



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMADOC-1700519818-3272044

Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Opdualag

International non-proprietary name: nivolumab / relatlimab

Procedure no.: EMA/PAM/0000349901

Marketing authorisation holder (MAH): Bristol-Myers Squibb Pharma EEIG

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



Status of this report and steps taken for the assessment			
Current step	Description	Planned date	Actual Date
☐	Start date	22 June 2026	22 Jun 2026
☐	CHMP Rapporteur AR	27 July 2026	27 Jul 2026
☐	CHMP comments	10 August 2026	n/a
☐	Updated CHMP Rapporteur AR	13 August 2026	13 Aug 2026
☒	CHMP outcome	20 August 2026	20 August 2026

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1. Introduction

On 22 May 2026, the MAH submitted a completed paediatric study for Opdualag, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study CA224069 (RELATIVITY-069) is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Relatlimib and nivolumab were administered as intravenous infusion. In the flat dosing cohort relatlimab 160 mg + nivolumab 480 mg IV Q4W was administered. In the age/weight based dosing cohort relatlimab 2 mg/kg (max 160 mg) + nivolumab 6 mg/kg (max 480 mg) Q4W was administered. Please refer to section 2.3 for more details.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- CA224069 (RELATIVITY-069): A Phase I/II study of the safety tolerability, pharmacokinetics and preliminary efficacy of relatlimab plus nivolumab in pediatric and young adult participants with recurrent or refractory classical Hodgkin Lymphoma and Non-Hodgkin Lymphoma

2.3.2. Clinical study

CA224069 (RELATIVITY-069): A Phase I/II study of the safety tolerability, pharmacokinetics and preliminary efficacy of relatlimab plus nivolumab in pediatric and young adults

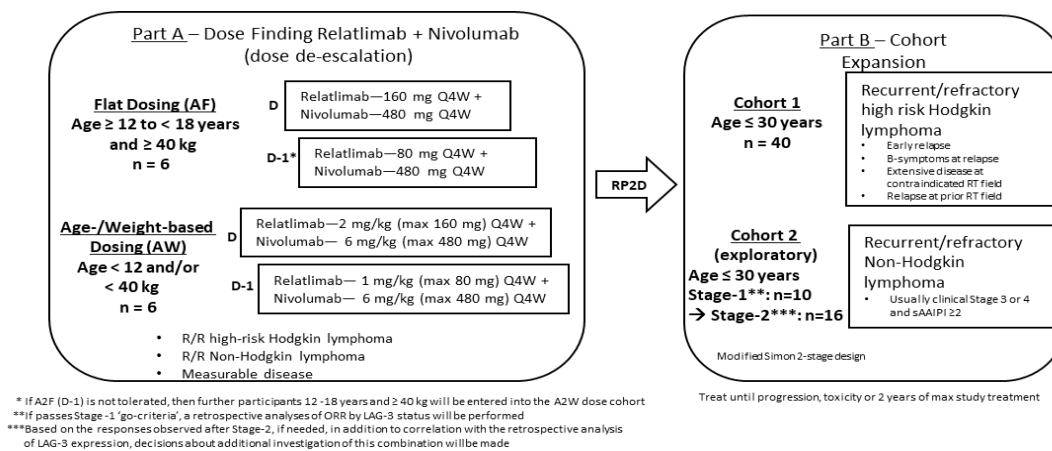
Description

Study CA224069 was a Phase 1/2 pediatric study of relatlimab + nivolumab to evaluate safety and tolerability in R/R cHL and NHL. The study was planned to be conducted in 2 parts: Part A (safety evaluation and dose determination) and Part B (cohort expansion). The study design is shown in Figure 1. Only Part A of the study was initiated prior to early study termination by the Sponsor; Part B was not initiated. The study was terminated early by the Sponsor due to the following reasons:

- Recent biomarker data indicating limited relevance of LAG-3 inhibition in lymphoma, particularly in the R/R setting.
- Enrollment feasibility challenges due to changes in treatment landscape for cHL. As a result of the addition of more targeted therapies into first-line treatment (anti-PD-1 therapy) there have been a decreased number of pediatric patients progressing to R/R disease.

- Limited interest from Investigators to enroll subjects, due to concurrent competing clinical trials and the expanding availability of alternative treatment options.

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



Methods

Study participants

Part A included pediatric subjects (< 18 years of age) with R/R cHL or R/R NHL.

Inclusion criteria:

1. Signed written informed consent
2. Type of Participant and Target Disease Characteristics
 - a. Participants must have measurable disease, documented by pathological and radiographic criteria.
 - b. For both cHL and NHL, recurrent/relapsed and refractory disease is defined as follows:
 - i. Recurrent/relapsed disease is defined as achieving a CR to previous therapy but then progressing 3 months or more after completion of that therapy.
 - ii. Refractory disease is defined as never achieving a CR to previous therapy or achieving
 - iii. a CR but then progressing within 3 months of completion of that therapy.
 - iv. Participants must have measurable or evaluable disease based on the Lugano 2014 Classification criteria.
 - v. Participants must have FDG-PET-avid and bidimensional measurable disease of at least 1.5 cm in longest axis as documented by radiographic technique (contrast-enhanced CT preferred).
 - vi. Karnofsky ≥ 60 for participants ≥ 16 years of age or Lansky ≥ 60 for participants < 16 years of age. Must be performed within 14 days prior to treatment assignment. Participants who are unable to walk because of neurologic deficits but who are in a wheelchair will be considered ambulatory for the purpose of assessing the performance score.

