26 April 2023
EMA/228393/2023
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Columvi

International non-proprietary name: glofitamab

Procedure No. EMEA/H/C/005751/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibody
ASCT	Autologous stem cell transplant
BOR	best overall response
CCOD	clinical cut-off date
CNS	central nervous system
CR	complete response
CRR	complete response rates
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography (scan)
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOCR	duration of complete response
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
FACT-Lym LymS	Functional Assessment of Cancer Therapy – Lymphoma Subscale
FDG-PET	fluorodeoxyglucose (FDG)-positron emission tomography (PET)
FL	follicular lymphoma
GL	guideline
Gpt	Gazyva® / Gazyvaro® (obinutuzumab) pre-treatment
HGBCL	high-grade B-cell lymphoma
HRQoL	health-related quality of life
IRC	Independent Review Committee
ITT	intent-to-treat
INV	Investigator
IV	intravenous
mDA CRM EWOC	modified data-augmentation continual reassessment method of escalation with overdose control
MoA	mechanism of action
MTD	maximum tolerated dose

NALT	new anti-lymphoma treatment
NE	not evaluable
NHL	non-Hodgkin’s lymphoma
NOS	not otherwise specified
OBD	optimal biological dose
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography (scan)
PFS	progression-free survival
PK	pharmacokinetic
PMBCL	primary mediastinal B-cell lymphoma
PopPK	population pharmacokinetics
PR	partial response
PT	preferred term
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
R/R	relapsed or refractory
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SCT	stem cell transplantation
SD	stable disease
SOC	system organ class
TFCR	time to first complete response
TFOR	time to first overall response
TOCR	time to first complete response
trFL	transformed follicular lymphoma

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration GmbH submitted on 25 March 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Columvi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 September 2020.

Columvi, was designated as an orphan medicinal product EU/3/21/2497 on 15 October 2021 in the following condition: diffuse large B-cell lymphoma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Columvi as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/columvi.

The applicant applied for the following indication "Columvi as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy".

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0094/2020 on the agreement of a paediatric investigation plan (PIP).

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation and Accelerated assessment

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

The applicant requested accelerated assessment in accordance with Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance glofitamab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
31/01/2019	EMEA/H/SA/4023/1/2018/I	Walter Janssens and Alexandre Moreau
12/12/2019	EMEA/H/SA/4023/2/2019/III	Kristian Wennmalm and Olli Tenhunen
30/01/2020	EMEA/H/SA/4023/3/2019/III	Alexandre Moreau and Paolo Foggi
23/07/2020	EMEA/H/SA/4023/2/FU/1/2020/II	Alexandre Moreau and Ole Weis Bjerrum

The scientific advice pertained to the following non-clinical, clinical aspects:

- The value of conducting and possibility to waive a 13-week toxicity study and a non-human primate ePPND study for MAA in B-cell hematologic malignancies expressing CD20 (R/R and first-line).
- The non-clinical program and clinical development aspects for MAA in diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL) after two or more lines of systemic therapy, in particular: dose and treatment schedule, the proposed clinical pharmacology plan; the design of study GO41944 Phase I expansion part to support a MAA (study population, clinical endpoints, sample size, timing of the efficacy analysis and inclusion of supplementary data with longer follow up time from a second dosing regimen); the proposal to assess the clinical activity of the single agent RO7082859; the proposed supportive RWD study to provide additional evidence for clinical benefit; the proposed total patient exposure for a MAA in the targeted population.
- The non-clinical program and clinical development aspects for MAA in relapsed or refractory B-cell lymphoma, in particular, the design of the Phase Ib study GO41943 to confirm the dose and dosing schedule and to provide preliminary safety and tolerability information on the combination of

RO7082859 with gemcitabine and oxaliplatin; the Phase III study GO41944 to support full approval (choice of endpoints, patient population, use of R-GemOx as comparator, stratification factors, statistical analysis plan); the use of EORTC QLC-C30 and FACT-LymS to demonstrate maintenance of health-related quality of life (HRQoL); the anticipated safety database to support approval, as well as the proposed strategy for safety monitoring and risk mitigation.

- In view of a MAA in relapsed or refractory diffuse large B cell lymphoma (DLBCL), high grade B cell lymphoma (HGBCL) and primary mediastinal large B-cell lymphoma (PMBCL): the design of the RWD study GO41485, in particular, the use of Flatiron Health's database as source of external data; data analysis using propensity score methods; the choice of prognostic factors to be used as covariates in a propensity score model; the assessments and handling of missing data; the sensitivity analyses to test the assumptions related to the comparability between the glofitamab and the RWD cohort; the timing of the analyses.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: Jan Mueller-Berghaus

The application was received by the EMA on	25 March 2022
The procedure started on	19 May 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 August 2022
The CHMP Co-Rapporteur's critique on the CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	23 August 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 August 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 September 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 December 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 January 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	9 February 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	23 February 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 March 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 April 2023

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Columvi on	26 April 2023
The CHMP adopted a report on similarity of Columvi with Kymriah, Yescarta, Minjuvi & Polivy on	26 April 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product on	26 April 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant is seeking marketing authorization for:

Columvi is indicated as monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.

