



RESEARCH AND DEVELOPMENT

NIVOLUMAB + RELATLIMAB FDC

RISK MANAGEMENT PLAN

Version Number: 6.0

Data-lock Point for this RMP: 17-Mar-2025

Date of final sign off: 16-Mar-2026

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TABLE OF CONTENTS

TITLE PAGE	1
TABLE OF CONTENTS.....	2
LIST OF TABLES	4
LIST OF APPENDICES.....	5
LIST OF ANNEXES	6
LIST OF ABBREVIATIONS.....	7
EU RMP FOR NIVOLUMAB + RELATLIMAB FDC.....	9
1 PART 1: PRODUCT OVERVIEW	12
2 PART II: SAFETY SPECIFICATION.....	13
2.1 Epidemiology of the Indication(s) and Target Population(s)	13
2.2 Nonclinical Part of the Safety Specification.....	16
2.3 Clinical Trial Exposure	17
2.3.1 Nivolumab + relatlimab FDC.....	18
2.4 Populations Not Studied in Clinical Trials	18
2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme	18
2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes.....	20
2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes.....	20
2.5 Post-Authorisation Experience	21
2.5.1 Method Used to Calculate Exposure	22
2.5.2 Exposure	22
2.6 Additional EU Requirements for the Safety Specification.....	22
2.6.1 Potential for Misuse for Illegal Purposes.....	22
2.7 Identified and Potential Risks	23
2.7.1 Identification of Safety Concerns in the Initial RMP Submission.....	23
2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP	23
2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP	24
2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP.....	25
2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information.....	25
2.7.3.1 Presentation of Important Identified and Important Potential Risks	25
.....	25
2.7.3.2 Presentation of the Missing Information	34
2.8 Summary of the Safety Concerns	34
3 PART III: PHARMACOVIGILANCE PLAN	34
3.1 Routine Pharmacovigilance Activities.....	34
3.2 Additional Pharmacovigilance Activities	34
3.3 Summary Table of Additional Pharmacovigilance Activities	36
4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES	37

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES).....	37
5.1 Routine Risk Minimisation Measures.....	37
5.2 Additional Risk Minimisation Measures	37
5.3 Summary of Risk Minimisation Measures	38
6 SUMMARY OF THE RISK MANAGEMENT PLAN.....	39

LIST OF TABLES

Table 1-1: Product Details	12
Table 2.1-1: Epidemiologic Characteristics of Metastatic Melanoma.....	13
Table 2.2-1: Summary of Significant Non-clinical Safety Findings	16
Table 2.3-1: Nivolumab + Relatlimab FDC Clinical Studies Supporting Exposure and Safety Analyses in the RMP	17
Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies	18
Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes.....	20
Table 2.7.1-1: Safety Concerns in the Initial RMP.....	23
Table 2.7.1.1-1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP	23
Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP	24
Table 2.7.3.1-1: Important Identified Risk: Immune-related ARs (including immune- related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)	25
Table 2.7.3.1-2: Important Potential Risk: Embryofetal Toxicity	33
Table 2.7.3.2-1: Missing Information	34
Table 2.8-1: Summary of Safety Concerns	34
Table 3.2-1: Post-Authorisation Safety Studies Short Name Summary	35
Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities.....	36
Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern	37
Table 5.2-1: Additional Risk Minimisation Measures.....	38
Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities	38

LIST OF APPENDICES

APPENDIX 1: REFERENCES	46
APPENDIX 2: CLINICAL TRIAL EXPOSURE TABLES	51

LIST OF ANNEXES

ANNEX 1: EUDRAVIGILANCE INTERFACE	58
ANNEX 2: TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME	60
ANNEX 3: PROTOCOLS FOR PROPOSED, ON-GOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN	63
ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS.....	64
ANNEX 5: PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV	65
ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)	67
ANNEX 7: OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL).....	69
ANNEX 8: SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME	72

LIST OF ABBREVIATIONS

Term	Definition
ADA	Anti-drug antibodies
AE(s)	Adverse event(s)
ALT	Alanine transaminase
AR(s)	Adverse reaction(s)
ASR	Age-standardized rate
AST	Aspartate transaminase
BMS	Bristol-Myers Squibb
CDC	Center for Disease Control
CMV	Cytomegalovirus
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
DMTR	Dutch Melanoma Treatment Registry
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDC	Fixed dose combination
GVHD	Graft-versus-host disease
HLH	Hemophagocytic lymphohistiocytosis
HSCT	Haematopoietic stem cell transplant
IARC	International Agency for Research on Cancer
ILD	Interstitial lung disease
IO	Immuno-oncology
irARs	Immune-related adverse reactions
LAG-3	Lymphocyte-activation gene-3
MAA	Marketing Authorisation Approval
mAbs	Monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia gravis
MOA	Mechanism of action
N/A	not applicable
NCI	National Cancer Institute
Nivo	Nivolumab
NPCR	National Program of Cancer Registries

Term	Definition
OS	Overall survival
PASS	Post-authorisation safety study
PBRER	Periodic Benefit Risk Evaluation Report
PC	Patient card
PD-1	Programmed death–1
PFS	Progression-free survival
PI	Package Insert
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic
PS	Performance status
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QPPV	Qualified person responsible for pharmacovigilance
RMP	Risk management plan
SEER	Surveillance, Epidemiology, and End Results
SJS	Stevens-Johnson syndrome
SOC	System Organ Classes
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TEN	Toxic Epidermal Necrolysis
TSH	Thyroid stimulating hormone
ULN	Upper limit of the normal
UK	United Kingdom
US	United States of America
VKH	Vogt Koyanagi-Harada syndrome
2QW	Twice weekly
WHO	World Health Organization
WOCBP	Women of childbearing potential

EU RMP FOR NIVOLUMAB + RELATLIMAB FDC

RMP version to be assessed as part of this application:

Version Number: 6.0

Data-lock Point for this RMP: 17-Mar-2025

Date of Final Sign-off: 16-Mar-2026

Rationale for submitting an updated RMP:

- Updated [Table 2.7.3.1-1](#) to include SJS/TEN under the ‘Skin irARs’ important identified risk category.
- Updated [Annex 7 Table 7-1](#): Summary of MedRA terms.

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	NA	V1.2 / 15-Sep-2022
SII Non-clinical part of the safety specification	NA	V1.2 / 15-Sep-2022
SIII Clinical trial exposure	NA	V1.2 / 15-Sep-2022
SIV Populations not studied in clinical trials	NA	V1.2 / 15-Sep-2022
SV Post-authorisation experience	NA	V5.1 / 12-Feb-2026
SVI Additional EU requirements for the safety specification	NA	V1.2 / 15-Sep-2022
SVII Identified and potential risks	Updated Table 2.7.3.1-1 to include SJS/TEN under the ‘Skin irARs’ important identified risk category	V6.0 / pending
SVIII Summary of the safety concerns	NA	V1.2 / 15-Sep-2022
Part III Pharmacovigilance Plan	NA	V4.0 / 24-Nov-2025
Part IV Plan for post-authorisation efficacy studies	NA	V1.2 / 15-Sep-2022
Part V Risk Minimisation Measures	NA	V2.0 / 11-Jul-2025
Part VI Summary of the Risk Management Plan	Updated to reflect changes in the RMP	V6.0 / pending
Part VII Annexes		
ANNEX 2 Tabulated summary of planned,	NA	V4.0 / 24-Nov-2025

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
ongoing, and completed pharmacovigilance study programme		
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	NA	V4.0 / 24-Nov-2025
ANNEX 4 Specific adverse drug reaction follow-up forms	NA	V1.2 / 15-Sep-2022
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	NA	V1.2 / 15-Sep-2022
ANNEX 6 Details of proposed additional risk minimisation activities	NA	V1.2 / 15-Sep-2022
ANNEX 7 Other supporting data	Updated Annex 7 Table 7-1 : Summary of MedRA terms	V6.0 / pending
ANNEX 8 Summary of changes to the risk management plan over time	Updated to include version 6.0	V6.0 / pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
Version 3.0	06-Oct-2025	EMA/VR/0000303785

Details of the currently approved RMP:

Version number: 5.1

Approved with procedure: EMA/VR/0000314728

Date of approval: 12-Feb-2026

EU RMP Contact Person: PharmD. Roberta Di Menno Di Bucchianico, EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	Nivolumab + Relatlimab
Pharmacotherapeutic group(s) (ATC Code)	L01FY02
Marketing Authorisation	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Opdualag
Marketing authorisation procedure	Centralized
Brief description of the product	Opdualag™ is a first in class, next generation immunotherapy combining two immunotherapies, nivolumab (anti-PD-1) + relatlimab (anti-LAG-3) drug products at a 3:1 protein-mass ratio in the same vial (FDC; BMS-986213) for use in adults and adolescents 12 years of age and older with advanced (unresectable or metastatic) melanoma. Nivolumab and relatlimab are immune checkpoint inhibitors. Nivolumab is a human IgG4 mAb that binds to the PD-1 receptor, blocks interaction with its ligands PD-L1 and PD-L2 and reduces PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. Relatlimab is a human IgG4 mAb that binds to the LAG-3 receptor, blocks its interaction with ligands, including MHC II and reduces LAG-3 pathway-mediated inhibition of the immune response. The combination of nivolumab (anti-PD-1) and relatlimab (anti-LAG-3) results in increased T-cell activation compared to the activity of either antibody alone. In murine syngeneic tumour models, LAG-3 blockade potentiates the anti-tumour activity of PD-1 blockade, inhibiting tumour growth and promoting tumour regression.
Hyperlink to the Product Information	Refer to proposed PI
Indication(s) in the EEA	Current: Opdualag is indicated for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%. Proposed: N/A
Dosage in the EEA	Current: The recommended dose for adults and adolescents 12 years of age and older is 480 mg nivolumab and 160 mg relatlimab every 4 weeks administered as an intravenous infusion over 30 minutes. This dose is established for adolescent patients weighing at least 30 kg. Proposed: N/A

