EU RISK MANAGEMENT PLAN FOR COLUMVI/GLOFITAMAB

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Rationale for Submitting an Updated RMP

The glofitamab European Union Risk Management Plan (EU RMP) Version 1.2 is submitted in response to the Committee for Medicinal Products for Human Use (CHMP) Day 180 list of questions for MAA procedure EMEA/H/C/005751. Safety data has been updated to include patients within the primary safety population or overall safety population who received at least one dose of glofitamab. This update aligns with the presentation of glofitamab-exposed patients in the primary safety population in the Summary of Product Characteristics (SmPC) (N=145).

Summary of Significant Changes in This RMP

Part I	Invented name for product, Columvi, added. Aligned with information in the SmPC.
Part II: SII	Data under Relevance to Human Usage updated to include patients within the primary safety population who received at least one dose of glofitamab.
Part II: SIII	The following sections were updated to include patients within the primary safety population or overall safety populations who received at least one dose of glofitamab: -descriptions of populations and number of patients for whom safety data is provided -exposure by dose by cycle
Part II: SIV.1	References to SmPC updated under rationale for important exclusion criteria.
Part II: SIV.3	Exposure in special populations updated to include patients within the primary safety population or overall safety population who received at least one dose of glofitamab.
Part II: SVII	Data on safety concerns and risks not considered important updated to include patients within the primary safety population or overall safety population who received at least one dose of glofitamab. The missing information of Long-term Safety was updated to include evaluation of safety data by sex as part of the long-term safety data analysis in Study NP30179. The missing information of Safety in Patients with Prior CAR-T Therapy was updated to specify analysis in Study NP30179 as an additional pharmacovigilance activity.
Part III.1	Monitoring and reporting of safety data by sex in the PBRER was added a routine pharmacovigilance activity beyond adverse reactions reporting and signal detection for the missing information of Long-term Safety.
Parts III.2 and III.3	Study NP30179 was re-classified as a Category 2 PASS. Safety in Patients with Prior CAR-T Therapy was included as a safety concern addressed by PASS NP30179. Evaluation of safety data by sex was included as part of the long-term safety data analysis in PASS NP30179. Milestone dates for Study BO43309 were updated.
Part V.2	Date of the final report for Study BO43309 was updated.
Part V.3	Updated to align with any changes to pharmacovigilance activities in Part III of the RMP.
Part VI	Updated to reflect the changes made in this EU RMP.

Annex 2	Updated to reflect changes in Part III.3 of the RMP. Study NP30179 was re-classified as a Category 2 PASS. Safety in Patients with Prior CAR-T Therapy was included as a safety concern addressed by PASS NP30179. Evaluation of safety data by sex was included as part of the long-term safety data analysis in PASS NP30179. Milestone dates for Study BO43309 were updated.
Annex 3	Updated draft protocol synopsis included for Study BO43309.
Annex 6	Key messages/elements of educational materials edited to align more closely with information in the EU PI.
Annex 7	Outputs updated to include patients within the primary safety population or overall safety population who received at least one dose of glofitamab.
Annex 8	Updated to reflect the changes made to this version of the EU RMP.

CAR-T = chimeric antigen receptor T-cell; EU PI= European Union Product Information; EU RMP = European Union Risk Management Plan; PASS = post-authorization safety study; PBRER = Periodic Benefit-Risk Evaluation Report; SmPC = Summary of Product Characteristics.

Other RMP Versions under Evaluation

Not applicable

Details of Currently Approved RMP

Not applicable

See page 1 for signature and date

PPD (Deputy QPPV)	Date

See page 1 for signature and date

PPD	Date

PART I: PRODUCT(S) OVERVIEW

Table 1 Product(s) Overview

Active Substance(s) (INN or common name)	glofitamab
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	Columvi
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Glofitamab is a humanized anti-CD20 anti-CD3 bispecific monoclonal antibody.
	Summary of mode of action: Glofitamab is a bispecific monoclonal antibody that binds bivalently to CD20 expressed on the surface of B cells, and monovalently to CD3 in the T-cell receptor complex expressed on the surface of T cells. By simultaneous binding to CD20 on the B cell and CD3 on the T cell, glofitamab mediates the formation of an immunological synapse with subsequent T-cell activation and proliferation, secretion of cytokines and release of cytolytic proteins that results in the lysis of CD20-expressing B cells.
	Important information about its composition: Glofitamab is a humanized anti-CD20 anti-CD3 bispecific monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.
Hyperlink to the Product Information	EU PI
Indication(s) in the EEA	Current: Not applicable
	Proposed: Columvi as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, after two or more lines of systemic therapy.
Dosage in the EEA	Current: Not applicable
	Proposed:

<table>
<tr><td></td><td>The step-up dosing schedule for Columvi (after pretreatment with obinutuzumab on Cycle 1 Day1) is shown below. Each cycle is 21 days.
<table>
<tr><th colspan="2">Treatment cycle, Day</th><th>Dose of Columvi</th><th>Duration of infusion</th></tr>
<tr><td rowspan="3">Cycle 1
(Pre-treatment and step-up dose)</td><td>Day 1</td><td colspan="2">Pretreatment with obinutuzumab</td></tr>
<tr><td>Day 8</td><td>2.5 mg</td><td rowspan="3">4 hours</td></tr>
<tr><td>Day 15</td><td>10 mg</td></tr>
<tr><td>Cycle 2</td><td>Day 1</td><td>30 mg</td></tr>
<tr><td>Cycle 3 to 12</td><td>Day 1</td><td>30 mg</td><td>2 hours</td></tr>
</table></td></tr>
<tr><td rowspan="2">Pharmaceutical form(s) and strengths</td><td>Current:
Not applicable</td></tr>
<tr><td>Proposed:
Concentrate for solution for infusion (sterile concentrate)
Colourless, clear solution with a pH of 5.5 and osmolality of 270-350 mOsmol/kg.
<u>Columvi 2.5 mg concentrate for solution for infusion</u>
Each vial of 2.5 mL of concentrate contains 2.5 mg of glofitamab at a concentration of 1 mg/mL

<u>Columvi 10 mg concentrate for solution for infusion</u>
Each vial of 10 mL of concentrate contains 10 mg of glofitamab at a concentration of 1 mg/mL.</td></tr>
<tr><td>Is or will the product be subject to additional monitoring in the European Union?</td><td>Yes</td></tr>
</table>

EEA = European Economic Area; INN=International non-proprietary name.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ASCT	autologous stem cell transplantation
AST	aspartate amino transferase
ASTCT	American Society for Transplantation and Cellular Therapy
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T-cell
CCOD	clinical cut-off date
CHMP	Committee for Medicinal Products for Human Use
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
COVID-19	Coronavirus Disease 2019
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
DLBCL-NOS	DLBCL-not otherwise specified
DSR	Drug Safety Report
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
E.U. RMP	E.U. Risk Management Plan
FDA	Food and Drug Administration
Gpt	Gazyva®/Gazyvaro® pretreatment
GVP	Good Pharmacovigilance Practice
HCP	healthcare professional
HIV	Human Immunodeficiency Virus
HLH	hemophagocytic lymphohistiocytosis
IARC	International Agency for Research on Cancer
IB	Investigator's Brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector-cell encephalopathy
ICU	intensive care unit
IRR	infusion-related reaction
LFT	liver function test

Abbreviation	Definition
MAA	Marketing Authorisation Application
mAB	monoclonal antibody
NAE	neurologic adverse event
NHL	Non-Hodgkin's lymphoma
NI-PASS	non-interventional post-authorization safety study
PASS	post-authorization safety study
PBRER	Periodic Benefit Risk Evaluation Report
PI	Product Information
PIP	Pediatric Investigation Plan
PSUR	Periodic Safety Update Report
PT	preferred term
PV	pharmacovigilance
R-CHOP	rituximab in combination with CHOP
RMP	Risk Management Plan
R/R	relapsed or refractory
SAE	serious adverse event
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TF	tumor flare
TLS	tumor lysis syndrome
ULN	upper limit of normal
USPI	United States Package Insert
WHO	World Health Organization

PART II: SAFETY SPECIFICATION

PART II: MODULE SI— EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 DIFFUSE LARGE B-CELL LYMPHOMA

Incidence

Non-Hodgkin's lymphoma: According to the International Agency for Research on Cancer (IARC), Non-Hodgkin's lymphoma (NHL) is the 11th most common cancer worldwide with more than 540,000 incident cases (all ages) estimated in 2020, accounting for an age-standardized incidence of 5.8 per 100,000 population worldwide. In Europe as well, NHL is the 11th most common cancer among all cancer types, accounting for an age-standardized incidence of 8.4 per 100,000 population in 2020. In the United States, NHL is the seventh most common cancer with an age-standardized incidence of 12.1 per 100,000 population in 2020 (GLOBOCAN 2020). Table 2 describes the incidence of NHL worldwide, in the United States, Europe, Asia and Africa (available from Global Cancer Observatory [GLOBOCAN] 2020 database, World Health Organization [WHO]).

Diffuse large B-cell lymphoma: Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL, representing approximately one-third of all cases worldwide. According to the Surveillance, Epidemiology, and End Results (SEER) cancer statistics, the annual age-adjusted incidence of DLBCL in the US was 5.6 per 100,000 for both sexes between 2014 and 2018 (SEER Cancer Stat Facts). Based on the data from French Network of Cancer Registries, the crude incidence rate of DLBCL in 2018 was reported to be 8.8 per 100,000 PY for men and 6.8 per 100,000 PY for women, while the age-standardized incidence rate of DLBCL was reported to be 4.7 and 3.2 per 100,000 PY for men and women respectively (Defossez et al. 2019). According to the Hematological Malignancy Research Network, UK, the annual incidence of DLBCL-not otherwise specified (NOS) was reported to be 7.3 per 100,000 (7.9 for males vs 6.8 for females) between 2010 and 2016 (Hematological Malignancy Research Network). A study by Smith and colleagues reported an annual age-standardized incidence of 6.6 per 100,000 population for DLBCL between 2004 and 2012 using UK's population-based Hematological Malignancy Research Network database (Smith et al. 2015). A study in Sweden reported that the incidence of DLBCL increased by 2.2% annually between 2004 and 2016 (Ekberg et al. 2020). Although the curability rate is high for DLBCL patients, 30-40% of patients will relapse or exhibit refractory disease (Sarkozy and Sehn 2018). A study aimed to assess relapsed/refractory (R/R) DLBCL epidemiology in Sweden based on the cohort of 4243 DLBCL patients from Swedish Lymphoma Register between 2007 and 2014 found that the progression or relapse is 18.9% at 2 years and 23.1% at 5 years of all DLBCL patients (Harrysson et al. 2021). Another retrospective study (REAL-TREND) identified 2778 patients with newly diagnosed DLBCL between 2010 and 2015 in China. The estimated 5-year cumulative incidence of refractory DLBCL patients was 20% (Wang et al. 2021). Throughout the world, the incidence

increases with age; for example, in the US, rates rise from 0.3/100,000/year (in patients that are 0−19 years old) to 4.6/100,000/year (20−64 years) and to 33.5/100,000/year (ages 65+) (SEER Cancer Statistics Review 1975-2015).

Prevalence

Non-Hodgkin's lymphoma: The IARC estimates that over 1.5 million people are living with NHL (all ages) globally with a 5-year prevalence proportion of 19.8 per 100,000 population in 2020. In Europe, the 5-year prevalence was 52.0 per 100,000 population in 2020, while the prevalence was 72.6 per 100,000 population in the US (GLOBOCAN 2020). Table 2 describes the prevalence of NHL worldwide, in the US, Europe, Asia and Africa (available from GLOBOCAN 2020 database and fact sheets, WHO).

Diffuse large B-cell lymphoma: A population-based study (Hematological Malignancy Research Network, UK) between 2004 and 2012 reported that the 3-year, 5-year and 10-year prevalence proportion of DLBCL was 17.6, 25.9 and 43.3 per 100,000 respectively (Smith et al. 2015). Another population-based study in Sweden reported that the 2-year, 5-year and 10-year prevalence of DLBCL in 2016 was 13.0, 28.4 and 46.2 per 100,000 population respectively. The 5-year prevalence increased by 66% between 2004 and 2016 with an average annual increase of 3.9% (Ekberg et al. 2020).

Table 2 Estimates of Non-Hodgkin's Lymphoma Incidence, Mortality, and 5-Year Prevalence in 2020 (All Ages) in Different Geographic Locations

Country	Incidence per 100,000 population (World age-standardized rate)	Mortality per 100,000 population (World age-standardized rate)	5-year Prevalence proportion (per 100,000 population)
Worldwide	5.8	2.6	19.8
Europe	8.4	2.6	52.0
United States	12.1	2.7	72.6
Asia	4.4	2.4	13.8
Africa	5.2	3.5	8.3

Source: Cancer Today-Global Cancer Observatory (GLOBOCAN 2020)

The Main Existing Treatment Options

According to the European Society for Medical Oncology 2015 guidelines (Tilly et al. 2015) and National Comprehensive Cancer Network 2019 guidelines on DLBCL (Zelenetz et al. 2019), the current standard of care for first-line treatment for DLBCL is a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) in combination with an anti-CD20 monoclonal antibody (mAb) rituximab (R-CHOP). An intensification of chemotherapy with rituximab, doxorubicin, vindesine, cyclophosphamide, bleomycin and prednisolone, given every 2 weeks followed by

sequential consolidation is also recommended alternatively in young patients with bulky disease.

For patients who are not cured with first-line therapy, high-dose chemotherapy with autologous stem cell transplantation (ASCT) is appropriate second-line treatment for R/R DLBCL that is chemotherapy-sensitive at relapse and in patients who are candidates for transplant. Patients not suitable for high-dose therapy may be treated with the same or other salvage regimens such as rituximab, gemcitabine, and oxaliplatin. Patients who relapse after second-line therapy are unlikely to respond to subsequent therapy and therefore generally are not eligible for ASCT (Tilly et al. 2015, Zelenetz et al. 2019). Patients who are not candidates for transplant should ideally be treated in the context of a clinical trial. Standard options include gemcitabine-based regimens ± rituximab, bendamustine ± rituximab, or brentuximab vedotin for CD30-positive disease. Lenalidomide ± rituximab and ibrutinib are appropriate options at relapse, particularly for patients with non–germinal center B-cell–like DLBCL. Patients who are not candidates for transplant and experience a partial response to second-line therapy, those with refractory disease during second-line therapy (regardless of transplant eligibility), and those who experience disease relapse following high dose chemotherapy plus ASCT or allogeneic hematopoietic cell transplantation should be managed with third-line systemic therapy, palliative radiotherapy, or best supportive care (Zelenetz et al. 2019).

Axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel are anti-CD19 chimeric antigen receptor (CAR) T-cell therapies approved by FDA (Food and Drug Administration) and EMA (European Medicines Agency) for the treatment of adult patients with relapsed/refractory DLBCL (Zelenetz et al. 2019).

Risk Factors for the Disease

Older age is a strong risk factor for NHL, with most cases occurring in people aged >65 years. Globally, men have over double the cumulative lifetime risk of developing NHL. Greater prevalence of certain risk factors, such as obesity, human immunodeficiency virus (HIV), and chemical exposure among men may help explain the increased risk. In the United States, white and non-Hispanic people are at highest risk of NHL, while Asian/Pacific Islander, American Indian and black populations are at the lowest risk. Family history of hematological malignancy, and certain autoimmune diseases such as Sjögren's syndrome, systemic lupus erythematosus, celiac disease, and scleroderma have been associated with various subtypes of NHL (Thandra et al. 2021).

In a pooled analysis of 4667 DLBCL cases from 19 studies, it was reported that DLBCL was associated with B-cell activating autoimmune diseases, hepatitis C virus seropositivity, family history of non-Hodgkin lymphoma, higher young adult body mass index, higher recreational sun exposure, any atopic disorder, and higher socioeconomic status. Additional risk factors for women were occupation as field crop/vegetable farm worker, hairdresser, and seamstress/embroider, low adult body mass index, hormone replacement therapy started at least at 50 years of age, and oral contraceptive use

before 1970. Additional risk factors for men were occupation as material handling equipment operator, lifetime alcohol consumption, and previous blood transfusion (Cerhan et al. 2014).

Natural History of the Indicated Condition in the (Untreated) Population

Non-Hodgkin's lymphoma ranks as the 11th most common cause of death among all cancers worldwide. An estimated 259,793 deaths were attributed to NHL in 2020 worldwide, with an age-standardized mortality rate of 2.6 per 100,000 population. It is the 12th most common cancer death in Europe, with 49,684 deaths, and eighth most common in the US, with 20,858 deaths in 2020 (GLOBOCAN 2020). Table 2 describes the mortality due to NHL worldwide, in the US, Europe, Asia and Africa (available from GLOBOCAN 2020 database and fact sheets, WHO). Based on the SEER Explorer database, from 2000 to 2017, the 5-year and 10-year survival rate of NHL is 71.5% and 64.4% respectively, since the time of diagnosis (SEER Explorer Database).

Nearly 40% of patients with DLBCL will eventually die of relapsed disease or disease that is refractory to first-line therapy. Per SEER cancer statistics, the 5-year relative survival for patients with DLBCL was 63.9% in the US between 2011 and 2017. The 5-year relative survival was 73.6% for Stage I and Stage II, 63.7% for stage III and 53.2% for Stage IV DLBCL (SEER Cancer Stat Facts). In a population-based cohort of 4243 relapsed/refractory DLBCL patients in Sweden, 5-year overall survival for patients treated with curative intent was 65.3% (Harrysson et al. 2021).

Important Co-Morbidities

A retrospective study identified 3905 adult patients diagnosed with DLBCL (2007–2013) through the Swedish Lymphoma Register. The most prevalent comorbid conditions were cardiovascular diseases (14%), solid cancer (13%), diabetes (10%), cerebrovascular diseases (9%), chronic pulmonary disease (7%), and rheumatologic disease (5%) (Wasterlid et al. 2019). Another retrospective study identified 181 DLBCL patients between 2010 and 2012 in Austria. The most common comorbid conditions were solid cancer (3.9%), diabetes (3.9%), chronic pulmonary disease (3.9%), connective tissue disease (3.3%), congestive heart disease (2.2%), and cerebrovascular disease (2.2%) (Kocher et al. 2020).

PART II: MODULE SII— NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key findings with glofitamab identified in single- and repeat-dose toxicity studies up to 4-weeks in duration in cynomolgus monkeys included B-cell depletion, transient post-dose cytokine release, primarily after the first dose and changes secondary to cytokine release (clinical signs, acute phase reactions, changes in leukocytes and an increase in heart rate and body temperature).

Cynomolgus monkeys with severe cytokine release syndrome (CRS) after a single dose (≥ 100 μg/mL) without obinutuzumab pretreatment (Gpt) had epithelial degeneration/ single cell necrosis in the exocrine pancreas and stomach mucosa or erosions in the gastrointestinal tract and inflammatory cell infiltrates in some organs. These findings were likely secondary to cytokine release or cytokine-induced immune-cell activation.

Gpt resulted in the attenuation of cytokine release allowing at least a 10x higher initial dose in cynomolgus monkeys. Administration of a low-dose prior to administering higher doses (step-up dosing) also mitigated the dose-limiting cytokine response.

Reproductive and developmental toxicity studies have not been conducted with glofitamab. The available nonclinical and clinical data for glofitamab and the known risks associated with anti-CD20 antibodies indicate an overall risk to pregnancy (due to cytokine release and/or infections) but a low risk for teratogenicity.

Key safety findings from nonclinical studies and relevance to human usage

- **Cytokine Release Syndrome**

Post-dose clinical signs were observed following the first dose of glofitamab, and included emesis, pale skin, decreased activity, and hunched posture. In most cases these clinical signs were mild and reversible, except for some animals given an initial dose of ≥ 100 mg/kg without Gpt, which did not recover and had to be euthanized. Clinical signs correlated with high cytokine levels, increased C-reactive protein, bilirubin and triglycerides, and decreased albumin and cholesterol, as well as mildly to moderately increased fibrinogen, partial thromboplastin time, and activated partial thromboplastin time, consistent with an acute phase response.

Relevance to human usage: Yes

Discussion: The mechanism of action of glofitamab is driven by B cell-dependent T-cell activation and subsequent T-cell-mediated B-cell killing. As observed with other CD3 engagers such as blinatumomab and CAR T-cell therapy, T-cell activation may lead to an excess of systemic cytokine release which may lead to serious and even fatal events (Blinatumomab United States Product Insert [USPI] and Summary of Product Characteristics [SmPC]; Hopfinger 2019). Signs or symptoms of CRS most frequently reported (≥ 5% of patients who experienced CRS of any grade [by American Society for Transplantation and Cellular Therapy {ASTCT} 2019 grading] in glofitamab-treated patients in the primary safety population) in Study NP30179 include pyrexia, tachycardia, hypotension, chills, hypoxia, headache, and nausea (Annex 7B.1). Cytokine release syndrome is an important identified risk for glofitamab. Serious and life-threatening CRS events occurred in patients treated with glofitamab; however, none were fatal (Module SVII.3). The majority of CRS events occurred in the first cycle of glofitamab administration, mostly associated either with the Cycle 1 Day 8 or Cycle 1 Day 15 doses.

- **B cell depletion and hematologic effects**

Consistent with the pharmacological mechanism of action, a reduction of B lymphocytes as well as activation and expansion of T-cell subsets (memory CD8 > naïve CD8 > CD4 > T_{reg}) was observed. Animals dosed with glofitamab had dose-dependent decreased cellularity of lymphoid follicles of the spleen, mesenteric, and mandibular lymph nodes, correlating immunohistochemically with decreased numbers of CD20+ B cells.

Concurrent with T-cell activation and cytokine release, a transient decrease in total white blood cell counts, lymphocytes, neutrophils, monocytes, basophils, and platelets could be observed, consistent with immune cell activation, margination, and redistribution. In addition, a decrease in red blood cells and an increase in reticulocytes was evident.

Relevance to human usage: Yes

Discussion: Neutropenia is a known class effect with other CD20-targeted therapies. Patients with severe neutropenia have an increased risk of infection. Neutropenia has been very commonly reported as an adverse drug reaction in patients treated with glofitamab, which may be attributed to the mechanism of action of glofitamab. Neutropenia is clinically manageable and reversible with Granulocyte Colony Stimulating Factor use. Neutropenia is an identified risk for glofitamab (Module SVII.1).

- **Cardiovascular effects**

Administration of glofitamab was associated with sustained dose-dependent increases in heart rate (beginning as early as 30 minutes post dose up to 20 hours post dose) and body temperature in nonhuman primates. These findings are consistent with cytokine release and acute phase reactions. There was no effect of glofitamab administration on QRS duration or QTc interval.