2.1.2. Epidemiology and risk factors

DLBCL is the most common NHL diagnosed in Western Europe and the United States, accounting for approximately 30-58% of NHL cases (Tilly et al. 2015). The disease causes approximately 8500 new cases in Europe (Sant et al. 2010) and an estimated 4000 deaths per year (Marcos-Gragera et al. 2011, De Angelis et al. 2015, Howlader et al. 2016). Throughout the world, the incidence increases with age; for example, in the United States, 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+).

A family history of lymphoma, autoimmune disease, human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) seropositivity, a high body mass as a young adult and some occupational exposures have been identified as risk factors of DLBCL (Morton el al. 2014).

2.1.3. Biologic features

Non-Hodgkin lymphoma represents a biologically and clinically heterogeneous group of lymphoproliferative malignancies which in 90% of cases are derived from B-cells. As in the majority of other mature B-cell lymphomas, DLBCL is characterized by the expression of a surface membrane antigen, CD20. CD20 is an attractive target for anti-lymphoma therapies, being B-cell-specific, highly and stably expressed, exhibiting a low rate of internalization, and not being present on hematopoietic stem cells. The concept of targeting CD20 as an effective anti-lymphoma strategy has been validated by clinical data for the anti-CD20 monoclonal antibody rituximab (R), showing prolonged survival in DLBCL when added to intensive cytotoxic chemotherapeutic regimens (Sehn et al. 2015).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

DLBCL is a life-threatening disease with an aggressive natural history and is fatal if left untreated. The incidence of DLBCL increases with age, with a median age of 64 years at diagnosis. Patients typically present with rapidly enlarging masses at nodal or extranodal sites and 45-60% of patients present with advanced-stage disease (Ann Arbor Stage III or IV). The clinical course can be debilitating due to constitutional symptoms, local symptoms of lymphadenopathy and bone marrow failure that may lead to infections, anemia, thrombocytopenia, organ failure, and death. Relapses of DLBCL are characterized by increasing refractoriness and decreasing duration of response to subsequent lines of therapy.

The current standard of care for first-line treatment for DLBCL is nowadays difficult to define in the EU. CHOP in combination with an anti-CD20 monoclonal antibody (mAb) rituximab (R-CHOP) (Coiffier et al. 2010) has been the standard of care for almost three decades, which is still reflected e.g. in the ESMO and NCCN guidelines. The reason for this is, that ESMO guidelines have been published prior to the approval of Polatuzumab vedotin in the 1L setting and the approval status in the US still does not contain this 1L indication (Polivy USPI, access date 17.08.2022).

According to consulted experts, the up-to-date trend could be to treat patients with the Pola+R-CHP in 1L and this could possibly be considered a new standard of care despite it not being reflected in the ESMO or NCCN guidelines. If there is indeed a shift to Pola-R-CHP in 1L, this change in treatment paradigm could be used by the applicant to additionally justify the MTA, as for patients pre-treated with Pola in the first line, there might be less willingness in the real-life setting to retreat them with Pola+BR in subsequent lines.

Despite significant therapeutic progress with the use of immunochemotherapy as first-line treatment for DLBCL, many patients will eventually relapse. For patients who are not cured with first-line (1L) therapy, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) offers a second chance for cure (Philip et al. 1995; NCCN 2021; Tilly et al. 2015). However, this is only available 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 (Seyfarth et al. 2006; Gisselbrecht et al. 2010). Patients with primary refractory disease or who relapse after transplant fare particularly poorly (Rochewski et al. 2022).

National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2021) and European Society for Medical Oncology (ESMO) guidelines (Tilly et al. 2015) suggest that patients who relapse after second-line therapy are unlikely to respond to subsequent therapy and therefore generally are not eligible for ASCT. The outcome in patients not eligible for ASCT is dismal with generally no chance of prolonged periods of disease control (Thieblemont and Coiffier, 2007). Poor outcomes have been reported for patients with R/R DLBCL who respond to salvage therapy, but are ineligible for transplant based on one or more factors, such as age > 65 years, inadequate response or early relapse after salvage therapy, relapse after second or greater line of therapy, failure to mobilize stem cells for ASCT, or presence of comorbidities or unresolved toxicities. In these patients, overall survival (OS) rates were 4-13 months (Colosia et al. 2014; Feugier et al. 2005; Crump et al. 2004; Sehn et al. 2020).

Published analyses of large-scale outcome data from patients with refractory DLBCL are limited. Refractory patients receiving second- or third-line with chemotherapy obtain an objective response rate of around 20-30% with short progression-free survival (PFS) (Gisselbrecht et al. 2018; Crump et al. 2017; Maurer et al. 2015; Telio et al. 2012).

Taken together, there remains an unmet medical need for patients with R/R DLBCL and the availability of new treatment options that can extend the duration of remission and overcome resistance to existing therapies, while providing acceptable safety and tolerability.

2.1.5. Management

Patients with R/R DLBCL who are not candidates for stem cell transplant, or who choose not to have a stem cell transplant, may be treated with chemotherapies such as bendamustine or gemcitabine. See ESMO recommendation (Table 1/ESMO GL, below).