Table 1-1: Product Details

Pharmaceutical form (s) and strength(s)	Current: Concentrate for solution for infusion (sterile concentrate); 240 mg/80 mg Each mL of concentrate for solution for infusion contains 12 mg nivolumab and 4 mg relatlimab One vial of 20 mL contains 240 mg nivolumab and 80 mg relatlimab
Is/will the product be subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

Table 2.1-1: Epidemiologic Characteristics of Metastatic Melanoma

Metastatic Melanoma	
Overview	Incidence, prevalence, and survival estimates for metastatic melanoma have changed over time based on increased detection at early stages and improved treatments for advanced stage III/IV disease. However, there is an unmet need for additional treatment options that offer the potential to boost efficacy of anti-PD-1 monotherapy and overcome anti-PD-1 resistance, regardless of BRAF status and inclusive of those with poor prognostic factors, while improving on the safety profile of currently available IO combinations.
Incidence	International incidence varies widely across populations.^{1,2} Please note that estimated 2020 rates are projected from prior years and do not account for systemic interruptions caused by the COVID-19 pandemic. - The WHO's IARC has estimated that there were approximately 324,635 incident melanoma cases worldwide.³ In 2020, an estimated 57,043 people died from melanoma.⁴ - The highest worldwide incidence of melanoma has been reported for Australia and New Zealand with an estimated ASR for 2020 of 30.5 per 100,000 women and 41.6 per 100,000 men.⁴ - IARC estimated that there were approximately 150,627 incident melanoma cases in the WHO European Region in 2020, making it the 6th most common cancer.⁴ The ASR for melanoma in Europe was 11.4 per 100,000.⁵ The estimated ASR of melanoma for various regions within Europe are:⁵ - Central and Eastern Europe: 5.6 per 100,000 - Northern Europe: 17.8 per 100,000 - Southern Europe: 9.0 per 100,000 - Western Europe: 18.9 per 100,000 The six European countries with the highest estimated age-standardized (world) incidence rates of melanoma (2020) were:⁵ - Denmark: 29.7 per 100,000 - The Netherlands: 27.0 per 100,000 - Norway: 26.4 per 100,000 - Sweden: 23.3 per 100,000

Table 2.1-1: Epidemiologic Characteristics of Metastatic Melanoma

Metastatic Melanoma	
	– Switzerland: 21.6 per 100,000 – Germany: 20.5 per 100,000 • Analyses of US-based cancer registry data (the CDC’s NPCR; NCI’s SEER) estimated the age-adjusted (to 2000 US standard population) incidence of melanoma for 2016 to be 21.8 per 100,000 persons.⁶ The rate varied considerably across race/ethnicity and gender, with highest rates among non-Hispanic white males (34.9 per 100,000), and the lowest among black females (0.9 per 100,000). As of 2019, ASR incidence has shown continued annual increases in US whites (1.7%), the UK (2.7%), Sweden (4.8%), and Norway (4.5%). ASR incidence may have plateaued in Denmark. Rates are declining only in Australia and New Zealand (due to behavioral changes such as reduced use of tanning beds).⁷ Aging populations are likely to offset any decreases due to preventative measures in most of the world.⁸ Note that projections of future incidence rates will depend highly on the standardizing population for this reason.
Prevalence	Prevalence of melanoma, like incidence, varies substantially worldwide. According to GLOBOCAN 2020 data from the IARC, the 1-year and 5-year prevalence estimates for melanoma for Europe were 18.3 and 69.1 per 100,000, respectively.⁵ The approximate 1- and 5-year prevalence estimates for 2020 for melanoma ranged within and across the various regions of Europe as follows:⁵ • Central and Eastern Europe: – 1-year: 8.0 per 100,000 – 5-year: 30.2 per 100,000 • Northern Europe: – 1-year: 29.5 per 100,000 – 5-year: 111.3 per 100,000 • Southern Europe: – 1-year: 13.8 per 100,000 – 5-year: 52.3 per 100,000 • Western Europe: – 1-year: 31.1 per 100,000 – 5-year: 117.4 per 100,000
Demographics of the population: age, gender, racial and/or ethnic origin	Incidence, poorer prognosis, and mortality all increase with increasing age.² Incidence increases in white populations residing at lower latitudes (eg, incidence rates are higher among Australians than among Europeans).
Risk factors for the disease	Risk factors for cutaneous melanoma may be genetic or environmental:^{9,10,11,12,13} • Atypical nevi (moles) are a strong indication for melanoma, but only 20-30% of cases arise in association with a nevus • Skin that is fair, has multiple freckles, and does not tan • History of sunburn, particularly at an early age • Intense, even if intermittent, exposure to ultraviolet radiation

Table 2.1-1: Epidemiologic Characteristics of Metastatic Melanoma

Metastatic Melanoma	
	• Prior melanoma or family history of melanoma • Genetic alterations such as mutation of BRAF or KIT gene or amplification of cyclin D1 or cyclin-dependent kinase 4 gene • Geographic location, particularly latitude
Main treatment options	Although progress has been made over the past decade, treatment of metastatic melanoma continues to represent a considerable unmet medical need. Prior to 2011, approved systemic therapies for the treatment of metastatic melanoma were limited to chemotherapy (dacarbazine) and immunotherapy (IL-2). Checkpoint inhibitors contributed to a change in the treatment landscape for patients with unresectable and metastatic melanoma with the initial approval of ipilimumab in 2011, increasing the median OS for patients from 6-9 months^{14,15,16} to 20 months.¹⁷ Two checkpoint inhibitors (nivolumab and pembrolizumab) targeting the PD-1 pathway have built on the foundation of ipilimumab, extending the median OS to > 30 months and incurring a lower frequency and severity of side effects.^{17,18,19} Further benefit was realized with the addition of ipilimumab to nivolumab, with the combination demonstrating a 5 year OS rate of 52%,¹⁷ and a 6.5 year OS rate of 49% for patients with advanced melanoma.²⁰ However, this was at the expense of increased toxicity, with high grade (Grade 3-4) treatment-related adverse events observed in 59% of those treated with the combination; treatment-related AEs led to discontinuation in 42%.¹⁷ In addition to immunotherapy, treatment options for patients with BRAF mutated melanoma include targeted BRAF/MEK combination therapies. Initially developed as monotherapies, BRAF inhibitors are recommended in combination with MEK inhibitors to delay MAPK-driven acquired resistance resulting in a longer duration of response. Currently available BRAF/MEK combinations include dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib. While these agents are effective in a high proportion of patients with BRAF mutated disease, most patients acquire resistance over time. Recently, approaches to combine targeted therapy with immunotherapy have demonstrated improved PFS and duration of response; however, the impact on OS is not yet known and increased toxicity is observed. While immunotherapy has become a cornerstone of the melanoma treatment armamentarium, there is still a considerable proportion of patients who fail to respond to these therapies or respond but then relapse. There are no standard approaches to treating these patients once they progress after receiving anti-PD-1 therapy. An unmet need therefore exists to improve upon the outcomes of patients treated with anti-PD-1 monotherapy and overcome anti-PD-1 resistance but with a reduced burden of toxicity compared to available combination therapies. This need includes adolescent patients, in whom current therapeutic strategies for adults are applied due to the similarity of disease and a paucity of dedicated clinical trials.
Mortality and morbidity (natural history)	Survival rates for cutaneous melanoma have improved over recent decades, due in part to earlier detection and treatment, and improved the treatments for advanced disease. Five-year relative survival rates have improved in most EU countries, particularly in Eastern Europe.²¹ EUROCARE-5 found a slight improvement from 82% in 1999–2001 to 85% in 2005-2007. The absolute difference in

Table 2.1-1: Epidemiologic Characteristics of Metastatic Melanoma

Metastatic Melanoma	
	survival estimates between 2005–2007 and 1999–2001 ranged from +1% for Northern Europe to +5% for Eastern Europe.²² According IARC the estimated age-standardized 2020 mortality rate for melanoma for Europe was 1.6 per 100,000.⁵ Estimated 2020 ASR mortality rates for melanoma for various regions within Europe were:⁵ • Central and Eastern Europe: 1.7 per 100,000 • Northern Europe: 1.9 per 100,000 • Southern Europe: 1.4 per 100,000 • Western Europe: 1.5 per 100,000 Overall 5-year survival for US patients diagnosed with metastatic melanoma over the 2008-2014 period is estimated to be 98% in early-stage disease, 64% in regional disease, and 22% in stage IV disease.²³ Survival for advance disease was 15% during the 2001-2007 period.²⁴ In Canada, numbers are similar.²⁵ There has been a steep decline in death rates in the US (6.4% per year from 2013-2017) after the introduction of checkpoint inhibitors and targeted therapies for metastatic disease.^{3,26,27}
Important co-morbidities	There are no identified comorbid conditions specifically or more frequently associated with metastatic melanoma compared to the general population. Second primary malignancies that are more common in melanoma survivors are: breast cancer, prostate cancer, and non-Hodgkin lymphoma.^{28,29}