- vii. Substantial recovery (ie, $\leq$ Grade 1 or resolves to baseline) from prior therapy.
 - viii. An interval ("wash-out period") prior to administration of first study treatment is recommended as follows:
 - Biologic agents and targeted therapies: At least 4 weeks after the last dose of biologic or targeted therapy.
 - Chemotherapy: At least 4 weeks after the last dose of most myelosuppressive chemotherapy. For nitrosoureas, at least 6 weeks is recommended.
 - Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (eg, Neulasta) or 7 days for short-acting growth factor. For agents that have known AEs occurring beyond 7 days after administration, this period must be extended beyond the time during which AEs are known to occur. The duration of this interval must be discussed with the BMS Medical Monitor.
 - c. A FFPE tissue block (preferred) or a minimum of 15 unstained slides of tumor tissue from an excisional biopsy, core biopsy or surgical specimen obtained during screening, or prior to treatment assignment and within 3 months of enrollment with no intervening systemic anticancer treatment between time of acquisition and enrollment, must be sent to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable.
 - d. Participants with pathologically confirmed high-risk R/R cHL, after non-response to or failure of 1 or more lines of standard therapy.
 - e. Participants with pathologically confirmed R/R NHL after non-response to or failure of 1 or more lines of standard therapy, including, but not limited to, R/R primary mediastinal B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), mediastinal gray zone lymphoma (MGZL), anaplastic large cell lymphoma (ALCL), or peripheral T-cell lymphoma (PTCL).
 - f. Participants with pathologically confirmed R/R NHL after non-response to or failure of 2 or more lines of standard therapy, including Burkitt lymphoma (blast count < 25% malignant Burkitt cells and/or per the investigator's clinical assessment of risk status), lymphoblastic lymphoma (blast count < 25% of marrow nucleated cells and/or per the investigator's clinical assessment of risk status), NK/T-cell lymphoma (nasal and non-nasal NK/T-cell lymphoma subtypes, but not aggressive NK/T-cell leukemia/lymphoma subtype).
3. Age of Participant
- a. For enrollment in Part A, participant must be 0 to less than 18 years of age at the time of signing the informed consent (or assent, as applicable).
 - b. For enrollment in Part B, participant must be 0 to 30 years of age inclusive at the time of signing the informed consent (or assent, as applicable).
4. Not of childbearing potential or contraceptive requirements for female participants. No contraception requirements for nivolumab and relatlimab for male participants are mandated.

Exclusion criteria:

1. Medical conditions

- a. Secondary CNS lymphoma (ie, from systemic NHL) involving the brain, spinal cord, or with leptomeningeal seeding.
- b. Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the participant from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results (eg, a condition associated with diarrhea or acute diverticulitis).
- c. History of progressive multifocal leukoencephalopathy.
- d. Pre-existing neuropathy of $\geq$ Grade 2.
- e. Active infection requiring systemic therapy within 14 days prior to the first dose of study treatment; routine antimicrobial prophylaxis is permitted. There should be no sequelae that would place the participant at a higher risk from receiving investigational treatment.
- f. Participants with a history of myocarditis, irrespective of etiology.
- g. Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to treatment assignment (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before treatment assignment and the participant has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.
- h. Concurrent or active graft versus host disease (GVHD) or previous history of Grade > 2 GVHD.
- i. Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- j. Participants with a condition requiring systemic treatment with either corticosteroids (daily doses of > 10 mg or > 0.12 mg/kg prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of treatment assignment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily (or > 0.12 mg/kg daily) prednisone equivalent are permitted in the absence of active autoimmune disease.
- k. Participants with an immunodeficiency that existed prior to diagnosis, such as primary immunodeficiency syndromes, organ transplant recipients, and participants on current systemic immunosuppressive agents.
- l. Participants with serious or uncontrolled medical disorders.
- m. Primary CNS lymphoma of the brain or spinal cord.