However, none of these agents or regimens are specifically indicated for patients with DLBCL. In a large, international, retrospective study evaluating the outcomes in patients with refractory DLBCL (SCHOLAR-1), an overall response rate (ORR) of 26%, a CR rate of 7%, and a median OS of 6.3 months with existing therapies was reported among patients who were resistant to chemotherapy or who had a relapse within 12 months after ASCT (Crump et al. 2017).

Platinum containing regimens such as R-ICE, R-DHAP, and R-GDP were evaluated in clinical trials focused on transplant-eligible patients as salvage regimens (Gisselbrecht et al. 2010; Crump et al. 2014). These regimens may be considered in transplant-ineligible patients in clinical practice as the studies were designed to evaluate the salvage regimens followed by high-dose chemotherapy (HDT)-ASCT; however, these regimens may not be generalizable for most transplant-ineligible patients, as the reasons for ineligibility are typically advanced age, comorbidities, or frailty.

Gemcitabine/platinum-based therapies are also an option for patients with R/R DLBCL (Mounier et al 2013, Cazelles et al 2021).

Bendamustine is widely used in combination with rituximab (BR) in EU clinical practice for the treatment of patients with R/R DLBCL.

Three CAR-Ts (Yescarta, Kymriah and Breyanzi) are approved in the EU for patients with R/R DLBCL who have received two or more lines of systemic therapy (Kochenderfer et al. 2015, Pegram et al. 2015). However, despite the promising CAR-T data, ensuring the consistency, quality, and dose of autologous cell-based therapies remain challenging, the treatment is also restricted to specialized centers, as well as there may be logistical issues, making it difficult to treat patients who require rapid disease control (Thieblemont et al. 2019, Nastoupil et al. 2018).

Another approved option is Pixantrone (Pixuvri) as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive NHL.

Recently Polivy (polatuzumab vedotin), a CD79b-directed antibody-drug conjugate received conditional approval in the EU, in combination with bendamustine and rituximab for the treatment of adult patients with R/R DLBCL who are not candidates for hematopoietic stem cell transplant. Polivy is now fully approved as the conditions for the CMA have been fulfilled.

Minjuvi (tafasitamab) received a conditional approval in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with R/R DLBCL who are not eligible for ASCT.

Achieving a response to therapy (CR rate) remains highly prognostic for the overall outcome (PFS and OS) of patients with R/R DLBCL (Lee et al, 2011). Available therapies have limitations and generally, OS is short. Taken together, this highlights the unmet medical need and the need to improve further treatment outcomes in these patients to extend the duration of remission and overcome resistance to existing therapies, while providing acceptable safety and tolerability.

2.2. About the product

Glofitamab (also known as RO7082859, RG6026, CD20 CD3, CD20 CD3 TCB, CD20 TCB, or CD20-TCB) is a full-length, fully humanized, immunoglobulin G1 (IgG1), T-cell-engaging bispecific antibody (TCB). As a TCB targeting CD20-expressing B cells, glofitamab binds to CD20 expressed on target B cells and

CD3 epsilon chain (CD3ε) present on effector T cells. By simultaneously binding to human CD20-expressing tumor cells and to the CD3ε of the T-cell receptor (TCR) complex on T cells, it induces tumor cell lysis, in addition to T-cell activation, proliferation and cytokine release. Nonclinical studies conducted with glofitamab have demonstrated that it is a potent molecule with proven in vitro and in vivo activity to completely eliminate B-cells from the peripheral blood and secondary lymphoid organs, and to induce regression of aggressive lymphoma tumors.

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on considerations of the draw backs of a SAT and the availability of several other treatment options with comparable response rates, however, it was acknowledged that Glofitamab has a novel MoA and addresses a high unmet need in a population of RR DLBCL with varying comorbidities; moreover the initial results from a Phase I/II single arm trial (SAT) are encouraging from a clinical point of view.

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data. To confirm the clinical benefit and convert the CMA to a standard marketing authorisation (MA), the applicant proposes to submit Study GO41944, a Phase III open-label, multicenter, randomized controlled trial in patients with R/R DLBCL. Approximately 270 eligible patients will be randomized in a 2:1 ratio to receive either Glofitamab-Gemcitabine-Oxaliplatin (Glofit-GemOx) or Rituximab-Gemcitabine-Oxaliplatin (R-GemOx). The primary endpoint is OS. The secondary endpoints in this study are PFS, CR rate, ORR, DOR, DOCR, time to deterioration in physical functioning and/or fatigue, and time to deterioration in lymphoma-specific symptoms. Prior CHMP scientific advice (EMEA/H/SA/4023/2/2019/III), considered that a randomized controlled trial in an earlier treatment line may be considered an appropriate specific obligation
- Unmet medical needs will be addressed, as Glofitamab is a novel bispecific antibody with a new mechanism of action for R/R DLBCL patients, redirecting T-cells against the cancer cells. Glofitamab monotherapy met the primary endpoint of CRR by IRC assessment in NP30179 Cohort D_3 in a high unmet need population; a population of heavily pre-treated high-risk patients with R/R DLBCL who have received at least two prior systemic therapies and are refractory to multiple classes of prior therapy (including refractory to CAR-T). The CRR and durability were clinically meaningful compared to available therapies in the enrolled populations, and there was a favorable and well tolerated safety profile, supporting a positive benefit risk profile for glofitamab monotherapy in this population. In addition to its positive benefit-risk, glofitamab monotherapy is a readily available ('off-the-shelf') chemotherapy-free regimen with a fixed duration of treatment length to treat R/R DLBCL patients with ≥2 prior therapies.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  Based on the aggressiveness of, and poor prognosis associated with, R/R DLBCL as well as the fact that the risk-benefit balance of Columvi is positive, the benefits to public health of immediate availability outweigh the risks.