2.2 Nonclinical Part of the Safety Specification

The scope and results of the nonclinical toxicity and exposure studies support the clinical use of nivolumab + relatlimab FDC at the proposed dose and dosing regimen. Risks of inflammatory AEs, and effects on maintenance of pregnancy and infant viability were identified in the relatlimab and/or nivolumab nonclinical program (Table 2.2-1). Excluding clinical observations associated with treatment-emergent ADA observed in 1 animal in a 3-month toxicity study, no relatlimab alone-related findings were observed in standard clinical evaluations of cardiovascular, respiratory, neurologic, and ophthalmologic function conducted in cynomolgus monkeys. When nivolumab and relatlimab were administered in combination, clinical signs of toxicity, related to CNS vasculitis were observed.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
Inflammatory AEs: When nivolumab and relatlimab were administered in combination, inflammatory AEs (CNS vasculitis and epididymitis) were observed.	Increased incidences and severities of inflammatory AEs involving several organ systems have been observed in patients treated with nivolumab, relatlimab, and the combination of the two.
Reproductive Toxicity: The combination of nivolumab and relatlimab was not evaluated for potential reproductive toxicity. However, effects of	The cause of adverse pregnancy outcomes and infant mortality associated with nivolumab administration are unknown as are the clinical implications of these

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

nivolumab on prenatal and postnatal development were investigated in ePPND study in pregnant cynomolgus monkeys. Nivolumab treatment at 10 mg/kg and 50 mg/kg (administered 2QW) dosed from GD 20-22 through parturition was associated with increases in third trimester abortions, stillbirths, and/or death/euthanasia of premature infants. No AEs were observed in surviving offspring through the 6-month evaluation phase. Pregnant mouse studies with surrogate anti-mouse LAG3 antibodies did not identify toxicity associated with blockade of murine LAG-3.	findings. There are no data on the use of nivolumab in pregnant women. Nivolumab + relatlimab FDC is not recommended during pregnancy. WOCBP should use effective contraception if treatment with nivolumab + relatlimab FDC is recommended. It is unknown whether nivolumab and/or relatlimab are excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, nivolumab + relatlimab FDC could be used during breast-feeding if clinically needed.
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2.3 Clinical Trial Exposure

Opdualag™ (nivolumab and relatlimab; BMS-986213) is a FDC drug product that contains nivolumab (BMS-936558) and relatlimab (BMS-986016) co-formulated in the same vial at a protein-mass ratio of 3:1, respectively.

An overview of the clinical program summarized in this RMP supporting the safe and effective use of nivolumab + relatlimab FDC is in [Table 2.3-1](#).

Safety data from CA224047 and CA224020 (Part D1 cohort) are included in [Section 2.7.3.1](#) for the Presentation of the Important Identified and Important Potential Risks. Exposure data from CA224047 and CA224020 (Part D1 cohort) are included in [Appendix 2](#). In CA224020 Part D1 cohort, subjects with unresectable or metastatic melanoma who previously progressed on anti-PD-1 were treated with nivolumab 480 mg + relatlimab 160 mg FDC Q4W, the proposed dosing regimen.

In addition, data from CA224047 and CA224020 Part D1 were pooled and presented in [Section 2.7.3.1](#) and Appendix 2. The pooled data set provides the extent of exposure and safety data for nivolumab + relatlimab FDC in melanoma.

Table 2.3-1: Nivolumab + Relatlimab FDC Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number (Indication)	Study Title	Number Treated Subjects
Nivolumab + Relatlimab FDC (BMS-986213; 480 mg nivolumab + 160 mg relatlimab)		
CA224047 ³⁰ (melanoma)	Adaptive Phase 2/3 randomized, double-blind study of BMS-986213 (FDC vial) vs nivolumab in subjects with previously untreated metastatic or unresectable melanoma.	Nivolumab + relatlimab FDC: 355 Nivo: 359

Table 2.3-1: Nivolumab + Relatlimab FDC Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number (Indication)	Study Title	Number Treated Subjects
CA224020 ³¹ (melanoma)	Phase 1/2a, open-label, multicenter, multidose, dose-escalation and expansion study of anti-LAG-3 mAb (BMS-986016) administered alone and in combination with anti-PD-1 mAb (BMS-936558) or administered as nivolumab + relatlimab FDC (BMS-986213) in advanced solid tumors: (Parts A [dose expansion for Part A1] and B), dose expansion (Part C), dose expansion in melanoma participants who progressed on prior IO therapy (Part D - Part D1 and Part D2), and exposure/response expansion in participants with previously untreated melanoma or who progressed on prior IO (Part E).	Part D1 FDC Cohort (Nivolumab + relatlimab FDC): 82

2.3.1 Nivolumab + relatlimab FDC

Clinical trial exposure analyses for nivolumab + relatlimab FDC individual studies and pooled analyses are provided in [Appendix 2](#).

2.4 Populations Not Studied in Clinical Trials**2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme****Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies**

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Age < 12 years	Initial clinical development of nivolumab + relatlimab limited to adult and adolescent patients.	No	The safety and efficacy of nivolumab/relatlimab in patients < 12 years of age have not been established. The EMA has waived the obligation to conduct studies with nivolumab/relatlimab in patients less than 12 years of age in treatment of melanoma. This patient population is not part of the proposed indication.
Active autoimmune disease	Further immune activation may increase risk of immune-related adverse events.	No	This patient population is addressed in the SmPC (Sections 4.4 and 5.1). There are no proposed risk minimisation activities recommending specific clinical measures, or risk minimisation measures beyond the PI. Increasing evidence suggests immune toxicities are frequent in patients with pre-existing autoimmune disease treated with immune checkpoint inhibition but are most frequently mild and manageable without discontinuing therapy. ^{32,33}

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			Well-established immune-related adverse event management algorithms and guidelines are available globally.
Subjects requiring systemic treatment with immunosuppressants including corticosteroids (≥ 10 mg prednisolone equivalent) before starting nivolumab + relatlimab FDC	Systemic immunosuppressants could interfere with the nivolumab + relatlimab MOA.	No	This patient population is addressed in the SmPC (Sections 4.4 and 5.1). There are no proposed risk minimisation activities recommending specific clinical measures, or risk minimisation measures beyond the PI. Increasing evidence suggests that immunosuppressive therapy to control autoimmune disease has a minimal impact on the efficacy of immune checkpoint inhibitors. ³⁴
History of severe renal and/or hepatic impairment	Baseline impairment may increase risk to patient safety in event of a hepatic or renal AE development.	No	This patient population is addressed in the SmPC (Sections 4.2 and 5.2). As nivolumab + relatlimab FDC is a biologic agent, it is not metabolized by the liver nor cleared by the kidney; in addition, there is no suggestion that the product cross-reacts with components of the kidney. Based on a population pharmacokinetics analyses, no clinically important differences in the clearance of relatlimab were found between patients with mild or moderate renal impairment and patients with normal renal function, nor between patients with mild or moderate hepatic impairment and normal hepatic function. The impact of severe renal and hepatic impairment on the pharmacokinetics of nivolumab and relatlimab is unknown.
History of myocarditis	Cardiac risk for nivolumab + relatlimab FDC was unknown. In the preclinical setting, lethal myocarditis was observed a LAG-3 and PD-1 double knockout mouse model. ³⁵	No	This patient population is addressed in the SmPC (Sections 4.4 and 5.1). Immune-related myocarditis is included in the important identified risk of immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs).
ECOG PS ≥ 2	Potential for higher risk to patient safety with development of AEs in this group	No	This patient population is addressed in the SmPC (Sections 4.4 and 5.1).

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
	compared with lower performance status.		
Pregnant or breastfeeding females	Effect on foetus and nursing baby were unknown.	No	Embryofetal toxicity is included as an important potential risk.
Patients with active or untreated brain or leptomeningeal metastases	Subpopulation with a significantly worse prognosis.	No	This patient population is addressed in the SmPC (Sections 4.4 and 5.1). There are no proposed risk minimisation activities recommending specific clinical measures, nor risk minimisation measures beyond the PI.
Uveal melanoma	Subpopulation with a significantly worse prognosis.	No	This patient population is addressed in the SmPC (Sections 4.4 and 5.1). Based on the improved responses to combination IO therapy compared with single agent checkpoint inhibition observed in clinical practice, ³⁶ uveal melanoma may be responsive to nivolumab + relatlimab FDC. Limited treatment options available for this disease type.

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme for nivolumab + relatlimab FDC is unlikely to detect rare and very rare ARs that may occur with nivolumab + relatlimab FDC exposure. Continuing clinical development and post-marketing safety monitoring will support the identification of new ARs related to nivolumab + relatlimab FDC.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women: Based on animal reproductive studies, nivolumab + relatlimab FDC is not recommended during pregnancy.	No clinical studies conducted
Breastfeeding women: It is unknown whether nivolumab and/or relatlimab are excreted in human milk. Human IgGs are known to be excreted in breast milk	No clinical studies conducted

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period.	
Patients with relevant comorbidities:	
Patients with hepatic impairment	No clinical studies conducted which included patients with AST/ALT > 3x ULN or total bilirubin > 1.5xULN at baseline
Patients with renal impairment	No clinical studies conducted which included patients with serum creatinine > 1.5x ULN or calculated creatinine clearance < 40 mL/min at baseline
Patients with cardiovascular impairment	Not applicable
Immunocompromised patients	No clinical studies conducted
Patients with a disease severity different from inclusion criteria in clinical trials	
• ECOG PS of ≥ 2, uveal melanoma, active or untreated CNS metastases	No clinical studies conducted
Population with relevant different ethnic origin	No clinical studies conducted with nivolumab + relatlimab FDC but ongoing phase 1 CA224034 trial, an open-label multi-dose, dose-escalation safety study of relatlimab with and without nivolumab in adult subjects with advance solid tumors in Japan.
Subpopulations carrying relevant genetic polymorphisms	No clinical studies conducted
Other	
Adolescent patients ≥ 12 years	Adolescent patients ≥ 12 years were permitted to enroll into studies CA224047 and CA224020. Although rare, melanoma in adolescents behaves similarly to the disease in adults,³⁷ and treatment with immune checkpoint inhibition, including nivolumab + relatlimab FDC, is expected to have equivalent risk: benefit in this population. No adolescent patients were enrolled into either the CA224047 or the CA224020 studies.
Paediatric patients ≤ 12 years	A PIP has been agreed with the EMA. The EMA has waived the obligation to conduct studies with nivolumab/relatlimab in patients less than 12 years of age in treatment of melanoma.

