

## EU RISK MANAGEMENT PLAN FOR COLUMVI/GLOFITAMAB

RMP version to be assessed as part of this application: EMEA/H/C/005751/II/0005

RMP Version number: 5.0

Data lock point for this RMP: 10 February 2025

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
21-Feb-2025 07:54:05	Deputy QPPV	Tanrikulu, Yusuf (tanrikuy)
21-Feb-2025 11:41:24	Company Signatory (PV)	PPD

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## Rationale for Submitting an Updated RMP

The glofitamab Risk Management Plan (RMP) Version 5.0 is prepared to consolidate information from the following RMP versions:

- Version 3.1, current Committee for Medicinal Products for Human Use (CHMP)-approved version as of 9 January 2025, which includes the addition of the important identified risk of immune effector cell-associated neurotoxicity syndrome (ICANS) per Pharmacovigilance Risk Assessment Committee's (PRAC's) recommendation on signals adopted on 11 July 2024 (EPITT No. 20058)
- Versions 2.0, 2.1, and 2.2, prepared to support an application for the extension of indication for Columvi (glofitamab), in combination with gemcitabine and oxaliplatin, for adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplant (ASCT) based on data from pivotal study GO41944 and supportive study GO41943.
- Version 4.0 prepared to remove Study NP30179, a multicenter, open-label study to evaluate the safety, efficacy, tolerability, and pharmacokinetics of escalating doses of glofitamab in patients with relapsed/refractory B-cell non-Hodgkin's lymphoma (NHL), from the list of required additional pharmacovigilance activities pertaining to the missing information of "Long-term safety" and "Safety in patients with prior chimeric antigen receptor T-cell (CAR-T) therapy". Following the submission of the Update Clinical Study Report (CSR) for Study NP30179, there are no further additional pharmacovigilance activities pertaining to the safety concerns of "Long-term safety" and "Safety in patients with prior CAR-T therapy", which are no longer considered missing information.

## Summary of Significant Changes in This RMP

Part I	Aligned dosage in European Economic Area (EEA) information with latest SmPC submitted to European Medicines Agency (EMA).
Part II: SIII	Clinical trial exposure data updated with the latest CCOD data (17 May 2024) for Study NP30179.
Part II: SIV.3	The exposure for "patients with hepatic impairment and renal impairment" in Table 21 for Study NP30179 was clarified as aligned with the previous CCOD (15 June 2022) because data with the latest CCOD of 17 May 2024 is not available at the time of preparation of this RMP. The patients with major protocol deviations from Study NP30179 in footnote "g" for Table 21 was aligned with the latest CCOD data (17 May 2024).
Part II: SV	Updated to reflect post-authorization exposure information from latest PBRER.
Part II: SVII.2, SVII.3, and SVIII	"Long-term safety" and "Safety in patients with prior CAR-T therapy" are no longer considered Missing information. Added rationale for removing these from the list of safety concerns (Missing Information) and removed related content.
Part III	Removed Study NP30179 as no longer required in pharmacovigilance plan. Title for Study BO44309 aligned with most recent study protocol.

Part V	Part V.3 updated to align with any changes to Part II Module SVII and Part III.
Part VI	Updated to reflect the changes made in this RMP.
Annex 2	Study NP30179 moved to completed studies. Title for Study BO44309 aligned with most recent study protocol.
Annex 3	Removed protocol for Study NP30179 from Annex 3 as no longer required in the pharmacovigilance plan.
Annex 5	Updated to reflect changes to Part IV.
Annex 7	Added latest available post-marketing exposure data. Updated outputs added to Annex 7B for Study NP30179 to reflect latest CCOD of 17 May 2024. Reference for Update CSR 1131971 added to Annex 7A.
Annex 8	Updated to reflect the changes made to this version of the RMP.
Other	Of note, Roche pregnancy follow-up process and the methodology and summary tabulations of prospective and retrospective ICSRs on pregnancy, included in v4.0, are not included in this version based on PRAC recommendation.

ASCT = autologous stem cell transplant; CAR-T = chimeric antigen receptor T-cell; DLBCL = diffuse large B-cell lymphoma; EU RMP = European Union Risk Management Plan; HCP = healthcare professional;; NOS = not otherwise specified; PBRER = Periodic Benefit-Risk Evaluation Report; SmPC = Summary of Product Characteristics.

## Other RMP Versions under Evaluation

RMP Version 2.2

Submitted on 4 February 2025

Procedure Number EMEA/H/C/005751/II/0005

## Details of Currently Approved RMP

RMP Version Number 3.1

Approved with Procedure Number EMEA/H/C/005751/IB/0009

Date of approval (opinion date): 09 January 2025

See [page 1](#) for signature and date

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Yusuf Tanrikulu (Deputy QPPV)

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Date

See [page 1](#) for signature and date

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PPD

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Date

## **PART I: PRODUCT(S) OVERVIEW**

**Table 1 Product(s) Overview**

Active Substance(s) (INN or common name)	Glofitamab
Pharmacotherapeutic group(s) (ATC Code)	L01FX28
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	<a href="#">EU PI</a>
Indication(s) in the EEA	Current: 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.
	Proposed: Columvi in combination with gemcitabine and oxaliplatin is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplantation (ASCT).

# Dosage in the EEA

## Current:

The step-up dosing schedule for Columvi (after pretreatment with obinutuzumab 1000 mg on Cycle 1 Day1) is shown below. Each cycle is 21 days.

Treatment cycle, Day		Dose of Columvi	Duration of infusion
<b>Cycle 1</b> (Pre-treatment and step-up dose)	Day 1	Pre-treatment with obinutuzumab 1000 mg	
	Day 8	2.5 mg	4 hours
	Day 15	10 mg	
<b>Cycle 2</b>	Day 1	30 mg	4 hours
<b>Cycle 3 to 12</b>	Day 1	30 mg	
			2 hours

## Proposed:

The step-up schedule for Columvi in combination with gemcitabine and oxaliplatin for patients with relapsed or refractory DLBCL is shown below. Each cycle is 21 days. In Cycles 1–8, administer gemcitabine before oxaliplatin. In Cycles 2–8, administer Columvi before gemcitabine and oxaliplatin. Gemcitabine and oxaliplatin may be given on Day 1 or 2.

Treatment cycle, Day		Dose of Columvi (duration of infusion)	Dose of gemcitabine	Dose of oxaliplatin
<b>Cycle 1</b> (pre-treatment and step-up dose)	Day 1	Pretreatment with obinutuzumab 1000 mg		
	Day 2	--	1000 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>
	Day 8	2.5 mg (4 hours)	--	--
	Day 15	10 mg (4 hours)		
<b>Cycle 2</b>	Day 1	30 mg (4 hours)	1000 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>
<b>Cycle 3 to 8</b>	Day 1	30 mg (2 hours)	1000 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>
<b>Cycle 9 to 12</b>	Day 1	30 mg (2 hours)	--	--

Pharmaceutical form(s) and strengths	<p>Current:</p> <p>Concentrate for solution for infusion (sterile concentrate)</p> <p>Colorless, clear solution with a pH of 5.5 and osmolality of 270-350 mOsmol/kg.</p> <p><u>Columvi 2.5 mg concentrate for solution for infusion</u></p> <p>Each vial of 2.5 mL of concentrate contains 2.5 mg of glofitamab at a concentration of 1 mg/mL</p> <p><u>Columvi 10 mg concentrate for solution for infusion</u></p> <p>Each vial of 10 mL of concentrate contains 10 mg of glofitamab at a concentration of 1 mg/mL.</p> <hr/> <p>Proposed: Not applicable</p>
Is or will the product be subject to additional monitoring in the European Union?	Yes

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

## GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AEGT	adverse event group term
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
CNS	central nervous system
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
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector-cell encephalopathy
ICU	intensive care unit
IRR	infusion-related reaction



<b>Abbreviation</b>	<b>Definition</b>
LFT	liver function test
mAB	monoclonal antibody
MAH	marketing authorization holder
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
PRAC	Pharmacovigilance Risk Assessment Committee
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 ([Defosse 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**

The historical standard of care for first-line (1L) treatment for DLBCL is based on a therapeutic backbone of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in combination with an anti-CD20 monoclonal antibody (mAb) rituximab (R-CHOP) ([Coiffier et al. 2010](#)). The Phase III POLARIX study met its primary endpoint demonstrating a statistically significant and clinically meaningful improvement in investigator (INV)-assessed progression-free survival (PFS) with POLIVY® (polatuzumab vedotin) + rituximab, cyclophosphamide, doxorubicin, and prednisolone (pola + R-CHP) compared to R-CHOP in patients with previously untreated DLBCL ([Tilly et al. 2022](#))

resulting in the approvals of pola + R-CHP as a new standard of care. Despite the availability of treatment regimens in 1L DLBCL, up to 40% of patients will ultimately relapse following R-CHOP, pola-R-CHP, or similar regimens, and patients with primary refractory disease or who relapse after transplant fare particularly poorly ([Roschewski et al. 2022](#)).

For patients who are not cured with 1L therapy, high-dose chemotherapy salvage followed by ASCT represents the historical standard of care for second line (2L) therapy among transplant candidates and offers a second chance for cure ([Philip et al. 1995](#); [NCCN 2024](#); [Tilly et al. 2015](#)). While no universal criteria exist to define transplant candidacy, this procedure is typically reserved for younger, fit patients who demonstrate chemosensitive disease ([Tilly et al. 2015](#)). Less than half of patients who are eligible for transplant will be cured, with markedly worse outcomes in patients who are refractory to frontline therapy or relapse within 12 months of treatment ([Seyfarth et al. 2006](#); [Gisselbrecht et al. 2010](#)). Chimeric antigen receptor T cells (CAR T) therapy directed against CD19 represents a novel therapeutic option for R/R DLBCL. Randomized Phase III trials of axicabtagene ciloleucel and lisocabtagene maraleucel have demonstrated superior event-free survival (EFS) relative to ASCT ([Kamdar et al. 2022](#); [Locke et al. 2022](#); [Yescarta USPI](#) and [SmPC](#); [Breyanzi USPI](#) and [SmPC](#)). Although CAR-T therapy represents a key advance in treating R/R DLBCL, ensuring the consistency, quality, and dose of autologous cell based therapies remain challenging and thus limits the broad adoption of this therapy beyond specialized centers. In addition, CAR-Ts are manufactured on an individualized basis with significant wait times, and many patients with DLBCL require rapid control of their aggressive disease and are thus unlikely to be suitable candidates for this therapy ([Thieblemont et al. 2019](#); [Nastoupil et al. 2018](#); [Hoffmann et al. 2023](#)).

Current treatments in R/R DLBCL outside of ASCT or CAR-T generally aim to achieve durable disease control/remission but are not considered to be curative. Almost all patients eventually relapse and become resistant to available treatment, where the remission duration generally decreases with each subsequent treatment regimen. Such patients are at increased risk of death due to progressive disease compared to younger, fitter, and less heavily pre-treated individuals. While numerous other therapies have emerged in recent years to provide additional options, these commonly pose challenges in terms of safety profile, complexity and accessibility, and critically none have demonstrated an overall survival benefit for ASCT-ineligible patients in a randomized Phase III study. Thus, the need for additional effective and tolerable treatment options in R/R DLBCL remains a key priority for this vulnerable population.

Current options for the treatment of DLBCL are presented in [Table 3](#).

**Table 3 Glofit-GemOx and Currently Available Treatment Options Based on Line of Therapy**

Patient segment	1L	2L	3L and beyond
All patients	R-CHOP or R-CHOP-like regimens Pola + R-CHP		
Transplant-eligible		Intensive salvage chemotherapy (R-DHAP/ICE/GDP)	
		HDCT + ASCT <sup>a</sup>	
		allogeneic transplant <sup>c</sup>	
		CAR-T therapies: lisocabtagene maraleucel <sup>b</sup> , axicabtagene ciloleucel <sup>b</sup> ,	
Transplant-ineligible		platinum-based and/or gemcitabine-based regimens (R-GemOx) pola + BR tafasitamab + lenalidomide <b>Glofitamab-GemOx</b>	
All patients			<b>glofitamab monotherapy</b> tisagenlecleucel loncastuximab tesirine selinexor epcoritamab odronextamab
			clinical trials (new MoAs)

ASCT=autologous stem cell transplant; BR=bendamustine+rituximab; CAR=chimeric antigen receptor; Glofit-GemOx=glofitamab + gemcitabine and oxaliplatin; HDCT=high dose chemotherapy; MoA=mechanism of action; polatuzumab vedotin=pola; R-CHOP=rituximab+cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP=rituximab, cyclophosphamide, doxorubicin, and prednisone; R-DHAP=rituximab+dexamethasone, cytarabin, cisplatin; R-GDP=rituximab+gemcitabine, cisplatin, dexamethasone; R-ICE=rituximab+ifosfamide, carboplatin, etoposide.

<sup>a</sup> ESMO (Tilly et al. 2015) guidelines suggest patients who relapse after 2L therapy are unlikely to respond to subsequent therapy and therefore generally are not eligible for ASCT.

<sup>b</sup> Refractory within 12 months.

<sup>c</sup> Consider allogeneic transplantation in patients relapsed after R-HDCT with ASCT or in patients with poor-risk factors at relapse (Tilly et al. 2015). Allogeneic transplant potentially available as consolidation after achieving sufficient response to salvage therapy.

Breyanzi® (lisocabtagene maraleucel) [SmPC](#)

Kymriah® (tisagenlecleucel) [SmPC](#)

Minjuvi® (tafasitamab) [SmPC](#)

Ordspono (odronextamab) [SmPC](#)

Polivy® (polatuzumab vedotin) [SmPC](#)

Tepkinly® (epcoritamab) [SmPC](#)

Xpovio™ (selinexor) [SmPC](#)

Yescarta® (axicabtagene ciloleucel) [SmPC](#)

Zynlonta® (loncastuximab tesirine) [SmPC](#)

ESMO Guidelines (Tilly et al. 2015)

### **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 11<sup>th</sup> 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 12<sup>th</sup> 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 ( $\geq 100 \mu\text{g/kg}$ ) 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  $\geq 100 \mu\text{g/kg}$  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](#)). 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<sup>+</sup> naïve CD8<sup>+</sup> CD4<sup>+</sup> T<sub>reg</sub>) 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<sup>+</sup> 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  $\leq 450$  ms. Thirteen patients (9.2%) had post-baseline QTcF values  $> 450$  ms -  $\leq 480$  ms, 1 patient (0.7%) had post-baseline QTcF values  $> 480$  ms -  $\leq 500$  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.

In Studies GO41944 and GO41943, among patients in the glofitamab-exposed safety population who had at least one post-baseline QTcF value (N=143), 126/143 patients (88.1%) had a maximum post-baseline QTcF value  $\leq 450$  msec, 14/143 patients (9.8%) a maximum post-baseline QTcF value  $> 450 - \leq 480$  msec, 1/143 patients (0.7%) a maximum post-baseline QTcF value  $> 480 - \leq 500$  msec, and 2/143 patients (1.4%) had a maximum post-baseline QTcF value  $> 500$  msec ([t\\_eg\\_cat\\_SERO](#)). Of the patients with  $> 480$  msec QTcF values (3/143), one patient from Study GO41944 had a cardiac AE with a QTcF interval at C2D1 of 467.27 msec and experienced non-serious Grade 1 arrhythmia which resolved without treatment after 7 days. No other patients with  $> 480$  msec QTcF values had cardiac AEs 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  $\geq 100$   $\mu\text{g/kg}$  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](#)). ICANS, including Grade 3 and higher, has been reported in patients treated with glofitamab in clinical trials and with post-marketing experience. ICANS is considered an important identified risk for glofitamab ([Module SVII.2](#)).

Endoscopy biopsy of the colon revealed T-cell infiltration and lymphangiectasia in a patient treated with glofitamab from Study NP30179.

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 4](#)).

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 17 May 2024 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 5](#), and R/R NHL, [Table 6](#)) who received at least one dose of glofitamab.

### **Relapsed / Refractory DLBCL Patients who have Received $\geq 2$ 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 registrational dose) in the current indication (patients with R/R DLBCL who have received  $\geq 2$  prior lines of systemic therapy) pooled from cohorts D<sub>2</sub> Subcohort 2 ([Sub. 2], Part II), D<sub>3</sub> (Part III) and D<sub>5</sub> (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 5](#), receiving glofitamab doses  $\geq 0.60$  mg (fixed dosing and step-up dosing) in the current indication (R/R DLBCL patients,  $\geq 2$  prior lines of systemic therapy).

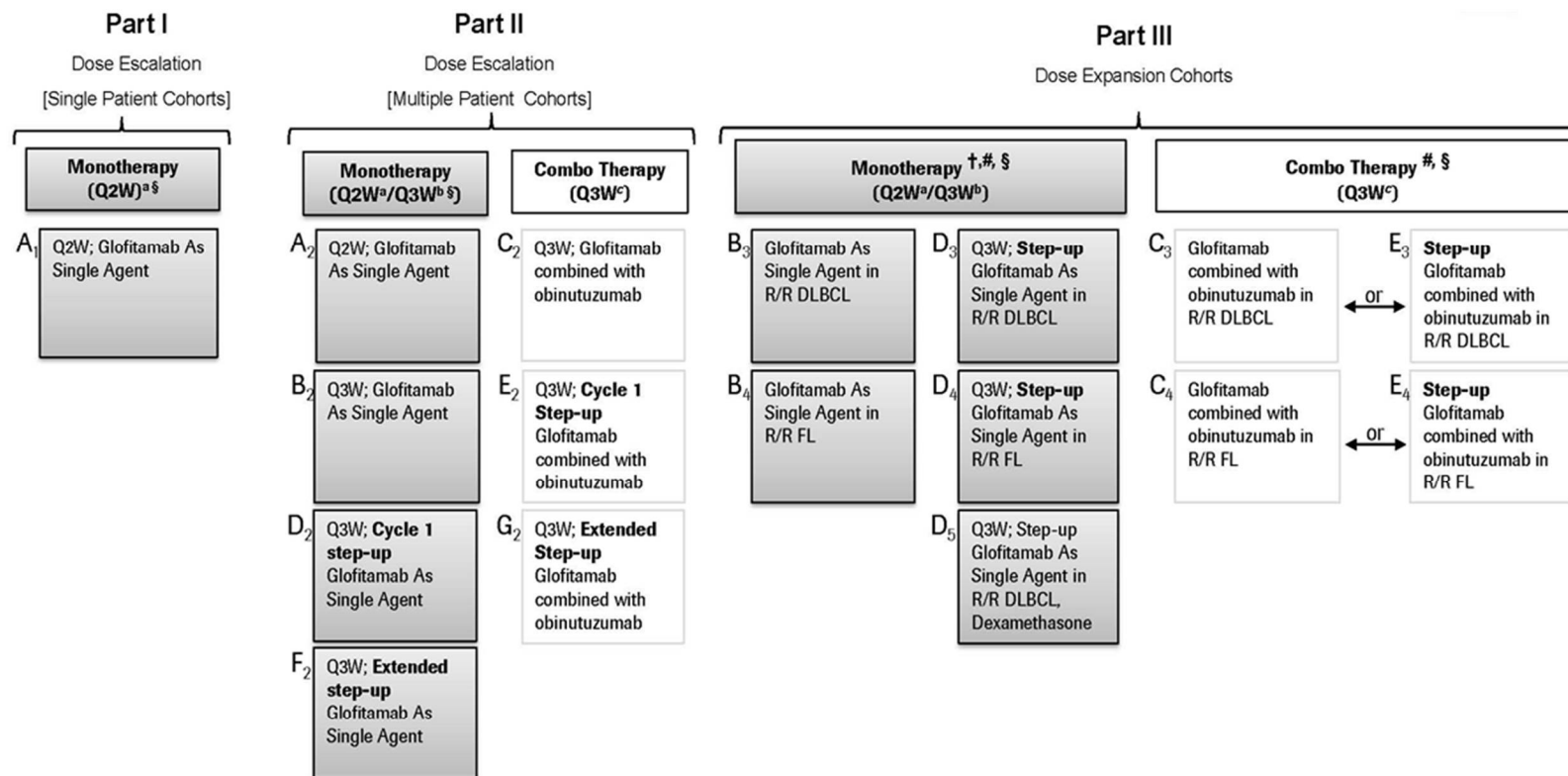
### **Relapsed / Refractory NHL Patients (All Histologies; for list, see footnote to [Table 6](#))**

- **Overall safety population:** Data from all enrolled patients in Study NP30179 glofitamab monotherapy  $\geq 0.6$  mg dosing cohorts who have received at least one dose of study medication (Gpt or glofitamab), irrespective of histology (N=485 patients with R/R NHL; see footnote to [Table 6](#)). These patients support the primary safety population to provide a comprehensive overview of the safety profile of

glofitamab monotherapy. Of these 485 patients, 467 received at least one dose of glofitamab.