2.4. Quality aspects

2.4.1. Introduction

Glofitamab is a novel T cell bispecific humanised monoclonal antibody that binds to human CD20 on tumor cells and to the human CD3 epsilon subunit (CD3ε) of the T-cell receptor complex on T cells.

Glofitamab is produced in CHO cells based on a human IgG1 framework. Two Fab domains bind to CD20 and one Fab domain binds to CD3ε. The antibody consists of two different heavy chains and two different light chains. The Fc region of glofitamab bears a proprietary modification, which abrogates its binding to Fc gamma receptors (FcγR) and prevents FcγR-mediated co-activation of innate immune effector cells including natural killer cells, monocytes/macrophages, and neutrophils without changes in functional binding to FcRn (neonatal Fc receptor).

Columvi finished product is provided as a sterile liquid concentrate for solution for intravenous infusion. The finished product is composed of 1 mg/mL glofitamab in L-histidine/L-histidine hydrochloride buffer, D-sucrose, L-methionine, polysorbate 20, pH 5.5.

The finished product is available in two strengths provided in two vial configurations: 2.5 mg/2.5mLfilled in a 6 mL single-use glass vial and 10 mg/10mL filled in a 15 mL single-use glass vial.

2.4.2. Active substance

2.4.2.1. General Information

Glofitamab (INN) is a [2+1] or 2:1 bispecific humanised monoclonal antibody produced in CHO cells based on a human IgG1 framework. Two Fab domains bind to CD20 and contain heavy chain V_H1 and light chain $V_L$kappa2 subgroup sequences. One Fab domain binds to CD3ε and contains heavy chain V_H3 and light chain $V_L$lambda7 subgroup sequences. Glofitamab consists of two different heavy chains and two different light chains, composed of LC1, 2 times LC2, HC1, and HC2.

Point mutations in the CH3 domain ("Knobs into holes") promote the assembly of two different heavy chains. Exchange of the V_H and V_L domains in the CD3 binding Fab (CrossMab approach) and point mutations in the C_H and C_L domains ("charged variants") in the CD20 binding Fabs promote the correct assembly of the two different light chains. The "Knobs into holes" mutations consist of amino acid exchanges Y351C, T368S, L370A, and Y409V in the heavy chain HC1 and of amino acid exchanges S581C and T593W in the heavy chain HC2. The "charged variants" mutations consist of amino acid exchanges E128R and Q129K in the light chain LC2 and amino acid exchanges K149E and K215E in the heavy chains HC1 and HC2. The Fc region bears a proprietary modification ("PG LALA" mutation), which abrogates its binding to Fc gamma receptors (FcγR) and to the first protein component (C1q) of the complement cascade. Thereby, FcγR-mediated effector functions, including co-activation of innate immune effector cells like natural killer (NK) cells, monocytes/macrophages, and neutrophils are prevented, without changes in functional binding to neonatal Fc receptor (FcRn). The "PG LALA" mutations consist of amino acid exchanges P331G, L236A, and L237A in the heavy chain HC1 and amino acid exchanges P556G, L461A, and L462A in the heavy chain HC2.

The molecular mass of intact glofitamab is approximately 194 kDa.

2.4.2.2. Manufacture, process controls and characterisation

Manufacturing process and process controls

The glofitamab active substance is manufactured at Roche Diagnostics GmbH, Nonnenwald 2, 82377, Penzberg, Germany. Sufficient proof of GMP compliance has been provided for all sites involved in the active substance manufacturing and/or control.

Glofitamab is manufactured using an upstream process resembling a standard process for monoclonal antibody manufacturing based on fed-batch culturing of cell lines. The production bioreactor content is harvested by centrifugation and filtration to remove cells and cell debris prior to further purification.

Glofitamab is purified and final conditioned using a combination of chromatography and filtration steps and additional steps for removal and inactivation of potential viral contaminants prior to filling into the container closure system.

Control of materials

Apart from the production cells, no raw material of animal or human origin is used for the manufacture of glofitamab active substance.

Preparation of master cell bank (MCB) and WCB is described in sufficient detail.

Overall, the generation and characterisation of the MCB, WCB and cells at an *in vitro* age comply with the requirements set in the ICH Q5A, Q5B and Q5D guidelines.

Process characterisation and validation

The process was developed using a quality by design strategy combining science- and risk-based approaches. This includes glofitamab-specific studies as well as prior knowledge gained from similar molecules and processes. Process validation studies were conducted both at the commercial manufacturing site and scale and in qualified scale-down models (SDMs).

The glofitamab active substance manufacturing process has been validated in accordance with relevant guidelines and the control strategy is acceptable.