Relevance to human usage: Yes

Discussion: Hypotension and tachycardia have been reported as symptoms of CRS in patients treated with glofitamab. In Study NP30179, among patients in the primary safety population who received at least one dose of glofitamab and had at least one post-baseline QTcF value (N = 141), 125 patients (88.7%) had maximum QTcF values post-baseline ≤ 450 ms. Thirteen patients (9.2%) had post-baseline QTcF values > 450 ms - ≤ 480 ms, 1 patient (0.7%) had post-baseline QTcF values > 480 ms - ≤ 500 ms, and 2 patients (1.4%) had a post-baseline QTcF value > 500 ms. (Annex 7B.2, Annex 7B.3). All but one of the post-baseline QTcF values >450 ms were assessed as not of clinical significance by the investigator. The one patient with a clinically significant post-baseline QTcF value had heavily confounding factors at baseline and immediately prior to the QTcF being reported.

- **Systemic inflammatory cell infiltration**

Mononuclear cell infiltrates in some organs (heart, salivary gland, kidney, perivascular spaces of meninges, choroid plexus, and parenchyma of the brain - some with minimal gliosis) were increased in incidence among glofitamab-dosed animals as compared to controls.

Histopathological changes associated with the modality (independent of the tumor associated antigen) are mononuclear or mixed cell infiltrates, which may occur in any tissue (Saber et al., 2017; Kamperschroer et al., 2020).

Animals with very high levels of proinflammatory cytokines following doses ≥100 μg/kg without Gpt had epithelial degeneration/ single cell necrosis in the exocrine pancreas and stomach mucosa or erosions in the gastrointestinal tract and mixed-cell and/or neutrophilic infiltrates in the spleen, sinusoids of the liver and sporadically in some other organs including lung interstitium, choroid plexus, and adrenal gland.

Relevance to human usage: Yes

Discussion: Described or characterized by data from CD19-directed CAR-T therapies, symptoms of immune effector cell-associated neurotoxicity syndrome (ICANS) include tremor, dysgraphia, expressive aphasia, impaired attention, and apraxia (Lee et al. 2019). The etiology of toxicity in these settings is not well known and may not be responsive to cytokine-directed therapy such as tocilizumab, but has generally improved with treatment discontinuations and corticosteroids (Kochenderfer et al. 2015). Endoscopy biopsy of the colon revealed T-cell infiltration and lymphangiectasis in a patient treated with glofitamab from Study NP30179.

Neurologic adverse events (defined as Preferred Terms [PTs] in MedDRA System Organ Classes [SOCs] Nervous system disorders and Psychiatric disorders) have occurred in patients treated with glofitamab. Neurologic adverse events are considered a potential risk for glofitamab. Colitis has also been observed in Study NP30179 (Module SVII.1)

- **Reproductive/developmental toxicity**

Reproductive and developmental toxicity studies have not been conducted with glofitamab. A risk assessment for embryofetal development has been performed, using a weight-of-evidence approach. Based on a low placental transfer of antibodies during the first trimester, the mechanism of action and available nonclinical and clinical data, and available data on the anti-CD20 antibody class, the risk for teratogenicity is low. Prolonged B-cell depletion can lead to increased risk of opportunistic infection, which may cause fetal loss (obinutuzumab [Gazyvaro®] SmPC ocrelizumab [Ocrevus] SmPC, rituximab [MabThera] SmPC). Transient cytokine release associated with glofitamab administration may also be harmful to pregnancy.

Relevance to human usage: Yes

Discussion: No clinical studies have been performed in pregnant women. Women of childbearing potential are advised to use highly effective contraception to avoid pregnancy while undergoing glofitamab treatment and for at least three months after the last dose. Contraception use in male patients receiving glofitamab is not required. No pregnancies have been reported in patients treated with glofitamab.

- **Genotoxicity**

In accordance with the current ICH guidance on the preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6(R1) 2011), genotoxicity studies have not been conducted with glofitamab. It is not expected that glofitamab would interact directly with DNA or other chromosomal material.

- **Carcinogenicity**

No carcinogenicity studies have been conducted with glofitamab.

PART II: MODULE SIII— CLINICAL TRIAL EXPOSURE

Study NP30179 is a Phase I/II, multicenter, open-label, dose-escalation study evaluating the efficacy, safety, tolerability, and pharmacokinetics of glofitamab administered by IV infusion as a single agent and in combination with obinutuzumab following pretreatment with a fixed dose of obinutuzumab (Gpt) in patients with R/R NHL. Patients with a history of a R/R hematologic malignancy that is expected to express the CD20 antigen, including DLBCL and follicular lymphoma, are being enrolled. Multiple dosing schedules are being explored in Study NP30179 with the goal of minimizing treatment-emergent toxicities and maximizing the benefit/risk profile of glofitamab (see Figure 1 and Table 3).

Safety data from Study NP30179 presented in this RMP support the use of glofitamab monotherapy for the treatment of adult patients with R/R DLBCL, after two or more lines of systemic therapy.

Safety and exposure data in the RMP are presented up to the clinical cut-off date (CCOD) of 15 June 2022 from the monotherapy cohorts of Study NP30179 (Figure 1) for patients within the populations listed below (R/R DLBCL [patients treated with $\geq$2 prior lines of systemic therapy], Table 4, and R/R NHL, Table 5) who received at least one dose of glofitamab.

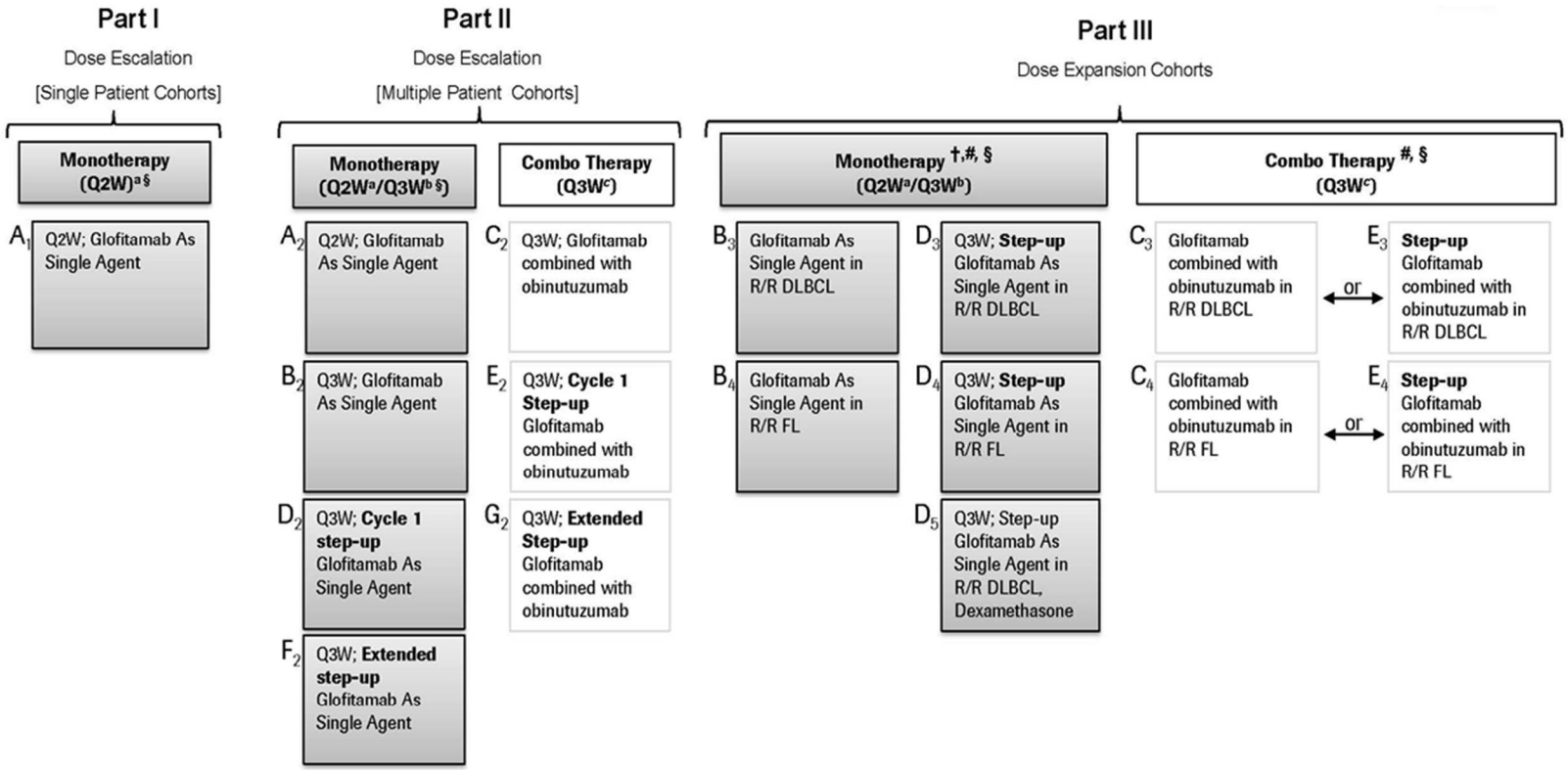
Relapsed / Refractory DLBCL Patients who have Received ≥2 Prior Lines of Systemic Therapy

- **Primary safety population**: Data from safety-evaluable patients (i.e. patients who have received at least one dose of study medication [Gpt or glofitamab]) treated with 2.5/10/30 mg step-up doses of glofitamab (the proposed registrational dose) in the proposed indication (patients with R/R DLBCL who have received ≥2 prior lines of systemic therapy) pooled from cohorts D_2 Subcohort 2 ([Sub. 2], Part II), D_3 (Part III) and D_5 (Part III) (N=154 patients). Of these 154 patients, 145 received at least one dose of glofitamab.
- Supporting data from the populations shown in Table 4, receiving glofitamab doses ≥0.60 mg (fixed dosing and step-up dosing) in the proposed indication (R/R DLBCL patients, ≥2 prior lines of systemic therapy).

Relapsed / Refractory NHL Patients (All Histologies; for list, see footnote to Table 5**)**

- **Overall safety population:** Data from all enrolled patients in Study NP30179 glofitamab monotherapy ≥0.6 mg dosing cohorts who have received at least one dose of study medication (Gpt or glofitamab), irrespective of histology (N=469 patients with R/R NHL; see footnote to Table 5). These patients support the primary safety population to provide a comprehensive overview of the safety profile of glofitamab monotherapy. Of these 469 patients, 450 received at least one dose of glofitamab.
- Supporting data from patients treated with glofitamab step-up dosing 2.5/10/30 mg (the proposed registrational dose) in Cohort D_3, Cohort D_2 [Sub 2] and Cohort D_5 from all R/R NHL histologies (see footnote to Table 5) (N=195). Of these 195 patients, 185 received at least one dose of glofitamab.

Figure 1 Study Design and Dose Escalation and Expansion Cohorts in Study NP30179



Refer to the Protocol Schedule of assessments appendices for dosing schedules:
a. Appendix 1 – Q2W Monotherapy schedule
b. Appendix 2 – Q3W Monotherapy schedule
c. Appendix 3 – Q3W Combination schedule

Q2W = Every 2 weeks; Q3W = Every 3 weeks

†Patients in Part III dose expansion monotherapy cohorts may receive Glofitamab on a Q2W or Q3W dosing schedule with fixed dosing or Q3W with step-up dosing (Cycle 1 Step-up or Extended Step-up), if supported by emerging data and/or recommended by the IMC.

#Based on determined MTD/OBD, both or one expansion cohort may be selected for monotherapy B_3 and/or D_3, B_4 and/or D_4, while C_3 or E_3 and C_4 or E_4 may be selected.

§ The shaded glofitamab monotherapy cohorts are included in the interim Clinical Study Report (CSR). Combo therapy cohorts will be presented in a subsequent CSR. Cohort D4 will only be reported for safety and not for efficacy in the interim CSR.

Table 3 Summary of Studies Included in the Risk Management Plan

Study No. and Phase	Study Design, Control Type	Population	No. of Patients	Dose, Route, and Regimen
NP30179 Phase I/II ongoing (clinical cutoff date: 15 June 2022)	Open-label, multicenter, dose-escalation and expansion study.	Patients with R/R NHL	Primary Safety Population [a]: 154 R/R DLBCL patients Overall Safety Population [b]: 469 R/R NHL patients	Glofitamab dosing regimen (2.5/10/30 mg): 2.5 mg administered on Day 8 and 10 mg administered on Day 15 within Cycle 1, followed by 30 mg on Day 1 in Cycles 2-12 (21-day cycles [Q3W]). Treatment is administered via IV infusion following a single dose of obinutuzumab (Gazyvaro® / Gazyva®) 1000 mg pretreatment (Gpt) administered via IV infusion, on Cycle 1 Day 1, 7 days before initial dosing of glofitamab.

DLBCL=diffuse large B-cell lymphoma; IV=intravenous; NHL=non-Hodgkin's lymphoma; Q3W=every 3 weeks; R/R=relapsed or refractory.

[a] Primary safety population includes patients pooled from cohorts D_2 Subcohort 2 (Part II), D_3 (Part III) and Cohort D_5 (Part III) treated at the proposed registrational dose (2.5/10/30 mg) in the proposed indication (R/R DLBCL patients who have received ≥2 prior lines of systemic therapy).

[b] Overall safety population includes all enrolled patients with R/R NHL in Study NP30179 in the glofitamab monotherapy ≥0.6 mg dosing cohorts who have received at least one dose of study medication (obinutuzumab pretreatment or glofitamab), irrespective of histology.

Table 4 Description of Cohorts/Groups Presented for Patients with Relapsed/Refractory DLBCL who have Received ≥2 Prior Systemic Therapies (Safety-Evaluable Population)

	Patients with R/R DLBCL who have Received ≥2 Prior Systemic Therapies					
Group/cohort	**Cohort D_3**	**Cohort D_5**	**≥0.6 mg dose**	**≥10 mg Target dose**	**Cohort D_2 Subcohort 2 + Cohort D_3**	**Cohort D_2 Subcohort 2, D_3 and D_5**
Analysis Population	Primary Efficacy Population	Supportive Safety	Supportive Safety	Supportive Efficacy / Safety	Supportive Efficacy / Safety	Primary Safety Population
	N = 107 [e]	N = 40 [f]	N = 287 [d]	N = 100 [g]	N = 114 [e]	N = 154 [e]
Source of patients	Cohort D_3 (Part III, dose expansion)	Cohort D_5 (Part III dose expansion)	All cohorts except Cohort A_1	Cohorts B_2 (Part II, dose escalation), Cohort B_3 (Part III) and Cohort D_2 Subcohort 1 (Part II, dose escalation)	Cohort D_2 subcohort 2 (Part II dose escalation) + Cohort D_3 (Part III dose expansion)	Cohort D_2 subcohort 2 (Part II dose escalation) + Cohort D_3 and Cohort D_5 (Part III dose expansion)
No. of pts receiving at least one dose of glofitamab	N = 101	N = 37	N = 273	N = 97	N = 108	N = 145
Dose (mg)	Step-up dosing, 2.5/10/30[a] mg glofitamab [h]	Step-up dosing, 2.5/10/30[a] mg glofitamab (Dex premedication [f h])	Fixed dosing, 0.6, 1,1.6, 4, 10, 16, 25 mg or 10/16[b] mg; step-up dosing, 2.5/10/16[c] mg or 2.5/10/30[a] mg glofitamab [h]	Fixed dosing, 10mg, 16mg, 25mg or 10/16[b] mg, step-up dosing, 2.5/10/16[c] mg glofitamab [h]	Step-up dosing, 2.5/10/30[a] mg glofitamab [h]	Step-up dosing, 2.5/10/30 [a] mg glofitamab (Cohort D_5, Dex premedication [f h])

Table 4 Description of Cohorts/Groups Presented for Patients with Relapsed/Refractory DLBCL who have Received ≥2 Prior Systemic Therapies (Safety-Evaluable Population) (cont.)

	Patients with R/R DLBCL who have Received ≥2 Prior Systemic Therapies					
Patient population	R/R DLBCL Patients with ≥2 prior therapies	R/R DLBCL Patients with ≥2 prior therapies	R/R DLBCL Patients with ≥2 prior therapies	R/R DLBCL Patients with ≥2 prior therapies	R/R DLBCL Patients with ≥2 prior therapies	R/R DLBCL Patients with ≥2 prior therapies
Histologies included	DLBCL NOS, HGBCL, trFL and PMBCL	DLBCL NOS, HGBCL, trFL and PMBCL	DLBCL NOS, HGBCL, trFL and PMBCL	DLBCL NOS, HGBCL, trFL and PMBCL	DLBCL NOS, HGBCL, trFL and PMBCL	DLBCL NOS, HGBCL, trFL and PMBCL

Dex = dexamethasone; DLBCL = diffuse large B-cell lymphoma; HGBCL = high-grade B-cell lymphoma; NHL = non-Hodgkin's lymphoma; NOS = not otherwise specified; PMBCL = primary mediastinal B-cell lymphoma; R/R = relapsed/refractory; trFL = transformed follicular lymphoma.

[a] 2.5 mg on C1D8, 10 mg on C1D15, 30 mg C2D1 and subsequent Q3W cycles.

[b] 10 mg on C1D1, 16 mg on C2D1 and subsequent Q3W cycles.

[c] 2.5 mg on C1D1, 10 mg on C1D8, 16 mg C2D1 and subsequent Q3W cycles.

[d] Includes patients treated with two doses of obinutuzumab (Gazyva®, double Gpt [DGpt]) in Cohort D_2, Subcohort.4.

[e] Safety population (R/R DLBCL) in Cohort D_3 excludes one FL patient and one patient who did not receive any study treatment with Gpt or glofitamab (enrolled in error).

[f] Safety population (R/R DLBCL) in Cohort D_5 excludes one FL patient enrolled in error.

[g] Safety population in ≥10 mg target dose cohort excludes one patient assigned to 10/16 mg treatment who did not receive any study treatment with Gpt or glofitamab.

[h] Premedication with corticosteroids prior to glofitamab was mandatory for all patients in the study. In Cohort D_5, dexamethasone was pre-specified per protocol while in the other cohorts, the type of corticosteroid was at the discretion of the investigator who had the option to use any of the following agents (methylprednisolone, prednisone or dexamethasone).

Table 5 Description of Cohorts/Groups Presented for Relapsed/Refractory NHL Patients (All Histologies, Safety-Evaluable Population)

	Patients with R/R NHL (All Histologies)	
Group/cohort	Cohort D_2 Subcohort 2, D_3 and D_5 Step-up dosing, 2.5/10/30[a] mg	All patients ≥0.6 mg
Analysis Population	Supportive Safety N = 195	Overall Safety Population [d] N = 469
Source of patients	Cohort D_2 subcohort 2 (Part II dose escalation) + Cohort D_3 and Cohort D_5 (Part III dose expansion) (Cohort D_5, Dex premedication)	Cohorts A_2, B_2, D_2, F_2, B_3, B_4, D_3, D_4, D_5
No. of pts receiving at least one dose of glofitamab	N = 185	N = 450
Dose (mg)	Step-up dosing, 2.5/10/30[a] mg glofitamab [g]	Fixed dosing, 0.6, 1, 1.6, 4, 10, 16, 25 mg or 10/16[b] mg; step-up dosing, 2.5/10/16[c] mg, 2.5/10/30[a,d] mg or 0.5/2.5/10/30[e] mg glofitamab [g]
Patient population	Patients with R/R NHL	Patients with R/R NHL
Histologies included	All NHL histologies per protocol [f]	All NHL histologies per protocol [f]

Dex = dexamethasone; DLBCL = diffuse large B-cell lymphoma; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory

[a] 2.5 mg on C1D8, 10 mg on C1D15, 30 mg C2D1 and subsequent Q3W cycles.

[b] 10 mg on C1D1, 16 mg on C2D1 and subsequent Q3W cycles.

[c] 2.5 mg on C1D1, 10 mg on C1D8, 16 mg C2D1 and subsequent Q3W cycles.

[d] Includes patients treated with two doses of obinutuzumab (Gazyva®, double Gpt [DGpt]) in Cohort D_2, Subcohort.4.

[e] 0.5 mg on C1D8, 2.5 mg on C1D15, 10 mg on C2D1, 30 mg C3D1 and subsequent Q3W cycles.

[f] Non-Hodgkin's Lymphoma (NHL) including: Grades 1-3b follicular lymphoma (FL), Marginal zone lymphoma (splenic; nodal; extra-nodal), mantle cell lymphoma (MCL), Diffuse Large B Cell lymphoma (DLBCL) not otherwise specified (NOS), high grade B cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma (PMBCL), Richter's transformation and/or transformed FL (tr FL).

[g] Premedication with corticosteroids prior to glofitamab was mandatory for all patients in the study. In Cohort D_5, dexamethasone was pre-specified per protocol while in the other cohorts, the type of corticosteroid was at the discretion of the investigator who had the option to use any of the following agents (methylprednisolone, prednisone or dexamethasone)

Clinical trial exposure data from Study NP30179 supporting the MAA for the proposed indication are presented in the tables below.

Duration of Exposure

Primary Safety Population

A total of 145 patients (45.80 patient-years of exposure) with R/R DLBCL in the primary safety population (Cohorts D_2 [Sub.2], D_3, and D_5) received at least one dose of glofitamab. Of these patients, 74 (51.0%) received glofitamab for ≤ 3 months (Table 6). A majority of patients (61.4%) received <8 cycles of glofitamab (Table 8). Exposure in Cohort D_5 is low as enrollment started later than other cohorts.

Overall Safety Population

A total of 450 patients (154.64 patient-years of exposure) with mixed R/R NHL histologies in the overall safety population received at least one dose of ≥0.60 mg glofitamab. Of these patients, 53.3% received glofitamab from >3 to ≤ 9 months and 44.7% received glofitamab for ≤ 3 months (Table 7). A total of 170 patients (37.8%) received > 8 cycles of glofitamab (Table 9).

Table 6 Duration of Exposure - Patients with R/R DLBCL (≥2 Prior Systemic Therapies)

Summary of Duration of Exposure, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohort D3 (N=101)		Glofitamab 2.5/10/30 mg Cohort D5(a) (N=37)		Glofitamab Doses >=0.60 mg (N=273)		Glofitamab Doses >=10 mg(b) (N=97)	
Duration of exposure	Patients (N=101)	Person time*	Patients (N=37)	Person time*	Patients (N=273)	Person time*	Patients (N=97)	Person time*
0 <= 1 month	26 (25.7%)	0.76	9 (24.3%)	0.23	67 (24.5%)	2.05	23 (23.7%)	0.81
> 1 <= 3 months	30 (29.7%)	5.13	8 (21.6%)	1.38	74 (27.1%)	12.41	26 (26.8%)	4.25
> 3 <= 6 months	18 (17.8%)	6.58	6 (16.2%)	2.09	62 (22.7%)	23.16	24 (24.7%)	8.95
> 6 <= 9 months	25 (24.8%)	15.86	14 (37.8%)	8.92	67 (24.5%)	41.75	23 (23.7%)	14.06
> 9 <= 12 months	2 (2.0%)	1.64	0	NE	3 (1.1%)	2.51	1 (1.0%)	0.86
Total patients numbers/person time	101 (100%)	29.97	37 (100%)	12.62	273 (100%)	81.88	97 (100%)	28.94

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of Glofitamab) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 6 Duration of Exposure - Patients with R/R DLBCL (≥2 Prior Systemic Therapies) (cont.)

