or FDG-PET-MRI should occur at Day 49 (± 7 days), Day 105 (± 7 days) and Day 161 (± 7 days) starting from the date of first dose and corresponding with Day 21 (± 7 days) of Cycles 2, 4 and 6. In case of CMR before or after 6 cycles by FDG-PET-CT or FDG-PET-MRI, imaging may be performed using diagnostic quality MRI/CT scans every 12 weeks (± 7 days) from the last on-treatment scan date until PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death. If progressive disease (PD) is suspected

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based on clinical or MRI/CT findings, a confirmatory FDG-PET-CT or FDG-PET-MRI should be obtained to confirm PMD.

PMR participants at the end of 6 cycles proceeding to receive Investigator's choice of continuing relatlimab + nivolumab will be followed up by FDG-PET-CT or FDG-PET-MRI imaging every 12 weeks (± 7 days) from the last on-treatment scan date until CMR, PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death.

Participants continuing treatment based on Investigator's discretion, for example in the case of NMR, will be allowed to switch imaging modality from being PET-based to diagnostic quality CT or MRI scans every 12 weeks (± 7 days) from the last on-treatment scan date until PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death. In case of suspected CR based on CT/MRI, FDG-PET-CT or FDG-PET-MRI scan must be performed to confirm CMR. If PD is suspected on CT or MRI, an additional FDG-PET-CT or FDG-PET-MRI scan must be performed to confirm PMD.

The study consists of a screening, treatment, and long-term follow-up periods. Based on the response-driven regimen, participants will be allowed to continue study therapy until disease progression, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, for a maximum of [redacted] of study treatment, the participant is lost to follow-up, or study termination by the Sponsor (Figure 1). Participants for whom pseudoprogession is considered a likely clinical explanation of their PMD on imaging may be allowed to continue therapy. If additional imaging confirms the PMD, participants will be taken off study and the time of progression will be assessed as the date of the initial scan demonstrating progression.

The proposed treatment duration is until metabolic progression or for a flexible number of cycles based on Investigator's discretion up to a maximum of [redacted]. This proposed treatment duration is intended to allow for regional differences in duration of therapy and maximize treatment benefit while ensuring the safety of the study participants.

Participants who discontinue treatment will enter a clinical safety (30-day and 135-day) and survival (up to approximately [redacted]) follow-up periods. The post-treatment clinical observation period is intended to last approximately 5 elimination half-lives of relatlimab and nivolumab.

Number of Participants:

The total sample size of the study is estimated to be between approximately [redacted] to [redacted] treated participants. The minimal accrual of [redacted] participants would be based on both age groups not tolerating either dose of relatlimab + nivolumab and the study not proceeding to Part B. If the study proceeds to Part B, participants in Part A will be counted towards the accrual goals of Part B if they are treated at the same dose (RP2D) selected for Part B. [redacted] If both age/weight groups in Part A require a dose de-escalation, then up to [redacted] participants (in addition to when A2F is not tolerated) would be treated in Part A; leading to a maximum of [redacted] participants in the study. The minimum number

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of participants expected in those children that are < 12 years of age and/or below 40 kg is [redacted] if no DLTs are observed. Likewise, the minimum number of participants anticipated in pediatric participants from 12 to < 18 and at least 40 kg is [redacted], if no DLTs are observed. This minimum number considers scenarios where only Part A is completed for safety or toxicity reasons.

It is estimated that approximately between [redacted] and [redacted] enrolled participants will be required to achieve between [redacted] and [redacted] participants needed to be treated in Part A and Part B of the study.

Study Population:

Main inclusion criteria:

- Male and female participants less than 18 years of age (Part A), and less than or equal to 30 years of age (Part B) with R/R cHL (Cohort 1) and NHL (Cohort 2).
- Participants with pathologically confirmed high-risk R/R cHL, after non-response to or failure of 1 or more lines of standard therapy. See Appendix 5 for country-specific requirements for France.
  - High-risk for cHL is defined by early relapse, extranodal disease or B symptoms at relapse, extensive disease where radiation therapy was contraindicated at relapse, and/or relapse in a prior radiation field.
- Participants with pathologically confirmed R/R NHL after non-response to or failure of 1 or more lines of standard therapy, including, but not limited to, R/R primary mediastinal B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), mediastinal gray zone lymphoma (MGZL), anaplastic large cell lymphoma (ALCL), or peripheral T-cell lymphoma (PTCL). See Appendix 5 for country specific requirements for France.
  - High-risk for NHL is defined as applicable (eg, in young adults) by a second-line therapy age-adjusted International Prognostic Index score of ≥ 2 factors.
- Participants with pathologically confirmed R/R NHL after non-response to or failure of 2 or more lines of standard therapy, including Burkitt lymphoma (blast count < 25% malignant Burkitt cells and/or per the investigator's clinical assessment of risk status), lymphoblastic lymphoma (blast count < 25% of marrow nucleated cells and/or per the investigator's clinical assessment of risk status), NK/T-cell lymphoma (nasal and non-nasal NK/T-cell lymphoma subtypes, but not aggressive NK/T-cell leukemia/lymphoma subtype).
  - High-risk for NHL is defined as applicable (eg, in young adults) by a second-line therapy age-adjusted International Prognostic Index score of ≥ 2 factors.
- The participant’s current disease state must be R/R to standard therapy.
- Participants must have measurable PET positive disease in both cHL and NHL cohorts.

Main exclusion criteria:

- Primary CNS lymphoma of the brain or spinal cord, and secondary CNS lymphoma (ie, from systemic non-Hodgkin lymphoma) involving the brain, spinal cord, or with leptomeningeal seeding.

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- Prior treatment with an anti-cytotoxic T-lymphocyte-associated protein 4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways, with the exception of anti-PD(L)-1 targeted therapies.
- Prior treatment with LAG-3-targeted agents.
- Participants with a history of allogeneic bone marrow transplantation.
- Participants with clinically significant systemic illnesses unrelated to the cancer as judged by the investigators, which would compromise the participant's ability to tolerate the study treatment.
- Participants with autoimmune disease.
- Participants who are pregnant or breastfeeding.

Intervention Groups and Duration:

Study Intervention:

Study Intervention for CA224069		
Medication	**Potency**	**IP/Non-IP**
Relatlimab Injection 80 mg/vial	10 mg/mL	IP
Nivolumab Injection 100 mg/vial	10 mg/mL	IP

Abbreviation: IP = Investigational Product.

Co-administration of Relatlimab Injection and Nivolumab Injection

Relatlimab (BMS-986016) injection (10 mg/mL) is co-administered with nivolumab (BMS-936558) injection by mixing in the same infusion bag and administered as an IV infusion through a compatible low-protein-binding in-line filter at the protocol-specified doses over approximately 30 minutes. Relatlimab injection combined with nivolumab injection can be diluted with 0.9% normal saline or dextrose 5% in water to a total protein concentration no lower than [redacted] mg/mL ([redacted] mg/mL of relatlimab and [redacted] mg/mL of nivolumab).

Based on expected comparable PK and safety of relatlimab + nivolumab in adults and adolescents, the adult dose of relatlimab + nivolumab can be extrapolated to the adolescent population. Relatlimab + nivolumab was administered as a flat dose in adults, therefore, a minimum body weight threshold in adolescents (≥ 40 kg) is defined to receive the same adult flat dose to prevent exceeding target adult exposures. Adolescents < 40 kg will be administered body weight adjusted relatlimab and nivolumab doses, up to the respective maximum adult flat doses.

Approved v4.0 930165609 4.0

Statistical Methods

Sample Size:

Part A (dose determination): Up to [redacted] participants will be enrolled for each of the two age/weight groups to assess safety and dose determination of relatlimab + nivolumab. The MTD/RP2D will be assessed based on the number of DLTs observed at each dose level.

Part B (cohort expansion): Approximately [redacted] response-evaluable participants in the cHL participants (Cohort 1) will be enrolled and used to assess the CMR (cHL). [redacted] summarizes the different boundaries of the exact 90% CI (based on Clopper-Pearson method) for different observed CMR rates in [redacted] response-evaluable cHL participants.

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The total sample size of the study is estimated to be between approximately [redacted] and [redacted] treated participants, depending on dose de-escalation contingencies in Part A and cohort expansions in Part B.

Analyses

In Part A, DLTs will be assessed during the first [redacted] (1 cycle) of treatment with relatlimab + nivolumab. PK samples will be collected at pre-defined time points for the duration of the treatment period. PK parameters at Cycle 1 and at steady state will be assessed. Tumor assessment will be performed every 12 weeks (± 7 days) while on treatment.

The MTD/RP2D in Part A, will be assessed based on the number of DLTs observed at each dose level. Incidences of AEs, serious adverse events (SAEs), AEs leading to discontinuation, deaths, and laboratory abnormalities will be assessed by the frequency distribution of treated participants with AEs, using the worst Common Technology Criteria grade.

The PK parameters will be summarized by doses of relatlimab/nivolumab. Geometric means and coefficients of variation will be presented for Cmax, Ctrough, and AUC(TAU). Medians and ranges will be presented for Tmax. Means and standard deviations will be provided for the other PK parameters.

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For Part B the preliminary efficacy of relatlimab in combination with nivolumab at the RP2D from Part A will be assessed using CMR. The CMR rate and exact 2-sided 90% CI (based on Clopper-Pearson method) will be summarized separately for Cohort 1 and Cohort 2.

Data Monitoring Committee and Other Committees: Yes

Brief Summary:

Study CA224069 is a Phase 1/2 pediatric study of relatlimab + nivolumab to evaluate safety and tolerability in participants with recurrent or refractory classical Hodgkin lymphoma and non-Hodgkin lymphoma. The purpose of this study is first to characterize during dose finding (Part A) the safety, tolerability, pharmacokinetics and define the maximum tolerated dose or recommended Phase 2 dose for relatlimab + nivolumab in pediatric participants less than 18 years of age with recurrent/relapsed or refractory Hodgkin lymphoma and non-Hodgkin lymphoma; then during cohort expansion (Part B) to assess the preliminary efficacy of relatlimab + nivolumab based on the recommended Phase 2 dose from Part A in participants less than or equal to 30 years old with cHL (Cohort 1) and [redacted] participants with non-Hodgkin lymphoma (Cohort 2). Study details include:

Study Duration: The maximum duration for a participant on-study is [redacted].

Study Intervention Duration: Each dosing cycle lasts [redacted]. Study drug is administered on Day 1 ± 3 days until disease progression or for a flexible number of cycles based on Investigator's discretion up to a maximum of [redacted].

Study Visit Frequency: In each dosing cycle of [redacted], the participant will attend a dosing visit on Day 1. During the first 2 cycles, non-dosing visits occur every 2 weeks for safety assessments. Tumor assessments during the treatment period are every 12 weeks (± 7 days).

Approved v4.0 930165609 4.0

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline for Part A and Part B (CA224069)

Procedure	Screening [redacted]	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific IRB/IEC-approved informed consent (or assent, as applicable) is signed and dated. 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.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to treatment assignment.
Medical History	X	Includes medical history relevant to disease under study.
Prior Anticancer Therapy	X	Includes all prior cancer therapies, including radiation therapies.
[redacted]		
Tumor Assessment Imaging: FDG-PET-CT or FDG-PET-MRI	X	To be performed within 31 days prior to first dose. FDG-PET-CT or FDG-PET-MRI whole-body (at least from the base of skull to proximal femurs) and all known/suspected sites of disease will be used for metabolic response assessment. In addition, contrast-enhanced CT or MRI may be performed as part of standard-of-care practice per Investigator discretion. If CNS involvement is suspected, perform brain MRI without and with Gadolinium contrast at baseline to exclude participants with brain involvement. Refer to Section 9.1.
Tumor Biopsy or Tumor Sample Submission or Archived Tumor Tissue Sample	X	A FFPE tissue block (preferred) or a minimum of [redacted] unstained slides* of tumor tissue from an excisional biopsy, core biopsy or surgical specimen obtained during screening, or prior to treatment assignment [redacted] must be sent to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable. Central lab must provide confirmation of receipt of tumor tissue prior to participant treatment assignment.

Approved v4.0 930165609 4.0

Table 2-1: Screening Procedural Outline for Part A and Part B (CA224069)

Procedure	Screening [redacted]	Notes
		*If despite best efforts, a minimum of [redacted] slides is not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with the Sponsor or designee. [redacted]
IRT Assignment	X	Each participant will be assigned a unique participant number after signing the ICF.
Safety Assessments		
Complete Physical Examination	X	Including but not limited to skin and mucus membranes, regional lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), abdominal organs (eg, spleen, liver), and neurological examination.
Physical Measurements	X	Weight, height, RR, and BSA (ie, Mosteller formula)
Vital Signs	X	Temperature, BP, HR, RR, and oxygen saturation at rest by pulse oximetry at screening only. Must be collected within 14 days prior to treatment assignment.
Assessment of Signs and Symptoms	X	Within 14 days prior to treatment assignment.
ECG	X	12-lead ECGs should be recorded after the participant has been supine for at least 5 minutes. Within 14 days prior to treatment assignment. Note: Repeated for confirmation if any of the criteria in Section 6.2.4 j) is met.
ECHO	X	LVEF assessment with documented LVEF ≥ 50% by either TTE (preferred test) or MUGA scan within 6 months from first study drug administration. Participants with other significant abnormalities on ECHO/MUGA scan should be discussed with the Sponsor Medical Monitor prior to enrollment.
Laboratory Tests		Refer to Section 9.4.6.
Clinical Laboratory Assessments	X	On-site or off-site local laboratory tests must be performed within 14 days prior to treatment assignment.

Approved v1.0 930165609 4.0

Table 2-1: Screening Procedural Outline for Part A and Part B (CA224069)

Procedure	Screening [redacted]	Notes
		Includes clinical hematology, general chemistry, urinalysis, thyroid function and serology/viral testing. Refer to Section 9.4.6 for list of laboratory tests to conduct. Note: [redacted]. For HIV: testing at sites where locally mandated (see Appendix 5 for country-specific requirements for countries where exclusion of HIV positive participants is locally mandated).
[redacted]		
Pregnancy Test (for WOCBP only)	X	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 approximately 1 day prior to first dose of study treatment.
[redacted]		
Adverse Event Reporting		
AE Assessments (including SAEs)	X	AEs will be graded according to the NCI-CTCAE version 5.0. Record from the time of informed consent (or assent, as applicable). All AEs (SAEs or non-serious AEs), must be collected continuously throughout the treatment period and for a minimum of 135 days after last dose of study treatment (Appendix 3).
Concomitant Medication Use	X	Within 14 days prior to treatment assignment. Live/attenuated vaccine use within 30 days prior to first study treatment.

Abbreviations: AE = adverse event; BMS = Bristol-Myers Squibb Company; BP = blood pressure; BSA = body surface area; CNS = central nervous system; [redacted] CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECHO = echocardiogram; FDG = [^{18}F]fluorodeoxyglucose; FFPE = formalin-fixed paraffin-embedded; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; HR = heart rate; ICF = informed consent form; IEC = Independent Ethics Committee; IgG = Immunoglobulin; IRB = Institutional Review Board; IRT = Interactive Response Technology; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; NCI = National Cancer Institute; PET = positron emission tomography; [redacted] RR = respiration rate; SAE = serious adverse event; TTE = transthoracic electrocardiogram; WOCBP = women of child bearing potential.

Approved v4.0 930165609 4.0

Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069)

Procedure	[redacted]				Notes
Safety Assessments					
Targeted Physical Examination	X	X	X	X	Including but not limited to skin and mucus membranes, regional lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), abdominal organs (eg, spleen, liver), and neurological examination.
Physical Measurements	X		X* (See notes)	X* (See notes)	Weight on the day of dosing. If the participant's weight on the day of dosing differs by > 10% from baseline or the weight used for the previous dose calculation, the dose must be recalculated. Height every 6 months.
Vital Signs	X	X	X	X	Vital signs (BP, HR, RR and temperature). Monitor and record vital signs at predose and within 30 minutes after administration of study treatment.
[redacted]					
ECGs	As clinically indicated [redacted]				

Approved v1.0 930165609 4.0

Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069)

Procedure	[redacted]	Notes
Adverse Event Reporting		
AE Assessments (including SAEs)	Continuously	AEs will be graded according to the NCI-CTCAE version 5.0. Record at each visit. All AEs (SAEs or non-serious AEs) must be collected continuously throughout the treatment period and for a minimum of 135 days after last dose of study treatment (Appendix 3).
Concomitant Medication Use	Continuously	Record at each visit.
Laboratory Tests		Refer to Section 9.4.6.
Clinical Laboratory Assessments	X X X X	Perform on-site or off-site local laboratory testing within 3 days prior to each dose. For the first treatment visit, labs do not need to be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility. Refer to Section 9.4.6 for the list of laboratory tests to be conducted.
Pregnancy Test (for WOCBP only)	X X X X	Serum or urine within approximately 24 hours prior to first dose and then every 4 weeks (± 1 week) irrespective of dosing schedule.
[redacted]		

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Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069)

Procedure	[redacted]	Notes
	[redacted]	[redacted]

Approved v1.0 930165609 4.0

Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069)

Procedure	[redacted]	Notes
PK [redacted] Assessments		
PK [redacted] Collections	X	Refer to Section 9.5, [redacted] for the PK sampling schedule. PK sampling on non-dosing visits on Days 2, 4, 8 and 15 of Cycle 1 are also mandatory.
[redacted]		
Efficacy Assessments		
Tumor Assessments (Part A)	See notes	During the treatment period, FDG-PET-CT whole-body or FDG-PET-MRI should occur at Day 49 (± 7 days), Day 105

Approved v1.0 930165609 4.0

Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069)

Procedure	[redacted]	Notes
FDG-PET-CT or FDG-PET-MRI		(± 7 days) and Day 161 (± 7 days) starting from the date of first dose and corresponding with Day 21 (± 7 days) of Cycles 2, 4 and 6, then every 12 weeks (± 7 days) after Cycle 6 assessment until PMD or treatment discontinuation (EOT), whichever occurs later, participant withdrawal, or death.[b,c,d,e,f]
Tumor Assessments (Part B) FDG-PET-CT or FDG-PET-MRI	See notes	During the treatment period, tumor assessments by FDG-PET-CT or FDG-PET-MRI should occur at Day 49 (± 7 days), Day 105 (± 7 days) and Day 161 (± 7 days) starting from the date of first dose and corresponding with Day 21 (± 7 days) of Cycles 2, 4 and 6. In case of CMR before or after 6 cycles by FDG-PET-CT or FDG-PET-MRI, imaging may be performed using diagnostic quality MRI/CT scans every 12 weeks (± 7 days) from the last on-treatment scan date until PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death. If PD is suspected based on clinical or MRI/CT findings, a confirmatory FDG-PET-CT or FDG-PET-MRI should be obtained to confirm PMD.[f]

Approved v4.0 930165609 4.0

Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069)

Procedure	[redacted]				Notes
					PMR participants at the end of 6 cycles proceeding to receive Investigator's choice of continuing relatlimab + nivolumab will be followed up by FDG-PET-CT or FDG-PET-MRI imaging every 12 weeks (± 7 days) from the last on-treatment scan date until CMR, PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death. Participants continuing treatment based on investigator's discretion, for example in case of NMR, will be allowed to switch imaging modality from being PET-based to diagnostic quality CT or MRI scans every 12 weeks (± 7 days) from the last on -treatment scan date until PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death. In case of suspected CR based on CT/MRI, FDG-PET-CT or FDG-PET-MRI scan must be performed to confirm CMR. If PD is suspected on CT or MRI, an additional FDG-PET-CT or FDG-PET-MRI scan must be performed to confirm PMD.
Study Intervention					
IRT Drug Assignment	X		X	X	Participant must receive the first dose of study medication within 3 calendar days from treatment assignment.

Approved v4.0 930165609 4.0

Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069)

Procedure	[redacted]				Notes
Relatlimab (BMS-986016) administration	X		X	X	First dose to be administered within 3 calendar days following treatment assignment. Study therapy may be administered within 3 days before or after the scheduled dose. Refer to Section 7.1. For weight-based dosing, use body weight for dosing calculations. If the participant's weight on the day of dosing differs by >10% from baseline or the weight used for the previous dose calculation, the dose must be recalculated. Round all doses to the nearest milligram.
Nivolumab (BMS-936558) administration	X		X	X	First dose to be administered within 3 calendar days following treatment assignment. Study therapy may be administered within 3 days before or after the scheduled dose. Refer to Section 7.1. For weight-based dosing, use body weight for dosing calculations. If the participant's weight on the day of dosing differs by > 10% from baseline or the weight used for the previous dose calculation, the dose must be recalculated. Round all doses to the nearest milligram.

Abbreviations: AE = adverse event; BP = blood pressure; CMR = complete metabolic response; [redacted] CR = complete response; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; EOT = end of treatment; FDG = [^{18}F]fluorodeoxyglucose; HR = heart rate; [redacted] IRT = Interactive Response Technology; MRI = magnetic resonance imaging; NCI = National Cancer Institute; NMR = no metabolic response; PD - progressive disease; PET = positron emission tomography; PK = pharmacokinetics;

Approved v4.0 930165609 4.0

PMD = progressive metabolic disease; PMR = partial metabolic response; [redacted] RR = respiratory rate; SAE = serious adverse event; WOCBP = women of child bearing potential.

[a] For participants who require blood draw volume modifications for low body weight or other reasons, blood collection volumes will be appropriately reduced per guidelines outlined in the laboratory manual to meet pediatric institutional or national guidelines for maximum daily and monthly blood draw limits.

[b] EOT is defined as the visit where decision is made to discontinue the participant from treatment.

[c] For participants who complete all schedules of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit or Follow-up Visit 1.

[d] For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit. If all safety and response data is available, the EOT visit does not need to be repeated, and will be considered the start of Week 1 of the Clinical Safety Follow-up.

[e] Participants with Q8W x 2, then Q12W imaging frequency at enrollment will maintain their imaging schedule throughout the study.

[f] Imaging assessment should follow indicated schedule even if dose is omitted or delayed.

Approved v4.0 930165609 4.0

Table 2-3: Long-term Follow-up Procedural Outline (CA224069)

Procedure	[redacted]			Notes
Safety Assessments				
Targeted Physical Examination	X	X		Including but not limited to skin and mucus membranes, regional lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), abdominal organs (eg, spleen, liver), and neurological examination.
Vital Signs	X	X		Blood pressure, heart rate and temperature.
[redacted]				
Concomitant Medication Use	X	X		Record at each visit.
Adverse Event and SAE Assessment	X	X	*	Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2.6), 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 8.3). Record at each visit. Collect continuously throughout the treatment period and for a minimum of 135 days following discontinuation of dosing. *Beyond 135 days from the last dose of study therapy, 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.
Subsequent Cancer Therapy	X	X	X	Include documentation of subsequent cancer therapy (ie, systemic therapy, stem cell transplantation, tumor-directed surgery, or radiation therapy).
Laboratory Tests				Refer to Section 9.4.6
Clinical Laboratory Assessments	X			To be performed at Follow-Up Visit 1, repeat at Follow-Up Visit 2 if study drug-related toxicity persists. Refer to Section 9.4.6 Clinical Safety Laboratory Assessments for the list of laboratory tests.

Approved v4.0 930165609 4.0

Table 2-3: Long-term Follow-up Procedural Outline (CA224069)

Procedure	[redacted]			Notes
Pregnancy Test	X	X		Serum or urine. Pregnancy testing is only required at Safety Follow Up Visits 1 and 2 unless increased frequency and duration is required per local regulations.
[redacted]				
PK [redacted] Assessments				
PK [redacted] Samples	X	X		Refer to [redacted] Section 9.5 [redacted] for the PK [redacted] sampling schedule.
[redacted]				

Approved v4.0 930165609 4.0

Table 2-3: Long-term Follow-up Procedural Outline (CA224069)

Procedure	[redacted]			Notes
[redacted]				
Efficacy Assessments				
Survival Status	X	X	X	During the Safety follow-up period (Follow-up Visits 1 and 2) and then every 3 months (clinic visit or by telephone) ± 14 days during Survival Follow-Up. Include documentation of subsequent therapy. Participants will be followed until death, lost to follow-up, withdrawal of consent, conclusion of the study, or a maximum of [redacted] from last study treatment.
Tumor Assessment FDG-PET-CT or FDG-PET-MRI	X			During follow-up, all participants are allowed to switch imaging modality from being PET-based to diagnostic quality CT or MRI every 12 weeks (± 7 days) for the first 52 weeks, and every 24 weeks (± 7 days) thereafter from the last on--treatment scan date until PMD, participant withdrawal, or death. If PD is suspected on CT or MRI, an additional FDG-PET-CT or FDG-PET-MRI scan must be performed to confirm PMD.

Abbreviations: AE = adverse event; CT = computed tomography; FDG = [^{18}F]fluorodeoxyglucose; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PK = pharmacokinetics; PMD = progressive metabolic disease; [redacted] SAE = serious adverse event.

Approved v4.0 930165609 4.0

In the event that multiple procedures are required at a single time point, the electrocardiogram (ECG) may be obtained up to 15 minutes earlier, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory samples may be obtained up to 5 minutes earlier than the nominal time point, ensuring that the pharmacokinetic (PK) samples can be collected on time.

3 INTRODUCTION

Study CA224069 is a Phase 1/2 pediatric study of relatlimab + nivolumab to evaluate safety and tolerability in recurrent or refractory classical Hodgkin lymphoma (cHL) and non-Hodgkin lymphoma (NHL).

Pediatric hematologic malignancies including cHL and select subtypes of NHL may modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. Immune checkpoint blockade has recently demonstrated clinical efficacy in several cancer types, including melanoma, hepatocellular (HCC), gastric cancer, non-small cell lung cancer (NSCLC), and hematologic malignancies.[1,2,3]

Relatlimab (BMS-986016) is a fully human lymphocyte activation gene 3 (LAG-3) specific antibody that was isolated following immunization of transgenic mice expressing human immunoglobulin (Ig) genes. Relatlimab binds to LAG-3 receptors expressed on T-cells with high affinity and prevents binding of this receptor to cells bearing its ligands, major histocompatibility complex (MHC) Class II[4] and fibrinogen-like protein 1 (FGL-1).[5] Relatlimab binding inhibits the negative regulatory function of LAG-3 mediated through its interaction with ligands in vitro. By blocking the inhibitory LAG-3 signaling pathway, relatlimab enhances the anti-tumor immune response and, thus, has the potential to inhibit the growth of multiple malignancies when administered in combination with other therapeutic immuno-oncology (IO) agents. Dual checkpoint inhibition with relatlimab and nivolumab results in enhanced T-cell effector function that is greater than the effects of either antibody alone in murine syngeneic tumor models.[6]

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype monoclonal antibody that binds the programmed death-ligand 1 (PD-1) receptor on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and programmed death-ligand 2 (PD-L2) (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. In early clinical trials, nivolumab has demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLC.[7]

3.1 Study Rationale

LAG-3 (CD223) is a checkpoint receptor and expressed on several immune cell types including activated CD4+ and CD8+ T cells, memory T cells, Tregs, and natural killer (NK) cells.[4] Activation of the LAG-3 pathway occurs when LAG-3 interacts with its ligands, such as MHC Class II or other emerging ligands (eg, FGL-1), which triggers inhibitory activity that reduces the function of effector T cells.[4, 5]

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LAG-3 is often expressed on chronically exhausted T-cells and is frequently co-expressed with PD-1 on tolerized tumor infiltrating lymphocytes (TILs) across many tumor types.[8,9,10] Increased expression of LAG-3 on TILs, especially in the context of PD-1 expression, further promotes T cell exhaustion, leading to an impaired ability to attack tumor cells and an increased potential for tumor growth.[4,11] Preclinical studies indicate that inhibition of the LAG-3 pathway may restore effector function of exhausted T cells, promoting proinflammatory cytokine signaling, and ultimately, an anti-tumor response. The combination of LAG-3 and PD-1 inhibition demonstrated enhanced anti-tumor activity by targeting independent pathways with distinct functions.[4]

Relatlimab is a blocking antibody specific to the LAG-3 receptor. Relatlimab is being investigated in different indications and lines of therapies in combination with nivolumab. Nivolumab and relatlimab have been shown to have encouraging clinical activity as combination therapy, with few overlapping toxicities.[6] In the CA224020 Phase 1/2a study, the combination of nivolumab and relatlimab demonstrated tolerability, and preliminary clinical activity in advanced melanoma participants that had been previously treated with anti-PD-1/PD-L1 therapy.[6,12,13]

3.1.1 LAG-3 Expression in Pediatric Tumors

[redacted] The LAG-3^{+} Treg subset co-expressed cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) but not PD-1. PD-1^{+} T cells did not co-express LAG-3. More recently, patients with pediatric Hodgkin lymphoma (HL) with tumor samples from Children's Oncology Group clinical trial AHOD0031 with matched patient outcome data were analyzed for the expression of LAG-3 and PD-L1 using immunohistochemistry.[16] [redacted] Collectively, these observations support a rationale for combination therapy of pediatric hematologic malignancies targeting both PD-1 and LAG-3 immune checkpoints.

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3.1.2 Overview of Select Pediatric Hematologic Malignancies

3.1.2.1 Classical Hodgkin Lymphoma

Classical Hodgkin lymphoma is characterized by rare malignant Reed Sternberg cells surrounded by an extensive but ineffective inflammatory immune cell infiltrate.[17,18,19] Recent work has demonstrated that chromosome 9p24.1/CD274 (PD-L1)/PDCD1LG2(PD-L2) genetic alterations increase the PD-1 ligands expression, and are described as a defining feature of cHL.[20] The 9p24 amplicon also contains JAK2, and copy number-dependent JAK2-signal transducers and activators of transcription which can further increase PD-1 ligand expression.[18]

[redacted]

Hodgkin lymphoma has a bimodal age distribution with peak incidence at 15-34 years of age and again at 50-60 years of age. A significant proportion of cases occur in the pediatric age group, the majority of which present in adolescents, and a minority of the cases are seen in patients younger than 10 years of age.[18] It is divided into 2 broad categories by pathology: cHL and nodular lymphocyte predominant HL.

Selection of chemotherapy regimen with or without radiotherapy is usually risk based and response adapted, with risk stratification evolving. National Comprehensive Cancer Network (NCCN) guidelines recommend low, intermediate- or high-risk groups related to clinical staging and certain factors from clinical study data,[19] whereas EuroNet guidelines propose an assessment of the pre-salvage prognostic factors time to relapse, first line treatment, and stage at relapse to allocate participants to low- or a standard risk groups.[20] High-risk assessment for this protocol is determined by the following factors: early relapse, B-symptoms at relapse, extensive disease at contraindicated radiotherapy (RT) field, and/or relapse at prior RT field.

There are multiple standard chemotherapeutic regimens for first-line treatment in newly diagnosed pediatric cHL that vary between the US and Europe, making the direct comparison of outcomes from different studies difficult.[21,22,23,24] Positron emission tomography (PET) response to therapy prior to high-dose chemotherapy followed by autologous stem cell transplantation (HDCT/ASCT) has also been recognized as an important prognostic factor.[25] The most predictive prognostic factors identified for pediatric patients with recurrent/relapsed or refractory (R/R) cHL include primary progression or early relapse, chemotherapy-resistant disease at relapse, and the presence of disease prior to ASCT.[26]

Participants achieving a complete metabolic response (CMR) after salvage chemotherapy have a long-term relapse-free survival of ~75% post-ASCT whereas those with evidence of residual disease prior to HDCT/ASCT have a long-term relapse-free survival that is only ~25%.[27] Because results from salvage therapy influence long-term EFS post-ASCT, it is important to develop well-tolerated regimens that increase complete response (CR) rates pre-ASCT.[27,28,29]

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Given that brentuximab vedotin (Bv) and nivolumab both have documented high single-agent response rates and also work through distinct mechanisms of action, the ongoing CA209744 (NCT02927769) study evaluates the safety and antitumor activity of combination therapy with nivolumab + brentuximab vedotin (N+Bv) in participants with cHL relapsed or refractory after failure of standard frontline chemotherapy. [redacted] Participants with early relapse, or extranodal disease, or B symptoms at relapse have worse prognosis and are classified as high-risk (R2 cohort). For the high-risk cohort only participants who attain CMR to salvage therapy proceed to HDCT/ASCT. Thus, an unmet medical need remains in these high-risk patients.