2.5 Post-Authorisation Experience

Nivolumab + relatlimab FDC is authorized for marketing in 42 countries/regions for the treatment of unresectable or metastatic melanoma.

2.5.1 Method Used to Calculate Exposure

There is no readily available information on the number of patients treated with marketed nivolumab + relatlimab FDC. However, an estimate of the number of treated patients can be derived from available sales figures. Vendors provide nivolumab + relatlimab FDC sales figures to the Company on a quarterly basis that are generally available 3 months after the close of a calendar quarter. Although these data represent the bulk of the Company's worldwide sales of nivolumab + relatlimab FDC, they are only an estimation of the total quantity of product sold based on the total amount of product distributed in all countries worldwide. The sales data only capture an estimated 80% to 85% of the true total worldwide sales data. Additionally, the sales data from vendors may vary from one reporting period to another because of changes to both the subscription agreements and to the number of data channels available within a given country (eg, direct-to-consumer sales, hospital sales, and home care sales).

2.5.2 Exposure

Considering an estimation of the available sales data and the assumptions, cumulative from the first quarter of 2022 through the fourth quarter of 2024, a total of 144,094 vials of nivolumab + relatlimab FDC have been sold.

Cumulative treated months from the first quarter of 2022 through the fourth quarter of 2024:

$$144,094 \text{ vials sold} \div 2 \text{ vials/patient per treatment cycle} = 72,047 \text{ treated months}$$

The total cumulative, post-marketing patient exposure for nivolumab + relatlimab FDC was estimated to be 19,265 patients. The estimated person-month exposure for nivolumab + relatlimab FDC based on the estimated 19,265 patients cumulatively exposed from the first quarter of 2022 through the second quarter of 2024 is:

$$144,094 \text{ vials sold} \div 19,265 \text{ patients} \div 2 \text{ vials/patient} = 3.74 \text{ person-months}$$

Given the above-mentioned limitations and assumptions, this estimate of the cumulative number of patients treated from the first quarter of 2022 through the fourth quarter of 2024 should be interpreted with caution.

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

Nivolumab + relatlimab FDC is not a controlled substance. It is administered by medical personnel in a hospital or clinic environment. No specific nonclinical or clinical studies have been performed on the effects of the potential for nivolumab + relatlimab for misuse for illegal purposes, enhancing performance, causing dependence, or facilitating assault.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Table 2.7.1-1: Safety Concerns in the Initial RMP

<i>Important identified risks</i>	Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)
<i>Important potential risks</i>	Embryofetal toxicity
<i>Missing information</i>	Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.1-1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)

Immunogenicity - Because both nivolumab and relatlimab contain only human immunoglobulin protein sequences, they have a low risk of inducing immunogenicity or associated infusion or hypersensitivity reactions. The effect of immunogenicity on safety was assessed in the CA224047 study. The occurrence of either nivolumab or relatlimab ADA was low and did not have an effect on the safety of the regimens. Most of the hypersensitivity/infusion reactions occurred after the first dose, were transient, and independent of ADA status. None of the relatlimab ADA positive subjects had hypersensitivity/infusion reactions. Among those positive for nivolumab ADA, there were only 1 and 2 subjects with hypersensitivity/infusion reactions in the nivolumab + relatlimab FDC and nivolumab monotherapy arms, respectively.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated

None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised)

Severe infusion reactions - Among the drug-related select AEs, hypersensitivity/ infusion-related reactions were of low frequency, with less than a 2.3% difference in any grade events (6.8% vs 4.5% in the nivolumab + relatlimab FDC arm and nivolumab monotherapy arms, respectively).

The events were manageable with no high grade or serious hypersensitivity/ infusion-related reactions in the nivolumab + relatlimab FDC arm, compared with 0.3% high grade events in the nivolumab monotherapy arm. The two infusion reaction events that led to discontinuation were in the nivolumab arm, with no infusion reaction events leading to discontinuation of treatment with nivolumab + relatlimab FDC. Management guidance for infusion related reactions are addressed in the SmPC. Healthcare professionals are aware of the risk of severe infusion reactions and will have the appropriate measures in place as part of clinical practice.

No clinically meaningful differences in the frequency of hypersensitivity/infusion-related are expected when nivolumab + relatlimab FDC is administered over a 30 minute infusion compared with the 60 minute infusion. This is supported by lack of associations between dose and hypersensitivity or infusion or hypersensitivity

Table 2.7.1.1-1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

reactions, higher studied infusion rates (up to 1440 mg over 60 minutes) and predicted equivalent PK profiles of nivolumab and relatlimab following 30- and 60-minute infusion.
Known risks that do not impact the risk-benefit profile
None
Other reasons for considering the risks not important
None

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Important identified risks	
Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)	The most clinically significant treatment-related ARs associated with nivolumab + relatlimab FDC are irARs, which are inflammatory in nature. Severe irARs are of low frequency, can be serious and life-threatening. Prompt recognition of signs and symptoms and implementation of the recommended management guidelines may prevent serious complications.
Important potential risks	
Embryofetal toxicity	Preclinical results of studies with nivolumab suggest potential risk of third trimester fetal loss and premature birth with increased neonatal mortality. Therefore, nivolumab + relatlimab FDC is not recommended during pregnancy and in WOCBP not using effective contraception unless the clinical benefit outweighs the potential risk.
Missing Information	
Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age	The effects of nivolumab + relatlimab FDC in adolescent patients greater than 12 years of age or older are not known. Although rare, melanoma in adolescents behaves similarly to the disease in adults, ³⁴ and treatment with immune checkpoint inhibition, including nivolumab + relatlimab FDC, is expected to have equivalent risk: benefit in this population. Long term safety follow-up of Grade 3-4 AEs (including irARs) experienced by paediatric patients, their management, and outcome are to be evaluated. Immune related endocrinopathies that can affect the pituitary gland and hormones important for growth and development (eg. growth hormone - stature/appearance, TSH - metabolic homeostasis, gonadotropin hormones - reproductive organ function) are of particular importance.

2.7.2 ***New Safety Concerns and Reclassification with a Submission of an Updated RMP***

Not applicable.

2.7.3 ***Details of Important Identified Risks, Important Potential Risks, and Missing Information***

The important identified and potential risks as well as missing information are listed below.

Important Identified Risks

- Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

Important Potential Risks

- Embryofetal toxicity

Missing Information

- Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age

2.7.3.1 ***Presentation of Important Identified and Important Potential Risks***

Table 2.7.3.1-1: Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)	
Potential mechanisms	Relatlimab is a human IgG4 mAb that binds to the T cell LAG-3 receptor and releases the LAG-3 mediated inhibition of immune response by blocking interaction with its ligands. By blocking the downregulatory pathway of T cells, 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 IO mAbs; however, T cell upregulation may also result in immune related AEs.
Evidence source and strength of evidence	Pneumonitis Immune-related pneumonitis or ILD cases were observed with nivolumab + relatlimab FDC. The majority of cases reported were Grade 1-2. Severe (Grade 3-4) cases were more common with nivolumab + relatlimab FDC than with nivolumab monotherapy. One fatal case of pneumonitis was reported with nivolumab + relatlimab FDC.³⁰ Severe pneumonitis can be life-threatening if not diagnosed early and managed appropriately. Colitis Immune-related colitis cases were observed with nivolumab + relatlimab FDC. The majority of subjects had mild to moderate (Grade 1-2) diarrhoea or colitis. Severe diarrhoea or colitis (Grade 3-4) cases were more common with nivolumab + relatlimab FDC than with nivolumab monotherapy. Diarrhoea/colitis was manageable using the established management guidelines. The majority of cases resolved with drug interruption and/or, immunosuppressive therapy. Severe or persistent diarrhoea and colitis can be life-threatening if not recognized early and managed appropriately.

Table 2.7.3.1-1: Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

Hepatitis

Immune-related hepatitis cases were observed with nivolumab + relatlimab FDC. The majority of cases reported were Grade 1-2. Severe (Grade 3-4) cases were more common with nivolumab + relatlimab FDC than with nivolumab monotherapy. Subjects may be also asymptomatic. In clinical studies, hepatotoxicities manifesting as transaminase elevations was the most frequently observed hepatic AE and was detectable with liver function testing and signs and symptoms monitoring. Immune-related hepatitis can be serious or life-threatening and even fatal if not treated promptly. Subjects with immune-related hepatitis are generally managed clinically with steroid therapy or other immunosuppressants with resolution of the event. Prompt review of blood tests, recognition of signs and symptoms, and implementation of the recommended management guidelines may prevent serious complications.

Endocrinopathies

Immune-related endocrinopathies have been observed with nivolumab + relatlimab FDC and thyroid disorders, adrenal disorders, pituitary disorders were more common with nivolumab and relatlimab FDC than with nivolumab monotherapy. The most common thyroid disorders were hypothyroidism and hyperthyroidism, however, no severe (Grade 3-4) thyroid disorders were reported. Severe (Grade 3-4) adrenal, pituitary and diabetes cases have been observed but all at low frequency.

Patients are typically well-managed with hormone replacement and/or steroid treatment. Lifelong hormone replacement may be required. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may prevent serious complications.

Nephritis and renal dysfunction

Immune-related nephritis and renal dysfunction have been observed with nivolumab + relatlimab FDC. Most cases were Grade 1-2. Severe nephritis and renal dysfunction cases were more common with nivolumab + relatlimab FDC than with nivolumab monotherapy. Immune-related nephritis and renal dysfunction can be serious or life-threatening. Subjects with immune-related nephritis and renal dysfunction are generally managed clinically with steroid therapy with resolution of the event. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may prevent serious complications.