Manufacturing process performance qualification (PPQ)

Critical process parameters (CPPs) and non-CPPs were monitored in the PPQ batches to demonstrate that the active substance manufacturing process could be executed within the established process parameter acceptable ranges. Critical quality attributes (CQAs), IPCs and key performance indicators (KPIs) were also evaluated.

Overall, the presented PPQ data demonstrate that the manufacturing process provides a product that consistently meets its predefined quality attributes at the commercial manufacturing site and scale and that the process performs as designed. The process is therefore considered as validated at the commercial manufacturing site and scale.

Process parameter ranges and CPPs

A risk ranking and filtering (RRF) assessment was conducted for each unit operation to assess the criticality of all process parameters based on relevant prior knowledge and product-specific development data. A process parameter was identified as critical if it had an impact on any CQA or KPI. Acceptable ranges for CPPs were then established based on manufacturing-scale data or existing process validation data. Alternatively, a process parameter would be further investigated in a process validation study to assess its criticality and to validate its acceptable range. If no impact on any CQA or KPI has been observed or is expected, this process parameter was directly classified as a non-CPP and an acceptable range was established based on the RRF or product-specific development data.

Process characterisation studies were multifactor studies planned and evaluated using design of experiment concepts (DOE) in qualified SDMs. The identified CPPs in the different process steps are considered acceptable.

Scale-down models

The scale down models (SDMs) used in validation of the active substance manufacturing process were designed to deliver performance that is representative of the manufacturing-scale process.

Process hold times

Acceptable ranges for in-process hold times were determined using both microbial and biochemical stability studies performed at manufacturing scale with PPQ batches. For the biochemical stability studies, the impact of the proposed hold times was evaluated on selected CQAs.

Process impact assessment

Process impact (PI) assessments have been performed to assess the risk of the manufacturing process on CQAs. PI assessments are based on data from small-scale studies to support process performance acceptable ranges and criticality, biochemical in-process pool hold studies, and process linkage studies, as well as data from manufacturing-scale batches. The level of each CQA at different process steps was compared to an established limit The majority of the CQAs have been assessed to have a low residual risk, meaning that they are well controlled during the manufacturing process and/or effectively removed during the manufacturing process.The data presented in the PI assessment support the conclusion that the manufacturing process produces active substance of consistent quality and as such the PI assessment is seen as support to the comparability study.

Sufficient information is provided on the potential residual levels of raw materials, potential leachables from product-contacting materials, as well as reuse, regeneration and sanitisation procedures of resins and membranes.

Manufacturing process development

Developmental history

different versions of the active substance manufacturing process were developed.

A comparability exercise between the process versions was performed to assess the impact of the manufacturing process changes on product quality.

Overall, the results of the comparability exercise demonstrated that the manufacturing process changes did not have an adverse impact on the quality, safety, or efficacy of glofitamab.

Characterisation

Overall, the structural, physiochemical and biological characterisation of glofitamab active substance is considered comprehensive and sufficient.

The structural confirmation and characterisation of the physicochemical properties of glofitamab have been performed using the reference standard. The characterisation studies were performed using the proposed commercial release analytical methods and extended characterisation methods to assess the primary, secondary and higher order structure, as well as post-translational modifications. Methods to assess the biological properties include the proposed method used for commercial release as well as extended characterisation methods.

Impurities

Product-related variants have been adequately characterised and assessed. The removal of process-related impurities has been sufficiently assessed.

2.4.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The commercial release and shelf life specification for glofitamab active substance were provided.

The release specification includes general tests appearance, test for identity, purity and impurity tests for product-related impurities, test for excipient, test for protein content, test for potency, as well as tests for safety.

Justification for specifications and acceptance criteria at release and shelf life is provided and discussed covering finished product specification. Overall, the parameters included in the active substance specification are found adequate to control the quality of glofitamab active substance at release and during shelf life.

Analytical procedures

The analytical procedures used for release of glofitamab active substance are a combination of compendial and non-compendial methods.

The panel of methods used to assure the quality of the active substance is in accordance with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008. The analytical procedures are described in sufficient details. Information on reference standard is included where relevant. The methods are considered suitable for their intended use.

The compendial analytical procedures Bioburden and Bacterial endotoxins are performed in accordance with the methods described in the relevant pharmacopoeia and were verified for their suitability.

The non-compendial analytical procedures are described in sufficient details. A summary of method validation has been provided and demonstrates that the methods were adequately validated for their suitability for intended use according to ICH Q2 guideline.

Batch analysis

During the pharmaceutical development of glofitamab, three different processes were used for manufacture of nonclinical and clinical active substance material.

Batch analyses data have been provided for all active substance batches produced by the three different processes. All batch data complied with the specifications valid at the time of testing. Overall, it is found that the batch data confirm batch-to-batch consistency and process comparability.

Reference standards

See finished product (the same reference standard is used for finished product and active substance testing).

Container closure

Glofitamab active substance is filled and stored. Specification of the drug substance storage container from the vendor is provided and includes the following requirements; USP <661> Plastic packaging systems and their materials of construction, USP <87> Biological reactivity tests, in vitro, USP <88> Biological reactivity tests, in vivo and Ph. Eur. 3.1.7 Poly(ethylene-vinyl acetate) for containers and tubing for total parenteral nutrition preparations.

The approach described for assessment of extractables and leachables from the active substance container closure system is found adequate. The results support the safety of glofitamab drug substance stored frozen in the container closure system.