Summary of Duration of Exposure, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=108)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=145)	
Duration of exposure	Patients (N=108)	Person time*	Patients (N=145)	Person time*
0 <= 1 month	27 (25.0%)	0.76	36 (24.8%)	1.00
> 1 <= 3 months	30 (27.8%)	5.13	38 (26.2%)	6.51
> 3 <= 6 months	20 (18.5%)	7.39	26 (17.9%)	9.47
> 6 <= 9 months	29 (26.9%)	18.27	43 (29.7%)	27.18
> 9 <= 12 months	2 (1.9%)	1.64	2 (1.4%)	1.64
Total patients numbers/person time	108 (100%)	33.19	145 (100%)	45.80

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of Glofitamab) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 7 Duration of Exposure - Patients with R/R NHL– All Histologies

Summary of Duration of Exposure, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5 and Total Doses >= 0.60 mg, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab Doses >=0.60 mg (N=450)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)	
Duration of exposure	Patients (N=450)	Person time*	Patients (N=185)	Person time*
0 <= 1 month	90 (20.0%)	2.92	40 (21.6%)	1.13
> 1 <= 3 months	111 (24.7%)	18.46	45 (24.3%)	7.86
> 3 <= 6 months	97 (21.6%)	36.52	34 (18.4%)	12.68
> 6 <= 9 months	143 (31.8%)	89.32	63 (34.1%)	39.92
> 9 <= 12 months	9 (2.0%)	7.43	3 (1.6%)	2.45
Total patients numbers/person time	450 (100%)	154.64	185 (100%)	64.03

Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of Glofitamab) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 8 Exposure by Number of Cycles- Patients with R/R DLBCL (≥2 Prior Systemic Therapies)

Summary of Number of Visit Cycles, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohort D3 (N=101)		Glofitamab 2.5/10/30 mg Cohort D5(a) (N=37)		Glofitamab Doses >=0.60 mg (N=273)		Glofitamab Doses >=10 mg(b) (N=97)	
Number of Cycles	Patients (N=101)	Person time*	Patients (N=37)	Person time*	Patients (N=273)	Person time*	Patients (N=97)	Person time*
<8 Cycles	66 (65.3%)	9.17	21 (56.8%)	2.87	166 (60.8%)	22.36	59 (60.8%)	8.07
8 Cycles	7 (6.9%)	2.83	1 (2.7%)	0.38	22 (8.1%)	8.76	11 (11.3%)	4.68
9-11 Cycles	1 (1.0%)	0.47	1 (2.7%)	0.44	12 (4.4%)	5.82	7 (7.2%)	3.51
12 Cycles	27 (26.7%)	17.51	14 (37.8%)	8.92	73 (26.7%)	44.94	20 (20.6%)	12.68
Total patients numbers/person time	101 (100%)	29.97	37 (100%)	12.62	273 (100%)	81.88	97 (100%)	28.94

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of Glofitamab) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ex_cycles_rmp.sas
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Table 8 Exposure by Number of Cycles- Patients with R/R DLBCL (≥2 Prior Systemic Therapies) (cont.)

Summary of Number of Visit Cycles, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=108)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=145)	
Number of Cycles	Patients (N=108)	Person time*	Patients (N=145)	Person time*
<8 Cycles	68 (63.0%)	9.52	89 (61.4%)	12.40
8 Cycles	7 (6.5%)	2.83	8 (5.5%)	3.21
9-11 Cycles	3 (2.8%)	1.48	4 (2.8%)	1.93
12 Cycles	30 (27.8%)	19.35	44 (30.3%)	28.27
Total patients numbers/person time	108 (100%)	33.19	145 (100%)	45.80

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of Glofitamab) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ex_cycles_rmp.sas
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Table 9 Exposure by Number of Cycles - Patients with R/R NHL– All Histologies

Summary of Number of Visit Cycles, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5 and Total Doses >= 0.60 mg, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab Doses >=0.60 mg (N=450)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)	
Number of Cycles	Patients (N=450)	Person time*	Patients (N=185)	Person time*
<8 Cycles	241 (53.6%)	34.83	103 (55.7%)	15.21
8 Cycles	39 (8.7%)	16.28	13 (7.0%)	5.43
9-11 Cycles	21 (4.7%)	10.27	6 (3.2%)	2.85
12 Cycles	149 (33.1%)	93.26	63 (34.1%)	40.54
Total patients numbers/person time	450 (100%)	154.64	185 (100%)	64.03

Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of Glofitamab) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ex_cycles_rmp.sas
Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/Adhocs_Interim_15JUN2022/prod/output/t_ex_cycles_rmp_I_RMP2_SERO_15JUN2022_30179.out
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Exposure by Age Group and Gender

Primary Safety Population

Of the patients who received at least one dose of glofitamab in the primary safety population (N = 145), 45.5% (66/145 patients) were ≥18 to ≤64 years of age and 65.5% (95/145 patients) were male. Male patients had 27.4 patient-years of exposure versus 18.4 patient-years in female patients (Table 10).

Overall Safety Population

Of the patients who received at least one dose of glofitamab ≥0.60 mg in the overall safety population (N = 450), 48.9% (220/450 patients) were ≥18 to ≤64 years of age and 62.0% (279/450 patients) were male. Male patients had 92.7 patient-years of exposure versus 62.0 patient-years in female patients (Table 11).

Table 10 Exposure by Age Group and Gender - Patients with R/R DLBCL (≥2 Prior Systemic Therapies)

Summary of Exposure by Age Group and Gender, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy),
Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

Age group (years)	Patients			Person time*		
	Male	Female	Total	Male	Female	Total
Glofitamab 2.5/10/30 mg Cohort D3 (N=101)						
>=18 <=64	31 (44.3%)	14 (45.2%)	45 (44.6%)	9.83	4.67	14.51
> 64 <=74	26 (37.1%)	13 (41.9%)	39 (38.6%)	5.71	5.04	10.74
> 74 <=84	11 (15.7%)	4 (12.9%)	15 (14.9%)	2.34	1.90	4.24
> 84	2 (2.9%)	0	2 (2.0%)	0.49	NE	0.49
Total patients numbers/person time	70 (100%)	31 (100%)	101 (100%)	18.36	11.61	29.97
Glofitamab 2.5/10/30 mg Cohort D5(a) (N=37)						
>=18 <=64	12 (54.5%)	4 (26.7%)	16 (43.2%)	4.79	0.39	5.18
> 64 <=74	5 (22.7%)	2 (13.3%)	7 (18.9%)	1.13	0.67	1.80
> 74 <=84	4 (18.2%)	8 (53.3%)	12 (32.4%)	1.60	3.19	4.79
> 84	1 (4.5%)	1 (6.7%)	2 (5.4%)	0.46	0.38	0.85
Total patients numbers/person time	22 (100%)	15 (100%)	37 (100%)	7.99	4.63	12.62

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. Age and Sex information is shown for all patients who received Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of Glofitamab) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 10 Exposure by Age Group and Gender - Patients with R/R DLBCL (≥2 Prior Systemic Therapies) (cont.)

Summary of Exposure by Age Group and Gender, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy),
Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

Age group (years)	Patients			Person time*		
	Male	Female	Total	Male	Female	Total
Glofitamab						
Doses						
>=0.60 mg (N=273)						
>=18 <=64	90 (50.6%)	47 (49.5%)	137 (50.2%)	25.98	13.81	39.79
> 64 <=74	64 (36.0%)	24 (25.3%)	88 (32.2%)	18.44	8.09	26.53
> 74 <=84	21 (11.8%)	22 (23.2%)	43 (15.8%)	4.79	8.81	13.60
> 84	3 (1.7%)	2 (2.1%)	5 (1.8%)	0.95	1.00	1.95
Total patients numbers/person time	178 (100%)	95 (100%)	273 (100%)	50.16	31.72	81.88
Glofitamab						
Doses						
>=10 mg(b) (N=97)						
>=18 <=64	33 (50.8%)	17 (53.1%)	50 (51.5%)	7.99	4.79	12.77
> 64 <=74	27 (41.5%)	7 (21.9%)	34 (35.1%)	10.64	1.81	12.45
> 74 <=84	5 (7.7%)	8 (25.0%)	13 (13.4%)	0.65	3.07	3.72
Total patients numbers/person time	65 (100%)	32 (100%)	97 (100%)	19.27	9.67	28.94

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. Age and Sex information is shown for all patients who received Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of Glofitamab) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 10 Exposure by Age Group and Gender - Patients with R/R DLBCL (≥2 Prior Systemic Therapies) (cont.)

Summary of Exposure by Age Group and Gender, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy),
Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

Age group (years)	Patients			Person time*		
	Male	Female	Total	Male	Female	Total
Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=108)						
>=18 <=64	34 (46.6%)	16 (45.7%)	50 (46.3%)	10.86	5.63	16.49
> 64 <=74	26 (35.6%)	13 (37.1%)	39 (36.1%)	5.71	5.04	10.74
> 74 <=84	11 (15.1%)	5 (14.3%)	16 (14.8%)	2.34	2.51	4.85
> 84	2 (2.7%)	1 (2.9%)	3 (2.8%)	0.49	0.62	1.11
Total patients numbers/person time	73 (100%)	35 (100%)	108 (100%)	19.38	13.80	33.19
Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=145)						
>=18 <=64	46 (48.4%)	20 (40.0%)	66 (45.5%)	15.65	6.02	21.67
> 64 <=74	31 (32.6%)	15 (30.0%)	46 (31.7%)	6.83	5.71	12.54
> 74 <=84	15 (15.8%)	13 (26.0%)	28 (19.3%)	3.94	5.70	9.64
> 84	3 (3.2%)	2 (4.0%)	5 (3.4%)	0.95	1.00	1.95
Total patients numbers/person time	95 (100%)	50 (100%)	145 (100%)	27.37	18.43	45.80

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. Age and Sex information is shown for all patients who received Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of Glofitamab) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 11 Exposure by Age Group and Gender- Patients with R/R NHL– All Histologies

Summary of Exposure by Age Group and Gender, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5 and Total Doses >= 0.60 mg, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

Age group (years)	Patients			Person time*		
	Male	Female	Total	Male	Female	Total
Glofitamab Doses >=0.60 mg (N=450)						
>=18 <=64	142 (50.9%)	78 (45.6%)	220 (48.9%)	46.95	27.27	74.22
> 64 <=74	93 (33.3%)	51 (29.8%)	144 (32.0%)	30.49	17.93	48.42
> 74 <=84	40 (14.3%)	40 (23.4%)	80 (17.8%)	14.12	15.77	29.89
> 84	4 (1.4%)	2 (1.2%)	6 (1.3%)	1.11	1.00	2.11
Total patients numbers/person time	279 (100%)	171 (100%)	450 (100%)	92.66	61.98	154.64
Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)						
>=18 <=64	55 (46.2%)	26 (39.4%)	81 (43.8%)	19.85	9.14	28.99
> 64 <=74	41 (34.5%)	23 (34.8%)	64 (34.6%)	11.12	8.75	19.87
> 74 <=84	20 (16.8%)	15 (22.7%)	35 (18.9%)	6.67	6.55	13.22
> 84	3 (2.5%)	2 (3.0%)	5 (2.7%)	0.95	1.00	1.95
Total patients numbers/person time	119 (100%)	66 (100%)	185 (100%)	38.60	25.43	64.03

Sub = subcohort. Age and Sex information is shown for all patients who received Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of Glofitamab) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Exposure by Dose

Primary Safety Population

Of the patients who received glofitamab in the primary safety population (N = 145), 87.6% (127/145 patients, 40.0 patient-years of exposure) received the highest dose of 30 mg of glofitamab (Table 12). A summary of the doses for each cohort group is appended (Annex 7B.4). The majority of patients who received glofitamab in the primary safety population received all doses in accordance with the planned dose and cycles; only 9.0% of patients (13/145 patients) received at least one dose of glofitamab outside of the planned cycle or at an unplanned dose level (different from the intended dose) (Table 14).

Overall Safety Population

Of the patients who received glofitamab in the overall safety population (N = 450), 56.0% (252/450 patients, 87.9 patient-years of exposure) received the highest dose of 30 mg of glofitamab (Table 13). A summary of the doses for each cohort group is appended (Annex 7B.5). Of the subgroup of patients in the overall safety population assigned to receive glofitamab step-up dosing 2.5/10/30 mg in Cohorts D_2 [Sub. 2], D_3 and D_5 and who received at least one dose of glofitamab (N = 185), the majority received all doses in accordance to the planned dose and cycles; only 15.1% (28/185 patients) received at least one dose outside of the planned cycle or at an unplanned dose level Table 15.

Table 12 Exposure by Dose (maximum dose received) - Patients with R/R DLBCL (≥2 Prior Systemic Therapies)

Summary of Exposure by Maximum Dose, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohort D3 (N=101)		Glofitamab 2.5/10/30 mg Cohort D5(a) (N=37)		Glofitamab Doses >=0.60 mg (N=273)		Glofitamab Doses >=10 mg(b) (N=97)	
Maximum Dose	Patients (N=101)	Person time*	Patients (N=37)	Person time*	Patients (N=273)	Person time*	Patients (N=97)	Person time*
0.6 mg	0	NE	0	NE	10 (3.7%)	1.96	0	NE
1.0 mg	0	NE	0	NE	5 (1.8%)	0.99	0	NE
1.8 mg	0	NE	0	NE	7 (2.6%)	1.94	0	NE
2.5 mg	6 (5.9%)	0.11	3 (8.1%)	0.01	10 (3.7%)	0.12	0	NE
4.0 mg	0	NE	0	NE	8 (2.9%)	2.14	0	NE
9.4 mg	1 (1.0%)	0.00	0	NE	1 (0.4%)	0.00	0	NE
10.0 mg	5 (5.0%)	0.01	2 (5.4%)	0.01	23 (8.4%)	3.57	16 (16.5%)	3.55
16.0 mg	0	NE	0	NE	74 (27.1%)	21.32	74 (76.3%)	21.32
18.0 mg	0	NE	0	NE	1 (0.4%)	0.00	1 (1.0%)	0.00
20.0 mg	0	NE	0	NE	1 (0.4%)	0.00	1 (1.0%)	0.00
25.0 mg	0	NE	0	NE	5 (1.8%)	1.65	5 (5.2%)	1.65
30.0 mg	89 (88.1%)	25.69	32 (86.5%)	11.29	128 (46.9%)	39.96	0	NE
Total patients numbers/person time	101 (100%)	25.82	37 (100%)	11.30	273 (100%)	73.67	97 (100%)	26.52

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first dose of Glofitamab at the reported Maximum dose level to the day prior to the next different dose level, except if the last dose at the Maximum level) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 12 Exposure by Dose (maximum dose received) - Patients with R/R DLBCL (≥2 Prior Systemic Therapies) (cont.)

S ummary of Exposure by Maximum Dose, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=108)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=145)	
Maximum Dose	Patients (N=108)	Person time*	Patients (N=145)	Person time*
0.6 mg	0	NE	0	NE
1.0 mg	0	NE	0	NE
1.8 mg	0	NE	0	NE
2.5 mg	7 (6.5%)	0.11	10 (6.9%)	0.12
4.0 mg	0	NE	0	NE
9.4 mg	1 (0.9%)	0.00	1 (0.7%)	0.00
10.0 mg	5 (4.6%)	0.01	7 (4.8%)	0.02
16.0 mg	0	NE	0	NE
18.0 mg	0	NE	0	NE
20.0 mg	0	NE	0	NE
25.0 mg	0	NE	0	NE
30.0 mg	95 (88.0%)	28.67	127 (87.6%)	39.96
Total patients numbers/person time	108 (100%)	28.80	145 (100%)	40.11

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first dose of Glofitamab at the reported Maximum dose level to the day prior to the next different dose level, except if the last dose at the Maximum level) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 13 Exposure by Dose (maximum dose received) - Patients with R/R NHL– All Histologies

Summary of Exposure by Maximum Dose, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5 and Total Doses >= 0.60 mg, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab Doses >=0.60 mg (N=450)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)	
Maximum Dose	Patients (N=450)	Person time*	Patients (N=185)	Person time*
0.6 mg	14 (3.1%)	3.11	0	NE
1.0 mg	8 (1.8%)	1.50	0	NE
1.8 mg	9 (2.0%)	2.87	0	NE
2.5 mg	14 (3.1%)	0.24	11 (5.9%)	0.13
4.0 mg	9 (2.0%)	2.30	0	NE
9.4 mg	1 (0.2%)	0.00	1 (0.5%)	0.00
10.0 mg	34 (7.6%)	4.96	7 (3.8%)	0.02
12.0 mg	1 (0.2%)	0.04	0	NE
16.0 mg	99 (22.0%)	30.90	0	NE
18.0 mg	1 (0.2%)	0.00	0	NE
20.0 mg	1 (0.2%)	0.00	0	NE
25.0 mg	7 (1.6%)	2.42	0	NE
30.0 mg	252 (56.0%)	87.86	166 (89.7%)	56.14
Total patients numbers/person time	450 (100%)	136.21	185 (100%)	56.28

Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first dose of Glofitamab at the reported Maximum dose level to the day prior to the next different dose level, except if the last dose at the Maximum level) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 14 Exposure by Dose by Cycle - Patients with R/R DLBCL (≥2 Prior Systemic Therapies)

Summary of Exposure Within Each Dose Level, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohort D3 (N=101)		Glofitamab 2.5/10/30 mg Cohort D5(a) (N=37)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=108)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=145)	
Dose level	Patients (N=101)	Person time*	Patients (N=37)	Person time*	Patients (N=108)	Person time*	Patients (N=145)	Person time*
Obinutuzumab (C1D1)**	101 (100%)	0.00	37 (100%)	0.00	108 (100%)	0.00	145 (100%)	0.00
2.5mg (C1D8)	97 (96.0%)	2.15	35 (94.6%)	0.61	104 (96.3%)	2.27	139 (95.9%)	2.88
10 mg (C1D15)	93 (92.1%)	1.93	34 (91.9%)	0.67	99 (91.7%)	2.05	133 (91.7%)	2.72
30 mg(C2+D1)	89 (88.1%)	25.69	32 (86.5%)	11.29	95 (88.0%)	28.67	127 (87.6%)	39.96
Glofitimab (other)	10 (9.9%)	0.20	3 (8.1%)	0.04	10 (9.3%)	0.20	13 (9.0%)	0.24
Obinutuzumab (other)**	8 (7.9%)	0.00	1 (2.7%)	0.00	9 (8.3%)	0.00	10 (6.9%)	0.00

(a) Dexamethasone pretreated.
"C1D1"="Cycle 1 Day 1". "C1D8"="Cycle 1 Day 8". "C1D15"="Cycle 1 Day 15". "C2+D1"="Cycle X Day 1" where X includes all Cycles from 2 to 12 inclusively. Sub = subcohort.
* Person-time is defined as the sum of the exposure time (from first dose of Glofitamab at the reported dose level to the day prior to the next different dose level, except if the last dose is at the reported level) for every patient in unit: Years.
Patients are only counted as having received a particular dose of Glofitamab of 2.5mg, 10mg or 30mg if it was received at the planned cycle. All doses received outside of the planned cycles, or at unplanned levels, have been considered as "Glofitamab (other)".
** Person Time is not calculated for Obinutuzumab. All patients who received Obinutuzumab at Cycle 1 Day 1 are shown under C1D1,regardless of the dose. Patients who received a dose at any other visit are counted in "Obinutuzumab (other)".
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 15 Exposure by Dose by Cycle - Patients with R/R NHL– All Histologies; Cohorts D_2 [Sub. 2], D_3, and D_5

Summary of Exposure Within Each Dose Level, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

Dose level	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)	
	Patients (N=185)	Person time*
Obinutuzumab (C1D1)**	185 (100%)	0.00
2.5mg (C1D8)	167 (90.3%)	3.44
10 mg (C1D15)	169 (91.4%)	3.65
30 mg(C2+D1)	166 (89.7%)	56.13
Glofitimab (other)	28 (15.1%)	0.81
Obinutuzumab (other)**	14 (7.6%)	0.00

"C1D1"="Cycle 1 Day 1". "C1D8"="Cycle 1 Day 8". "C1D15"="Cycle 1 Day 15". "C2+D1"="Cycle X Day 1" where X includes all Cycles from 2 to 12 inclusively. Sub = subcohort.
* Person-time is defined as the sum of the exposure time (from first dose of Glofitamab at the reported dose level to the day prior to the next different dose level, except if the last dose is at the reported level) for every patient in unit: Years.
Patients are only counted as having received a particular dose of Glofitamab of 2.5mg, 10mg or 30mg if it was received at the planned cycle. All doses received outside of the planned cycles, or at unplanned levels, have been considered as "Glofitamab (other)".
** Person Time is not calculated for Obinutuzumab. All patients who received Obinutuzumab at Cycle 1 Day 1 are shown under C1D1,regardless of the dose. Patients who received a dose at any other visit are counted in "Obinutuzumab (other)".
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Exposure by Ethnic or Racial Origin

Primary Safety Population

Of the patients who received glofitamab in the primary safety population (N = 145), the majority were White (112/145 patients [77.2%], 35.1 patient-years of exposure) and of ethnicity Not Hispanic or Latino (114/145 patients [78.6%], 37.7 patient-years of exposure (Table 16, Table 18).

Overall Safety Population

Of the patients who received glofitamab in the overall safety population (N = 450), the majority were White (354/450 patients [78.7%], 120.5 patient-years of exposure) and of ethnicity Not Hispanic or Latino (351/450 patients [78.0%], 123.0 patient-years of exposure (Table 17, Table 19).

Table 16 Exposure by Race- Patients with R/R DLBCL (≥2 Prior Systemic Therapies)

Summary of Exposure by Racial Origin, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohort D3 (N=101)		Glofitamab 2.5/10/30 mg Cohort D5(a) (N=37)		Glofitamab Doses >=0.60 mg (N=273)		Glofitamab Doses >=10 mg(b) (N=97)	
Race	Patients (N=101)	Person time*	Patients (N=37)	Person time*	Patients (N=273)	Person time*	Patients (N=97)	Person time*
Asian	6 (5.9%)	2.12	1 (2.7%)	0.61	11 (4.0%)	4.79	4 (4.1%)	2.06
Black or African American	0	NE	2 (5.4%)	1.27	3 (1.1%)	1.33	1 (1.0%)	0.06
White	75 (74.3%)	23.03	32 (86.5%)	9.99	225 (82.4%)	66.18	84 (86.6%)	24.57
Unknown	20 (19.8%)	4.82	2 (5.4%)	0.74	34 (12.5%)	9.58	8 (8.2%)	2.26
Total patients numbers/person time	101 (100%)	29.97	37 (100%)	12.62	273 (100%)	81.88	97 (100%)	28.94

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of study drug) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 16 Exposure by Race- Patients with R/R DLBCL (≥2 Prior Systemic Therapies) (cont.)