2. Reproductive status (Women with a positive pregnancy test at screening or who are breastfeeding)
3. Prior/concomitant therapy
 - a. Inability to comply with restrictions and prohibited treatments.
 - b. Prior radiation therapy within 2 weeks prior to first study treatment. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study treatment.
 - c. Prior treatment with an anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways, with the exception of anti-PD(L)-1 targeted therapies.
 - d. Prior treatment with LAG-3 targeted agents
 - e. Prior allogeneic bone marrow transplantation.
 - f. Treatment with any live/ attenuated vaccine within 30 days of first study treatment.
 - g. Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to first study treatment. Such medications are permitted if they are used as supportive care.
 - h. Participants currently in other interventional trials, including those for coronavirus disease 2019 (COVID-19), may not participate in BMS clinical trials until the protocol specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the investigator and the Medical Monitor.
 - i. Prior CAR-T therapy within 6 months of first study treatment.
4. Physical and Laboratory Test Findings
 - a. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population
 - b. Inadequate bone marrow function
 - c. Blood creatinine outside of reference values
 - d. Serum creatinine $> 1.5 \times 97.5$ th percentile
 - e. AST/ALT: $> 3.0 \times \text{ULN}$.
 - f. TB $> 1.5 \times \text{ULN}$ (except participants with Gilbert Syndrome who must have a TB level of $< 3.0 \times \text{ULN}$).
 - g. Troponin T (TnT) or I (TnI) $> 2 \times \text{institutional ULN}$.
 - h. Any positive test result for hepatitis B virus indicating presence of virus, eg Hepatitis B surface antigen (HBsAg, Australia antigen) positive.

- i. Any positive test result for hepatitis C virus (HCV) indicating presence of active viral replication (detectable HCV-RNA). Note: Participants with positive HCV antibody and an undetectable HCV RNA are eligible to enroll.
 - j. Positive urine screen for drugs of abuse as clinically indicated.
 - k. Left ventricular ejection fraction (LVEF) assessment with documented LVEF < 50% by either transthoracic echocardiogram (TTE) or multigated acquisition (MUGA) scan (TTE preferred test) within 6 months prior to start of study treatment.
5. Allergies and adverse drug reactions
- a. History of allergy or hypersensitivity to study drug components.
 - b. History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).
6. Other
- a. Prisoners or participants who are involuntarily incarcerated.
 - b. Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.
 - c. Inability to comply with lifestyle restrictions.
 - d. Any major surgery within 4 weeks of study intervention administration unrelated to the underlying disease except as approved in consultation with the Medical Monitor or designee.

Treatments

Part A consisted of two cohorts (Figure 2 and Figure 3):

- Flat dosing (AF) cohort included subjects ≥ 12 years of age who weighed ≥ 40 kg:
 - D = Relatlimab 160 mg + nivolumab 480 mg IV Q4W (A1F); if the starting dose was found to be not tolerated, the relatlimab dose was to be decreased to D-1
 - D-1 = Relatlimab 80 mg + nivolumab 480 mg IV Q4W (A2F)
- Age/weight based dosing (AW) cohort included subjects ≥ 12 years of age who weighed < 40 kg and/or subjects < 12 years of age irrespective of weight:
 - D = Relatlimab 2 mg/kg (max 160 mg) + nivolumab 6 mg/kg (max 480 mg) Q4W (A1W); if the starting dose was found to be not tolerated, then the relatlimab dose was to be decreased to D-1
 - D-1 = Relatlimab 1 mg/kg (max 80 mg) with nivolumab 6 mg/kg (max 480 mg) Q4W (A2W)

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

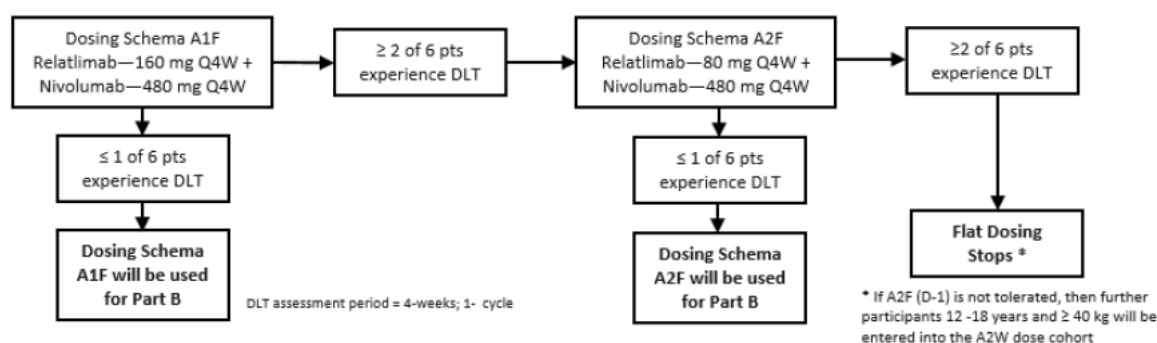
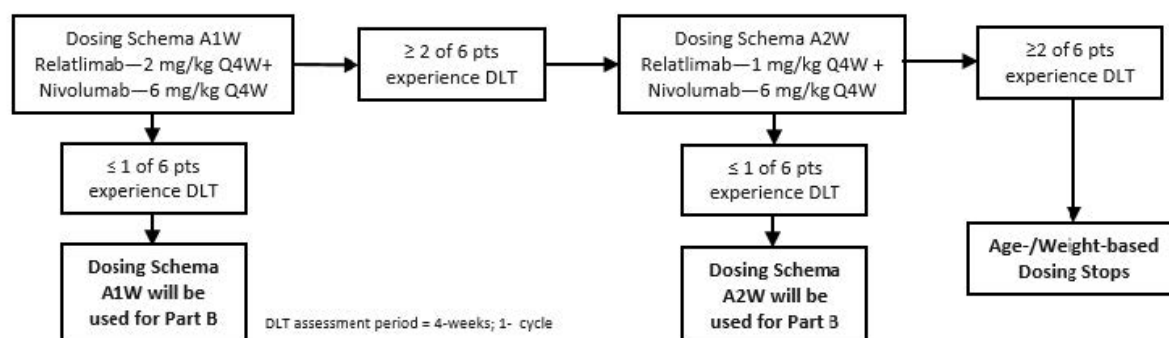