2.4.2.4. Stability

The stability studies are designed in accordance with the ICH Q5C guideline. A shelf life of 48 months is proposed at a storage condition.

The post-approval stability protocol and stability commitment are acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and Pharmaceutical Development

Description of the product

Columvi concentrate for solution for infusion is formulated as a sterile, preservative-free, concentrate for solution for infusion at a concentration of 1 mg/mL. The finished product is presented in two configurations; 2.5 mg/2.5 ml and 10 mg/10 ml. The concentrate is a colourless aqueous solution of glofitamab, presented in single-dose Type I glass vials.

Glofitamab active substance solution is diluted to 1 mg/mL with formulation buffer to produce finished product.

Pharmaceutical development

The finished product formulation is identical to the active substance formulation with the exception of the concentration of glofitamab. Excipients used in the formulation are L-histidine, L-histidine hydrochloride monohydrate, L-methionine, D-sucrose, and polysorbate 20. No novel excipients or excipients of human or animal origin have been identified. Compatibility of active substance with the excipients is considered demonstrated by stability studies.

The formulation remained unchanged with respect to excipient composition and concentration across all development phases including the commercial formulation.

Columvi finished product manufacturing process consists of thawing of the active substance, optional pooling and mixing, buffer preparation, dilution and mixing, bioburden reduction filtration, sterile filtration, aseptic filling of vials and stoppering, capping & crimping and 100% final visual inspection before storage/transportation and secondary packaging.

Three different finished product manufacturing processes comprising three different finished product formulations were used in clinical studies during development.

The comparability studies demonstrate that finished products are comparable.

The proposed commercial finished product container closure system consists of a 6 mL Type I glass vial, stoppered with rubber stopper for the 2.5 mg/vial finished product, and a 15 mL Type I glass vial stoppered with rubber stopper for the 10 mg/vial finished product.

The results of the extractable studies performed with commercial stoppers and vials and the results of the leachable studies performed with the finished product demonstrate that the primary packaging components are suitable and safe for use for the finished product. Glofitamab is compatible with the primary packaging components in the container closure system, as demonstrated by long-term

stability data for the finished product incl. testing of container closure integrity and sterility. The leachables studies are ongoing and will be continued until end of shelf life of the finished product to confirm the suitability of the commercial primary packaging configuration for the finished product.

Columvi finished product does not contain preservatives or antioxidants. The finished product is sterile filtered using an aseptic filling process.

The compatibility of dose solution with IV bags and infusion lines has been demonstrated. Stability and compatibility studies were conducted to confirm the physicochemical stability of the solutions for infusion under recommended in-use conditions.

The in-use studies demonstrated that glofitamab is physicochemically stable after dilution into 0.9% or 0.45% sodium chloride solution and after holding for 72 hours at 2°C-8°C and for an additional 24 hours at 30°C at ambient room light conditions, followed by a maximum infusion time of 8 hours.

The following is applied to glofitamab: From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C-8°C, unless preparation of the solution for infusion has taken place in controlled and validated aseptic conditions.

2.4.3.2. Manufacture of the product and process controls

Manufacturing process and process controls

Columvi finished product is manufactured (including filling/primary packaging) by Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA. This site is also performing in-process control testing and quality control testing (bacterial endotoxins only). No concerns regarding GMP of finished product manufacturing sites have been identified during review of the quality documentation.

The finished product manufacturing process is standard and consists of thawing of the active substance, pooling and mixing, bioburden reduction filtration, sterile filtration and aseptic vial filling, stoppering and capping, vial inspection and secondary packaging and storage. A detailed description of the manufacturing process is presented in the dossier. For several manufacturing process steps the product may be stored before the next step. Storage temperature and maximum storage time for each step is presented. No refreezing is allowed.

Process parameters for finished product manufacturing were evaluated for their criticality with respect to predetermined quality attributes. The evaluated parameters cover the manufacturing process from thawed active substance to final vial inspection.

Process validation

The data from the PPQ batches demonstrate that the process runs consistently within the defined process parameter acceptable ranges and produces material that meets the commercial release acceptance criteria across the range of batch sizes.

Media fill runs and environmental monitoring are described and found acceptable.

Shipping qualification studies are presented for several passive and active thermal shipping systems. The results indicate that the finished product is adequately protected during shipping and that mechanical stress conditions have no impact on product quality.

2.4.3.3. Product specification, analytical procedures, batch analysis

Specifications

The proposed finished product release and shelf life specifications for Columvi have been provided for both vial configurations (2.5 mg/2.5ml and 10 mg/10 ml).

The release specification includes general tests: appearance, test for identity, tests for product-related impurities, test for excipient, test for protein content, test for potency, as well as tests for safety. Overall, the parameters included in the finished product specification are found adequate to control the quality of the Columvi finished product.

The justification of the acceptance criteria is based on a combination of different information such as clinical experience, product-specific knowledge, applicant's experience with related molecules, formulation development studies, storage and process effects, regulatory guidelines and manufacturing experience. Overall, the approach used to set the acceptance criteria for the finished product is accepted.