Summary of Exposure by Racial Origin, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=108)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=145)	
Race	Patients (N=108)	Person time*	Patients (N=145)	Person time*
Asian	6 (5.6%)	2.12	7 (4.8%)	2.73
Black or African American	0	NE	2 (1.4%)	1.27
White	80 (74.1%)	25.07	112 (77.2%)	35.07
Unknown	22 (20.4%)	5.99	24 (16.6%)	6.73
Total patients numbers/person time	108 (100%)	33.19	145 (100%)	45.80

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of study drug) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 17 Exposure by Race- Patients with R/R NHL– All Histologies

Summary of Exposure by Racial Origin, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5 and Total Doses >= 0.60 mg, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab Doses >=0.60 mg (N=450)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)	
Race	Patients (N=450)	Person time*	Patients (N=185)	Person time*
Asian	19 (4.2%)	8.64	8 (4.3%)	3.39
Black or African American	5 (1.1%)	2.17	2 (1.1%)	1.27
White	354 (78.7%)	120.51	140 (75.7%)	48.13
Unknown	72 (16.0%)	23.32	35 (18.9%)	11.24
Total patients numbers/person time	450 (100%)	154.64	185 (100%)	64.03

Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of study drug) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 18 Exposure by Ethnic Origin - Patients with R/R DLBCL (≥2 Prior Systemic Therapies)

Summary of Exposure by Ethnic Origin, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohort D3 (N=101)		Glofitamab 2.5/10/30 mg Cohort D5(a) (N=37)		Glofitamab Doses >=0.60 mg (N=273)		Glofitamab Doses >=10 mg(b) (N=97)	
Ethnicity	Patients (N=101)	Person time*	Patients (N=37)	Person time*	Patients (N=273)	Person time*	Patients (N=97)	Person time*
Hispanic or Latino	5 (5.0%)	0.24	3 (8.1%)	1.01	11 (4.0%)	1.80	0	NE
Not Hispanic or Latino	78 (77.2%)	24.74	32 (86.5%)	10.87	220 (80.6%)	68.18	83 (85.6%)	25.34
Not Stated	16 (15.8%)	4.36	2 (5.4%)	0.74	31 (11.4%)	8.50	7 (7.2%)	2.00
Unknown	2 (2.0%)	0.62	0	NE	11 (4.0%)	3.40	7 (7.2%)	1.61
Total patients numbers/person time	101 (100%)	29.97	37 (100%)	12.62	273 (100%)	81.88	97 (100%)	28.94

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of study drug) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 18 Exposure by Ethnic Origin - Patients with R/R DLBCL (≥2 Prior Systemic Therapies) (cont.)

Summary of Exposure by Ethnic Origin, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=108)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=145)	
Ethnicity	Patients (N=108)	Person time*	Patients (N=145)	Person time*
Hispanic or Latino	5 (4.6%)	0.24	8 (5.5%)	1.25
Not Hispanic or Latino	82 (75.9%)	26.78	114 (78.6%)	37.65
Not Stated	17 (15.7%)	4.37	19 (13.1%)	5.11
Unknown	4 (3.7%)	1.80	4 (2.8%)	1.80
Total patients numbers/person time	108 (100%)	33.19	145 (100%)	45.80

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of study drug) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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Table 19 Exposure by Ethnic Origin - Patients with R/R NHL– All Histologies

Summary of Exposure by Ethnic Origin, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5 and Total Doses >= 0.60 mg, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab Doses >=0.60 mg (N=450)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)	
Ethnicity	Patients (N=450)	Person time*	Patients (N=185)	Person time*
Hispanic or Latino	19 (4.2%)	5.07	11 (5.9%)	1.92
Not Hispanic or Latino	351 (78.0%)	123.01	139 (75.1%)	50.30
Not Stated	58 (12.9%)	18.78	26 (14.1%)	8.06
Unknown	22 (4.9%)	7.79	9 (4.9%)	3.75
Total patients numbers/person time	450 (100%)	154.64	185 (100%)	64.03

Sub = subcohort. The "N" value under "Patients" shows the number of patients receiving Glofitamab. The "N" value in the main column headers also includes patients who only received Obinutuzumab.
* Person-time is defined as the sum of the exposure time (from first to last administration of study drug) for every patient in unit: Years.
NE means that there were no subjects in the category.
Data Cutoff Date: 15JUN2022

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PART II: MODULE SIV— POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 20 Important Exclusion Criteria in Pivotal Studies in the Development Program [a]

Criterion	Reason for Exclusion	Is it to be included as missing information ? (Yes/No)	Rationale *(if not included as missing information)*
Patients with chronic lymphocytic leukemia [b], Burkitt lymphoma, and lymphoplasmacytic lymphoma	These histologies might require urgent treatment with chemotherapy	No	This exclusion criterion was not related to the safety of the patient
Current or past history of progressive multifocal leukoencephalopathy	Prevent exacerbation of patient's condition and minimize the risk of a therapy that is known to cause neutropenia and B-cell depletion. This could also interfere with the determination of safety or efficacy of study treatment.	No	Given the life-threatening nature of R/R DLBCL, treatment with glofitamab should be an option for such patients. No specific warning is included in the SmPC, as it is considered part of routine oncology practice to assess a patient's fitness for treatment. Section 5.1 of the SmPC states that Study NP30179 excluded patients with progressive multifocal leukoencephalopathy.
Current or past history of CNS lymphoma	CNS penetration/activity of glofitamab is unknown.	No	Given the life-threatening nature of the proposed indications, treatment with glofitamab should be an option for such patients. No specific warning is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment. Section 5.1 of the SmPC states that Study NP30179 excluded patients with current or a history of CNS lymphoma.

Criterion	Reason for Exclusion	Is it to be included as missing information ? (Yes/No)	Rationale *(if not included as missing information)*
Patients with a known or suspected history of HLH	Prevent exacerbation of patient's condition and to minimize the risk of a therapy that was potentially immune activating. This could also interfere with the determination of safety of study treatment.	No	Given the life-threatening nature of the proposed indications, treatment with glofitamab should be an option for such patients. No specific warning is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment. Section 5.1 of the SmPC states that Study NP30179 excluded patients with a history of HLH.
Patients with acute bacterial, viral, or fungal infection at baseline, confirmed by a positive blood culture within 72 hours prior to Gpt infusion or by clinical judgment in the absence of a positive blood culture	The comorbidities could affect compliance with the protocol or interpretation of results, especially with safety. Minimize possible risks of glofitamab that are known to cause neutropenia and B-cell depletion. Additionally, infections may exacerbate immune-related safety risks associated with glofitamab.	No	Section 4.4 of SmPC warns regarding infections, including severe and life-threatening having been reported, and need for close monitoring during treatment, for signs of bacterial, fungal, and viral infections. Glofitamab must not be administered to patients with an active infection.
Patients with known active infection, or reactivation of a latent infection, whether bacterial, viral (including, but not limited to, EBV, cytomegalovirus, hepatitis B, hepatitis C, and HIV), fungal, mycobacterial, or other pathogens (excluding fungal infections of nail beds) or any major episode of infection	The comorbidities could affect compliance with the protocol or interpretation of results, especially with safety. To minimize possible risks of glofitamab that is known to cause neutropenia and B-cell depletion.	No	Section 4.4 of SmPC warns regarding infections, including severe and life-threatening having been reported, and need for close monitoring during treatment, for signs of bacterial, fungal, and viral infections. Glofitamab must not be administered to patients with an active infection.

Criterion	Reason for Exclusion	Is it to be included as missing information ? (Yes/No)	Rationale *(if not included as missing information)*
requiring hospitalization or treatment with IV antibiotics (for IV antibiotics this pertains to completion of last course of antibiotic treatment) within 4 weeks of dosing	Additionally, infections may exacerbate immune-related safety risks associated with glofitamab.		Section 5.1 of the SmPC states that Study NP30179 excluded patients with active infections.
History of treatment-emergent immune-related adverse events associated with prior immunotherapeutic agents, as follows: Grade ≥ 3 adverse events with the exception of Grade 3 endocrinopathy managed with replacement therapy; Grade 1–2 adverse events that did not resolve to baseline after treatment discontinuation	To minimize the risk of exacerbating ongoing immune-related AEs associated with prior therapies.	No	Given the life-threatening nature of the proposed indications, treatment with glofitamab should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment
Prior allogeneic SCT, prior solid organ transplant	These patients were excluded to minimize effects of possible early and late complications from prior transplant or long-term treatment with immunosuppressives that could confound study results	No	This exclusion criterion was not related to the safety of the patient. Section 5.1 of the SmPC states that Study NP30179 excluded patients with prior allogeneic stem cell transplant or prior organ transplantation.
Autologous SCT within 100 days prior to Gpt infusion	To minimize the effect of the prior transplant that could affect interpretation of efficacy and safety results.	No	Given the life-threatening nature of the proposed indications, treatment with glofitamab should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment

Criterion	Reason for Exclusion	Is it to be included as missing information ? (Yes/No)	Rationale *(if not included as missing information)*
Current or past history of CNS disease, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease. [c]	CNS penetration/activity of glofitamab is unknown. CNS diseases, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease could confound safety data.	No	Given the life-threatening nature of the proposed indications, treatment with glofitamab should be an option for such patients. No specific warning is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment. Section 5.1 of the SmPC states that Study NP30179 excluded patients with current or a history of CNS disease.
Pregnant, breast-feeding, or intending to become pregnant during the study	Reproductive and developmental toxicity studies have not been conducted with glofitamab. The available nonclinical and clinical data for glofitamab and the known risks associated with anti-CD20 antibodies indicate an overall risk to pregnancy (due to cytokine release and/or infections), but a low risk for teratogenicity	No	Section 4.6 (Fertility, pregnancy and lactation) of the SmPC advises women of childbearing potential to avoid pregnancy, and breastfeeding women to discontinue while receiving glofitamab and for 2 months after the final dose of glofitamab. Pregnancy and lactation cases will be followed per routine activities and presented in the PBRER.
Significant or extensive history of cardiovascular disease such as New York Heart Association Class III or IV or Objective Class C or D cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina	Prevent exacerbation of patient's condition. Also, the comorbidities could affect the compliance with study treatment or affect the safety or efficacy of study treatment.	No	Given the life-threatening nature of the proposed indications, treatment with glofitamab should be an option for such patients. No specific warning is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment.

Criterion	Reason for Exclusion	Is it to be included as missing information ? (Yes/No)	Rationale *(if not included as missing information)*
			Section 5.1 of the SmPC states that Study NP30179 excluded patients with significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina).
Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including diabetes mellitus, history of relevant pulmonary disorders (bronchospasm, obstructive pulmonary disease), and known autoimmune diseases	The comorbidities could affect the compliance with study treatment or interpretation of results especially with safety.	No	Given the life-threatening nature of the proposed indications, treatment with glofitamab should be an option for such patients. No specific warning is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment. Section 5.1 of the SmPC states that Study NP30179 excluded patients with significant active pulmonary disease or active autoimmune disease requiring immunosuppressive therapy.
History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins) and in part III dexamethasone cohort, patients with hypersensitivity to dexamethasone or systemic corticosteroids	Such patients cannot be treated with study treatment. To warrant patient safety.	No	Glofitamab contains a humanized IgG1 monoclonal antibody, therefore such patients should not be treated with glofitamab. Hypersensitivity to glofitamab, obinutuzumab, or any of the excipients is listed as a contraindication in the SmPC

Criterion	Reason for Exclusion	Is it to be included as missing information ? (Yes/No)	Rationale *(if not included as missing information)*
Major surgery or significant traumatic injury < 28 days prior to the Gpt infusion (excluding biopsies) or anticipation of the need for major surgery during study treatment	Minimize risks the therapy may have to surgical healing and to the risk of infection in an acutely post-surgical patient. In addition, post-surgical complications may confound interpretation of results.	No	Given the life-threatening nature of the proposed indications, treatment with glofitamab should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment
Patients with another invasive malignancy in the last 2 years (with the exception of basal cell carcinoma and tumors deemed by the investigator to be of low likelihood for recurrence)	Patients with a history of malignancies that had a high risk of relapsing early could confound efficacy data.	No	Given the life-threatening nature of the proposed indications, treatment with glofitamab should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment
Received systemic immunosuppressive medications (including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to Gpt infusion. Treatment with corticosteroid < 25 mg/day prednisone or equivalent is allowed. Inhaled and topical steroids are permitted.	These patients were excluded to minimize effects of possible early and late complications of long-term treatment with immunosuppressives that could confound study results.	No	Given the life-threatening nature of the proposed indications, treatment with glofitamab should be an option for such patients. No specific warning is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment. Section 5.1 of the SmPC states that Study NP30179 excluded patients with active autoimmune disease requiring immunosuppressive therapy.

Criterion	Reason for Exclusion	Is it to be included as missing information ? (Yes/No)	Rationale *(if not included as missing information)*
Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that would contraindicate the use of an investigational drug.	Such patients were excluded because these conditions, as per the investigator, could contraindicate the use of an investigational drug.	No	Given the life-threatening nature of the proposed indications, treatment with glofitamab should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment
Vaccination with a live vaccine within 4 weeks prior to treatment	To minimize the risk of a therapy that was potentially immunosuppressive	No	Section 4.4 of SmPC warns of immunization. Immunization with live vaccines is not recommended during glofitamab therapy.

AE=adverse event, CNS=central nervous system, DLBCL=diffuse large B-cell lymphoma, Gpt= Gazyva®/Gazyvaro® pretreatment, HIV= human immunodeficiency virus, HLH=hemophagocytic lymphohistiocytosis, IgG= immunoglobulin G, IV=intravenous, R/R=relapsed/refractory, SmPC=Summary of Product Characteristics, SCT=stem cell transplantation.

[a] Exclusion criteria are from Study NP30179 protocol version 11.

[b] The exclusion of patients with chronic lymphocytic leukemia reduced the risk of tumor lysis syndrome and infusion-related reactions, which are more likely to occur in patients with high peripheral B cell counts.

[c] Patients with a history of stroke who have not experienced a stroke or transient ischemic attack in the past 2 years and have no residual neurologic deficits, as judged by the investigator, are allowed.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

The clinical trial development program for glofitamab was unable to detect adverse drug reactions that are

- rare adverse reactions
- caused by prolonged exposure
- caused by cumulative exposure
- or that have a long latency

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Table 21 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure [a]
Pregnant women	None
Breastfeeding women	None
Patients with relevant comorbidities:	
Patients with hepatic impairment [b]	Mild hepatic impairment [d]: n=21 Moderate hepatic impairment [d]: n=0 Severe hepatic impairment [d]: n=1
Patients with renal impairment [c]	Mild renal impairment [d]: n=50 Moderate renal impairment [d]: n=21 Severe renal impairment [d]: n=2
Patients with cardiovascular impairment [e]	Not included
Immunocompromised patients [f]	Very limited [g]
Patients with a disease severity different from inclusion criteria in clinical trials	Very limited [h]
Population with relevant different ethnic origin	Refer to Table 18
Subpopulations carrying relevant genetic polymorphisms	Not included
Other:	Not included

Table 21 Exposure of Special Populations Included or Not in Clinical Trial Development Program (cont.)

AST = aspartate aminotransferase; TB = total bilirubin; ULN = upper limit of normal.

[a] Exposure and information regarding inclusion are provided for Study NP30179

[b] Hepatic impairment categories:

Normal: TB & AST ≤ ULN

Mild hepatic impairment (TB > ULN to 1.5 x ULN or AST > ULN)

Moderate hepatic impairment (TB >1.5–3 x ULN, any AST)

Severe hepatic impairment (TB >3 - 10 x ULN, any AST)

[c] Excluded patients with creatinine > ULN and a measured creatinine clearance < 60 mL/min.

Renal impairment category is based on estimated creatinine clearance per FDA guidance

Normal: ≥ 90 mL/min

Mild: 60-89 mL/min

Moderate: 30-59 mL/min

Severe: 15-29 mL/min

One patient was not assessed because it appeared that incorrect units were recorded by the site.

[d] Numbers are based on the primary safety population, i.e. patients with R/R DLBCL who have received ≥2 prior lines of systemic therapy, treated with glofitamab step-up dosing 2.5/10/30 mg (Cohorts D_2 [sub2], D_3, and D_5; N = 145).

[e] Patients with significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) were excluded.

[f] Patients with positive serologic test results for HIV infection were excluded.

[g] In patients in the primary safety population treated with glofitamab (N = 145), hypogammaglobulinemia was reported in the previous or concurrent medical history for 3 patients.

[h] In patients in the overall safety population treated with glofitamab (N = 450), at least one of the following major protocol deviations was reported in 13 patients: current or past history of CNS disease, history of autoimmune disease, other invasive malignancy within the last 2 years, significant uncontrolled disease, active or latent infection within 4 weeks of Gpt; non-adequate hematological function; non-adequate liver function.

Source: Annex 7B.6; Annex 7B.7;
Annex 7B.44 Annex 7B.8.

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

This section is not applicable, because glofitamab has not yet been approved in any country.

SV.1.2 Exposure

This section is not applicable, because glofitamab has not yet been approved in any country.

PART II: MODULE SVI— ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Drugs that have a potential for misuse for illegal purposes are expected to share general characteristics such as psychoactive, stimulant, or sedative effects, or less commonly, anabolic effects or enhancement of hemoglobin levels.

For glofitamab, there is neither nonclinical nor current clinical evidence supporting psychostimulatory effects or dependency, which would induce misuse for illegal purposes.

A review of safety information obtained in patients exposed to glofitamab concluded that there was no indication of abuse or dependence-related adverse events (AEs).

Therefore, the potential for glofitamab to be misused for illegal purposes is low.

PART II: MODULE SVII— IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for NOT including an identified or potential risk 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):

- Pyrexia

Pyrexia occurring within 24 hours from administration of glofitamab should be recorded as CRS. Pyrexia is an identified risk, and was reported in 23 patients (15.9%) who received glofitamab in the primary safety population (N = 145); all events were Grade ≤2 (Annex 7B.9). Pyrexia is common in patients with DLBCL.

- Infusion Related Reactions

Infusion related reactions (IRRs) are expected based on experience of other CD20 agents (Gazyvaro®, Polivy, MabThera/Rituxan Summaries of Product Characteristics [SmPCs]). For glofitamab, IRRs may be clinically indistinguishable from manifestations of CRS. For all events with clinical presentation of IRR/CRS with onset within 24 hours from the end of glofitamab infusion (e.g., fever, nausea, chills, headache, hypotension,

hypoxia or organ toxicity) investigators were instructed to report using the preferred term “cytokine release syndrome”, unless no systemic increase of cytokines was detected (IRR could be recorded if no systemic increase of cytokines was detected). Therefore, the number of IRRs reported are minimal.

Among patients in the primary safety population who received at least one dose of glofitamab, IRR was reported for 10/145 patients (6.9%); all events were Grade ≤2 (Grade 1, 4 patients [2.8%], Grade 2, 6 patients [4.1%]). Of the ten patients with IRRs, five experienced IRRs after Gpt and prior to the first glofitamab dose (assessed as related to Gpt); the remaining five patients experienced IRRs after glofitamab use (four assessed as related to glofitamab). Of the four patients with IRRs related to glofitamab, one patient had IRR reported concomitantly with CRS (the same onset date); cytokine levels for the other three patients were within normal ranges. These IRRs resolved on either the same day or the day after glofitamab use. (Annex 7B.9, Annex 7B.10). A serious IRR was reported in one patient (the event was not considered related to glofitamab but related to Gpt). IRR led to dose modification in one patient (Annex 7B.11, Annex 7B.12).

- Immunogenicity

A key immunogenicity risk factor for glofitamab includes its novel bispecific antibody structure. Since the expected mechanism of action for glofitamab is to deplete B-cell production, it should limit the development of anti-drug antibodies (ADAs). Therefore, the overall immunogenicity risk for glofitamab is considered low. A total of 442 patients were evaluable for immunogenicity assessment with a baseline sample and at least one post dose sample. The majority of patients (418/442 patients [94.6%]) were negative at baseline and remained negative on treatment. Nineteen patients (4.3%) had a positive ADA sample at baseline and became negative after glofitamab treatment. Three patients (0.7%) positive at baseline had at least one subsequent positive ADA sample on treatment. Two patients (0.5%) that were negative at baseline, developed ADAs while on study, one at Treatment Completion/ET Visit and one at Follow Up till Progression visit of 12 months. It is important to note that in both cases the ADA titer was <10 which is reported for samples that were screening positive and could be confirmed; however, in the titer assay, the value was below the minimum required dilution.

Adverse reactions with clinical consequences, even serious but occurring with a low frequency or not occurring, and considered to be acceptable in relation to the severity of the indication treated:

- Risk of bleeding/ hemorrhage due to thrombocytopenia

A total of 35/145 patients (24.1%) who received at least one dose of glofitamab in the primary safety population reported an event under the grouped terms of thrombocytopenia/platelet count decreased. Thrombocytopenia was reported in 30

patients (20.7%), of whom 22 patients (15.2%) reported Grade 1-2 events and 8 patients (5.5%) reported Grade 3-4 events. A total of 5 patients (3.4%) reported platelet count decreased, of whom 3 patients (2.1%) reported Grade 1-2 events, and 2 patients reported Grade 3-4 events (Annex 7B.13). Thrombocytopenia (Grade 4) was reported as a serious AE in one patient. No platelet count decreased AEs were reported as serious (Annex 7B.11).

In the primary safety population, hemorrhagic events are defined as preferred terms from 'Haemorrhagic central nervous system vascular conditions [SMQ]', 'Haemorrhage laboratory terms [SMQ]' or 'Haemorrhage terms [excl laboratory terms] [SMQ]') concurrent with thrombocytopenia/platelet count decreased. A hemorrhagic event was reported in only one patient (0.7%) (Annex 7B.14) who experienced Grade 4 gastrointestinal hemorrhage (resolved; treatment received for the AE [octreotide and RBC transfusions]) concurrent with Grade 1 thrombocytopenia (resolved; no treatment received for the AE).

- Risk of hepatic injury

Among patients in the primary safety population who received at least one dose of glofitamab (N=145), liver and pancreatic AEs were reported in 18 patients (12.4%); 5 patients (3.4%) reported events of Grade 3-4 severity (Annex 7B.15). No events were reported as serious (Annex 7B.11). One patient reported a liver or pancreatic AE which required their glofitamab dose to be interrupted. (Annex 7B.16).

Liver function test (LFT) AEs reported as signs/symptoms concurrently with CRS in patients who received at least one dose of glofitamab in the primary safety population were reported in 6/145 patients (4.1%) (Annex 7B.17). Grade 1-2 LFT AEs were experienced by 4 patients (2.8%). At the CCOD, Grade 1-2 LFT AEs were unresolved in 1 patient. Two patients experienced a Grade ≥3 event; one patient experienced Grade 3 aspartate amino transferase (AST) increased and one patient experienced Grade 3 alanine aminotransferase (ALT) increased. At the time of the CCOD, both Grade 3 events had resolved (Annex 7B.18). One patient in the primary safety population who experienced an LFT AE concurrent with CRS, had elevated liver laboratory parameter values consistent with a potential Hy's Law case (Annex 7B.16).