Skin ARs

Immune-related skin ARs have been observed with nivolumab + relatlimab FDC. Skin immune-related reactions were higher for nivolumab + relatlimab FDC than with nivolumab monotherapy with the majority being mild to moderate (Grade 1-2). The severe (Grade 3-4) immune related skin ARs (rash) were of low frequency with nivolumab + relatlimab FDC and nivolumab monotherapy. Cases of SJS and TEN, some of them with fatal outcome, have been reported with nivolumab + relatlimab FDC. Early detection and timely treatment are key to recovery and to prevent severe complications.

Myocarditis

Myocarditis was observed with a low frequency in patients treated with nivolumab + relatlimab FDC, and the majority of cases were mild to moderate (Grade 1-2). Severe myocarditis was also observed, however, all cases in patients receiving nivolumab +

Table 2.7.3.1-1: Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

relatlimab FDC were manageable within established irAR management practices and resolved. Myocarditis can be life-threatening if not managed appropriately.

Some asymptomatic cases of myocarditis were detected through troponin lab monitoring in patients receiving nivolumab + relatlimab, however, troponin is a sensitive, but non-specific, marker of cardiac pathology and myocarditis accounted for a minority of the troponin elevation events observed within the study, most of which required no immunosuppression. The risk of immune-mediated myocarditis with IO agents is now well-recognised among clinical practitioners, and guidelines for IO toxicity management including myocarditis are available globally. Careful patient follow-up, a high index of suspicion, and management according to well-established IO treatment algorithms are appropriate to detect myocarditis and prevent poor outcomes.

Other irARs

Selected other irARs, which are considered important identified risks, include uveitis, pancreatitis, Guillain-Barre syndrome, myositis/ rhabdomyolysis, MG, Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome, encephalitis, hemolytic anemia,³⁰ VKH, HLH³⁰ were observed with nivolumab + relatlimab FDC.

Additionally, gastritis has been reported with nivolumab + relatlimab FDC.

The following clinically significant irARs have been reported with nivolumab monotherapy or nivolumab in combination with other approved agents: demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenic syndrome, aseptic meningitis, sarcoidosis, duodenitis, hypoparathyroidism, and cystitis noninfective.

Solid organ transplant rejection has been reported in the post marketing setting in patients treated with PD-1 inhibitors.

In patients treated with nivolumab before or after allogeneic HSCT, rapid onset and severe GVHD, some with fatal outcome, have been reported.

Severe (Grade 3-4) other irARs were reported in minority of patients. Other irARs can be serious and life threatening. Patients are usually clinically managed with steroids/other immunosuppressants and the events generally resolved.

The majority of cases for uveitis or pancreatitis were not severe, therefore, not considered to be standalone risks. The frequency for uveitis and pancreatitis was similar between the nivolumab + relatlimab FDC and nivolumab monotherapy arms.

Table 2.7.3.1-1: Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

Characterization of risk (Percent; All Treated)

Pneumonitis

I. Nivolumab + Relatlimab FDC

Melanoma	Nivolumab + Relatlimab FDC	Nivolumab mono	DIFF (95% CI)
CA224047			
Any Grade	5.1	2.8	2.3 (-0.97, 5.54)
Grade 3-4	0.8	0.3	0.6 (-0.69, 1.82)

Melanoma Nivolumab + Relatlimab FDC

CA224020			
Any Grade		4.9	
Grade 3-4		0	

Pooled BMS-986213 studies (N = 437) (CA224047 and CA224020)

- Any Grade: 5.0%
- Grade 3-4: 0.7%
- Grade 5: 0

Colitis

I. Nivolumab + Relatlimab FDC

Melanoma	Nivolumab + Relatlimab FDC	Nivolumab mono	DIFF (95% CI)
CA224047			
Any Grade	15.8	10.3	5.5 (-0.17, 11.10)
Grade 3-4	2.0	0.6	1.4 (-0.46, 3.29)

Melanoma Nivolumab + Relatlimab FDC

CA224020			
Any Grade		9.8	
Grade 3-4		3.7	

Pooled BMS-986213 studies (N = 437) (CA224047 and CA224020)

- Any Grade: 14.6%
- Grade 3-4: 2.3%
- Grade 5: 0

Hepatitis

I. Nivolumab + Relatlimab FDC

Melanoma	Nivolumab + Relatlimab FDC	Nivolumab mono	DIFF (95% CI)
CA224047			
Any Grade	13.2	9.2	4.0 (-1.24, 9.33)

Table 2.7.3.1-1: Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)**Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)**

Grade 3-4	3.9	1.7	2.3 (-0.50 , 5.04)
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Melanoma	Nivolumab + Relatlimab FDC
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CA224020

Any Grade	6.1
Grade 3-4	1.2

Pooled BMS-986213 studies (N = 437) (CA224047 and CA224020)

- Any Grade: 11.9%
- Grade 3-4: 3.4%
- Grade 5: 0

Endocrinopathies**I. Nivolumab + Relatlimab FDC**

Melanoma	Nivolumab + Relatlimab FDC	Nivolumab mono	DIFF (95% CI)
CA224047			
Any Grade	26.5	20.9	5.6 (-1.53 , 12.71)
<i>(nivolumab + relatlimab FDC: thyroid disorder 20.8%, adrenal disorder 4.8%, pituitary disorder 2.5%, and diabetes 0.3%)</i>			
Grade 3-4	2.0	0.8	1.1 (-0.84 , 3.11)
<i>(nivolumab + relatlimab FDC: adrenal disorder 1.4%, diabetes 0.3%, and pituitary disorder 0.3%)</i>			

Melanoma	Nivolumab + Relatlimab FDC
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CA224020

Any Grade	13.4
<i>(nivolumab + relatlimab FDC: thyroid disorder 11.0%, pituitary disorder 2.4%, adrenal disorder 1.2%, and diabetes 1.2%)</i>	
Grade 3-4	2.4
<i>(nivolumab + relatlimab FDC: pituitary disorder 2.4%, and diabetes 1.2%)</i>	

Pooled BMS-986213 studies (N = 437) (CA224047 and CA224020)

- Any Grade: 24.0%
 - *(thyroid disorder 19.0%, adrenal disorder 4.1%, pituitary disorder 2.5%, and diabetes 0.5%)*
- Grade 3-4: 2.1%
 - *(adrenal disorder 1.1%, pituitary disorder 0.7%, and diabetes 0.5%)*
- Grade 5: 0

Table 2.7.3.1-1: Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)**Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)****Nephritis and renal dysfunction****I. Nivolumab + Relatlimab FDC**

Melanoma	Nivolumab + Relatlimab FDC	Nivolumab mono	DIFF (95% CI)
CA224047			
Any Grade	4.5	1.7	2.8 (-0.06 , 5.73)
Grade 3-4	1.4	0.3	1.1 (-0.40, 2.66)

Melanoma	Nivolumab + Relatlimab FDC
CA224020	
Any Grade	2.4
Grade 3-4	0

Pooled BMS-986213 studies (N = 437) (CA224047 and CA224020)

- Any Grade: 4.1%
- Grade 3-4: 1.1%
- Grade 5: 0

Skin ARs**I. Nivolumab + Relatlimab FDC**

Melanoma	Nivolumab + Relatlimab FDC	Nivolumab mono	DIFF (95% CI)
CA224047			
Any Grade	45.1	36.8	8.3 (0.08 , 16.52)
Grade 3-4	1.4	1.9	-0.5 (-2.70 , 1.61)

Melanoma	Nivolumab + Relatlimab FDC
CA224020	
Any Grade	26.8
Grade 3-4	1.2

Pooled BMS-986213 studies (N = 437) (CA224047 and CA224020)

- Any Grade: 41.6%
- Grade 3-4: 1.4%
- Grade 5: 0

Myocarditis**I. Nivolumab + Relatlimab FDC**

Melanoma	Nivolumab + Relatlimab FDC	Nivolumab mono	DIFF (95% CI)
CA224047			

Table 2.7.3.1-1: Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)			
Any Grade	1.4	0.6	0.9 (-0.80, 2.51)
Grade 3-4	0.6	0	0.6 (-0.33, 1.45)

Melanoma	Nivolumab + Relatlimab FDC
CA224020	
Any Grade	0
Grade 3-4	0

Pooled BMS-986213 studies (N = 437) (CA224047 and CA224020)

- Any Grade: 1.1%
- Grade 3-4: 0.5%
- Grade 5: 0

Other irARs

I. Nivolumab + Relatlimab FDC

Melanoma	Nivolumab + Relatlimab FDC	Nivolumab mono
CA224047		
Any Grade		
Guillain-Barre syndrome	0.3	0
Pancreatitis	1.4	1.1
Uveitis	1.7	1.4
Encephalitis	0.6	0.6
Myositis/Rhabdomyolysis	0.6	0
Grade 3-4		
Guillain-Barre syndrome	0	0
Pancreatitis	0	0.3
Uveitis	0.3	0.6
Encephalitis	0.6	0.6
Myositis/Rhabdomyolysis	0.3	0

Myocarditis is presented above under Myocarditis.

Melanoma	Nivolumab + Relatlimab FDC (Part D1)
CA224020	
Any Grade	
Guillain-Barre syndrome	0
Pancreatitis	0
Uveitis	0
Encephalitis	1.2

Table 2.7.3.1-1: Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)	
Myositis/Rhabdomyolysis	0
Grade 3-4	
Guillain-Barre syndrome	0
Pancreatitis	0
Uveitis	0
Encephalitis	1.2
Myositis/Rhabdomyolysis	0

Myocarditis is presented above under Myocarditis.