3.1.2.2 Non-Hodgkin Lymphoma

Non-Hodgkin lymphomas (NHLs) constitute 10% to 12% of cancers and represent nearly two-thirds of the lymphomas diagnosed in children.[30] Approximately 70% of children with NHL present with advanced disease and/or have metastatic involvement, including bone marrow, central nervous system (CNS), and/or bone,[31] as opposed to NHL in adults, which tends to present as low- or intermediate-grade. NHL of childhood and adolescence fall into 3 main histological categories: mature B-cell (Burkitt and Burkitt-like lymphomas [30%] and diffuse large B-cell lymphoma [DLBCL; 10 to 20%]), lymphoblastic lymphoma (20%), and anaplastic large cell lymphoma (10%). Other types are only rarely diagnosed in children.[32] Childhood NHL occurs most commonly in the second decade of life and infrequently at under than 3 years of age. In children, NHLs consist predominantly of mature, aggressive B-cell lymphomas, with Burkitt lymphoma (BL) being most common in 5- to 14-year-olds and DLBCL predominating in 15- to 19-year-olds. The outcome at diagnosis is usually superior relative to adults but those with R/R disease do poorly and need novel approaches.[32,33,34,35]

Compared with adults, children and adolescents with DLBCL have a better overall survival (OS). One factor may be the difference in biology, because pediatric DLBCL shares multiple features with BL, including high proliferation, increased MYC expression, decreased B-cell lymphoma 2 expression, higher incidence of MYC translocation, and germinal center phenotype (75%).[36,37] In addition, using gene expression profile, Deffenbacher et al[38] recently reported a 3:1 predominance of the germinal center B-cell-like (GCB) versus the activated B-cell-like (ABC) subtype in pediatric DLBCL. Adult participants with the GCB subtype have a significantly better OS than those with the ABC subtype.[38,39,40,41] Lymphoblastic lymphomas (20% of childhood NHLs) are usually positive for terminal deoxynucleotidyl transferase, with more than 75% having a T-cell immunophenotype and the remainder having a precursor B-cell phenotype.[42] Chromosomal abnormalities are not well characterized in patients with lymphoblastic lymphoma. Anaplastic large cell lymphoma (ALCL) accounts for approximately 10% of childhood NHL.[43] All ALCL cases are CD30-positive, and more than 90% of pediatric ALCL cases have a

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chromosomal rearrangement involving the anaplastic lymphoma kinase (ALK) gene. The other types of lymphoma, more commonly seen in adults, occur rarely in children.

The primary therapy for childhood NHL is multi-agent chemotherapy, and the intensity and length of therapy are usually determined by the subtype and stage of disease. The OS for NHL in children across all age groups has continued to steadily improve, with a 5-year survival from 2004 to 2010 of 86.5%. Children with limited-stage NHL have an excellent prognosis with an estimated 5-year EFS of 90% to 95%.[44,45] The prognosis for advanced-stage disease has also improved and varies based on subtype (60% to 90% 5-year EFS).[45,46,47,48,49] The following are known prognostic factors in pediatric NHL: age, site of disease, chromosomal abnormalities, tumor burden, and early response to therapy.[43] The International Prognostic Index was shown to have significant prognostic value for newly diagnosed adults with aggressive NHL, especially if over the age of 60 years (median age in study 56 years, range 16-92 years).[50] An age-adjusted model for younger patients known as the age-adjusted International Prognostic Index was also developed since subjects younger than 60 years of age had a different clinical outcome.[50] The applicability of it in pediatric lymphoma below 16 years of age is not well studied; components of the index such as lactate dehydrogenase (LDH) may have prognostic significance whereas performance status tends not to be routinely used in planning therapy in newly diagnosed NHL in children, and type of lymphoma may have more prognostic influence.[51] Additionally, neither index has been extensively evaluated as a prognostic tool in the relapsed/primary refractory setting. Subsequently, a second-line therapy age-adjusted International Prognostic Index (sAAIPI) has been developed for assessing risk in the relapsed/ primary refractory setting with the therapeutic goal of achieving transplantation (HDCT/ASCT)[52] (Appendix 9). Definitions were similar, with changes from Eastern Cooperative Group to Karnofsky Performance Status, an update from Ann Arbor staging to the Cotswold modification version, incorporation of International Working Group (IWG) response criteria to include functional imaging for response assessment,[53] and modelling was performed on participants with a median age of 49 (range, 16-86) years. In younger children with relapsed or refractory NHL, the prognosis is not as promising, and the best treatment approach for this poor-risk group continues to be a challenge.[54,55] There is little consistency in therapeutic approaches, and there is no formal recommendation on the best approach for this poor prognostic subgroup; new treatment options are needed. An unmet medical need thus remains for these high-risk patients.

3.2 Background

While the treatment of cHL has improved dramatically over the past 2 decades, with reported 5-year EFS rates between 80%-90%, there is still a subset of patients who either relapse or in whom first-line treatment fails. Ten percent to 15% of patients with localized disease and 25% of patients with advanced cHL have recurrent disease after first-line treatment.[56,57,58] Patients with cHL who are refractory to initial therapy, or relapse after primary initial chemotherapy, have a poor clinical outcome.[26, 59] There is currently no consensus or identified best salvage chemotherapy regimen in pediatric and adolescent participants with R/R cHL. Recent clinical trial

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literature of immune checkpoint inhibitors in R/R cHL are summarized in Table 3.2-1 and show encouraging clinical activity with objective response rate (ORR) in the range of approximately 60-80%.

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Table 3.2-1: Clinical Trials of Immune Checkpoint Inhibitors in Relapsed or Refractory cHL

Study	Drug, dose	Design	Phase	Clinical Setting	Participants (n)	ORR (%)	CR (%)	PFS
Cole et al. (Study CA209744), ASCO 2020[60]	Nivolumab (N), 3 mg/kg IV on Day 1 of Cycle Q3W Brentuximab vedotin (Bv), 1.8 mg/kg IV on Day 1 of Cycle Q3W Bendamustine (B), 90 mg/m2 IV on Days 1-2 of Cycle Q3W	Prospective (pediatric) Cohort R1 (low risk) - N+Bv for 2 Cycles, if PD off study treatment, all others 2 more cycles N+Bv Cohort R2 (standard risk) - N+Bv for 2 Cycles, all others 2 more cycles N+Bv Participants who achieved CMR proceeded to HDCT/ASCT After 4 cycles of N+Bv, participants with PMR/NMR received Bv+B intensification prior to HDCT/ASCT (or RT)	2	R/R Low risk Standard risk	 N/A 44	 N/A 82%+	 N/A 59%++ (CMR), DoCMR pending; 9%++ (PMR)	 N/A 91% (@ 12 mos)
Armand et al. (CheckMate 205 updated results), ASH 2018[61]	Nivolumab, 3 mg/kg IV every 2 weeks until PD, etc.* Participants in cohort C discontinue nivolumab after 1 year in persistent CR and could resume treatment if they relapsed within 2 years of the last dose	Prospective Cohort A (no exposure to Bv) Cohort B (treatment with Bv after auto-HSCT) Cohort C (treatment with Bv before and/or after ASCT failure)	2	R/R after prior ASCT	243 (overall) 63 80 100	69 (overall) 65 68 73	16 (overall) 29 13 12	mPFS 15 mos (overall) mPFS 17 mos (A) mPFS 12 mos (B) mPFS 15 mos (C)

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Table 3.2-1: Clinical Trials of Immune Checkpoint Inhibitors in Relapsed or Refractory cHL

Study	Drug, dose	Design	Phase	Clinical Setting	Participants (n)	ORR (%)	CR (%)	PFS
Maruyama et al. 2017, 2018[62]	Nivolumab, 3 mg/kg IV on Day 1 each 14-day cycle.	Prospective	2	R/R	17	81.3	23.5	60% (@6 months)
Herbaux et al. 2017[63]	Nivolumab, 3 mg/kg IV once every 2 weeks without premedication until PD, etc.	Retrospective	-	R/R after allo- HCT	20	95	42	58.2% (@12 mos)
Haverkos et al. 2017[64]	Nivolumab 3 mg/kg IV every 2 weeks or Pembrolizumab 200 mg IV every 3 weeks	Retrospective	-	R/R cHL and NHL after allo-HCT	31 (29 cHL, 2 NHL)	79	50	mPFS 591 days
Ansell et al. (CheckMate 039), 2015[65]	Nivolumab, 3 mg/kg IV every 2 weeks until CR, PD, etc.	Prospective	1	R/R	23	87	17	86% (@24 weeks)
Kuruvilla et al. (Keynote-204), ASCO 2020[66]	Pembrolizumab 200 mg IV Q3W	Prospective (pediatric)	3	R/R	304 (overall) 148 (pembro) 152 (Bv)	65.6% (pembro)	24.5% (pembro)	mPFS 13.2 months
Geoerger et al. (Keynote-051), 2020[67]	Pembrolizumab 2 mg/kg IV every 3 weeks (pediatric RP2D)	Prospective (pediatric)	1-2	R/R solid tumors and NHL cHL	154 total 136	 5.9% 60% (2 CR +7 PR)	NA NA	NA NA
Zinzani et al. (Keynote-087 updated	Pembrolizumab, 200 mg IV every 3 weeks without premedication for a	Prospective Cohort 1 (progression after auto-HSCT and Bv) Cohort 2 (progression after	2	R/R	210 total 69 81	71.9 76.8 66.7	27.6 26.1 25.9	mPFS 13.7 mos mPFS 16.4 mos mPFS 11.1 mos

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Table 3.2-1: Clinical Trials of Immune Checkpoint Inhibitors in Relapsed or Refractory cHL

Study	Drug, dose	Design	Phase	Clinical Setting	Participants (n)	ORR (%)	CR (%)	PFS
results), ASH 2018[68]	maximum of 24 months or until confirmed PD, etc.	salvage chemotherapy and Bv, but ineligible for ASCT because of chemoresistant disease) Cohort 3 (progression after auto-HSCT, without Bv)			 60	 73.3	 31.7	 19.4
Armand et al. (Keynote 013), 2016[69]	Pembrolizumab IV at a dose of 10 mg/kg every 2 weeks	Prospective	1	R/R	31	65	16	69% (@24 weeks) 46% (@52 weeks)
Geoerger et al. (iMATRIX), 2019[70]	Atezolizumab 1200 mg or 15 mg/kg IV every 3 weeks until PD or loss of clinical benefit	Prospective (pediatric) cHL	1-2	R/R solid tumors or NHL, cHL	87 total 9	4.6% 22% (2 PR)	NA NA	NA NA
Shi et al. (ORIENT-1), 2019[71]	Sintilimab, 200 mg IV once every 3 weeks, until PD, etc., for a maximum of 24 months	Prospective Single arm, multicenter, 2L+	2	R/R	92	80.4	34	77.6% (@12 mos)

Abbreviations: allo-HCT = allogeneic hematopoietic cell therapy; ASCO = American Society of Clinical Oncology; ASCT= autologous hematopoietic stem cell transplantation; B = bendamustine; BICR = Blinded Independent Central Review; Bv = brentuximab vedotoxin; cHL = classical Hodgkin lymphoma; CR= complete response; HSCT = hematopoietic stem cell trasplant; IV = intravenously; m= median; mos = months; n = number; N = nivolumab; NA = Not Available; NHL = non-Hodgkin lymphoma; NMR = no metabolic response; ORR= objective response rate; PD = progressive disease; PFS= progression free survival; PMR = partial metabolic response; PR = partial response; R/R= recurrent/relapsed or refractory disease; RP2D = recommended Phase 2 dose; RT = radiotherapy.
+ Prior to consolidation by BICR; ++ After having received 4 cycles of N+Bv treatment.
∗Amendment (July 2014): participants continued treatment beyond progression if certain-predefined criteria were met (ie, SD status and deriving perceived clinical benefit). Participants treated beyond initial progression were required to discontinue in the event of further progression (>10% further increase in tumor burden).

Note: Entries are organized by checkpoint inhibitor then reverse chronologically.

Modified and updated from De Goycoechea et al (2019).[72].

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Nearly two-thirds of the lymphomas diagnosed in children are NHL. In children, NHL is distinct from the common lymphomas observed in adults and is almost always high grade at presentation. Approximately 70% of children with NHL present with advanced disease and/or have metastatic involvement, including bone marrow, CNS, and/or bone, as opposed to NHL in adults, which tends to present as low or intermediate grade. Although the outcome for NHL at diagnosis is excellent using treatment strategies that are tailored to the specific patient and disease subtype, those with recurrent or refractory disease do poorly and need novel approaches. The data on NHL subtypes has shown that the clinical activity of checkpoint inhibitors is more modest in the range of 20-40% response rates.[73]



3.2.2 Nivolumab Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (IgG4-S228P) 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, PD-L1 and 2 PD-L2, results in the downregulation 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.

Nivolumab (OPDIVO^{TM}) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

3.2.3 Relatlimab Combined with Nivolumab Preclinical Activity

LAG-3 has been shown to be expressed in TILs of several tumor types, including melanoma, HCC, breast, ovarian, and lung cancers, often in connection with increased PD-1+ T cells.[74] Preclinical data presented in recent years illustrate a clear synergy between the inhibitory receptors LAG-3

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and PD-1 in controlling immune homeostasis, preventing autoimmunity, and enforcing tumor-induced tolerance.[6,75] 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.

[redacted]

3.2.4 Relatlimab Combined with Nivolumab 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. [redacted]

The Phase 1/2a study CA224020 is investigating the safety, tolerability, and effectiveness of relatlimab, with and without nivolumab, to treat various solid tumors. Initial results show encouraging clinical activity when relatlimab is combined with nivolumab in the treatment of participants with solid tumors.[6,12,13] The combination dose of relatlimab [redacted] mg every [redacted] + nivolumab [redacted] mg [redacted] induced responses in previously heavily treated advanced solid tumors and effected responses in tumors that had demonstrated resistance to nivolumab therapy. [redacted] Refer to the Relatlimab IB for further information.[6]

[redacted]

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3.2.6 Nivolumab Clinical Activity

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including NSCLC, melanoma, RCC, cHL, SCLC, gastric cancer, SCCHN, urothelial cancer, HCC, and colorectal cancer (CRC). 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 SCCHN. Details of the clinical activity in these various malignancies are provided in the United States prescribing information and Summary of Product Characteristics.

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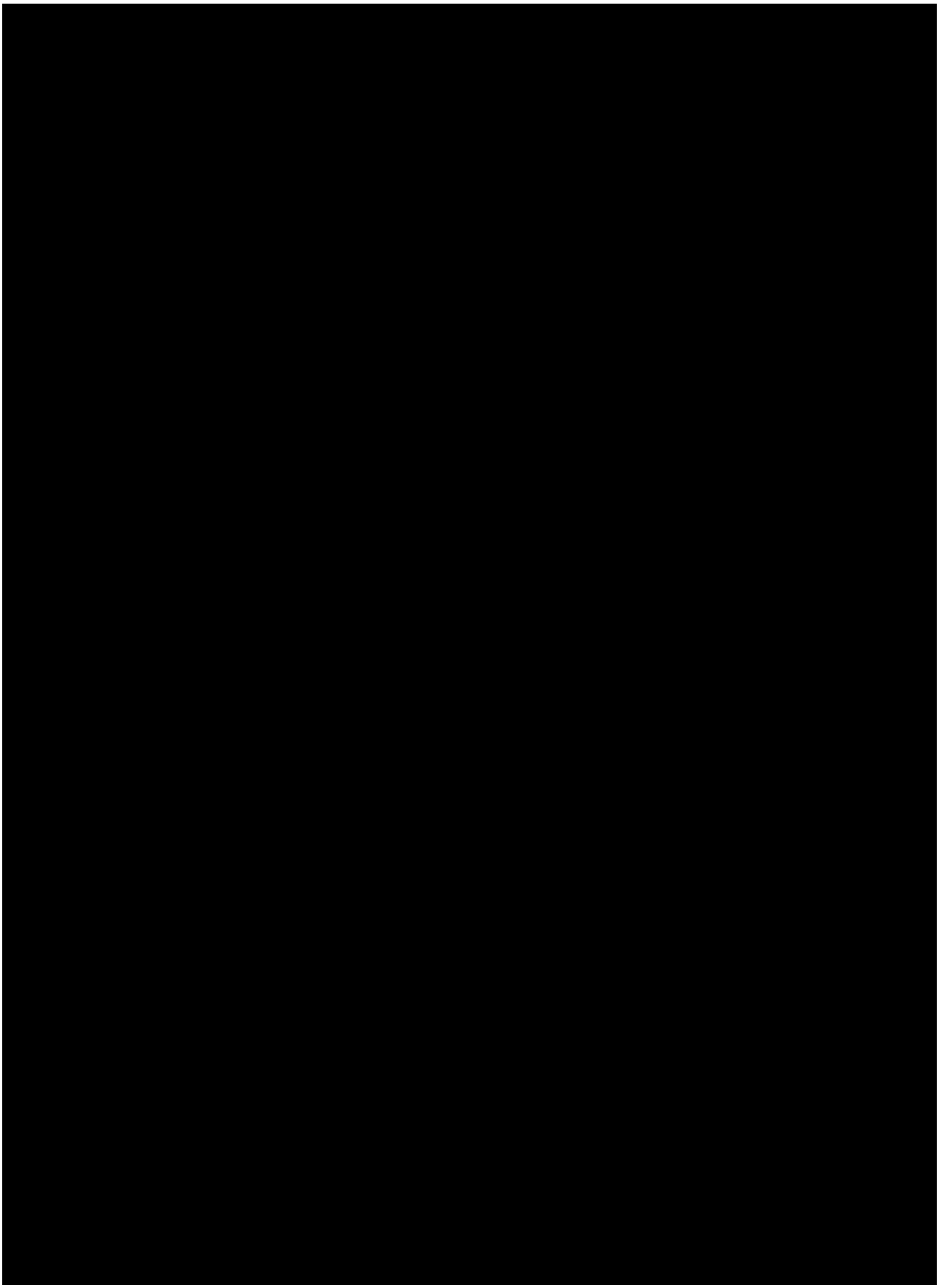
3.2.7 Relatlimab Combined with Nivolumab Clinical Safety

The combination therapy of relatlimab plus nivolumab has been tested in [redacted] dosing intervals in Part B (dose escalation) of CA224020 study. Refer to the IB Table 5.5.1-1 for details of the dose levels and dose-limiting toxicities (DLTs) for participants treated in the Part B (combination therapy escalation).[6] [redacted]

Of note, at the dose level of [redacted] mg relatlimab + [redacted] mg nivolumab [redacted], there were 2 DLTs of Grade 3 aseptic meningitis and Grade 4 myocarditis.[6] The Grade 4 myocarditis event led to additional on-treatment surveillance given the clinical significance of myocarditis.[6] Increased cardiac surveillance during the first 2 months of therapy [redacted] was instituted, as well as the exclusion of participants with a history of myocarditis and ECG monitoring, in subsequent expansion cohorts in the CA224020, CA224022, CA224034, CA224087, and CA224048 studies. Nevertheless, serious myocarditis reactions are uncommon, with an incidence rate of 0.69% in combined data from monotherapy and in combination with nivolumab [redacted].[6]

[redacted]

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[redacted]

More information can be found in the relatlimab IB.[6]

[redacted]

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[redacted]

3.3 Benefit/Risk Assessment

3.3.1 Risk Assessment

Table 3.3.1-1: Risk Assessment of CA224069 Study Conduct

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Study Interventions: Relatlimab + Nivolumab		
Immune-Mediated AEs (eg, pneumonitis, colitis, hepatitis, nephritis, endocrinopathy, neurologic and skin AEs)	IB Section 7.1.1.1[6]	Recommended IMAE management algorithms are included [redacted] or as per institutional protocol/Investigator discretion.
Neurological AEs (eg, aseptic meningitis and encephalitis)	IB Section 7.1.1.2	Cerebrospinal fluid analysis and in the absence of identifiable infectious etiology, steroid therapy with taper or management as per institutional protocol/Investigator discretion.
Potential Infusion Related Reaction and Cytokine Release	IB Section 7.1.1.3	Recommended management algorithms are included [redacted] or as per institutional protocol/Investigator discretion.
Opportunistic Infections Due to Immunosuppression	IB Section 7.1.1.4	Prophylactic antibiotics and/or antifungal agents if indicated, laboratory tests or procedures, and management per institutional protocol/Investigator discretion.
Cardiovascular AEs (ie, myocarditis)	IB Section 7.1.2	ECG monitoring, [redacted], and management per Myocarditis AE Management Algorithm [redacted] or as per institutional protocol/Investigator discretion.
Potential developmental toxicity	IB Section 4.3.4	Exclusion criteria, pregnancy testing, contraception per protocol, physical measurements per Section 2.
Study Procedures		
Tumor Biopsy (eg, pain, infection)	IB Section 7.1.3	Per institutional protocol/ Investigator discretion.

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Table 3.3.1-1: Risk Assessment of CA224069 Study Conduct

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
FDG-PET-CT (ie, irradiation)	NCCN Clinical Practice Guidelines for B-cell Lymphomas v 4.2020 (Aug 13, 2020)	Algorithm to limit radiation exposure during imaging procedures in follow-up phase by permitting imaging per SoC and Investigator discretion, protocol Section 5.1.3.
Phlebotomy (eg, pain, ecchymosis, bleeding, syncope)	IB Section 7.1.3	Per institutional protocol/ Investigator discretion.
Other (if applicable)		
Allergy to contrast agent (eg, reaction to anaphylaxis)	Not applicable	Prophylaxis and/or treatment per institutional protocol/Investigator discretion.

Abbreviations: AE = adverse event; ECG = electrocardiogram; FDG-PET-CT = [^{18}F] fluorodeoxyglucose-positron emission tomography-computed tomography; IB = Investigator Brochure; IMAE = immune-mediated adverse event; NCCN = National Comprehensive Cancer Network; SoC = standard of care.

3.3.2 Benefit Assessment

Although salvage with standard-dose chemotherapy (SDCT) followed by HDCT/ASCT in R/R cHL is often considered the standard of care (SoC) in adult practice, pediatric practice adopts a more individualized risk-stratified and response-adapted approach to salvage therapy with greater use of non-transplant salvage. The NCCN and EuroNet guidelines recommend low- and standard-salvage risk groups categorization at the point of relapse, based on time to relapse, prior treatment in first line therapy, and stage at relapse.[23,25] The definition of high-risk as used in this protocol contains elements of high-risk from the NCCN guidelines and also standard risk from the EuroNet guidelines.[23,25] Achieving a CMR, defined as a Deauville score 1–3, is the goal of salvage SDCT. FDG-PET response is crucial in deciding whether salvage treatment within low- and standard-risk group is continued or altered. Due to the associated poor prognosis of failure to achieve CMR (as compared with those participants who achieve negative FDG-PET imaging prior to HDCT/ASCT), participants who have failed to achieve CMR after 2 lines of SDCT are classified as high-risk.[25] Due to the lack of an evidence-based recommendation in this group, NCCN and EuroNet guidelines recommend considering multiple re-induction and subsequent therapy regimens before HDCT/ASCT, to minimize disease burden with a goal of achieving a metabolic CR prior to transplant, including experimental (ie, clinical study) options. Bv, an anti-CD30 antibody conjugated to auristatin (Monomethyl auristatin E [MMAE]), is highly effective in R/R cHL. Single agent Bv reported in the Phase 1/2 pediatric trial investigating single agent Bv in CD30-positive R/R HL and anaplastic large cell lymphoma (ClinicalTrials.gov number NCT01492088) demonstrated an ORR of 47% and CR rate 33% in cHL participants.[80] The immune checkpoint inhibitors targeting the PD-1/PDL-1 axis are an option in patients refractory to 2 initial lines of salvage therapy, and thus are reserved for high-risk patients. Single agent nivolumab showed promising results in a small study (n=23) in R/R HL with ORR of 87%

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(CR 17% and partial response [PR] 70%).[81] The rate of progression free survival (PFS) was 86% (95% confidence interval [CI] 62 to 95) in 20 participants with an objective response. These patients were very heavily pre-treated, 78% had prior ASCT and 78% had prior Bv. Nivolumab has substantial therapeutic activity and an acceptable safety profile in heavily pre-treated cHL however the CR rate as monotherapy was only 17%. Therefore, combination therapies with other agents, including Bv, has been a recent focus in order to achieve better CR rates. The CA209-744 trial in R/R pediatric cHL investigating immunotherapy as the first line salvage with induction Bv + nivolumab followed by intensification with Bv + B in poor initial responders (CA209-744 trial, AHOD1721; NCT02927769) demonstrated a CMR rate per blinded independent central review (BICR) of 59% after 4 cycles of nivolumab + Bv.[82]



The addition of relatlimab to nivolumab has been shown to have encouraging clinical activity as combination therapy in multiple tumor types.[6] Furthermore, given the superior clinical outcomes of a negative FDG-PET response in pediatric participants with R/R cHL,[27,28,29] treatment with relatlimab + nivolumab is hypothesized to minimize disease burden with the goal of achieving CMR prior to transplant.

3.3.3 Overall Benefit/Risk Conclusion

The diseases being studied include pediatric R/R cHL and NHL of high-risk. Pediatric cHL and NHL may be fatal if not cured. Approximately 50% of participants treated even with ASCT eventually relapse and other treatment options remain limited. Thus, an unmet medical need remains for this group of patients.



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[redacted]

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[redacted] preliminary indications of efficacy across multiple tumor types and the significant unmet medical need in pediatric R/R cHL and NHL populations, the continuing evaluation of the combination of relatlimab + nivolumab is justified for the patient population in this protocol.

Investigators and the Sponsor will utilize continuous safety assessments to determine whether additional safety measures or termination from the study is 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 (WS) representatives to monitor for any safety signals or trends. As relatlimab is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur; however, data shows that the combination of relatlimab and nivolumab is safe and tolerable at relatlimab [redacted] mg + nivolumab [redacted] mg [redacted] in other studies.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided [redacted]. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of relatlimab and nivolumab, including results from other clinical studies, are also available in the relatlimab IB.[6]

Considering the risks of toxicities in a pediatric population, the study incorporates a weight-based dosing schema for prepubescent (< 12 years old) and lower weight (< 40 kg) participants who may display differences in PK compared to adults. Additionally, a Data Monitoring Committee (DMC) will provide oversight of safety during the study conduct and ensure the protection of participants based on benefit/risk assessment of the combination (refer to Section 5.1.4). A third risk mitigation is by allowing the termination of flat dosing (A1F) if the de-escalated dose (A2F) is not tolerated, and the inclusion of further participants between ages 12 to 18 years and weighing at least 40 kg into a weight-based dosing cohort (A2W). [redacted]

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with relatlimab + nivolumab appear justified by the anticipated benefits that may be afforded to participants with R/R cHL and NHL. The Sponsor will continue to evaluate the risk/benefit profile of the study based on all available safety data including AEs or other safety trends in this or other pertinent clinical studies of BMS-986016; or and new nonclinical data

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suggesting significant risk of illness or injury. [redacted]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• **Part A:** To characterize the safety, tolerability, and define the MTD or RP2D for the combination of relatlimab + nivolumab in pediatric participants less than 18 years of age with R/R cHL and NHL.	• DLTs, MTD/RP2D, and incidences of AEs, SAEs, AEs leading to discontinuation, deaths and laboratory abnormalities
• **Part A:** To characterize the PK of relatlimab for the combination of relatlimab + nivolumab in pediatric participants less than 18 years of age with R/R cHL and NHL.	• Cmax, Ctrough, Tmax, and AUC(TAU) for relatlimab
• **Part B:** To assess the preliminary efficacy of relatlimab + nivolumab based on the RP2D from Part A in participants less than or equal to 30 years old with cHL (Cohort 1).	• CMR rate – The CMR rate is defined as the proportion of all response-evaluable participants who achieve the best response of CMR using Lugano 2014 criteria.
Secondary	
• **Part B:** To assess the safety of relatlimab + nivolumab in R/R cHL (Cohort 1) and NHL (Cohort 2)	• Incidence of AEs, SAEs, AEs leading to discontinuation, deaths, and laboratory abnormalities
• **Part B:** To evaluate the ORR of relatlimab + nivolumab in participants ≤ 30 years of age with cHL (Cohort 1)	• ORR – ORR is defined as the proportion of all response-evaluable participants who achieve a best response of CMR or PMR using the Lugano 2014 classification.

[redacted]

Approved v4.0 930165609 4.0

[redacted]

Abbreviations: AE = adverse event; AUC(TAU) = area under the curve within a dosing interval; cHL = classical Hodgkin lymphoma; [redacted] Cmax = maximum observed serum concentration; Ctrough = trough observed concentration; CMR = complete metabolic response; DLT = dose-limiting toxicity; [redacted] MTD = maximum tolerated dose; NHL = non-Hodgkin lymphoma; ORR = overall response rate; [redacted] PK = pharmacokinetic; PMR = partial metabolic response; R/R = recurrent/relapsed or refractory; RP2D = recommended Phase 2 dose; SAE= serious adverse event; [redacted] Tmax = time to maximum concentration.

Approved v4.0 930165609 4.0

5 STUDY DESIGN

5.1 Overall Design

CA224069 is an open-label, Phase 1/2 clinical trial of relatlimab + nivolumab in children, adolescents, and young adults with R/R cHL and NHL. Part A will encompass safety and dose determination of relatlimab + nivolumab. Part B will be composed of an expansion cohort of cHL (Cohort 1) and [redacted] in NHL (Cohort 2). A schematic of the study design showing the relationship between dose finding (Part A) and cohort expansion (Part B) is shown in Figure 5.1-1.

Participants will continue treatment until progressive metabolic disease (PMD), death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, for a maximum of [redacted] of study treatment, the participant is lost to follow-up, or study termination by the Sponsor.

***Part A*:** Pediatric participants with R/R cHL or R/R NHL less than 18 years of age will be recruited.

The proposed dosing regimen for the starting dose of relatlimab + nivolumab is based upon all available clinical safety/efficacy data. Because pediatric participants vary in age and weight, the proposed starting doses of relatlimab + nivolumab will be determined separately based on age and/or weight. Participants less than 12 years of age and/or weighing less than 40 kg will be given a weight-based dose of relatlimab + nivolumab (Figure 5.1-3), and participants aged ≥ 12 to < 18 years and weighing at least 40 kg will be given a flat dose of relatlimab + nivolumab (Figure 5.1-2).

Part A: [redacted] participants per age/weight group

Flat-dosing (AF) cohort will include the following: participants ≥ 12 years old who weigh ≥ 40 kg:

- D = Relatlimab 160 mg + nivolumab 480 mg intravenous (IV) Q4W (A1F); if the starting dose is found to be not tolerated, then the relatlimab dose will be decreased as follows:
- D-1 = Relatlimab 80 mg + nivolumab 480 mg IV Q4W (A2F).

Age/weight-based dosing (AW) cohort will include the following: participants ≥ 12 years old who weigh < 40 kg and/or participants < 12 years old irrespective of weight:

- D = Relatlimab 2 mg/kg (max 160 mg) + nivolumab 6 mg/kg (max 480 mg) Q4W (A1W); if the starting dose is found to be not tolerated, then the relatlimab dose will be decreased as follows:
- D-1 = Relatlimab 1 mg/kg (max 80 mg) with nivolumab 6 mg/kg (max 480 mg) Q4W (A2W).