Analysis of laboratory results identified 6 patients who had received at least one dose of glofitamab in the primary safety population as potential Hy's law cases due to corresponding laboratory results > 3 x upper limit of normal (ULN) for AST and ALT and/or > 2 x ULN for total bilirubin. All these potential Hy's law cases occurred either in the context of the reported CRS, or occurred concurrently with disease progression. Therefore there were no confirmed Hy's law cases (Annex 7B.19, Annex 7B.20).

- Hemophagocytic lymphohistiocytosis

No events of suspected hemophagocytic lymphohistiocytosis were reported in Study NP30179 at the time of the CCOD. Hemophagocytic lymphohistiocytosis (HLH) is a rare condition characterized by inappropriate immune activation and cytokine release. HLH shares clinical features with severe CRS, and has been reported with blinatumomab as well as CAR T-cell therapy (Teachey 2013; Lee et al. 2014; Blinatumomab United States Package Insert [USPI] and SmPC). HLH should be included in the differential diagnosis for patients who develop a sepsis-like syndrome or severe or prolonged CRS.

Based on the mechanism of action of glofitamab and data available from the primary safety population, HLH is considered a potential risk that will be followed up by routine pharmacovigilance.

- Colitis

Among patients in the primary safety population who received at least one dose of glofitamab (N=145), one patient reported a Grade 4 colitis serious adverse event (SAE). The SAE was considered related to glofitamab study treatment by the investigator. The time to onset from the first glofitamab dose was 104.0 days (Annex 7B.9, Annex 7B.21). There was no interruption to glofitamab study treatment as a result of the event and, at the time of the CCOD, the event was ongoing and considered to be resolving/recovering.

A Good Laboratory Practices toxicity study has shown changes in gastrointestinal tract (erosions and single cell necrosis) occurred in 3 cynomolgus monkeys following 100 μg/kg of glofitamab (without Gpt) (Module SII). Adverse events of colitis occurred at very low frequency in patients exposed to glofitamab and will be followed up by routine pharmacovigilance.

Known risks that require no further characterization and are followed up via routine pharmacovigilance—namely, through signal detection and adverse reaction reporting—and for which the risk-minimization messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized):

- Neutropenia /Febrile Neutropenia

Among patients in the primary safety population who received at least one dose of glofitamab, 58 of 145 patients (40.0%) reported at least one neutropenia/neutrophil count decreased AE. Grade 3-4 events were reported in 42 (29.0%) patients (Annex 7B.27). The median time to onset of the first neutropenia AE overall was 29.0 days (range: 1–203) (Annex 7B.28). Neutropenia AEs lasting longer than 30 days occurred in 17 patients (11.7%) (Annex 7B.29).

Among patients in the primary safety population who received at least one dose of glofitamab, 14 patients (9.7%) experienced infections concurrent with neutropenia (infections which started on or after the onset/start date, and before the end date of the

neutropenia event) (Annex 7B.25). Four patients (2.8%) reported febrile neutropenia, including 3 patients (2.1%) with serious febrile neutropenia (Annex 7B.9; Annex 7B.11).

Neutropenia is included in the SmPC Section 4.8 Undesirable Effects.

Known risks that have a low impact on the risk-benefit profile:

- Tumor lysis syndrome

Tumor lysis syndrome (TLS) occurred with a low frequency in patients treated with glofitamab, i.e., 2 of 145 patients (1.4%) in the primary safety population experienced TLS, both reporting Grade 3 events. No Grade 4 events were reported. The time to onset from the first glofitamab dose was 2.0 days. At the time of the CCOD, both events had resolved (Annex 7B.21).

In the overall safety population among patients who received at least one dose of glofitamab (N = 450), Grade ≥ 3 TLS was reported by 10 patients (2.2%); 8 patients (1.8%) reported a Grade 3 event and 2 patients (0.4%) reported a Grade 4 event (Annex 7B.30).

While TLS can be life threatening/fatal, the impact on the benefit-risk balance of glofitamab is considered low, since the incidence of severe TLS is low and the risk is well characterized, the concept of TLS well understood. Measures to prevent/reduce TLS are described in the SmPC Section 4.4 (Warnings and Precautions), and include prophylaxis: adequate hydration, premedication with allopurinol or rasburicase per local guidelines. TLS is further presented in Section 4.8 (Undesirable Effects). Therefore, the known risk of TLS will be followed up via routine pharmacovigilance which, together with adherence by prescribers to risk-minimization messages in the product information (routine risk minimization measures), are considered sufficient for this risk.

Potential risks that are followed up via routine pharmacovigilance

- Neurological adverse events

Neurologic toxicity has been reported frequently with other T-cell engaging therapies such as blinatumomab and CAR T-cell therapy. Some of these events were life-threatening or fatal (Blincyto [blinatumomab] SmPC and USPI, Maude et al. 2014 Kochenderfer et al. 2015). The etiology of toxicity in these settings is not well known and may not be responsive to cytokine-directed therapy such as tocilizumab, but has generally improved with treatment discontinuations and corticosteroids (Blincyto (blinatumomab SmPC and USPI; Maude et al. 2014; Kochenderfer et al. 2015).

In Study NP30179, neurologic AEs (NAEs) include PTs reported from the Nervous system disorders and Psychiatric disorders SOCs. Neurologic AEs (of any grade) were reported in 58/145 patients who received at least one dose of glofitamab (40.0%) in the primary safety population (Annex 7B.31). Neurologic AEs reported as signs/symptoms concurrently with CRS were reported in 10/145 patients (6.9%).

Seven patients (4.8%) reported Grade 1-2 NAEs concurrently with CRS, and 3 patients (2.1%) reported at least one Grade ≥3 event (Annex 7B.32). One patient reported Grade 3 somnolence (considered unrelated to study treatment by the investigator), one patient reported Grade 4 myelitis (considered related to study treatment by the investigator) and one patient had a Grade 5 NAE (delirium; considered unrelated to study treatment by the investigator). At the time of the CCOD, NAEs concurrent with CRS were resolved in the majority of patients; in 4 patients events were ongoing (myelitis, muscular weakness, hyperventilation and somnolence in the same patient, and peripheral neuropathy).

A similar frequency of neurologic AEs of any grade (40.9%) was reported in patients who received at least one dose of glofitamab in the overall safety population, as compared to the primary safety population (Annex 7B.33).

NAEs consistent with ICANS event rates (non-concurrent and concurrent with CRS) are generally low, and the majority were Grade 1-2 and considered unrelated to glofitamab study treatment. NAEs consistent with ICANS events concurrent to CRS also occurred infrequently (2.8%) in the primary safety population, mainly in the first cycle of glofitamab treatment (Annex 7B.34).

Considering the low frequency of NAEs consistent with ICANS events and the fact that the CAR-T-cell-therapy-associated toxicity 10-point (CARTOX10) and immune effector-cell encephalopathy (ICE) scoring systems were not used in Study NP30179, the neurological adverse events with PTs reported from the nervous system disorders and psychiatric disorders SOCs above represent a more appropriate characterization of the adverse events.

Despite the total frequency of NAEs, events that were Grade 3 or higher were reported in 1.4% of patients. This risk is considered to have minimal clinical impact on patients (in relation to the severity of the indication treated). NAEs such as headache, somnolence, tremor, confusional state and myelitis are included in Section 4.8 of SmPC. Therefore, NAE is considered a potential risk for glofitamab that will be followed up by routine pharmacovigilance.

SVII.1.2Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk of Cytokine Release Syndrome

Risk-benefit impact:

The mechanism of action of glofitamab is driven by T-cell activation against CD20-expressing cells. T-cell activation may lead to an excess of systemic cytokine release from cells targeted by antibodies, immune effector cells recruited to the tumor area and the subject’s immune cells activated during this process.

In the primary safety population, 98 of 145 patients (67.6%) who received at least one dose of glofitamab experienced a total of 168 cytokine release syndrome (CRS) events,

on the basis of ASTCT 2019 grading criteria (Lee et al. 2019) (Table 22). The majority of patients with CRS had events of Grade 1 as the maximum grade (50.3% of patients), which were fever with/without constitutional symptoms. Grade 2 CRS was reported in 13.1% of patients, Grade 3 CRS in 2.8%, and Grade 4 CRS in 1.4%. There were no Grade 5 CRS events. All CRS events except one ASTCT Grade 4 event had resolved at the CCOD (the patient died due to progressive disease with CRS still ongoing at time of death). One patient had glofitamab treatment withdrawn and one patient interrupted glofitamab treatment due to a CRS event (0.7% each).

In the primary safety population among patients who received at least one dose of glofitamab (N = 145), the vast majority of CRS events resolved with appropriate management, including use of tocilizumab (31/98 patients with CRS; 31.6%), corticosteroids (28.6%), tocilizumab and corticosteroids (16.3%), and oxygen (10.2%). Rates of intensive care unit (ICU) admission were low (7/99 patients with CRS; 7.1%) and no patient required the use of multiple pressors (Annex 7B.35).

Grade ≥2 CRS was reported in 17.2% of patients and the frequency of Grade 3-4 CRS was low (4.1%); however, due to the potential impact of higher grade CRS events on the benefit-risk balance of glofitamab, appropriate comprehensive labeling and patient educational materials as a risk-minimization activity are proposed to increase the likelihood of an early diagnosis of CRS followed by appropriate treatment.

In glofitamab-treated patients who received dexamethasone premedication (n=39) versus another glucocorticoid premedication (n=106), CRS of any grade occurred in 48.7% vs. 56.6% of patients, Grade 1 CRS in 38.5% vs 43.4% of patients, Grade 2 CRS in 7.7% vs 9.4% of patients, Grade 3 CRS in 2.6% vs 1.9% of patients and Grade 4 CRS in 0% vs 1.9% of patients after the 2.5 mg dose of glofitamab at Cycle 1 Day 8. After the 10 mg dose at Cycle 1 Day 15 (n=36 for dexamethasone premedication, n=99 for another glucocorticoid premedication), any grade CRS occurred in 22.2% vs 37.4% of patients, Grade 1 CRS in 22.2% vs 30.3% of patients, Grade 2 CRS in 0% vs 6.1% of patients and Grade 3 CRS in 0% vs 1% of patients. After the 30 mg dose at Cycle 2 Day 1 (n=32 for dexamethasone premedication, n=95 for another glucocorticoid premedication) any grade CRS occurred in 6.3% vs 33.7% of patients, Grade 1 CRS in 6.3% vs 32.6% of patients, and Grade 2 CRS in 0% vs 1.1% of patients (Annexes 7B.36, 7B.37, 7B.38).

Important Identified Risk of Tumor Flare

Risk-benefit impact:

Tumor flare (TF) is likely due to the influx of T-cells into tumor sites following glofitamab administration. Manifestations include localized pain at sites of lymphoma lesions, and possible volumetric increase of lymphoma lesions leading to local compression and accompanying organ dysfunction.

As of the 15 June 22 CCOD, seventeen patients (11.7%) experienced any grade TF in the primary safety population among patients who received at least one dose of glofitamab (N=145) (Table 26). Eleven patients (7.6%) experienced 11 events of Grade ≥2 TF (Annex 7B.21). All 11 events were assessed as related to glofitamab by the investigator (Annex 7B.10); 7 patients (4.8%) had Grade 2 events and 4 patients (2.8%) had Grade 3 events. Most of the events of tumor flare occurred in the inguinal node and maxillary lymph node and were associated with/characterized by localized pain, swelling, and worsening pleural effusion.

Among the 6 patients with Grade 1 tumor flare, 3 patients received treatment with analgesics, and no treatment was reported for the remaining 3 patients with Grade 1 tumor flare; all patients recovered from this event at CCOD (Annex 7B.39)

Among the 11 patients with Grade≥ 2 tumor flare, 9 patients received treatment. Of the 9 patients who received treatment, 2 patients received analgesics only, 6 patients received corticosteroids and analgesics including morphine derivatives, and 1 patient received corticosteroids and anti-emetics as treatment. Two Grade≥2 events did not require treatment. None of the patients who experienced tumor flare needed prophylactic intubation for safe administration of glofitamab due to the critical location of their lymphoma (as recommended in Study NP30179 protocol, v11.0). At the 15 June 2022 CCOD, Grade≥2 tumor flare events were resolved in 10 of the 11 patients.

None of the TF events led to withdrawal of glofitamab treatment or dose interruption. One patient required the glofitamab dose to be modified due to TF events. Overall, the median time to onset of ‘any grade’ TF was 2.00 days (range: 1.0-16.0 days). The median duration of TF was 3.50 days (range: 1.0 – 35.0) (Annex 7B.40).

Considering the low incidence of TF events, and that the majority of events resolved without glofitamab treatment modification, the impact on the benefit-risk profile is considered to be minimal. However, there is a potential for clinically significant impact based on anatomical site of lesions secondary to mass effect. Patients with bulky tumors located in close proximity to airways and/or a vital organ are at heightened risk, of which prescribers should be warned. Therefore, TF represents an important identified risk for glofitamab. Appropriate comprehensive labeling and prescriber educational materials as a risk-minimization activity, increase the likelihood of early recognition and allow planning for mitigations in patients with tumors at critical anatomic locations, reducing the impact of TF on the benefit-risk balance of the glofitamab.

Important Identified Risk of Serious Infections

Risk-benefit impact:

In the primary safety population among patients who received at least one dose of glofitamab (N=145), adverse events from the grouped terms of infections and infestation were reported in 57 patients (39.3%) (Annex 7B.22). The median time to onset of the

first infection and infestation event from the first glofitamab dose (Cycle1 Day 8) was 5.0 days (range: 2.0–15.0), and the median duration of the first infection and infestation AE from the first glofitamab dose (Cycle 1 Day 8) was 6.0 days (range: 3.0–59.0) (Annex 7B.23).

Under the grouped terms of infections and infestations AEs, 23 patients (15.9%) reported SAEs. The SAEs reported in ≥ 2% patients were sepsis (6 patients [4.1%]), COVID-19 (5 patients [3.4%]), and COVID-19 pneumonia (4 patients [2.8%]). Grade 1-2 SAEs were reported in 3 patients (2.1%), Grade 3-4 SAEs in 13 patients (9.0%), and Grade 5 SAEs in 7 patients (4.8%) (Annex 7B.11). Serious AEs related to glofitamab were reported in four patients (2.8%) (Annex 7B.24). No Grade 5 AEs were considered related to glofitamab treatment. Four patients (2.8%) reported a serious infection concurrent with Grade 3–4 neutropenia (Annex 7B.25).

In the overall safety population among patients who received at least one dose of glofitamab (N = 450), AEs in the Infections and infestations SOC were reported in 45.6% of patients (Annex 7B.26).

Due to its anticipated mode of action (MoA) resulting in profound B-cell depletion, glofitamab may be associated with an increased risk of infections. Infections have been reported in other CD20 directed therapies. The concept of serious infections is well understood with oncology treatments. Although the risk is expected/known due to MoA, some infections could be life threatening and/or fatal. Consequently, serious infections has been discussed and presented in SmPC Section 4.4 Warning and Precautions, and further presented in Section 4.8 Undesirable Effects. Patients with a history of chronic or recurrent infection or those who have conditions or had treatment that may predispose them to infections should be monitored before and during glofitamab treatment for the emergence of new or reactivated infections. Therefore, the known risk of infections will be followed up via routine pharmacovigilance which, together with adherence by prescribers to risk-minimization messages in the product information (routine risk minimization measures), are considered sufficient for this risk.

Important Potential Risks

Not applicable

Missing Information of Long-term safety

Risk-benefit impact:

At the 15 June 2022 CCOD, all patients in the primary safety population had either completed initial study treatment or had discontinued initial study treatment. Median duration of follow-up for patients in the primary safety population who had received at least one dose of glofitamab was 13.5 months (range: 0–28 months) (Annex 7B.45). Limited data are available in terms of long-term safety of patients treated with glofitamab; long-term safety is therefore considered missing information. Long-term

safety data is being collected from the ongoing NP30179 study that is included as an additional pharmacovigilance activity for long-term safety. To address this missing information, a minimum of two years follow-up from the end of treatment of the last patient enrolled in the primary safety population of Study NP30179, including an analysis of safety by sex shall be provided.

Missing Information of Safety in Patients with Prior CAR-T Therapy

Risk-benefit impact:

Based on the 15 June 2022 CCOD, among patients in the primary safety population who had received at least one dose of glofitamab (N=145), more patients had not received prior CAR-T therapy (N=98 [67.6%]) compared to patients who had received prior CAR-T therapy (N=47 [32.4%]).

Serious AEs were reported in a higher proportion of patients who previously received CAR-T therapy compared with those who had not (55.3% vs. 44.9%; Annex 7B.41). Conversely, in patients who had not received prior CAR-T therapy compared to those who had, a higher proportion of patients reported AEs leading to dose modification/interruption (21.4% vs. 12.8%). However, the difference in the sample sizes of these subgroups could potentially be a reason for the observed imbalances. The incidence of Grade 3-5 AEs was comparable across both groups (65.3% in patients who had not received prior CAR-T therapy vs. 61.7% in those who had) and there were similar rates of CRS (65.3% in patients who had not received prior CAR-T therapy vs. 72.3% in those who had).

Characterization of the safety profile of patients with prior CAR-T therapy is limited and is therefore considered missing information. Analysis of future safety information in this patient population in Study NP30179, as an additional pharmacovigilance activity, is planned.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Information on Important Identified Risks

Cytokine Release Syndrome

Potential mechanisms:

CRS results from the release of cytokines from cells targeted by antibodies, immune effector cells recruited to the tumor area, and the subject's immune cells activated during this process. The release of cytokines results in a variety of clinical manifestations

including cardiac, gastrointestinal, hepatic, coagulation, renal, respiratory, skin, and constitutional (fever, rigors, headaches, malaise, fatigue, arthralgia, nausea, and vomiting) signs and symptoms.

Evidence source(s) and strength of evidence:

– Nonclinical studies, showing transient T-cell activation and cytokine release, primarily limited to the first dose (see Module SII)

– Phase I/II clinical trial data (Study NP30179)

– Class effect: As observed with other CD3 engagers such as blinatumomab and CAR T-cell therapy, T-cell activation may lead to an excess of systemic cytokine release which may lead to serious and even fatal events (Blincyto [blinatumomab] SmPC and USPI; Hopfinger 2019).

Characterization of the risk:

Overview of CRS by ASTCT 2019 Grading Criteria

- Primary safety population

In the primary safety population, 98 of 145 patients (67.6%) who received at least one dose of glofitamab experienced a total of 168 cytokine release syndrome (CRS) events (Table 22), on the basis of ASTCT 2019 grading criteria (Lee et al. 2019). The majority of patients with CRS had events of Grade 1 maximum severity (50.3% of patients), which were fever with/without constitutional symptoms. Grade 2 CRS was reported in 13.1% of patients, Grade 3 CRS in 4 patients (2.8%), and Grade 4 CRS in 2 patients (1.4%). There were no Grade 5 CRS events. Of a total of 168 CRS events, all were considered related to glofitamab. At least one serious event of CRS was experienced by 32 patients (22.1%). All CRS events except one ASTCT Grade 4 event had resolved at the CCOD (the patient died due to progressive disease with CRS still ongoing at time of death). One patient had glofitamab treatment withdrawn and one patient had glofitamab treatment interrupted due to a glofitamab-related CRS event (0.7% each).

In the subpopulations comprising the primary safety population among patients who received at least one dose of glofitamab, i.e., patients with R/R DLBCL with ≥ 2 prior therapies who received 2.5/10/30 mg step-up dosing in Part II Cohort D_2 [Sub. 2] and Part III Cohort D_3 (N=108), and in Part III Cohort D_3 (N=101), the profile of CRS events was consistent with the primary safety population (Table 22). However, at the CCOD, patients in Cohort D_5 showed a trend to reduction in the incidence of all grade and Grade ≥ 2 CRS with each glofitamab step-up dose, as compared to patients in Cohort D_3 (Annexes 7B.42 and 7B.43).

Premedication with corticosteroids prior to glofitamab was mandatory for all patients in the study. In Cohort D_5, dexamethasone was pre-specified per protocol while in the other cohorts, the type of corticosteroid was at the discretion of the investigator who had the

option to use any of the following agents: methylprednisolone, prednisone or dexamethasone.

In patients who received dexamethasone premedication (n=39) versus another glucocorticoid premedication (n=106), CRS of any grade occurred in 48.7% vs. 56.6% of patients, Grade 1 CRS in 38.5% vs 43.4% of patients, Grade 2 CRS in 7.7% vs 9.4% of patients, Grade 3 CRS in 2.6% vs 1.9% of patients and Grade 4 CRS in 0% vs 1.9% of patients after the 2.5 mg dose of glofitamab at Cycle 1 Day 8. After the 10 mg dose at Cycle 1 Day 15 (n=36 for dexamethasone premedication, n=99 for another glucocorticoid premedication), any grade CRS occurred in 22.2% vs 37.4% of patients, Grade 1 CRS in 22.2% vs 30.3% of patients, Grade 2 CRS in 0% vs 6.1% of patients and Grade 3 CRS in 0% vs 1% of patients. After the 30 mg dose at Cycle 2 Day 1 (n=32 for dexamethasone premedication, n=95 for another glucocorticoid premedication) any grade CRS occurred in 6.3% vs 33.7% of patients, Grade 1 CRS in 6.3% vs 32.6% of patients, and Grade 2 CRS in 0% vs 1.1% of patients (Annexes 7B.36, 7B.37, 7B.38) .

- Overall safety population

In the overall safety population, among patients who received at least one dose of glofitamab (N=450), CRS events of any grade were reported in 299 patients (66.4%) by ASTCT 2019 grading (Table 23). The majority of patients who reported CRS had events of Grade 1-2 maximum severity by ASTCT 2019 grading (275 patients [61.1%]). Grade 3–4 CRS AEs were reported in 24 patients (5.3%). No Grade 5 CRS AEs were reported. Of a total of 522 CRS events, 516 were considered related to glofitamab. At least one serious event of CRS was experienced by 146 patients (32.4%). Only one patient had glofitamab treatment withdrawn due to a glofitamab-related CRS event. Glofitamab-related CRS events led to dose modification/interruption in 15 (3.3%) patients. At the time of the CCOD, 3 patients had CRS events that had not resolved.

In the subgroup of patients with R/R NHL treated with glofitamab step-up dosing 2.5/10/30 mg in Cohort D_3, Cohort D_2 [Sub. 2] and Cohort D_5 (N=185), the CRS profile was generally consistent with the overall safety population.