- Supporting data from patients treated with glofitamab step-up dosing 2.5/10/30 mg (the registrational dose) in Cohort D<sub>3</sub>, Cohort D<sub>2</sub> [Sub 2] and Cohort D<sub>5</sub> from all R/R NHL histologies (see footnote to [Table 6](#)) (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

<sup>†</sup>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.

<sup>§</sup>Based on determined MTD/OBD, both or one expansion cohort may be selected for monotherapy B<sub>3</sub> and/or D<sub>3</sub>, B<sub>4</sub> and/or D<sub>4</sub>, while C<sub>3</sub> or E<sub>3</sub> and C<sub>4</sub> or E<sub>4</sub> may be selected.

<sup>§</sup> 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 D<sub>4</sub> will only be reported for safety and not for efficacy in the interim CSR.

**Table 4 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: 17 May 2024)	Open-label, multicenter, dose-escalation and expansion study.	Patients with R/R NHL	<u>Primary Safety Population</u> <sup>a</sup> : 154 R/R DLBCL patients <u>Overall Safety Population</u> <sup>b</sup> : 485 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.
GO41944 (also known as STARGLO) Phase III (CCOD:16 February 2024)	Open-label, multicenter, randomized study	R/R DLBCL	Enrolled: Glofit-GemOx N = 183 R-GemOx N = 91 Safety-Evaluable: Glofit-GemOx N = 172 R-GemOX N = 88	Glofit-GemOx <sup>c</sup> Glofit: IV, 2.5 mg (C1D8)/10 mg (C1D15)/30 mg (C2-12D1) q 21 days Obi: IV, 1000 mg (C1D1) <sup>d</sup> GemOx: Gem: IV, 1000 mg/m <sup>2</sup> , Ox: IV, 100 mg/m <sup>2</sup> (C1D2), (C2-8D1) q 21 days R-GemOx <sup>c</sup> R: IV, 375 mg/m <sup>2</sup> (C1-8D1) GemOx: see above.

Study No. and Phase	Study Design, Control Type	Population	No. of Patients	Dose, Route, and Regimen
GO41943 Phase Ib completed (CCOD: 8 December 2021)	Open-label, multicenter, two-treatment arm study with non-randomized arms <sup>e</sup>	R/R B-cell lymphoma, including: DLBCL, NOS; HGBCL with MYC, BCL2, and/or BCL6 rearrangement, and HGBCL, NOS	Enrolled: Glofit-GemOx N = 17  Safety Evaluable: Glofit-GemOx N = 16	Glofit-GemOx <sup>c</sup> Glofit: IV, 2.5 mg (C1D8)/10 mg (C1D15)/30 mg (C2-12D1) q 21 days Obi: IV, 1000 mg (C1D1) <sup>d</sup> GemOx: Gem: IV, 1000 mg/m <sup>2</sup> ; Ox: IV, 100 mg/m <sup>2</sup> (C1D2), (C2-8D1) q 21 days

C = cycle; CCOD = clinical cutoff date; D = Day; DLBCL = diffuse large B-cell lymphoma; Glofit = glofitamab; Glofit-GemOx = glofitamab in combination with gemcitabine and oxaliplatin; Gpt = obinutuzumab (Gazyvaro®/ Gazyva®) pretreatment; HGBCL = high grade B-cell lymphoma; IV = intravenous; LPLV = last patient's last visit; ; Mosun-GemOx = mosunetuzumab in combination with gemcitabine and oxaliplatin; NHL = non-Hodgkin's lymphoma; NOS = not otherwise specified; Q3W = every 3 weeks; R/R = relapsed or refractory; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; R/R = relapsed or refractory.

<sup>a</sup> Primary safety population includes patients pooled from cohorts D<sub>2</sub> Subcohort 2 (Part II), D<sub>3</sub> (Part III) and Cohort D<sub>5</sub> (Part III) treated at the registrational dose (2.5/10/30 mg) in the current indication (R/R DLBCL patients who have received ≥2 prior lines of systemic therapy).

<sup>b</sup> 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.

<sup>c</sup> Gemcitabine was administered before oxaliplatin on the same day in Cycles 1-8. Gemcitabine and oxaliplatin were administered on Day 1 or 2 (per local practice) in Cycles 2-8 and were given after glofitamab/rituximab.

<sup>d</sup> A single dose of obinutuzumab 1000 mg pretreatment was administered intravenously on Cycle 1 Day 1, 7 days prior to the first administration of glofitamab.

<sup>e</sup> Patients were non-randomly assigned to treatment with Glofit-GemOx or mosunetuzumab in combination with GemOx (Mosun-GemOx). Data from the Mosun-GemOx arm from Study GO41943 are not discussed in this RMP as these data are out of scope for the RMP.

**Table 5 Study NP30179: Description of Cohorts/Groups Presented for Patients with Relapsed/Refractory DLBCL who have Received  $\geq 2$  Prior Systemic Therapies (Safety-Evaluable Population)**

	Patients with R/R DLBCL who have Received $\geq 2$ Prior Systemic Therapies					
Group/cohort	Cohort D <sub>3</sub>	Cohort D <sub>5</sub>	$\geq 0.6$ mg dose	$\geq 10$ mg Target dose	Cohort D <sub>2</sub> Subcohort 2 + Cohort D <sub>3</sub>	Cohort D <sub>2</sub> Subcohort 2, D <sub>3</sub> and D <sub>5</sub>
Analysis Population	Primary Efficacy Population N = 107 <sup>e</sup>	Supportive Safety N = 40 <sup>f</sup>	Supportive Safety N = 287 <sup>d</sup>	Supportive Efficacy / Safety N = 100 <sup>g</sup>	Supportive Efficacy / Safety N = 114 <sup>e</sup>	Primary Safety Population N = 154 <sup>e</sup>
Source of patients	Cohort D <sub>3</sub> (Part III, dose expansion)	Cohort D <sub>5</sub> (Part III dose expansion)	All cohorts except Cohort A <sub>1</sub>	Cohorts B <sub>2</sub> (Part II, dose escalation), Cohort B <sub>3</sub> (Part III) and Cohort D <sub>2</sub> Subcohort 1 (Part II, dose escalation)	Cohort D <sub>2</sub> subcohort 2 (Part II dose escalation) + Cohort D <sub>3</sub> (Part III dose expansion)	Cohort D <sub>2</sub> subcohort 2 (Part II dose escalation) + Cohort D <sub>3</sub> and Cohort D <sub>5</sub> (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 <sup>a</sup> mg glofitamab <sup>h</sup>	Step-up dosing, 2.5/10/30 <sup>a</sup> mg glofitamab (Dex premedication <sup>f h</sup> )	Fixed dosing, 0.6, 1, 1.6, 4, 10, 16, 25 mg or 10/16 <sup>b</sup> mg; step-up dosing, 2.5/10/16 <sup>c</sup> mg or 2.5/10/30 <sup>a</sup> mg glofitamab <sup>h</sup>	Fixed dosing, 10mg, 16mg, 25mg or 10/16 <sup>b</sup> mg, step-up dosing, 2.5/10/16 <sup>c</sup> mg glofitamab <sup>h</sup>	Step-up dosing, 2.5/10/30 <sup>a</sup> mg glofitamab <sup>h</sup>	Step-up dosing, 2.5/10/30 <sup>a</sup> mg glofitamab (Cohort D <sub>5</sub> , Dex premedication <sup>f h</sup> )



**Table 5 Study NP30179: Description of Cohorts/Groups Presented for Patients with Relapsed/Refractory DLBCL who have Received  $\geq 2$  Prior Systemic Therapies (Safety-Evaluable Population) (cont.)**

	Patients with R/R DLBCL who have Received $\geq 2$ Prior Systemic Therapies					
Patient population	R/R DLBCL Patients with $\geq 2$ prior therapies	R/R DLBCL Patients with $\geq 2$ prior therapies	R/R DLBCL Patients with $\geq 2$ prior therapies	R/R DLBCL Patients with $\geq 2$ prior therapies	R/R DLBCL Patients with $\geq 2$ prior therapies	R/R DLBCL Patients with $\geq 2$ 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.

<sup>a</sup> 2.5 mg on C1D8, 10 mg on C1D15, 30 mg C2D1 and subsequent Q3W cycles.

<sup>b</sup> 10 mg on C1D1, 16 mg on C2D1 and subsequent Q3W cycles.

<sup>c</sup> 2.5 mg on C1D1, 10 mg on C1D8, 16 mg C2D1 and subsequent Q3W cycles.

<sup>d</sup> Includes patients treated with two doses of obinutuzumab (Gazyva<sup>®</sup>, double Gpt [DGpt]) in Cohort D<sub>2</sub>, Subcohort.4.

<sup>e</sup> Safety population (R/R DLBCL) in Cohort D<sub>3</sub> excludes one FL patient and one patient who did not receive any study treatment with Gpt or glofitamab (enrolled in error).

<sup>f</sup> Safety population (R/R DLBCL) in Cohort D<sub>5</sub> excludes one FL patient enrolled in error.

<sup>g</sup> Safety population in  $\geq 10$  mg target dose cohort excludes one patient assigned to 10/16 mg treatment who did not receive any study treatment with Gpt or glofitamab.

<sup>h</sup> Premedication with corticosteroids prior to glofitamab was mandatory for all patients in the study. In Cohort D<sub>5</sub>, 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 6 Study NP30179: 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 <sub>2</sub> Subcohort 2, D <sub>3</sub> and D <sub>5</sub> Step-up dosing, 2.5/10/30 <sup>a</sup> mg	All patients ≥0.6 mg
Analysis Population	Supportive Safety N = 195	Overall Safety Population <sup>d</sup> N = 485
Source of patients	Cohort D <sub>2</sub> subcohort 2 (Part II dose escalation) + Cohort D <sub>3</sub> and Cohort D <sub>5</sub> (Part III dose expansion) (Cohort D <sub>5</sub> , Dex premedication)	Cohorts A <sub>2</sub> , B <sub>2</sub> , D <sub>2</sub> , F <sub>2</sub> , B <sub>3</sub> , B <sub>4</sub> , D <sub>3</sub> , D <sub>4</sub> , D <sub>5</sub>
No. of pts receiving at least one dose of glofitamab	N = 185	N = 467
Dose (mg)	Step-up dosing, 2.5/10/30 <sup>a</sup> mg glofitamab <sup>g</sup>	Fixed dosing, 0.6, 1, 1.6, 4, 10, 16, 25 mg or 10/16 <sup>b</sup> mg; step-up dosing, 2.5/10/16 <sup>c</sup> mg, 2.5/10/30 <sup>a,d</sup> mg or 0.5/2.5/10/30 <sup>e</sup> mg glofitamab <sup>g</sup>
Patient population	Patients with R/R NHL	Patients with R/R NHL
Histologies included	All NHL histologies per protocol <sup>f</sup>	All NHL histologies per protocol <sup>f</sup>

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

<sup>a</sup> 2.5 mg on C1D8, 10 mg on C1D15, 30 mg C2D1 and subsequent Q3W cycles.

<sup>b</sup> 10 mg on C1D1, 16 mg on C2D1 and subsequent Q3W cycles.

<sup>c</sup> 2.5 mg on C1D1, 10 mg on C1D8, 16 mg C2D1 and subsequent Q3W cycles.

<sup>d</sup> Includes patients treated with two doses of obinutuzumab (Gazyva<sup>®</sup>, double Gpt [DGpt]) in Cohort D<sub>2</sub>, Subcohort.4.

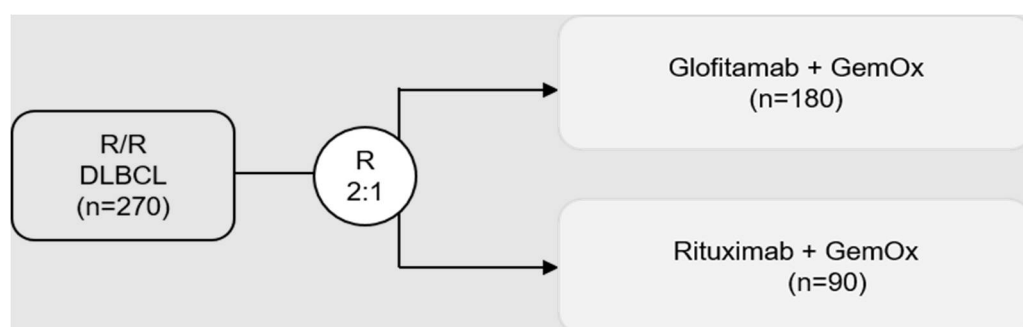
<sup>e</sup> 0.5 mg on C1D8, 2.5 mg on C1D15, 10 mg on C2D1, 30 mg C3D1 and subsequent Q3W cycles.

<sup>f</sup> 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).

<sup>g</sup> Premedication with corticosteroids prior to glofitamab was mandatory for all patients in the study. In Cohort D<sub>5</sub>, 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)

Pivotal Study GO41944 is a Phase III, open-label, multicenter, randomized study evaluating the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin (Glofit-GemOx) versus rituximab in combination with gemcitabine and oxaliplatin (R-GemOx) in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL). An overview of the design is shown in [Figure 2](#).

**Figure 2 Overview of GO41944 Study Design**



DLBCL = diffuse large B-cell lymphoma; GemOx = gemcitabine plus oxaliplatin; R = randomized; R/R = relapsed or refractory.

Supportive study GO41943 was an open-label, multicenter, two-treatment arm Phase Ib study with non-randomized arms evaluating the safety and preliminary efficacy of Glofit-GemOx or mosunetuzumab in combination with gemcitabine plus oxaliplatin (Mosun-GemOx) in patients with R/R large B-cell lymphoma and high-grade large B-cell lymphoma (HGBCL).

Exposure and AE data in this RMP are presented up to the clinical cutoff date of 16 February 2024 for Study GO41944 and 8 December 2021 for Study GO41943 ([Table 4](#)) for the populations listed below.

- GO41944 (Rituximab–GemOx arm)
  1. Patients with R/R DLBCL receiving Rituximab–GemOx (N=88)
- GO41944 (Glofitamab–GemOx arm)
  2. Patients with R/R DLBCL receiving Glofit–GemOx, Glofit Exposed (N= 172)
- GO41943 (Glofitamab–GemOx arm)
  3. Patients with R/R DLBCL<sup>a</sup> receiving Glofit–GemOx, Glofit Exposed (N= 16)
- GO41944 + GO41943 (All Glofitamab–GemOx)
  4. Patients with R/R DLBCL<sup>a</sup> receiving Glofit–GemOx, Glofit Exposed (N= 188)

<sup>a</sup> Includes patients with HGBCL in study GO41943

The primary presentation of exposure and safety data in this RMP focuses on patients who received Gpt and at least one dose of glofitamab in Studies GO41944 and

GO41943 (N=188). This is denoted as “glofitamab-exposed” in the relevant tables of this RMP. “Modified safety-evaluable patients” in tables refers to patients who received either Rituximab-GemOx or Glofitamab-Gemox from the 4 populations described above.

### **Study NP30179**

Clinical trial exposure data from Study NP30179 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<sub>2</sub> [Sub.2], D<sub>3</sub>, and D<sub>5</sub>) received at least one dose of glofitamab. Of these patients, 74 (51.0%) received glofitamab for  $\leq 3$  months ([Table 7](#)). A majority of patients (61.4%) received  $<8$  cycles of glofitamab ([Table 9](#)).

#### **Overall Safety Population**

A total of 467 patients (154.64 patient-years of exposure) with mixed R/R NHL histologies in the overall safety population received at least one dose of  $\geq 0.60$  mg glofitamab. Of these patients, 57.8% received glofitamab from  $>3$  to  $\leq 9$  months and 39.4% received glofitamab for  $\leq 3$  months ([Table 8](#)). A total of 207 patients (44.3%) received  $>8$  cycles of glofitamab ([Table 10](#)).

**Table 7 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: 17MAY2024

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**Table 7 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: 17MAY2024

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**Table 8 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  $\geq 0.60$  mg, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab  
Protocol: NP30179  
Risk Management Plan

Duration of exposure	Glofitamab Doses $\geq 0.60$ mg (N=467)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)	
	Patients (N=467)	Person time*	Patients (N=185)	Person time*
0 $\leq$ 1 month	83 (17.8%)	2.69	40 (21.6%)	1.13
> 1 $\leq$ 3 months	101 (21.6%)	17.21	45 (24.3%)	7.86
> 3 $\leq$ 6 months	97 (20.8%)	36.31	34 (18.4%)	12.68
> 6 $\leq$ 9 months	173 (37.0%)	109.26	62 (33.5%)	39.26
> 9 $\leq$ 12 months	11 ( 2.4%)	9.05	3 ( 1.6%)	2.45
>12 months	2 ( 0.4%)	2.42	1 ( 0.5%)	1.00
Total patients numbers/person time	467 ( 100%)	176.95	185 ( 100%)	64.38

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: 17MAY2024

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**Table 9 Exposure by Number of Cycles- Patients with R/R DLBCL (≥2 Prior Systemic Therapies)**

Summary of Exposure by Number of 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: 17MAY2024

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**Table 9 Exposure by Number of Cycles- Patients with R/R DLBCL (≥2 Prior Systemic Therapies) (cont.)**

Summary of Exposure by Number of 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: 17MAY2024

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**Table 10 Exposure by Number of Cycles - Patients with R/R NHL– All Histologies**

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

Number of Cycles	Glofitamab Doses $\geq 0.60$ mg (N=467)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)	
	Patients (N=467)	Person time*	Patients (N=185)	Person time*
<8 Cycles	223 (47.8%)	32.40	102 (55.1%)	14.56
8 Cycles	37 ( 7.9%)	14.94	13 ( 7.0%)	5.43
9-11 Cycles	22 ( 4.7%)	12.30	6 ( 3.2%)	2.85
12 Cycles	185 (39.6%)	117.31	64 (34.6%)	41.54
Total patients numbers/person time	467 ( 100%)	176.95	185 ( 100%)	64.38

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: 17MAY2024

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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  $\geq 18$  to  $\leq 64$  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 11](#)).