Pooled BMS-986213 studies (N = 437) (CA224047 and CA224020)

Nivolumab + Relatlimab FDC	
Any Grade	
Guillain-Barre syndrome	0.2
Pancreatitis	1.1
Uveitis	1.4
Encephalitis	0.7
Myositis/Rhabdomyolysis	0.5
Grade 3 - 4	
Guillain-Barre syndrome	0
Pancreatitis	0
Uveitis	0.2
Encephalitis	0.7
Myositis/Rhabdomyolysis	0.2
Grade 5	0

Myocarditis is presented above under Myocarditis.

Risk factors and risk groups

Pneumonitis

Risk factors for ILD include older age, reduced lung function, smoking history, concomitant or previous lung infection,^{38,39} previous radiotherapy or chemotherapy, and pulmonary resection.

Colitis

Patients with active inflammatory bowel disease.

Hepatitis

Active autoimmune hepatitis.

Endocrinopathies

Active autoimmune diseases of the endocrine glands.

Nephritis and renal dysfunction

Active autoimmune diseases with potential for renal involvement.

Table 2.7.3.1-1: Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

Important Identified Risk: Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)	
	Skin ARs Active autoimmune skin disorders. Myocarditis The risks are unknown. Other irARs Active autoimmune diseases.
Preventability	In the event of immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis, and other irARs), prompt recognition of signs and symptoms and implementation of the recommended management guidelines may prevent serious complications. Monitor patients for signs and symptoms of irARs. Refer to Section 5.2 for additional risk minimisation measures.
Impact on the risk-benefit balance of the product	Nivolumab + relatlimab FDC can increase the risk of immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis, and other irARs). Early recognition and appropriate management are important to prevent more severe complications and ensure the benefits of the medicine continue to outweigh the risks. An additional educational material is intended to ensure that patients are aware of these risks.
Public health impact	For nivolumab + relatlimab FDC, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids/other immunosuppressants as outlined in the SmPC.
MedDRA terms	See Annex 7

Table 2.7.3.1-2: Important Potential Risk: Embryofetal Toxicity

Important Potential Risk: Embryofetal Toxicity	
Potential mechanisms	Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to increase foetal loss.
Evidence source and strength of evidence	Effective contraception should be used for WOCBP during nivolumab + relatlimab FDC clinical trials and post-marketing. Nivolumab + relatlimab FDC has not been evaluated in pregnant monkeys; however, preclinical data suggests potential risk of third trimester fetal loss and premature birth with increased neonatal mortality if exposed to nivolumab during pregnancy. Based on the MOA, potential risks of nivolumab and relatlimab during pregnancy include increased rates of abortion and stillbirth.
Characterization of risk (Percent; All Treated)	None
Risk factors and risk groups	Exposure during pregnancy.

Table 2.7.3.1-2: Important Potential Risk: Embryofetal Toxicity

Important Potential Risk: Embryofetal Toxicity	
Preventability	Preventable with contraception.
Impact on the risk-benefit balance of the product	Dosing during pregnancy is not recommended. WOCBP receiving nivolumab + relatlimab FDC should use effective contraception for a period of at least 5 months after the last dose of nivolumab + relatlimab FDC.
Public health impact	None
MedDRA terms	See Annex 7

2.7.3.2 Presentation of the Missing Information

Table 2.7.3.2-1: Missing Information

Missing Information	Evidence Source
Population in need of further characterisation:	
Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age	The long term effects of nivolumab + relatlimab FDC in adolescent patients greater than 12 years of age or older are not known. A PIP has been agreed with the EMA

2.8 Summary of the Safety Concerns

Table 2.8-1: Summary of Safety Concerns

Important identified risks	Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)
Important potential risks	Embryofetal toxicity
Missing information	Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age

3 PART III: PHARMACOVIGILANCE PLAN

The PV plan provides details of PV activities/studies that are intended to proactively identify and/or characterize safety concerns and will inform risk mitigation strategies for the important and potential risks.

3.1 Routine Pharmacovigilance Activities

There are no routine PV activities beyond adverse reaction reporting and signal detection.

3.2 Additional Pharmacovigilance Activities

A summary of Category 1-3 safety study protocols/activities in the nivolumab + relatlimab FDC PV plan is provided in [Table 3.2-1](#). A summary of all PV study protocols in the PV programme is provided in [Annex 2](#).

Table 3.2-1: Post-Authorisation Safety Studies Short Name Summary

Study short name and title	Rationale and study objectives	Study design	Study population	Milestone(s)	Due Date(s)
CA224122: Long-term follow-up of paediatric patients exposed to nivolumab + relatlimab FDC in the DMTR. Voluntary PASS Category 3	Rationale: Patients are followed long-term to assess survival. The primary objective is to evaluate Grade 3-4 AEs (which includes irARs) experienced by paediatric patients, their management, and outcome. Secondary objectives include evaluating long-term outcomes (with emphasis on growth and development).	Observational, national, retrospective study.	Paediatric patients ≥ 12 to < 18 years of age treated with nivolumab + relatlimab FDC for advanced (unresectable or metastatic) melanoma.	1. Protocol synopsis submission	13-Sep-2021
				2. Full Protocol submission	2Q2023
				3. Interim reports ^a	1Q2029 1Q2032 1Q2035 1Q2038
				4. Final report ^a	1Q2041

^a Milestone(s) due dates are based on the anticipated reimbursement approval for the nivolumab + relatlimab FDC in the Netherlands.

3.3 Summary Table of Additional Pharmacovigilance Activities

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CA224122: Long-term follow-up of paediatric patients exposed to nivolumab + relatlimab FDC in the DMTR. Planned Voluntary PASS	The primary objective is to evaluate Grades 3-4 AEs (which includes irARs) experienced by paediatric patients ≥ 12 to < 18 years of age, along with their management, and outcome. Secondary objectives include evaluating long-term outcomes (with emphasis on growth and development).	Long term safety (including growth and development disorders) in paediatric patients ≥ 12 to < 18 years of age. Use in these patients is part of the proposed on-label indication for Opdualag but there is no data from clinical development in this patient population.	1. Protocol synopsis submission	13-Sep-2021
			2. Full Protocol submission	2Q2023
			3. Interim reports ^a	1Q2029 1Q2032 1Q2035 1Q2038
			4. Final report ^a	1Q2041

^a Milestone(s) due dates are based on the anticipated reimbursement approval for the nivolumab + relatlimab FDC in the Netherlands.

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned or ongoing post-authorisation efficacy studies.

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

5.1 Routine Risk Minimisation Measures

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)	Routine risk communication: The SmPC warns of the risks of irARs in Sections 4.4 and 4.8. In addition, the package leaflet also includes specific warnings and descriptions of the most important irARs in the language suitable for patients. Routine risk minimisation activities recommending specific clinical measures to address the risk: Specific guidance on monitoring and management, including treatment delay or discontinuation and intervention with corticosteroids or other immunosuppressive therapy, are provided in SmPC Sections 4.2, 4.4 and 4.8, as appropriate. Other routine risk minimisation measures beyond the Product Information: None
Embryofetal toxicity	Routine risk communication: SmPC includes embryofetal toxicity in Sections 4.6 and 5.3. In addition, the package leaflet also includes warnings that nivolumab + relatlimab FDC could harm an unborn baby and relevant advice regarding contraception for patients. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age	Routine risk communication: The SmPC includes information for the paediatric population in Section 4.2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None

5.2 Additional Risk Minimisation Measures

Details of proposed additional risk minimisation measures are provided in [Annex 6](#).

Table 5.2-1: Additional Risk Minimisation Measures

Additional Risk Minimisation:	Objectives/Rational:
Educational Material Patient Card	Objectives: To further raise awareness of patients on signs and symptoms of important risks of irARs. Rationale for the additional risk minimisation measure: This communication tool will provide the opportunity for reinforcing the key messages to ensure early recognition and appropriate management of important identified risks of irARs to maintain favorable benefit/risk of nivolumab + relatlimab FDC in market use. Target audience and planned distribution path: Patients via healthcare professionals. Plans to evaluate the effectiveness of the interventions and criteria for success: Routine PV activities will provide information on any changes in the occurrence, severity, and outcome of important identified risks as it relates to the established safety profile, and will be reported in future regulatory safety reports (eg, PBRERs/PSURs).

5.3 Summary of Risk Minimisation Measures

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 Package Leaflet Section 2 Additional risk minimisation measures: Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Embryofetal toxicity	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3 Package Leaflet Section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age	Routine risk minimisation measures: SmPC Section 4.2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS CA224122

6 SUMMARY OF THE RISK MANAGEMENT PLAN

This is a summary of the risk management plan (RMP) for Opdualag (nivolumab + relatlimab FDC). The RMP details important risks of Opdualag, how these risks can be minimised, and how more information will be obtained about Opdualag's risks and uncertainties (missing information).

Opdualag's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Opdualag should be used.

This summary of the RMP for Opdualag should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Opdualag's RMP.