CRS events by Dose Cycle

In the primary safety population among patients who received at least one dose of glofitamab, CRS events occurred predominantly in Cycle 1 and were mainly associated with Day 8 and Day 15 dose administrations, with a higher frequency of CRS of any grade observed following the Day 8 (2.5 mg) dose (79 of 145 patients who received the Day 8 dose [54.5%]) compared with the Day 15 (10 mg) dose (45 of 135 patients who received the Day 15 dose, [33.3%]) (Table 24). CRS events occurred less frequently in Cycle 2 (34 of 127 patients who received glofitamab doses in Cycle 2 [26.8%]), and infrequently in Cycle 3 and beyond (3 of 107 patients who received glofitamab doses in Cycle 3 and beyond [2.8%]). Serious CRS events also occurred predominantly in Cycle 1, with a higher frequency observed following the Day 8 (2.5 mg) dose (21 of 145 patients who received the Day 8 dose [14.5%]) compared with the Day 15 (10 mg) dose (9 of 135 patients who received the Day 15 dose [6.7%]) (Table 24). Nine of 127 patients who received glofitamab doses in Cycle 2 (7.1%) and 2 of 107 patients who received glofitamab doses in Cycle 3 and beyond (1.9%) experienced serious CRS events. Glofitamab-related CRS events leading to withdrawal of glofitamab treatment occurred only following the Cycle 1 Day 8 dose (1 patient). Glofitamab-related CRS events leading to dose interruption were observed only following the Cycle 1 Day 15 dose (1 patient).

Similar results were observed in patients from all NHL histologies who received at least one dose of glofitamab and were treated at the proposed registrational dose (2.5/10/30 mg) in Cohort D_3, Cohort D_2 [Sub. 2], and Cohort D_5 (N = 185) (Table 25).

Note that CRS events by dose cycle have not been shown for the ≥0.6 mg and ≥10 mg cohorts that combine groups with fixed and step-up dosing regimens. As fixed dosing regimens are not given on the same cycle days as step-up dosing, combined data is not an accurate description of the CRS event.

Risk factors and risk groups:

The risk of CRS may be influenced by factors related to the type of therapy and treatment dose, the underlying disease (type, tumor burden, and tumor cell location [e.g., peripheral blood vs. bone marrow]), patient characteristics (age, general health status, and comorbidity burden; basal inflammatory state), and degree of T-cell activation and expansion (Shimabukuro-Vornhagen et al. 2018, Wang and Han 2018). Disease burden is among the most important predictors of severe CRS after CAR T-cell therapy and the bispecific T-cell engager blinatumomab (Teachey et al. 2016; Topp et al. 2015).

Preventability:

To reduce the occurrence of CRS with glofitamab use, patients must be pretreated with obinutuzumab seven days prior to initiation of glofitamab step-up dosing, and should be

premedicated with an anti-pyretic, antihistamine, and a glucocorticoid. As described in the SmPC (section 4.2), all patients must be monitored for signs and symptoms of potential CRS during infusion and for at least 10 hours after completion of the infusion of the first glofitamab dose (2.5 mg on Cycle 1 Day 8). Patients who experienced Grade ≥2 CRS with their previous infusion should be monitored after completion of the infusion. Data on the time to CRS onset of Grade ≥2 CRS following 10 mg and 30 mg doses is provided in the SmPC (section 4.8) to inform prescribers.

Healthcare professionals (HCPs) should have immediate on-site access to tocilizumab. At least one dose of tocilizumab must be available prior to glofitamab infusion for use in the event of CRS. Access to an additional dose of tocilizumab within 8 hours of each previous tocilizumab dose must be ensured.

All patients must be given a Patient Card (Table 41), counselled on the risk and signs and symptoms of CRS, and advised to contact the healthcare provider immediately, should they experience signs and symptoms of CRS.

Impact on the benefit-risk balance of the product:

CRS events have been manageable and reversible with supportive measures. The impact on benefit/risk balance is considered low. Grade ≥2 events require medical intervention. Grade ≥3 CRS events require hospitalization for more aggressive treatment, and patients may need ICU admission. The impact on the benefit/risk balance might be considered significant for Grade ≥2 CRS.

The majority of CRS events were of Grade 1-2 intensity and resolved with appropriate management. Although the frequency of severe and life-threatening CRS events of Grade 3-4 intensity was low, the impact on the benefit-risk balance of glofitamab may differ depending on the grade and severity of CRS. Guidance regarding premedication, careful monitoring, and management provided in the product label reduce the risk of CRS.

In addition to comprehensive product labeling, additional risk-minimization measures include educational material for patients in the form of a Patient Card. These measures, together with routine pharmacovigilance activities and the survey for prescribers to measure effectiveness of additional risk minimization measures, are considered adequate to manage the risk of CRS.

Public health impact:

No public health impact is envisaged in view of the population treated and the limitations placed upon administration of glofitamab by virtue of the warnings and precautions and dosage instructions in the product label. Use outside of controlled environments by non-healthcare professionals is not anticipated.

Table 22 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R DLBCL who have Received ≥2 Prior Systemic Therapies

Seriousness, Outcomes, Severity, Frequency of AEs, Cytokine Release Syndrome AEs, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohort D3 (N=101)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=37)	Glofitamab Doses >=0.60 mg (N=273)	Glofitamab Doses >=10 mg(b) (N=97)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=108)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=145)
Number of patients with at least one AE	74 (73.3%)	19 (51.4%)	172 (63.0%)	64 (66.0%)	79 (73.1%)	98 (67.6%)
95% CI for % of patients with at least one AE	(63.54%, 81.59%)	(34.40%, 68.08%)	(56.98%, 68.74%)	(55.66%, 75.30%)	(63.76%, 81.22%)	(59.32%, 75.12%)
Total number of AEs	135	25	274	92	143	168
Total number of AEs related to Glofit	135	25	271	89	143	168
Number of patients with at least one AE by worst grade						
Grade 1	55 (54.5%)	15 (40.5%)	110 (40.3%)	32 (33.0%)	58 (53.7%)	73 (50.3%)
Grade 2	14 (13.9%)	3 (8.1%)	49 (17.9%)	27 (27.8%)	16 (14.8%)	19 (13.1%)
Grade 3	3 (3.0%)	1 (2.7%)	9 (3.3%)	4 (4.1%)	3 (2.8%)	4 (2.8%)
Grade 4	2 (2.0%)	0	4 (1.5%)	1 (1.0%)	2 (1.9%)	2 (1.4%)
Grade 5	0	0	0	0	0	0
Number of patients with at least one serious AE	25 (24.8%)	6 (16.2%)	80 (29.3%)	39 (40.2%)	26 (24.1%)	32 (22.1%)
Number of patients with at least one AE by outcome						
Fatal outcome	0	0	0	0	0	0
Unresolved	1 (1.4%)	0	2 (1.2%)	1 (1.6%)	1 (1.3%)	1 (1.0%)
Recovering/Resolving	0	0	0	0	0	0
Recovered/Resolved	73 (98.6%)	19 (100%)	171 (99.4%)	64 (100%)	78 (98.7%)	97 (99.0%)
Resolved with sequelae	0	0	1 (0.6%)	1 (1.6%)	0	0
Unknown outcome	0	0	0	0	0	0
Glofit related AE leading to withdrawal from treatment	1 (1.0%)	0	1 (0.4%)	0	1 (0.9%)	1 (0.7%)
Glofit related AE leading to dose interruption	1 (1.0%)	0	2 (0.7%)	0	1 (0.9%)	1 (0.7%)
Glofit related AE leading to dose modification	0	0	1 (0.4%)	1 (1.0%)	0	0

Table 22 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R DLBCL who have Received ≥2 Prior Systemic Therapies (cont.)

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. ASTCT grading is used for this output and only Treatment (either Glofitamab or Obinutuzumab) Emergent CRS AEs with a valid ASTCT grade
are included.
Investigator text for AEs encoded using MedDRA version 25.0.
Data Cutoff Date: 15JUN2022

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Table 23 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R NHL– All Histologies

Seriousness, Outcomes, Severity, Frequency of AEs, Cytokine Release Syndrome AEs, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5 and Total Doses >= 0.60 mg, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab Doses >=0.60 mg (N=450)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)
Number of patients with at least one AE	299 (66.4%)	132 (71.4%)
95% CI for % of patients with at least one AE	(61.87%, 70.80%)	(64.26%, 77.75%)
Total number of AEs	522	245
Total number of AEs related to Glofit	516	245
Number of patients with at least one AE by worst grade		
Grade 1	177 (39.3%)	91 (49.2%)
Grade 2	98 (21.8%)	30 (16.2%)
Grade 3	17 (3.8%)	7 (3.8%)
Grade 4	7 (1.6%)	4 (2.2%)
Grade 5	0	0
Number of patients with at least one serious AE	146 (32.4%)	53 (28.6%)
Number of patients with at least one AE by outcome		
Fatal outcome	0	0
Unresolved	3 (1.0%)	2 (1.5%)
Recovering/Resolving	0	0
Recovered/Resolved	297 (99.3%)	130 (98.5%)
Resolved with sequelae	1 (0.3%)	0
Unknown outcome	0	0
Glofit related AE leading to withdrawal from treatment	1 (0.2%)	1 (0.5%)
Glofit related AE leading to dose interruption	10 (2.2%)	3 (1.6%)
Glofit related AE leading to dose modification	5 (1.1%)	2 (1.1%)

Sub = subcohort. ASTCT grading is used for this output and only Treatment (either Glofitamab or Obinutuzumab) Emergent CRS AEs with a valid ASTCT grade are included.
Investigator text for AEs encoded using MedDRA version 25.0.
Data Cutoff Date: 15JUN2022

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Table 24 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R DLBCL, ≥2 Prior Systemic Therapies; Cohorts D_2 [Sub. 2], D_3, and D_5

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Cytokine Release Syndrome AEs, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Cycle 1 Day 8 (N=145)	Cycle 1 Day 15 (N=135)	Cycle 2 (N=127)	Cycle 3-12 (N=107)
Number of patients with at least one AE	79 (54.5%)	45 (33.3%)	34 (26.8%)	3 (2.8%)
95% CI for % of patients with at least one AE	(46.01%, 62.77%)	(25.46%, 41.96%)	(19.31%, 35.35%)	(0.58%, 7.98%)
Total number of AEs	80	47	34	7
Total number of AEs related to Glofitamab	80	47	34	7
Number of patients with at least one AE by worst grade				
Grade 1	61 (42.1%)	38 (28.1%)	33 (26.0%)	3 (2.8%)
Grade 2	13 (9.0%)	6 (4.4%)	1 (0.8%)	0
Grade 3	3 (2.1%)	1 (0.7%)	0	0
Grade 4	2 (1.4%)	0	0	0
Grade 5	0	0	0	0
Number of patients with at least one serious AE	21 (14.5%)	9 (6.7%)	9 (7.1%)	2 (1.9%)
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	1 (1.3%)	0	0	0
Recovering/ Resolving	0	0	0	0
Recovered/Resolved	78 (98.7%)	45 (100%)	34 (100%)	3 (100%)
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0
Glofitamab related AE leading to withdrawal from treatment	1 (0.7%)	0	0	0
Glofitamab related AE leading to dose interruption	0	1 (0.7%)	0	0
Glofitamab related AE leading to dose modification	0	0	0	0

Sub = subcohort.
ASTCT grading is used for this output and only CRS AEs with a valid ASTCT grade starting after the first dose of Glofitamab are included.
Investigator text for AEs encoded using MedDRA version 25.0.
Data Cutoff Date: 15JUN2022

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Table 25 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R NHL (All Histologies); Cohorts D_2 [Sub. 2], D_3, and D_5

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Cytokine Release Syndrome AEs, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Cycle 1 Day 8 (N=185)	Cycle 1 Day 15 (N=174)	Cycle 2 (N=166)	Cycle 3-12 (N=142)
Number of patients with at least one AE	104 (56.2%)	64 (36.8%)	45 (27.1%)	9 (6.3%)
95% CI for % of patients with at least one AE	(48.75%, 63.48%)	(29.61%, 44.41%)	(20.51%, 34.54%)	(2.94%, 11.69%)
Total number of AEs	106	66	45	28
Total number of AEs related to Glofitamab	106	66	45	28
Number of patients with at least one AE by worst grade				
Grade 1	72 (38.9%)	52 (29.9%)	41 (24.7%)	8 (5.6%)
Grade 2	23 (12.4%)	9 (5.2%)	3 (1.8%)	1 (0.7%)
Grade 3	6 (3.2%)	3 (1.7%)	0	0
Grade 4	3 (1.6%)	0	1 (0.6%)	0
Grade 5	0	0	0	0
Number of patients with at least one serious AE	34 (18.4%)	15 (8.6%)	15 (9.0%)	5 (3.5%)
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	1 (1.0%)	0	1 (2.2%)	0
Recovering/ Resolving	0	0	0	0
Recovered/Resolved	103 (99.0%)	64 (100%)	44 (97.8%)	9 (100%)
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0
Glofitamab related AE leading to withdrawal from treatment	1 (0.5%)	0	0	0
Glofitamab related AE leading to dose interruption	1 (0.5%)	2 (1.1%)	0	0
Glofitamab related AE leading to dose modification	2 (1.1%)	0	0	0

Sub = subcohort.
ASTCT grading is used for this output and only CRS AEs with a valid ASTCT grade starting after the first dose of Glofitamab are included.
Investigator text for AEs encoded using MedDRA version 25.0.
Data Cutoff Date: 15JUN2022

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Tumor Flare

Potential mechanisms:

Adverse events associated with TF have been reported with some anti-cancer therapies (e.g. immunomodulating agents, T-cell engaging therapies, checkpoint inhibitors), where the mechanism of action that includes redirecting the immune response towards tumor killing results in the activation and trafficking of immune cells to tumor sites. Tumor flare is a phenomenon whereby symptoms present due to effects of influx of immune cells in response to treatment with glofitamab. Tumor pseudoprogression is primarily a radiological diagnosis, in contrast to the clinical manifestations with relatively short onset and duration that characterize tumor flare (Taleb 2019). Manifestations of tumor flare include localized pain at sites of lymphoma lesions, and possible volumetric increase of lymphoma lesions leading to local compression and accompanying organ dysfunction. Patients with tumors at critical anatomic locations should be closely monitored for TF, and considerations dependent on the anatomic locations of lymphoma lesions need to be applied and specific mitigations planned with collaboration of multidisciplinary teams.

Evidence source(s) and strength of evidence:

Tumor flare has been observed in clinical data (Study NP30179) with glofitamab. It is a known risk with other immunomodulating agents, T-cell engaging therapies, checkpoint inhibitor therapies (Taleb 2019).

Characterization of the risk:

Overview of Tumor Flare Events

- Primary safety population

Seventeen patients (11.7%) experienced any grade TF among patients in the primary safety population who received at least one dose of glofitamab (N=145) (Table 26). Eleven patients (7.6%) experienced 11 events of Grade ≥2 TF (Annex 7B.21). All 11 events were assessed as related to study treatment by the investigator (Annex 7B.10); 7 patients (4.8%) had Grade 2 events and 4 patients (2.8%) had Grade 3 events. Tumor flare events resolved in the majority of patients (94.1%); in one patient, events were unresolved at the time of reporting. None of the TF events led to withdrawal of glofitamab treatment or dose interruption. One patient required the glofitamab dose to be modified due to TF events. Overall, the median time to onset of any grade tumor flare was 2.0 days (range: 1.0-16.0 days). The median duration of tumor flare was 3.5 days (range: 1.0 – 35.0) (Annex 7B.40).

Tumor flare was reported involving lymph nodes in the head and neck presenting with pain, and involving lymph nodes in the thorax with symptoms of breathlessness due to development of pleural effusion.

- Overall safety population

In the overall safety population, among patients who received at least one dose of glofitamab (N=450), TF events of any grade were reported in 44 patients (9.8%) (Table 27). The majority of patients who reported TF had events of Grade 1-2 maximum severity (34 patients [7.6%]). Grade 3 TF AEs were reported in 10 patients (2.2%). No Grade 4 or Grade 5 TF AEs were reported. Of a total of 53 TF events, 51 were considered related to glofitamab, as assessed by the investigator. At least one SAE was experienced by 10 patients (2.2%). At the time of the CCOD, two patients (4.5%) had TF events that had not resolved.

In the subgroup of patients treated with glofitamab step-up dosing 2.5/10/30 mg in Cohort D_3, Cohort D_2 [Sub. 2], and Cohort D_5 from all histologies (N=185), frequencies of tumor flare events and serious tumor flare events were comparable with the overall safety population.

Tumor Flare Events by Dose Cycle

In the primary safety population, among patients who received at least one dose of glofitamab (N=145), TF events occurred predominantly in Cycle 1. Tumor flare was mainly associated with Day 8 dose administrations, with 13 of 145 patients who received a glofitamab dose at Day 8 (9.0%) reporting TF events of any grade following the Day 8 dose (2.5 mg) compared with 3 of 135 patients who received a glofitamab dose at Day 15 (2.2%) reporting events following the Day 15 (10 mg) dose (Table 28). Tumor flare events occurred infrequently in Cycle 2 (3 of 127 patients who received glofitamab doses in Cycle 2 [2.4%]) and were not observed in Cycle 3 and beyond. Serious TF events occurred only in Cycle 1, with 4 of 145 patients who received a glofitamab dose at Day 8 (2.8%) reporting serious TF events of any grade following the Day 8 dose (2.5 mg) compared with 1 of 135 patients who received a glofitamab dose at Day 15 (0.7%) reporting serious events following the Day 15 (10 mg) dose. Tumor flare events leading to dose modification occurred only following the Cycle 1 Day 8 dose (1 patient).

Similar results were observed in patients from all R/R NHL histologies treated at the proposed registrational dose (2.5/10/30 mg) in Cohort D_3, Cohort D_2 [Sub. 2], and Cohort D_5 (Table 29).

Note that tumor flare events by dose cycle have not been shown for the ≥0.6 mg and ≥10 mg cohorts that combine groups with fixed and step-up dosing regimens. As fixed dosing regimens are not given on the same cycle days as step-up dosing, combined data is not an accurate description of the TF event.

Risk factors and risk groups:

Treatment with immunomodulatory agents is associated with TF, and more frequent with hematologic malignancies than in patients with solid tumors (Taleb 2019).

Preventability:

Patients with tumors at critical anatomic locations should be closely monitored for tumor flare, and considerations dependent on the anatomic locations of lymphoma lesions need to be applied and specific mitigations planned with collaboration of multidisciplinary teams. Depending on the nature of the tumor inflammation, further medical and/or surgical management may be necessary (e.g., anti-inflammatory agents, airway management, decompression, prolonged hospitalization, etc.). Important differential diagnosis needs to be made with disease progression.

In Study NP30179, tumor flare was broadly managed with simple interventions, including events that resolved without any treatment, and no patients had prophylactic intubation for safe administration of glofitamab.

Section 4.4 of the SmPC provides monitoring and management advice for tumor flare, and Section 4.8 provides a description of tumor flare to reduce the potential for negative outcomes in patients experiencing the event. Additionally, the Applicant proposes to provide supplementary information in the HCP brochure to further increase awareness around tumor flare.

Impact on the benefit-risk balance of the product:

Based on safety data collected, TF associated with glofitamab administration has manifested as new or worsening pleural effusions, and localized pain and swelling at sites of lymphoma lesions. Considering the low incidence of TF events, and that the majority of events resolved without glofitamab treatment modification, the impact on benefit/risk balance is considered to be minimal.

To enhance the early recognition and management of TF, additional risk-minimization measures include educational material in the form of a HCP brochure, and the SmPC provides comprehensive guidance for patient management of TF. These measures are considered adequate to manage the risk.

Public health impact:

Given the low frequency of serious events, coupled with the responsiveness to TF management, the impact of TF on public health is considered to be low.

Table 26 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R DLBCL who have Received ≥2 Prior Systemic Therapies

Seriousness, Outcomes, Severity, Frequency of AEs, Tumour Flare Adverse Events, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic
Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohort D3 (N=101)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=37)	Glofitamab Doses >=0.60 mg (N=273)	Glofitamab Doses >=10 mg(b) (N=97)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=108)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=145)
Number of patients with at least one AE	13 (12.9%)	3 (8.1%)	27 (9.9%)	8 (8.2%)	14 (13.0%)	17 (11.7%)
95% CI for % of patients with at least one AE	(7.04%, 21.00%)	(1.70%, 21.91%)	(6.62%, 14.06%)	(3.63%, 15.61%)	(7.27%, 20.79%)	(6.98%, 18.11%)
Total number of AEs	15	3	31	10	16	19
Total number of AEs related to Glofit	15	3	29	8	16	19
Number of patients with at least one AE by worst grade						
Grade 1	6 (5.9%)	0	7 (2.6%)	1 (1.0%)	6 (5.6%)	6 (4.1%)
Grade 2	5 (5.0%)	1 (2.7%)	11 (4.0%)	3 (3.1%)	6 (5.6%)	7 (4.8%)
Grade 3	2 (2.0%)	2 (5.4%)	9 (3.3%)	4 (4.1%)	2 (1.9%)	4 (2.8%)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
Number of patients with at least one serious AE	4 (4.0%)	0	7 (2.6%)	2 (2.1%)	5 (4.6%)	5 (3.4%)
Number of patients with at least one AE by outcome						
Fatal outcome	0	0	0	0	0	0
Unresolved	1 (7.7%)	0	2 (7.4%)	1 (12.5%)	1 (7.1%)	1 (5.9%)
Recovering/Resolving	0	0	0	0	0	0
Recovered/Resolved	12 (92.3%)	3 (100%)	25 (92.6%)	7 (87.5%)	13 (92.9%)	16 (94.1%)
Resolved with sequelae	0	0	0	0	0	0
Unknown outcome	0	0	0	0	0	0
Glofit related AE leading to withdrawal from treatment	0	0	0	0	0	0
Glofit related AE leading to dose interruption	0	0	0	0	0	0
Glofit related AE leading to dose modification	1 (1.0%)	0	1 (0.4%)	0	1 (0.9%)	1 (0.7%)

Table 26 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R DLBCL who have Received ≥2 Prior Systemic Therapies (cont.)