Enrollment in the two dosing cohorts (A1F and A1W) will be initiated in parallel. Up to [redacted] participants for each age/weight group will be assessed for safety and PK. The observation period for DLTs (DLT-evaluation period) will be one cycle, defined as [redacted]. Participants will be

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monitored for safety using Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 criteria. If DLT (as defined in Section 7.4.5) is observed in [redacted] or more participants, the dose will be de-escalated to D-1 (A2F and A2W) and an additional [redacted] participants will be evaluated for toxicity and exposure, for another ≥ 2 DLTs. If no DLTs are observed, a minimum of [redacted] participants will be enrolled in A1F and A1W, respectively.

- If, in Part A, a safe dose in pediatric participants cannot be identified, Part B may not be initiated in some age/weight subsets.

If the AF cohort is not tolerated at A1F and A2F dose levels, accrual into this cohort will be terminated. Additional participants aged 12 and above and at least 40 kg will be enrolled onto dose level-1 (A2W) in the age/weight-based dosing schema, and if found to be tolerated, A2W will be declared as the recommended Phase 2 dose (RP2D) for this age/weight group. The participants aged < 12 years and/or weighing < 40 kg would continue to be enrolled and evaluated in parallel.

Part B: Expansion cohort in Hodgkin lymphoma (Cohort 1) and [redacted] in Non-Hodgkin lymphoma (Cohort 2)

The doses of relatlimab + nivolumab are the RP2D or MTD from Part A. Male and female participants with R/R cHL (Cohort 1) or NHL (Cohort 2) less than or equal to 30 years of age will be recruited.

The goal of Part B is to evaluate the preliminary efficacy of relatlimab + nivolumab at its RP2D from Part A in pediatric participants with high-risk R/R cHL (Cohort 1) and in a cohort of R/R NHL (Cohort 2). Participants in Part A will be counted towards the accrual goals of Part B if they are treated at the same dose selected for Part B. Details of the analyses will be specified in the statistical analysis plan (SAP). Due to the heterogeneity of NHL tumors resulting in differences in treatment and outcome, analysis as a single cohort with cHL is not optimal. As such, the expansion portion of the trial (Part B) will enroll approximately [redacted] NHL participants will be enrolled in Stage 1 and Stage 2, respectively, at the RP2D or MTD as defined above.

The total duration of the study follow-up is up to [redacted] from the last study treatment of the last participant (ie, Last Participant Last Treatment), or until the time of primary CMR analysis, whichever occurs later.

The primary objective of Part B is to evaluate preliminary efficacy in cHL (Cohort 1) [redacted]. Preliminary efficacy in cHL (Cohort 1) will be evaluated using the estimated CMR rate and exact 2-sided 90% CI in the [redacted] response-evaluable participants. [redacted]

[redacted]

Approved v4.0 930165609 4.0

[redacted]

Participants who have an initial increase in target lesions but eventually show a response according to the Lugano 2014 lymphoma metabolic response criteria (Appendix 7) will be considered responders for defining response. Parameters for response and progression will be calculated relative to baseline or nadir measurements according to the applicable response criteria. All participants will undergo baseline tumor assessments by [^{18}F] fluorodeoxyglucose-positron emission tomography computed tomography (FDG-PET-CT) or by [^{18}F] fluorodeoxyglucose positron emission tomography magnetic resonance imaging (FDG-PET-MRI) per protocol requirements. If CNS involvement is suspected, in addition to lumbar puncture for CSF evaluation that may be performed as part of standard of care (SoC) practice, brain magnetic resonance imaging (MRI) without and with Gadolinium contrast will be performed at baseline to exclude participants with brain involvement. In addition, contrast-enhanced computed tomography (CT) or MRI may be performed as part of SoC practice per Investigator discretion.

Part A: During the treatment period, FDG-PET-CT whole-body or FDG-PET-MRI should occur at Day 49 (± 7 days), Day 105 (± 7 days) and Day 161 (± 7 days) starting from the date of first dose and corresponding with Day 21 (± 7 days) of Cycles 2, 4 and 6, then every 12 weeks (± 7 days) after Cycle 6 until PMD or treatment discontinuation (EOT), whichever occurs later, participant withdrawal, or death.

Part B: During the treatment period, tumor assessments by FDG-PET-CT or FDG-PET-MRI should occur at Day 49 (± 7 days), Day 105 (± 7 days) and Day 161 (± 7 days) starting from the date of first dose and corresponding with Day 21 (± 7 days) of Cycles 2, 4 and 6. The imaging modality should remain the same for each participant during this phase of the study. In case of CMR before or after 6 cycles by FDG-PET-CT or FDG-PET-MRI, imaging may be performed using diagnostic quality MRI/CT scans every 12 weeks (± 7 days) from the last on-treatment scan date until PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death. If PD is suspected based on clinical or MRI/CT findings, a confirmatory FDG-PET-CT or FDG-PET-MRI should be obtained to confirm PMD.

PMR participants at the end of 6 cycles proceeding to receive Investigator's choice of continuing relatlimab + nivolumab will be followed up by FDG-PET-CT or FDG-PET-MRI imaging every 12 weeks (± 7 days) from the last on-treatment scan date until CMR, PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death.

During follow-up, all participants are allowed to switch imaging modality from being PET-based to diagnostic quality CT or MRI every 12 weeks (± 7 days) for the first 52 weeks, and every 24 weeks (± 7 days) thereafter from the last on- treatment scan date until PMD, participant withdrawal, or death. If PD is suspected on CT or MRI, an additional FDG-PET-CT or FDG-PET-MRI scan must be performed to confirm PMD.

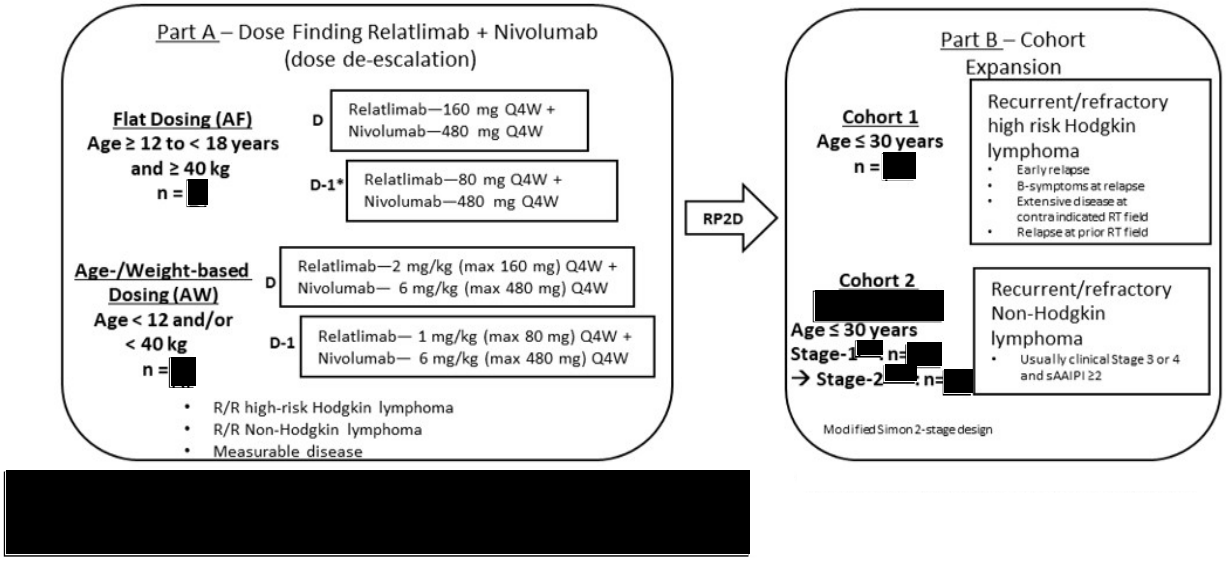
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The study consists of a screening, treatment, and long-term follow-up periods. Based on the response -driven regimen, participants will be allowed to continue study therapy until PMD, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, for a maximum of [redacted] of study treatment, the participant is lost to follow-up, or study termination by the Sponsor. Participants for whom pseudoprogession is considered a likely clinical explanation of their PMD on imaging may be allowed to continue therapy. If additional imaging confirms the PMD, participants will be taken off study, and the time of progression will be assessed as the date of the initial scan demonstrating progression.

The proposed treatment duration is until metabolic progression or for a flexible number of cycles based on Investigator's discretion up to a maximum of [redacted]. This proposed treatment duration is intended to allow for regional differences in duration of therapy and maximize treatment benefit while ensuring the safety of the study participants. Participants who discontinue treatment will enter a clinical safety (30-day and 135-day) and survival (up to approximately [redacted]) follow-up periods. The post-treatment clinical observation period is intended to last approximately 5 elimination half-lives of relatlimab and nivolumab.

The study design schematics are presented in Figure 5.1-1 to Figure 5.1-4.

Figure 5.1-1: Study Design Showing Dose Finding (Part A) and Cohort Expansion (Part B)

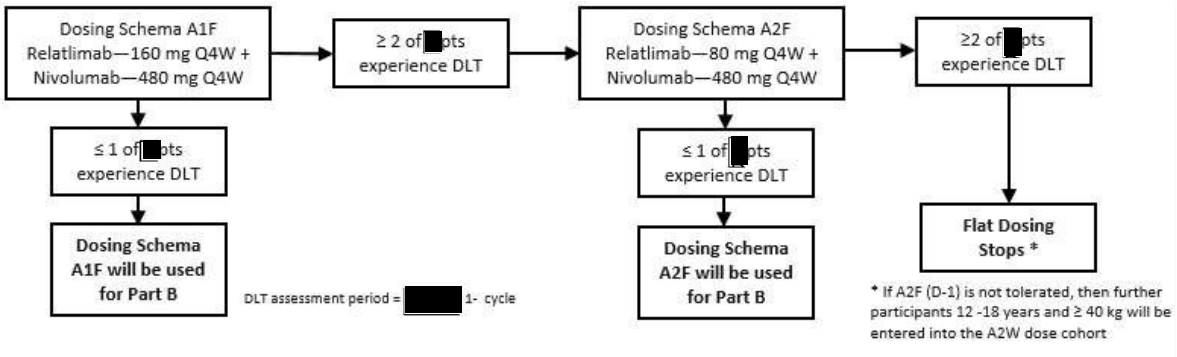


Participants will continue treatment until PMD, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, for a maximum of [redacted] of study treatment, the participant is lost to follow-up, or study termination by the Sponsor.

Abbreviations: AF = flat dosing; AW = age/weight-based dosing; [redacted] PMD = progressive metabolic disease; Q4W = every 4 weeks; RP2D = recommended Phase 2 dosing; R/R = recurrent/relapsed or refractory; RT = radiotherapy; sAAIPI = second-line therapy age-adjusted International Prognostic Index (score).

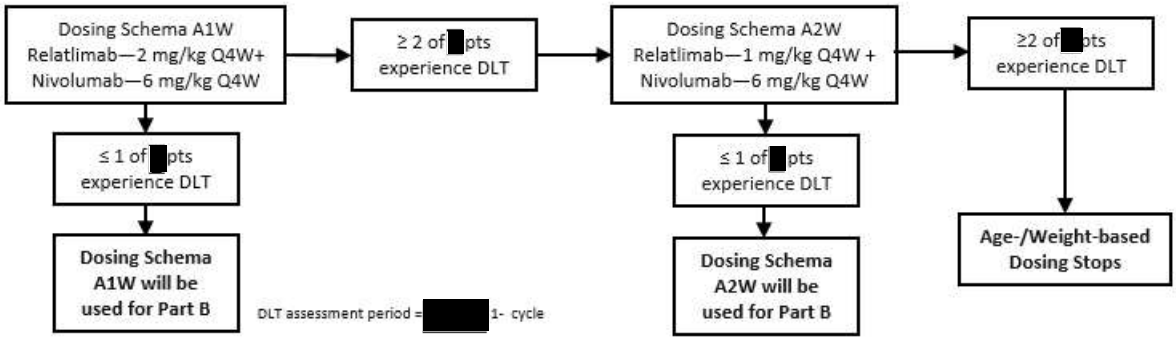
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Figure 5.1-2: Dose-finding Study Design for Flat Dosing (AF) in Part A



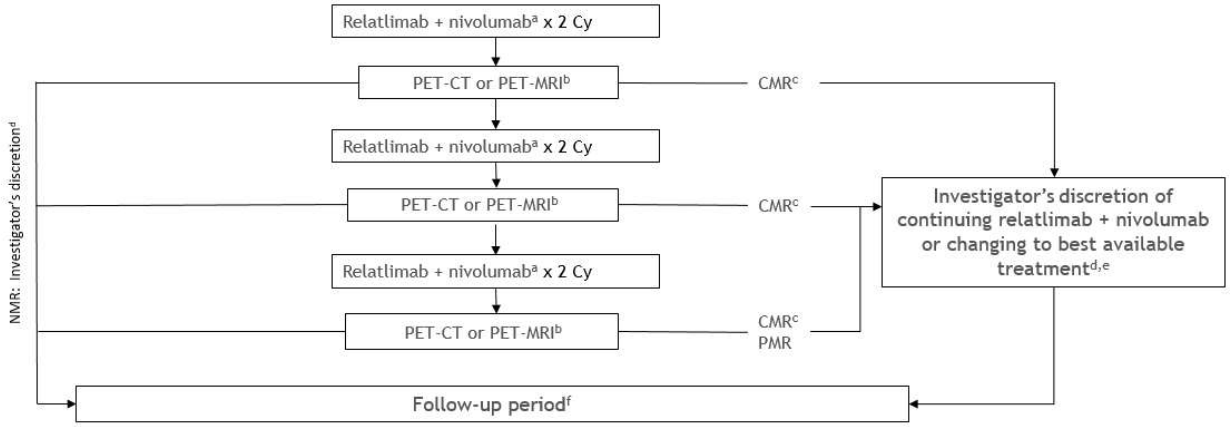
Abbreviations: DLT = dose limiting toxicity; pts = participants; Q4W = every 4 weeks.

Figure 5.1-3: Dose-finding Study Design for Age- and Weight-based Dosing (AW) in Part A



Abbreviations: DLT = dose limiting toxicity; pts = participants; Q4W = every 4 weeks.

Figure 5.1-4: Schematic of Cohort Expansion (Part B) Individual Participant Duration of Treatment Decision Tree



Approved v4.0 930165609 4.0

Abbreviations: ASCT = autologous stem cell transplantation; CAR-T = chimeric antigen receptor T-cells; cHL = classic Hodgkin lymphoma; CMR = complete metabolic response; Cy = (4W) cycle (s); DOT = duration of treatment; EOT = end of treatment; HDCT = high-dose chemotherapy; FDG-PET-CT = [^{18}F]fluorodeoxyglucose-positron emission tomography (PET) – computed tomography (CT) combination; FDG-PET-MRI = [^{18}F]fluorodeoxyglucose-positron emission tomography (PET) – magnetic resonance imaging (MRI); MM = Medical Monitor; MRI = magnetic resonance imaging; NHL = non-Hodgkin lymphoma; NMR = no metabolic response; PMD = progressive metabolic disease; PMR = partial metabolic response; QxW = every x weeks; RP2D = recommended Phase 2 dose; SoC = standard of care; W = week.

[a] RP2D (Part A).

[b] FDG-PET-CT or FDG-PET-MRI at Days 49, 105 and 161 (± 7 days), respectively, then Q12W until CMR, PMD, or treatment discontinuation, whichever occurs later, participant withdrawal, or death.

[c] Per Lugano 2014 criteria (see Appendix 7) where CMR includes Deauville 1–3 or qPET < 1.3.

[d] Investigator's discretion including but not limited to continuing relatlimab + nivolumab with a flexible DOT to accommodate differences in regional SoC for up to a total of [redacted] maximum study treatment, HDCT/ASCT (ie, cHL), CAR-T (ie, NHL) or other best available (eg, definitive) treatment, following consultation with BMS MM. Participants are to be followed with diagnostic quality CT or MRI scans every 12 weeks (± 7 days) from the last on-treatment scan date until PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death.

[e] PMR participants at the end of 6 cycles proceeding to receive Investigator's choice of continuing relatlimab + nivolumab will be followed up by FDG-PET-CT or FDG-PET-MRI imaging every 12 weeks (± 7 days) from the last on-treatment scan date until CMR, PMD, or treatment discontinuation, whichever occurs later, participant withdrawal, or death.

[f] After EOT (Follow-Up), CT or MRI every then Q12W until suspected progression, after which PMD must be confirmed by FDG-PET-CT or FDG-PET-MRI.

5.1.1 Screening Phase

Written informed consent (and assent where appropriate) must be obtained before starting any protocol-specified procedures or evaluations not considered to be part of the participants' standard care. Once informed consent/assent is received, participants will be evaluated for entry criteria during the screening period within [redacted] prior to the administration of the study drug unless stated otherwise (eg, tumor assessment imaging will be performed within 31 days prior to the first dose). Refer to Table 2-1. Re-enrollment after screen failure will be allowed (refer to Section 6.4.1).

A 12-lead ECG is required within 14 days prior to treatment assignment. An echocardiogram within 6 months up to study drug administration is required.

Sufficient, recent tumor tissue (formalin-fixed paraffin-embedded [FFPE] block or minimum of [redacted] unstained slides, obtained from an excisional biopsy, core biopsy or surgical specimen) obtained within [redacted] prior to enrollment, from a nodal or extranodal site which has not been previously irradiated will be submitted to the central laboratory. Central lab must provide confirmation of receipt of tumor tissue prior to treatment assignment. [redacted] Tissue submitted during screening must have an associated pathology report. Fine needle aspiration, plural effusion drainage, and bone marrow/bone lesions are unacceptable for submission. Refer to Section 6.1 [redacted] for

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specifications. [redacted]

5.1.2 Treatment Phase

Part A (Phase 1): Dose-finding cohort by age/weight group

For Part A, up to [redacted] participants will be enrolled in each dosing schema (total maximum of [redacted] participants) starting with dosing schemas A1F (flat dosing) and A1W (age/weight-based dosing) for 1 cycle (each cycle is [redacted]).

Flat-dosing (AF) cohort will include participants ≥ 12 years old who weigh ≥ 40 kg:

- D = Relatlimab 160 mg + nivolumab 480 mg IV Q4W (A1F); if the starting dose is found to be not tolerated, then the relatlimab dose will be decreased as follows:
- D-1 = Relatlimab 80 mg + nivolumab 480 mg IV Q4W (A2F).

Age/weight-based dosing (AW) cohort will include participants ≥ 12 years old who weigh < 40 kg and participants < 12 years old irrespective of weight:

- D = Relatlimab 2 mg/kg (max 160 mg) + nivolumab 6 mg/kg (max 480 mg) Q4W (A1W); if the starting dose is found to be not tolerated, then the relatlimab dose will be decreased as follows:
- D-1 = Relatlimab 1 mg/kg (max 80 mg) with nivolumab 6 mg/kg (max 480 mg) Q4W (A2W).

Assessments for the flat dosing and for the age/weight-based dosing schemas will run concurrently and are independent of each other. Any dosing level in which ≥ 2 participants experience 1 or more DLTs identified in Cycle 1 will be reviewed in conjunction with the Investigators (Section 5.1.4) before accrual into the dose-reduced schema proceeds for flat dosing or age/weight-based, respectively, as outlined in Figure 5.1-2 (A2F; flat dosing) and Figure 5.1-3 (A2W; age/weight-based dosing).

Since the flat dosing schemas (A1F/A2F) and age/weight-based dosing schemas (A1W/A2W) are independent from each other, they will be evaluated for DLTs separately. If dosing in one schema must be reduced or stopped due to DLTs, the other schema will continue as outlined. Participants will continue treatment until PMD, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment (eg, due to CMR enabling participants proceeding to definitive treatment such as (HDCT/ASCT), the participant's decision to discontinue treatment or withdraw consent (or assent, as applicable), the participant is lost to follow-up, conclusion of the study by the Sponsor, or for up to a flexible number of cycles based on Investigator's discretion up to a maximum of [redacted]. Individual participants with confirmed CMR may be given the opportunity to discontinue study therapy on a case-by-case basis after consultation and agreement

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between the Investigator and BMS Medical Monitor in settings where benefit-risk analysis justifies discontinuation of study therapy.

Participants in Part A treated at the dose level used in Part B can be counted in the accrual goals for Part B. The selection of the optimal dose level for Part B will be made at the completion of Part A and can occur separately for the 2 dosing schemas (flat dosing and age/weight-based, respectively) and may be made by the Sponsor in conjunction with the Investigator.

Part B (Phase 2): Expansion cohort in Hodgkin lymphoma (Cohort 1) and [redacted] in non-Hodgkin lymphoma (Cohort 2)

[redacted] participants with high-risk, R/R cHL will be enrolled into Cohort 1, and [redacted] and [redacted] participants with high-risk R/R NHL will be enrolled into Stages 1 and 2, respectively, in Cohort 2 using the optimal dosing schemas (RP2D) identified in Part A. During the treatment period, tumor assessments by FDG-PET-CT or FDG-PET-MRI should occur at Day 49 (± 7 days), Day 105 (± 7 days) and Day 161 (± 7 days) starting from the date of first dose and corresponding with Day 21 (± 7 days) of Cycles 2, 4 and 6.

In case of CMR before or after 6 cycles by FDG-PET-CT or FDG-PET-MRI, imaging may be performed using diagnostic quality MRI/CT scans every 12 weeks (± 7 days) from the last on-treatment scan date until PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death. If PD is suspected based on clinical or MRI/CT findings, a confirmatory FDG-PET-CT or FDG-PET-MRI should be obtained to confirm PMD.

PMR participants at the end of 6 cycles proceeding to receive Investigator's choice of continuing relatlimab + nivolumab will be followed up by FDG-PET-CT or FDG-PET-MRI imaging every 12 weeks (± 7 days) from the last on-treatment scan date until CMR, PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death.

In case of treatment discontinuation, all participants will be allowed to switch modality from being PET-based to diagnostic quality CT or MR scans every 12 weeks (± 7 days) for the first 52 weeks, and every 24 weeks (± 7 days) thereafter from the last on-treatment scan date until PMD, participant withdrawal, or death. If PD is suspected on CT or MRI, an additional FDG-PET-CT or FDG-PET-MRI scan must be performed to confirm PMD.

In certain circumstances, participants with PMD using disease-specific and imaging criteria, but with otherwise stable or improved performance and clinical status, may continue to be treated for a total of [redacted] from Cycle 1 Day 1, in the event of a perceived benefit per Investigator; refer to Section 8.1.1 for treatment beyond progression criteria.

Dose-limiting Toxicities

For the purpose of guiding decisions regarding dose de-escalations in Part A and subject management in Part B, DLTs will be defined based on the incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT period will start on Cycle 1 Day 1 and end at Day [redacted] ([redacted] period). The severity of AEs will be graded according to National Cancer Institute (NCI) CTCAE v5.0. In addition to DLTs, the Sponsor will evaluate the overall

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tolerability, in consultation with the Investigators, of the dose determination in Part A before deciding if Part B will be evaluated in this participant population.

For the purpose of participant management, DLTs that occur at any time will result in study drug being delayed pending evaluation of the event in relation to study drug, in accordance with Section 7.4.5. A participant is considered DLT evaluable after receiving 1 dose of relatlimab + nivolumab.

Participants who withdraw from the study during the [redacted] DLT evaluation period for reasons other than a DLT may be replaced with a new participant at the same dose level. The incidence of DLT(s) during the [redacted] DLT evaluation period will be used to help guide de-escalation decisions and to define the MTD/RP2D. AEs occurring after the [redacted] DLT period will be considered for the purposes of defining the RP2D upon agreement between the Sponsor and Investigators. Participants experiencing a DLT will be evaluated to determine if they are eligible to continue study drug at modified dosing (Section7.4) or if they should discontinue from the study.

5.1.3 Follow-up Phase

Long-term follow-up should continue until withdrawal of consent, death, study termination by the Sponsor, or up to a maximum of [redacted], whichever occurs earlier. Timing for long-term follow-up will be as follows:

- Assessments should continue as described in Table 2-3.
- Participants must be followed for at least 135 days after the last dose of study treatment. The first 2 follow-up visits should be conducted in person.
  - Follow-up Visit 1 should occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 42 days from the last dose.
  - Follow-up Visit 2 occurs approximately 135 days (± 7 days) from the last dose of study treatment.
- Additional assessments may occur when the decision is made to discontinue treatment.
- After Follow-up Visit 2, all participants will be contacted for survival every 3 months (± 14 days). BMS may request that survival data be collected on all treated participants outside of the 3-month specified window. Additional assessments described in Table 2-3 will also be collected. During follow-up, all participants will be allowed to switch modality from being PET-based to diagnostic quality CT or MR scans every 12 weeks (± 7 days) for the first 52 weeks, and every 24 weeks (± 7 days) thereafter from the last on-treatment scan date until PMD, participant withdrawal, or death. If PD is suspected on CT or MRI, an additional FDG-PET-CT or FDG-PET-MRI scan must be performed to confirm PMD.
- Per clinical judgment, the participant may come in earlier to all follow-up visits.
- In case of a clinically significant AE, the participant will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drugs (relatlimab and/or nivolumab). If the participant discontinues study drug for an AE, the participant will be followed until resolution of the AE or the event is considered to be stable and/or chronic. Tumor scans will also continue as described in Section 9.1.2.

Approved v4.0 930165609 4.0

5.1.4 *Data Monitoring Committee and Other Committees*

A Data Monitoring Committee (DMC) will be utilized in the study to provide oversight of safety and provide necessary recommendations for the continued protection of participants considering the assessed risk-benefit profile of relatlimab + nivolumab. The DMC will have access to periodic interim reports of safety and/or efficacy. The DMC charter will describe the procedures related to the committee operations in greater detail.

A Study Steering Committee (SSC) will be established to provide guidance and oversight of the study, and it may assist with certain aspects of management. The SSC will be an independent committee comprised of international subject matter experts. The SSC Committee charter will describe the procedures related to the committee operations in greater detail.

5.2 Number of Participants

The total sample size of the study is estimated to be between approximately [redacted] to [redacted] treated participants. The minimal accrual of [redacted] participants would be based on both age groups not tolerating either dose of relatlimab + nivolumab and the study not proceeding to Part B. If the study proceeds to Part B, participants in Part A will be counted towards the accrual goals of Part B if they are treated at the same dose (RP2D) selected for Part B. In Part B, the study is expected to treat [redacted]. If both age/weight groups in Part A require a dose de-escalation, then up to [redacted] participants (in addition to when A2F is not tolerated) would be treated in Part A; leading to a maximum of [redacted] participants in the study. The minimum number of participants expected in those children that are < 12 years of age and/or below 40 kg is [redacted] if no DLTs are observed. Likewise, the minimum number of participants anticipated in pediatric participants from 12 to < 18 and at least 40 kgs is [redacted], if no DLTs are observed. This minimum number considers scenarios where only Part A is completed for safety or toxicity reasons. Additional details regarding sample size determination are provided in Section 10.2.

It is estimated that approximately between [redacted] and [redacted] enrolled participants will be required to achieve between [redacted] and [redacted] participants needed to be treated in Part A and Part B of the study.

5.3 End of Study Definition

The start of the trial is defined as the first visit for first participant screened. End of trial is defined as the last participant last visit in the survival follow-up period.

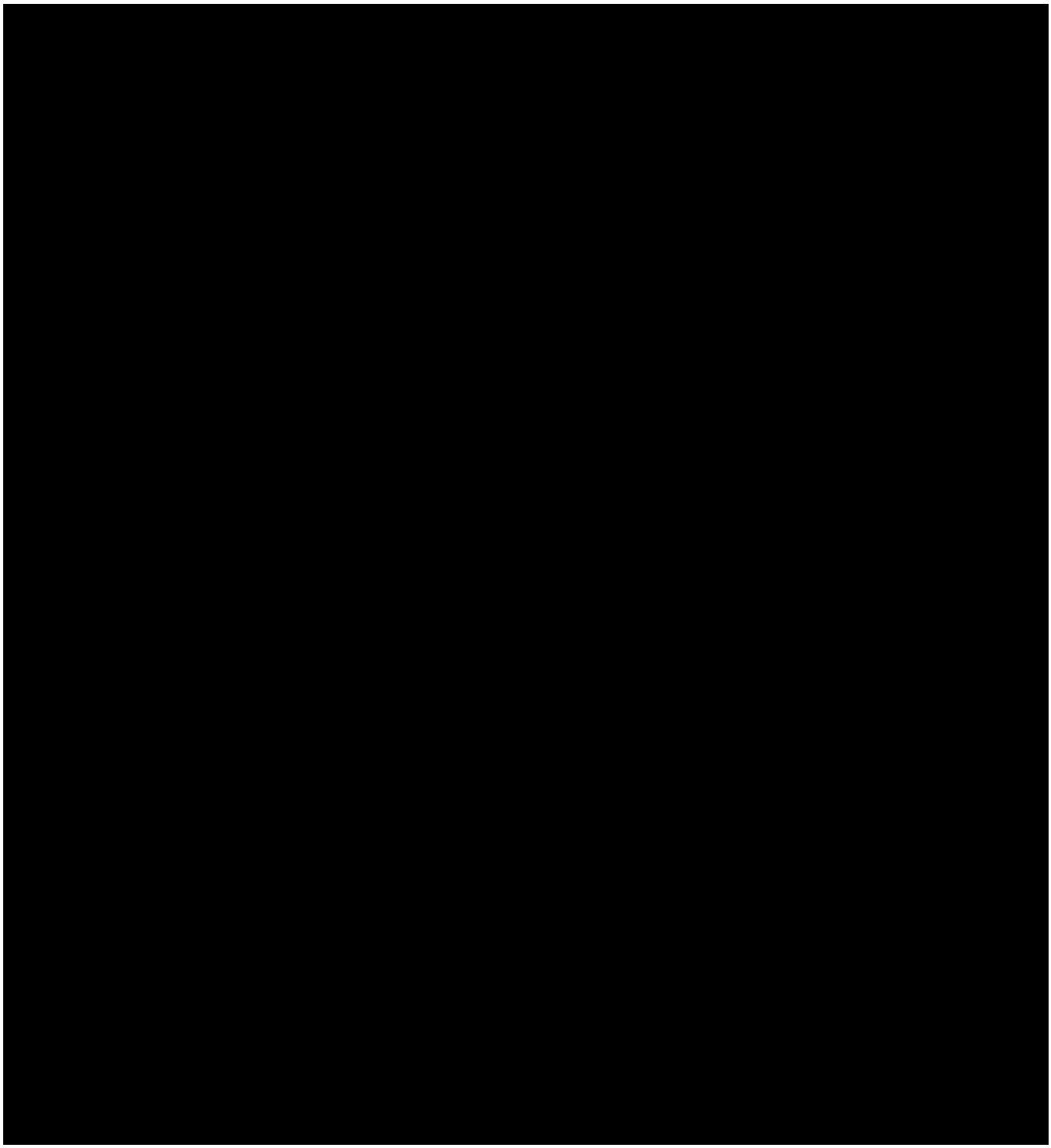
Study completion is defined as the final date on which data for the primary endpoint was or are expected to be collected if this is not the same.

A participant is considered to have completed the study if he/she has completed the last procedure shown in the Schedule of Activities in Section 2 (Table 2-3).