### **Overall Safety Population**

Of the patients who received at least one dose of glofitamab  $\geq 0.60$  mg in the overall safety population (N=467), 47.5% (222/467 patients) were  $\geq 18$  to  $\leq 64$  years of age and 62.7% (293/467 patients) were male. Male patients had 106.6 patient-years of exposure versus 70.3 patient-years in female patients ([Table 12](#)).

**Table 11 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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_aggnr\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/

t\_ex\_aggnr\_rmp\_I\_RMP\_SERO\_17MAY2024\_30179.out

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**Table 11 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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_aggnr\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun20247prod/output/

t\_ex\_aggnr\_rmp\_I\_RMP\_SERO\_17MAY2024\_30179.out

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**Table 11 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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_aggnr\_rmp.sas  
Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/  
t\_ex\_aggnr\_rmp\_I\_RMP\_SERO\_17MAY2024\_30179.out  
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**Table 12 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=467)						
>=18 <=64	144 (49.1%)	78 (44.8%)	222 (47.5%)	51.63	30.97	82.60
> 64 <=74	103 (35.2%)	54 (31.0%)	157 (33.6%)	37.67	20.77	58.43
> 74 <=84	41 (14.0%)	40 (23.0%)	81 (17.3%)	15.58	17.60	33.19
> 84	5 ( 1.7%)	2 ( 1.1%)	7 ( 1.5%)	1.72	1.00	2.73
Total patients numbers/person time	293 ( 100%)	174 ( 100%)	467 ( 100%)	106.60	70.34	176.95
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%)	7.02	6.55	13.57
> 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%)	38.95	25.43	64.38

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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_aggnr\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/

t\_ex\_aggnr\_rmp\_I\_RMP2\_SERO\_17MAY2024\_30179.out

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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 13](#)). A summary of the exposure by 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 15](#)).

### **Overall Safety Population**

Of the patients who received glofitamab in the overall safety population (N=467), 58.9% (275/467 patients, 109 patient-years of exposure) received the highest dose of 30 mg of glofitamab ([Table 14](#)). A summary of the exposure by 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<sub>2</sub> [Sub. 2], D<sub>3</sub> and D<sub>5</sub> 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 16](#)).



**Table 13 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	101 ( 100%)	25.82	37 ( 100%)	11.30	273 ( 100%)	73.67	97 ( 100%)	26.52
numbers/person time								

(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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_dose1\_rmp.sas  
Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/  
t\_ex\_dose1\_rmp\_I\_RMP\_SERO\_17MAY2024\_30179.out  
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**Table 13 Exposure by Dose (maximum dose received) - Patients with R/R DLBCL (≥2 Prior Systemic Therapies)  
(cont.)**

Summary of Exposure by Maximum Dose, Initial Treatment Phase, (R/R DLBCL Patients, ≥2 Prior Lines of Systemic Therapy), Safety-Evaluatable 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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_dose1\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/

t\_ex\_dose1\_rmp\_I\_RMP\_SERO\_17MAY2024\_30179.out

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**Table 14 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

Maximum Dose	Glofitamab Doses >=0.60 mg (N=467)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)	
	Patients (N=467)	Person time*	Patients (N=185)	Person time*
0.6 mg	14 ( 3.0%)	3.11	0	NE
1.0 mg	8 ( 1.7%)	1.50	0	NE
1.8 mg	9 ( 1.9%)	2.87	0	NE
2.5 mg	12 ( 2.6%)	0.13	11 ( 5.9%)	0.13
4.0 mg	9 ( 1.9%)	2.30	0	NE
9.4 mg	1 ( 0.2%)	0.00	1 ( 0.5%)	0.00
10.0 mg	30 ( 6.4%)	4.95	7 ( 3.8%)	0.02
12.0 mg	1 ( 0.2%)	0.04	0	NE
16.0 mg	99 (21.2%)	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 ( 1.5%)	2.42	0	NE
30.0 mg	275 (58.9%)	109.07	166 (89.7%)	56.45
Total patients numbers/person time	467 ( 100%)	157.30	185 ( 100%)	56.60

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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_dose1\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/

t\_ex\_dose1\_rmp\_I\_RMP2\_SERO\_17MAY2024\_30179.out

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**Table 15 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
Glofitamab (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	8 ( 7.4%)	0.00	9 ( 6.2%)	0.00

(a) Dexamethasone pretreated.

Sub = subcohort. "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.

\* 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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_dose3\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/

t\_ex\_dose3\_rmp\_I\_RMP\_SERO\_17MAY2024\_30179.out

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**Table 16 Exposure by Dose by Cycle - Patients with R/R NHL– All Histologies; Cohorts D2 [Sub. 2], D3, and D5**

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

Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)			
Dose level	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%)	56.45	
Glofitimab (other)	28 (15.1%)	0.84	
Obinutuzumab (other)**	13 ( 7.0%)	0.00	

Sub = subcohort. "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.

\* 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: 17MAY2024

Program: root/clinical studies/RO7082859/CDT70029/NP30179/share/data analysis/prod/program/t ex dose3\_rmp.sas

Output: root/clinical studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun20247/prod/output/

t\_ex\_dose3\_rmp\_I\_RMP2A\_SERO\_17MAY2024\_30179.out

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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 17](#), [Table 19](#)).

### **Overall Safety Population**

Of the patients who received glofitamab in the overall safety population (N=467), the majority were White (370/467 patients [79.2%], 139.1 patient-years of exposure) and of ethnicity Not Hispanic or Latino (365/467 patients [78.2%], 140.7 patient-years of exposure ([Table 18](#), [Table 20](#)).

**Table 17 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	101 ( 100%)	29.97	37 ( 100%)	12.62	273 ( 100%)	81.88	97 ( 100%)	28.94
numbers/person time								

(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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_race\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/

t\_ex\_race\_rmp\_i\_RMP\_SERO\_17MAY2024\_30179.out

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**Table 17 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

Race	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)	
	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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_race\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/

t\_ex\_race\_rmp\_i\_RMP\_SERO\_17MAY2024\_30179.out

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**Table 18 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

Race	Glofitamab Doses >=0.60 mg (N=467)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)	
	Patients (N=467)	Person time*	Patients (N=185)	Person time*
Asian	19 ( 4.1%)	9.51	8 ( 4.3%)	3.73
Black or African American	5 ( 1.1%)	2.17	2 ( 1.1%)	1.27
White	370 (79.2%)	139.08	140 (75.7%)	48.13
Unknown	73 (15.6%)	26.19	35 (18.9%)	11.24
Total patients numbers/person time	467 ( 100%)	176.95	185 ( 100%)	64.38

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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_race\_rmp.sas  
Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/  
t\_ex\_race\_rmp\_I\_RMP2\_SERO\_17MAY2024\_30179.out  
24OCT2024\_18:09

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**Table 19 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

Ethnicity	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)	
	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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_ethnic\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/

t\_ex\_ethnic\_rmp\_I\_RMP\_SERO\_17MAY2024\_30179.out

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**Table 19 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

Ethnicity	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)	
	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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_ethnic\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/

t\_ex\_ethnic\_rmp\_I\_RMP\_SERO\_17MAY2024\_30179.out

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**Table 20 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

Ethnicity	Glofitamab Doses >=0.60 mg (N=467)		Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)	
	Patients (N=467)	Person time*	Patients (N=185)	Person time*
Hispanic or Latino	20 ( 4.3%)	6.14	11 ( 5.9%)	1.92
Not Hispanic or Latino	365 (78.2%)	140.74	139 (75.1%)	50.65
Not Stated	60 (12.8%)	22.27	26 (14.1%)	8.06
Unknown	22 ( 4.7%)	7.79	9 ( 4.9%)	3.75
Total patients numbers/person time	467 ( 100%)	176.95	185 ( 100%)	64.38

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: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ex\_ethnic\_rmp.sas  
Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/  
t\_ex\_ethnic\_rmp\_I\_RMP2\_SERO\_17MAY2024\_30179.out  
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### **Studies GO41944 and GO41943**

Clinical trial exposure data from Studies GO41944 and GO41943 are presented in the tables below.

### **Duration of Exposure**

In Studies GO41944 and GO41943 (N= 188), all 188 patients (82.6 patient-years of exposure) with R/R DLBCL received 2.5/10/30 mg glofitamab. Of these patients, the majority received glofitamab for  $\leq 9$  months (96.3%, 181/188 patients) ([Table 21](#)). Fifty-seven percent (57.0%) of patients received 11 or fewer cycles of glofitamab ([Table 22](#)).

**Table 21 Duration of Exposure (Studies GO41944 and GO41943)**

Summary of Duration of Exposure, Modified Safety-Evaluable Patients  
Protocol: GO41944 & GO41943  
Risk Management Plan

Study Treatment Duration of exposure	R-GemOx (GO41944) (N=88)		Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)		Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)		Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)	
	Patients (N=88)	Person time*	Patients (N=172)	Person time*	Patients (N=16)	Person time*	Patients (N=188)	Person time*
Gemcitabine								
0 <= 1 month	33 (37.5%)	1.22	24 (14.0%)	0.71	1 ( 6.3%)	0.06	25 (13.3%)	0.77
> 1 <= 3 months	24 (27.3%)	4.04	24 (14.0%)	3.97	8 (50.0%)	1.56	32 (17.0%)	5.53
> 3 <= 6 months	30 (34.1%)	12.00	115 (66.9%)	46.96	6 (37.5%)	2.39	121 (64.4%)	49.35
> 6 <= 9 months	1 ( 1.1%)	0.50	9 ( 5.2%)	4.97	1 ( 6.3%)	0.54	10 ( 5.3%)	5.51
> 9 <= 12 months	0	NE	0	NE	0	NE	0	NE
Glofitamab								
0 <= 1 month	0	NE	23 (13.4%)	0.66	1 ( 6.3%)	0.04	24 (12.8%)	0.70
> 1 <= 3 months	0	NE	25 (14.5%)	3.97	8 (50.0%)	1.40	33 (17.6%)	5.37
> 3 <= 6 months	0	NE	28 (16.3%)	10.66	2 (12.5%)	0.71	30 (16.0%)	11.37
> 6 <= 9 months	0	NE	90 (52.3%)	57.31	4 (25.0%)	2.40	94 (50.0%)	59.71
> 9 <= 12 months	0	NE	6 ( 3.5%)	4.67	1 ( 6.3%)	0.75	7 ( 3.7%)	5.42
Oxaliplatin								
0 <= 1 month	33 (37.5%)	1.22	24 (14.0%)	0.71	1 ( 6.3%)	0.06	25 (13.3%)	0.77
> 1 <= 3 months	24 (27.3%)	4.04	26 (15.1%)	4.38	8 (50.0%)	1.56	34 (18.1%)	5.94
> 3 <= 6 months	30 (34.1%)	12.00	115 (66.9%)	46.90	6 (37.5%)	2.39	121 (64.4%)	49.29
> 6 <= 9 months	1 ( 1.1%)	0.50	7 ( 4.1%)	3.88	1 ( 6.3%)	0.54	8 ( 4.3%)	4.42
> 9 <= 12 months	0	NE	0	NE	0	NE	0	NE
Rituximab								
0 <= 1 month	33 (37.5%)	1.27	0	NE	0	NE	0	NE
> 1 <= 3 months	24 (27.3%)	4.11	0	NE	0	NE	0	NE
> 3 <= 6 months	30 (34.1%)	12.07	0	NE	0	NE	0	NE
> 6 <= 9 months	1 ( 1.1%)	0.50	0	NE	0	NE	0	NE
> 9 <= 12 months	0	NE	0	NE	0	NE	0	NE

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.

\* 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.

Program: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ex\_dur\_rmp.sas  
Output: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/output/t\_ex\_dur\_rmp\_RMP\_SERO.out  
02MAY2024 15:55 Page 1 of 1

**Table 22 Exposure by Number of Cycles (Studies GO41944 and GO41943)**

Summary of Exposure by Number of Cycles, Modified Safety-Evaluable Patients  
Protocol: GO41944 & GO41943  
Risk Management Plan

Study Treatment Number of Cycles	R-GemOx (GO41944) (N=88)		Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)		Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)		Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)	
	Patients (N=88)	Person time*	Patients (N=172)	Person time*	Patients (N=16)	Person time*	Patients (N=188)	Person time*
Gemcitabine								
<8 Cycles	62 (70.5%)	6.84	68 (39.5%)	11.54	10 (62.5%)	1.95	78 (41.5%)	13.49
8 Cycles	26 (29.5%)	10.92	103 (59.9%)	44.47	6 (37.5%)	2.60	109 (58.0%)	47.07
9-11 Cycles	0	NE	1 ( 0.6%)	0.61	0	NE	1 ( 0.5%)	0.61
12 Cycles	0	NE	0	NE	0	NE	0	NE
Glofitamab								
<8 Cycles	0	NE	61 (35.5%)	8.86	10 (62.5%)	1.75	71 (37.8%)	10.61
8 Cycles	0	NE	11 ( 6.4%)	4.84	1 ( 6.3%)	0.40	12 ( 6.4%)	5.24
9-11 Cycles	0	NE	23 (13.4%)	13.00	1 ( 6.3%)	0.52	24 (12.8%)	13.52
12 Cycles	0	NE	77 (44.8%)	50.57	4 (25.0%)	2.64	81 (43.1%)	53.20
Oxaliplatin								
<8 Cycles	62 (70.5%)	6.84	71 (41.3%)	12.34	10 (62.5%)	1.95	81 (43.1%)	14.28
8 Cycles	26 (29.5%)	10.92	100 (58.1%)	42.92	6 (37.5%)	2.60	106 (56.4%)	45.52
9-11 Cycles	0	NE	1 ( 0.6%)	0.61	0	NE	1 ( 0.5%)	0.61
12 Cycles	0	NE	0	NE	0	NE	0	NE
Rituximab								
<8 Cycles	62 (70.5%)	6.98	0	NE	0	NE	0	NE
8 Cycles	26 (29.5%)	10.98	0	NE	0	NE	0	NE
9-11 Cycles	0	NE	0	NE	0	NE	0	NE
12 Cycles	0	NE	0	NE	0	NE	0	NE

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.

\* 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.

Program: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ex\_cycles\_rmp.sas  
Output: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/output/  
t\_ex\_cycles\_rmp\_RMP\_SERO.out  
02MAY2024 15:54

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### **Exposure by Age Group and Gender**

In Studies GO41944 and GO41943 (N =188), of the patients who received 2.5/10/30 mg glofitamab, 41% (77/188 patients) were <65 years of age and 59% (111/188 patients) were male. Male patients had 45.9 patient-years of exposure versus 36.7 patient-years in female patients ([Table 23](#)).



**Table 23 Exposure by Age Group and Gender, Glofit-Exposed Safety-Evaluable Patients (Studies GO41944 and GO41943)**

Summary of Duration of Exposure by Age Group and Gender, Modified Safety-Evaluable Patients  
Protocol: GO41944 & GO41943  
Risk Management Plan

Study Treatment Age group (years)	Patients			Person time*		
	Male	Female	Total	Male	Female	Total
Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)						
Gemcitabine						
<65	42 (37.8%)	35 (45.5%)	77 (41.0%)	12.30	11.45	23.76
65-74	45 (40.5%)	23 (29.9%)	68 (36.2%)	13.70	7.17	20.88
75-84	24 (21.6%)	18 (23.4%)	42 (22.3%)	9.35	6.74	16.08
85+	0	1 (1.3%)	1 (0.5%)	NE	0.45	0.45
Total	111 (100%)	77 (100%)	188 (100%)	35.35	25.82	61.17
Glofitamab						
<65	42 (37.8%)	35 (45.5%)	77 (41.0%)	15.21	16.11	31.33
65-74	45 (40.5%)	23 (29.9%)	68 (36.2%)	18.19	10.53	28.71
75-84	24 (21.6%)	18 (23.4%)	42 (22.3%)	12.50	9.35	21.85
85+	0	1 (1.3%)	1 (0.5%)	NE	0.68	0.68
Total	111 (100%)	77 (100%)	188 (100%)	45.90	36.67	82.57
Obinutuzumab						
<65	42 (37.8%)	35 (45.5%)	77 (41.0%)	1.43	2.19	3.62
65-74	45 (40.5%)	23 (29.9%)	68 (36.2%)	1.34	1.60	2.94
75-84	24 (21.6%)	18 (23.4%)	42 (22.3%)	0.33	1.00	1.33
85+	0	1 (1.3%)	1 (0.5%)	NE	0.00	0.00
Total	111 (100%)	77 (100%)	188 (100%)	3.10	4.80	7.90
Oxaliplatin						
<65	42 (37.8%)	35 (45.5%)	77 (41.0%)	12.30	11.46	23.76
65-74	45 (40.5%)	23 (29.9%)	68 (36.2%)	13.55	7.12	20.67
75-84	24 (21.6%)	18 (23.4%)	42 (22.3%)	9.16	6.38	15.53
85+	0	1 (1.3%)	1 (0.5%)	NE	0.45	0.45
Total	111 (100%)	77 (100%)	188 (100%)	35.01	25.40	60.42
Rituximab						
<65	0	0	0	NE	NE	NE
65-74	0	0	0	NE	NE	NE
75-84	0	0	0	NE	NE	NE
85+	0	0	0	NE	NE	NE
Total	0	0	0	NE	NE	NE

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.

Age and Sex information is shown for all patients who received study drug.

\* Person-time is defined as the sum of the exposure time (from first to last administration of study drug) for every

**Table 23 Exposure by Age Group and Gender, Glofit-Exposed Safety-Evaluable Patients (Studies GO41944 and GO41943)**

patient in unit: Years.

NE means that there were no subjects in the category.

Program: root/clinical\_studies/R07082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ex\_aggnr\_age\_rmp.sas

Output: Adapted from [t\\_ex\\_aggnr\\_age\\_rmp\\_RMP\\_SERO.out](#)

### **Exposure by Dose**

All patients in the glofitamab-exposed safety population in Studies GO41944 and GO41943 (N= 188) received 2.5/10/30 mg glofitamab.

### **Exposure by Ethnic or Racial Origin**

In Studies GO41944 and GO41943 (N= 188), of the patients that received glofitamab, the majority were White (87/188 patients [46.3%] and 36.3 patient-years of exposure) or Asian (87/188 patients [46.3%] and 40.4 patient-years of exposure) and of non-Hispanic or Latino ethnicity (165/188 patients [87.8%] and 73.9 patient-years of exposure) ([Table 24](#) and [Table 25](#)).