Figure 3 Dose-finding Study Design for Age- and Weight-based Dosing (AW) in Part A



Enrollment in the 2 dosing cohorts (A1F and A1W) was initiated in parallel. Up to 6 subjects for both age/weight cohorts were planned to be assessed for safety and PK. The observation period for DLTs (DLT-evaluation period) was 1 cycle, defined as 28 days. Subjects were monitored for safety using CTCAE v.5.0 criteria. If DLT with CTCAE v5.0 criteria of Grade 3 or higher severity was observed in 2 or more subjects, the dose was to be de-escalated to D-1 (A2F and A2W) and an additional 6 subjects were planned to be evaluated for toxicity and exposure, for another ≥ 2 DLTs. If no DLTs were observed, a minimum of 6 subjects were to be enrolled in A1F and A1W, respectively. Both AF and AW dosing schemas were independent of each other and were evaluated for DLTs separately. Blood samples were drawn on days of infusion for all pre-dose and end of infusion.

The proposed treatment duration was until metabolic progression or toxicity up to a maximum of 2 years.

No intra-subject dose reductions or escalations for immunotherapy were permitted. Dose delay criteria applied for all drug-related AEs for both relatlimab and nivolumab.

Objectives and endpoints

The study objectives and endpoints are described in Table 1.

Objectives	Endpoints	Endpoint Description
Primary		
To characterize the safety, tolerability for the combination of relatlimab + nivolumab in pediatric subjects less than 18 years of age with R/R cHL and NHL	DLTs and incidences of AEs, SAEs, AEs leading to discontinuation, deaths and laboratory abnormalities	DLTs were defined based on the incidence, intensity, and duration of AEs for which no clear alternative cause was identified. The DLT period started on Cycle 1 Day 1 and ended at Day 28 (4-week period). Incidences of AEs, SAEs, AEs leading to discontinuation, deaths, and laboratory abnormalities occurring within 135 days of last dose of study treatment were assessed by using CTCAE Version 5.0.
To characterize the PK of relatlimab for the combination of relatlimab + nivolumab in pediatric subjects less than 18 years of age with R/R cHL and NHL	Cmax, Ctrough, Tmax, and AUC (TAU) for relatlimab	The PK of relatlimab were derived from serum concentration versus time measurements.
Exploratory		
To characterize the PK of nivolumab for the combination of relatlimab + nivolumab in pediatric subjects less than 18 years of age with R/R cHL and NHL	Ctrough and Ceoi	Individual subject PK parameter values were derived by non-compartmental and, if appropriate, by population PK methods.

Table 1 Objectives and Endpoints of Study Part A

Sample size

The sample size of Part A was not based on statistical considerations and there was no statistical hypothesis tested. Though it was expected to treat up to 6 subjects in each age/weight dose level, the actual number treated in Part A depended on the accepted toxicity profile of each dose being assessed.

Randomisation and blinding (masking)

Treatment assignment to subjects was performed using interactive response technology. There was no randomization or blinding.

Statistical Methods

Since the treated population number was limited to 5 subjects, by-subject listings were provided for the safety analyses.

PK parameters were summarized descriptively by doses of relatlimab/nivolumab. Mean, geometric mean, and CV were presented for Cmax, Ctrough, and AUC(TAU). Medians and ranges were presented for Tmax. Means and SD were provided for the other PK parameters such as Ceoi and Ctrough. The PK of relatlimab and nivolumab was derived from serum concentration versus time measurements.

Results

Participant flow

Seven pediatric subjects were enrolled and 5 of them received study treatment. Among the treated subjects, 4 subjects were assigned to the AF cohort and received treatment with relatlimab 160 mg or 80 mg + nivolumab 480 mg Q4W. One subject received treatment with relatlimab 2 mg/kg or 1 mg/kg (max 160 mg) + nivolumab 6 mg/kg (max 480 mg) Q4W in the AW cohort.

All 4 subjects treated in the AF cohort discontinued study treatment (2 due to disease progression, 1 due to achieving maximum clinical benefit, and 1 due to other reason). All 4 subjects subsequently discontinued the study due to 'other' reasons.

The subject treated in the AW cohort discontinued study treatment due to disease progression and discontinued from the study due to death.

Recruitment

Refer to Table 1 for the key dates and follow-up.