Approved v4.0 930165609 4.0

[redacted]

Approved v4.0 930165609 4.0



5.5 Justification for Dose

The proposed 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, pharmacodynamics, and extensive nivolumab monotherapy clinical experience.[97]

Based on PPK analysis, relatlimab baseline CL in participants receiving relatlimab monotherapy and nivolumab + relatlimab SAV (sequential or co-administered) was similar to participants

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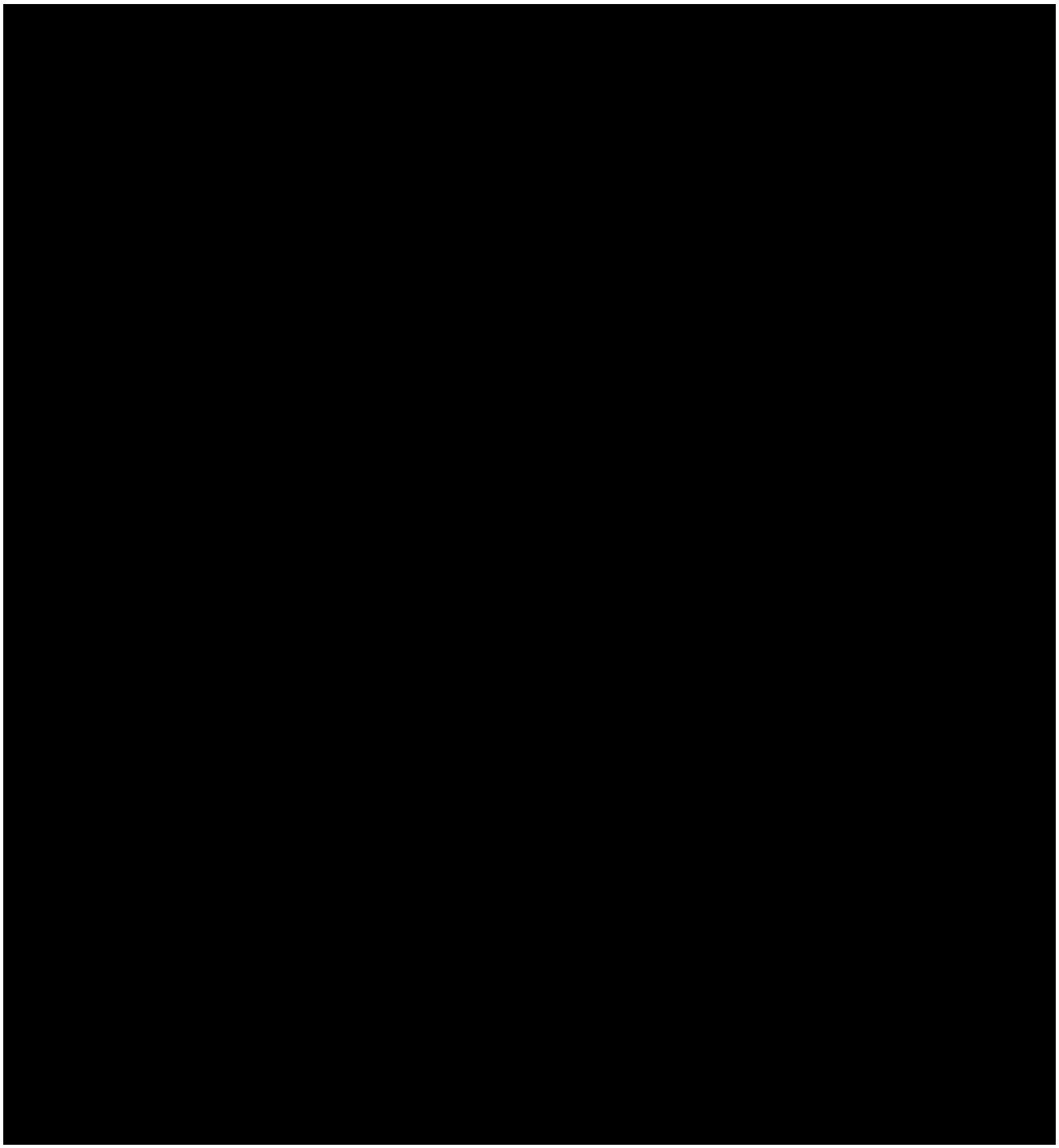
receiving nivolumab + relatlimab FDC (≤ 5% and ≤ 18% difference, respectively). Similarly, nivolumab baseline CL in participants receiving nivolumab monotherapy or nivolumab + relatlimab was similar (≤ 5% difference) to participants receiving nivolumab + relatlimab FDC, thus indicating no clinically relevant effect of FDC formulation on relatlimab or nivolumab PK. Both nivolumab and relatlimab exhibit time-varying CL associated with improving disease status over time in the metastatic solid tumor patient population.

In addition, overall exposure in adolescent participants is expected to be well within established adult safe and tolerable exposure margin. Relatlimab flat doses of [redacted] to [redacted] mg [redacted] as monotherapy and up to [redacted] mg [redacted] in combination with nivolumab have been studied in adults across the weight range of 40 to 120 kg;[91] additional higher doses of relatlimab continue to be evaluated. With regards to nivolumab, a recent analysis has demonstrated that the benefit-risk profile for nivolumab [redacted] mg [redacted] was predicted to be similar to that of [redacted] mg/kg [redacted] across multiple tumor types while providing a more convenient and flexible option for patients and their caregivers.

Based on expected comparable PK and safety of relatlimab and nivolumab combination between adults and adolescent, the adult dose of relatlimab when administered in combination with nivolumab can be extrapolated to the adolescent population. Relatlimab + nivolumab was administered as flat dosing in adults, therefore, a minimum body weight threshold in adolescents (≥ 40 kg) is defined to receive the same adult flat dose to prevent exceeding target adult exposures. Adolescents < 40 kg will be administered body weight adjusted relatlimab and nivolumab doses, up to the respective maximum adult flat doses.

In addition, nivolumab PK in pediatrics was previously characterized.[92] Pediatric and adult HL subjects had similar baseline CL. Pediatric and adult HL subjects had similarly lower (34% and 32%, respectively) CL than adult melanoma subjects, after adjusting for the effect of other covariates, including body size. In the covariate analysis, CHL, HL, and NHL were combined as a single tumor category of lymphoma (HL) due to the small sample size of each of the sub-categories. The predicted exposures of nivolumab for pediatric patients < 12 years old with HL at [redacted] mg/kg Q4W nivolumab monotherapy are shown [redacted]. The predicted nivolumab exposures (Cavgss, Cminss, and Cmaxss) were mostly contained within the range of adult exposures supporting the [redacted] mg/kg Q4W dose. Similar to nivolumab, a relatlimab dose of [redacted] mg/kg Q4W in pediatric patients < 12 years old is expected to provide relatlimab exposures within the range of adult exposures and the intensive PK data generated from Part A of this current study would enable adequate characterization of relatlimab PK in pediatrics.

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Flat-dosing (AF) cohort will include participants ≥ 12 years old who weigh ≥ 40 kg:

- D = Relatlimab 160 mg + nivolumab 480 mg IV Q4W (A1F); if the starting dose is found to be not tolerated, then the relatlimab dose will be decreased as follows:
- D-1 = Relatlimab 80 mg + nivolumab 480 mg IV Q4W (A2F).

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Age/weight-based dosing (AW) cohort will include participants ≥ 12 years old who weigh < 40 kg and/or participants < 12 years old:

- D = Relatlimab 2 mg/kg (max 160 mg) + nivolumab 6 mg/kg (max 480 mg) Q4W (A1W); if the starting dose is found to be not tolerated, then the relatlimab dose will be decreased as follows:
- D-1 = Relatlimab 1 mg/kg (max 80 mg) with nivolumab 6 mg/kg (max 480 mg) Q4W (A2W).

5.5.1 Justification for the 30 Minute Infusion Duration

Co-administration of SAV products (3:1) using a 30-minute infusion time has not been evaluated in participants with cancer. Nevertheless, no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions are expected when the SAV is administered over a 30-minute infusion compared with the 60-minute infusion based on experience with an FDC product.[98] Clinical studies of the FDC (3:1) for the treatment of cancer used a 60-minute infusion duration, wherein the FDC (3:1) has been safely administered over long treatment periods. Infusion reactions, including high-grade hypersensitivity reactions, were uncommon across the relatlimab clinical program. The length of infusion of 30 minutes or 60 minutes is not expected to impact the PK profile of nivolumab and relatlimab. Overall, an infusion duration of 30 minutes for the FDC (3:1) is likewise not anticipated to present significant safety concerns (ie, the frequency of hypersensitivity/infusion-related reactions). The shorter infusion will provide patient convenience by reducing the overall infusion duration and chair time.

Study CA224020 provides a robust safety experience with nivolumab + relatlimab over the broad dose range of [redacted] mg and [redacted] mg to [redacted] mg and [redacted] mg [redacted] levels, respectively. Nivolumab + relatlimab was safely administered sequentially (nivolumab was given first, followed by relatlimab within 15 to 30 minutes of completing the infusion of nivolumab) up to doses of nivolumab [redacted] mg + relatlimab [redacted] mg [redacted] which provides a similar infusion rate of ~[redacted] mg/min as the proposed infusion of nivolumab + relatlimab SAV (3:1) in this study.[98]

No apparent dose association was observed for infusion and hypersensitivity reactions (no cases reported at nivolumab [redacted] mg + relatlimab [redacted] mg [redacted] dose level [0/17 participants] and 1 event [1/15 participants] at nivolumab [redacted] mg + relatlimab [redacted] mg [redacted] dose level was Grade 1/2 and manageable).

All infusion-related reactions reported with co-administration of nivolumab [redacted] mg + relatlimab [redacted] mg infused over 60 minutes were Grade 1-2 adverse events and were manageable.[98]

5.6 Clinical Pharmacology Summary

5.6.1 Nivolumab Clinical Pharmacology Summary

Nivolumab PK was assessed using a PPK approach for single-agent nivolumab.

Nivolumab as a single agent: The PK of single-agent nivolumab was studied in patients over a dose range of [redacted] to [redacted] mg/kg administered as a single dose or as multiple doses of nivolumab as a 60-minute intravenous infusion every 2 or 3 weeks. Nivolumab CL decreases over time, with a

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mean maximal reduction (% coefficient of variation [CV%]) from baseline values of [redacted]% ([redacted]%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of [redacted] mL/h ([redacted]%) 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 [redacted]% lower in this patient population compared with patients with metastatic melanoma at steady state. The geometric mean volume of distribution at steady state (Vss) (CV%) is [redacted] L ([redacted]%), and geometric mean elimination half-life (t1/2) is [redacted] ([redacted]%). Steady-state concentrations of nivolumab were reached [redacted]. The exposure to nivolumab increases dose proportionally over the dose range of [redacted] to [redacted] mg/kg administered every [redacted] weeks. The predicted exposure (Cavg and Cmax) of nivolumab after a 30 minute infusion is comparable to that observed with a 60 minute infusion.

Specific Populations: The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), gender, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2), moderate (eGFR 30 to 59 mL/min/1.73 m^2), or severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by PPK analyses in patients with HCC and in patients with other tumors with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal (ULN) and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) and in HCC patients with moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). No clinically important differences in the clearance of nivolumab were found between patients with mild/moderate hepatic impairment.

Full details on the clinical pharmacology aspects of nivolumab can be found in the IB and product label.[59,98]

Nivolumab doses of [redacted] mg and [redacted] mg/kg are approved in multiple solid tumors and cHL progressing after ASCT and Bv or after 3 or more lines of systemic therapy, including ASCT[98], and it will therefore be used in this study.

In addition, nivolumab PK was characterized in adults and pediatric participants with solid tumors who received nivolumab alone and in combination with relatlimab. Nivolumab exhibits linear and time-varying PK. Nivolumab baseline CL in participants receiving nivolumab monotherapy or nivolumab + relatlimab was similar (≤ 5% difference) to participants receiving nivolumab + relatlimab FDC. The magnitude of the reductions in nivolumab CL over time were also similar

Approved v4.0 930165609 4.0

between relatlimab in combination with nivolumab and nivolumab monotherapy with a maximal reduction of 21.1% in adult 1L melanoma participants. Thus, no PK interaction between nivolumab and relatlimab was observed when these agents were given in combination.



6 STUDY POPULATION

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

6.1 Inclusion Criteria

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

1) Signed Written Informed Consent

a) Participants, or for minors, parents (both, if required by local law), guardians, or legally acceptable representatives (LAR) must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent

Approved v4.0 930165609 4.0

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) Assent from minor participants, where appropriate, should be obtained per local laws and regulations and should be documented in accordance with local requirements.

c) **Not Applicable per Protocol Amendment 01**

d) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study, including disease assessment by FDG-PET-CT.

2) Type of Participant and Target Disease Characteristics

a) Participants must have measurable disease, documented by pathological and radiographic criteria.

b) **Not Applicable per Protocol Amendment 02:** Refer to inclusion criterion 2) l).

i) **Not Applicable per Protocol Amendment 02:** Refer to inclusion criterion 2) l) i).

ii) **Not Applicable per Protocol Amendment 02:** Refer to inclusion criterion 2) l) ii).

c) **Not Applicable per Protocol Amendment 01**: Refer to inclusion criterion 2) m).

i) **Not Applicable per Protocol Amendment 01**: Refer to inclusion criterion 2) m) i).

ii) **Not Applicable per Protocol Amendment 01**: Refer to inclusion criterion 2) m) ii).

d) For both cHL and NHL, recurrent/relapsed and refractory disease is defined as follows:

i) Recurrent/relapsed disease is defined as achieving a CR to previous therapy but then progressing 3 months or more after completion of that therapy.

ii) Refractory disease is defined as never achieving a CR to previous therapy or achieving a CR but then progressing within 3 months of completion of that therapy.

e) Participants must have measurable or evaluable disease based on the Lugano 2014 Classification criteria (Appendix 7).

f) Participants must have FDG-PET-avid and bidimensional measurable disease of at least 1.5 cm in longest axis as documented by radiographic technique (contrast-enhanced CT preferred).

g) [redacted]
Participants who are unable to walk because of neurologic deficits but who are in a wheelchair will be considered ambulatory for the purpose of assessing the performance score [redacted].

h) Substantial recovery (ie, ≤Grade 1 or resolves to baseline) from prior therapy.

i) An interval ("wash-out period") prior to administration of first study treatment is recommended as follows:

i) Biologic agents and targeted therapies: At least 4 weeks after the last dose of biologic or targeted therapy.

ii) Chemotherapy: At least 4 weeks after the last dose of most myelosuppressive chemotherapy. For nitrosoureas, at least 6 weeks is recommended.

iii) Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (eg, Neulasta) or 7 days for short-acting growth factor. For agents that

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have known AEs occurring beyond 7 days after administration, this period must be extended beyond the time during which AEs are known to occur. The duration of this interval must be discussed with the BMS Medical Monitor.

j) A FFPE tissue block (preferred) or a minimum of [redacted] unstained slides of tumor tissue from an excisional biopsy, core biopsy or surgical specimen obtained during screening, or prior to treatment assignment [redacted] must be sent to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable.
   i) Central lab must provide confirmation of receipt of tumor tissue prior to participant treatment assignment.
   ii) If despite best efforts, a minimum of [redacted] slides is not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with Sponsor Medical Monitor or designee. [redacted]
   iii) Please refer [redacted] for additional details on tumor tissue requirements.
   iv) Biopsies of bone lesions that do not have a soft tissue component are not acceptable.

k) **Not Applicable per Protocol Amendment 02**: Refer to inclusion criterion 2) m).
   i) **Not Applicable per Protocol Amendment 02**: Refer to inclusion criterion 2) m) i).
   ii) **Not Applicable per Protocol Amendment 02**: Refer to inclusion criterion 2) m) ii).

l) Participants with pathologically confirmed high-risk R/R cHL, after non-response to or failure of 1 or more lines of standard therapy. See Appendix 5 for country-specific requirements for France.
   i) Clinical stages of cHL permitted include IIB with bulky disease, IIIA with E-lesions with or without bulky disease, IIIB and IV; where E-lesions are defined as localized involvement of extralymphatic tissue (by contiguous growth from, or in close anatomic relation to, an involved lymph node) that is treatable by irradiation, and where IIB with bulk has been upstaged to high-risk based on the more recent series of Children's Oncology Group clinical trials. (Refer to AHOD0031, AHOD1331, and EuroNet-PHL-C1 per NCCN Guidelines Version 2.2021, Pediatric Hodgkin Lymphoma).[23]
   ii) High-risk in cHL for this protocol, which differs from the NCCN or EuroNet Guidelines,[25] is defined by the following characteristics: early relapse, extranodal disease or B symptoms at relapse, extensive disease where radiation therapy was contraindicated at relapse, and/ or relapse in a prior radiation field.

m) **Not Applicable per Protocol Amendment 03**: Refer to inclusion criteria 2 n) and 2) o).

n) Participants with pathologically confirmed R/R NHL after non-response to or failure of 1 or more lines of standard therapy, including, but not limited to, R/R primary mediastinal B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), mediastinal gray zone lymphoma (MGZL), anaplastic large cell lymphoma (ALCL), or peripheral T-cell

Approved v4.0 930165609 4.0

lymphoma (PTCL). Refer also to exclusion criterion 1) r) (Section 6.2). See Appendix 5 for country-specific requirements for France.

i) For the purpose of this study clinical stages of NHL permitted include clinical Stage III or Stage IV per the Lugano 2014 Classification.

ii) High-risk NHL where defined as applicable (eg, in young adults) by sAAIPI scale, based on factors of decreased performance status, elevated LDH, and Stage III/IV disease, with a score of ≥ 2 factors (refer to Appendix 9).[52]

o) Participants with pathologically confirmed R/R NHL after non-response to or failure of 2 or more lines of standard therapy, including Burkitt lymphoma (blast count < 25% malignant Burkitt cells and/or per the investigator's clinical assessment of risk status), lymphoblastic lymphoma (blast count < 25% of marrow nucleated cells and/or per the investigator's clinical assessment of risk status), NK/T-cell lymphoma (nasal and non-nasal NK/T-cell lymphoma subtypes, but not aggressive NK/T-cell leukemia/lymphoma subtype).

i) For the purpose of this study clinical stages of NHL permitted include clinical Stage III or Stage IV per the Lugano 2014 Classification.

ii) High-risk NHL where defined as applicable (eg, in young adults) by sAAIPI scale, based on factors of decreased performance status, elevated LDH, and Stage III/IV disease, with a score of ≥ 2 factors (refer to Appendix 9).[52]

3) Age of Participant

a) For enrollment in Part A, participant must be 0 to less than 18 years of age at the time of signing the informed consent (or assent, as applicable).

b) For enrollment in Part B, participant must be 0 to 30 years of age inclusive at the time of signing the informed consent (or assent, as applicable).

4) **Reproductive Status**

- Investigators shall counsel women of childbearing potential (WOCBP) participants on the importance of pregnancy prevention and the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study intervention to a developing fetus.
- The Investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants:

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

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

iii) WOCBP must have a negative highly sensitive urine or serum as required by local regulations pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human

Approved v4.0 930165609 4.0

chorionic gonadotropin) within approximately 1 day prior to the start of study intervention.

(1) If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

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

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

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

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

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

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, as described in Appendix 4, during the intervention period and for the duration of treatment with relatlimab and nivolumab plus 5 half-lives of study treatment for a total of 5 months post-treatment completion and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

b) **Male Participants:**

i) No contraception requirements for nivolumab and relatlimab for male participants are mandated.

Note: Pregnancy reporting from female partners of childbearing potential of male participants is not required unless an additional Investigational Medicinal Product (IMP) is genotoxic or can be present in relevant amount in seminal fluid to cause fetotoxicity.

6.2 Exclusion Criteria

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

1) Medical Conditions

a) **Not Applicable per Protocol Amendment 01**: Refer to exclusion criterion 1) r).

b) Secondary CNS lymphoma (ie, from systemic NHL) involving the brain, spinal cord, or with leptomeningeal seeding.

c) Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the participant from adhering to the protocol or would increase the risk associated with study participation or study drug administration or

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interfere with the interpretation of safety results (eg, a condition associated with diarrhea or acute diverticulitis).

d) History of progressive multifocal leukoencephalopathy.

e) Pre-existing neuropathy of ≥ Grade 2.

f) Active infection requiring systemic therapy within 14 days prior to the first dose of study treatment; routine antimicrobial prophylaxis is permitted. There should be no sequelae that would place the participant at a higher risk from receiving investigational treatment.

g) **Not Applicable per Protocol Amendment 01**

h) **Not Applicable per Protocol Amendment 01**

i) Participants with a history of myocarditis, irrespective of etiology.

j) **Not Applicable per Protocol Amendment 01**

k) 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.

l) Concurrent or active graft versus host disease (GVHD) or previous history of Grade > 2 GVHD.

m) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

n) Participants with a condition requiring systemic treatment with either corticosteroids (daily doses of > 10 mg or > 0.12 mg/kg prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of treatment assignment. Inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily (or > 0.12 mg/kg daily) prednisone equivalent are permitted in the absence of active autoimmune disease.

o) Participants with an immunodeficiency that existed prior to diagnosis, such as primary immunodeficiency syndromes, organ transplant recipients, and participants on current systemic immunosuppressive agents.

   i) Known human immunodeficiency virus (HIV) positive with an AIDS defining opportunistic infection within the last year, or a current CD4 count <350 cells/µL. Participants with HIV are eligible if:

      (1) they have received antiretroviral therapy (ART) for at least 4 weeks prior to treatment assignment as clinically indicated while enrolled on study.

      (2) they continue on ART as clinically indicated while enrolled on study.

      (3) 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 5).

p) Participants with serious or uncontrolled medical disorders.

q) **Not Applicable per Protocol Amendment 02.** Refer to exclusion criterion 1) r).

Approved v4.0 930165609 4.0

r) Primary CNS lymphoma of the brain or spinal cord.

2) Reproductive Status

a) Women with a positive pregnancy test at Screening or who are breastfeeding.

3) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7 Concomitant Therapy.

b) Prior radiation therapy within 2 weeks prior to first study treatment. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study treatment.

c) Prior treatment with an anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways, with the exception of anti-PD(L)-1 targeted therapies.

d) Prior treatment with LAG-3 targeted agents.

e) **Not applicable per Protocol Amendment 02.**

f) Prior allogeneic bone marrow transplantation.

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

h) 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. Refer to Section 7.7.1 for prohibited therapies.

i) 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, enrollment 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.

j) Prior CAR-T therapy within 6 months of first study treatment.

4) Physical and Laboratory Test Findings

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

b) Inadequate bone marrow function defined as the following:

i) For participants with known bone marrow involvement.

(1) Participants with cytopenias secondary to known bone marrow involvement are not excluded irrespective of absolute neutrophil count (ANC) or platelet counts.

(2) Participants may be administered red cell or platelet transfusions, provided they are not known to be refractory.

(3) Participants with bone marrow involvement will not be evaluated for hematologic toxicity irrespective of ANC or platelet count at the time of diagnosis.

ii) For participants without known bone marrow involvement.

(1) White blood cells < 2000/µL

Approved v4.0 930165609 4.0

(2) Neutrophils < 1500/µL
(3) Platelets < 100 x 10^3/µL
(4) Hemoglobin < 9.0 g/dL

c) Blood creatinine

Serum or plasma specimens for creatinine are acceptable, Reference values for more commonly performed serum creatinine are indicated in the following subsections. [redacted]

i) Reference values for serum creatinine reported for healthy infants are as follows:

Age	Median	2.5th %ile	10th %ile	90th %ile	97.5 %ile
Day 1	55	37	43	70	81
Day 2	47	32	36	60	69
Day 3	42	29	33	54	62
Day 4	39	27	31	50	58
Day 5	37	25	29	48	55
Day 6	36	24	28	46	53
Day 7	34	23	27	44	51
Week 1	31	21	24	40	46
Week 2	28	19	22	36	41
Week 4	25	17	20	32	37
Month 2	22	15	17	29	33
Month 3	20	14	16	26	30
Months 4-6	20	14	16	26	30
Months 7-9	20	14	16	26	30
Months 10-12	21	15	17	27	32

Notes: The values in this table were predicted from the Boer et al. formula[93] modeled from 12,205 determinations of serum creatinine that met inclusion criteria for infants less than 1 year of age. Values are given as micromoles per litre (µmol/L). To express serum creatinine values in milligrams per decalitre (mg/dL) divide by 88.4. The absence of a relationship with gender, weight and height suggests that equations to estimate glomerular filtration rate may be less useful for participants of this age group.

d) Serum creatinine > 1.5 x 97.5th percentile.

i) Serum creatinine based on age/gender for children and adolescents as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4

Approved v4.0 930165609 4.0

≥ 16 years to < 18 years	1.7	1.4

Note: the threshold values in this table were derived from the Schwartz formula for estimating GFR,[94] utilizing child length and stature data published by the US Centers for Disease Control and Prevention

ii) Serum creatinine in young adults ≥ 18 - 30 years of age > 1.5 x ULN, unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockcroft-Gault formula).

iii) Reference ranges for less commonly performed plasma creatinine are as referenced,[95,96] where available, or if not, local reference ranges are acceptable.

e) AST/ALT: > 3.0 x ULN.

f) TB > 1.5 x ULN (except participants with Gilbert Syndrome who must have a TB level of < 3.0x ULN).

[redacted]

h) Any positive test result for hepatitis B virus indicating presence of virus, eg Hepatitis B surface antigen (HBsAg, Australia antigen) positive.

i) Any positive test result for hepatitis C virus (HCV) indicating presence of active viral replication (detectable HCV-RNA). Note: Participants with positive HCV antibody and an undetectable HCV RNA are eligible to enroll.

j) Positive urine screen for drugs of abuse as clinically indicated.

k) Not Applicable per Protocol Amendment 01

l) Left ventricular ejection fraction (LVEF) assessment with documented LVEF < 50% by either transthoracic echocardiogram (TTE) or multigated acquisition (MUGA) scan (TTE preferred test) within 6 months prior to start of study treatment.

5) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components.

b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

6) Other Exclusion Criteria

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

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

c) Inability to comply with restrictions as listed in Section 6.3 (Lifestyle Restrictions).

Approved v4.0 930165609 4.0

d) Any major surgery within 4 weeks of study intervention administration unrelated to the underlying disease except as approved in consultation with the Medical Monitor or designee.

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

6.3 Lifestyle Restrictions

No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently treated 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.

6.4.1 Retesting During Screening or Lead-in Period

Participant Re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment failure (ie, participant has not been treated). If re-enrolled, the participant must be re-consented and study inclusion will be assessed based on the participant's most current, clinical state. Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value). The most current result prior to administration of study intervention is that by which study inclusion will be assessed, because it represents the participant's most current clinical state. Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline, may be repeated in an effort to find all possible well-qualified participants. FDG-PET-CT performed within 8 weeks of re-enrollment does not have to be repeated unless clinically indicated. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) as indicated in Table 7-1.

Approved v4.0 930165609 4.0

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

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the SoC for a given diagnosis, may be considered as IPs.

In this protocol, the IPs are the following:

- Relatlimab
- Nivolumab
- Both drugs used in this open-label study qualify as IPs, and the description and storage information are described in Table 7-1.

Table 7-1: Study Treatments for CA224069

Product Description / Class and Dosage Form	Potency	IP/ Non-IP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Relatlimab (BMS-986016) Solution for Injection	10 mg/mL	IP	Open-label	[redacted]-mL vial. Colorless to pale yellow liquid, clear to slightly opalescent, light (few) particulates (consistent in appearance to protein particulates) may be present	Refer to the label on container and/or pharmacy manual.
Nivolumab (BMS-936558-01) Solution for Injection	10 mg/mL	IP	Open-label	[redacted]-mL vial. Clear to opalescent, colorless to pale yellow liquid. May contain particles.	Refer to the label on container and/or pharmacy manual.

Abbreviation: IP = investigational product.

7.1 Study Interventions Administered

Table 7.1-1: Selection and Timing of Doses

Study Treatment	Dose Levels	Frequency of Administration	Route of Administration
Relatlimab	160 mg and 80 mg 2 mg/kg and 1 mg/kg	Q4W	IV
Nivolumab	480 mg 6 mg/kg	Q4W	IV

Abbreviations: IV = intravenous; Q4W = every 4 weeks.

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Co-administration of Relatlimab Injection and Nivolumab Injection

Relatlimab (BMS-986016) injection (10 mg/mL) is co-administered with nivolumab (BMS-936558) injection by mixing in the same infusion bag and administered as an IV infusion through a compatible low-protein-binding in-line filter at the protocol-specified doses over approximately 30 minutes. Relatlimab injection combined with nivolumab injection can be diluted with 0.9% normal saline or dextrose 5% in water to a total protein concentration no lower than [redacted] mg/mL [redacted].

Based on expected comparable PK and safety of relatlimab + nivolumab [redacted]. Relatlimab + nivolumab was administered as a flat dose in adults, therefore, a minimum body weight threshold [redacted].

Study treatment should be administered in an area with access to resuscitation equipment. Dosing calculations should be based on the actual body weight assessed at baseline. It is not necessary to recalculate subsequent doses if the participant's weight is within 10% of the weight used to calculate the previous dose. All doses will be rounded up to the nearest milligram or per institutional standard.

After participants are assigned to an initial dosing cohort (either age/weight-based [A1W or A2W] or flat dosing [A1F or A2F]), participants should remain on that dosing cohort for the duration of the study.

Participants should be carefully monitored for infusion reactions during study treatment administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.4.

Doses of study treatment may be interrupted during infusion (refer to Section 7.4.4), delayed (refer to Section 7.4.1), or discontinued (refer to Section 8.1) depending on how the participant tolerates treatment. Dosing visits (cycles) are not skipped or omitted, but they may be delayed. Within an allocated dosing schema, there will be no dose escalations or reductions of relatlimab and nivolumab allowed. Premedications are not recommended for the first dose of study therapy. Study therapy may be administered within 3 days before or after the scheduled dose.

7.1.1 Relatlimab Combined with Nivolumab Administration

Participants will receive nivolumab and relatlimab on Day 1 of every 4-week cycle. Nivolumab will be co-administered with relatlimab in a single bag IV over approximately 30 minutes.

- There will be no dose escalations or reductions of immunotherapy allowed outside of dosing schema in Table 2-2 and Table 2-3 during Part A.
- Premedications are not recommended routinely for the first dose of immunotherapy.
- Participants should be carefully monitored for infusion reactions during immunotherapy administration.

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- If an acute infusion reaction is noted, participants should be managed according to Section 7.4.4.
- Participants should receive immunotherapy until progression, unacceptable toxicity, withdrawal of consent (or assent, where applicable), or a flexible number of cycles based on Investigator's discretion up to a maximum of [redacted]
- Doses of immunotherapy may be interrupted, 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. Refer to Section 7.4 and Section 8.1.
- If a participant meets criteria for discontinuation and the Investigator is unable to determine whether the event is related to all or any 1 study drug, the participant should discontinue all study drugs and be taken off the treatment phase of the study.

The study drug injections can be infused undiluted or diluted. All infusions must be promptly followed by a diluent flush to clear the line of IP before starting infusion(s) of any additional treatment. Instruction for dilution and infusion of study drug injections will be provided in the Pharmacy Manual. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. For details on prepared drug storage, preparation, and administration, please refer to the IBs and/or Pharmacy Manual. The selection and timing of dose for each participant is provided in Table 7.1-1.

Study treatment will be dispensed by IRT at the study visits as listed in Section 2 (Schedule of Activities). Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

7.2 Method of Study Intervention Assignment

Before the study is initiated at an investigative site, each user will receive login information and directions on how to access the IRT. Each participant will be assigned a unique participant number after signing the ICF. Participant numbers will be used on all participants' study information. Participant numbers will not be reassigned. An IRT will be employed to manage participant dosing (either age/weight-based or flat dosing). The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained.
- Year of birth.