**Table 24 Summary of Exposure by Race (Studies GO41944 and GO41943)**

Study Treatment Race	R-GemOx (GO41944) (N=88)		Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)		Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)		Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)	
	Patients (N=88)	Person time*	Patients (N=172)	Person time*	Patients (N=16)	Person time*	Patients (N=188)	Person time*
Gemcitabine								
Asian	50 (56.8%)	7.98	85 (49.4%)	29.52	2 (12.5%)	0.65	87 (46.3%)	30.16
Black or African American	1 ( 1.1%)	0.40	2 ( 1.2%)	0.56	0	NE	2 ( 1.1%)	0.56
White	31 (35.2%)	8.28	73 (42.4%)	22.90	14 (87.5%)	3.90	87 (46.3%)	26.81
Unknown	6 ( 6.8%)	1.11	12 ( 7.0%)	3.64	0	NE	12 ( 6.4%)	3.64
Glofitamab								
Asian	0	NE	85 (49.4%)	39.81	2 (12.5%)	0.61	87 (46.3%)	40.43
Black or African American	0	NE	2 ( 1.2%)	0.76	0	NE	2 ( 1.1%)	0.76
White	0	NE	73 (42.4%)	31.58	14 (87.5%)	4.69	87 (46.3%)	36.27
Unknown	0	NE	12 ( 7.0%)	5.12	0	NE	12 ( 6.4%)	5.12
Obinutuzumab								
Asian	0	NE	85 (49.4%)	4.85	2 (12.5%)	0.01	87 (46.3%)	4.86
Black or African American	0	NE	2 ( 1.2%)	0.01	0	NE	2 ( 1.1%)	0.01
White	0	NE	73 (42.4%)	2.56	14 (87.5%)	0.18	87 (46.3%)	2.74
Unknown	0	NE	12 ( 7.0%)	0.29	0	NE	12 ( 6.4%)	0.29
Oxaliplatin								
Asian	50 (56.8%)	7.98	85 (49.4%)	29.27	2 (12.5%)	0.65	87 (46.3%)	29.92
Black or African American	1 ( 1.1%)	0.40	2 ( 1.2%)	0.41	0	NE	2 ( 1.1%)	0.41
White	31 (35.2%)	8.28	73 (42.4%)	22.91	14 (87.5%)	3.90	87 (46.3%)	26.81
Unknown	6 ( 6.8%)	1.11	12 ( 7.0%)	3.28	0	NE	12 ( 6.4%)	3.28
Rituximab								
Asian	50 (56.8%)	8.07	0	NE	0	NE	0	NE
Black or African American	1 ( 1.1%)	0.41	0	NE	0	NE	0	NE
White	31 (35.2%)	8.36	0	NE	0	NE	0	NE
Unknown	6 ( 6.8%)	1.12	0	NE	0	NE	0	NE

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.

\* 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.

Program: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ex\_race\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/output/t\_ex\_race\_rmp\_RMP\_SERO.out

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**Table 25 Summary of Exposure by Ethnicity (Studies GO41944 and GO41943)**

Study Treatment Ethnicity	R-GemOx (GO41944) (N=88)		Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)		Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)		Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)	
	Patients (N=88)	Person time*	Patients (N=172)	Person time*	Patients (N=16)	Person time*	Patients (N=188)	Person time*
Gemcitabine								
Hispanic or Latino	5 ( 5.7%)	1.51	11 ( 6.4%)	2.81	0	NE	11 ( 5.9%)	2.81
Not Hispanic or Latino	79 (89.8%)	15.33	149 (86.6%)	50.44	16 (100%)	4.55	165 (87.8%)	54.99
Not Stated	3 ( 3.4%)	0.53	12 ( 7.0%)	3.38	0	NE	12 ( 6.4%)	3.38
Unknown	1 ( 1.1%)	0.40	0	NE	0	NE	0	NE
Glofitamab								
Hispanic or Latino	0	NE	11 ( 6.4%)	4.02	0	NE	11 ( 5.9%)	4.02
Not Hispanic or Latino	0	NE	149 (86.6%)	68.58	16 (100%)	5.30	165 (87.8%)	73.89
Not Stated	0	NE	12 ( 7.0%)	4.67	0	NE	12 ( 6.4%)	4.67
Unknown	0	NE	0	NE	0	NE	0	NE
Obinutuzumab								
Hispanic or Latino	0	NE	11 ( 6.4%)	0.56	0	NE	11 ( 5.9%)	0.56
Not Hispanic or Latino	0	NE	149 (86.6%)	6.85	16 (100%)	0.19	165 (87.8%)	7.04
Not Stated	0	NE	12 ( 7.0%)	0.29	0	NE	12 ( 6.4%)	0.29
Unknown	0	NE	0	NE	0	NE	0	NE
Oxaliplatin								
Hispanic or Latino	5 ( 5.7%)	1.51	11 ( 6.4%)	2.81	0	NE	11 ( 5.9%)	2.81
Not Hispanic or Latino	79 (89.8%)	15.33	149 (86.6%)	50.05	16 (100%)	4.55	165 (87.8%)	54.60
Not Stated	3 ( 3.4%)	0.53	12 ( 7.0%)	3.01	0	NE	12 ( 6.4%)	3.01
Unknown	1 ( 1.1%)	0.40	0	NE	0	NE	0	NE
Rituximab								
Hispanic or Latino	5 ( 5.7%)	1.52	0	NE	0	NE	0	NE
Not Hispanic or Latino	79 (89.8%)	15.50	0	NE	0	NE	0	NE
Not Stated	3 ( 3.4%)	0.54	0	NE	0	NE	0	NE
Unknown	1 ( 1.1%)	0.41	0	NE	0	NE	0	NE

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.

\* 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.

**Table 25 Summary of Exposure by Ethnicity (Studies GO41944 and GO41943)**

NE means that there were no subjects in the category.  
Program: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ex\_ethnic\_rmp.sas  
Output: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/output/  
t\_ex\_ethnic\_rmp\_RMP\_SERO.out  
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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 26 Important Exclusion Criteria in Pivotal Studies in the Development Program <sup>a</sup>**

<b>Criterion</b>	<b>Reason for Exclusion</b>	<b>Is it to be included as missing information? (Yes/No)</b>	<b>Rationale (if not included as missing information)</b>
Patients with chronic lymphocytic leukemia <sup>b</sup> , 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
Patients with HGBCL with MYC and BCL2 and/or BCL6 rearrangements, and HGBCL NOS (GO41944)	Potential therapeutic benefit of control arm in GO41944 (R-GemOx) was thought to be insufficient in this population	No	This exclusion criterion was not related to the safety of the patient
History of transformation of indolent disease to DLBCL (GO41944)	Because of better outcomes in patients with transformed lymphoma treated with R-GemOx relative to those with <i>de novo</i> disease, glofit-GemOx was deemed by the study team to have insufficient potential additive benefit over R-GemOx in patients with transformed lymphoma	No	This exclusion criterion was not related to the safety of the patient
Primary mediastinal B-cell lymphoma (GO41944)	Potential therapeutic benefit of control arm in GO41944 (R-GemOx) was thought to be insufficient in this population	No	This exclusion criterion was not related to the safety of the patient

<b>Criterion</b>	<b>Reason for Exclusion</b>	<b>Is it to be included as missing information? (Yes/No)</b>	<b>Rationale (if not included as missing information)</b>
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	<p>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.</p> <p>Section 5.1 of the SmPC states that Studies NP30179 and GO41944 excluded patients with progressive multifocal leukoencephalopathy.</p>
Current or past history of CNS lymphoma	CNS penetration/activity of glofitamab is unknown.	No	<p>Given the life-threatening nature of the current and 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.</p> <p>Section 5.1 of the SmPC states that Studies NP30179 and GO41944 excluded patients with current or a history of CNS lymphoma.</p>



<b>Criterion</b>	<b>Reason for Exclusion</b>	<b>Is it to be included as missing information? (Yes/No)</b>	<b>Rationale (if not included as missing information)</b>
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 current and 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 Studies NP30179 and GO41944 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	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.

<b>Criterion</b>	<b>Reason for Exclusion</b>	<b>Is it to be included as missing information? (Yes/No)</b>	<b>Rationale (if not included as missing information)</b>
any major episode of infection 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 Studies NP30179 and GO41944 excluded patients with active infections.
History of treatment-emergent immune-related adverse events associated with prior immunotherapeutic agents, as follows: Grade $\geq$ 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 (Study NP30179 only)	To minimize the risk of exacerbating ongoing immune-related AEs associated with prior therapies.	No	Given the life-threatening nature of the current and 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 Studies NP30179 and GO41944 excluded patients with prior allogeneic stem cell transplant or prior organ transplantation.

<b>Criterion</b>	<b>Reason for Exclusion</b>	<b>Is it to be included as missing information? (Yes/No)</b>	<b>Rationale (if not included as missing information)</b>
Autologous SCT within 100 days prior to Gpt infusion (Study NP30179 only)	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 current and 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
Current or past history of CNS disease, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease. <sup>c</sup>	<p>CNS penetration/activity of glofitamab is unknown.</p> <p>CNS diseases, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease could confound safety data.</p>	No	<p>Given the life-threatening nature of the current and 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.</p> <p>Section 5.1 of the SmPC states that Studies NP30179 and GO41944 excluded patients with current or a history of CNS disease.</p>
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.

<b>Criterion</b>	<b>Reason for Exclusion</b>	<b>Is it to be included as missing information? (Yes/No)</b>	<b>Rationale (if not included as missing information)</b>
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	<p>Given the life-threatening nature of the current and 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.</p> <p>Section 5.1 of the SmPC states that Studies NP30179 and GO41944 excluded patients with significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction (within the last 3 months for Study GO41944 and last 6 months for Study NP30179), unstable arrhythmias, or unstable angina).</p>
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	<p>Given the life-threatening nature of the current and 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.</p>

<b>Criterion</b>	<b>Reason for Exclusion</b>	<b>Is it to be included as missing information? (Yes/No)</b>	<b>Rationale (if not included as missing information)</b>
			Section 5.1 of the SmPC states that Study NP30179 excluded patients with significant active pulmonary disease or active autoimmune disease requiring immunosuppressive therapy, and that Study GO41944 excluded patients with 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 (NP30179 only), 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
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 current and 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

<b>Criterion</b>	<b>Reason for Exclusion</b>	<b>Is it to be included as missing information? (Yes/No)</b>	<b>Rationale (if not included as missing information)</b>
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 current and 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 (30 mg/day in Study GO41944) 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 current and 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 Studies NP30179 and GO41944 excluded patients with active autoimmune disease requiring immunosuppressive therapy.
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 current and 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

<b>Criterion</b>	<b>Reason for Exclusion</b>	<b>Is it to be included as missing information? (Yes/No)</b>	<b>Rationale (if not included as missing information)</b>
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.

<sup>a</sup> Exclusion criteria are from Study NP30179 protocol version 11 and Study GO41944 protocol version 7.

<sup>b</sup> 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.

<sup>c</sup> 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 27 Exposure of Special Populations Included or Not in Clinical Trial Development Program**

Type of Special Population	NP30179 Exposure	GO41944 and GO41943 Exposure
Pregnant women	None	None
Breastfeeding women	None	None
Patients with relevant comorbidities:		
Patients with hepatic impairment <sup>a</sup>	Mild hepatic impairment <sup>c</sup> : n=21 Moderate hepatic impairment <sup>c</sup> : n=0 Severe hepatic impairment <sup>c</sup> : n=1	Mild hepatic impairment <sup>h</sup> : n=27 Moderate hepatic impairment <sup>h</sup> : n=0 Severe hepatic impairment <sup>h</sup> : n=0
Patients with renal impairment <sup>b</sup>	Mild renal impairment <sup>c</sup> : n=50 Moderate renal impairment <sup>c</sup> : n=21 Severe renal impairment <sup>c</sup> : n=2	Mild renal impairment <sup>h</sup> : n=75 Moderate renal impairment <sup>h</sup> : n=35 Severe renal impairment <sup>h</sup> : n=1
Patients with cardiovascular impairment <sup>d</sup>	Not included	Not included
Immunocompromised patients <sup>e</sup>	Very limited <sup>f</sup>	Limited <sup>i</sup>
Patients with a disease severity different from inclusion criteria in clinical trials	Very limited <sup>g</sup>	Very limited <sup>j</sup>
Population with relevant different ethnic origin	Refer to <a href="#">Table 19</a>	Refer to <a href="#">Table 25</a>
Subpopulations carrying relevant genetic polymorphisms	Not included	Not included

**Table 27 Exposure of Special Populations Included or Not in Clinical Trial Development Program**

Other:	Not included	Not included
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AST = aspartate aminotransferase; NOS = not otherwise specified; TB = total bilirubin; ULN = upper limit of normal.

<sup>a</sup> 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)

<sup>b</sup> Excluded patients with creatinine > ULN and a measured creatinine clearance < 60 mL/min.

Renal impairment category is based on estimated creatinine clearance per U.S. Food and Drug Administration (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.

<sup>c</sup> Numbers are based on the primary safety population (as of CCOD 15 June 2022), 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<sub>2</sub> [sub2], D<sub>3</sub>, and D<sub>5</sub>; N = 145). The data with the latest CCOD of 17 May 2024 is not available at this time.

<sup>d</sup> 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.

<sup>e</sup> Patients with positive serologic test results for HIV infection were excluded.

<sup>f</sup> 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.

<sup>g</sup> In patients in the overall safety population treated with glofitamab (N = 467), at least one of the following major protocol deviations was reported in 15 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.

<sup>h</sup> Numbers are based on the glofitamab-exposed safety population (N = 188).

<sup>i</sup> In patients in the glofitamab-exposed safety population (N = 188), the following were reported in the previous or concurrent medical history: seasonal allergy (6 patients), drug sensitivity (4 patients), hypogammaglobulinemia (3 patients), immunodeficiency, hypersensitivity, iodine allergy (1 patient each). All patients were from Study GO41944.

<sup>j</sup> In patients in the glofitamab-exposed safety population (N = 188), one major protocol deviation was reported in 1 patient from Study GO41944: Histologically confirmed as not diffuse large B-cell lymphoma, NOS.

## Table 27 Exposure of Special Populations Included or Not in Clinical Trial Development Program

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Source: [Annex 7B.6](#); [Annex 7B.7](#);

[t\\_mh\\_PM2S\\_SE\\_17MAY2024\\_30179](#), [t\\_dv\\_PM2S\\_SE\\_17MAY2024\\_30179](#), [l\\_mh\\_IMMMH\\_SERO](#), [l\\_dv\\_EXC\\_SERO](#).

## **PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE**

### **SV.1 POST-AUTHORIZATION EXPOSURE**

#### **SV.1.1 Method used to calculate exposure**

The data presented below are derived from the glofitamab Periodic Benefit-Risk Evaluation Report (PBRER 1131825) with data lock point (DLP) of 23 September 2024. Patient exposure from post-authorization experience is approximated from the volume of glofitamab sold. The volume sold by Roche is sourced from Roche supply chain and financial systems (Controlling Profitability Analysis [COPA]). The sales data are provided on a monthly basis; therefore, exposure data is available from the International Birth Date (IBD) of 24 March 2023 to the nearest point of DLP (i.e., 31 October 2024).

To convert vials volume into commercial patient exposure data, factors such as epidemiology, treatment duration, dosing and patient compliance from the best available sources are used.

#### **Methodology: European Economic Area (EEA) and Rest of World (RoW)**

For EEA and RoW patient exposure estimation, the dosage per patient was calculated from dosage administration suggested in the EMA label. As per the Columvi SmPC, the dosage of Columvi is for 12 cycles with each cycle being 3 weeks long. First cycles have 2.5 mg in the first week, 10 mg in the second week, and 30 mg in the third week. Second cycle has 30 mg and the subsequent cycles have 30 mg each. From the above, it is safe to assume that a patient with DLBCL starting treatment with Columvi has to consume one 2.5 mg vial. Based on this analogy, we consider the consumption of 2.5 mg vials to indicate patients who start Columvi.

To estimate the exposure in each individual country, monthly volume sales of 2.5 mg vials patient consumption is used. The output is further divided by the considered loading dosage (2.5 mg) to obtain the number of new patients who start Columvi. Based on clinical trial data, we are using the median duration of treatment (5.5 cycles, i.e. 4 months).

#### **Methodology: United States**

Each patient starting on Columvi receives one 2.5 mg vial per the dosing instructions. Thus, the data sources used 2.5 mg vial sales as a proxy of patient initiation.

#### **SV.1.2 Exposure**

Since the IBD until the data lock point (DLP) of PBRER 1131825 (23 September 2024), an estimated cumulative total of 3687 patients have received glofitamab from marketing experience (see [Annex 7C](#)).

## **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  $\leq 2$  ([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](#)<sup>®</sup>, [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  $\leq 2$  (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  $\geq 3$  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  $> 3 \times$  upper limit of normal (ULN) for AST and ALT and/or  $> 2 \times$  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  $\geq 3$  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 ([Blinicyto \[blinatumomab\] 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 (Blinicyto (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 System Organ Class (SOC). 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  $\geq 3$  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.1.2 Risks 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 American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading criteria ([Lee et al. 2019](#)) ([Table 28](#)). 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  $\geq 2$  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 34](#)). Eleven patients (7.6%) experienced 11 events of Grade  $\geq 2$  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  $\geq 2$  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  $\geq 2$  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  $\geq 2$  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  $\geq 2\%$  patients were sepsis (6 patients [4.1%]), corona virus disease-2019 (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**

“Long-term safety” and “Safety in patients with prior CAR-T therapy” is no longer considered missing information.

#### **Background on Study NP30179:**

Study NP30179 was listed as an additional pharmacovigilance activity to evaluate long-term safety and safety in patients with prior CAR-T therapy in patients with R/R B-cell NHL.



The safety and efficacy results supporting the initial marketing applications were based on data collected up to and including 14 September 2021 for the primary analysis and a first updated interim analysis was conducted approximately 9 months later with a CCOD of 15 June 2022.

To address the missing information of the long-term safety of patients treated with glofitamab, and safety in patients with prior CAR-T therapy, an updated CSR (referred to as the second updated analysis [Update Clinical Study Report (CSR) Report No. [1131971](#)]) has been recently conducted based on a CCOD of 17 May 2024, which provides 2-year follow-up from the end of treatment of the last patient enrolled in the primary safety population of the study. The safety profile of this updated analysis was consistent with known glofitamab treatment effects with respect to the incidence and types of AEs, with no new safety signals identified.

It has been concluded that the updated safety analysis from Study NP30179 addresses the safety concerns of “long-term safety” and “safety in patients with prior CAR-T therapy” as missing information following the completion of Update CSR (Report No. [1131971](#)) and no further additional pharmacovigilance activities are necessary, as the long-term safety data and the safety data of glofitamab use in patients with prior CAR-T therapy from this study continue to support the tolerability of glofitamab in patients with complex comorbidities.

Further details supporting each safety concern is summarized below:

### **Long-Term Safety**

Reasons for changes (removal) to the list of safety concerns:

- Changes in the level of scientific evidence for the causal association or benefit-risk impact

The main population for the assessment of long-term safety in the second updated analysis of Study NP30179 is the primary safety population, comprising of patients with R/R DLBCL (DLBCL-NOS, transformed follicular lymphoma [trFL], primary mediastinal B-cell lymphoma [PMBCL], high-grade B-cell lymphoma [HGBCL]) with  $\geq 2$  prior lines of systemic therapy assigned to receive glofitamab monotherapy 2.5/10/30 mg every 3 weeks (Q3W) in Cohorts D2 [Sub. 2], D3, and D5 (N=154; safety-evaluable population). Additional supportive data was also provided for the overall safety population (R/R NHL [mixed histologies; 1 prior line of systemic therapy];  $\geq 0.60$  mg glofitamab monotherapy) (N=485; safety-evaluable population), for the glofitamab-exposed primary safety population and the overall safety population (145 and 467 patients, respectively).