Last Subject Randomized Date	02-Jan-2025
Clinical cutoff/ LPLV	03-Dec-2025
Clinical DBL	10-Feb-2026

Table 2 Key Dates and Follow-up

Baseline data

AF cohort: All 4 subjects were ≥ 12 years old (range: 15-17 years) and weighed ≥ 40 kg (range: 46.8-70.1 kg) at baseline. 3 subjects were male and 1 subject was female and all were White. At the time of study entry, 2 subjects were diagnosed with Stage IV R/R cHL, 1 subject was diagnosed with Stage II R/R cHL, and 1 subject was diagnosed with Stage IV R/R NHL. The performance score at baseline using either Lansky or Karnofsky, as appropriate based on the subject age, was 100 for all subjects.

AW cohort: The subject enrolled in the AW cohort was a 13 year-old male with a baseline weight of 34.9 kg, diagnosed with Stage III R/R NHL at the time of study entry. At baseline, the subject had a performance score of 100 .

Number analysed

The enrolled population consisted of 7 patients. In total 5 patients received at least 1 dose of study treatment (Table 3).

Study population	Number of subjects
Enrolled Population: All subjects, or their LARs, who have agreed to participate in the study following completion of the informed consent process, unless otherwise specified by the protocol	7
Treated Population: All subjects who received at least 1 dose of study treatment	5
PK Population: All treated subjects with available PK data	5

Table 3 Study populations

Efficacy results

There were no planned primary or secondary efficacy endpoints for Part A of the study. However, per protocol, subjects enrolled in Part A who continued to receive treatment post DLT period could have contributed BOR results to Part B accrual, as Part B had a BOR-related primary objective. Although Part B was never initiated, BOR results from Part A are provided here for completeness.

At the clinical data cutoff, BOR per investigator (Lugano 2014 criteria) was available for all 4 subjects in the AF cohort. For the subject in the AW cohort, BOR was not available, as the subject discontinued the study prior to final BOR assessment using PET/CT scan (Table 4).

Cohort	BOR	Progression (Y/N)	Subsequent Therapy (Y/N)
AF	CMR	Y	Not reported
AF	PMR	Y	Y
AF	NMR	Not reported	Not reported
AF	PMR	Not reported	Y
AW	Not available (subject discontinued the study prior to final BOR assessment)	Y	Y

Table 4 BOR per Investigator- All Treated Subjects in the AF and AW Cohorts

Safety results

Exposure

AF cohort: In the AF cohort, all 4 subjects received 5-8 cycles (4-week period/cycle) of relatlimab 160 mg and nivolumab 480 mg. There were no dose delays, interruptions, or rate reductions reported.

AW cohort: The subject in the AW cohort received 2 cycles of weight-based relatlimab and nivolumab treatment. There were no dose delays, interruptions, or rate reductions reported.

Safety summary

The safety summary is shown in Table 5. All subjects in both AF and AW cohorts reported at least 1 all-causality AE. One subject in the AW cohort was reported with a fatal (Grade 5) AE of malignant neoplasm progression. The event was reported in the follow-up period.

Three subjects (2 subjects in the AF cohort and 1 subject in the AW cohort) reported SAEs including pyrexia, skin infection, facial pain, spinal cord compression, and malignant neoplasm progression. None of these SAEs were considered related to the study treatment.

Four subjects reported at least 1 drug-related AE (all from AF cohort). The drug-related AEs were of low grade (Grade 1-2). There were no Grade 3-5 drug-related AEs reported.

No AEs leading to dose delay or dose discontinuation were reported in either cohort.

The majority of changes in laboratory parameters were related to hematological parameters and were of Grade 1-2 in severity. Only 1 Grade ≥ 3 laboratory abnormality was reported across both cohorts (Grade 3 increase in absolute lymphocytes reported in the AF cohort).

AE/SAE	N = 5	Grade 1-2	Grade 3-4	Grade 5
Deaths within 135 days of the last dose				
AW Cohort				
Malignant neoplasm progression	1	0	0	1
All-causality SAEs within 135 days of the last dose				
AF Cohort				
Pyrexia*	1	0	1	0
Skin infection	1	0	1	0
AW Cohort				
Facial pain	1	0	1	0
Spinal cord compression	1	0	1	0
Malignant neoplasm progression	1	0	0	1
Drug-related AEs within 135 days of the last dose				
AF Cohort				
Lymphopenia	2	2	0	0
Thrombocytopenia	1	1	0	0
ALT increased	1	1	0	0
AST increased	1	1	0	0
Anaemia	1	1	0	0
Non-cardiac chest pain	1	1	0	0
Hyperthyroidism	1	1	0	0
Blood thyroid stimulating hormone increased	1	1	0	0
Hypothyroidism	1	1	0	0
AW Cohort				
	0	0	0	0

Table 5 Safety Summary - All Treated Subjects in Part A. *The event of pyrexia was reported during the screening period.

Adverse events

AF cohort:

All-causality AEs (any grade) were reported by all subjects (100%) in the AF cohort, with the majority of AEs reported as single events (Table 6). The most frequently reported AE within 30 days of the last study dose was lymphopenia, reported in 2 subjects.

At least 1 drug-related AE was reported in each subject in the AF cohort within 30 days of the last study dose. The events included ALT increased, anaemia, AST increased, blood thyroid stimulating hormone increased, hyperthyroidism, hypothyroidism, lymphopenia, non-cardiac chest pain, and thrombocytopenia.