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. Only Treatment (either Glofitamab or Obinutuzumab) Emergent AEs with a preferred term (encoded using MedDRA version 25.0) of Tumour Flare are included.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ae_out1_rmp.sas
Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/Adhocs_Interim_15JUN2022/prod/output/t_ae_out1_rmp_TF_I_RMP_SERO_15JUN2022_30179.out
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Table 27 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R NHL– All Histologies

Seriousness, Outcomes, Severity, Frequency of AEs, Tumour Flare Adverse Events, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5 and Total Doses >= 0.60 mg, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab Doses >=0.60 mg (N=450)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)
Number of patients with at least one AE	44 (9.8%)	20 (10.8%)
95% CI for % of patients with at least one AE	(7.19%, 12.90%)	(6.73%, 16.20%)
Total number of AEs	53	22
Total number of AEs related to Glofit	51	22
Number of patients with at least one AE by worst grade		
Grade 1	18 (4.0%)	8 (4.3%)
Grade 2	16 (3.6%)	8 (4.3%)
Grade 3	10 (2.2%)	4 (2.2%)
Grade 4	0	0
Grade 5	0	0
Number of patients with at least one serious AE	10 (2.2%)	7 (3.8%)
Number of patients with at least one AE by outcome		
Fatal outcome	0	0
Unresolved	2 (4.5%)	1 (5.0%)
Recovering/Resolving	0	0
Recovered/Resolved	42 (95.5%)	19 (95.0%)
Resolved with sequelae	0	0
Unknown outcome	0	0
Glofit related AE leading to withdrawal from treatment	0	0
Glofit related AE leading to dose interruption	0	0
Glofit related AE leading to dose modification	1 (0.2%)	1 (0.5%)

Sub = subcohort. Only Treatment (either Glofitamab or Obinutuzumab) Emergent AEs with a preferred term (encoded using MedDRA version 25.0) of Tumour Flare are included.
Data Cutoff Date: 15JUN2022

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Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/Adhocs_Interim_15JUN2022/prod/output/t_ae_out1_rmp_TF_I_RMP2_SERO_15JUN2022_30179.out
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Table 28 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R DLBCL, ≥2 Prior Systemic Therapies; Cohort D_2 [Sub. 2], D_3 and D_5, (Primary Safety Population)

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Tumour Flare Adverse Events, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Cycle 1 Day 8 (N=145)	Cycle 1 Day 15 (N=135)	Cycle 2 (N=127)	Cycle 3-12 (N=107)
Number of patients with at least one AE	13 (9.0%)	3 (2.2%)	3 (2.4%)	0
95% CI for % of patients with at least one AE	(4.86%, 14.84%)	(0.46%, 6.36%)	(0.49%, 6.75%)	(0.00%, 3.39%)
Total number of AEs	13	3	3	0
Total number of AEs related to Glofitamab	13	3	3	0
Number of patients with at least one AE by worst grade				
Grade 1	5 (3.4%)	1 (0.7%)	2 (1.6%)	0
Grade 2	4 (2.8%)	2 (1.5%)	1 (0.8%)	0
Grade 3	4 (2.8%)	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Number of patients with at least one serious AE	4 (2.8%)	1 (0.7%)	0	0
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	1 (7.7%)	0	0	0
Recovering/ Resolving	0	0	0	0
Recovered/Resolved	12 (92.3%)	3 (100%)	3 (100%)	0
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0
Glofitamab related AE leading to withdrawal from treatment	0	0	0	0
Glofitamab related AE leading to dose interruption	0	0	0	0
Glofitamab related AE leading to dose modification	1 (0.7%)	0	0	0

Sub = subcohort.
Only Treatment (either Glofitamab or Obinutuzumab) Emergent AEs with a preferred term (encoded using MedDRA version 25.0) of Tumour Flare are included.
Data Cutoff Date: 15JUN2022

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Table 29 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R NHL (All Histologies) Cohorts D_2 [Sub. 2], D_3, and D_5

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Tumour Flare Adverse Events, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Cycle 1 Day 8 (N=185)	Cycle 1 Day 15 (N=174)	Cycle 2 (N=166)	Cycle 3-12 (N=142)
Number of patients with at least one AE	14 (7.6%)	5 (2.9%)	3 (1.8%)	0
95% CI for % of patients with at least one AE	(4.20%, 12.37%)	(0.94%, 6.58%)	(0.37%, 5.19%)	(0.00%, 2.56%)
Total number of AEs	14	5	3	0
Total number of AEs related to Glofitamab	14	5	3	0
Number of patients with at least one AE by worst grade				
Grade 1	6 (3.2%)	2 (1.1%)	2 (1.2%)	0
Grade 2	4 (2.2%)	3 (1.7%)	1 (0.6%)	0
Grade 3	4 (2.2%)	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Number of patients with at least one serious AE	4 (2.2%)	3 (1.7%)	0	0
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	1 (7.1%)	0	0	0
Recovering/ Resolving	0	0	0	0
Recovered/Resolved	13 (92.9%)	5 (100%)	3 (100%)	0
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0
Glofitamab related AE leading to withdrawal from treatment	0	0	0	0
Glofitamab related AE leading to dose interruption	0	0	0	0
Glofitamab related AE leading to dose modification	1 (0.5%)	0	0	0

Sub = subcohort.
Only Treatment (either Glofitamab or Obinutuzumab) Emergent AEs with a preferred term (encoded using MedDRA version 25.0) of Tumour Flare are included.
Data Cutoff Date: 15JUN2022

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Serious Infections

Potential mechanisms:

The mechanism of action of glofitamab results in B-cell depletion, which is associated with an increased risk of infections. Infections have been reported in patients receiving other CD20-directed therapies. Serious, life-threatening, and fatal infections occurred in patients receiving glofitamab, and contributory factors may include glofitamab-induced B-cell depletion, as well as the patient's immunocompromised status due to the underlying disease, and prior immunosuppressive treatment that may predispose to infections.

Evidence source(s) and strength of evidence:

Serious infections have been observed in clinical data (Study NP30179) with glofitamab.

Characterization of the risk:

Overview of Serious Infections

- Primary safety population

In the primary safety population among patients who received at least one dose of glofitamab (N=145), adverse events from the grouped terms of infections and infestation were reported in 57 patients (39.3%) (Annex 7B.22). The median time to onset of the first infection and infestation event from the first glofitamab dose (Cycle1 Day 8) was 5.0 days (range: 2.0–15.0), and the median duration of the first infection and infestation AE from the first glofitamab dose (Cycle 1 Day 8) was 6.0 days (range: 3.0–59.0) (Annex 7B.23).

Under the grouped terms of infections and infestations AEs, 23 patients (15.9%) reported SAEs. The SAEs reported in ≥ 2% patients were sepsis (6 patients [4.1%]), COVID-19 (5 patients [3.4%]), and COVID-19 pneumonia (4 patients [2.8%]). Grade 1-2 SAEs were reported in 3 patients (2.1%), Grade 3-4 SAEs in 13 patients (9.0%), and Grade 5 SAEs in 7 patients (4.8%) (Annex 7B.11). Serious AEs related to glofitamab were reported in four patients (2.8%) (Annex 7B.24). No Grade 5 AEs were considered related to glofitamab treatment. Four patients (2.8%) reported a serious infection concurrent with Grade 3–4 neutropenia (Annex 7B.25). Serious infection and infestation events resolved in the majority of patients (69.6%); in two patients, events were unresolved at the time of reporting and seven patients experienced fatal events. One patient had treatment withdrawn and one patient interrupted glofitamab treatment due to glofitamab-related serious infection and infestation events, that were myelitis and peritonitis, respectively.

- Overall safety population

In the overall safety population among patients who received at least one dose of glofitamab (N = 450), AEs in the Infections and infestations SOC were reported in 205 patients (45.6%) (Annex 7B.26); 79 patients (17.6%) reported SAEs. Most patients with infection and infestation SAEs had Grade 3 events (47 patients [10.4%]); Grade 4 SAEs were reported in 6 patients (1.3%) and Grade 5 in 13 patients (2.9%). The SAEs reported in ≥ 1% of patients included: COVID-19 (11 patients [2.4%]), pneumonia (10 patients [2.2%]), COVID-19 pneumonia (9 patients [2.0%]), and sepsis (7 patients [1.6%]) (Annex 7B.46). Only one patient had treatment withdrawn due to a glofitamab-related SAE (Table 30). Glofitamab-related SAEs led to dose interruption in 5 patients (1.1%). At the time of the CCOD, 6 patients had SAEs that had not resolved.

In the subgroup of patients with R/R NHL treated with glofitamab step-up dosing 2.5/10/30 mg in Cohort D_3, Cohort D_2 [Sub. 2] and Cohort D_5 (N=185), the profile of infection and infestation SAEs was generally consistent with the overall safety population (Table 31).

Serious Infections by Dose Cycle

In the primary safety population, among patients who received at least one dose of glofitamab (N=145), infection and infestation SAEs occurred predominantly in Cycle 3 and beyond. Of 107 patients who received glofitamab doses in Cycle 3 and beyond, 11 patients (10.3%) reported infection and infestation SAEs. In Cycle 1, of 145 patients who received a glofitamab dose at Day 8 (2.5 mg), 4 patients (2.8%) reported infection and infestation SAEs following the Day 8 dose; of 135 patients who received a glofitamab dose at Day 15 (10 mg), 4 patients (3.0%) reported infection and infestation SAEs following the Day 15 dose. Among 127 patients who received glofitamab doses in Cycle 2, 3 patients (2.4%) reported infection and infestation SAEs (Table 32).

Similar results were observed in patients from all R/R NHL histologies treated with glofitamab at the proposed registrational dose (2.5/10/30 mg) in Cohort D_3, Cohort D_2 [Sub. 2], and Cohort D_5 (Table 33).

Note that infection and infestation SAEs by dose cycle have not been shown for the ≥0.6 mg and ≥10mg cohorts that combine groups with fixed and step-up dosing regimens. As fixed dosing regimens are not given on the same cycle days as step-up dosing, combined data is not an accurate description of the infection and infestation event.

Risk factors and risk groups:

Serious infections is a recognized risk associated with B-cell depletion treatment effect and a major cause of morbidity and mortality in patients with hematological malignancies. Underlying medical conditions in the patient population including history of recurring or chronic infections (e.g., chronic, active Epstein-Barr Virus) and prior immunosuppressive treatment are risk factors that may predispose to infections.

Preventability:

Guidance is provided in the SmPC that glofitamab should not be administered to patients with an active infection. Patients with a history of chronic or recurrent infection or those who have conditions or had treatment that may predispose them to infections should be monitored before and during glofitamab treatment for the emergence of new or reactivated infections.

Impact on the benefit-risk balance of the product:

Serious infections are anticipated with glofitamab administration due to its mode of action resulting in B-cell depletion. However, the risk is well recognized by healthcare professionals for the patient population in view of underlying conditions and/or prior immunosuppressive treatment that may predispose to infections. The management of serious infections in the patient population does not differ from routine oncology practice and the standard of care.

The known risk of infections will be followed up via routine pharmacovigilance which, together with adherence by prescribers to risk-minimization messages in the Product Information (routine risk minimization measures), are considered sufficient for this risk.

Public health impact:

Given that the appropriate guidance associated with glofitamab treatment is included in the SmPC and that serious infection and infestation events resolved in 69.6% of patients who received at least one dose of glofitamab in the primary safety population, the impact of serious infections on public health is considered to be low.

Table 30 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R DLBCL who have Received ≥2 Prior Systemic Therapies

Seriousness, Outcomes, Severity, Frequency of AEs, Infection and infestation, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab 2.5/10/30 mg Cohort D3 (N=101)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=37)	Glofitamab Doses >=0.60 mg (N=273)	Glofitamab Doses >=10 mg(b) (N=97)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=108)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=145)
Number of patients with at least one AE	41 (40.6%)	12 (32.4%)	114 (41.8%)	43 (44.3%)	45 (41.7%)	57 (39.3%)
95% CI for % of patients with at least one AE	(30.93%, 50.82%)	(18.01%, 49.79%)	(35.84%, 47.85%)	(34.24%, 54.77%)	(32.25%, 51.55%)	(31.31%, 47.76%)
Total number of AEs	60	18	180	69	74	92
Total number of AEs related to Glofit	8	0	27	8	16	16
Number of patients with at least one AE by worst grade						
Grade 1	2 (2.0%)	3 (8.1%)	20 (7.3%)	10 (10.3%)	2 (1.9%)	5 (3.4%)
Grade 2	24 (23.8%)	5 (13.5%)	54 (19.8%)	21 (21.6%)	25 (23.1%)	30 (20.7%)
Grade 3	6 (5.9%)	2 (5.4%)	27 (9.9%)	11 (11.3%)	8 (7.4%)	10 (6.9%)
Grade 4	4 (4.0%)	0	5 (1.8%)	0	5 (4.6%)	5 (3.4%)
Grade 5	5 (5.0%)	2 (5.4%)	8 (2.9%)	1 (1.0%)	5 (4.6%)	7 (4.8%)
Number of patients with at least one serious AE	17 (16.8%)	4 (10.8%)	42 (15.4%)	13 (13.4%)	19 (17.6%)	23 (15.9%)
Number of patients with at least one AE by outcome						
Fatal outcome	5 (12.2%)	2 (16.7%)	8 (7.0%)	1 (2.3%)	5 (11.1%)	7 (12.3%)
Unresolved	10 (24.4%)	7 (58.3%)	29 (25.4%)	6 (14.0%)	11 (24.4%)	18 (31.6%)
Recovering/Resolving	1 (2.4%)	0	2 (1.8%)	1 (2.3%)	1 (2.2%)	1 (1.8%)
Recovered/Resolved	29 (70.7%)	6 (50.0%)	84 (73.7%)	35 (81.4%)	32 (71.1%)	38 (66.7%)
Resolved with sequelae	1 (2.4%)	0	4 (3.5%)	3 (7.0%)	1 (2.2%)	1 (1.8%)
Unknown outcome	0	0	0	0	0	0
Glofit related AE leading to withdrawal from treatment	1 (1.0%)	0	1 (0.4%)	0	1 (0.9%)	1 (0.7%)
Glofit related AE leading to dose interruption	2 (2.0%)	0	5 (1.8%)	2 (2.1%)	3 (2.8%)	3 (2.1%)

Table 30 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R DLBCL who have Received ≥2 Prior Systemic Therapies (cont.)

Glofit related AE leading to dose modification	0	0	0	0	0	0

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Sub = subcohort. Only Treatment (either Glofitamab or Obinutuzumab) Emergent AEs with a preferred term (encoded using MedDRA version 25.0) of Infection and infestation are included.
Data Cutoff Date: 15JUN2022

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Table 31 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R NHL– All Histologies

Seriousness, Outcomes, Severity, Frequency of AEs, Serious Infections and Infestations, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5 and Total Doses >= 0.60 mg, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Glofitamab Doses >=0.60 mg (N=450)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)
Number of patients with at least one AE	79 (17.6%)	35 (18.9%)
95% CI for % of patients with at least one AE	(14.15%, 21.39%)	(13.55%, 25.32%)
Total number of AEs	105	45
Total number of AEs related to Glofit	22	10
Number of patients with at least one AE by worst grade		
Grade 1	4 (0.9%)	1 (0.5%)
Grade 2	9 (2.0%)	5 (2.7%)
Grade 3	47 (10.4%)	15 (8.1%)
Grade 4	6 (1.3%)	5 (2.7%)
Grade 5	13 (2.9%)	9 (4.9%)
Number of patients with at least one serious AE	79 (17.6%)	35 (18.9%)
Number of patients with at least one AE by outcome		
Fatal outcome	13 (16.5%)	9 (25.7%)
Unresolved	5 (6.3%)	2 (5.7%)
Recovering/Resolving	1 (1.3%)	0
Recovered/Resolved	62 (78.5%)	27 (77.1%)
Resolved with sequelae	4 (5.1%)	0
Unknown outcome	0	0
Glofit related AE leading to withdrawal from treatment	1 (0.2%)	1 (0.5%)
Glofit related AE leading to dose interruption	5 (1.1%)	2 (1.1%)
Glofit related AE leading to dose modification	0	0

Sub = subcohort. Only Treatment (either Glofitamab or Obinutuzumab) Emergent AEs with a preferred term (encoded using MedDRA version 25.0) of Serious Infection and infestation are included.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ae_out1_rmp.sas
Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/Adhocs_Interim_15JUN2022/prod/output/t_ae_out1_rmp_SINFEST_I_RMP2_SERO_15JUN2022_30179.out
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Table 32 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R DLBCL, ≥2 Prior Systemic Therapies; Cohorts D_2 [Sub. 2], D_3, and D_5

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Serious Infections and Infestations, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Cycle 1 Day 8 (N=145)	Cycle 1 Day 15 (N=135)	Cycle 2 (N=127)	Cycle 3-12 (N=107)
Number of patients with at least one AE	4 (2.8%)	4 (3.0%)	3 (2.4%)	11 (10.3%)
95% CI for % of patients with at least one AE	(0.76%, 6.91%)	(0.81%, 7.41%)	(0.49%, 6.75%)	(5.24%, 17.65%)
Total number of AEs	4	6	4	14
Total number of AEs related to Glofitamab	1	1	1	3
Number of patients with at least one AE by worst grade				
Grade 1	0	0	0	0
Grade 2	2 (1.4%)	0	0	0
Grade 3	1 (0.7%)	2 (1.5%)	1 (0.8%)	4 (3.7%)
Grade 4	1 (0.7%)	1 (0.7%)	1 (0.8%)	2 (1.9%)
Grade 5	0	1 (0.7%)	1 (0.8%)	5 (4.7%)
Number of patients with at least one serious AE	4 (2.8%)	4 (3.0%)	3 (2.4%)	11 (10.3%)
Number of patients with at least one AE by outcome				
Fatal outcome	0	1 (25.0%)	1 (33.3%)	5 (45.5%)
Unresolved	0	1 (25.0%)	0	1 (9.1%)
Recovering/ Resolving	0	0	0	0
Recovered/Resolved	4 (100%)	3 (75.0%)	3 (100%)	5 (45.5%)
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0
Glofitamab related AE leading to withdrawal from treatment	0	1 (0.7%)	0	0
Glofitamab related AE leading to dose interruption	0	0	1 (0.8%)	0
Glofitamab related AE leading to dose modification	0	0	0	0

Sub = subcohort.
Only Treatment (either Glofitamab or Obinutuzumab) Emergent AEs with a preferred term (encoded using MedDRA version 25.0) of Serious Infections and infestations are included.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ae_out2_rmp.sas
Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/Adhocs_Interim_15JUN2022/prod/output/t_ae_out2_rmp_SINFEST_I_RMPD_SERO_15JUN2022_30179.out
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Table 33 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R NHL (All Histologies); Cohorts D_2 [Sub. 2], D_3, and D_5

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Serious Infections and Infestations, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D2(Sub 2), D3, D5, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab
Protocol: NP30179
Risk Management Plan

	Cycle 1 Day 8 (N=185)	Cycle 1 Day 15 (N=174)	Cycle 2 (N=166)	Cycle 3-12 (N=142)
Number of patients with at least one AE	5 (2.7%)	5 (2.9%)	5 (3.0%)	19 (13.4%)
95% CI for % of patients with at least one AE	(0.88%, 6.19%)	(0.94%, 6.58%)	(0.99%, 6.89%)	(8.25%, 20.10%)
Total number of AEs	5	7	6	23
Total number of AEs related to Glofitamab	1	1	3	5
Number of patients with at least one AE by worst grade				
Grade 1	0	0	0	1 (0.7%)
Grade 2	2 (1.1%)	0	0	2 (1.4%)
Grade 3	2 (1.1%)	3 (1.7%)	3 (1.8%)	7 (4.9%)
Grade 4	1 (0.5%)	1 (0.6%)	1 (0.6%)	2 (1.4%)
Grade 5	0	1 (0.6%)	1 (0.6%)	7 (4.9%)
Number of patients with at least one serious AE	5 (2.7%)	5 (2.9%)	5 (3.0%)	19 (13.4%)
Number of patients with at least one AE by outcome				
Fatal outcome	0	1 (20.0%)	1 (20.0%)	7 (36.8%)
Unresolved	0	1 (20.0%)	0	1 (5.3%)
Recovering/ Resolving	0	0	0	0
Recovered/Resolved	5 (100%)	4 (80.0%)	5 (100%)	11 (57.9%)
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0
Glofitamab related AE leading to withdrawal from treatment	0	1 (0.6%)	0	0
Glofitamab related AE leading to dose interruption	0	0	1 (0.6%)	1 (0.7%)
Glofitamab related AE leading to dose modification	0	0	0	0

Sub = subcohort.
Only Treatment (either Glofitamab or Obinutuzumab) Emergent AEs with a preferred term (encoded using MedDRA version 25.0) of Serious Infections and infestations are included.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ae_out2_rmp.sas
Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/Adhocs_Interim_15JUN2022/prod/output/t_ae_out2_rmp_SINFEST_I_RMP2A_SERO_15JUN2022_30179.out
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Information on Important Potential Risks

Not applicable

SVII.3.2. Presentation of the Missing Information

Information on Missing Information

Long-term safety

At the 15 June 2022 CCOD, all patients in the primary safety population had either completed initial study treatment or discontinued initial study treatment. Median duration of follow-up for patients in the primary safety population who had received at least one dose of glofitamab was 13.5 months (range: 0–28 months) (Annex 7B.45). Limited data are available in terms of long-term safety of patients treated with glofitamab; long-term safety is therefore considered missing information.

Evidence Source:

Population in need of further characterization

The assessment of long-term safety of glofitamab is not fully understood and ongoing analysis of future safety information is needed. Thus, long-term safety data is being collected from the ongoing NP30179 study (see Part III.2). To address this missing information, a minimum of two years follow-up from the end of treatment of the last patient enrolled in the primary safety population of Study NP30179, including an analysis of safety by sex shall be provided.

Safety in Patients with Prior CAR-T Therapy

Based on the 15 June 2022 CCOD, among patients in the primary safety population who received at least one dose of glofitamab (N=145), more patients had not received prior CAR-T therapy (N=98 [67.6%]) compared to patients who had received prior CAR-T therapy (N=47 [32.4%]).

Serious AEs were reported in a higher proportion of patients who previously received CAR-T therapy compared with those who had not (55.3% vs. 44.9%; Annex 7B.41). Conversely, in patients who had not received prior CAR-T therapy compared to those who had, a higher proportion of patients reported AEs leading to dose modification/interruption (21.4% vs. 12.8%). However, the difference in the sample sizes of these subgroups could potentially be a reason for the observed imbalances. The incidence of Grade 3-5 AEs was comparable across both groups (65.3% in patients who had not received prior CAR-T therapy vs. 61.7% in those who had) and there were similar rates of CRS (65.3% in patients who had not received prior CAR-T therapy vs. 72.3% in those who had).

Characterization of the safety profile of patients with prior CAR-T therapy is limited and is therefore considered missing information. Analysis of future safety information in this

patient population in Study NP30179, as an additional pharmacovigilance activity is planned.

Evidence Source:

Population in need of further characterization

The safety profile in patients with prior CAR-T therapy is limited and ongoing analysis of future safety information in this patient population through routine pharmacovigilance activities is planned.

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 34 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Cytokine release syndrome • Tumor Flare • Serious Infections
Important potential risks	None
Missing information	• Long-term safety • Safety in patients with prior CAR-T therapy

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

ROUTINE PHARMACOVIGILANCE ACTIVITIES BEYOND ADVERSE REACTIONS REPORTING AND SIGNAL DETECTION

Specific adverse reaction follow-up questionnaires:

None

Other forms of routine pharmacovigilance activities for the missing information of Long-term safety:

Safety in male patients versus female patients will be monitored as part of long-term safety, and data presented in Periodic safety update reports (PSURs)/Periodic benefit-risk evaluation reports (PBRERs).