I. The medicine and what it is used for

Opdualag is authorised for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older (see SmPC for the full indication). It contains nivolumab and relatlimab as the active substances as part of a FDC and it is given by intravenous infusion. Further information about the evaluation of Opdualag's benefits can be found in Opdualag's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: <https://www.ema.europa.eu/en/medicines/what-we-publishwhen/european-public-assessment-reports-background-context>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Opdualag, together with measures to minimise such risks and the proposed studies for learning more about Opdualag's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In the case of Opdualag, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Opdualag is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Opdualag are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Opdualag. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

<i>Important identified risks</i>	Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)
<i>Important potential risks</i>	Embryofetal toxicity
<i>Missing information</i>	Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age

II.B Summary of important risks

Important identified risks

Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

Evidence for linking the risk to the medicine	Pneumonitis
	Immune-related pneumonitis or interstitial lung disease (ILD) cases were observed with nivolumab + relatlimab FDC. The majority of cases reported were Grade 1-2. Severe (Grade 3-4) cases were more common with nivolumab + relatlimab FDC than with nivolumab monotherapy. One fatal case of pneumonitis was reported with nivolumab + relatlimab FDC. Severe pneumonitis can be life-threatening if not diagnosed early and managed appropriately.
	Colitis
	Immune-related colitis cases were observed with nivolumab + relatlimab FDC. The majority of subjects had mild to moderate (Grade 1-2) diarrhoea or colitis. Severe diarrhoea or colitis (Grade 3-4) cases were more common with nivolumab + relatlimab FDC than with nivolumab monotherapy. Diarrhoea/colitis was manageable using the established management guidelines. The majority of cases resolved with drug interruption and/or, immunosuppressive therapy. Severe or persistent diarrhoea and colitis can be life-threatening if not recognized early and managed appropriately.
	Hepatitis
	Immune-related hepatitis cases were observed with nivolumab + relatlimab FDC. The majority of cases reported were Grade 1-2. Severe (Grade 3-4) cases were more common with nivolumab + relatlimab FDC than with nivolumab monotherapy. Subjects may be also asymptomatic. In clinical studies, hepatotoxicities manifesting as transaminase elevations was the most frequently

Important identified risks

Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

observed AE and was detectable with liver function testing and signs and symptoms monitoring. Immune-related hepatitis can be serious or life-threatening and even fatal if not treated promptly. Subjects with immune-related hepatitis are generally managed clinically with steroid therapy or other immunosuppressants with resolution of the event. Prompt review of blood tests, recognition of signs and symptoms, and implementation of the recommended management guidelines may prevent serious complications.

Endocrinopathies

Immune-related endocrinopathies have been observed with nivolumab + relatlimab FDC and thyroid disorders, adrenal disorders, pituitary disorders were more common with nivolumab and relatlimab FDC than with nivolumab monotherapy. The most common thyroid disorders were hypothyroidism and hyperthyroidism, however, no severe (Grade 3-4) thyroid disorders were reported. Severe (Grade 3-4) adrenal, pituitary and diabetes cases have been observed but all at low frequency.

Patients are typically well-managed with hormone replacement and/or steroid treatment. Lifelong hormone replacement may be required. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may prevent serious complications.

Nephritis and renal dysfunction

Immune-related nephritis and renal dysfunction have been observed with nivolumab + relatlimab FDC. Most cases were Grade 1-2. Severe nephritis and renal dysfunction cases were more common with nivolumab + relatlimab FDC than with nivolumab monotherapy. Immune-related nephritis and renal dysfunction can be serious or life-threatening. Subjects with immune-related nephritis and renal dysfunction are generally managed clinically with steroid therapy with resolution of the event. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may prevent serious complications.

Skin ARs

Immune-related skin ARs have been observed with nivolumab + relatlimab FDC. Skin immune-related reactions were higher for nivolumab + relatlimab FDC than with nivolumab monotherapy with the majority being mild to moderate (Grade 1-2). The severe (Grade 3-4) immune related skin ARs (rash) were of low frequency with nivolumab + relatlimab FDC and nivolumab monotherapy. Cases of SJS and TEN, some of them with fatal outcome, have been reported with nivolumab + relatlimab FDC. Early detection and timely treatment are key to recovery and to prevent severe complications.

Myocarditis

Myocarditis was observed with a low frequency in patients treated with nivolumab + relatlimab FDC, and the majority of cases were mild to moderate (Grade 1-2). Severe myocarditis was also observed, however, all cases in patients receiving nivolumab + relatlimab FDC were manageable within established irAR management practices and resolved. Myocarditis can be life-threatening if not managed appropriately.

Some asymptomatic cases of myocarditis were detected through troponin lab monitoring in patients receiving nivolumab + relatlimab, however, troponin is a sensitive, but non-specific, marker of cardiac pathology and myocarditis accounted for a minority of the troponin elevation events observed within the study, most of which required no immunosuppression. The risk of immune-mediated myocarditis with IO agents is now well-recognised among clinical practitioners, and guidelines for IO toxicity management including myocarditis are available globally. Careful patient follow-up, a high index of suspicion, and management according to well-

Important identified risks

Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

established IO treatment algorithms are appropriate to detect myocarditis and prevent poor outcomes.

Other irARs

Selected other irARs, which are considered important identified risks, include uveitis, pancreatitis, Guillain-Barre syndrome, myositis/ rhabdomyolysis, myasthenia gravis (MG), Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome, encephalitis, hemolytic anemia, Vogt Koyanagi-Harada syndrome (VKH), hemophagocytic lymphohistiocytosis (HLH) were observed with nivolumab + relatlimab FDC.

Additionally, gastritis has been reported with nivolumab + relatlimab FDC.

The following clinically significant irARs have been reported with nivolumab monotherapy or nivolumab in combination with other approved agents: demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenic syndrome, aseptic meningitis, sarcoidosis, duodenitis, hypoparathyroidism, and cystitis noninfective.

Solid organ transplant rejection has been reported in the post marketing setting in patients treated with PD 1 inhibitors.

In patients treated with nivolumab before or after allogeneic HSCT, rapid onset and severe graft versus host disease (GVHD), some with fatal outcome, have been reported.

Severe (Grade 3-4) other irARs were reported in minority of patients. Other irARs can be serious and life threatening. Patients are usually clinically managed with steroids/other immunosuppressants and the events generally resolved.

The majority of cases for uveitis or pancreatitis were not severe, therefore, not considered to be standalone risks. The frequency for uveitis and pancreatitis was similar between the nivolumab + relatlimab FDC and nivolumab monotherapy arms.

Risk factors
and risk
groups

Pneumonitis

Risk factors for ILD include older age, reduced lung function, smoking history, concomitant or previous lung infection, previous radiotherapy or chemotherapy, and pulmonary resection.

Colitis

Patients with active inflammatory bowel disease.

Hepatitis

Active autoimmune hepatitis.

Endocrinopathies

Active autoimmune diseases of the endocrine glands.

Nephritis and renal dysfunction

Active autoimmune diseases with potential for renal involvement.

Skin ARs

Active autoimmune skin disorders.

Myocarditis

The risks are unknown.

Other irARs

Active autoimmune diseases.

Risk
minimisation
measures

Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8; Package Leaflet Section 2

Additional risk minimisation measures: Patient Card

Important identified risks

Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)

Additional PV activities	None See section II.C of this summary for an overview of the post-authorisation development plan.
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Important potential risks

Embryofetal toxicity

Evidence for linking the risk to the medicine	Effective contraception should be used for women of childbearing potential (WOCBP) during nivolumab + relatlimab FDC clinical trials and post-marketing. Nivolumab + relatlimab FDC has not been evaluated in pregnant monkeys; however, preclinical data suggests potential risk of third trimester fetal loss and premature birth with increased neonatal mortality if exposed to nivolumab during pregnancy. Based on the mechanism of action, potential risks of nivolumab + relatlimab during pregnancy include increased rates of abortion and stillbirth.
Risk factors and risk groups	Exposure during pregnancy.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3; Package Leaflet Section 2 Additional risk minimisation measures: None
Additional PV activities	None See section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information

Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2. Additional risk minimisation measures: None
Additional PV activities	PASS CA224122 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Opdualag.

II.C.2 Other studies in post-authorisation development plan

Category 3 planned additional pharmacovigilance activities

Study short name and title	Rationale and study objectives
CA224122: Long-term follow-up of paediatric patients exposed to nivolumab + relatlimab FDC in the DMTR. Planned	The primary objective is to evaluate Grades 3-4 AEs (which includes irARs) experienced by paediatric patients ≥ 12 to < 18 years of age, along with their management, and outcome. Secondary objectives include evaluating long-term outcomes (with emphasis on growth and development). Long term safety (including growth and development disorders) in paediatric patients ≥ 12 to < 18 years of age. Use in these patients is part of the proposed on-label indication for Opdualag but there is no data from clinical development in this patient population.

APPENDIX 2: CLINICAL TRIAL EXPOSURE TABLES

1 NIVOLUMAB + RELATLIMAB FDC

Clinical trial exposure analyses include cumulative dose and clinical exposure by duration, age, sex, and racial origin from Study CA224047 and CA224020 (Part D1 Cohort). In CA224020 Part D1 cohort, subjects with unresectable or metastatic melanoma who previously progressed on anti-PD-1 were treated with nivolumab 480 mg + relatlimab 160 mg FDC Q4W, the proposed dosing regimen.

For nivolumab + relatlimab FDC, individual and pooled clinical trial exposure analyses are presented in the following tables. The pooled data set provides the extent of exposure for nivolumab + relatlimab FDC in melanoma.

- [Table 1-1](#) through [Table 1-4](#) for CA224047, CA224020 (Part D1 Cohort) and pooled analyses (melanoma)

Table 1-1: Clinical Exposure in Person Time; BMS-986213 All Treated Subjects, CA224047 and CA224020 and Pooled

Duration of Exposure (Months)	BMS-986213: CA224047 N = 355		BMS-986213: CA224020 N = 82		Pooled BMS-986213 CA224047 and CA224020 N = 437	
	Persons (%)	Person Time of Exposure (1) (Months)	Persons (%)	Person Time of Exposure (1) (Months)	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 3	85 (23.9)		22 (26.8)		107 (24.5)	
0 - < 6	150 (42.3)		50 (61.0)		200 (45.8)	
0 - < 9	175 (49.3)		58 (70.7)		233 (53.3)	
0 - < 12	205 (57.7)		62 (75.6)		267 (61.1)	
0 - < 18	265 (74.6)		67 (81.7)		332 (76.0)	
0 - < 24	308 (86.8)		76 (92.7)		384 (87.9)	
0 - < 30	322 (90.7)		82 (100)		404 (92.4)	
0 - < 36	348 (98.0)		82 (100)		430 (98.4)	
0 - ≤ 28.55 (A)			82 (100)	703.96		
0 - ≤ 39.06 (A)	355 (100)	4219.21			437 (100)	4923.17

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.