No Grade 3-5 drug-related AEs were reported within 30 days of the last study dose.

AW cohort:

The subject in the AW cohort reported Grade 2 all-causality AEs of toothache, otitis media, and pyrexia within 30 days of the last study dose (Table 6). None of these AEs were considered related to the study treatment by the investigator.

The subject in this cohort reported 1 Grade 3 SAE (facial pain) and 1 Grade 4 SAE (spinal cord compression) during the treatment period. During the follow-up period, the subject was reported with a fatal (Grade 5) AE of malignant neoplasm progression. The event was considered as an SAE.

System Organ Class Preferred Term	Part A - AF Cohort N=4			Part A - AW Cohort N=1		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Total Subjects With an Event	4 (100.0)	2 (50.0)	0	1 (100.0)	1 (100.0)	0
Infections and infestations	3 (75.0)	1 (25.0)	0	1 (100.0)	0	0
Influenza	1 (25.0)	0	0	0	0	0
Nasopharyngitis	1 (25.0)	0	0	0	0	0
Skin infection	1 (25.0)	1 (25.0)	0	0	0	0
Viral upper respiratory tract infection	1 (25.0)	0	0	0	0	0
Otitis media	0	0	0	1 (100.0)	0	0
Blood and lymphatic system disorders	2 (50.0)	0	0	0	0	0
Lymphopenia	2 (50.0)	0	0	0	0	0
Anaemia	1 (25.0)	0	0	0	0	0
Thrombocytopenia	1 (25.0)	0	0	0	0	0
Gastrointestinal disorders	2 (50.0)	0	0	1 (100.0)	0	0
Dental caries	1 (25.0)	0	0	0	0	0
Diarrhoea	1 (25.0)	0	0	0	0	0
Toothache	0	0	0	1 (100.0)	0	0
Investigations	2 (50.0)	0	0	0	0	0
ALT increased	1 (25.0)	0	0	0	0	0
AST increased	1 (25.0)	0	0	0	0	0
Blood bilirubin increased	1 (25.0)	0	0	0	0	0
Blood thyroid stimulating hormone increased	1 (25.0)	0	0	0	0	0
Gamma-glutamyl transferase increased	1 (25.0)	0	0	0	0	0
Skin and subcutaneous tissue disorders	2 (50.0)	1 (25.0)	0	0	0	0

System Organ Class Preferred Term	Part A - AF Cohort N=4			Part A - AW Cohort N=1		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Rash maculo-papular	1 (25.0)	1 (25.0)	0	0	0	0
Seborrhoeic dermatitis	1 (25.0)	0	0	0	0	0
Endocrine disorders	1 (25.0)	0	0	0	0	0
Hyperthyroidism	1 (25.0)	0	0	0	0	0
Hypothyroidism	1 (25.0)	0	0	0	0	0
General disorders and administration site conditions	1 (25.0)	0	0	1 (100.0)	1 (100.0)	0
Non-cardiac chest pain	1 (25.0)	0	0	0	0	0
Facial pain	0	0	0	1 (100.0)	1 (100.0)	0
Pyrexia	0	0	0	1 (100.0)	0	0
Immune system disorders	1 (25.0)	1 (25.0)	0	0	0	0
Hypersensitivity	1 (25.0)	1 (25.0)	0	0	0	0
Injury, poisoning and procedural complications	1 (25.0)	0	0	0	0	0
Infusion related reaction	1 (25.0)	0	0	0	0	0
Metabolism and nutrition disorders	1 (25.0)	0	0	0	0	0
Hypoalbuminaemia	1 (25.0)	0	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (25.0)	0	0	0	0	0
Back pain	1 (25.0)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (25.0)	0	0	0	0	0
Rhinitis allergic	1 (25.0)	0	0	0	0	0
Nervous system disorders	0	0	0	1 (100.0)	1 (100.0)	0
Spinal cord compression	0	0	0	1 (100.0)	1 (100.0)	0

Table 6 Any Adverse Events Summary by Worst CTCAE Grade (Any Grade, Grade 3-4, Grade 5) with 5% Cutoff - All Treated Subjects

Deaths

AF cohort: No deaths were reported in the AF cohort.

AW cohort: The subject in the AW cohort died due to a Grade 5 AE of malignant neoplasm progression which was reported in the follow-up period.

Serious Adverse Events

AF cohort: A total of 2 subjects reported 2 Grade 3 SAEs (pyrexia [reported in the screening period] and skin infection [reported in the treatment period]). None of the SAEs were considered related to the study treatment by the Investigator.

AW cohort: The subject in this cohort reported 1 Grade 3 SAE (facial pain), 1 Grade 4 SAE (spinal cord compression) during the treatment period, and 1 Grade 5 SAE (malignant neoplasm progression) during the follow-up period. None of the SAEs were considered related to the study treatment by the Investigator

Adverse Events Leading to Discontinuation or Dose Modifications of Study Therapy

There were no AEs which led to dose delay or discontinuation in the AF and AW cohorts. There were no DLTs or dose reductions reported, and all subjects were treated at the initial starting dose (AF or AW).