The acceptance criteria set for the qualitative and quantitative attributes have been sufficiently justified and can be accepted. A risk evaluation concerning the presence of nitrosamine impurities was provided, which concluded that no risk of the presence of nitrosamines was identified for the active substance, or finished product.

Analytical procedures

The analytical procedures used for release of the finished product are a combination of compendial and non-compendial methods. The panel of methods used to assure the quality of the finished product is in accordance with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008. The analytical procedures are described in sufficient details. Information on reference standard is included where relevant. The methods are considered suitable for their intended use.

The compendial analytical procedures are performed in accordance with the methods described in the relevant pharmacopoeia.

The non-compendial methods were adequately validated for their suitability for intended use according to ICH Q2 guideline.

Characterisation of impurities

The finished product manufacturing process consists of thawing the active substance, pooling (optional), dilution, filtration, and aseptic filling and capping, with no change to the formulation compared to the active substance. No new impurities are generated during the finished product manufacturing process and all impurities observed in the finished product were characterised for the active substance. A risk assessment for elemental impurities was conducted in accordance with ICH Q3D guideline. Test results for the 10 elements recommended for consideration for parenteral products showed that there are no concerns related to elemental impurities in the finished product produced at the site of commercial manufacture.

Batch analysis

Batch analysis results for finished product batches are presented in the dossier.

All results were compliant with the acceptance criteria valid at the time of release and were consistent across the batches. In addition, the finished product PPQ batches met the acceptance criteria of the

proposed commercial specification acceptance criteria. The batch release data demonstrate consistent quality of the finished product throughout development and for commercial purpose.

Reference standards

A two-tiered reference material system has been established. Three different reference standards (RS) – initial, primary and secondary – have been used throughout the development of Columvi. Information on the batches (number, source, date of manufacture) and the use are included. Qualification of the RS included active substance release methods as well as additional characterisation.

A protocol for preparation of future secondary reference standards and the qualification hereof is described.

2.4.3.4. Stability of the product

The proposed shelf life for both finished product configurations is: 24 months at 2°C-8°C, protected from light.

6 months accelerated data are presented for all primary batches.

Primary stability studies are performed using the same analytical procedures as for finished product release testing. Additionally, container closure integrity testing is included for finished product stability studies.

Generally, no significant trends are observed at 5±3 °C.

The applicant commits to place one batch in long-term stability per year with yearly time points and testing according to the stability specification defined in section 3.2.P.5.1.

An ICH Q1B photostability study has been conducted. Based on this, the applicant concluded that the finished product is photosensitive and should be stored in its outer carton to protect it from light, which is considered satisfactory.

A temperature excursion study has been. The batch was exposed sequentially to varying temperature conditions before being placed on long-term stability (-20°C to + 30°C). The data confirm stability of finished product under conditions that might occur during manufacturing, shipping, and handling.

Glofitamab is intended for IV administration after dilution in 0.9% or 0.45% sodium chloride via IV bag infusion. Stability and compatibility studies were conducted to confirm the physicochemical stability of the solutions for infusion under recommended in-use conditions. The studies demonstrated that the glofitamab solutions for infusion are stable during typical preparation and administration procedures and may be held for 72 hours at 2°C-8°C and an additional 24 hours at 30°C at ambient room light conditions followed by a maximum infusion time of 8 hours.

The finished product does not contain any antimicrobial preservative; therefore, sterility of the solution must be ensured during in-use handling by maintaining appropriate aseptic conditions. Standard SmPC wording is applied.

Based on the data provided, the shelf life and storage conditions for both finished product configurations are: 2 years at 2°C-8°C, protected from light are acceptable. The in-use shelf life and storage conditions are: 72 hours at 2°C-8°C and 24 hours at 30°C, with maximum infusion time of 8 hours.

2.4.3.5. Post approval change management protocol(s)

Not applicable.

2.4.3.6. Adventitious agents

Apart from the production cell line no material from animal/human origin has been used in the manufacture of glofitamab active substance and finished product.

Cell banks have been tested for nonviral and viral adventitious agents according to ICH Q5A guideline. The cell banks are therefore considered safe for use in the manufacture of glofitamab with regard to the risk of viral and non-viral adventitious agents and endogenous retroviruses.

Testing for nonviral and viral adventitious agents is conducted in the routine manufacture of glofitamab active substance at different stages of production. The testing conducted during manufacture and at release is considered sufficient and in line with current requirements.

The viral clearance capacity of the glofitamab active substance purification process was evaluated by conducting viral clearance studies, using qualified SDMs in accordance with ICH Q5A guideline.

Overall, the risk of contamination with adventitious agents, including TSE, mycoplasma, bacteria, fungi, and viruses, is considered well contained based on selection of safe raw materials, demonstration of absence of adventitious (and endogenous) agents in cell banks, testing at relevant stages of the process, and finally the substantial virus clearance capacity, demonstrated for the glofitamab purification process. In conclusion, Columvi is considered safe for commercial purposes with regard to risk of contamination with adventitious non-viral or viral agents or with endogenous viruses.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The dossier presented in support of the Marketing Authorisation Application for Columvi is of good quality.