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

[redacted]

Approved v4.0 930165609 4.0

[redacted]

7.4 Dosage Modification

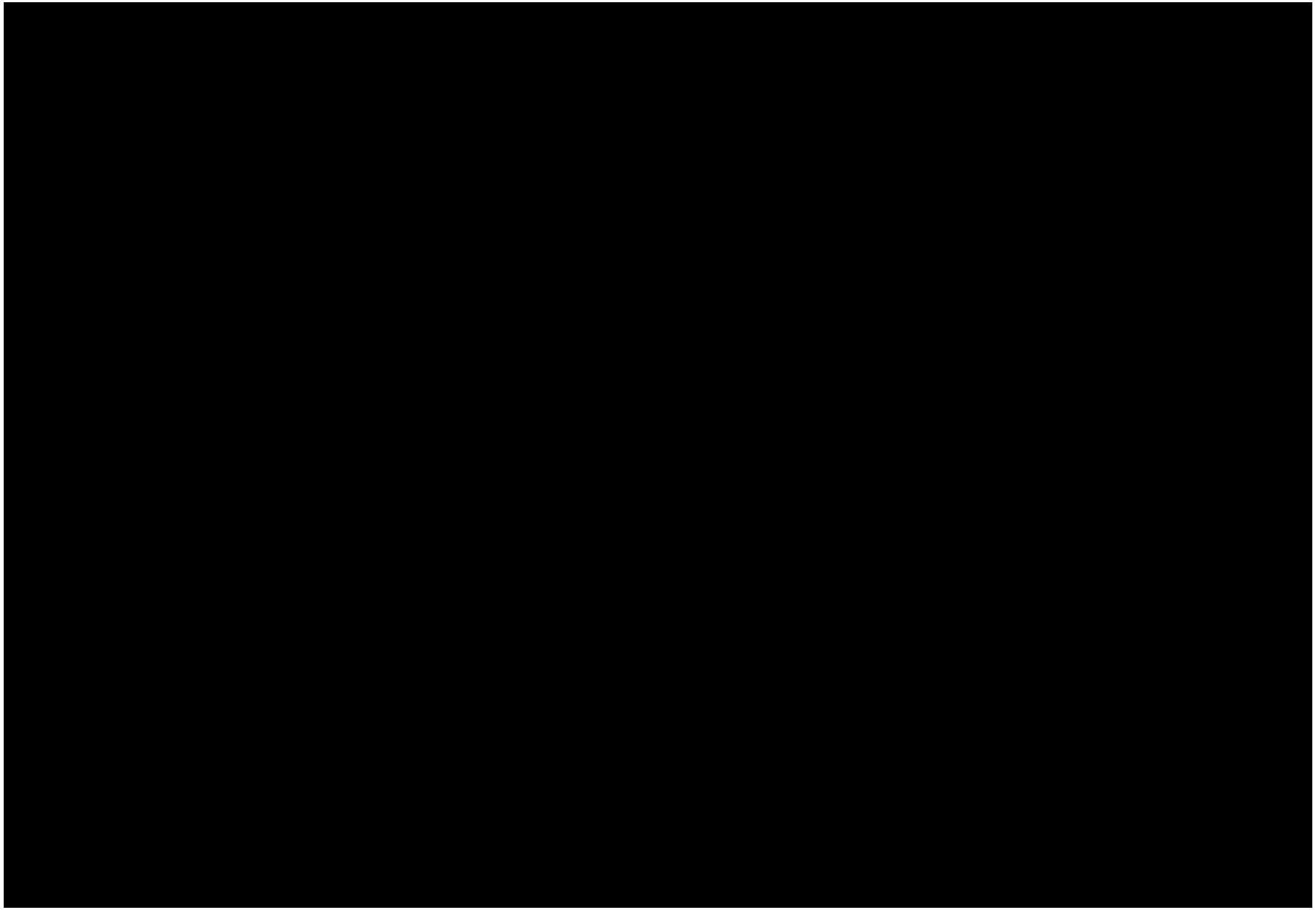
No intra-participant dose reductions or escalations for immunotherapy are permitted.

7.4.1 Dose Modification Criteria for Relatlimab and Nivolumab

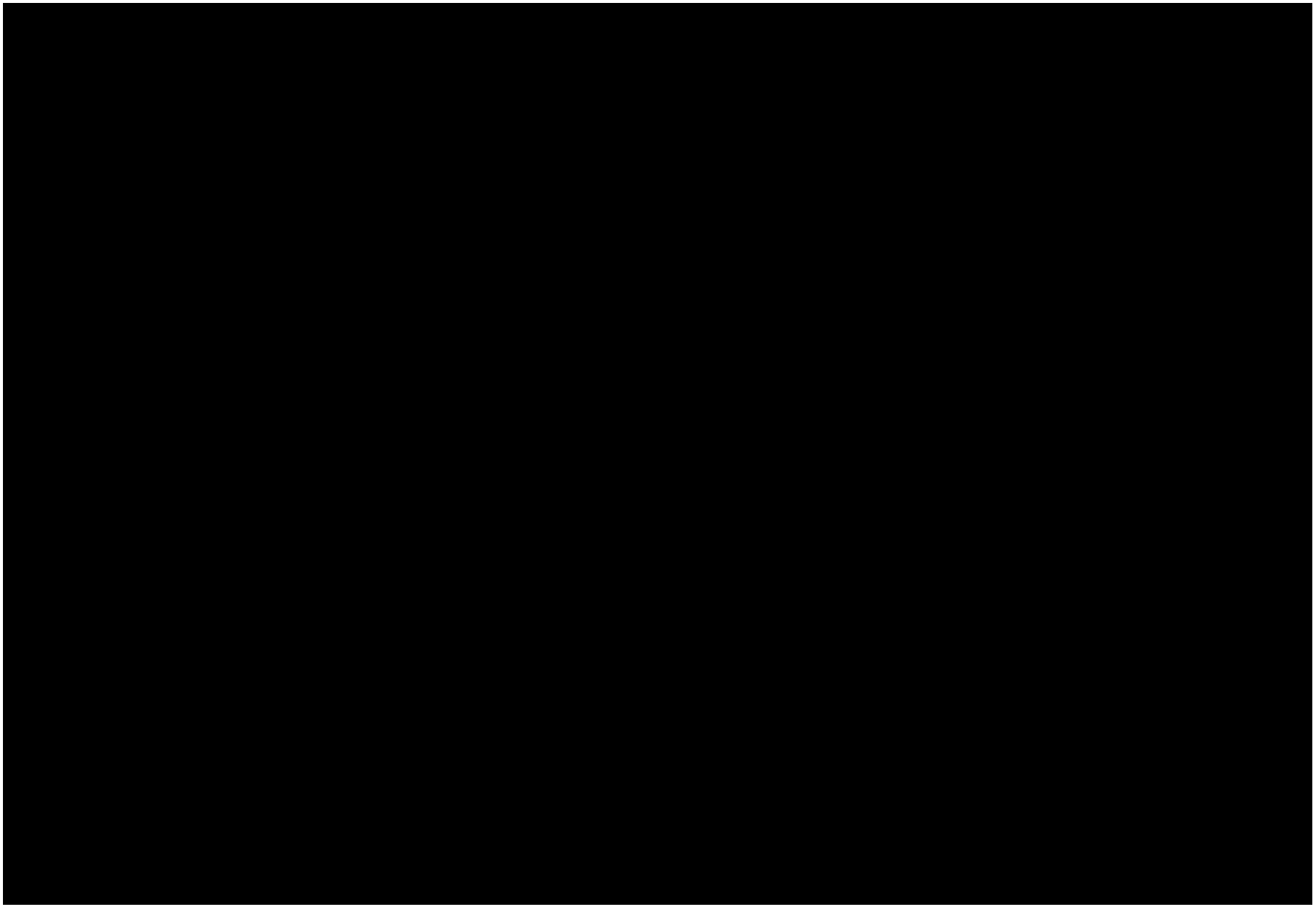
Dose delay criteria apply for all drug-related AE. Delay administration of both relatlimab and nivolumab if any of the delay criteria [redacted] are met. Delay relatlimab and nivolumab dosing for any AE, laboratory abnormality, or intercurrent illness which, in the judgement of the Investigator, warrants delaying the dose of study medication.

For participants who require delay of relatlimab and nivolumab, re-evaluate weekly, or more frequently, if clinically indicated, and resume dosing when criteria to resume treatment are met (refer to Section 7.4.2). Continue tumor assessments per protocol even if dosing is delayed.

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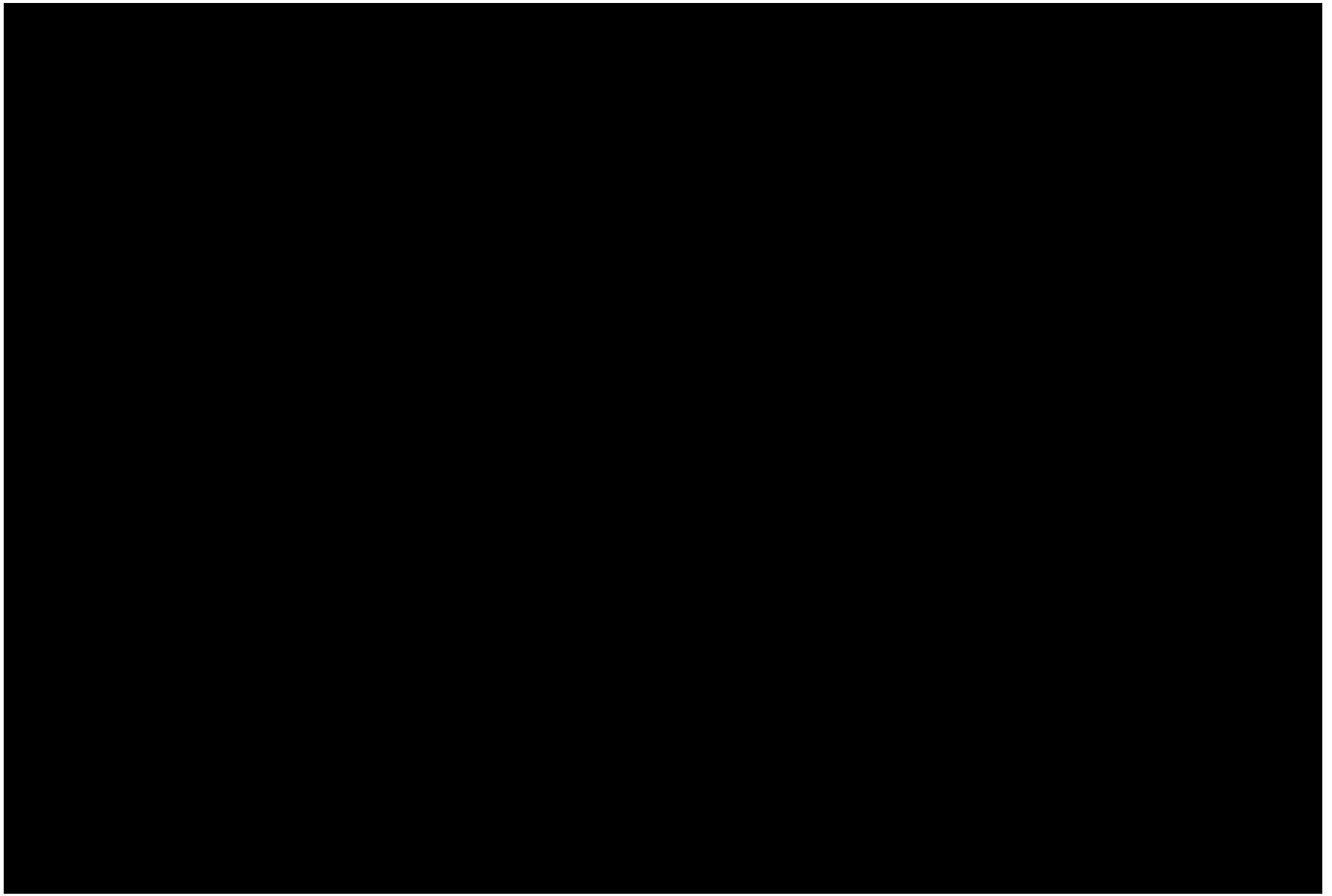
Approved v4.0 930165609 4.0



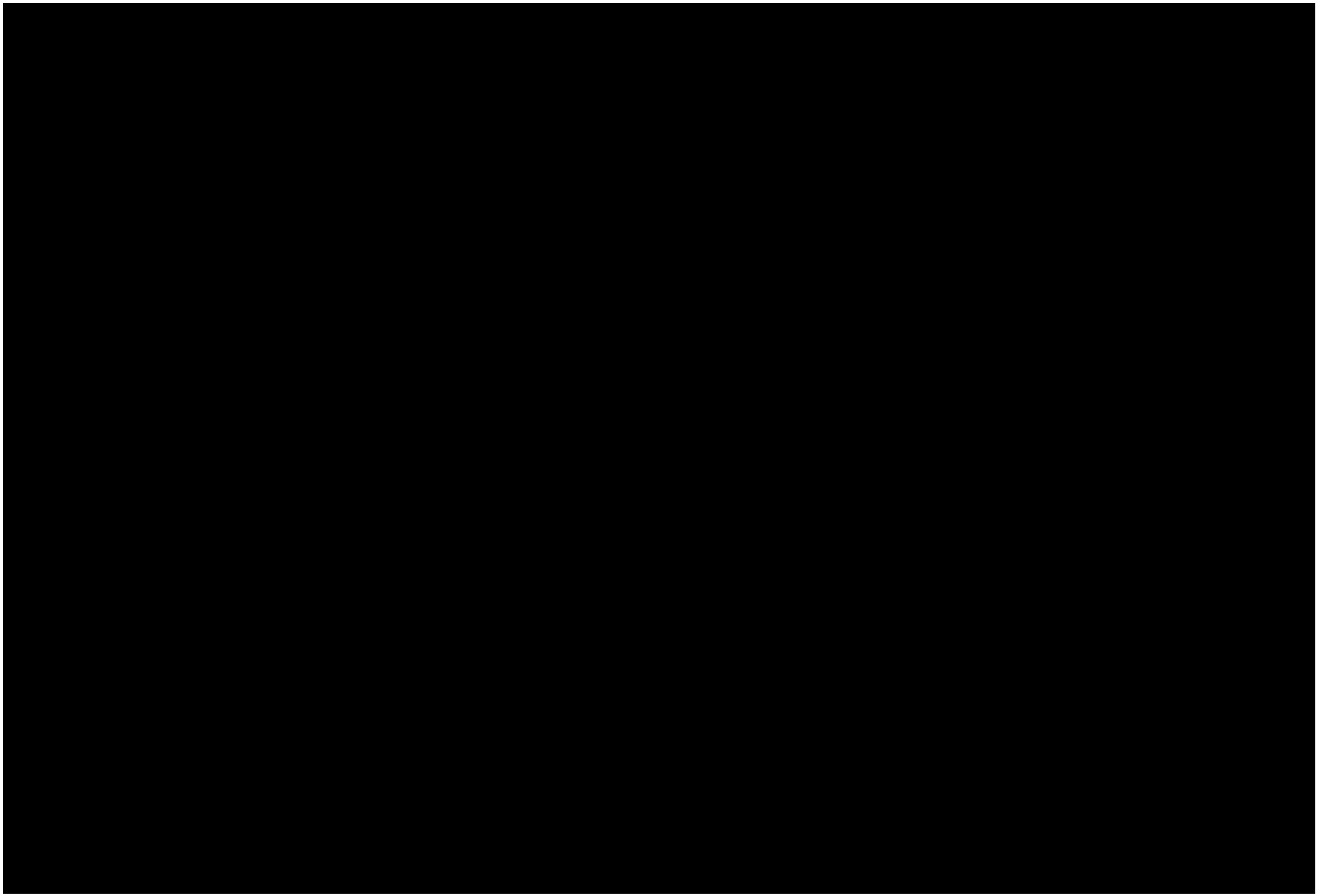
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[redacted]

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7.4.2 Criteria to Resume Treatment

Participants may resume treatment with study drug if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg or > 0.12 mg/kg daily, whichever is lower, prednisone or equivalent, and meet the requirements [redacted].

Prior to re-initiating treatment in a participant with a dosing delay lasting [redacted], the Medical Monitor (or designee) must be consulted. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies [redacted] or more frequently if clinically indicated during such dosing delays.

7.4.3 Management Algorithms for Relatlimab and Nivolumab

IO agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Relatlimab and nivolumab are considered IO agents and the management algorithms [redacted] provide guidance on assessing and managing the following groups of AEs:

[redacted]

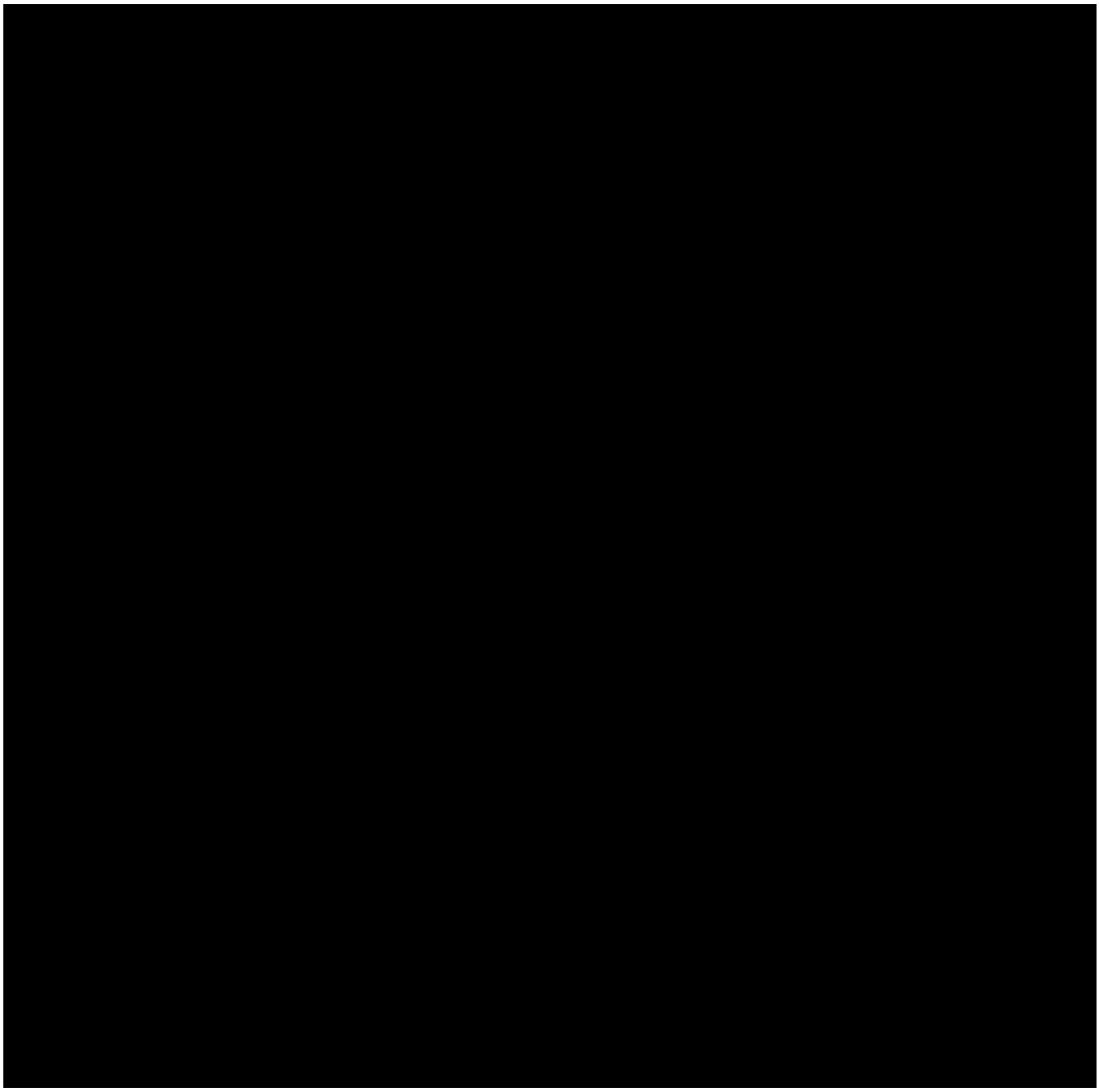
7.4.4 Treatment of Related Infusion Reactions

Since relatlimab and nivolumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Report all Grade 3 or 4 infusion reactions within 24 hours as an SAE if it meets the criteria.

Treatment recommendations are provided below based on CTCAE v5.0 grading definitions and may be modified based on local treatment standards and guidelines, as appropriate:

[redacted]

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7.4.5 Dose-Limiting Toxicities

For the purpose of guiding decisions regarding combination dose de-escalation in Part A DLTs will be determined based on the incidence, intensity, and duration of AEs that are related to study drug and that occur within [redacted] initiation of study drug (ie, the DLT evaluation period which begins on the first day of treatment and ends on Day [redacted]). Participants must have received at least 1 dose of relatlimab + nivolumab to be considered DLT-evaluable. Participants who withdraw from the study during the DLT evaluation period will not be considered as DLT-evaluable and may be replaced with new participants at the same dose level.

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Adverse events will be graded according to the National Cancer Institute CTCAE v5.0. For the purpose of subject management, any AE that meets DLT criteria, irrespective of the cycle in which it occurs, will lead to dose delays pending evaluation of the event's relatedness to study drug, severity, and duration, and in accordance to Section 7.4.1. Participants must meet criteria for resuming treatment prior to re-initiation of study treatment (refer to Section 7.4.2). De-escalation of doses will be based on the number of DLTs experienced during the DLT evaluation interval as determined by the Medical Monitor and Investigators.

7.4.5.1 Rationale for [redacted] DLT Period

The identification of acute DLTs that occur after administration of a study drug is crucial for the safety of the patients enrolled in a clinical trial. The length of the DLT is usually established based on the availability of pre-clinical data. When clinical data are available, the risk/benefit evaluation used to define the appropriate DLT period must be reassessed and should incorporate a critical analysis of all, clinical and pre-clinical data. For the purpose of this study, the DLT period will be [redacted] (one infusion) in light of the availability of preliminary clinical data from previously initiated ongoing clinical studies.

Correlation between AEs and duration of treatment

The safety profile of relatlimab as monotherapy is well manageable and generally consistent across the 2 ongoing clinical studies (CA224020 and CA224022) with no MTD reached at the 4 doses tested, up to [redacted] mg in dose escalation monotherapy. Only 1 subject experienced a related high-grade AE (asymptomatic Grade 3 lipase increased), fifteen days post the first administration of the study drug in CA224020. There were no related SAEs reported in the monotherapy in either study.

A preliminary analysis of the clinical data from the combination arm of Study CA224020 in which 24 participants were treated with relatlimab + nivolumab showed that there was no relationship between the incidence, severity, or causality of AEs and the dose level of study drugs. Seven participants received [redacted] mg relatlimab/[redacted] mg nivolumab [redacted], nine subjects were treated with [redacted] mg relatlimab/[redacted] mg nivolumab [redacted] and eight participants received [redacted] mg relatlimab/[redacted] mg nivolumab [redacted].
Four acute treatment related AEs were observed (2 SAEs and 2 AEs), 3 of them occurred during the first 4 weeks of treatment, one single event occurred at Week 6 and no treatment related AEs were documented after Week 6. The treatment-emergent SAE reported at Week 6 (day + 42 post first dose) was a Grade 4 ventricular fibrillation that occurred in a participant with cervical cancer that receive [redacted] mg relatlimab/[redacted] mg nivolumab combination therapy. The event occurred spontaneously while the participant was shopping, and cardiopulmonary resuscitation was administered by paramedics for 10 minutes. At the initial clinical assessment, the participant showed no evidence of coronary artery abnormality, myocardial infarction, myocarditis, or pulmonary embolism. A previous peri-infusional Holter ECG recording on Cycle 1, Day 1 did not show an arrhythmia. The participant's history of cannabinoid ingestion, tobacco smoking, hypertension, chlorphenamine and caffeine use, and a prior episode of loss of consciousness were considered potential contributing factors for the event and suggested pre-existing cardiac disease

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or an arrhythmia, but in the absence of a clearly identified etiology, contribution from relatlimab and nivolumab could not be excluded. Study drug was discontinued, and defibrillator was successfully implanted. Of note, despite the possible immune-related mechanism, the participant never received steroids for the treatment of this AE. The participant has fully recovered with no sequelae and achieved a complete response after 3 doses of study drug. Due to the important role that the cannabinoids may have had is this event, the use of cannabinoids is now part of the exclusion criteria.

Effects of prolonged DLT period in a population with advanced cancer

The target populations for Phase 1/2 oncology studies are characterized by a high frequency of patients with advanced stage disease. Consequently, a relevant group of patients will progress rapidly after initiation of study drug. Across the 2 ongoing studies with relatlimab, administered as monotherapy or in combination with nivolumab (CA224020 and CA224022), 24% (9/38) of the participants enrolled in dose escalation cohorts experienced disease progression between Weeks 4 and 8 of the DLT period while only 2/38 (5%) of the participants progressed between Weeks 1 and 4. It is important to note that a participant that progresses during the DLT period is no longer evaluable for the purposes of safety adjudication and a new replacement participant must be enrolled at the same dose in order to complete the safety evaluation at that dose level.

In summary, the review of the safety data from the 2 ongoing studies at the time of writing this protocol strongly suggests that a [redacted] DLT period will provide an appropriate window to capture the acute, treatment related AEs and to ensure the safety of the participants enrolled in this clinical trial. Furthermore, it may limit the number of participants exposed to safe but suboptimal doses of the drugs due to progressive disease.

7.4.5.2 Definitions of DLTs

Hepatic, non-hematologic, and hematologic DLTs are defined separately as outlined below:

[redacted]

Approved v4.0 930165609 4.0

[redacted]

Note: Participants with bone marrow involvement will not be evaluated for hematologic toxicity.

Intra participant dose escalation is not allowed. In Part A, participants who receive at least 1 dose of both study drugs during the [redacted] evaluation interval will be considered evaluable for DLT determination. In Part B, participants who receive at least 1 dose of study drugs will be considered

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evaluable for DLT determination (occurrence of DLTs in this part may be used at Investigator discretion to help guide participant management). Participants who withdraw from the study during the DLT evaluation interval for reasons other than a DLT and/or for whom safety data are unavailable for the entire DLT evaluation interval may be replaced at the same dose level. If an infusion cannot be administered at a scheduled visit during the DLT evaluation interval, it must be administered as soon as possible. If the delay is between 1 and 3 days, the procedures at the originally scheduled visit should be performed and participants will be considered evaluable for DLT determination. If the delay is more than 3 days, the dose will be considered missed and will not be replaced. Participants with a delay of more than 3 days will not be considered evaluable for DLT determination. Unevaluable participants may be replaced at the same dose level.

7.5 Preparation/Handling/Storage/Accountability

The IP 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 is only dispensed to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

For nivolumab and relatlimab, refer to the current version of the IB and/or Pharmacy Manual for complete storage, handling, dispensing, and infusion information.

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

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

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

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the (Study Reference Manual or other specified location, Appendix 2).

For study interventions not provided by the Sponsor and obtained commercially by the site, storage should in accordance with the product label.

Approved v4.0 930165609 4.0

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

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

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

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability, as well as by recoding relatlimab (BMS-986016) and nivolumab (BMS-936558) in the participant's medical records and electronic case report form (eCRF). Study drug will be administered in the clinic by trained personnel. Drug accountability should be reviewed by the site study staff at each visit.

The date and time of start and end of infusion and the exact amount given at each infusion will be recorded. In case the treatment has to be interrupted during an infusion and the dosing is not resumed, the medical personnel should evaluate the percentage of dose received by the participant and document it in the participant record.

Any reason for noncompliance should also be documented.

7.7 Concomitant Therapy

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-986016 is unknown.

7.7.1 Prohibited and/or Restricted Treatments

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

- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids. Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses equivalent to > 10 mg daily or > 0.12 mg/kg daily, whichever is lower, prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Any concurrent systemic anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of cHL and NHL).

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- Any non-palliative radiation therapy. Radiation therapy administered with palliative intent (ie for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) is permitted.
- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 135 days post-last dose of study drug.
- The following are NOT considered live vaccines and the decision to vaccinate should be made by the investigator and participant: inactivated vaccines (eg, heat-killed and formalin-killed vaccines), subunit vaccines, toxoid vaccines, nucleic acid vaccines that do not encode potentially infectious virus (Pfizer/BioNTech and Moderna COVID-19 vaccines) and replication-incompetent recombinant vector vaccines.
- Use of cannabinoids or other recreational substances.

7.7.2 Other Restrictions and Precautions

The following other restrictions or precautions are recommended.

- Local prophylaxis guideline recommendations for opportunistic infections in this patient population should be followed.
- Participants are prohibited from enrolling in another clinical trial while they are participating in this study.

7.7.2.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and if so, which contrast agent and dose is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, eGFR < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis, therefore MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the image manual.

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

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

At the conclusion of the study, if the study treatment is not available as an approved treatment in the local country, participants who continue to demonstrate clinical benefit may be eligible to receive BMS-supplied study treatment for up to a maximum of [redacted] (Section 7.1). If the study

Approved v4.0 930165609 4.0

treatment is not available as an approved and available treatment, [redacted] requiring approval by the responsible Health Authority and Ethics Committee, or through another mechanism at the discretion of BMS.

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

8 DISCONTINUATION CRITERIA

If a participant receiving nivolumab and relatlimab combination therapy meets criteria for discontinuation [redacted], they must discontinue both nivolumab and relatlimab and be taken off the treatment phase of the study.

8.1 Discontinuation From Study Intervention

Nivolumab and relatlimab treatment must be permanently discontinued per criteria in [redacted] Section 7.4.

Discontinue nivolumab and relatlimab for any AE, laboratory abnormality, or intercurrent illness, which in the judgment of the Investigator presents a substantial clinical risk to the participant with continued nivolumab and relatlimab dosing.

Any event that leads to delay in dosing lasting [redacted] from the previous dose requires discontinuation of study drug, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related AE are allowed.
- Dosing delays lasting [redacted] from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor or designee.

Participants MUST discontinue IP (and potentially Non-IP 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 (or assent, as applicable) for any further contact with him/her or persons previously authorized by the participant to provide this information
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by the Sponsor
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under

Approved v4.0 930165609 4.0

specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and Sponsor approval is required.)

- 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.
- In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the Medical Monitor/designee of this event. The study treatment must be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety).

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

All participants who discontinue study intervention should comply with protocol-specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent (or assent, as applicable) 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 case report form (CRF) page.

8.1.1 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD).[97]

Participants treated with relatlimab plus nivolumab will be permitted to continue both immunotherapy treatments beyond initial metabolic PD by Lugano 2014 criteria, assessed by the Investigator for a flexible number of cycles based on Investigator's discretion up to a maximum of [redacted], whichever occurs earlier, from date of first dose as long as they meet the following criteria:

- Investigator-assessed clinical benefit.
- Tolerance of study treatment.
- Stable performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS involvement).
- Participant provides written informed consent (or assent, where appropriate) prior to receiving additional relatlimab + nivolumab treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

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If the Investigator feels that the participant treated with relatlimab + nivolumab continues to achieve clinical benefit by continuing study treatment, the participant should remain in the study and continue to receive monitoring according to Table 2-2.

With respect to the follow-up FDG-PET-CT scan, further progression is defined as a score, per Deauville Criteria (See Appendix 7), of 4 (uptake moderately > liver) or 5 (uptake markedly > liver and/or new lesions) with increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma; or new or recurrent FDG-avid foci in the bone marrow.

An individual node/lesion must be abnormal with longest diameter (LDi) > 1.5 cm and increase by ≥ 50% from perpendicular diameter nadir and an increase in LDi or shortest diameter from nadir at least 0.5 cm for lesions ≤ 2 cm, 1.0 cm for lesions > 2 cm. In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline; if no prior splenomegaly, the splenic length must increase by ≥ 2 cm from baseline.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

8.1.2 Post-study Treatment Study Follow-up

In this study, CMR is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study, at the Sponsor's discretion. Participants who discontinue study intervention must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

The Sponsor may request that survival data be collected on all treated participants outside of the protocol defined window (refer to Section 2, Schedule of Activities). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact or is lost to follow-up.