Clinical Laboratory Evaluations

Most treated subjects were reported with changes in baseline clinical laboratory test results (after the first dose and within 30 days of the last dose of study treatment). The majority of these changes were related to hematological parameters and were Grade 1-2 in severity.

AF cohort: A Grade 3 laboratory abnormality was reported in 1 subject (an increase in absolute lymphocytes) who had a Grade 2 abnormality in this parameter at baseline. All other changes from baseline were of low grade.

AW cohort: No Grade ≥ 3 hematological laboratory abnormalities were reported in the AW cohort

No Grade ≥ 3 serum chemistry laboratory abnormalities were reported in both AF and AW cohorts.

2.3.3. Pharmacokinetic results

AF cohort (n=4):

- For relatlimab, at Cycle 1, the geometric mean (% geometric CV) C_{max} was 51.83 $\mu\text{g/mL}$ (16%), the median t_{max} was 0.74 hours (range: 0.58-1.00), the geometric mean (% geometric CV) C_{tau} was 9.50 $\mu\text{g/mL}$ (68%), and the geometric mean (% geometric CV) ($AUC_{[TAU]}$ in first dosing interval) was 13160.63 $\text{h}\cdot\mu\text{g/mL}$ (32%).
- For nivolumab, the geometric mean observed C_{eoi} at Cycle 1 Day 1 was 161.57 $\mu\text{g/mL}$ and at Cycle 6 Day 1 was 282.85 $\mu\text{g/mL}$, whereas the geometric mean observed C_{trough} at Cycle 2 Day 1 was 40.32 $\mu\text{g/mL}$ and at Cycle 6 Day 1 was 91.87 $\mu\text{g/mL}$.

AW cohort (n=1):

- For relatlimab, at Cycle 1, the C_{max} was 40.00 $\mu\text{g/mL}$, the t_{max} was 0.50 hours, the C_{tau} was 2.39 $\mu\text{g/mL}$, and the $AUC_{[TAU]}$ in first dosing interval was 6745.58 $\text{h}\cdot\mu\text{g/mL}$.
- For nivolumab, the observed C_{eoi} at Cycle 1 Day 1 was 89.60 $\mu\text{g/mL}$, whereas the observed C_{trough} at Cycle 2 Day 1 was 17.80 $\mu\text{g/mL}$.

2.3.4. Discussion on clinical aspects

CA224069 (RELATIVITY-069) was a Phase I/II study of the safety tolerability, pharmacokinetics and preliminary efficacy of relatlimab plus nivolumab in paediatric and young adults.

Methods

The study included two parts aimed at dose finding (part A) and cohort expansion (part B). The dose finding was further subdivided in a flat dosing cohort for subjects ≥ 12 years of age who weighed ≥ 40 kg and an age/weight-based dosing cohort for subjects < 40 kg and/or subjects < 12 years of age. The aim was to include 6 subjects for both age/weight cohorts without any formal sample size calculation. The primary aim was to assess the safety and pharmacokinetics.

Study termination

The study was terminated early by the Sponsor; only part A of the study was initiated. The reasons for early study termination were recent biomarker data indicating limited relevance of LAG-3 inhibition in lymphoma, particularly in the R/R setting and feasibility issues due to changes in treatment landscape for cHL and competing clinical trials. The MAH provided the biomarker report for study CA224022 in support. Study CA224-022 was a Phase 1/2a, open-label study of relatlimab administered as monotherapy or in combination with nivolumab to subjects with advanced relapsed or refractory B-cell

malignancies. Data from study CA224022 were compared to two other cohorts consisting of newly diagnosed patients. The biomarker report described that cellular LAG-3 was highest in the immune tumor microenvironment of patients with newly diagnosed cHL, and significantly lower in biopsies from patients with relapsed disease post-chemotherapy, post-nivolumab and post-nivolumab+relatlimab. Nivolumab was recently approved in newly diagnosed patients with cHL aged 12 years and older and in children 5 years of age and older, adolescents and adults up to 30 years of age with relapsed or refractory classical Hodgkin lymphoma after one prior line of therapy ([SmPC Opdivo](#)). Therefore, the rationale for study termination can be followed in light of the potential lower relevance of LAG-3 inhibition in the R/R cHL setting in combination the feasibility issues due to the recent approvals of Opdivo for newly diagnosed and R/R cHL.

Study population

In total 5 patients received at least 1 dose of the study treatment. Four patients were included in the flat dosing cohort and one patient in the age/weight-based cohort. Patients were aged 13 – 17 and were diagnosed with R/R cHL (n=3) or R/R NHL (n=2). Overall, the study population is very small and only adolescents were included.

Efficacy

One complete metabolic response and two partial metabolic responses were observed. Therefore, Opdualag resulted in anti-tumour efficacy, although the efficacy data are considered too limited to draw further conclusions.

Safety

No DLTs were observed, however no conclusions can be drawn about the optimal dose, as the first dose cohort was not fully enrolled before termination of the study.