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 35 BO43309 Summary

Study/activity short name and title: BO43309 Evaluation of the Effectiveness of the Additional Risk Minimisation Measures for Glofitamab: A Survey Among Healthcare Professionals in 10 Countries in the European Economic Area.
Rationale and Study Objectives: This non-interventional study will assess effectiveness of additional risk minimization measures (HCP Brochure, Patient Card). These measures will be implemented to intensify communication and medical and patient education around the important identified risks of CRS (Patient Card) and tumor flare (HCP Brochure). The main objective of the study is to evaluate the following process and behavioural indicators: receipt of the educational materials (EMs), i.e., HCP Brochure and Patient Card, by the target population (glofitamab prescribers) and distribution of the Patient Card by prescribers to their patients; awareness, knowledge, comprehension, and self-reported adherence of prescribers with respect to TF information included in the HCP brochure.
Study design: The survey will be conducted in selected countries among HCPs who prescribed glofitamab according to the label at least once in the six months prior to taking the survey. The survey will be sent to the participating HCPs to collect information on their awareness, knowledge, comprehension, and adherence with respect to TF information included in the HCP brochure. Therefore, the survey will have different types of questions (Awareness, Knowledge/ Comprehension and Adherence). In order to evaluate the effectiveness of the risk-minimization measures, the following process and behavioural indicators will be considered: • Receipt of the EMs, i.e., HCP brochure and Patient Card, by the target population (glofitamab prescribers) and the distribution of Patient Card by prescribers to their patients (metrics on implementing steps of additional risk minimization measures). • Awareness questions will involve collection of HCPs' self-reported awareness of the risk of TF described in the HCP brochure and assess if HCPs have used the HCP brochure to gain awareness and knowledge of the risk of TF and whether HCPs have used the Patient Card to educate their patients about the risk of CRS associated with glofitamab and the risk mitigation measures for CRS. • Knowledge and comprehension questions will measure HCP knowledge/comprehension of the risk of TF that may occur with glofitamab use and on the specific guidance for risk minimization for TF, as described in the HCP brochure. • In the adherence questions, HCPs will be asked to self-assess their adherence to the guidance provided in the HCP brochure.
Study populations: A sample of HCPs who prescribed glofitamab according to the label, at least once in the six months prior to taking the survey.

Table 35 BO43309 Summary (cont.)

Milestones: Study status: Planned Start Date of Study (date of first data collection): Q1 2025 End of Study: Q4 2025 Final report: Q2 2026

CRS=cytokine release syndrome; HCP=healthcare professional; TBD=to be determined; TF= tumor flare.

Table 36 NP30179 Summary

Study/activity short name and title: NP30179 A multicenter, open-label, Phase I/II study to evaluate the safety, efficacy, tolerability and pharmacokinetics of escalating doses of glofitamab (RO7082859) as a single agent and in combination with obinutuzumab administered after a fixed, single dose pre-treatment of obinutuzumab (Gazyva®/Gazyvaro®) in patients with relapsed/refractory (R/R) B cell Non-Hodgkin's lymphoma (NHL)
Rationale and Study Objectives: A primary objective of the study is to evaluate the safety, tolerability, and pharmacokinetics of glofitamab as single agent (and in combination with obinutuzumab) following obinutuzumab pre-treatment (Gpt) in patients with R/R CD20+ B –cell NHL. The MAH shall provide a minimum of two years follow-up from the end of treatment of the last patient enrolled in the primary safety population of Study NP30179, including analyses of safety in patients with prior CAR-T therapy and safety by sex.
Study design: • A Phase I/II, multicenter, open-label, dose-escalation study designed to evaluate the efficacy, safety, tolerability, and pharmacokinetics of glofitamab, administered by IV infusion as a single agent and in combination with obinutuzumab following pre-treatment with a fixed dose of obinutuzumab (Gazyva®: Gpt) in patients with R/R NHL. • A minimum of two years follow-up from the end of treatment of the last patient enrolled in the primary safety population of Study NP30179, including analyses of safety in patients with prior CAR-T therapy and safety by sex shall be provided.
Study populations: Patients with R/R NHL
Milestones: Update CSR: Q4 2024

CSR = clinical study report; IV= intravenous; NHL= Non-Hodgkin's lymphoma.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 37 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 2—Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
NP30179 A multicenter, open-label, Phase I/II study to evaluate the safety, efficacy, tolerability and pharmacokinetics of escalating doses of glofitamab (RO7082859) as a single agent and in combination with obinutuzumab administered after a fixed, single dose pre-treatment of obinutuzumab (Gazyva®/Gazyvaro™) in patients with R/R B-cell NHL Ongoing	A primary objective of the study is to evaluate the safety, tolerability, and pharmacokinetics of glofitamab as single agent (and in combination with obinutuzumab) following obinutuzumab pre-treatment (Gpt) in patients with R/R CD20+ B –cell NHL. The MAH shall provide a minimum of 2 years follow-up from the end of treatment of the last patient enrolled in the primary safety population of Study NP30179, including analyses of safety in patients with prior CAR-T therapy and safety by sex.	Long-term safety Safety in patients with prior CAR-T therapy	Update CSR	Q4 2024

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimization activities				
BO43309 Evaluation of the Effectiveness of the Additional Risk Minimisation Measures for Glofitamab: A Survey Among Healthcare Professionals in 10 Countries in the European Economic Area Planned	The primary objective of this study is to assess, by survey: • the receipt of the educational materials, i.e., HCP brochure (for the important identified risk of TF) and Patient Card (for the important identified risk of CRS), by the target population (glofitamab prescribers) and the distribution of the Patient Card by prescribers to their patients • behavioral indicators (the level of awareness, knowledge, comprehension and adherence) of prescribers with respect to TF information included in the HCP brochure.	• Cytokine release syndrome • Tumor Flare	Final report	Q2 2026

CAR-T = chimeric antigen receptor T-cell; CRS = cytokine release syndrome; CSR= clinical study report; HCP= healthcare professional; NHL = Non-Hodgkin's lymphoma; R/R = relapsed/refractory; TF=tumor flare.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table 38 Planned and Ongoing Post-Authorization Imposed Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorization				
Not applicable				
Efficacy studies that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
GO41944 A Phase III, Open-Label, Multicenter, Randomized Study Evaluating the Efficacy and Safety of Glofitamab in Combination with Gemcitabine plus Oxaliplatin versus Rituximab in Combination with Gemcitabine and Oxaliplatin in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma Ongoing	- To evaluate the efficacy of Glofit-GemOx compared with R-GemOx on the basis of OS, PFS, CR rate, ORR, duration of OR, duration of CR, and time to deterioration in physical functioning and fatigue, and lymphoma symptoms - To evaluate the safety and tolerability of Glofit-GemOx compared with R-GemOx on the basis of the following endpoints:	Efficacy uncertainties addressed: Overall survival benefit Safety concerns addressed: CRS; Tumor Flare; Serious Infections	Primary CSR	Q3 2024

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
	• Incidence and severity of AEs (severity determined according to NCI CTCAE v5.0), including CRS, with severity determined according to ASTCT CRS grading criteria • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results • Tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of AEs			

AE=adverse event; ASTCT= American Society for Transplantation and Cellular Therapy; CR=complete response; CRS=cytokine release syndrome; CSR=clinical study report; Glofit-GemOx=glofitamab in combination with gemcitabine plus oxaliplatin; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; OR=objective response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; R-GemOx=rituximab in combination with gemcitabine plus oxaliplatin.

PART V: RISK-MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK-MINIMIZATION ACTIVITIES)

RISK-MINIMIZATION PLAN
V.1 ROUTINE RISK-MINIMIZATION MEASURES
Table 39 Description of Routine Risk-Minimization Measures by Safety Concern

Safety Concern	Routine Risk-Minimization Activities
Cytokine Release Syndrome	**Routine risk communication**: **SmPC:** • Section 4.2 Posology and method of administration • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects **Package Leaflet:** • Section 2 What you need to know before you are given Columvi • Section 4 Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** Recommendation for monitoring for the development of CRS is included in SmPC section 4.2. **Other risk minimization measures beyond the Product Information:** **Pack size:** None **Medicine's legal status:** Glofitamab is subject to restricted medical prescription.
Tumor Flare	**Routine risk communication:** **SmPC:** • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects **Package Leaflet:** • Section 2 What you need to know before you are given Columvi • Section 4 Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information**: **Pack size:** None **Medicine's legal status:** Glofitamab is subject to restricted medical prescription.

Safety Concern	Routine Risk-Minimization Activities
Serious Infections	**Routine risk communication:** **SmPC:** • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects **Package Leaflet:** • Section 2 What you need to know before you are given Columvi • Section 4 Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** Recommendation for monitoring for the development of Serious Infections is included in SmPC section 4.4. **Other risk-minimization measures beyond the Product Information:** **Pack size:** None **Medicine's legal status:** Glofitamab is subject to restricted medical prescription.
Long-term Safety	No risk-minimization measures required
Safety in patients with prior CAR-T therapy	No risk-minimization measures required

CAR-T= chimeric antigen receptor T-cell; CRS=cytokine release syndrome; SmPC=summary of product characteristics; TF= tumor flare.

V.2. ADDITIONAL RISK-MINIMIZATION MEASURES

Table 40 Additional Risk-Minimization Measures

Additional risk-minimization measure	Healthcare Professional Brochure
Objective(s)	The HCP brochure will aim to educate and raise HCPs' awareness and comprehension of the risk of TF, such that HCPs can detect and manage TF in a timely and appropriate manner. Optimizing the time to intervention and appropriate management of TF will prevent it from worsening and maximize recovery potential. The HCP brochure will provide a description of TF, and information on early recognition, appropriate diagnosis, and monitoring of TF.
Rationale for the additional risk-minimization activity	Based on the characterization of TF, additional risk-minimization measures in the form of the HCP Brochure can increase the likelihood of an early diagnosis followed by appropriate treatment, thereby reducing the impact of TF on the patient.

Additional risk-minimization measure	Healthcare Professional Brochure
Target audience and planned distribution path	The HCP Brochure is distributed to the physician who will provide treatment of glofitamab to adult patients with R/R DLBCL, after two or more lines of systemic therapy.
Plans for evaluating the effectiveness of the interventions and criteria for success	**How effectiveness will be measured**: • Metrics of distribution of HCP Brochure to HCPs • Survey to evaluate HCPs awareness, knowledge, comprehension, and adherence to the additional risk-minimization measures for the important identified risk of TF, as described in the HCP brochure • Periodic medical review of clinical trial and post-marketing cases in terms of reporting rate and severity to determine whether the additional risk minimization measures have led to improved patient outcomes **Milestones for reporting:** • Monitoring of reporting rate and severity, periodically in PBRERs • Final report for Study BO43309: Q2 2026

CRS=cytokine release syndrome; DLBCL= diffuse large B-cell lymphoma; HCP= healthcare professional; NI-PASS= non-interventional post-authorization safety study; PBRER= periodic benefit risk evaluation report; R/R DLBCL= relapsed/refractory diffuse large B-cell lymphoma; TF= tumor flare.

Table 41 Additional Risk-Minimization Measures

Additional risk-minimization measure	Patient Card
Objective(s)	Based on the characterization of CRS, the Patient Card will enable the patient to receive education facilitated by the treating physician, on the key recommendations to be followed during the treatment with glofitamab, with the aim of minimizing the worsening of adverse reactions relevant to the risk of CRS. The intent is that the Patient Card will remind patients of the signs and symptoms of CRS and encourage patients to seek immediate medical attention if signs and symptoms of CRS present. Optimizing the time to intervention, and appropriate management of the adverse reactions or preventing further worsening of the adverse reactions will maximize recovery potential. Furthermore, the Patient Card will alert HCPs that the patient is taking glofitamab (particularly useful if the patient is presenting at the emergency room).
Rationale for the additional risk-minimization activity	The Patient Card will promote awareness of the key signs and symptoms of CRS, thereby enabling early recognition of CRS by patients and timely reporting to their physicians, encouraging prompt intervention.

Additional risk-minimization measure	Patient Card
Target audience and planned distribution path	The Patient Card is targeted for use in adult patients with R/R DLBCL, after two or more lines of systemic therapy. The Patient Card will be provided to the physician for distribution to the patient prior to their first dose of glofitamab.
Plans for evaluating the effectiveness of the interventions and criteria for success	**How effectiveness will be measured:** • Metrics of distribution channel of Patient Card to HCP • Survey to confirm patient card was given to patient by HCP • Periodic medical review of clinical trial and post-marketing cases in terms of reporting rate and severity to determine whether the additional risk minimization measures have led to improved patient outcomes **Milestones for reporting:** • Monitoring of reporting rate and severity, periodically in PBRERs • Final report for Study BO43309: Q2 2026

CRS=cytokine release syndrome; DLBCL= diffuse large B-cell lymphoma; HCP = healthcare professional; NI-PASS= non-interventional post-authorization safety study; PBRER= periodic benefit risk evaluation report; R/R DLBCL= relapsed/refractory diffuse large B-cell lymphoma.

REMOVAL OF ADDITIONAL RISK-MINIMIZATION ACTIVITIES

Not applicable

V.3 SUMMARY OF RISK-MINIMIZATION MEASURES

Table 42 Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
Cytokine release syndrome	**Routine risk-minimization measures:** SmPC section 4.2, 4.4, and 4.8 Recommendation for monitoring for the development of CRS is included in SmPC section 4.2. Package leaflet sections 2 and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** No activities beyond routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** Study BO43309 Final report: Q2 2026

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
	Additional risk-minimization measures: Patient Card	
Tumor Flare	**Routine risk-minimization measures:** SmPC section 4.4 and 4.8 Package leaflet section 2 and 4 **Additional risk-minimization measures:** HCP brochure	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** No activities beyond routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** Study BO43309 Final report: Q2 2026
Serious Infections	**Routine risk-minimization measures:** SmPC section 4.4 and 4.8 Recommendation for monitoring for the development of Serious Infections is included in SmPC section 4.4. Package leaflet section 2 and 4 **Additional risk-minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** No activities beyond routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** None
Long-term safety	**Routine risk-minimization measures:** None **Additional risk-minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Monitoring and reporting of safety by sex in (PSURs)/PBRERs **Additional pharmacovigilance activities:** Study NP30179 Update CSR: Q4 2024

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
Safety in patients with prior CAR-T therapy	**Routine risk-minimization measures:** None **Additional risk-minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** No activities beyond routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** Study NP30179 Update CSR: Q4 2024

aRMM= additional risk-minimization measures; CAR-T = chimeric antigen receptor T-cell; CSR= clinical study report; HCP= healthcare professional; NI-PASS = non-interventional post-authorization safety study; PBRER= periodic benefit risk evaluation report; PSUR= periodic safety update report; SmPC= summary of product characteristics.

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PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR COLUMVI (GLOFITAMAB)

This is a summary of the risk-management plan (RMP) for Columvi. The RMP details important risks of Columvi, how these risks can be minimized, and how more information will be obtained about Columvi's risks and uncertainties (missing information).

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

This summary of the RMP for Columvi should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of 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 Columvi's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Columvi as monotherapy is authorized for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, after two or more lines of systemic therapy (see SmPC for the full indication). It contains *glofitamab* as the active substance and is administered as an intravenous infusion.

Further information about the evaluation of Columvi's benefits can be found in Columvi's EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's Web page.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

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

Measures to minimize 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 authorized pack size—The amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly.
- The medicine's legal status—The way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

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

In the case of Columvi, these measures are supplemented with *additional risk-minimization* measures mentioned under relevant risks below.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, 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 Columvi is not yet available, it is listed under “missing Information” below.

II.A List of Important Risks and Missing Information

Important risks of Columvi are risks that need special risk-management activities to further investigate or minimize 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 Columvi. 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 about the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• Cytokine release syndrome • Tumor Flare • Serious infections
Important potential risks	None
Missing information	• Long-term safety • Safety in patients with prior CAR-T therapy

II.B Summary of Important Risks

Important Identified Risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine	• Non-clinical studies, showing transient T-cell activation and cytokine release, primarily limited to the first dose • Phase I/II clinical trial data (Study NP30179) • Class effect: As observed with other CD3 engagers such as blinatumomab and CAR T-cell therapy, T-cell activation may lead to an excess of systemic cytokine release which may lead to serious and even fatal events
Risk factors and risk groups	The risk of CRS may be influenced by factors related to the type of therapy and treatment dose, the underlying disease (type, tumor burden, and tumor cell location [e.g., peripheral blood vs. bone marrow], patient characteristics (age, general health status, and comorbidity burden; basal inflammatory state), and degree of T-cell activation and expansion. Disease burden is among the most important predictors of severe CRS after CAR T-cell therapy and the bispecific T-cell engager blinatumomab.
Risk-minimization measures	**Routine risk-minimization measures:** SmPC section 4.2, 4.4 and 4.8 Recommendation for monitoring for the development of CRS is included in SmPC section 4.2. Package leaflet sections 2 and 4 **Additional risk-minimization measures:** Patient Card
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study BO43309 See Section II.C of this summary for an overview of the post-authorization development plan.

CAR-T=chimeric antigen receptor (CAR) T-cell therapy; CRS=cytokine release syndrome; SmPC=summary of product characteristics.

Important Identified Risk: Tumor Flare	
Evidence for linking the risk to the medicine	Tumor flare has been observed in clinical data (Study NP30179) with glofitamab. It is a known risk with other immunomodulating agents, T-cell engaging therapies, checkpoint inhibitor therapies.
Risk factors and risk groups	Treatment with immunomodulatory agents is associated with tumor flare, and more frequent with hematologic malignancies than in patients with solid tumors.
Risk-minimization measures	**Routine risk-minimization measures:** SmPC section 4.4 and 4.8 Package leaflet section 2 and 4 **Additional risk-minimization measures:** HCP brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study BO43309 See Section II.C of this summary for an overview of the post-authorization development plan.

HCP= healthcare professional; SmPC=summary of product characteristics; TF=tumor flare.

Important Identified Risk: Serious Infections	
Evidence for linking the risk to the medicine	Serious infections have been observed in clinical data (Study NP30179) with glofitamab.
Risk factors and risk groups	Serious infections is a recognized risk associated with B-cell depletion treatment effect and a major cause of morbidity and mortality in patients with hematological malignancies. Underlying medical conditions in the patient population including history of recurring or chronic infections (e.g., chronic, active Epstein-Barr Virus) and prior immunosuppressive treatment are risk factors that may predispose to infections.
Risk-minimization measures	Routine risk-minimization measures: SmPC section 4.4 and 4.8 Recommendation for monitoring for the development of Serious Infections is included in SmPC section 4.4. Package leaflet section 2 and 4 Additional risk-minimization measures: No additional risk minimization measures

SmPC=summary of product characteristics.

Missing Information: Long-term safety	
Risk-minimization measures	**Routine risk-minimization measures:** No routine risk minimization measures **Additional risk-minimization measures**: No additional risk minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study NP30179 See Section II.C of this summary for an overview of the post-authorization development plan.

Missing Information: Safety in patients with prior CAR-T therapy	
Risk-minimization measures	**Routine risk-minimization measures:** No routine risk minimization measures **Additional risk-minimization measures**: No additional risk minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study NP30179 See Section II.C of this summary for an overview of the post-authorization development plan.

CAR-T = chimeric antigen receptor (CAR) T-cell therapy

II.C Post-Authorization Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization.

Study NP30179:

Purpose of the study:

- To evaluate the safety, tolerability, and pharmacokinetics of glofitamab as single agent (and in combination with obinutuzumab) following obinutuzumab pre-treatment (Gpt) in patients with relapsed/refractory CD20 + B –cell Non-Hodgkin's Lymphoma

- The Marketing Authorization Holder shall provide a minimum of two years follow-up from the end of treatment of the last patient enrolled in the primary safety population of Study NP30179, including analyses of safety in patients with prior CAR-T therapy and safety by sex.

Study GO41944:

Purpose of the study:

- To evaluate the efficacy of glofitamab in combination with gemcitabine plus oxaliplatin compared with rituximab in combination with gemcitabine plus oxaliplatin on the basis of overall survival, progression-free survival, complete response rate, duration of objective response, duration of complete response, and time to deterioration in physical functioning and fatigue, and lymphoma symptoms
- To evaluate the safety and tolerability of glofitamab in combination with gemcitabine plus oxaliplatin compared with rituximab in combination with gemcitabine plus oxaliplatin on the basis of: incidence and severity of adverse events (severity determined according to NCI CTCAE v5.0), including cytokine release syndrome (CRS), with severity determined according to ASTCT CRS grading criteria; change from baseline in targeted vital signs; change from baseline in targeted clinical laboratory test results; tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of adverse events

II.C.2 Other Studies in Post-Authorization Development Plan

Study BO43309:

Purpose of the study:

- This non-interventional study will assess effectiveness of additional risk minimization measures (Healthcare Professional [HCP] Brochure, Patient Card). These measures will be implemented to intensify communication and medical and patient education around the important identified risks of CRS (Patient Card) and tumor flare (HCP Brochure).
- The main objective of the study is to evaluate the following process and behavioural indicators: receipt of the educational materials i.e., HCP Brochure and Patient Card, by the target population (glofitamab prescribers) and distribution of the Patient Card by prescribers to their patients; awareness, knowledge, comprehension, and self-reported adherence of prescribers with respect to tumor flare information included in the HCP brochure.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Specific Adverse Reactions Follow-Up Forms/Questionnaires

Not applicable

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

Draft Key Messages of the Additional Risk-Minimization Measures

Prior to the use of Columvi in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The educational program is aimed at

- Informing physicians to provide each patient with the patient card and educate the patient on its content, that includes a list of symptoms of cytokine release syndrome (CRS)
- Prompting patient actions, including seeking immediate medical attention, in case of the occurrence of symptoms of CRS
- Informing physicians of the risk of tumor flare (TF) and its manifestations

The objective of the program is to minimize the risks of TF and CRS and any resultant complications by encouraging prompt intervention.

The MAH shall ensure that in each Member State where Columvi is marketed, all healthcare professionals (HCPs) who are expected to prescribe, dispense, or use Columvi have access to/are provided with a Healthcare Professional Brochure. All patients who receive Columvi shall be provided with a Patient Card.

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1. HEALTHCARE PROFESSIONALS

1.1 HEALTHCARE PROFESSIONAL BROCHURE

The HCP Brochure for TF provides the following key elements:

- A description of TF, and information on early recognition, appropriate diagnosis, and monitoring of TF
- A reminder to provide each patient with the patient card, that includes a list of symptoms of CRS, to prompt patients to seek immediate medical attention in case of their occurrence

2. PATIENTS/CARERS

2.1 PATIENT CARD

Patients will be given a card that they should carry with them at all times. Physicians will educate patients about the key elements of the Patient Card when giving it to them.

The Patient Card provides the following key elements:

- Contact details of the Columvi prescriber
- List of symptoms of CRS to prompt patient actions, including seeking immediate medical attention in case of their occurrence
- Instructions that the patient should carry the Patient Card at all times and share it with HCPs involved in their care (i.e., urgent care HCPs, etc.)
- Information for the HCPs treating the patient that Columvi treatment is associated with the risk of CRS