(A) Max clinical exposure

Analyses are limited to subjects who received BMS986-213 FDC 160mg/480mg.

Study CA224020 data are from 25FEB2021 database lock.

Study CA224047 data are from 28OCT2021 database lock.

Program Source: BMS_GBS\CA224\DZA72884\Biostatistics\Production\Tables\EBR38\rt-ex-pt-durtrt.sas

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Table 1-2: Cumulative Dose of BMS-986213; BMS-986213 All Treated Subjects, CA224047 and CA224020 and Pooled

	BMS-986213: CA224047 N = 355	BMS-986213: CA224020 N = 82	Pooled BMS-986213 CA224047 and CA224020 N = 437
NUMBER OF DOSES RECEIVED/ SUBJECT			
MEAN (SD)	12.3 (10.71)	8.9 (8.48)	11.7 (10.41)
MEDIAN	10.0	5.0	8.0
MIN - MAX	1 - 43	1 - 29	1 - 43
CUMULATIVE DOSE (MG)/ SUBJECT			
MEAN (SD)	7886.706 (6852.5687)	5596.878 (5407.1469)	7457.035 (6660.2537)
MEDIAN	6400.000	2880.000	5120.000
MIN - MAX	640.00 - 27520.00	640.00 - 17920.00	640.00 - 27520.00

Cumulative dose (in mg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.

Analyses are limited to subjects who received BMS986-213 FDC 160mg/480mg.

Study CA224020 data are from 25FEB2021 database lock.

Study CA224047 data are from 28OCT2021 database lock.

Program Source: BMS_GBS\CA224\DZA72884\Biostatistics\Production\Tables\EBR38\rt-ex-cumdos.sas

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Table 1-3: Clinical Exposure in Person Time by Age Group and Sex; BMS-986213 All Treated Subjects: CA224047 and CA224020 and Pooled

Treatment group: BMS-986213: CA224047

AGE CATEGORY (YEARS)	PERSONS (%)			PERSON TIME OF EXPOSURE (MONTHS) (1)		
	MALE N = 210	FEMALE N = 145	TOTAL N = 355	MALE N = 210	FEMALE N = 145	TOTAL N = 355
>=18 and <65	103 (49.0)	84 (57.9)	187 (52.7)	1195.35	1027.93	2223.28
>=65 and <75	67 (31.9)	35 (24.1)	102 (28.7)	950.63	346.87	1297.50
>=75 and <85	37 (17.6)	23 (15.9)	60 (16.9)	414.20	220.60	634.80
>=85	3 (1.4)	3 (2.1)	6 (1.7)	42.60	21.03	63.63
TOTAL	210 (100)	145 (100)	355 (100)	2602.78	1616.43	4219.21

Treatment group: BMS-986213: CA224020

	PERSONS (%)			PERSON TIME OF EXPOSURE (MONTHS) (1)		
	MALE N = 56	FEMALE N = 26	TOTAL N = 82	MALE N = 56	FEMALE N = 26	TOTAL N = 82
>=18 and <65	25 (44.6)	15 (57.7)	40 (48.8)	256.75	53.57	310.32
>=65 and <75	21 (37.5)	8 (30.8)	29 (35.4)	237.09	55.53	292.62
>=75 and <85	8 (14.3)	3 (11.5)	11 (13.4)	86.66	7.66	94.32
>=85	2 (3.6)	0	2 (2.4)	6.70	N.A.	6.70
TOTAL	56 (100)	26 (100)	82 (100)	587.20	116.76	703.96

Treatment group: Pooled BMS-986213 CA224047 and CA224020

	PERSONS (%)			PERSON TIME OF EXPOSURE (MONTHS) (1)		
	MALE N = 266	FEMALE N = 171	TOTAL N = 437	MALE N = 266	FEMALE N = 171	TOTAL N = 437
>=18 and <65	128 (48.1)	99 (57.9)	227 (51.9)	1452.10	1081.50	2533.60
>=65 and <75	88 (33.1)	43 (25.1)	131 (30.0)	1187.72	402.40	1590.12
>=75 and <85	45 (16.9)	26 (15.2)	71 (16.2)	500.86	228.26	729.12
>=85	5 (1.9)	3 (1.8)	8 (1.8)	49.30	21.03	70.33
TOTAL	266 (100)	171 (100)	437 (100)	3189.98	1733.19	4923.17

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time

between first dose date and last known date alive and duration of treatment +30 days,
for subjects who are off treatment, and as time between first dose date and
last known date alive for subjects who are still on treatment.

Analyses are limited to subjects who received BMS986-213 FDC 160mg/480mg.

Study CA224020 data are from 25FEB2021 database lock.

Study CA224047 data are from 28OCT2021 database lock.

N.A.: Not Applicable.

Program Source: BMS_GBS\CA224\DZA72884\Biostatistics\Production\Tables\EBR38\rt-ex-pt-age.sas

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Table 1-4: Clinical Exposure in Person Time by Racial Origin and Sex; BMS-986213 All Treated Subjects: CA224047 and CA224020 and Pooled

Treatment group: BMS-986213: CA224047

RACE	PERSONS (%)			PERSON TIME OF EXPOSURE (MONTHS) (1)		
	MALE N = 210	FEMALE N = 145	TOTAL N = 355	MALE N = 210	FEMALE N = 145	TOTAL N = 355
WHITE	204 (97.1)	138 (95.2)	342 (96.3)	2533.78	1547.07	4080.85
BLACK OR AFRICAN AMERICAN	0	0	0	N.A.	N.A.	N.A.
ASIAN	0	0	0	N.A.	N.A.	N.A.
OTHER	4 (1.9)	3 (2.1)	7 (2.0)	51.16	22.97	74.13
NOT REPORTED	2 (1.0)	4 (2.8)	6 (1.7)	17.84	46.39	64.23
TOTAL	210 (100)	145 (100)	355 (100)	2602.78	1616.43	4219.21

Treatment group: BMS-986213: CA224020

	PERSONS (%)			PERSON TIME OF EXPOSURE (MONTHS) (1)		
	MALE N = 56	FEMALE N = 26	TOTAL N = 82	MALE N = 56	FEMALE N = 26	TOTAL N = 82
WHITE	53 (94.6)	23 (88.5)	76 (92.7)	526.06	98.10	624.16
BLACK OR AFRICAN AMERICAN	0	1 (3.8)	1 (1.2)	N.A.	10.22	10.22
ASIAN	2 (3.6)	2 (7.7)	4 (4.9)	33.94	8.44	42.38
OTHER	1 (1.8)	0	1 (1.2)	27.20	N.A.	27.20
NOT REPORTED	0	0	0	N.A.	N.A.	N.A.
TOTAL	56 (100)	26 (100)	82 (100)	587.20	116.76	703.96

Treatment group: Pooled BMS-986213 CA224047 and CA224020

	PERSONS (%)			PERSON TIME OF EXPOSURE (MONTHS) (1)		
	MALE N = 266	FEMALE N = 171	TOTAL N = 437	MALE N = 266	FEMALE N = 171	TOTAL N = 437
WHITE	257 (96.6)	161 (94.2)	418 (95.7)	3059.84	1645.17	4705.01
BLACK OR AFRICAN AMERICAN	0	1 (0.6)	1 (0.2)	N.A.	10.22	10.22
ASIAN	2 (0.8)	2 (1.2)	4 (0.9)	33.94	8.44	42.38
OTHER	5 (1.9)	3 (1.8)	8 (1.8)	78.36	22.97	101.33
NOT REPORTED	2 (0.8)	4 (2.3)	6 (1.4)	17.84	46.39	64.23
TOTAL	266 (100)	171 (100)	437 (100)	3189.98	1733.19	4923.17

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Analyses are limited to subjects who received BMS986-213 FDC 160mg/480mg.
Study CA224020 data are from 25FEB2021 database lock.
Study CA224047 data are from 28OCT2021 database lock.
N.A.: Not Applicable.
Program Source: BMS_GBS\CA224\DZA72884\Biostatistics\Production\Tables\EBR38\rt-ex-pt-race.sas

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ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Marketing Authorization Holder (MAH) shall ensure that in each Member State where Opdualag is marketed, all healthcare professionals (HCPs) and patients/caregivers who are expected to prescribe and use Opdualag have access to/are provided with the patient card.

The Patient Card shall contain the following key messages:

- Opdualag can cause serious immune-related adverse reactions that can affect various organ systems, lead to death, and which need to be addressed immediately
- Description of the main symptoms of the important immune-related adverse reactions and highlight the importance of notifying the treating physician or nurse immediately if these symptoms occur, persist or worsen
- The importance of not attempting to self-treat any symptoms without consulting their HCP first
- That signs or symptoms may be delayed and may occur weeks to months after the last treatment with Opdualag
- That it is recommended that the patient reads the package leaflet and includes the web link as appropriate
- Highlights the importance of carrying the patient card at all times to show at all medical visits to HCPs other than prescribers (eg, emergency HCPs)
- Prompts to enter contact details of the treating physician and to alert other physicians that the patient is being treated with Opdualag

The MAH shall agree about the format and content of the above educational material with the National Competent Authority prior to launch of Opdualag in each Member State.

Signature Page for VV-PVG-044734 v1.0

Approval Task Verdict: Approved	Roberta Di Menno di Bucchianico EU QPPV 18-Jun-2026 16:40:47 GMT+0000
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