The observed drug-related TEAEs were all low grade and in line with the known safety profile of relatlimab in combination with nivolumab. One fatal TEAE was observed of malignant neoplasm progression. This event occurred 55 days after the last dose was received and it is agreed that due to the timing and nature of the adverse event the fatal TEAE was most likely not drug-related. Three subjects reported SAEs and after assessment of the narratives it is agreed that none of these SAEs were drug-related. Therefore, it can be concluded that the data did not reveal any new safety concerns.

Pharmacokinetics

Four paediatric subjects (>12 years, >40 kg) received the same dose as approved in adults (i.e., relatlimab 160 mg Q4W + nivolumab 480 mg Q4W) for 5 to 8 cycles. In adults, steady-state is reached by 16 weeks (i.e., 4 cycles). Nivolumab C_{trough} geometric mean (CV%) at Cycle 4 Day 1 was 79.80 (53) µg/mL and relatlimab C_{trough} was 20.52 (66) µg/mL. C_{trough} concentrations at steady-state are somewhat higher compared to adults (i.e., Relatlimab C_{min} 15.3 (64.3) µg/mL and nivolumab C_{min} 59.7 (58.6) µg/mL. The paediatric nivolumab data cautiously supports the finding that nivolumab clearance in adolescent subjects is lower than those of adults.

SmPC

The MAH proposes no changes to the Opdualag SmPC based on the efficacy and safety data without providing a justification. Opdualag is approved in adolescents with advanced melanoma, this indication was entirely based on extrapolation from adult data and therefore there are no paediatric data in the SmPC ([EMA/H/C/005481/0000](#)). It is proposed to update the paediatric sub-section in 4.2 and 5.2, and to add a paediatric sub-section in section 4.8 and 5.1 (see proposal below).

3. Rapporteur's overall conclusion and recommendation

The MAH submitted the final report for study CA224069 in accordance with Article 46 of Regulation (EC) No1901/2006. The study was terminated early. Study CA224069 was a phase I/II study aimed at dose finding in paediatric subjects with R/R cHL or R/R NHL. No conclusions can be drawn about the optimal dose, as the first dose cohort was not fully enrolled before termination of the study. The efficacy data are considered insufficient as only 5 patients were included. The observed safety was in line with the known safety profile of relatlimab in combination with nivolumab.

The MAH proposes no changes to the Opdualag SmPC based on the efficacy and safety data, but a suggestion for updates to SmPC section 4.2, 4.8, 5.1, and 5.2 is provided. After agreement of the wording for the SmPC, the MAH is requested for a commitment to submit a variation shortly after finalisation of the procedure to implement the changes into the PI, as it is not possible to update the PI during a P46 procedure. Acknowledging the limited number of patients in study CA224069, including the paediatric data is in line with the [SmPC guidance](#).

☒ **Fulfilled**

In view of the available data regarding efficacy and safety of Opdualag in paediatric patients, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and **no later than 60 days after the receipt** of these conclusions

- **SmPC section 4.2:** The subsection "Paediatric population" states that no data are available in children below 12 years of age. In line with the [SmPC guideline](#), the MAH is requested to add the following sentence *"Currently available data in adolescents are described in section 4.8, 5.1 and 5.2. Due to limited data no recommendation on posology can be made."*
- **SmPC section 4.8:** In line with the [SmPC guideline](#), a paediatric sub-section should always be included (unless irrelevant). There is currently no paediatric sub-section in SmPC section 4.8 since the indication for adolescents was entirely based on extrapolation from adult data ([EMA/H/C/005481/0000](#)). The MAH is requested to add a paediatric sub-section with the following information: *"No new safety concerns were reported in 5 paediatric patients with relapsed or refractory classical Hodgkin lymphoma (R/R cHL) and R/R non-Hodgkin lymphoma (NHL) treated with Opdualag in study CA224069."*
- **SmPC section 5.1:** In line with the [SmPC guideline](#), a paediatric sub-section should be included. There is currently no paediatric sub-section in SmPC section 5.1 since the indication for adolescents was entirely based on extrapolation from adult data ([EMA/H/C/005481/0000](#)). The MAH is requested to add a paediatric sub-section.
- **SmPC section 5.2:** The subsection "Paediatric population" should include relevant obtained PK data in paediatrics as in line with the SmPC guideline. The MAH is requested to add the following information in the paediatric population section: *"In study CA224069, 4 paediatric patients with R/R cHL and NHL (>12 years, >40 kg) received relatlimab 160 mg Q4W + nivolumab 480 mg Q4W for 5 to 8 cycles. Nivolumab C_{trough} geometric mean (CV%) at Cycle 4 Day 1 was 79.80 (53) µg/mL and relatlimab C_{trough} was 20.52 (66) µg/mL."*

Annex. Line listing of all the studies included in the development program

Clinical studies

Product Name: Opdualag

Active substance: Nivolumab / Relatlimab

Study title	Study number	Date of completion	Date of submission of final study report
A Phase I/II study of the safety tolerability, pharmacokinetics and preliminary efficacy of relatlimab plus nivolumab in pediatric and young adults	CA224069 (RELATIVITY-069)	03-DEC-2025 (LPLV)	24-APR-2026 (report date)