Based on the cumulative safety data collected up to the CCOD of the second updated analysis (17 May 2024; Report No. [1131971](#)):

- In the primary safety population (R/R DLBCL [DLBCL NOS, HGBCL, trFL and PMBCL;  $\geq 2$  prior lines of systemic therapy]; glofitamab 2.5/10/30 mg Q3W, N=154):
  - There was a low rate of discontinuation due to AEs (9.1%), and 3.2% of patients discontinued due to AEs assessed as glofitamab-related.
  - The most frequently reported AEs by PT were CRS (ASTCT grading; the majority of which were Grade 1–2, limited to Cycle 1, manageable, and resolved), neutropenia, anemia, and thrombocytopenia.
- Pretreatment with obinutuzumab 1000 mg was well-tolerated, and no new safety signals were identified.
- The analysis of safety by sex showed that overall, the safety profile in male and female patients was similar; while some differences were observed between the respective subgroups (higher rates of Grade 5 AEs, serious AEs, and AEs leading to study discontinuation observed in male patients compared to female patients), they did not follow a consistent pattern, and could be attributable to the sample size of these subgroups. The differences do not suggest a concern regarding long-term safety in either male or female patients.
- The safety profile in the overall safety population (R/R NHL [mixed histologies;  $\geq 1$  prior line of systemic therapy];  $\geq 0.60$  mg glofitamab) was generally consistent with that of the primary safety population.

The safety profile was consistent with known glofitamab treatment effect with respect to the incidence and types of AEs, SAEs, adverse events of special interest (AESIs), laboratory data and vital signs, with no new safety signals. AESIs were not increased in patients typically considered to be at increased risk of immune-related AEs. Overall, the glofitamab step-up dosing regimen of 2.5/10/30 mg was well-tolerated, and continued to demonstrate a manageable safety profile with a longer follow up. No new safety concerns were identified.

- Previous regulatory request:

Following the assessment of the conditional marketing authorization application for Columvi (Procedure No. EMEA/H/C/005751/0000), a specific obligation was included in the Committee for Medicinal Products for Human Use (CHMP) Assessment Report (EMA/228393/2023) which stated that “The MAH shall provide the updated Clinical Study Report with 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 in scope of procedure EMEA/H/C/005751/0000.”

### **Safety in Patients with Prior CAR-T Therapy**

Reasons for changes (removal) to the list of safety concerns:

- Changes in the level of scientific evidence for the causal association or benefit-risk impact



An analysis of safety by prior CAR-T therapy for the glofitamab-exposed subpopulation of the primary safety population (N=145), with clinical cut-off date (CCOD) 17 May 2024, is included in the second updated analysis of Study NP30179 (Report No. [1131971](#)). In this subpopulation (N=145), 47 patients had received, and 98 patients had not received prior CAR-T therapy. ([t\\_cm\\_cart\\_PM2S\\_I\\_SE\\_17MAY2024\\_30179](#)).

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. 45.9%;

[t\\_ae\\_oview\\_subgrp\\_PCART\\_PM2S\\_I\\_SE\\_17MAY2024\\_30179](#)), mainly driven by CRS. The incidence of other common SAEs was similar between the subgroups, suggesting that there are no long term toxicities related to the previous exposure to CAR-T cell therapy. Conversely, a higher proportion of patients experienced an AE that led to study treatment discontinuation in patients who received prior CAR-T therapy compared with the patients who had not (4.3% vs. 8.2% respectively), and Grade 5 events were reported in a higher proportion in patients that did not receive prior CAR-T therapy (9.2%) versus 2.1% that received prior CAR-T therapy. The incidence of Grade 1–4 AEs was comparable across both groups. Overall, these differences did not follow a consistent pattern, and could be due to the sample sizes of these subgroups and other factors such as age and ECOG status at baseline ([Annex 7B.12](#)). The analysis of safety by prior CAR-T therapy does not suggest a concern regarding the safety of patients receiving prior CAR-T therapy treated with glofitamab.

- Previous regulatory request:

Following the assessment of the conditional marketing authorization application for Columvi (Procedure No. EMEA/H/C/005751/0000), the CHMP Assessment Report (EMA/228393/2023) included “Safety of patients with prior CAR-T therapy” as missing information in the RMP, with a Specific Obligation which stated “The applicant 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.”

### **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 and III clinical trial data (Studies NP30179, GO41944 and GO41943)
- 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 (Blinicyto [\[blinatumomab\]](#) SmPC and USPI; [Hopfinger 2019](#)).

#### **Characterization of the risk:**

##### **Results from Study NP30179**

##### **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 28](#)), 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  $\geq 2$  prior therapies who received 2.5/10/30 mg step-up dosing in Part II Cohort D<sub>2</sub> [Sub. 2] and Part III Cohort D<sub>3</sub> (N=108), and in Part III Cohort D<sub>3</sub> (N=101), the profile of CRS events was consistent with the primary safety population ([Table 2](#)). However, at the CCOD, patients in Cohort D<sub>5</sub> showed a trend to reduction in the incidence of all grade and Grade  $\geq 2$  CRS with each glofitamab step-up dose, as compared to patients in Cohort D<sub>3</sub> ([Annexes 7B.42](#) and [7B.43](#) ).

Premedication with corticosteroids prior to glofitamab was mandatory for all patients in the study. In Cohort D<sub>5</sub>, 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 29](#)). 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<sub>3</sub>, Cohort D<sub>2</sub> [Sub. 2] and Cohort D<sub>5</sub> (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 30). 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 30). 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 registrational dose (2.5/10/30 mg) in Cohort D<sub>3</sub>, Cohort D<sub>2</sub> [Sub. 2], and Cohort D<sub>5</sub> (N = 185) (Table 31).

Note that CRS events by dose cycle have not been shown for the  $\geq 0.6$  mg and  $\geq 10$  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.

## Results from Studies GO41944 and GO41943

### Overview of CRS by ASTCT 2019 Grading Criteria

In Studies GO41944 and GO41943 (N = 188), CRS events of any grade were reported in 84 patients (44.7%) by ASTCT 2019 grading criteria (Table 32). The majority of patients who reported CRS had events of Grade 1–2 maximum severity by ASTCT 2019 grading (79 patients [42.0%]). Grade 3 CRS AEs were reported in 5 patients (2.7%). No Grade 4 or 5 CRS AEs were reported. Of a total of 170 CRS events, all were considered related to glofitamab. At least one serious event of CRS was experienced by 37 patients (19.7%). One (0.5%) patient had glofitamab treatment withdrawn due to a glofitamab-related CRS event. Glofitamab-related CRS events led to dose interruption in 4 (2.1%) patients. At the time of the CCOD, one (0.5%) patient had CRS events that had not resolved.

## CRS events by Dose Cycle

In Studies GO41944 and GO41943 (N=188), CRS events occurred predominantly in Cycle 1 and was mainly associated with Day 8 dose administration. There was a higher frequency of CRS of any grade observed following Day 8 dose (67 patients, 35.6%) compared with Day 15 dose (28 patients, 15.3%) ([Table 33](#)). CRS events occurred less frequently in Cycle 2 (18 patients, 10.2%), and infrequently in Cycle 3 (11 patients, 6.7%), and Cycle 4 and beyond (17 patients, 10.8%). Serious CRS events also occurred predominantly in Cycle 1, with a higher frequency observed following the Day 8 (2.5mg) dose (28 patients, 14.9%) compared with Day 15 (10mg) dose (8 patients, 4.4%) ([Table 33](#)). In Cycle 2, 2 patients (1.1%), in Cycle 3, 1 patient (0.6%), and Cycle 4 and beyond 4 patients (2.5%) 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 following the Cycle 1 Day 8 dose (2 patients) and also after the Cycle 4 dose (1 patient). One additional patient received a C1D8 (2.5mg) dose prior to a serious CRS event occurring. This dose was however collected as an unscheduled visit instead of C1D8, meaning that the CRS event is displayed as occurring at C1D1 instead of at C1D8. This patient also had a glofitamab-related CRS event leading to dose interruption.

## 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  $\geq 2$  CRS with their previous infusion should be monitored after completion of the infusion. Data on the time to CRS onset of Grade  $\geq 2$  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 6](#)), 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  $\geq 2$  events require medical intervention. Grade  $\geq 3$  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  $\geq 2$  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 28 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 (Study NP30179)**

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 28 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 (Study NP30179) (cont.)**

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(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 29 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R NHL– All Histologies (Study NP30179)**

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  $\geq 0.60$  mg, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab  
Protocol: NP30179  
Risk Management Plan

	Glofitamab Doses $\geq 0.60$ 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 30 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R DLBCL,  $\geq 2$  Prior Systemic Therapies; Cohorts D<sub>2</sub> [Sub. 2], D<sub>3</sub>, and D<sub>5</sub> (Study NP30179)**

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Cytokine Release Syndrome AEs, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D<sub>2</sub> (Sub 2), D<sub>3</sub>, D<sub>5</sub>, (R/R DLBCL Patients,  $\geq 2$  Prior Lines of Systemic Therapy), Safety-Evaluatable 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 31 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R NHL (All Histologies); Cohorts D2 [Sub. 2], D3, and D5 (Study 30179)**

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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**Table 32 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI (Studies GO41944 & GO41943)**

Seriousness, Outcomes, Severity, Frequency of AEs, Cytokine Release Syndrome AEs, Modified Safety-Evaluable Patients  
Protocol: GO41944 & GO41943  
Risk Management Plan

	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Number of patients with at least one AE	76 (44.2%)	8 (50.0%)	84 (44.7%)
95% CI for % of patients with at least one AE	(36.63%, 51.94%)	(24.65%, 75.35%)	(37.44%, 52.09%)
Total number of AEs	152	18	170
Total number of AEs related to Glofit	152	18	170
Number of patients with at least one AE by worst grade			
Grade 1	54 (31.4%)	5 (31.3%)	59 (31.4%)
Grade 2	18 (10.5%)	2 (12.5%)	20 (10.6%)
Grade 3	4 ( 2.3%)	1 ( 6.3%)	5 ( 2.7%)
Grade 4	0	0	0
Grade 5	0	0	0
Number of patients with at least one serious AE	35 (20.3%)	2 (12.5%)	37 (19.7%)
Number of patients with at least one AE by outcome			
Fatal outcome	0	0	0
Unresolved	1 ( 1.3%)	0	1 ( 1.2%)
Recovering/Resolving	0	0	0
Recovered/Resolved	74 (97.4%)	8 ( 100%)	82 (97.6%)
Resolved with sequelae	1 ( 1.3%)	0	1 ( 1.2%)
Unknown outcome	0	0	0
Glofit related AE leading to withdrawal from treatment	1 ( 0.6%)	0	1 ( 0.5%)
Glofit related AE leading to dose interruption	3 ( 1.7%)	1 ( 6.3%)	4 ( 2.1%)
Glofit related AE leading to dose modification	0	0	0

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.

Percentages are based on N in the column headings.

Only Treatment Emergent AEs with a preferred term (encoded using MedDRA version 26.1) of CRS are included.

Adverse Events are graded by NCI CTCAE v5.0, CRS events are graded by ASTCT 2019.

Program: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ae\_outl\_rmp.sas  
Output: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/output/  
t\_ae\_outl\_rmp\_CRSAE\_RMP\_GLO\_SERO.out  
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**Table 33 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI by Dose Cycle (Studies GO41944 & GO41943)**

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Cytokine Release Syndrome AEs, Modified Safety-Evaluable Patients  
Protocol: GO41944 & GO41943  
Risk Management Plan

	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)					
	C1D1 (N=188)	C1D8 (N=188)	C1D15 (N=183)	C2 (N=177)	C3 (N=164)	C4+ (N=158)
Number of patients with at least one AE	1 (0.5%)	67 (35.6%)	28 (15.3%)	18 (10.2%)	11 (6.7%)	17 (10.8%)
95% CI for % of patients with at least one AE	(0.01%, 2.93%)	(28.80%, 42.93%)	(10.41%, 21.35%)	(6.14%, 15.60%)	(3.40%, 11.68%)	(6.39%, 16.67%)
Total number of AEs	1	69	28	18	11	43
Total number of AEs related to Glofitamab	1	69	28	18	11	43
Number of patients with at least one AE by worst grade						
Grade 1	0	44 (23.4%)	21 (11.5%)	15 ( 8.5%)	8 (4.9%)	13 ( 8.2%)
Grade 2	0	17 ( 9.0%)	2 ( 1.1%)	0	1 (0.6%)	2 ( 1.3%)
Grade 3	1 (0.5%)	3 ( 1.6%)	1 ( 0.5%)	0	0	0
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	1 (0.5%)	28 (14.9%)	8 ( 4.4%)	2 ( 1.1%)	1 (0.6%)	4 ( 2.5%)
Number of patients with at least one AE by outcome						
Fatal outcome	0	0	0	0	0	0
Unresolved	0	1 ( 1.5%)	0	0	0	0
Recovering/Resolving	0	0	0	0	0	0
Recovered/Resolved	1 (100%)	65 (97.0%)	28 ( 100%)	18 ( 100%)	11 (100%)	17 ( 100%)
Resolved with sequelae	0	1 ( 1.5%)	0	0	0	0
Unknown outcome	0	0	0	0	0	0

**Table 33 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI by Dose Cycle (Studies GO41944 & GO41943)**

Glofitamab related AE leading to withdrawal from treatment	0	1 ( 0.5%)	0	0	0	0
Glofitamab related AE leading to dose interruption	1 (0.5%)	2 ( 1.1%)	0	0	0	1 ( 0.6%)
Glofitamab related AE leading to dose modification	0	0	0	0	0	0

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Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.

Percentages are based on N in the column headings.

Only Treatment Emergent AEs with a preferred term (encoded using MedDRA version 26.1) of CRS are included.

Adverse Events are graded by NCI CTCAE v5.0, CRS events are graded by ASTCT 2019.

One patient from Study GO41944 received a 2.5 mg glofitamab dose prior to a serious Grade 3 CRS event. This dose was however collected as an unscheduled visit instead of C1D8, meaning that the CRS event is displayed as occurring at C1D1 instead of at C1D8.

Program: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ae\_out2\_rmp.sas

Output: Adapted from [t\\_ae\\_out2\\_rmp\\_CRSAE\\_RMP\\_GLO\\_SERO.out](#)

## **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 (Studies NP30179, GO41944, and GO41943) with glofitamab. It is a known risk with other immunomodulating agents, T-cell engaging therapies, checkpoint inhibitor therapies ([Taleb 2019](#)).

### **Characterization of the risk:**

#### **Results from Study NP30179**

##### **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 34](#)). Eleven patients (7.6%) experienced 11 events of Grade  $\geq 2$  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 35). 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<sub>3</sub>, Cohort D<sub>2</sub> [Sub. 2], and Cohort D<sub>5</sub> 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 36). 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 registrational dose (2.5/10/30 mg) in Cohort D<sub>3</sub>, Cohort D<sub>2</sub> [Sub. 2], and Cohort D<sub>5</sub> (Table 37).

Note that tumor flare events by dose cycle have not been shown for the  $\geq 0.6$  mg and  $\geq 10$  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.



## Results from Studies GO41944 and GO41943

### Overview of Tumor Flare Events

In Study GO41944, TF or suspected TF events of any grade were reported in 5 patients (2.7%) ([Table 38](#)). Out of these 5 patients who reported TF or suspected TF events, 4 patients (2.1%) had events of Grade 1 maximum severity (Grade 1 edema peripheral, Grade 1 cellulitis, Grade 1 cellulitis of male external genital organ, Grade 1 muscle atrophy, Grade 1 tumor flare) and 1 patient (0.5%) had a suspected TF event of Grade 3 maximum severity (Grade 3 cholestasis) ([t\\_xae\\_ctc\\_ph\\_TF\\_SERO](#)). No Grade 4 or Grade 5 TF AEs were reported. Of a total of 6 TF or suspected TF events, 1 was considered related to glofitamab, as assessed by the investigator. At least one SAE was experienced by 1 patient (0.5%). At the time of the CCOD, 3 patients (60%) had TF events that had not resolved. No events of TF or suspected TF events were reported in Study GO41943.

### Tumor Flare Events by Dose Cycle

In Study GO41944, TF or suspected TF events were associated with Cycle 1 Day 1 (1 patient, 0.5%) obinutuzumab pretreatment administration where the patient experienced a Grade 3 cholestasis event, and Cycle 1 Day 8 (1 patient, 0.5%), Cycle 3 (1 patient, 0.6%), and Cycle 4 and beyond (2 patients, 1.3%) dose administrations with all events being Grade 1 ([Table 39](#)). Tumor flare events did not occur in Cycle 2, and was thus observed in Cycle 1, Cycle 3, and Cycle 4 and beyond. Serious TF events occurred only in Cycle 1, with 1 patient (0.5%) reporting TF events of any grade following the Day 8 dose (2.5mg) compared with no patients reporting TF events following the Day 15 (10mg) dose. Tumor flare events did not lead to dose withdrawal or interruption.

### 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 Studies NP30179, GO41944, and GO41943, 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 34 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R DLBCL who have Received  $\geq 2$  Prior Systemic Therapies (Study NP30179)**

Seriousness, Outcomes, Severity, Frequency of AEs, Tumour Flare Adverse Events, Initial Treatment Phase, (R/R DLBCL Patients,  $\geq 2$  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 $\geq 0.60$ mg (N=273)	Glofitamab Doses $\geq 10$ 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 34 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R DLBCL who have Received  $\geq 2$  Prior Systemic Therapies (Study NP30179) (cont.)**

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(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\_outl\_rmp.sas  
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**Table 35 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R NHL– All Histologies (Study NP30179)**

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  $\geq 0.60$  mg, Safety-Evaluable Monotherapy Patients Dosed with Glofitamab  
Protocol: NP30179  
Risk Management Plan

	Glofitamab Doses $\geq 0.60$ 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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**Table 36 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R DLBCL,  $\geq 2$  Prior Systemic Therapies; Cohort D<sub>2</sub> [Sub. 2], D<sub>3</sub> and D<sub>5</sub>, (Primary Safety Population, Study NP30179)**

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Tumour Flare Adverse Events, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D<sub>2</sub>(Sub 2), D<sub>3</sub>, D<sub>5</sub>, (R/R DLBCL Patients,  $\geq 2$  Prior Lines of Systemic Therapy), Safety-Evaluatable 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 95% CI for % of patients with at least one AE	13 ( 9.0%) (4.86%, 14.84%)	3 (2.2%) (0.46%, 6.36%)	3 (2.4%) (0.49%, 6.75%)	0 (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 37 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R NHL (All Histologies) Cohorts D2 [Sub. 2], D3, D5, and D5 (Study NP30179)**

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

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/  
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**Table 38 Important Identified Risk of Tumor Flare Including Suspected Tumor Flare Events: Seriousness, Outcomes, Severity and Frequency with 95% CI (Studies GO41944 & GO41943)**

Seriousness, Outcomes, Severity, Frequency of AEs, Tumour Flare Adverse Events, Modified Safety-Evaluable Patients  
Protocol: GO41944 & GO41943  
Risk Management Plan

	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Number of patients with at least one AE	2 (2.3%)	5 ( 2.9%)	0	5 ( 2.7%)
95% CI for % of patients with at least one AE	(0.28%, 7.97%)	(0.95%, 6.65%)	(0.00%, 20.59%)	(0.87%, 6.10%)
Total number of AEs	2	6	0	6
Total number of AEs related to Glofit	0	1	0	1
Total number of AEs related to Rituximab	1	0	0	0
Number of patients with at least one AE by worst grade				
Grade 1	1 (1.1%)	4 ( 2.3%)	0	4 ( 2.1%)
Grade 2	1 (1.1%)	0	0	0
Grade 3	0	1 ( 0.6%)	0	1 ( 0.5%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Number of patients with at least one serious AE	0	1 ( 0.6%)	0	1 ( 0.5%)
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	0	3 (60.0%)	0	3 (60.0%)
Recovering/Resolving	0	0	0	0
Recovered/Resolved	2 (100%)	2 (40.0%)	0	2 (40.0%)
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0
Glofit related AE leading to withdrawal from treatment	0	0	0	0
Glofit related AE leading to dose interruption	0	0	0	0
Glofit related AE leading to dose modification	0	0	0	0
Rituximab related AE leading to withdrawal from treatment	0	0	0	0
Rituximab related AE leading to dose interruption	0	0	0	0



**Table 38 Important Identified Risk of Tumor Flare Including Suspected Tumor Flare Events: Seriousness, Outcomes, Severity and Frequency with 95% CI (Studies GO41944 & GO41943)**

Rituximab related AE leading to dose modification	0	0	0	0
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Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.