Additional subsequent cancer therapy details, such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression after next line of therapy, will be collected.

8.2 Discontinuation From the Study

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

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- Participants or for minors, parents (both, if required by local law), guardians, or LARs should notify the investigator of the decision to withdraw consent from future follow-up in-writing, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is from further treatment with study intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request or for minors, parents (both, if required by local law), guardians, or LARs, 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.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent (or assent, where applicable) for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

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

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

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- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before the first dose of study treatment. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed regional and/or institutional guidelines. For participants who require blood draw volume modifications for low body weight or other reasons, blood collection volumes will be appropriately reduced per guidelines outlined in the laboratory manual to meet pediatric institutional or national guidelines for maximum daily and monthly blood draw limits.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Perform additional measures, including non-study required laboratory tests, as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.

Evaluate 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

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assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

9.1.1 Efficacy Assessment for the Study

Imaging and response criteria are based on the International Lymphoma Working Group's revised recommendations for malignant lymphoma.[86,98] Primary response assessment will be evaluated using Lugano 2014 Classification (Appendix 7). ORR outcomes will be summarized using frequency tables together with 90% CIs. Time to event distribution [redacted] will be estimated using [redacted] as appropriate. [redacted] Refer to Section 10.

9.1.2 Imaging Assessment for the Study

Images will be submitted to a central imaging vendor for collection in a central repository and may undergo BICR at any time during and/or after the study. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the Imaging Manual provided by the central imaging vendor. Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) for response assessment by Lugano 2014 criteria must be collected and submitted to the central imaging vendor. Refer to Section 2 for further details.

Primary response assessment will be made using the Lugano 2014 Classification (Appendix 7).

Assessment will be performed by FDG-PET-CT or FDG-PET-MRI whole-body (at least from the base of skull to proximal femurs) and all known/suspected sites of disease, with disease involvement determined by focal FDG uptake in nodal and extranodal (including spleen, liver, bone marrow, and thyroid) sites that is consistent with lymphoma. A response of CMR, PMR, NMR or PMD will be determined based on the Lugano 2014 Classification. The FDG-PET scan metabolic uptake will be graded using the Deauville 5-point scale[91] with a score of < 4 considered to represent a CMR (refer to Appendix 7). If CNS involvement is suspected, perform brain MRI without and with Gadolinium contrast at baseline to exclude participants with brain involvement.

Part A: During the treatment period, FDG-PET-CT whole-body or FDG-PET-MRI should occur at Day 49 (± 7 days), Day 105 (± 7 days) and Day 161 (± 7 days) starting from the date of first dose and corresponding with Day 21 (± 7 days) of Cycles 2, 4 and 6, then every 12 weeks (± 7 days) after Cycle 6 assessment until PMD or treatment discontinuation (EOT), whichever occurs later, participant withdrawal, or death.

Part B: During the treatment period, tumor assessments by FDG-PET-CT or FDG-PET-MRI should occur at Day 49 (± 7 days), Day 105 (± 7 days) and Day 161 (± 7 days) starting from the date of first dose and corresponding with Day 21 (± 7 days) of Cycles 2, 4 and 6.

In case of CMR before or after 6 cycles by FDG-PET-CT or FDG-PET-MRI, imaging may be performed using diagnostic quality MRI/CT scans every 12 weeks (± 7 days) from the last on-treatment scan date until PMD or treatment discontinuation, whichever occurs later, participant

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withdrawal, or death. In case of suspected CR based on CT/MRI, FDG-PET-CT or FDG-PET-MRI scan must be performed to confirm CMR. If PD is suspected based on clinical or MRI/CT findings, a confirmatory FDG-PET-CT or FDG-PET-MRI should be obtained to confirm PMD. Imaging assessment should follow indicated schedule even if dose is omitted or delayed.

PMR participants at the end of 6 cycles proceeding to receive Investigator's choice of continuing relatlimab + nivolumab will be followed up by FDG-PET-CT or FDG-PET-MRI imaging every 12 weeks (± 7 days) from the last on-treatment scan date until CMR, PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death.

Participants continuing treatment based on Investigator's discretion, for example in the case of NMR, will be allowed to switch modality from being PET-based to diagnostic quality CT or MRI scans every 12 weeks (± 7 days) from the last on-treatment scan date until PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death. If PD is suspected on CT or MRI, an additional FDG-PET-CT or FDG-PET-MRI scan must be performed to confirm PMD.

In case of treatment discontinuation, all participants will be allowed to switch modality from being PET-based to diagnostic quality CT or MR scans every 12 weeks (± 7 days) for the first 52 weeks, and every 24 weeks (± 7 days) thereafter from the last on-treatment scan date until PMD, participant withdrawal, or death. If PD is suspected on CT or MRI, an additional FDG-PET-CT or FDG-PET-MRI scan must be performed to confirm PMD.

9.2 Adverse Events

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

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

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

Refer to Appendix 3 for SAE reporting.

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

IMAEs 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.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 135 days following discontinuation of dosing.

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

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent (or assent, as applicable) will be recorded on the appropriate section of the CRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The Investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

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

Appendix 1 in the IB represents the Reference Safety Information to determine expectedness of SAEs for expedited reporting.

All nonserious AEs (not only those deemed to be treatment related) should be collected continuously during the treatment period and for a minimum of 135 days following discontinuation of study treatment.

All SAEs must be collected from the time of signing the consent (or assent, as applicable), including those thought to be associated with protocol-specified procedures, for a minimum of 135 days of discontinuation of dosing. For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

All SAEs, and all AEs must be collected from the date of the participant's written consent until 135 days following discontinuation of dosing.

Contacts for SAE reporting are specified 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 or caregiver. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

Every AE must be assessed by the Investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's CRF.

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9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AEs of special interest (AESI) (as defined in Section 9.2) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

If, following initiation of the study intervention, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during, at least for 5 months after study product administration, the Investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

Serum or urine pregnancy tests will be performed on WOCBP according to the Schedule of Activities (Section 2). A negative pregnancy test result must be documented before the administration of the study drug(s) within approximately 1 day of the first dose, and then every 4 weeks (± 1 week) irrespective of dosing schedule.

If a female participant becomes pregnant, administration of the study drugs must be discontinued. Requirements for reporting a pregnancy are provided in Appendix 3.

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Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

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.

Not applicable for women not of child-bearing potential (WNOCBP) - protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

9.2.6 Adverse Events of Special Interest

An AESI is an AE of scientific and/or medical concern specific to the sponsor's product or development program, for which ongoing monitoring and expedited communication by the Investigator to the Sponsor may be appropriate.[99] An AESI may further be considered serious or nonserious based on its nature and outcome. Such an event might warrant further investigation to characterize and understand it. Depending on the nature of the event, expedited communication by the Sponsor to other parties (eg, health authorities) might also be warranted.

9.2.6.1 Definition of Immune-mediated Adverse Events

Immune-mediated adverse events (IMAEs) are specific events that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis) for which participants received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included irrespective of treatment since these events are often managed without immunosuppression.

IMAEs include events, irrespective of causality, occurring within 135 days of the last dose of study drugs. This list is subject to change based on Health Authority feedback or change of Medical Dictionary for Regulatory Activities (MedDRA) version. The final list used will be described in the clinical study report (CSR).

Table 9.2.6.1-1 below provides a summary of the IMAE categories and their respective preferred terms (PTs).

Table 9.2.6.1-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions

IMAE Category	PTs Included Under IMAE Category
Pneumonitis	Pneumonitis, Interstitial lung disease
Diarrhea/colitis	Diarrhea, Colitis, Enterocolitis
Hepatitis	Hepatotoxicity, Hepatitis, Hepatitis acute, Autoimmune hepatitis, AST increased, ALT increased, Bilirubin increased, ALP increased
Adrenal insufficiency	Adrenal insufficiency

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Table 9.2.6.1-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions

IMAE Category	PTs Included Under IMAE Category
Hypothyroidism/thyroiditis	Thyroiditis acute (collapsed with thyroiditis for frequency), Autoimmune thyroiditis (collapsed with thyroiditis for frequency)
Hyperthyroidism	Hyperthyroidism
Hypophysitis	Hypophysitis
Diabetes mellitus	Diabetes mellitus, Diabetic ketoacidosis
Nephritis and renal dysfunction	Nephritis, Nephritis allergic, Tubulointerstitial nephritis, Acute renal failure, Renal failure, Increased creatinine
Rash	Rash, Rash maculopapular

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphate; AST = aspartate aminotransferase; IMAE = immune mediated adverse event; PT = preferred term.

9.2.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE eCRF, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

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

It is expected that, wherever possible, the clinical (CTCAE term) rather than the Investigator reported laboratory term would be used by the reporting Investigator (eg, anemia versus hemoglobin decreased).

9.2.8 Potential Drug-induced Liver Injury

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

Potential DILI is defined as:



Approved v4.0 930165609 4.0

[redacted]

9.2.9 Other Safety Considerations

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

9.3 Overdose

For this study, any dose of relatlimab and/or nivolumab greater than planned dose within a 24-hour time period will be considered an overdose.

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

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor or designee immediately.
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities.
- Obtain a plasma sample for PK analysis as soon as possible within 5 days from the date of the last dose of study intervention if requested by the Medical Monitor or designee (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

9.4 Safety

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

9.4.1 Physical Examinations

Refer to Schedule of Activities (Section 2). BSA will be calculated using the Mosteller formula.[100,101]

9.4.2 Vital Signs

Refer to Schedule of Activities (Section 2). Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, and temperature. It is preferred that the same arm be used for all blood pressure readings, if possible.

Pulse oximetry will also be included at baseline only.

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9.4.3 Electrocardiograms

All participants will have 12-lead ECG done during Screening and as specified in the Schedule of Activities (Section 2).

9.4.4 Echocardiogram

Standard echocardiogram will be performed to assess cardiac function and LVEF according to the Schedule of Activities (Section 2). A MUGA scan can be performed to assess cardiac function and LVEF if a standard echocardiogram cannot be performed.

9.4.5 Pregnancy Tests

Serum or urine pregnancy tests will be performed on WOCBP as specified in the Schedule of Activities (Section 2).

9.4.6 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- On-site or off-site local laboratory performing the analyses must provide reference ranges for these tests.
- Results of clinical laboratory tests performed on Day -1 must be available and reviewed by the Investigator prior to dosing.

Table 9.4.6-1: Clinical Laboratory Assessments

Hematology – CBC	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen or serum UREA Glucose Albumin - screening only and as clinically indicated Sodium Potassium Chloride	Calcium Phosphorus [redacted] Amylase - screening and as clinically indicated Lipase - screening and as clinically indicated [redacted] TSH, free T3 and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment Uric acid
Serology	
Hepatitis B/C, HBVsAG, HCV antibody or HCV RNA), - screening only (Testing for HIV-1 and HIV-2 must be performed where mandated by local requirements)	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG).	
Urinalysis including specific gravity, pH, total protein, glucose, leukocyte esterase, and blood- screening only within 14 days prior to first dose and as clinically indicated	

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Table 9.4.6-1: Clinical Laboratory Assessments

Urine drug screen for drugs of abuse as clinically indicated (screening only)

Abbreviations: CBC = complete blood count; fT3 = free triiodothyronine; fT4 = free thyroxine; HBVsAG = hepatitis B (virus) surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HCV RNA = hepatitis C RNA viral load; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; [redacted] RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

9.4.7 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 as per standard medical/clinical judgment.

9.5 Pharmacokinetics

Full details on the clinical pharmacology aspects of nivolumab and relatlimab can be found in their respective IBs.[6,59]

The PK of relatlimab will be derived from serum concentration versus time measurements. The PK parameters to be assessed include:

- Cmax: Maximum observed serum concentration
- Tmax: Time of maximum observed serum concentration
- AUC(TAU): Area under the concentration-time curve within a dosing interval
- Ctrough: trough observed concentration

Individual participant PK parameter values will be derived by non-compartmental and, if appropriate, by population PK methods. Actual times of collection will be used in all PK analyses.

For nivolumab, PK parameters to be assessed include:

- Ctrough: trough observed concentration

[redacted]

Samples for PK [redacted] assessment from participants must be collected at the time points indicated [redacted]. All on-treatment PK time points are intended to align with days on which study treatment is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample does not need to be collected.

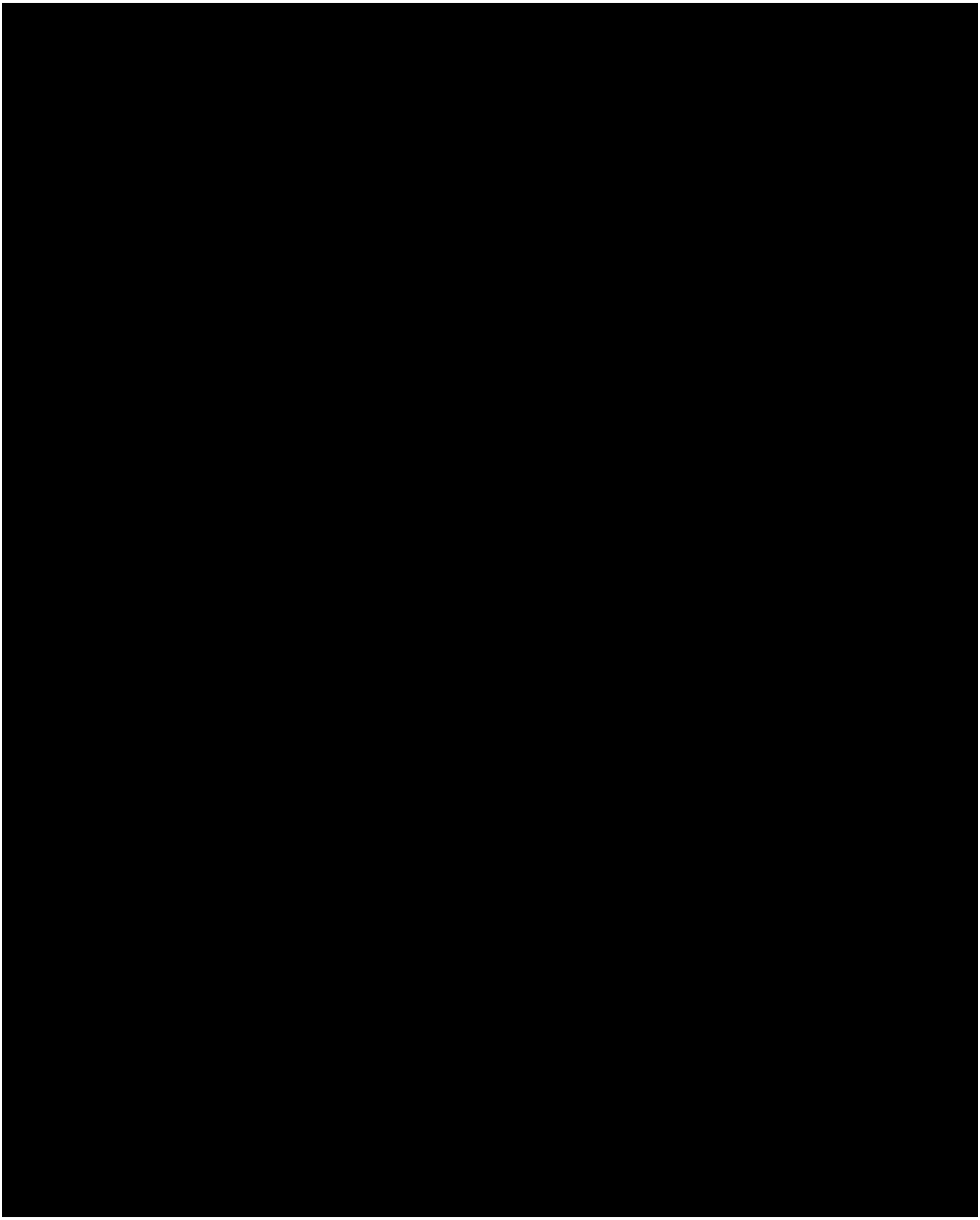
Blood samples must be drawn from a site other than the infusion site (ie, contralateral arm), including those participants with central venous access, on days of infusion for all [redacted] samples. Accurate documentation of the time and date of sample collection should be performed.

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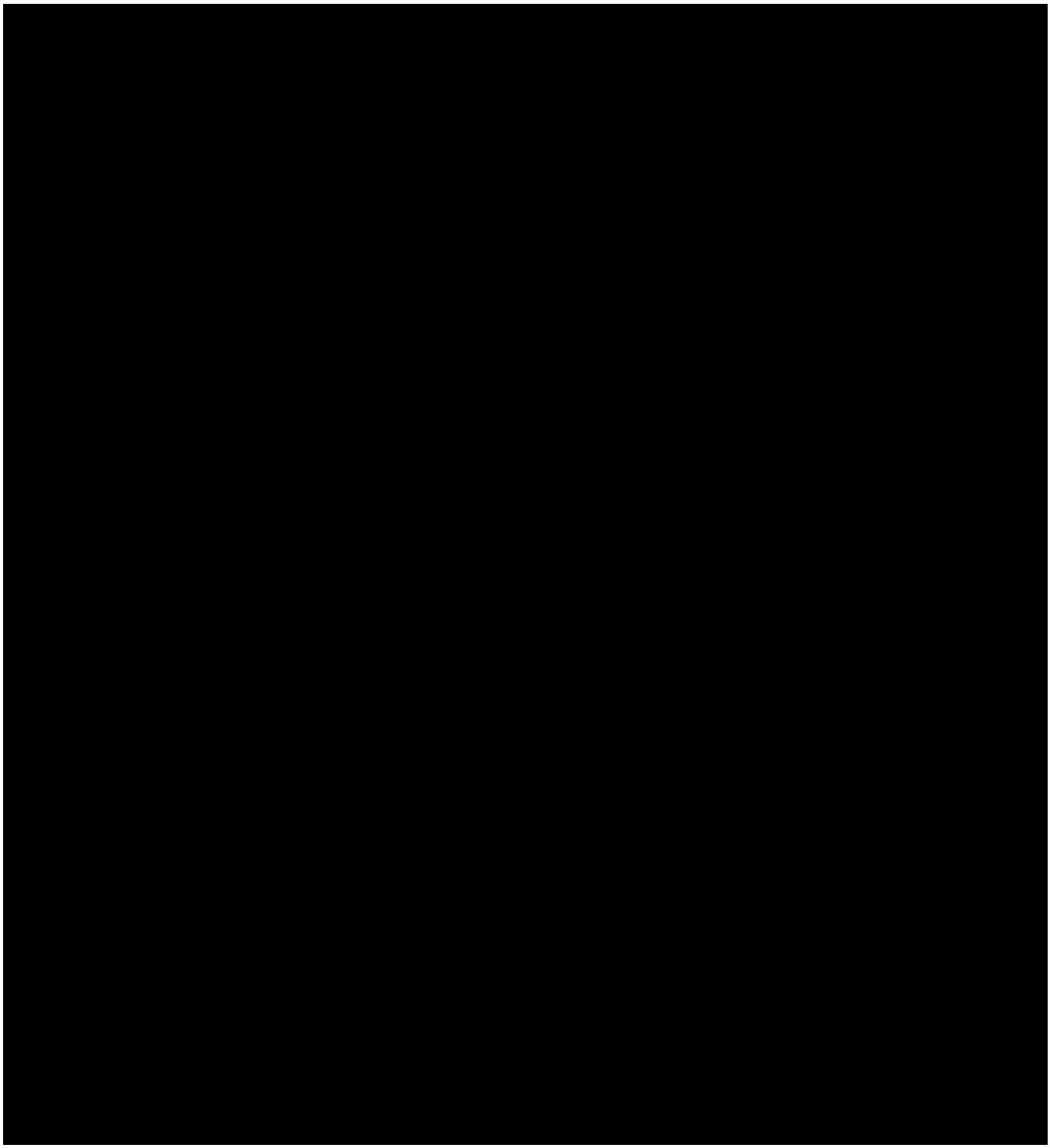
Further details of sample collection, processing, and shipment is provided in the laboratory procedures manual. For participants who require blood draw volume modifications for low body weight or other reasons, blood collection volumes will be appropriately reduced per guidelines outlined in the laboratory manual to meet pediatric institutional or national guidelines for maximum daily and monthly blood draw limits. In order to obtain the samples required for safety, PK, and PD evaluations specified at a time point, blood volumes for safety laboratory analysis should be minimized through the use of pediatric sample tubes, if possible. In the case that, despite using these measures, the blood volumes specified in the Schedule of Activities (Section 2) for a given time point would exceed those recommended in the laboratory manual, the Sponsor Medical Monitor (or delegate) must be contacted for further instructions as to which blood tests should be omitted or modified to meet volume requirements. Note that all required safety assessments must be performed.



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All on-treatment timepoints are intended to align with days on which study intervention is administered. If it is known that a dose is going to be delayed, then the predose sample for relatlimab and nivolumab, if appropriate, should be collected just prior to the delayed dose. However, if a predose sample for relatlimab and nivolumab is collected but the dose is subsequently delayed, an additional predose sample should not be collected. Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. If the

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infusion was interrupted, the interruption details will also be documented on the CRF. Further details of sample collection, processing, and shipment will be provided in the laboratory/procedure manual.

Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis and/or reanalysis of PK [redacted] samples.

Concentration analyses for relatlimab and nivolumab will be performed by validated bioanalytical method(s).

Bioanalytical samples designated for assessments (eg, [redacted] PK, [redacted]) from the same collection time point may be used interchangeably for analyses, if required (including, but not limited to, insufficient volume for complement assessment, to follow-up on suspected [redacted] AE, etc).

[redacted]

Detailed instructions for the PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

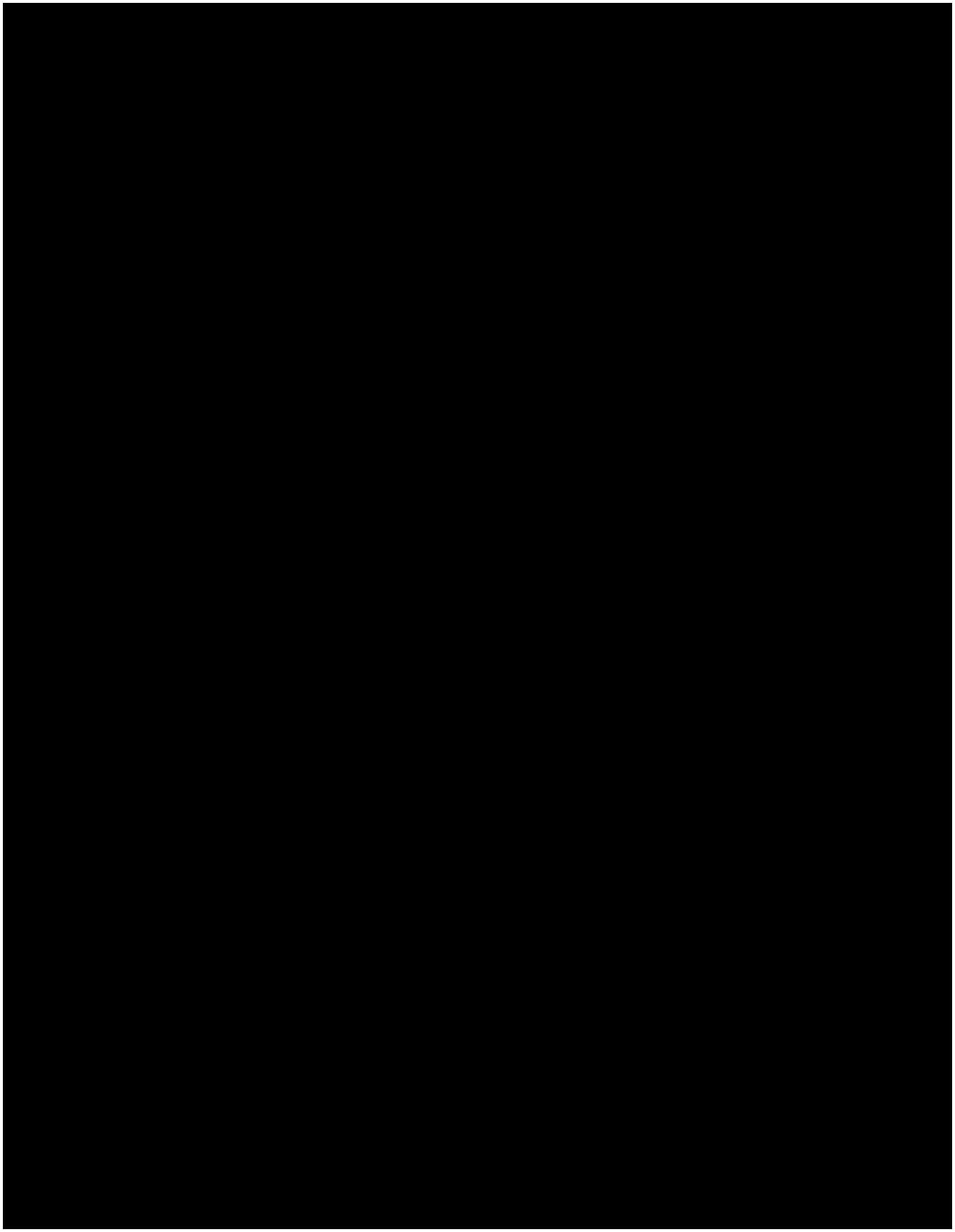
[redacted]

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9.10 [redacted]

[redacted]

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[redacted]

9.10.1.6 Tumor Samples

Tumor biopsy specimens will be obtained from consenting participants prior to treatment to characterize immune cell populations, evaluate expression of selected tumor and immune markers, and assess gene expression and tumor genomics.

Submission of an FFPE tumor block of diagnostic tumor tissue (preferred) or a minimum of [redacted] unstained slides acquired as a fresh biopsy during screening (preferred) or a recent archival FFPE tumor sample [redacted] prior to treatment assignment. Fine needle aspirations or other cytology samples are not acceptable. Submission of on-treatment and upon progression biopsy samples is strongly recommended and should be collected if medically feasible. If despite best efforts, a minimum of [redacted] unstained slides is not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with Sponsor or designee. [redacted]

Pathology reports associated with these tissues are also required and will be sent to the central pathology laboratory with the tissue and/or slides. The Sponsor will provide detailed instructions

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and materials for sample handling and shipping. Note that diagnosis based on fine needle aspirations is not considered acceptable pathologic data for entry into this study.

Eligibility will be based on local pathology review; confirmation of diagnosis by central pathology laboratory is not required for entry or initiation of treatment.

[redacted]

9.11 Additional Research

This protocol will include residual sample storage for additional research (AR).

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For All sites:

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

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

AR is intended to expand the R&D capability at BMS, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression, and response to treatment, etc.

Sample Collection and Storage

- Residual tumor biopsy or surgical samples, [redacted] and other materials (refer to Table 9.11-1) will also be retained for additional research purposes.

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

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, [redacted] after the end of the study or the maximum allowed by applicable law.

[redacted]

Further details of sample collection and processing will be provided to the site in the Procedure Manual.

Table 9.11-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
PK[redacted]	All
Tumor Biopsy	All

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Table 9.11-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
Surgical tissue	All
[redacted]	
Other derived/extracted materials from primary collection samples	All

Abbreviations: [redacted] PK = pharmacokinetics.

9.12 Health Economics OR Medical Resource Utilization and Health Economics

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

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

No prospective hypotheses are being formally evaluated in this study.

10.2 Sample Size Determination

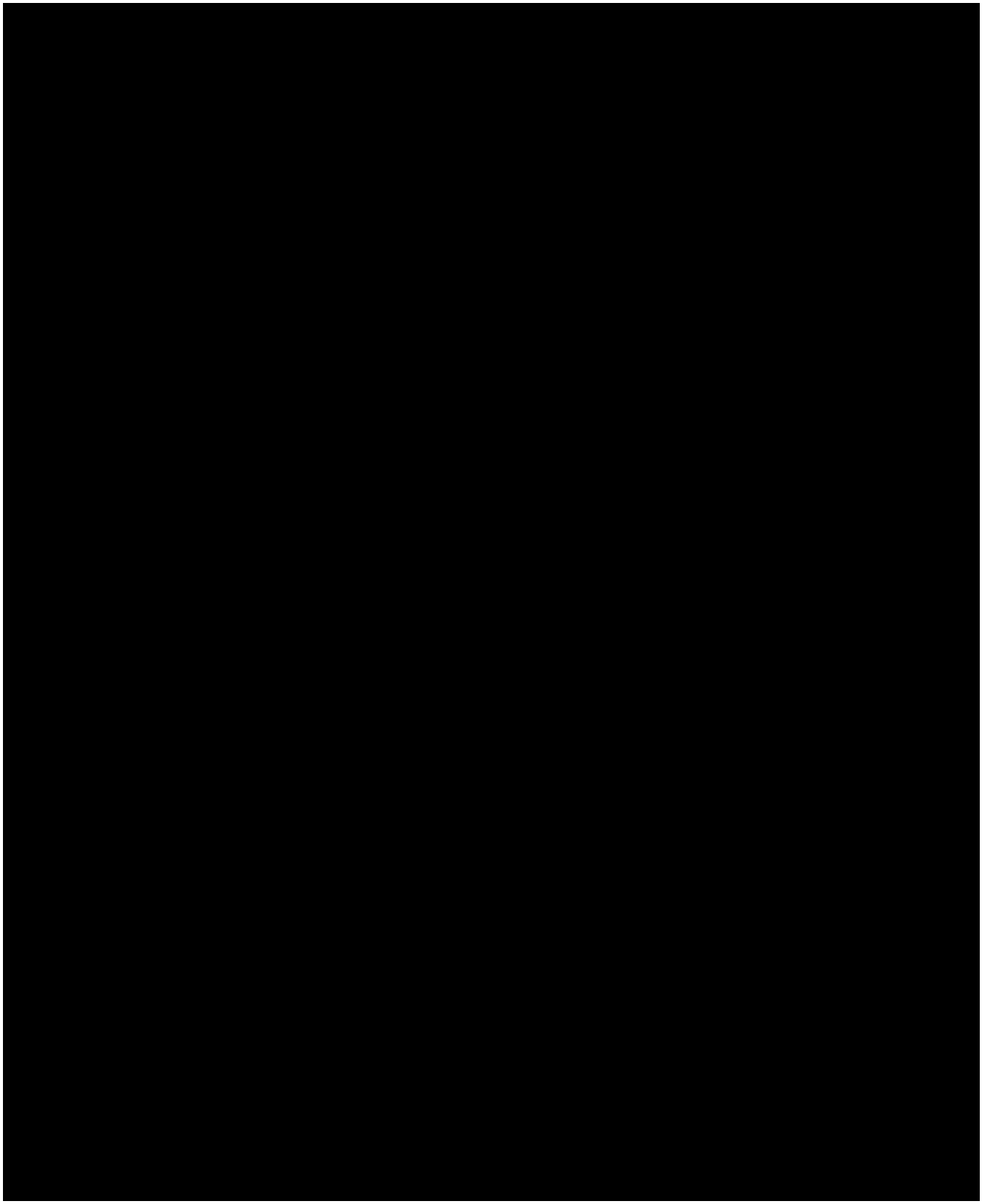
A maximum of between [redacted] and [redacted] participants will be enrolled to study such that approximately between [redacted] and [redacted] participants will be treated depending on dose de-escalation contingencies in Part A and cohort expansions in Part B.

The sample size of the Part A is not based on statistical considerations and there is no statistical hypothesis to be tested. [redacted]. The actual number treated in Part A will depend on the acceptable toxicity profile of each dose being assessed. At the minimum the total sample sizes in Part A should be appropriate to:

- support safety of the doses used in expansion cohorts.
- support doses and dose regimens for the subsequent therapeutic confirmatory study.