Percentages are based on N in the column headings.

Only Treatment Emergent AEs with a preferred term (encoded using MedDRA version 26.1) of Tumour Flare are included.

Adverse Events are graded by NCI CTCAE v5.0.

Program: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ae\_outl\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/output/

t\_ae\_outl\_rmp\_TF\_RMP\_SERO.out

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**Table 39 Important Identified Risk of Tumor Flare Including Suspected Tumor Flare Events: Seriousness, Outcomes, Severity and Frequency with 95% CI by Dose Cycle (Studies GO41944 & GO41943)**

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Tumour Flare Adverse Events, Modified Safety-Evaluable Patients  
Protocol: GO41944 & GO41943  
Risk Management Plan

	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)					
	C1D1 (N=188)	C1D8 (N=188)	C1D15 (N=183)	C2 (N=177)	C3 (N=164)	C4+ (N=158)
Number of patients with at least one AE	1 (0.5%)	1 (0.5%)	0	0	1 (0.6%)	2 (1.3%)
95% CI for % of patients with at least one AE	(0.01%, 2.93%)	(0.01%, 2.93%)	(0.00%, 2.00%)	(0.00%, 2.06%)	(0.02%, 3.35%)	(0.15%, 4.50%)
Total number of AEs	1	1	0	0	2	2
Total number of AEs related to Glofitamab	0	1	0	0	0	0
Number of patients with at least one AE by worst grade						
Grade 1	0	1 (0.5%)	0	0	1 (0.6%)	2 (1.3%)
Grade 2	0	0	0	0	0	0
Grade 3	1 (0.5%)	0	0	0	0	0
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	0	1 (0.5%)	0	0	0	0
Number of patients with at least one AE by outcome						
Fatal outcome	0	0	0	0	0	0
Unresolved	1 (100%)	0	0	0	0	2 (100%)
Recovering/Resolving	0	0	0	0	0	0
Recovered/Resolved	0	1 (100%)	0	0	1 (100%)	0
Resolved with sequelae	0	0	0	0	0	0
Unknown outcome	0	0	0	0	0	0

**Table 39 Important Identified Risk of Tumor Flare Including Suspected Tumor Flare Events: Seriousness, Outcomes, Severity and Frequency with 95% CI by Dose Cycle (Studies GO41944 & GO41943)**

Glofitamab related AE leading to withdrawal from treatment	0	0	0	0	0	0
Glofitamab related AE leading to dose interruption	0	0	0	0	0	0
Glofitamab related AE leading to dose modification	0	0	0	0	0	0

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Data Cutoff Dates: GO41943 – 08DEC2021, GO41944 – 16FEB2024.

Percentages are based on N in the column headings.

Only Treatment Emergent AEs with a preferred term (encoded using MedDRA version 26.1) of Tumour Flare are included.

Adverse Events are graded by NCI CTCAE v5.0.

Program: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ae\_out2\_rmp.sas

Output: Adapted from [t\\_ae\\_out2\\_rmp\\_TF\\_RMP\\_SERO.out](#)

## 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 (Studies NP30179, GO41944, and GO41943) with glofitamab.

### Characterization of the risk:

#### Results from Study NP30179

#### 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 (Cycle 1 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  $\geq 2\%$  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  $\geq 1\%$  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 40](#)). 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<sub>3</sub>, Cohort D<sub>2</sub> [Sub. 2] and Cohort D<sub>5</sub> (N=185), the profile of infection and infestation SAEs was generally consistent with the overall safety population ([Table 41](#)).

### 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 42](#)).

Similar results were observed in patients from all R/R NHL histologies treated with glofitamab at the registrational dose (2.5/10/30 mg) in Cohort D<sub>3</sub>, Cohort D<sub>2</sub> [Sub. 2], and Cohort D<sub>5</sub> ([Table 43](#)).

Note that infection and infestation SAEs by dose cycle have not been shown for the  $\geq 0.6$  mg and  $\geq 10$ 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 infection and infestation event.

## Results from Studies GO41944 and GO41943

### Overview of Serious Infections

In Studies GO41944 and GO41943, adverse events from the grouped terms of infections and infestation were reported in 102 patients (54.3%) ([Table 44](#)). The median time to

onset of the first infection and infestation event from the first glofitamab dose (Cycle 1 Day 8) was 3 days (range: 1–8 days), and the median duration of the first infection and infestation AE from the first glofitamab dose (Cycle 1 Day 8) was 7 days (range: 2–28 days) ([t\\_ae\\_aestat\\_dose\\_INFEST\\_SERO](#)).

Under the grouped terms of infections and infestations AEs, 43 patients (22.9%) reported SAEs ([Table 45](#)). The SAEs reported in  $\geq 2\%$  patients were pneumonia (10 patients [5.3%]), COVID-19 (8 patients [4.3%]), sepsis (6 patients [3.2%]), and lower respiratory tract infection (5 patients [2.7%]) ([t\\_ae\\_ctc\\_SER\\_SERO](#)). Grade 1-2 SAEs were reported in 8 patients (4.3%), Grade 3 SAEs in 29 patients (15.4%), and Grade 5 SAEs in 6 patients (3.2%). No Grade 4 SAEs were reported. Sixteen serious AEs and no Grade 5 AEs were related to glofitamab ([t\\_ae\\_ctc\\_SER\\_SERO](#), [t\\_ae\\_ctc\\_SER\\_REL\\_SERO](#)). Two patients (1.1%) reported a serious infection concurrent with Grade 3–4 neutropenia ([t\\_ae\\_inf\\_neut\\_SERO](#)). Serious infection and infestation events resolved in the majority of patients (69.8%); in 10 patients, events were unresolved at the time of reporting and 6 patients experienced fatal events. One patient had glofitamab treatment withdrawn and 7 patients had glofitamab treatment interrupted due to glofitamab-related serious infection and infestation events of pneumonia in 6 patients (3.2%), and lower respiratory tract infection and acinetobacter bacteremia in 1 patient each ([l\\_ae\\_rmp\\_SINFEST\\_INTDSC\\_RMP\\_SERO](#)).

### Serious Infections by Dose Cycle

In Studies GO41944 and GO41943, infection and infestation SAEs occurred predominantly in Cycle 2 and beyond ([Table 46](#)). Of 177 patients who received glofitamab doses in Cycle 2 and beyond, 40 patients (22.6%) reported infection and infestation SAEs ([Table 47](#)). In Cycle 1, of 188 patients who received a glofitamab dose at Day 8 (2.5 mg), 4 patients (2.1%) reported infection and infestation SAEs following the Day 8 dose; of 183 patients who received a glofitamab dose at Day 15 (10 mg), 2 patients (1.1%) reported infection and infestation SAEs following the Day 15 dose. Among 177 patients who received glofitamab doses in Cycle 2, 4 patients (2.3%) reported infection and infestation SAEs.

### 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 approximately 69% of patients who received at least one dose of glofitamab in the primary safety population in Study NP30179 or in the glofitamab-exposed safety population in Studies GO41944 and GO41943, the impact of serious infections on public health is considered to be low.

**Table 40 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 (Study NP30179)**

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 40 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 (Study NP30179) (cont.)**

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

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\_INFEST\_I\_RMP\_SERO\_15JUN2022\_30179.out  
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**Table 41 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R NHL– All Histologies (Study NP30179)**

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 42 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R DLBCL,  $\geq 2$  Prior Systemic Therapies; Cohorts D<sub>2</sub> [Sub. 2], D<sub>3</sub>, and D<sub>5</sub> (Study NP30179)**

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Serious Infections and Infestations, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D<sub>2</sub> (Sub 2), D<sub>3</sub>, D<sub>5</sub>, (R/R DLBCL Patients,  $\geq 2$  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 95% CI for % of patients with at least one AE	4 (2.8%) (0.76%, 6.91%)	4 (3.0%) (0.81%, 7.41%)	3 (2.4%) (0.49%, 6.75%)	11 (10.3%) (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/  
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Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/  
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t ae out2\_rmp\_SINFEST\_I\_RMPD\_SERO\_15JUN2022\_30179.out  
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**Table 43 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R NHL (All Histologies); Cohorts D<sub>2</sub> [Sub. 2], D<sub>3</sub>, and D<sub>5</sub> (Study NP30179)**

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Serious Infections and Infestations, Initial Treatment Phase, Glofitamab 2.5/10/30 mg Cohorts D<sub>2</sub> (Sub 2), D<sub>3</sub>, D<sub>5</sub>, 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  
09FEB2023 11:45

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**Table 44 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity, Frequency of AEs, Infection and Infestation, (Studies GO41944 & GO41943)**

Seriousness, Outcomes, Severity, Frequency of AEs, Infection and Infestation, Modified Safety-Evaluable Patients  
Protocol: GO41944 & GO41943  
Risk Management Plan

	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Number of patients with at least one AE	26 (29.5%)	95 (55.2%)	7 (43.8%)	102 (54.3%)
95% CI for % of patients with at least one AE	(20.29%, 40.22%)	(47.48%, 62.81%)	(19.75%, 70.12%)	(46.85%, 61.52%)
Total number of AEs	39	191	14	205
Total number of AEs related to Glofit	0	70	0	70
Total number of AEs related to Rituximab	13	0	0	0
Number of patients with at least one AE by worst grade				
Grade 1	7 ( 8.0%)	18 (10.5%)	2 (12.5%)	20 (10.6%)
Grade 2	8 ( 9.1%)	42 (24.4%)	1 ( 6.3%)	43 (22.9%)
Grade 3	6 ( 6.8%)	29 (16.9%)	4 (25.0%)	33 (17.6%)
Grade 4	2 ( 2.3%)	0	0	0
Grade 5	3 ( 3.4%)	6 ( 3.5%)	0	6 ( 3.2%)
Number of patients with at least one serious AE	11 (12.5%)	39 (22.7%)	4 (25.0%)	43 (22.9%)
Number of patients with at least one AE by outcome				
Fatal outcome	3 (11.5%)	6 ( 6.3%)	0	6 ( 5.9%)
Unresolved	10 (38.5%)	29 (30.5%)	3 (42.9%)	32 (31.4%)
Recovering/Resolving	0	0	0	0
Recovered/Resolved	17 (65.4%)	80 (84.2%)	5 (71.4%)	85 (83.3%)
Resolved with sequelae	1 ( 3.8%)	2 ( 2.1%)	0	2 ( 2.0%)
Unknown outcome	0	0	0	0
Glofit related AE leading to withdrawal from treatment	0	2 ( 1.2%)	0	2 ( 1.1%)
Glofit related AE leading to dose interruption	0	15 ( 8.7%)	0	15 ( 8.0%)
Glofit related AE leading to dose modification	0	0	0	0
Rituximab related AE leading to withdrawal from treatment	1 ( 1.1%)	0	0	0
Rituximab related AE leading to dose interruption	2 ( 2.3%)	0	0	0

**Table 44 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity, Frequency of AEs, Infection and Infestation, (Studies GO41944 & GO41943)**

Rituximab related AE leading to dose modification	0	0	0	0
<div><div>Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024. Percentages are based on N in the column headings. Only Treatment Emergent AEs with a preferred term (encoded using MedDRA version 26.1) of Infection and infestation are included. Adverse Events are graded by NCI CTCAE v5.0.</div><div>Program: root/clinical_studies/RO7082859/CDT30295/share/pool_SCS_Followup_Analysis_2024/prod/program/t_ae_outl_rmp.sas Output: root/clinical_studies/RO7082859/CDT30295/share/pool_SCS_Followup_Analysis_2024/prod/output/ t_ae_outl_rmp_INFEST_RMP_SERO.out 02MAY2024_15:46</div><div>Page 1 of 1</div></div>				

**Table 45 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity, Frequency of AEs, Serious Infections and Infestations, (Studies GO41944 & GO41943)**

Seriousness, Outcomes, Severity, Frequency of AEs, Serious Infections and Infestations, Modified Safety-Evaluable Patients  
Protocol: GO41944 & GO41943  
Risk Management Plan

	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Number of patients with at least one AE	11 (12.5%)	39 (22.7%)	4 (25.0%)	43 (22.9%)
95% CI for % of patients with at least one AE	(6.41%, 21.27%)	(16.65%, 29.67%)	(7.27%, 52.38%)	(17.07%, 29.55%)
Total number of AEs	14	46	6	52
Total number of AEs related to Glofit	0	16	0	16
Total number of AEs related to Rituximab	6	0	0	0
Number of patients with at least one AE by worst grade				
Grade 1	0	1 ( 0.6%)	0	1 ( 0.5%)
Grade 2	0	7 ( 4.1%)	0	7 ( 3.7%)
Grade 3	6 ( 6.8%)	25 (14.5%)	4 (25.0%)	29 (15.4%)
Grade 4	2 ( 2.3%)	0	0	0
Grade 5	3 ( 3.4%)	6 ( 3.5%)	0	6 ( 3.2%)
Number of patients with at least one serious AE	11 (12.5%)	39 (22.7%)	4 (25.0%)	43 (22.9%)
Number of patients with at least one AE by outcome				
Fatal outcome	3 (27.3%)	6 (15.4%)	0	6 (14.0%)
Unresolved	2 (18.2%)	9 (23.1%)	1 (25.0%)	10 (23.3%)
Recovering/Resolving	0	0	0	0
Recovered/Resolved	6 (54.5%)	27 (69.2%)	3 (75.0%)	30 (69.8%)
Resolved with sequelae	1 ( 9.1%)	0	0	0
Unknown outcome	0	0	0	0
Glofit related AE leading to withdrawal from treatment	0	1 ( 0.6%)	0	1 ( 0.5%)
Glofit related AE leading to dose interruption	0	7 ( 4.1%)	0	7 ( 3.7%)
Glofit related AE leading to dose modification	0	0	0	0
Rituximab related AE leading to withdrawal from treatment	1 ( 1.1%)	0	0	0
Rituximab related AE leading to dose interruption	1 ( 1.1%)	0	0	0

**Table 45 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity, Frequency of AEs, Serious Infections and Infestations, (Studies GO41944 & GO41943) (Cont.)**

Rituximab related AE leading to dose modification	0	0	0	0
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Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.

Percentages are based on N in the column headings.

Only Treatment Emergent AEs with a preferred term (encoded using MedDRA version 26.1) of Serious Infection and infestation are included.

Adverse Events are graded by NCI CTCAE v5.0.

Program: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ae\_out1\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/output/

t\_ae\_out1\_rmp\_SINFEST\_RMP\_SERO.out

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**Table 46 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Infection and Infestation, (Studies GO41944 & GO41943)**

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Infection and Infestation, Modified Safety-Evaluable Patients  
Protocol: GO41944 & GO41943  
Risk Management Plan

	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)					
	C1D1 (N=188)	C1D8 (N=188)	C1D15 (N=183)	C2 (N=177)	C3 (N=164)	C4+ (N=158)
Number of patients with at least one AE	5 (2.7%)	13 ( 6.9%)	8 ( 4.4%)	21 (11.9%)	12 ( 7.3%)	78 (49.4%)
95% CI for % of patients with at least one AE	(0.87%, 6.10%)	(3.73%, 11.53%)	(1.91%, 8.43%)	(7.50%, 17.56%)	(3.84%, 12.43%)	(41.33%, 57.43%)
Total number of AEs	6	13	8	24	13	141
Total number of AEs related to Glofitamab	0	1	4	9	2	54
Number of patients with at least one AE by worst grade						
Grade 1	1 (0.5%)	1 ( 0.5%)	1 ( 0.5%)	1 ( 0.6%)	2 ( 1.2%)	16 (10.1%)
Grade 2	1 (0.5%)	4 ( 2.1%)	3 ( 1.6%)	11 ( 6.2%)	4 ( 2.4%)	30 (19.0%)
Grade 3	1 (0.5%)	1 ( 0.5%)	2 ( 1.1%)	2 ( 1.1%)	1 ( 0.6%)	28 (17.7%)
Grade 4	0	0	0	0	0	0
Grade 5	0	2 ( 1.1%)	0	1 ( 0.6%)	1 ( 0.6%)	2 ( 1.3%)
Number of patients with at least one serious AE	2 (1.1%)	4 ( 2.1%)	2 ( 1.1%)	4 ( 2.3%)	3 ( 1.8%)	33 (20.9%)
Number of patients with at least one AE by outcome						
Fatal outcome	0	2 (15.4%)	0	1 ( 4.8%)	1 ( 8.3%)	2 ( 2.6%)
Unresolved	0	2 (15.4%)	2 (25.0%)	7 (33.3%)	1 ( 8.3%)	23 (29.5%)
Recovering/Resolving	0	0	0	0	0	0
Recovered/Resolved	5 (100%)	8 (61.5%)	6 (75.0%)	14 (66.7%)	10 (83.3%)	66 (84.6%)

**Table 46 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Infection and Infestation, (Studies GO41944 & GO41943)**

Resolved with sequelae	0	1 ( 7.7%)	0	0	0	1 ( 1.3%)
Unknown outcome	0	0	0	0	0	0
Glofitamab related AE leading to withdrawal from treatment	0	0	0	0	0	2 ( 1.3%)
Glofitamab related AE leading to dose interruption	0	0	1 ( 0.5%)	0	0	14 ( 8.9%)
Glofitamab related AE leading to dose modification	0	0	0	0	0	0

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Data Cutoff Dates: GO41943 – 08DEC2021, GO41944 – 16FEB2024.

Percentages are based on N in the column headings.

Only Treatment Emergent AEs with a preferred term (encoded using MedDRA version 26.1) of Infection and infestation are included.

Adverse Events are graded by NCI CTCAE v5.0.