For cohort expansion Part B, the sample size of approximately [redacted] response-evaluable participants in the cHL cohort (Cohort 1) will be used to assess the CMR rate and exact 2-sided 90% CI of relatlimab + nivolumab. [redacted]

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[redacted]

10.3 Analysis Sets

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

Population	Description
Enrolled	All participants, or their legally acceptable representative, if applicable, has agreed to participate in a clinical study following completion of the informed consent process, unless otherwise specified by the protocol.
Treated	All participants who received at least 1 dose of study treatment
[redacted]	
Response-Evaluable	All participants who receive at least 1 dose of study treatment, have a baseline tumor assessment with measurable disease, and 1 of the following: 1) at least 1 evaluable on-treatment tumor assessment, 2) clinical progression, or 3) death prior to the first on-treatment tumor evaluation

[redacted]

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[redacted]

10.4 Statistical Analyses

The SAP will be developed and finalized before primary endpoint database lock and will describe the selection of participants to be included in the analyses and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

A description of the participant population will be included in the CSR, including subgroups of age, gender, race, and other study specific populations and demographic characteristics. A description of participant disposition will also be included in the CSR.

10.4.1 General Considerations

A description of the participant population will be included in the statistical output reported, including subgroup of age, gender, and race. Table 10.4.1-1 defines the estimands for the primary and secondary endpoints.

Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized separately for Part A and Part B; the summaries for Part B will be presented by cohort.

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Table 10.4.1-1: Definition of Estimands for Primary and Secondary Endpoints

Objectives	Endpoints
Primary	
• **Part A**: To characterize the safety, tolerability, and define the MTD or RP2D for the combination of relatlimab + nivolumab in pediatric participants less than 18 years of age with R/R cHL and NHL.	• DLTs, MTD/RP2D, and incidences of AEs, SAEs, AEs leading to discontinuation, deaths and laboratory abnormalities
• **Part A**: To characterize the PK of relatlimab for the combination of relatlimab + nivolumab in pediatric participants less than 18 years of age with R/R cHL and NHL.	• Cmax Ctrough, Tmax, and, AUC(TAU)
• **Part B:** To assess the preliminary efficacy of relatlimab + nivolumab based on the RP2D from part A in participants less than or equal to 30 years old with cHL (Cohort 1).	• CMR rate
Secondary	
• **Part B**: To assess the safety of relatlimab + nivolumab in R/R cHL (Cohort 1) and NHL (Cohort 2)	• Incidences of AEs, SAEs, AEs leading to discontinuation, deaths and laboratory abnormalities
• **Part B:** To evaluate the ORR of relatlimab + nivolumab in participants ≤ 30 years of age with cHL (Cohort 1)	• Part B: ORR

[redacted]

Abbreviations: AE = adverse event; AUC(TAU) = area under the curve within a dosing interval; cHL = classical Hodgkin lymphoma; Cmax = maximum concentration; Ctrough = trough observed concentration, CMR = complete metabolic response; DLT = dose limiting toxicity; MTD = maximum tolerated dose; NHL = non-Hodgkin lymphoma; ORR = overall response rate; PK = pharmacokinetic; [redacted] R/R = recurrent/relapsed or refractory; RP2D = recommended Phase 2 dose; SAE = serious adverse event; Tmax=time to maximum concentration.

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10.4.2 Primary Endpoints

The primary safety and efficacy endpoints for the study are presented in Table 10.4.2-1.

Table 10.4.2-1: Endpoints

Primary Endpoint	Description	Timeframe
Part A: MTD/RP2D, Incidence of DLTS, SAEs, AEs, AEs leading to discontinuation, deaths and laboratory abnormalities	MTD/RP2D, Incidence of DLTs, SAEs, AEs leading to discontinuation, deaths and laboratory abnormalities	Up to 135 days after the last dose of study treatment
Part A: Pharmacokinetics of relatlimab – AUC(Tau), Cmax, Tmax, and Ctrough	As described in Section 9.5	NCA parameters from Cycle 1
Part B: CMR rate	The proportion of all response-evaluable participants who, achieve the best response of CMR using Lugano 2014 criteria.	Up to a maximum of 2 years from the last study treatment of the last participant (ie, Last Participant Last Treatment)

Abbreviations: AE = adverse event; AUC(TAU) = area under the curve within a dosing interval; Cmax = maximum concentration; CMR = complete metabolic response; DLT = dose limiting toxicity; NCA = non-compartmental analysis; SAE = serious adverse event; Tmax = time to maximum concentration.

10.4.2.1 Safety Analyses

All participants who receive study treatment will be evaluated for safety endpoints. All recorded AEs will be coded according to the most current version of MedDRA and be graded using the NCI CTCAE version 5.0. AEs will be listed and participants with AEs will be summarized based on the event with the CTCAE grade of highest severity by system organ class and preferred term, counting once at the preferred term level and once at the system organ class level, for each dose, dosing regimen, and overall. Vital signs and clinical laboratory test results will be listed and summarized. In addition, the worst grade of a laboratory measure observed on-study by the baseline grade (criteria per CTCAE v5.0) will also be generated for selected laboratory tests. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the Investigator and abnormalities, if present, will be listed.

10.4.2.2 Pharmacokinetic Analysis

The PK parameters will be summarized by doses of relatlimab/nivolumab. Geometric means and coefficients of variation will be presented for Cmax, Ctrough, and AUC(TAU). Medians and ranges will be presented for Tmax. Means and standard deviations will be provided for the other PK parameters.

10.4.2.3 Primary Efficacy Analysis

To assess the primary efficacy endpoint of CMR in Cohort 1 of Part B, the CMR rate and 2-sided exact 90% CI (based on Clopper-Pearson method) will be summarized.

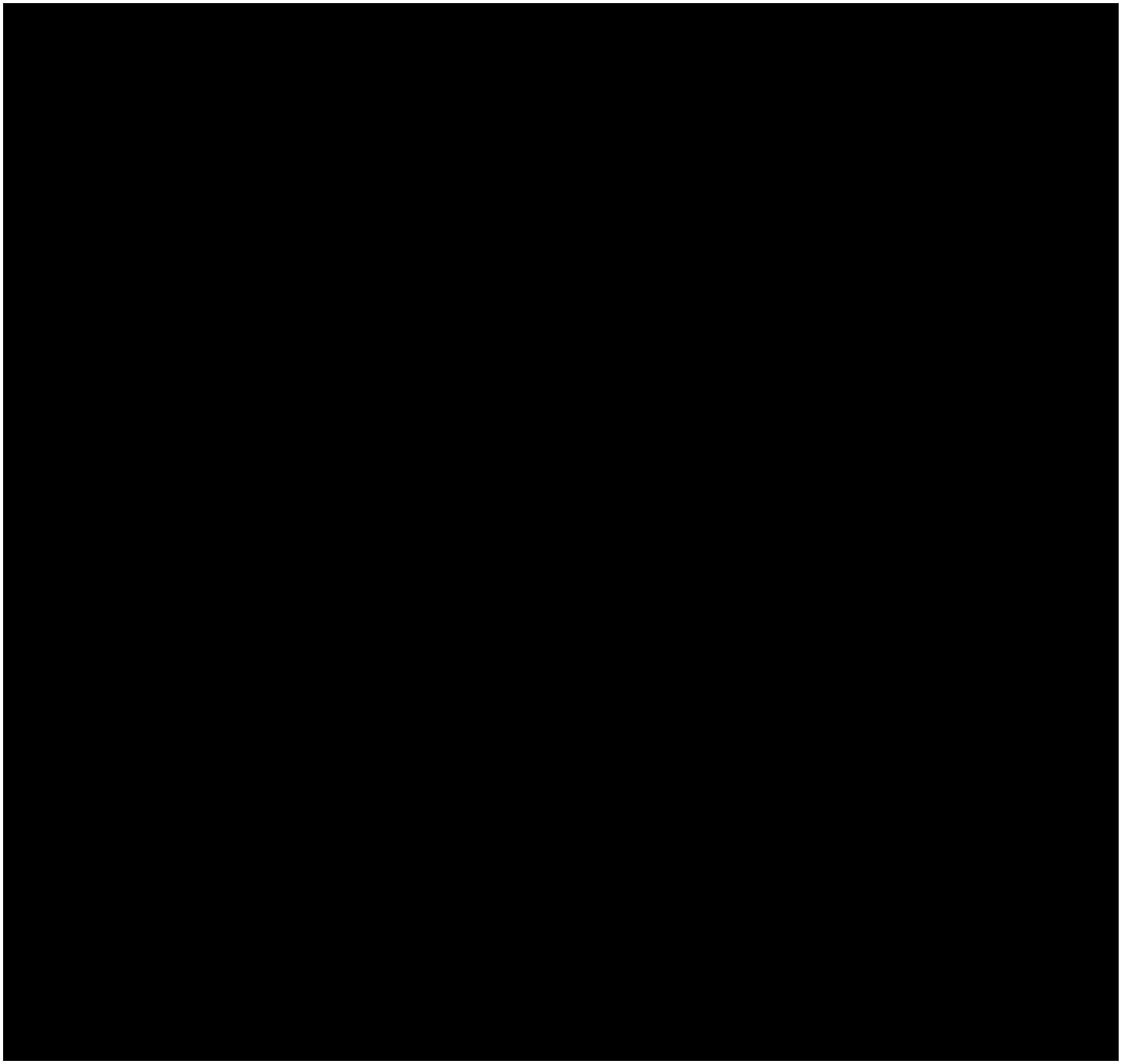
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10.4.3 Secondary Endpoint(s)

Similar safety analyses presented for the treated population in Part A (described in Section 10.4.2) will also be performed for the treated population in Part B. The safety analyses for Part B will be presented separately for participants treated in Cohort 1 and Cohort 2.

Objective Response Rate (ORR)

ORR based on Lugano 2014 criteria and defined as proportion of response-evaluable participants with a best overall response of CMR or PMR. ORR and 90% CI (based on Clopper-Pearson method) will be summarized. A summary of ORR by LAG-3 status will also be presented.



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Approved v4.0 930165609 4.0

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12 APPENDICES

Approved v4.0 930165609 4.0

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ABC	activated B-cell-like
[redacted]	
AE	adverse event
AF	flat-dosing
ALCL	anaplastic large cell lymphoma
allo-HCT	allogeneic hematopoietic cell therapy
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANSM	Agence nationale de sécurité du médicament et des produits de santé
AR	additional research
ART	antiretroviral therapy
ASCT	autologous stem cell transplant/transplantation
AST	aspartate aminotransferase
AT	aminotransferase
AUC_{tau}	area under the concentration-time curve in 1 dosing interval
AW	age/weight-based dosing
B	bendamustine
BICR	blinded independent central review
BL	Burkitt lymphoma
BMS	Bristol-Myers Squibb Company
BOR	best overall response
BP	blood pressure
BSA	body surface area
Bv	brentuximab vedotin
Cavgss	concentration at steady state
[redacted]	
Cmaxss	maximum concentration at steady state
CAR-T	chimeric antigen receptor T-cells
cHL	classical Hodgkin lymphoma
CI	confidence interval
CL	clearance
CLss	steady-state clearance

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Term	Definition
Cmax	maximum observed serum concentration
CMR	complete metabolic response
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTAgs	Clinical Trial Agreements
Ctau	concentration at the end of the dosing interval
CTCAE	Common Terminology Criteria for Adverse Event
[redacted]	
CTLA-4	cytotoxic T-lymphocyte associated protein 4
Ctrough	trough observed concentration
CV%	% coefficient of variation
DILI	drug-induced liver injury
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
[redacted]	
DOT	duration of treatment
DRESS	drug reaction with eosinophilia and systemic symptoms
E-R	exposure-response
[redacted]	
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EFS	event-free survival
EMA	European Medicines Agency
[redacted]	
EOT	end of treatment
EU-CTR	European Union-Clinical Trial Regulation

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Term	Definition
FDA	Food and Drug Administration
FDC	fixed dose combination
FDG	[^{18}F]fluorodeoxyglucose
FGL-1	fibrinogen-like protein 1
FFPE	formalin-fixed paraffin-embedded
GBS	Guillain-Barre syndrome
GCB	germinal center B-cell
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
[redacted]	
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCC	hepatocellular
HCV	hepatitis C virus
HDCT	high-dose chemotherapy
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HR	heart rate
HTLV	human T-lymphotrophic virus
IB	Investigator's Brochure
[redacted]	
ICF	informed consent form
IEC	Independent Ethics Committee
Ig	immunoglobulin
[redacted]	
IHC	immunohistochemistry/immunohistochemical
IMAE	immune-mediated adverse event
[redacted]	
IO	immuno-oncology
IP/IMP	Investigative Product/Investigative Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous

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Term	Definition
IWG	International Working Group
[redacted]	
LAG-3	lymphocyte activation gene-3
LAR	legally acceptable representative
LBL	lymphoblastic lymphoma
LDi	longest diameter
LDH	lactate dehydrogenase
LPFT	last patient first treatment
LVEF	left ventricular ejection fraction
m	median
[redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
MGZL	mediastinal gray zone lymphoma
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
N	number
NA	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NK	natural killer
NKTL	NK/T-cell lymphoma
NMR	no metabolic response
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
P	prospective
[redacted]	
PD	progression of disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1

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Term	Definition
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PMD	progressive metabolic disease
PMR	partial metabolic response
PPD	perpendicular diameter
PPK	population PK
[redacted]	
PTCL	peripheral T-cell lymphoma
QxW	every x weeks
[redacted]	
R/R	recurrent/relapsing or refractory
RCC	renal cell cancer
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RT	radiotherapy
[redacted]	
sAAIPI	second-line therapy age-adjusted International Prognostic Index
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	
SAV	single agent vial
SCCHN	squamous cell carcinoma head neck
[redacted]	
SDCT	standard dose of chemotherapy
SDi	shortest diameter
SJS	Stevens-Johnson syndrome
[redacted]	
SmPC	summary of product characteristics
SoC	standard of care
SUSAR	suspected, unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine

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Term	Definition
TB, T. bili	total bilirubin
TEN	toxic epidermal necrolysis
TIL	tumor infiltration lymphocytes
TMA	tissue microarray
Tmax	time to maximum concentration
[redacted]	
TSH	thyroid-stimulating hormone
TTE	transthoracic electrocardiogram
[redacted]	
ULN	upper limit of normal
US	United States
Vss	volume of distribution at steady state
WOCBP	women of childbearing potential
WNOCBP	women not of childbearing potential
WS	Worldwide Patient Safety

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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 International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws, regulations, and requirements

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

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

- ICH guidelines,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50),
- European Regulation 536/2014,
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC,
- and all other applicable local regulations.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

FINANCIAL DISCLOSURE

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

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INFORMED CONSENT PROCESS

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

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

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant or his/her legally acceptable representative and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant or his/her legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant or his/her legally acceptable representative to inquire about the details of the study.

Obtain an ICF signed and personally dated by participant or his/her legally acceptable representative and by the person who conducted the informed consent discussion.

- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or his/her legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

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

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

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

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

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the ICF approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time, should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written consent. Minors who reach the age of majority (legal adulthood) during the clinical trial must give their written consent.

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

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activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

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

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

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

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

SOURCE DOCUMENTS

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

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

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Examples of source documents may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records.

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

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

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

STUDY INTERVENTION RECORDS

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

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

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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 abnormalities that are reported or identified during the course of the study.

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

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

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

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

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

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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

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

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

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RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

If	Then
Study treatments supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused investigational medicinal product (IMP) must be reconciled by site monitor/Clinical Research Associate prior to destruction. If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors; eg, study treatments sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal of study interventions, provided that procedures for proper disposal have been established according to applicable federal,

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state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

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

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

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

STUDY AND SITE START AND CLOSURE

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

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

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DISSEMINATION OF CLINICAL STUDY DATA

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the clinical study report (CSR).

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

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

SCIENTIFIC PUBLICATIONS

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

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

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

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment that does not necessarily have a causal relationship with this treatment.

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

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SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below). NOTE: The following hospitalizations are not considered SAEs in Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.
Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

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

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint; if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Causality

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

- **Assessment of Intensity**

For the reporting of all AEs, including intensity or severity, on case report forms, please follow the definitions in Common Terminology Criteria for Adverse Event (CTCAE) v5.0.

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

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- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: worldwide.safety@BMS.com

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

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

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APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

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

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

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

End of Relevant Systemic Exposure

End of relevant systemic exposure is the timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

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

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

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

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

COLLECTION OF PREGNANCY INFORMATION

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

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APPENDIX 5 COUNTRY-SPECIFIC REQUIREMENTS

	Country-specific language
Requirement for France	Protocol summary and Section 6.1 Inclusion Criteria, Inclusion Criterion 2) l) to be modified From: Participants with pathologically confirmed high-risk R/R cHL, after non-response to or failure of 1 or more lines of standard therapy. To: Participants with pathologically confirmed high-risk R/R cHL, after non-response to or failure of 2 or more lines of standard therapy.
Requirement for France	Protocol summary and Section 6.1 Inclusion Criteria, Inclusion Criterion 2) m) to be modified From: Participants with pathologically confirmed R/R NHL after non-response to or failure of 1 or more lines of standard therapy, including but not limited to R/R primary mediastinal B-cell lymphoma, DLBCL, mediastinal gray zone lymphoma (MGZL), ALCL, Burkitt lymphoma (blast count < 25% malignant Burkitt cells and/or per the investigator's clinical assessment of risk status), lymphoblastic lymphoma (blast count < 25% of marrow nucleated cells and/or per the investigator's clinical assessment of risk status), NK/T-cell lymphoma (nasal and non-nasal NK/T-cell lymphoma subtypes, but not aggressive NK/T-cell leukemia/lymphoma subtype), or peripheral T-cell lymphoma (PTCL). To: Participants with pathologically confirmed R/R NHL after non-response to or failure of 2 or more lines of standard therapy, including but not limited to R/R primary mediastinal B-cell lymphoma, DLBCL, mediastinal gray zone lymphoma (MGZL), ALCL, Burkitt lymphoma (blast count < 25% malignant Burkitt cells and/or per the investigator's clinical assessment of risk status), lymphoblastic lymphoma (blast count < 25% of marrow nucleated cells and/or per the investigator's clinical assessment of risk status), NK/T-cell lymphoma (nasal and non-nasal NK/T-cell lymphoma subtypes, but not aggressive NK/T-cell leukemia/lymphoma subtype), or peripheral T-cell lymphoma (PTCL).

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Requirement for Countries Where Exclusion of HIV Positive Participants is Locally Mandated	Table 2-1: Screening Procedural Outline for Part A and Part B (CA224069); Laboratory Tests; Clinical Laboratory Assessments Add "HIV" to the list of laboratory tests
Requirement for Countries Where Exclusion of HIV Positive Participants is Locally Mandated	Section 6.2 Exclusion Criteria, Exclusion Criterion 1) o) i) "Known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome" to be replaced with "Positive test for HIV."

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APPENDIX 7 LUGANO 2014 RESPONSE CRITERIA

For positron emission tomography (PET)-based assessments, a clinical response of progressive metabolic disease (PMD), no metabolic response, partial metabolic response, or complete metabolic response (CMR) will be determined. PMD/progressive disease includes radiological evidence of progression per Lugano Classification Revised Staging System for malignant lymphoma. The PET scan metabolic uptake will be graded using the Deauville 5-point scale, with a score of ≤ 3 considered to represent a CMR.

Deauville 5-point scale: 1- no uptake above background; 2- uptake ≤ mediastinum; 3- uptake > mediastinum but ≤ liver; 4 = uptake moderately > liver; 5- uptake markedly higher than liver and/or new lesions; X- new areas of uptake unlikely to be related to lymphoma.

Table 1: CMR / CR

Response/Site	FDG-PET-CT-Based (Complete Metabolic Response)	CT-Based (CR)[a] All of the following:
Lymph nodes and extralymphatic sites	Score 1, 2 or 3 with or without a residual mass on 5-point-scale It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Abbreviations: CR = complete response; CT = computed tomography; FDG = [18F]fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest diameter; MRI = magnetic resonance imaging.

[a] CT-Based could also apply to MRI-based.

Note: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-68.

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Table 2: PMR / PR

Response/Site	FDG-PET-CT-Based (PMR)	CT-Based (PR)[a] All of the following:
Lymph nodes and extralymphatic sites	Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings suggest residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value; when no longer visible, 0 X 0 mm; for a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable

Abbreviations: CT = computed tomography; FDG = [18F]fluorodeoxyglucose; MRI = magnetic resonance imaging; PMR = partial metabolic response; PR = partial response.

[a] CT-Based could also apply to MRI-based.

Note: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-68.

Table 3: NMR / SD

Response/Site	FDG-PET-CT-Based (NMR)	CT-Based[a] (SD)
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites; no criteria for Progressive Disease met
Non-measured lesion	Not applicable	No increase consistent with Progression
Organ enlargement	Not applicable	No increase consistent with Progression

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Table 3: NMR / SD

Response/Site	FDG-PET-CT-Based (NMR)	CT-Based[a] (SD)
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Abbreviations: CT = computed tomography; FDG = [18F]fluorodeoxyglucose; MRI = magnetic resonance imaging; NMR = no metabolic response; SD = self diffusion; SPD = sum of the products of diameters.

[a] CT-Based could also apply to MRI-based.

Note: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-68.

Table 4: PMD / PD

Response/Site	FDG-PET-CT-Based (PMD)	CT-Based (PD)[a] At least one of the following:
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm & Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Non-measured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma.
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: CT = computed tomography; FDG = [18F]fluorodeoxyglucose; LDi = longest diameter; PD = progressive disease; PPD = perpendicular diameter; SDi MRI = shortest diameter magnetic resonance imaging.

[a] CT-Based could also apply to MRI-Based.

Note: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-68.