Program: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ae\_out2\_rmp.sas

Output: Adapted from [t\\_ae\\_out2\\_rmp\\_INFEST\\_RMP\\_SERO.out](#)

**Table 47 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Serious Infections and Infestations, (Studies GO41944 & GO41943)**

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Serious Infections and Infestations, Modified Safety-Evaluable Patients  
Protocol: GO41944 & GO41943  
Risk Management Plan

	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)					
	C1D1 (N=188)	C1D8 (N=188)	C1D15 (N=183)	C2 (N=177)	C3 (N=164)	C4+ (N=158)
Number of patients with at least one AE	2 (1.1%)	4 ( 2.1%)	2 ( 1.1%)	4 ( 2.3%)	3 ( 1.8%)	33 (20.9%)
95% CI for % of patients with at least one AE	(0.13%, 3.79%)	(0.58%, 5.36%)	(0.13%, 3.89%)	(0.62%, 5.68%)	(0.38%, 5.25%)	(14.83%, 28.06%)
Total number of AEs	2	4	2	4	3	37
Total number of AEs related to Glofitamab	0	0	1	1	0	14
Number of patients with at least one AE by worst grade						
Grade 1	0	0	0	0	1 ( 0.6%)	0
Grade 2	0	0	0	1 ( 0.6%)	0	6 ( 3.8%)
Grade 3	1 (0.5%)	1 ( 0.5%)	2 ( 1.1%)	2 ( 1.1%)	1 ( 0.6%)	24 (15.2%)
Grade 4	0	0	0	0	0	0
Grade 5	0	2 ( 1.1%)	0	1 ( 0.6%)	1 ( 0.6%)	2 ( 1.3%)
Number of patients with at least one serious AE	2 (1.1%)	4 ( 2.1%)	2 ( 1.1%)	4 ( 2.3%)	3 ( 1.8%)	33 (20.9%)
Number of patients with at least one AE by outcome						
Fatal outcome	0	2 (50.0%)	0	1 (25.0%)	1 (33.3%)	2 ( 6.1%)
Unresolved	0	0	1 (50.0%)	0	1 (33.3%)	8 (24.2%)
Recovering/Resolving	0	0	0	0	0	0
Recovered/Resolved	2 (100%)	2 (50.0%)	1 (50.0%)	3 (75.0%)	1 (33.3%)	24 (72.7%)
Resolved with sequelae	0	0	0	0	0	0

**Table 47 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity, Frequency of AEs by Dose, Serious Infections and Infestations, (Studies GO41944 & GO41943)**

Unknown outcome	0	0	0	0	0	0
Glofitamab related AE leading to withdrawal from treatment	0	0	0	0	0	1 ( 0.6%)
Glofitamab related AE leading to dose interruption	0	0	1 ( 0.5%)	0	0	6 ( 3.8%)
Glofitamab related AE leading to dose modification	0	0	0	0	0	0

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Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.

Percentages are based on N in the column headings.

Only Treatment Emergent AEs with a preferred term (encoded using MedDRA version 26.1) of Serious Infection and infestation are included.

Adverse Events are graded by NCI CTCAE v5.0.

Program: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ae\_out2\_rmp.sas

Output: Adapted from [t\\_ae\\_out2\\_rmp\\_SINFEST\\_RMP\\_SERO.out](#)

## Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

### Potential mechanisms:

ICANS is a known class effect of bispecific T-cell engaging antibodies. Although the exact mechanism of action is unclear, the proposed cascade of activating endogenous or infused T cells following an enhanced release of proinflammatory cytokines and neurotoxic substances, endothelial activation, and disruption of the blood-brain barrier offer a plausible explanation.

### Evidence source(s) and strength of evidence:

#### Nonclinical data:

- Studies in cynomolgus monkeys showed that increases in the release of granulocyte colony-stimulating factor (G-CSF), IFN- $\gamma$ , IL-10, IL-17, IL-1 receptor antagonist (IL-1RA), IL-2, IL-6, IL-8, MCP-1, macrophage inflammatory protein 1 beta (MIP-1 $\beta$ ) and TNF- $\alpha$  measured 4 hours post-dose generally returned to baseline 24 hours post-dose.
- A non-human primate study found that ICANS development was not CD19 antigen-specific, as CD20-targeted CAR T cells also led to ICANS in rhesus macaques ([Taraseviciute et al. 2018](#)).

#### Clinical trial data:

- Phase I/II/III clinical trial data (Study NP30179 [CCOD 17 May 2024 for ICANS], Study GO41944 [CCOD 16 February 2024], and Study GO41943 [CCOD 08 December 2021]).
- Data from glofitamab-treated CNS lymphoma patients showing CSF concentrations of glofitamab of 0.1%–0.4% (data on file).

#### Post-marketing data:

- Drug Safety Report ([DSR](#) 1130968, ICANS (CCOD 13 March 2024).

#### Class effect:

- ICANS is described in the EU Product Information for other bispecific T-cell engagers (epcoritamab, teclistamab, talquetamab, elrantamab), and classified as an Important Identified Risk in their RMPs.

### Characterization of the Risk:

Suspected ICANS cases were identified cumulatively in the clinical database and global safety database using the Roche adverse event group term (AEGT) 'CD3 bispecifics ICANS' based on [Lee et al. 2019](#), followed by adjudication considering concurrency with CRS, latency from glofitamab dosing, confounding factors, and alternate etiologies.

### Results from Study NP30179

#### Overview of ICANS

- Primary safety population

In Study NP30179, potential ICANS events were identified in 10/145 patients (6.9%) in the primary safety population using the AEGT. The incidence of potential ICANS events was generally low, and the majority were Grade 1–2 and considered unrelated to glofitamab study treatment ([Table 48](#)).

Following adjudication of these 10 cases, 7/145 patients (4.8%) in the primary safety population were considered to have ICANS. Among the 7 patients, 5 patients (3.4%) had ICANS occurring concurrently with CRS. Two patients reported Grade 1 confusional state (one of which was considered related to treatment by the Investigator) and 1 patient reported Grade 3 somnolence (considered unrelated to treatment) following the C1D8 (2.5 mg) dose (and prior to C1D15). One patient reported Grade 1 disorientation (considered related to glofitamab treatment) following the C2D1 (30 mg) dose (and prior to C3). One patient experienced Grade 5 delirium (considered unrelated to treatment and heavily confounded by concurrent opiate use) following the C1D15 (10 mg) dose (and prior to C2D1). At the CCOD, only the event of somnolence was unresolved (the patient died due to progressive disease with somnolence ongoing).

The remaining two patients (1.4%) had ICANS events which were non-concurrent with CRS. One patient reported Grade 1 somnolence (considered unrelated to treatment) following the C1D15 (10 mg) dose (and prior to C2D1), and 1 patient reported Grade 1 cognitive disorder (considered unrelated to glofitamab treatment) following a C4+ dose. At the CCOD, both events were resolved.

- Overall safety population

In the overall safety population, among 467 patients who received at least one dose of glofitamab (17 May 2024 CCOD), potential ICANS events were identified in 38 patients (8.1%) using the AEGT. The majority of patients had events of Grade 1-2 maximum severity (33 patients [7.1%]). Grade 3 ICANS events were reported in 4 patients (0.9%), and a Grade 5 ICANS (delirium) event was reported in 1 patient. There were no Grade 4 events reported. At the CCOD, 11/38 patients (28.9%) had ICANS 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 D3, Cohort D2 [Sub. 2] and Cohort D5 (N=185), the ICANS profile was generally consistent with that of the overall safety population ([Table 49](#)).

### **ICANS events by dose cycle**

Among patients in the primary safety population (N=145), ICANS events identified using the AEGT occurred mainly in the first cycle of glofitamab treatment ([Table 50](#)).

Of the five ICANS events which occurred concurrently with CRS, three were reported following the C1D8 (2.5 mg) glofitamab dose (and prior to C1D15). No ICANS events were reported after Cycle 2.

In patients from all R/R NHL histologies treated with glofitamab at the proposed registrational dose (2.5/10/30 mg) in Cohort D3, Cohort D2 [Sub. 2], and Cohort D5 (N=185), ICANS events identified by the AEGT similarly occurred mainly in the first cycle of glofitamab treatment ([Table 51](#)).

### **Results from Studies GO41944 and GO41943**

In Studies GO41944 and GO41943, potential ICANS events were reported in 18/188 patients (9.6%) ([Table 52](#)). These 18 potential cases were then adjudicated considering concurrency with CRS, latency from glofitamab dosing, management of the event, confounding factors, and alternate etiologies. Based on this adjudication, suspected ICANS events were reported in 4 patients (2.1% [4/188 patients]) in the glofitamab-exposed safety population. All 4 patients were from Study GO41944 and no events from Study GO41943 met the criteria. Out of the 4 patients, one patient (0.5%) experienced a confirmed non-serious Grade 2 ICANS event. The remaining 3 patients (1.6%) experienced events which were identified as suspected ICANS events based on the adjudication criteria described above. These events were Grade 1 confusional state, Grade 2 confusional state and Grade 3 delirium.

Of these 4 patients (2.1%) with suspected/confirmed ICANS due to glofitamab, 3 events were concurrent with CRS (Grade 1 confusional state in 1 patient and Grade 2 ICANS in 1 patient both of which occurred following the 2.5 mg C1D8 dose and prior to the 10 mg C1D15 dose, and Grade 3 delirium in 1 patient which occurred following the 10 mg C1D15 dose and prior to the 30 mg C2 dose). One patient had a suspected ICANS event which was non-concurrent with CRS (Grade 2 confusional state following the C1D8 2.5 mg glofitamab dose and prior to the C1D15 10 mg dose).

### **ICANS events by dose cycle**

In Studies GO41944 and GO41943, the majority of potential ICANS events identified using the AEGT occurred during the step-up dosing of glofitamab (C1D8 to C2) ([Table 53](#)). All 4 suspected/confirmed ICANS events through adjudication, described above, occurred during the step-up dosing of glofitamab. Events occurring after C2 (8/158 patients, 5.1%) were not considered to be suspected/confirmed ICANS events due to factors confounding the potential for ICANS and were typically low grade.

### **Post-marketing experience**

ICANS, including Grade 3 and higher, was reported with post-marketing experience ([DSR 1130968](#)). The most frequent clinical manifestation of ICANS were confusion, depressed level of consciousness, disorientation, seizure, aphasia, and dysgraphia. Based on the available data, the onset of neurologic toxicity was concurrent with CRS in the majority of cases.

The observed time to onset of majority of ICANS was 1–7 days with median of 2 days after the most recent dose. Only few events were reported to have occurred more than one month after the initiation of glofitamab.

**Risk factors and risk groups:**

Advanced disease, elderly population

**Preventability:**

As described in the SmPC (Section 4.2), patients must be monitored for signs and symptoms of ICANS following glofitamab administration. All patients must be given a Patient Card ([Table 60](#)), counselled on the risk and signs and symptoms of ICANS, and advised to contact the healthcare provider immediately should they experience signs and symptoms of ICANS at any time. Since patients with CRS may experience ICANS concurrently, measures to reduce the occurrence of CRS may also reduce the occurrence of ICANS.

At the first signs or symptoms of ICANS, manage according to the grading and management guidance for ICANS (non-concurrent and concurrent with CRS) provided in Section 4.2 of the SmPC. Treatment with glofitamab should be withheld or discontinued permanently as recommended.

**Impact on the benefit-risk balance of the product:**

ICANS is a known class effect of bispecific T-cell engagers. Considering that serious cases of ICANS which could be life-threatening or fatal have been reported in patients treated with glofitamab, there is an impact on the benefit-risk, however, the overall benefit-risk balance of glofitamab remains positive.

Comprehensive product labeling including monitoring and management guidance together with the additional risk-minimization measure of a Patient Card are considered adequate to mitigate and manage the risk.

**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 Information. Use outside of controlled environments by non-healthcare professionals is not anticipated.



**Table 48 Important Identified Risk of ICANS: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R DLBCL who have Received  $\geq 2$  Prior Systemic Therapies (Study NP30179)**

Seriousness, Outcomes, Severity, Frequency of AEs, ICANS Events, Initial Treatment Phase, (R/R DLBCL Patients,  $\geq 2$  Prior Lines of Systemic Therapy), Safety-Evaluatable 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 $\geq 0.60$ mg (N=273)	Glofitamab Doses $\geq 10$ 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	8 ( 7.9%)	2 (5.4%)	20 ( 7.3%)	8 ( 8.2%)	8 ( 7.4%)	10 ( 6.9%)
95% CI for % of patients with at least one AE	(3.48%, 15.01%)	(0.66%, 18.19%)	(4.53%, 11.09%)	(3.63%, 15.61%)	(3.25%, 14.07%)	(3.36%, 12.32%)
Total number of AEs	8	2	23	10	8	10
Total number of AEs related to Glofit	2	1	6	3	2	3
Number of patients with at least one AE by worst grade						
Grade 1	4 ( 4.0%)	2 (5.4%)	11 ( 4.0%)	4 ( 4.1%)	4 ( 3.7%)	6 ( 4.1%)
Grade 2	2 ( 2.0%)	0	6 ( 2.2%)	3 ( 3.1%)	2 ( 1.9%)	2 ( 1.4%)
Grade 3	1 ( 1.0%)	0	2 ( 0.7%)	1 ( 1.0%)	1 ( 0.9%)	1 ( 0.7%)
Grade 4	0	0	0	0	0	0
Grade 5	1 ( 1.0%)	0	1 ( 0.4%)	0	1 ( 0.9%)	1 ( 0.7%)
Number of patients with at least one serious AE	1 ( 1.0%)	0	2 ( 0.7%)	1 ( 1.0%)	1 ( 0.9%)	1 ( 0.7%)
Number of patients with at least one AE by outcome						
Fatal outcome	1 (12.5%)	0	1 ( 5.0%)	0	1 (12.5%)	1 (10.0%)
Unresolved	2 (25.0%)	0	6 (30.0%)	3 (37.5%)	2 (25.0%)	2 (20.0%)
Recovering/Resolving	0	0	1 ( 5.0%)	0	0	0
Recovered/Resolved	4 (50.0%)	2 (100%)	11 (55.0%)	5 (62.5%)	4 (50.0%)	6 (60.0%)
Resolved with sequelae	1 (12.5%)	0	1 ( 5.0%)	0	1 (12.5%)	1 (10.0%)
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

**Table 48 Important Identified Risk of ICANS: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R DLBCL who have Received ≥2 Prior Systemic Therapies (Study NP30179) (cont.)**

Glofit related AE leading to dose modification	0	0	0	0	0	0
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Immune effector cell-Associated Neurotoxicity Syndrome (ICANS) defined by the Roche AEGT.  
(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.  
Data Cutoff Date: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/t\_ae\_outl\_rmp.sas  
Output: root/clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/prod/output/  
t\_ae\_outl\_rmp\_ICANS\_I\_RMP\_SERO\_17MAY2024\_30179.out  
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**Table 49 Important Identified Risk of ICANS: Seriousness, Outcomes, Severity and Frequency with 95% CI - Patients with R/R NHL– All Histologies (Study NP30179)**

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

	Glofitamab Doses $\geq 0.60$ mg (N=467)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=185)
Number of patients with at least one AE	38 ( 8.1%)	17 ( 9.2%)
95% CI for % of patients with at least one AE	(5.82%, 11.00%)	(5.44%, 14.30%)
Total number of AEs	46	20
Total number of AEs related to Glofit	11	5
Number of patients with at least one AE by worst grade		
Grade 1	23 ( 4.9%)	10 ( 5.4%)
Grade 2	10 ( 2.1%)	5 ( 2.7%)
Grade 3	4 ( 0.9%)	1 ( 0.5%)
Grade 4	0	0
Grade 5	1 ( 0.2%)	1 ( 0.5%)
Number of patients with at least one serious AE	3 ( 0.6%)	1 ( 0.5%)
Number of patients with at least one AE by outcome		
Fatal outcome	1 ( 2.6%)	1 ( 5.9%)
Unresolved	11 (28.9%)	4 (23.5%)
Recovering/Resolving	1 ( 2.6%)	0
Recovered/Resolved	25 (65.8%)	12 (70.6%)
Resolved with sequelae	1 ( 2.6%)	1 ( 5.9%)
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	0	0

Immune effector cell-Associated Neurotoxicity Syndrome (ICANS) defined by the Roche AEGT.  
Data Cutoff Date: 17MAY2024

Program: root/clinical\_studies/RO7082859/CDT70029/NP30179/share/data\_analysis/prod/program/  
t\_ae\_outl\_rmp.sas  
Output: root/Clinical\_studies/RO7082859/CDT70029/NP30179/data\_analysis/CSRUpdate\_2yr\_Jun2024/  
prod/output/t\_ae\_outl\_rmp\_ICANS\_I\_RMP2\_SERO\_17MAY2024\_30179.out  
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**Table 50 Important Identified Risk of ICANS: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R DLBCL, ≥2 Prior Systemic Therapies; Cohorts D2 [Sub. 2], D3, and D5 (Study NP30179)**

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, ICANS 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	4 ( 2.8%)	2 ( 1.5%)	2 ( 1.6%)	1 (0.9%)
95% CI for % of patients with at least one AE	(0.76%, 6.91%)	(0.18%, 5.25%)	(0.19%, 5.57%)	(0.02%, 5.10%)
Total number of AEs	4	2	2	1
Total number of AEs related to Glofitamab	2	0	1	0
Number of patients with at least one AE by worst grade				
Grade 1	2 ( 1.4%)	1 ( 0.7%)	1 ( 0.8%)	1 (0.9%)
Grade 2	1 ( 0.7%)	0	1 ( 0.8%)	0
Grade 3	1 ( 0.7%)	0	0	0
Grade 4	0	0	0	0
Grade 5	0	1 ( 0.7%)	0	0
Number of patients with at least one serious AE	0	1 ( 0.7%)	0	0
Number of patients with at least one AE by outcome				
Fatal outcome	0	1 (50.0%)	0	0
Unresolved	2 (50.0%)	0	0	0
Recovering/Resolving	0	0	0	0
Recovered/Resolved	2 (50.0%)	1 (50.0%)	1 (50.0%)	1 (100%)
Resolved with sequelae	0	0	1 (50.0%)	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	0	0	0	0

Immune effector cell-Associated Neurotoxicity Syndrome (ICANS) defined by the Roche AEGT.  
Data Cutoff Date: 17MAY2024

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/CSRUpdate\_2yr\_Jun2024/  
prod/output/t\_ae\_out2\_rmp\_ICANS\_I\_RMPD\_SERO\_17MAY2024\_30179.out  
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**Table 51 Important Identified Risk of ICANS: Seriousness, Outcomes, Severity and Frequency with 95% CI by Cycle - R/R NHL (All Histologies); Cohorts D2 [Sub. 2], D3, D5 (Study NP30179)**

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, ICANS 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	8 ( 4.3%)	4 ( 2.3%)	2 ( 1.2%)	3 ( 2.1%)
95% CI for % of patients with at least one AE	(1.89%, 8.34%)	(0.63%, 5.78%)	(0.15%, 4.28%)	(0.44%, 6.05%)
Total number of AEs	8	5	2	3
Total number of AEs related to Glofitamab	4	0	1	0
Number of patients with at least one AE by worst grade				
Grade 1	4 ( 2.2%)	3 ( 1.7%)	1 ( 0.6%)	2 ( 1.4%)
Grade 2	3 ( 1.6%)	0	1 ( 0.6%)	1 ( 0.7%)
Grade 3	1 ( 0.5%)	0	0	0
Grade 4	0	0	0	0
Grade 5	0	1 ( 0.6%)	0	0
Number of patients with at least one serious AE	0	1 ( 0.6%)	0	0
Number of patients with at least one AE by outcome				
Fatal outcome	0	1 (25.0%)	0	0
Unresolved	2 (25.0%)	0	0	1 (33.3%)
Recovering/Resolving	0	0	0	0
Recovered/Resolved	6 (75.0%)	3 (75.0%)	1 (50.0%)	2 (66.7%)
Resolved with sequelae	0	0	1 (50.0%)	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	0	0	0	0

Immune effector cell-Associated Neurotoxicity Syndrome (ICANS) defined by the Roche AEGT.  
Data Cutoff Date: 17MAY2024

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/CSRUpdate\_2yr\_Jun2024/  
prod/output/t\_ae\_out2\_rmp\_ICANS\_I\_RMP2A\_SERO\_17MAY2024\_30179.out  
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**Table 52 Important Identified Risk of ICANS: Seriousness, Outcomes, Severity and Frequency with 95% CI - (Studies GO41944 & GO41943)**

Seriousness, Outcomes, Severity, Frequency of AEs, ICANS Events, Modified Safety-Evaluable Patients  
Protocol: GO41944 & GO41943  
Risk Management Plan

	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Number of patients with at least one AE	15 ( 8.7%)	3 (18.8%)	18 ( 9.6%)
95% CI for % of patients with at least one AE	(4.96%, 13.98%)	(4.05%, 45.65%)	(5.77%, 14.71%)
Total number of AEs	20	3	23
Total number of AEs related to Glofit	5	1	6
Number of patients with at least one AE by worst grade			
Grade 1	5 ( 2.9%)	2 (12.5%)	7 ( 3.7%)
Grade 2	7 ( 4.1%)	1 ( 6.3%)	8 ( 4.3%)
Grade 3	3 ( 1.7%)	0	3 ( 1.6%)
Grade 4	0	0	0
Grade 5	0	0	0
Number of patients with at least one serious AE	3 ( 1.7%)	0	3 ( 1.6%)
Number of patients with at least one AE by outcome			
Fatal outcome	0	0	0
Unresolved	5 (33.3%)	3 ( 100%)	8 (44.4%)
Recovering/Resolving	0	0	0
Recovered/Resolved	13 (86.7%)	0	13 (72.2%)
Resolved with sequelae	0	0	0
Unknown outcome	0	0	0
Glofit related AE leading to withdrawal from treatment	0	0	0
Glofit related AE leading to dose interruption	0	0	0
Glofit related AE leading to dose modification	0	0	0

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.

Percentages are based on N in the column headings.

Immune effector cell-Associated Neurotoxicity Syndrome (ICANS) defined by the Roche AEGT.

Only Treatment Emergent AEs with a preferred term (encoded using MedDRA version 26.1) of ICANS are included.

Adverse Events are graded by NCI CTCAE v5.0.

Program: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ae\_out1\_rmp.sas

Output: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/output/

t\_ae\_out1\_rmp\_ICANS\_RMP\_GLO\_SERO.out

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**Table 53 Important Identified Risk of ICANS: Seriousness, Outcomes, Severity and Frequency with 95% CI by Dose -(Studies GO41944 & GO41943)**

Seriousness, Outcomes, Severity, Frequency of AEs by Dose, ICANS Events, Modified Safety-Evaluable Patients  
Protocol: GO41944 & GO41943  
Risk Management Plan

	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)					
	C1D1 (N=188)	C1D8 (N=188)	C1D15 (N=183)	C2 (N=177)	C3 (N=164)	C4+ (N=158)
Number of patients with at least one AE	4 ( 2.1%)	5 (2.7%)	1 (0.5%)	3 ( 1.7%)	0	8 ( 5.1%)
95% CI for % of patients with at least one AE	(0.58%, 5.36%)	(0.87%, 6.10%)	(0.01%, 3.01%)	(0.35%, 4.87%)	(0.00%, 2.22%)	(2.21%, 9.73%)
Total number of AEs	5	5	1	3	0	8
Total number of AEs related to Glofitamab	0	3	0	2	0	1
Number of patients with at least one AE by worst grade						
Grade 1	2 ( 1.1%)	3 (1.6%)	0	1 ( 0.6%)	0	2 ( 1.3%)
Grade 2	1 ( 0.5%)	2 (1.1%)	0	1 ( 0.6%)	0	4 ( 2.5%)
Grade 3	0	0	0	1 ( 0.6%)	0	2 ( 1.3%)
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	0	1 (0.5%)	0	1 ( 0.6%)	0	1 ( 0.6%)
Number of patients with at least one AE by outcome						
Fatal outcome	0	0	0	0	0	0
Unresolved	4 ( 100%)	0	0	2 (66.7%)	0	2 (25.0%)
Recovering/Resolving	0	0	0	0	0	0
Recovered/Resolved	1 (25.0%)	5 (100%)	1 (100%)	1 (33.3%)	0	6 (75.0%)
Resolved with sequelae	0	0	0	0	0	0
Unknown outcome	0	0	0	0	0	0

**Table 53 Important Identified Risk of ICANS: Seriousness, Outcomes, Severity and Frequency with 95% CI by Dose -(Studies GO41944 & GO41943)(contd.)**

Glofitamab related AE leading to withdrawal from treatment	0	0	0	0	0	0
Glofitamab related AE leading to dose interruption	0	0	0	0	0	0
Glofitamab related AE leading to dose modification	0	0	0	0	0	0

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Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.

Percentages are based on N in the column headings.

Immune effector cell-Associated Neurotoxicity Syndrome (ICANS) defined by the Roche AEGT.

Only Treatment Emergent AEs with a preferred term (encoded using MedDRA version 26.1) of ICANS are included.

Adverse Events are graded by NCI CTCAE v5.0.

Program: root/clinical\_studies/RO7082859/CDT30295/share/pool\_SCS\_Followup\_Analysis\_2024/prod/program/t\_ae\_out2\_rmp.sas

Output: Adapted from [t\\_ae\\_out2\\_rmp\\_ICANS\\_RMP\\_GLO\\_SERO.out](#)



**Information on Important Potential Risks**  
**Not Applicable**

**SVII.3.2. Presentation of the Missing Information**  
**Not Applicable**

**PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS**

**Table 54 Summary of Safety Concerns**

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"><li>• Cytokine release syndrome</li><li>• Tumor Flare</li><li>• Serious Infections</li><li>• Immune effector cell-associated neurotoxicity syndrome (ICANS)</li></ul>
Important potential risks	None
Missing information	None

**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

None

## III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

**Table 55 BO44309 Summary**

<b>Study/Activity Short Name and Title:</b> BO44309 Evaluation of the Effectiveness of the Additional Risk Minimisation Measures for Glofitamab: A PASS Survey Among Healthcare Professionals in 10 European Countries
<b>Rationale and Study Objectives:</b> <p>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 and ICANS <sup>a</sup>(Patient Card) and tumor flare (HCP Brochure).</p> <p>The main objective of the study is to evaluate the following process and behavioral 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.</p>
<b>Study Design:</b> <p>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:</p> <ul style="list-style-type: none"><li>• 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).</li><li>• 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 risks of CRS and ICANS associated with glofitamab and the risk mitigation measures for CRS and ICANS.</li><li>• 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.</li><li>• In the adherence questions, HCPs will be asked to self-assess their adherence to the guidance provided in the HCP brochure.</li></ul>
<b>Study Population:</b> A sample of HCPs who prescribed glofitamab according to the label, at least once in the six months prior to taking the survey.

**Table 55 BO44309 Summary (cont.)**

<b>Milestones:</b> Study status: Planned Start Date of Study (date of first data collection): Q2 2026 (Planned) End of Study: Q4 2026 (Planned) Final report: Q4 2027 (Planned)
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CRS=cytokine release syndrome; HCP=healthcare professional; ICANS=immune effector cell-associated neurotoxicity syndrome; TBD=to be determined; TF= tumor flare.

<sup>a</sup> An update is planned to the design/questionnaire of this study to gather evidence on the effectiveness of the content for ICANS in addition to CRS and TF.

### III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

**Table 56 Ongoing and Planned Additional Pharmacovigilance Activities**

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
<b>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</b>				
BO44309 Evaluation of the Effectiveness of the Additional Risk Minimisation Measures for Glofitamab: A PASS Survey Among Healthcare Professionals in 10 European Countries  Planned	The primary objective of this study is to assess, by survey: <ul style="list-style-type: none"> <li>The receipt of the educational materials, i.e., HCP brochure (for the important identified risk of TF) and Patient Card (for the important identified risks of CRS and ICANS), by the target population (glofitamab prescribers) and the distribution of the Patient Card by prescribers to their patients</li> <li>Behavioral indicators (the level of awareness, knowledge, comprehension and adherence) of prescribers with respect to TF information included in the HCP brochure.</li> </ul>	<ul style="list-style-type: none"> <li>Cytokine release syndrome</li> <li>Tumor Flare</li> <li>ICANS <sup>a</sup></li> </ul>	Final report	Q4 2027 (Planned)

CAR-T=chimeric antigen receptor T-cell; CRS= cytokine release syndrome; CSR= clinical study report; HCP= healthcare professional; ICANS=immune effector cell-associated neurotoxicity syndrome; NHL= Non-Hodgkin's lymphoma; PASS=Post-Authorization Safety Study; R/R=relapsed/refractory; TF=tumor flare.

<sup>a</sup> An update is planned to the design/questionnaire of this study to gather evidence on the effectiveness of the content for ICANS in addition to CRS and TF.

## **PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES**

**Table 57 Planned and Ongoing Post-Authorization Imposed Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations**

<b>Study Status</b>	<b>Summary of Objectives</b>	<b>Efficacy uncertainties addressed</b>	<b>Milestones</b>	<b>Due Date</b>
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				
Not Applicable				

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

### **RISK-MINIMIZATION PLAN**

#### **V.1 ROUTINE RISK-MINIMIZATION MEASURES**

**Table 58 Description of Routine Risk-Minimization Measures by Safety Concern**

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

Safety Concern	Routine Risk-Minimization Activities
Serious Infections	<p><b>Routine risk communication:</b></p> <p><b>SmPC:</b></p> <ul style="list-style-type: none"> <li>• Section 4.4 Special warnings and precautions for use</li> <li>• Section 4.8 Undesirable effects</li> </ul> <p><b>Package Leaflet:</b></p> <ul style="list-style-type: none"> <li>• Section 2 What you need to know before you are given Columvi</li> <li>• Section 4 Possible side effects</li> </ul> <p><b>Routine risk-minimization activities recommending specific clinical measures to address the risk:</b></p> <p>Recommendation for monitoring for the development of Serious Infections is included in SmPC section 4.4.</p> <p><b>Other risk-minimization measures beyond the Product Information:</b></p> <p><b>Pack size:</b></p> <p>None</p> <p><b>Medicine's legal status:</b></p> <p>Glofitamab is subject to restricted medical prescription.</p>
Immune effector cell-associated neurotoxicity syndrome	<p><b>Routine risk communication:</b></p> <p><b>SmPC:</b></p> <ul style="list-style-type: none"> <li>• Section 4.2 Posology and method of administration</li> <li>• Section 4.4 Special warnings and precautions for use</li> <li>• Section 4.7 Effects on ability to drive and use machines</li> <li>• Section 4.8 Undesirable effects</li> </ul> <p><b>Package Leaflet:</b></p> <ul style="list-style-type: none"> <li>• Section 2 What you need to know before you are given Columvi</li> <li>• Section 4 Possible side effects</li> </ul> <p><b>Routine risk-minimization activities recommending specific clinical measures to address the risk:</b></p> <ul style="list-style-type: none"> <li>• Recommendation for monitoring for the development of ICANS is included in the SmPC Section 4.2</li> <li>• ICANS grading and management guidance is provided in SmPC Section 4.2</li> <li>• Recommendations for patients to avoid driving and operating machines is included in the SmPC Section 4.7</li> </ul> <p><b>Other risk minimization measures beyond the Product Information:</b></p> <p><b>Pack size:</b></p> <p>None</p> <p><b>Medicine's legal status:</b></p> <p>Glofitamab is subject to restricted medical prescription.</p>

CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; SmPC=summary of product characteristics; TBC =to be confirmed; TF= tumor flare.

## V.2. ADDITIONAL RISK-MINIMIZATION MEASURES

**Table 59 Additional Risk-Minimization Measures**

Additional risk-minimization measure	Healthcare Professional Brochure
Objective(s)	<p>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.</p> <p>The HCP brochure will provide a description of TF, and information on early recognition, appropriate diagnosis, and monitoring of TF.</p>
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.
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.
Plans for evaluating the effectiveness of the interventions and criteria for success	<p><b>How effectiveness will be measured:</b></p> <ul style="list-style-type: none"> <li>• Metrics of distribution of HCP Brochure to HCPs</li> <li>• 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</li> <li>• 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</li> </ul> <p><b>Milestones for reporting:</b></p> <ul style="list-style-type: none"> <li>• Monitoring of reporting rate and severity, periodically in PBRERs</li> <li>• Final report for Study BO44309: Q4 2027 (Planned)</li> </ul>

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 60 Additional Risk-Minimization Measures**

Additional risk-minimization measure	Patient Card
Objective(s)	<p>Based on the characterization of CRS and ICANS, 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 risks of CRS and ICANS. The intent is that the Patient Card will remind patients of the signs and symptoms of CRS and ICANS, and encourage patients to seek immediate medical attention if signs and symptoms of CRS and/or ICANS are 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.</p> <p>Furthermore, the Patient Card will alert HCPs that the patient is taking glofitamab (particularly useful if the patient is presenting at the emergency room).</p>
Rationale for the additional risk-minimization activity	<p>The Patient Card will promote awareness of the key signs and symptoms of CRS and ICANS, thereby enabling early recognition of CRS and ICANS by patients and timely reporting to their physicians, encouraging prompt intervention.</p>
Target audience and planned distribution path	<p>The Patient Card is targeted for use in adult patients with R/R DLBCL. The Patient Card will be provided to the physician for distribution to the patient prior to their first dose of glofitamab.</p>
Plans for evaluating the effectiveness of the interventions and criteria for success	<p><b>How effectiveness will be measured:</b></p> <ul style="list-style-type: none"> <li>• Metrics of distribution channel of Patient Card to HCP</li> <li>• Survey to confirm patient card was given to patient by HCP</li> <li>• 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</li> </ul> <p><b>Milestones for reporting:</b></p> <ul style="list-style-type: none"> <li>• Monitoring of reporting rate and severity, periodically in PBRERs</li> <li>• Final report for Study BO44309: Q4 2027 (Planned)</li> </ul>

CRS=cytokine release syndrome; HCP=healthcare professional; ICANS=immune effector cell-associated neurotoxicity syndrome; 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 61 Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern**

<b>Safety Concern</b>	<b>Risk-Minimization Measure(s)</b>	<b>Pharmacovigilance Activities</b>
Cytokine release syndrome	<b>Routine risk-minimization measures:</b> 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  <b>Additional risk-minimization measures:</b> Patient Card	<b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b> No activities beyond routine PSUR/PBRER reporting <b>Additional pharmacovigilance activities:</b> Study BO44309 Final report: Q4 2027 (Planned)
Tumor Flare	<b>Routine risk-minimization measures:</b> SmPC section 4.4 and 4.8  Package leaflet section 2 and 4  <b>Additional risk-minimization measures:</b> HCP brochure	<b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b> No activities beyond routine PSUR/PBRER reporting  <b>Additional pharmacovigilance activities:</b> Study BO44309 Final report: Q4 2027 (Planned)

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
Serious Infections	<b>Routine risk-minimization measures:</b> 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 <b>Additional risk-minimization measures:</b> None	<b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b> No activities beyond routine PSUR/PBRER reporting <b>Additional pharmacovigilance activities:</b> None
Immune effector cell-associated neurotoxicity syndrome	<b>Routine risk-minimization measures:</b> SmPC sections 4.2, 4.4, 4.7 and 4.8 Recommendation for monitoring for the development of ICANS is included in SmPC section 4.2. ICANS grading and management guidance is included in SmPC section 4.2. Package leaflet sections 2 and 4 <b>Additional risk-minimization measures:</b> Patient Card	<b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b> No activities beyond routine PSUR/PBRER reporting <b>Additional pharmacovigilance activities:</b> Study BO44309 Final report: Q4 2027 (Planned)

aRMM= additional risk-minimization measures; CSR= clinical study report; HCP= healthcare professional; ICANS=immune effector cell-associated neurotoxicity syndrome; NI-PASS = non-interventional post-authorization safety study; PBRER= periodic benefit risk evaluation report; PSUR= periodic safety update report; SmPC= summary of product characteristics.

## **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.

Columvi in combination with gemcitabine and oxaliplatin is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplant (ASCT).

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).

<b>List of Important Risks and Missing Information</b>	
Important identified risks	<ul style="list-style-type: none"> <li>• Cytokine release syndrome</li> <li>• Tumor Flare</li> <li>• Serious infections</li> <li>• Immune effector cell-associated neurotoxicity syndrome</li> </ul>
Important potential risks	None
Missing information	None

## II.B Summary of Important Risks

<b>Important Identified Risk: Cytokine release syndrome</b>	
Evidence for linking the risk to the medicine	<ul style="list-style-type: none"> <li>Non-clinical studies, showing transient T-cell activation and cytokine release, primarily limited to the first dose</li> <li>Phase I/II/III clinical trial data (Studies NP30179, GO41944, and GO41943)</li> <li>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</li> </ul>
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	<p><b>Routine risk-minimization measures:</b></p> <p>SmPC section 4.2, 4.4 and 4.8</p> <p>Recommendation for monitoring for the development of CRS is included in SmPC section 4.2.</p> <p>Package leaflet sections 2 and 4</p> <p><b>Additional risk-minimization measures:</b></p> <p>Patient Card</p>
Additional pharmacovigilance activities	<p><b>Additional pharmacovigilance activities:</b></p> <p>Study BO44309</p> <p>See Section II.C of this summary for an overview of the post-authorization development plan.</p>

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

<b>Important Identified Risk: Tumor Flare</b>	
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	<b>Routine risk-minimization measures:</b> SmPC section 4.4 and 4.8 Package leaflet section 2 and 4 <b>Additional risk-minimization measures:</b> HCP brochure
Additional pharmacovigilance activities	<b>Additional pharmacovigilance activities:</b> Study BO44309  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.

<b>Important Identified Risk: Serious Infections</b>	
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.

<b>Important Identified Risk: Immune effector cell associated neurotoxicity syndrome</b>	
Evidence for linking the risk to the medicine	<ul style="list-style-type: none"> <li>• Non-clinical data</li> <li>• Phase I/II/III clinical trial data (Studies NP30179, GO41944, and GO41943)</li> <li>• Post-marketing data</li> <li>• Class effect</li> </ul>
Risk factors and risk groups	Advanced disease, elderly population
Risk-minimization measures	<b>Routine risk-minimization measures:</b> SmPC section 4.2, 4.4, 4.7 and 4.8 Package leaflet sections 2 and 4 <b>Additional risk-minimization measures:</b> Patient Card
Additional pharmacovigilance activities	<b>Additional pharmacovigilance activities:</b> Study BO44309 See Section II.C of this summary for an overview of the post-authorization development plan.

SmPC=summary of product characteristics.

## **II.C Post-Authorization Development Plan**

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

Not Applicable

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

**Study BO44309:**

#### **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 and ICANS (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)

#### 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) and immune effector cell-associated neurotoxicity syndrome (ICANS)
- Prompting patient actions, including seeking immediate medical attention, in case of the occurrence of symptoms of CRS and/or ICANS
- Informing physicians of the risk of tumor flare (TF) and its manifestations

The objective of the program is to minimize the risks of TF, CRS, and ICANS, 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 and ICANS, 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 and ICANS 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 risks of CRS and ICANS