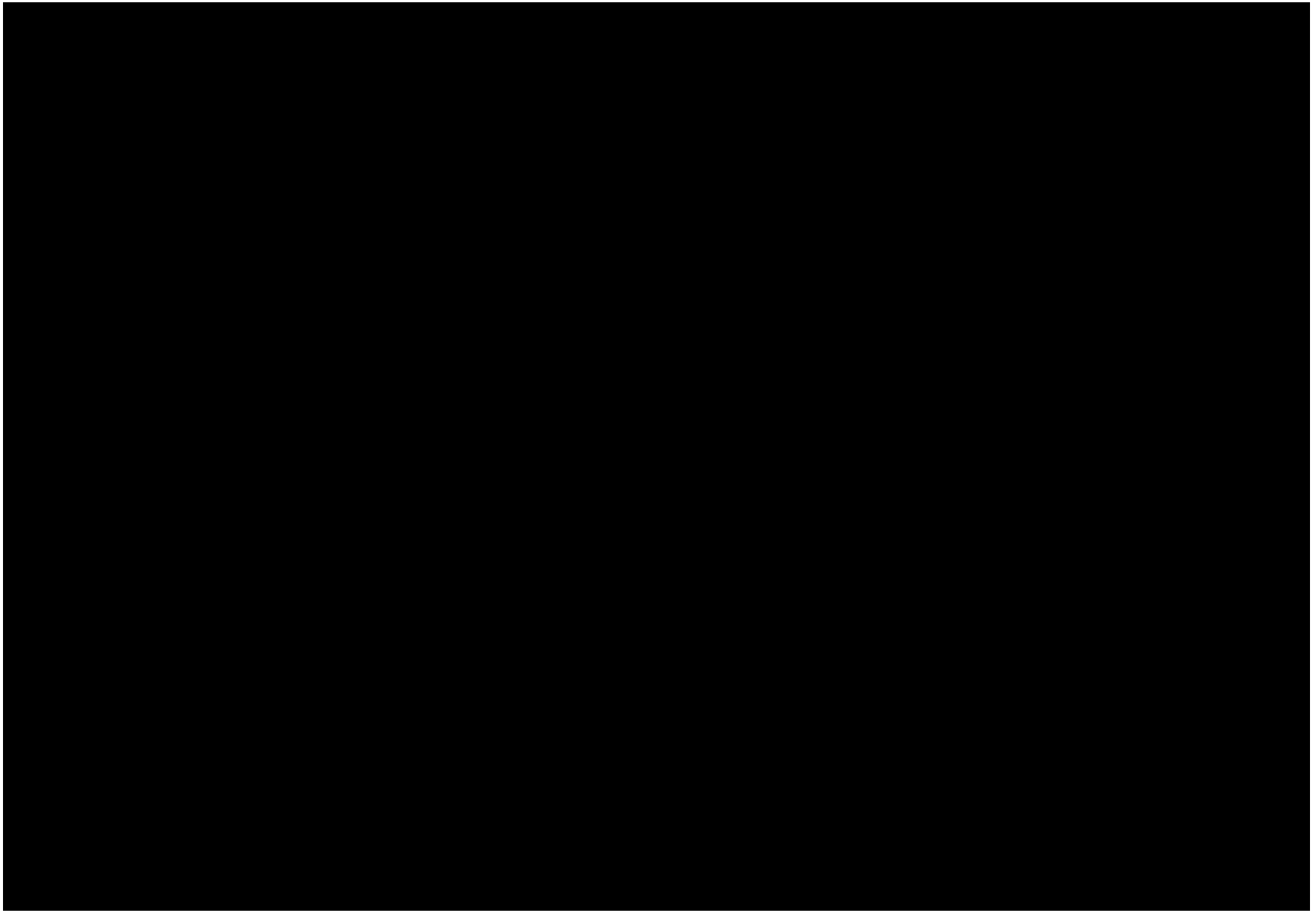
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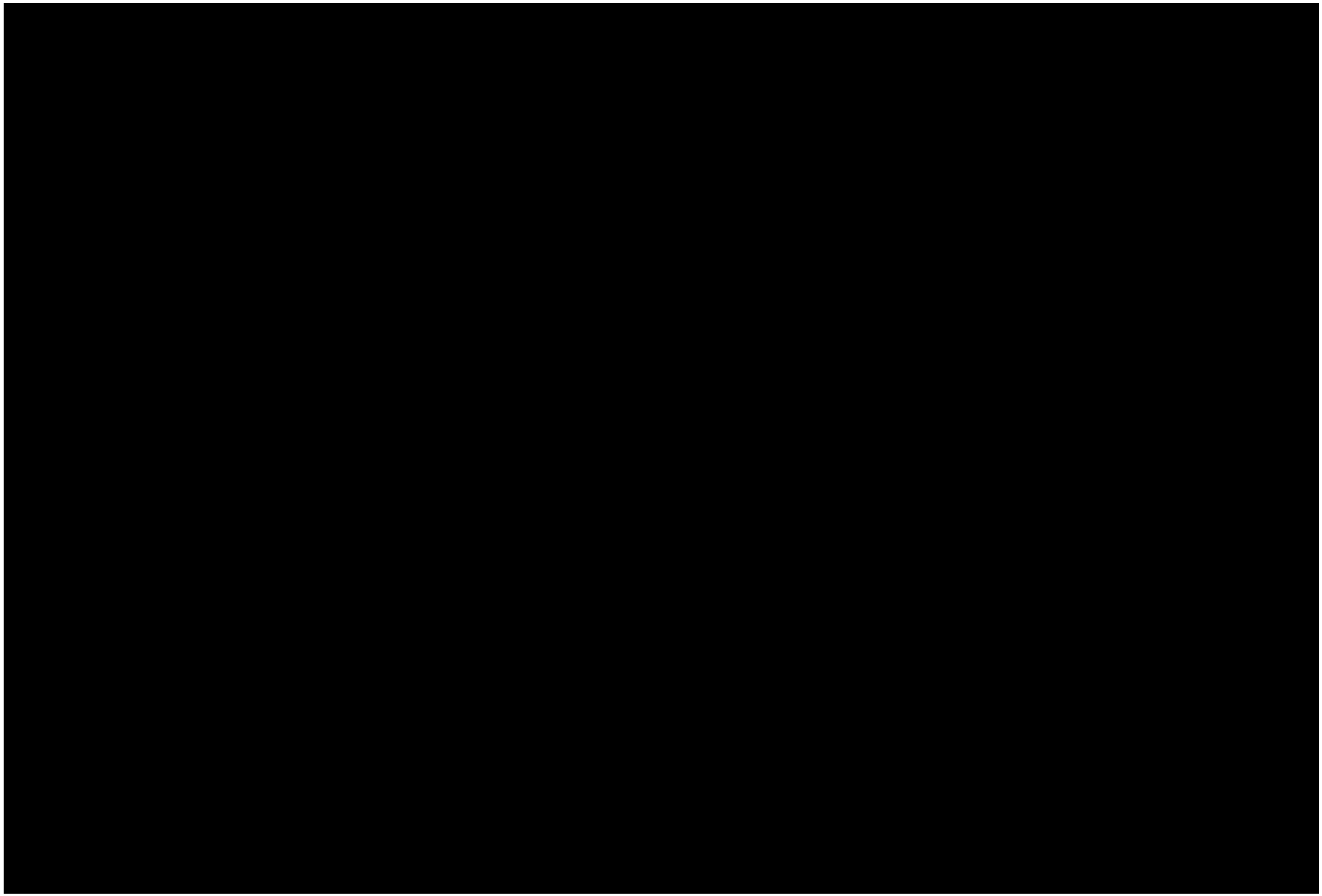
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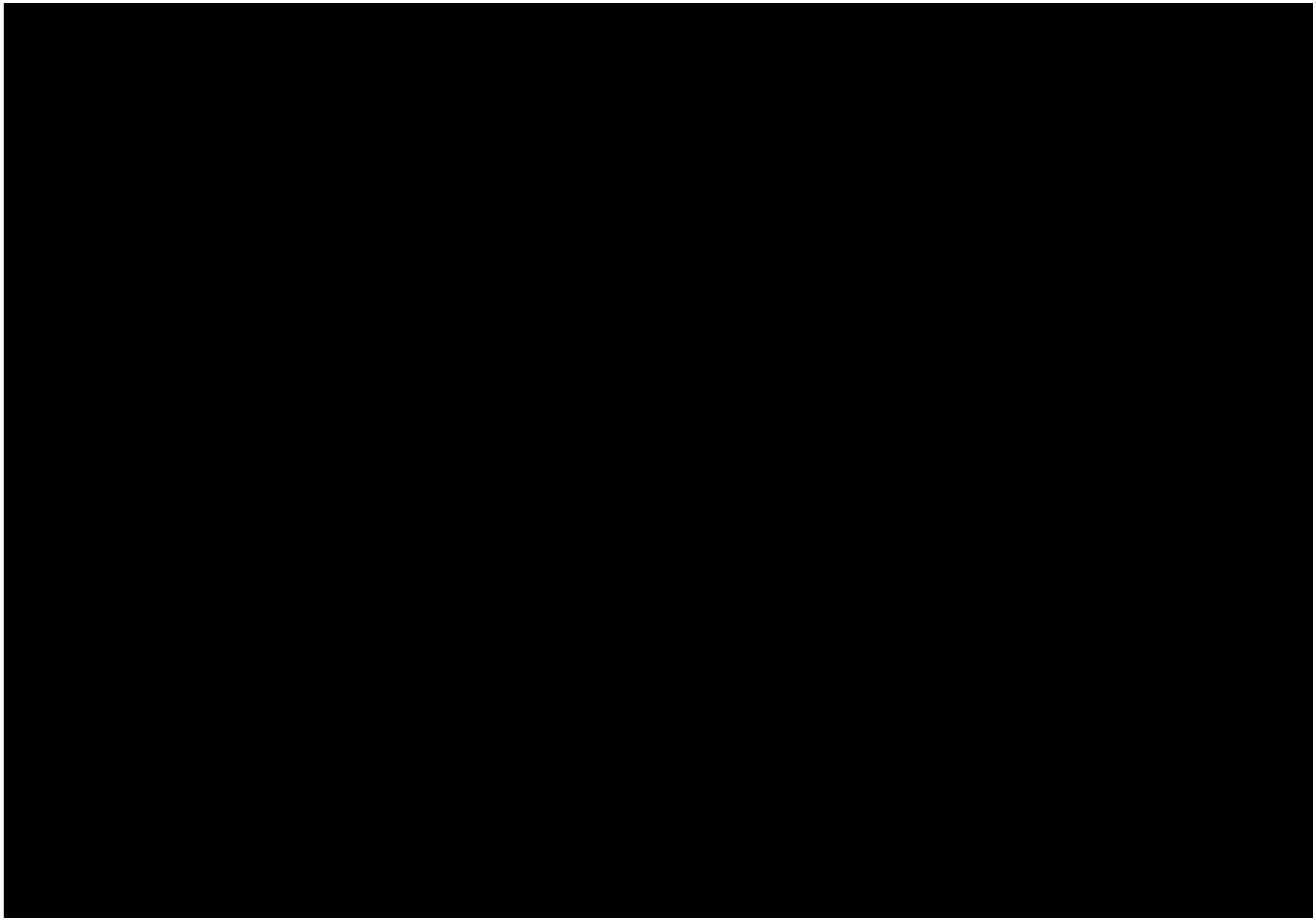
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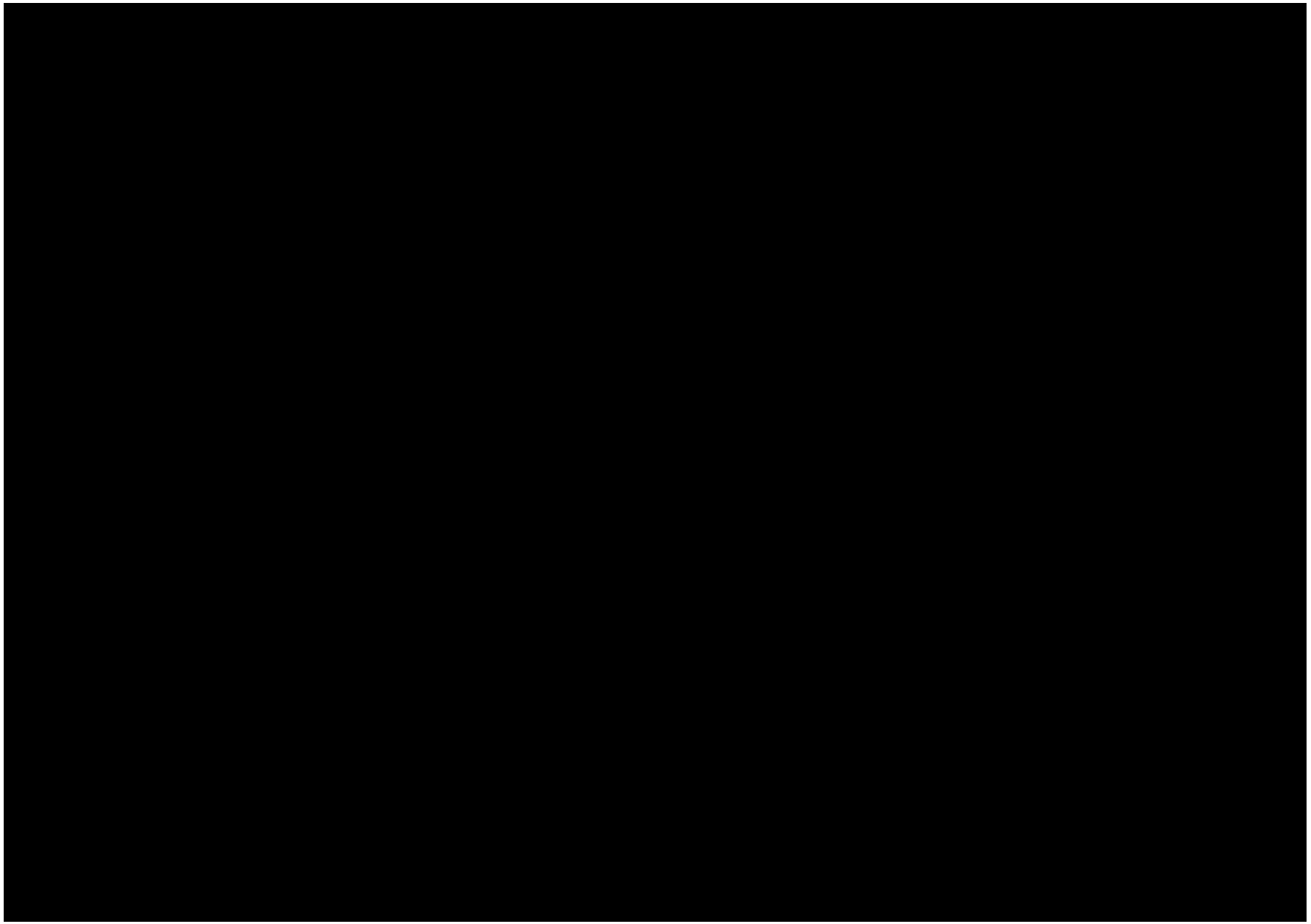
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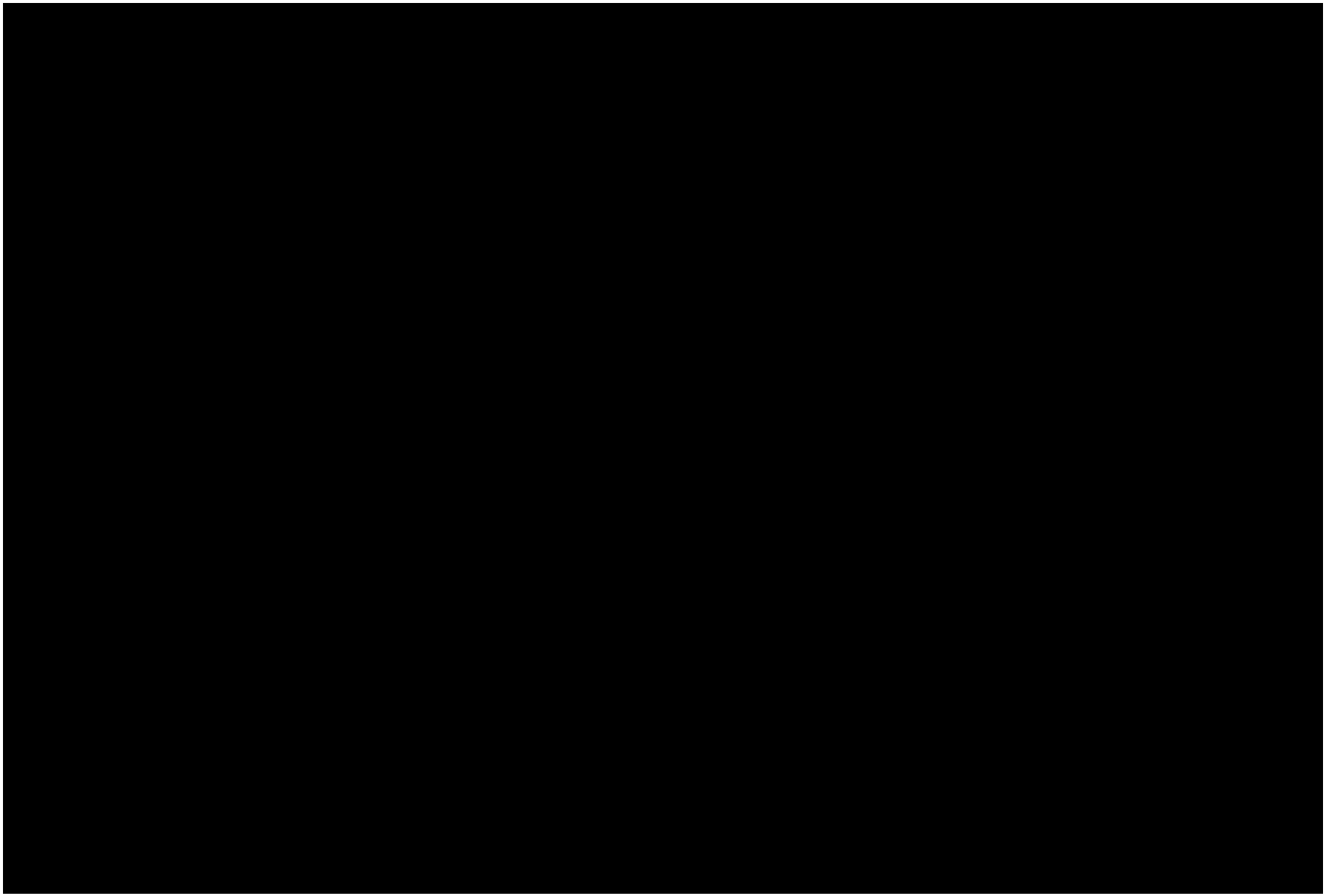
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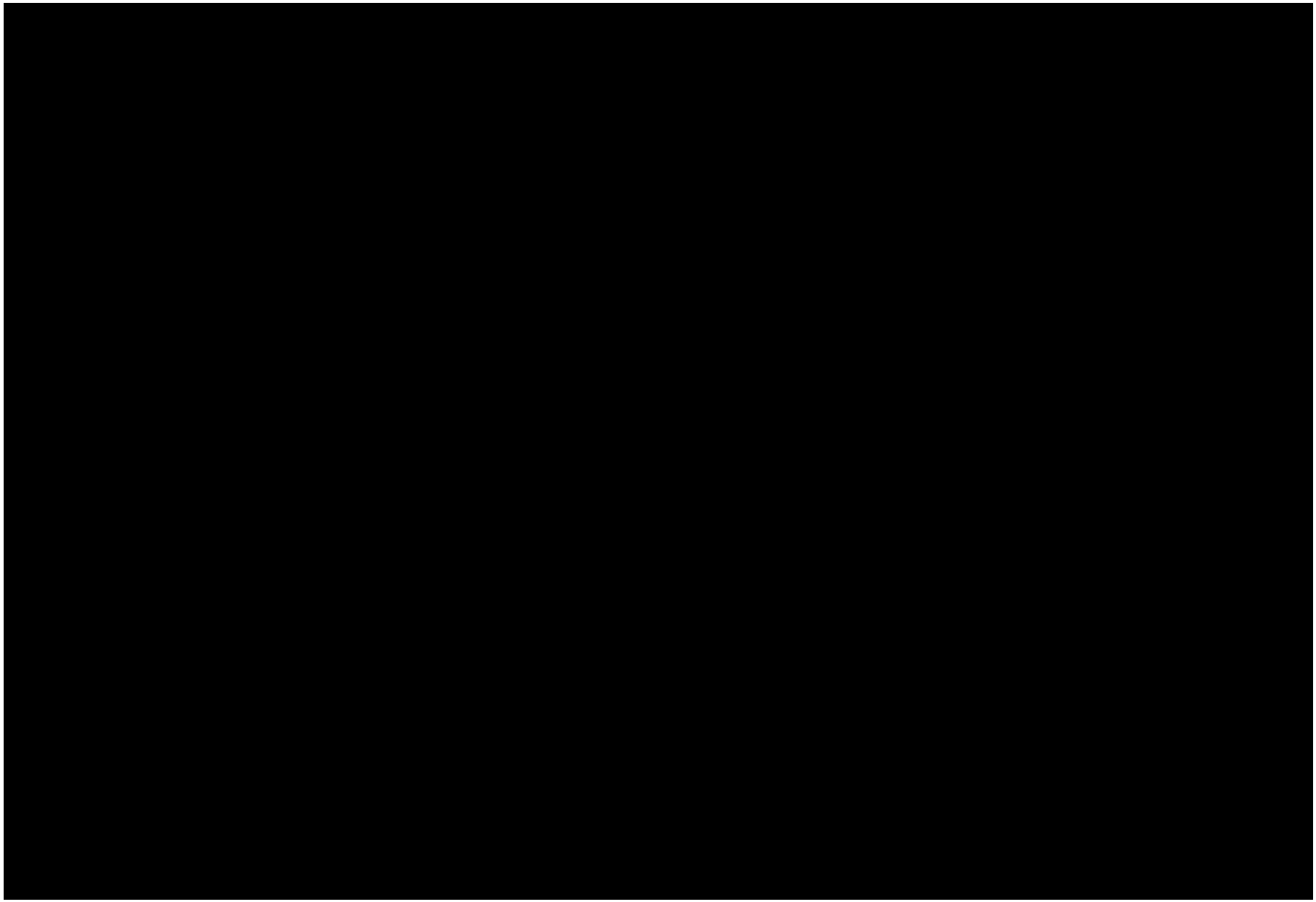
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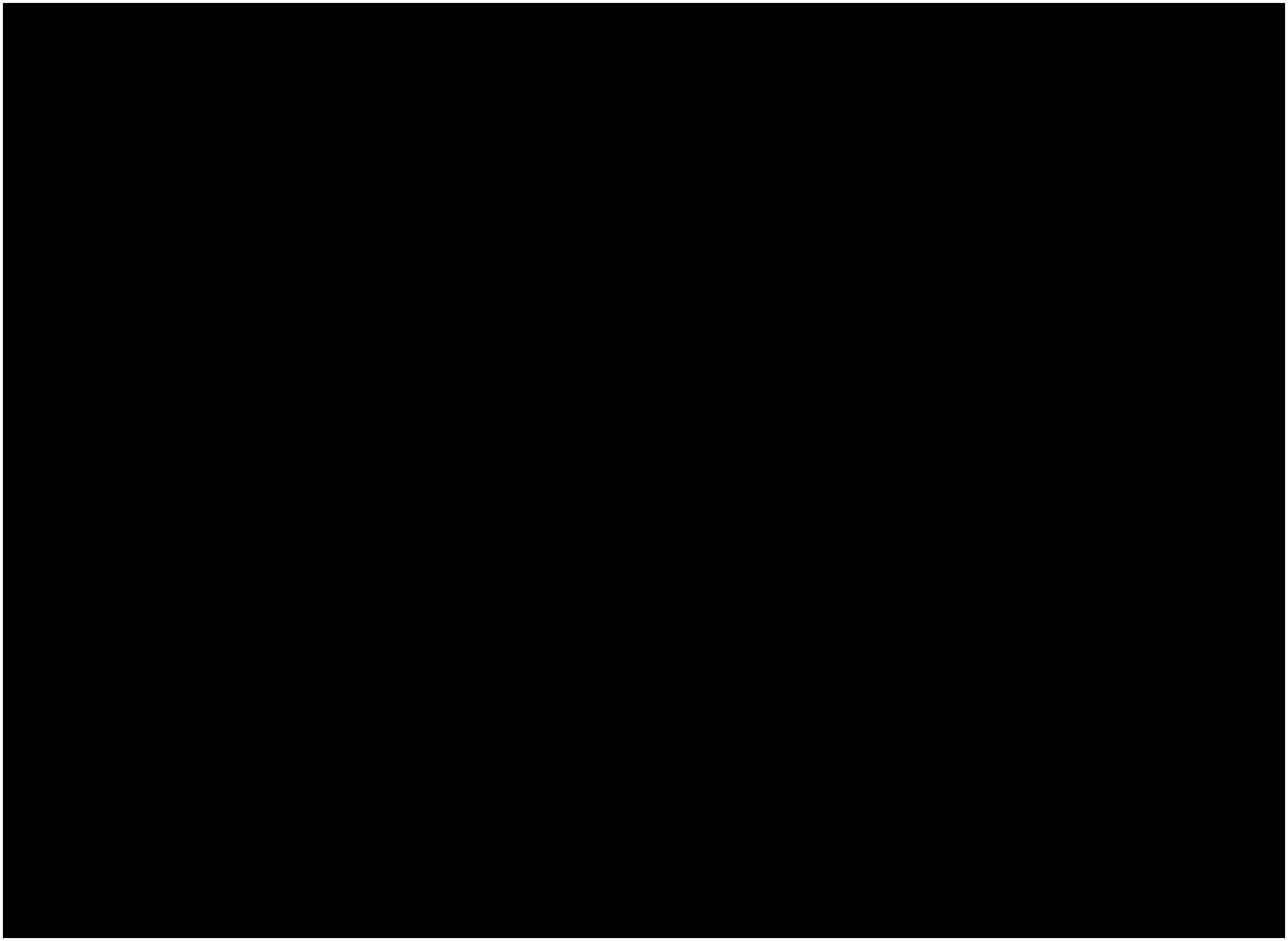
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APPENDIX 9 SECOND-LINE THERAPY AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX SCALE*

Composite score determined by assigning 1 point for each of the following factors:

[redacted]

- Elevated Serum lactate dehydrogenase
- Stage III/IV disease[1]

Risk Assessment:

- Low risk with 0 factors
- Low-intermediate risk with 1 factor
- High-Intermediate- risk with 2 factors
- High risk with all 3 factors present

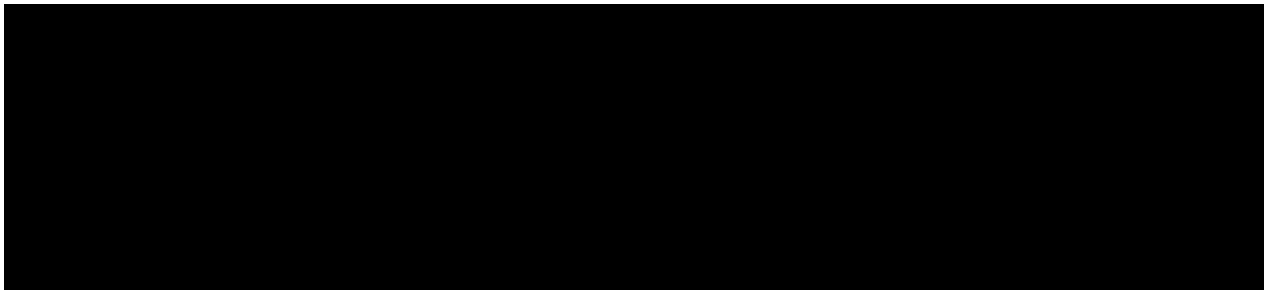
1. Ann Arbor staging, Cotswold 1989 modification

* Hamlin PA, Zelenetz AD, Kewalramani T, et al. Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. Blood. 2003;102:1989-96.

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APPENDIX 10 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 02, 27-Feb-2024



This amendment incorporates revisions from Protocol Amendment 01 EU, which consolidated Protocol Amendment 01 with France-specific requirements. Changes incorporated into the consolidated protocol are reflected within this global amendment.

Changes made throughout the protocol body have been incorporated into the Protocol Summary.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline for Part A and Part B (CA224069) Section 9.1.2, Imaging Assessment for the Study	Changed description of tumor assessment imaging for whole body to add "(at least from the base of skull to proximal femurs)".	Clarification to define anatomic extent of FDG-PET-MRI whole-body scan.
Section 2: Schedule of Activities, Table 2-1 Section 6.1: Inclusion Criteria, Criteria 2) b) and 2) k)	Included reference to Appendix 5 connecting country-specific requirements to the relevant sections of the protocol.	Connect country-specific requirements to the relevant sections of the protocol.

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SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069)	Changed from Cycles 7-12 to Cycles 7-24.	Correcting typographic error.
Section 3.1.2.1: Classical Hodgkin Lymphoma	[redacted]	Included clarification to define early relapse.

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SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 6.1: Inclusion Criteria	Modified criterion 2) l) from "first-line" to "1 or more lines"	To clarify that eligibility is not limited to immediately after failure of the first line of standard therapy alone and includes one or more lines of tberapy.
Section 6.1: Inclusion Criteria	Modified criterion 2) m), based on biological and clinical rationale, to include participants with specific subsets of Burkitt lymphoma (BL), lymphoblastic lymphoma (LBL), and NK/T-cell lymphoma (NKTL).	To broaden eligibility criteria.
Section 6.2: Exclusion Criteria	Modified exclusion criteria 1) q) to remove: Participants with certain aggressive B-cell lymphoma subtypes, including BL, LBL, NKTL.	To broaden eligibility criteria.
Section 6.2: Exclusion Criteria	Prior stem cell transplantation (high-dose chemotherapy [HDCT]/autologous stem cell transplantation [ASCT]) was deleted from exclusion criteria 3) e).	To broaden eligibility criteria.
[redacted]		

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SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Appendix 5: Country-specific Requirements	Added a description of the country-specific requirements.	Consolidate country-specific differences in one appendix.
Throughout	Minor editorial and formatting changes made throughout.	Editorial and formatting changes.

Overall Rationale for Protocol Amendment 01, 26-Aug-2022

[redacted] Investigator discretion includes, but is not limited to, continuing relatlimab + nivolumab with a flexible duration of treatment (DOT) to accommodate differences in regional standard of care (SoC) for up to a total of [redacted] maximum study treatment, high-dose chemotherapy (HDCT)/autologous stem cell transplantation (ASCT; eg, classic Hodgkin Lymphoma), CAR-T (eg, certain Non-Hodgkin Lymphoma subtypes) or change to other best available (eg, definitive) treatment, following consultation with the Medical Monitor.

Additional revisions, including in sections of the Protocol Summary, have been made to align the protocol with respect to these changes. This amendment also incorporates changes from the approved Administrative Letter 01, which is detailed in the Document History but not listed in the Summary of Key Changes below.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Table 2-1: Screening Procedural Outline for Part A and Part B (CA224069); Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069); Table 2-3: Long-term Follow-up Procedural Outline (CA224069); Section 5.1: Overall Design; Section 5.1.2: Treatment Phase; Section 9.1.2: Imaging Assessment for the Study	• Added [^{18}F]fluorodeoxyglucose-positron emission tomography magnetic resonance imaging (FDG-PET-MRI) to tumor assessment imaging. • Added (for Part A): During the treatment period, FDG-PET-CT whole-body or FDG-PET-MRI should occur at Day 49 (± 7 days), Day 105 (± 7 days) and Day 161 (± 7 days) starting from the date of first dose and corresponding with Day 21 (± 7 days) of Cycles 2, 4 and 6, then every 12 weeks (± 7 days) after Cycle 6 assessment until PMD or treatment discontinuation (EOT), whichever occurs later, participant withdrawal, or death. • Added (for Part B): During the treatment period, tumor assessments by FDG-PET-CT or FDG-PET-MRI should occur at Day 49 (± 7 days), Day 105 (± 7 days) and Day 161 (± 7 days) starting from the date of first dose and corresponding with Day 21 (± 7 days) of Cycles 2, 4 and 6.	• To align with a flexible duration of treatment (DOT) to accommodate differences in regional standard of care (SoC). • To adjust imaging frequency for Parts A and B, initiating Part A as is to keep current timelines and then harmonize Part A and Part B to enable timepoint-based analysis

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	In case of CMR before or after 6 cycles by FDG-PET-CT or FDG-PET-MRI, imaging may be performed using diagnostic quality MRI/CT scans every 12 weeks (± 7 days) from the last on treatment scan date until PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death. If PD is suspected based on clinical or MRI/CT findings, a confirmatory FDG-PET-CT or FDG-PET MRI should be obtained to confirm PMD. PMR participants at the end of 6 cycles proceeding to receive Investigator's choice of continuing relatlimab + nivolumab will be followed up by FDG-PET-CT or FDG PET-MRI imaging every 12 weeks (± 7 days) from the last on-treatment scan date until CMR, PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death. Participants continuing treatment based on investigator's discretion, for example in case of NMR, will be allowed to switch imaging modality from being PET-based to diagnostic quality CT or MRI scans every 12 weeks (± 7 days) from the last on treatment scan date until PMD or treatment discontinuation, whichever occurs later, participant withdrawal, or death. In case of suspected CR based on CT/MRI, FDG-PET-CT or FDG-PET-MRI scan must be performed to confirm CMR. If PD is suspected on CT or MRI, an additional FDG-PET-CT or FDG-PET-MRI scan must be performed to confirm PMD.	
Table 2-1: Screening Procedural Outline for Part A and Part B (CA224069); Section 9.4.1: Physical Examinations	• Clarified that body surface area (BSA) will be calculated using the Mosteller formula.	• Clarification.
[redacted]		

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Table 2-1: Screening Procedural Outline for Part A and Part B (CA224069); Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069); Section 5.1.1: Screening Phase; Section 6.1: Inclusion Criteria; [redacted] Tumor Samples	• Tissue slide requirement decreased [redacted].	• Based on pathologist recommendation as sites may not be able to obtain [redacted] slides from pediatric patient specimens. Lowering the requirement should allow patients with fewer slides to participate in the study without substantially affecting the planned [redacted] analysis.
Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069)	• Updated 'Cycles 3-26' column to [redacted] and added column for [redacted]. Updated '±2 days' visit window to '±3 days'. • Updated physical measurements regarding dose calculation based on weight. • Added row for Tumor Assessments (Part B).	• To align with updated study design. • Clarification. • Clarification.
Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069); Section 9.1.2: Imaging Assessment for the Study	• Added wording to indicate imaging assessment should follow indicated schedule even if dose is omitted or delayed.	• Clarification.
Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069); Section 9: Study Assessments and Procedures; Section 9.5: Pharmacokinetics; [redacted]	• Updated blood draw volume collection instructions.	• To accommodate participants who require blood draw volume modifications for low body weight or other reasons, and to meet pediatric institutional or national guidelines for maximum daily and monthly blood draw limits.
Table 2-1: Screening Procedural Outline for Part A and Part B (CA224069); Table 2-2: On Treatment Procedural Outline for Part A and Part B (CA224069); Table 2-3: Long-term Follow-up Procedural Outline (CA224069); Section 5.1: Overall Design;	• Updated the number of days study participants will be followed for adverse events (AEs)/serious adverse events (SAEs) from 100 to 135 days.	• To align with current Investigator's Brochure (IB) and accommodate 5 half-lives of relatlimab and nivolumab.

Approved v4.0 930165609 4.0

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.3: Follow-up Phase; Section 7.7.1 Prohibited and/or Restricted Treatments; Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information; Section 9.2.6.1: Definition of Immune-mediated Adverse Events; [redacted] Table 10.4.2-1: Endpoints		
Section 3.3.2: Benefit Assessment	• Added protocol definition of high-risk and standard risk.	• To align with EuroNet and National Comprehensive Cancer Network (NCCN) guidelines.
[redacted]		
Section 5.1: Overall Design; Section 5.1.3: Follow-up	• Total duration of study treatment updated to a maximum of [redacted].	• A maximum duration of treatment of up to [redacted] was selected based on current

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Phase; Table 10.4.2-1: Endpoints		treatment guidelines and evolving SoC, as well as to allow for Investigator's discretion with a flexible DOT to accommodate differences in regional SoC.
Section 5.1: Overall Design; Section 5.2: Number of Participants	• Imaging language for Part A and Part B added for clarification.	• To align with a flexible DOT to accommodate differences in regional SoC.
[redacted]		
Figure 5.1-4: Schematic of Cohort Expansion (Part B)	• Figure updated.	• To align with a flexible DOT to accommodate differences in regional SoC.
Section 5.1.1: Screening Phase	• Addition of 12-lead ECG, echocardiogram, and systemic anticancer treatment screening requirements.	• Clarification.
[redacted]		
Section 6.1: Inclusion Criteria	• Marked inclusion criterion 1) c) as Not Applicable per Protocol Amendment 01.	• To align with current nivolumab and relatlimab Essential Protocol Documents
Section 6.1: Inclusion Criteria	• Marked inclusion criterion 2) c), 2) c) i), and 2) c) ii) as Not Applicable per Protocol Amendment 01; added new inclusion criterion 2) k), 2) k) i), and 2) k) ii): "2) k) Participants with pathologically confirmed R/R NHL after failure or non-response to first-line therapy, including but not limited to primary mediastinal B-cell lymphoma, DLBCL, mediastinal gray zone lymphoma (MGZL), ALCL, or peripheral T-cell lymphoma (PTCL).	• To include additional lymphoma subtypes that remain unmet medical needs.

Approved v4.0 930165609 4.0

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Refer also to Exclusion Criteria 1) q) (Section 6.2). i) For the purpose of this study clinical stages of NHL permitted include clinical Stage III or Stage IV per the Lugano 2014 Classification. ii) High-risk NHL where defined as applicable (eg, in young adults) by sAAIPI scale, based on factors of decreased performance status, elevated LDH, and Stage III/IV disease, with a score of ≥ 2 factors (refer to Appendix 9).”	
Section 6.1: Inclusion Criteria; Section 9.2.5: Pregnancy	• Updated first bullet under inclusion criterion 4). • Added inclusion criterion 4) b) and 4) b) i): “4)b) Male Participants: 4)b)i) No contraception requirements for nivolumab and relatlimab for male participants are mandated. Note: Pregnancy reporting from female partners of childbearing potential of male participants is not required unless an additional Investigational Medicinal Product (IMP) is genotoxic or can be present in relevant amount in seminal fluid to cause fetotoxicity.”	• To align with current nivolumab and relatlimab male contraception language.
Section 6.1: Inclusion Criteria	• Updated inclusion criterion 2) c) ii) to clarify it applies to young adults. • Updated inclusion criterion 2) h) to clarify the definition of substantial recovery. • Updated inclusion criterion 2) i) to clarify the definition of “wash-out” period.	• Clarification.
Section 6.2: Exclusion Criteria	• Marked exclusion criterion 1) a) as Not Applicable per Protocol Amendment 01; added new exclusion criterion 1) q) to update the types of lymphoma that will result in exclusion from the study: “1) q) Participants with aggressive B-cell lymphomas subtypes including BL and lymphoblastic lymphoma, adult T-cell lymphoma/leukemia (human T-lymphotrophic virus [HTLV] 1+), NK-/T-cell lymphoma/leukemia, and primary CNS lymphoma of the brain or spinal cord.”	• To exclude certain aggressive subtypes that either do not express LAG-3 or would be expected to progress too quickly before response to immunotherapy.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2: Exclusion Criteria	• Marked exclusion criterion 1) g) as Not Applicable per Protocol Amendment 01. • Marked exclusion criterion 1) h) as Not Applicable per Protocol Amendment 01. • Marked exclusion criterion 1) j) as Not Applicable per Protocol Amendment 01. • Marked exclusion criterion 4) k) as Not Applicable per Protocol Amendment 01.	• To align with current nivolumab and relatlimab Essential Protocol Documents
Section 6.2: Exclusion Criteria	• Updated exclusion criterion 2) a) to exclude women with positive pregnancy test at Screening. • Updated exclusion criterion 3) f) to indicate all individuals with prior allogeneic bone marrow transplantation, regardless of graft versus host (GVHD) status, are to be excluded from study participation.	• Clarification.
Section 6.2: Exclusion Criteria	• Added exclusion criterion 3) j): "Prior CAR-T therapy within 6 months of first study treatment".	• To align with Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval of chimeric antigen receptor T-cell (CAR-T) therapy.
Section 7.7: Concomitant Therapy; Section 7.7.1: Prohibited and/or Restricted Treatments	• Added COVID-19 vaccination language.	• To align with current nivolumab and relatlimab COVID-19 language.
[redacted]		
Table 9.4.6-1: Clinical Laboratory Assessments	[redacted] • Added urine drug screen for drugs of abuse as clinically indicated at Screening.	• Clarification.
[redacted]		

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
[redacted] Tumor Samples	• Updated pathology requirements.	• Clarification.
[redacted]		
Table 10.4.1-1: Definition of Estimands for Primary and Secondary Endpoints	• Updated population wording.	• Clarification.
[redacted]		
Appendix 2: Study Governance Considerations	• Added 2 new sections: BMS Commitment to Diversity in Clinical Trials and Data Protection, Data Privacy, and Data Security.	• Added to align with BMS commitment to diversity in clinical trials and to comply with European Union Clinical Trials Regulation (EU-CTR) requirement.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 5: Country Specific Requirements	• Added France-specific protocol amendment.	• To include France-specific protocol amendment.
[redacted]		
All	• Minor formatting, clarification, and typographical corrections; additional updates to align the protocol with respect to key changes outlined above.	• Corrections for clarity and consistency within the document were minor, and therefore have not been summarized.

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