The control strategy for the glofitamab active substance manufacturing process was established in line with ICH 11 guidance. Overall, the manufacturing process is considered adequately described and the applied process parameters and in-process controls, as well as their ranges, and the control of starting materials are considered adequate to control the process and ensure formation of active substance of adequate and consistent quality. Overall, the approach taken to validate glofitamab manufacturing process is considered adequate. The process is demonstrated to perform consistently and glofitamab active substance meets all the biochemical, functional and microbiological acceptance criteria. The process development, including development of the control strategy, is considered adequately described and justified. Comparability studies confirm product comparability throughout development.

The selection of the attributes included in the active substance specification is based on the control strategy. Overall, the approach for selecting attributes and setting the acceptance criteria for both active substance and finished product specifications is endorsed and found in line with ICH Q6B.

The finished product manufacturing process is standard and consists of thawing of active substance, optional pooling and mixing, buffer preparation, dilution and mixing, bioburden reduction filtration, sterile filtration, aseptic filling of vials and stoppering, capping & crimping and 100% final visual inspection before storage/transportation and secondary packaging. The description is comprehensive and acceptable. The submitted validation data demonstrate that the process is generally well controlled.

A finished product shelf life of 24 months at 2-8°C is proposed. The provided finished product stability data confirm stability for up to 24 months.

The finished product is available in two configurations; 2.5 mg/2.5 ml and 10 mg/10 ml, presented in single-dose Type I glass vials. The compatibility of dose solution with intravenous bags and infusion lines has been demonstrated.

2.4.5. Conclusions on chemical, pharmaceutical and biological aspects

The overall quality of Columvi is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the marketing authorisation application for Columvi is considered approvable from the quality point of view.

2.5. Non-clinical aspects

2.5.1. Introduction

Glofitamab is designed to bind to two different antigens, namely CD20 expressed on target B cells and CD3 expressed on effector T cells. Glofitamab's activity and specificity was characterized in a wide range of nonclinical models:

- in vitro models: consisted of co-cultures of DLBCL tumor target cell lines expressing various levels of CD20 antigen and healthy donor peripheral blood mononuclear cells (PBMCs)
- ex vivo models: consisted of primary tumor samples derived from freshly isolated or previously frozen bone marrow samples from patients with non-Hodgkin's lymphoma (NHL)
- in vivo nonclinical pharmacology studies: consisted of the use of both non-tumor bearing human hematopoietic stem cell (HSC)-engrafted NOD/Shi scid/IL-2Rγ^{null} (HSC-NOG) mice [Hayakawa et al. 2009], and tumor-bearing HSC-NOG and HSC-engrafted NOD.Cg-Prkdc^{scid}Il2rg^{tm1Wjl}/SzJ [HSC-NSG] mice. The two DLBCL tumor cell line models utilized for in vivo studies were WSU-DLCL2 and OCI-Ly18.

The choice of the cynomolgus monkey as the pharmacological and toxicological species is considered justified as comparable cross-reactivity is observed between human and monkey B cells while no cross-reactivity is observed for rodent, dog or minipig CD20 or CD3ε.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro pharmacology

In vitro, glofitamab binds in a bivalent mode to both human and cynomolgus monkey CD20 on primary B cells with comparable EC_{50} values. Glofitamab does not cross-react to conventional toxicology species like rodent, dog, rabbit or minipig CD20. Glofitamab also binds to T cells monovalently, targeting CD3ε in the TCR complex, cross-reacting with both human and cynomolgus monkey CD3ε, as the binding epitope is conserved between human and cynomolgus monkey, but again not with CD3ε of

conventional toxicology species. It was demonstrated in vitro that only simultaneous binding of glofitamab to CD20 on tumor B cells and to CD3ε on T cells results in CD3ε cross-linking leading to T-cell activation and proliferation, and subsequent tumor cell lysis.

Table 1 EC50 Values of Tumor Cell Lysis Mediated by Glofitamab on a Panel of DLBCL Tumor Cell Lines Expressing Various Levels of CD20 Antigen

Cell line	Tumor Histology	CD20 (Antibody Binding Capacity/Cell)	EC_{50} of TCL (pM)	N (TCL, EC_{50})
SUDHL-8	DLBCL (GCB)	533	0.2985	9
Toledo	DLBCL (GCB)	96,833	0.5518	10
SUDHL-2	DLBCL (ABC)	162,455	0.9932	3
RC K8	DLBCL (GCB)	446,426	1.209	2
TMD8	DLBCL (ABC)	216,261	1.851	2
SUDHL-5	DLBCL (GCB)	134,586	1.873	4
U2932	DLBCL (ABC)	165,634	10.32	12
WSU-DLCL2	DLBCL (GCB)	769,676	59.38	8
Pfeiffer	DLBCL (GCB)	86,102	n.d.	4
SUDHL-4	DLBCL (GCB)	378,858	n.d.	2
SUDHL-6	DLBCL (GCB)	309,513	n.d.	4
ULA	DLBCL (GCB)	629,342	n.d.	2

ABC=activated B-cell; DLBCL=diffuse large B-cell lymphoma; EC_{50}=50% effective concentration (i.e., concentration resulting in one-half of the maximum effect); GCB=germinal center B cell; N=number of independent assays; n.d.=not determinable; TCL=tumor cell lysis.

Note: Antibody binding capacity values/cell are shown as averages from independent assays, and are dependent on culture conditions.

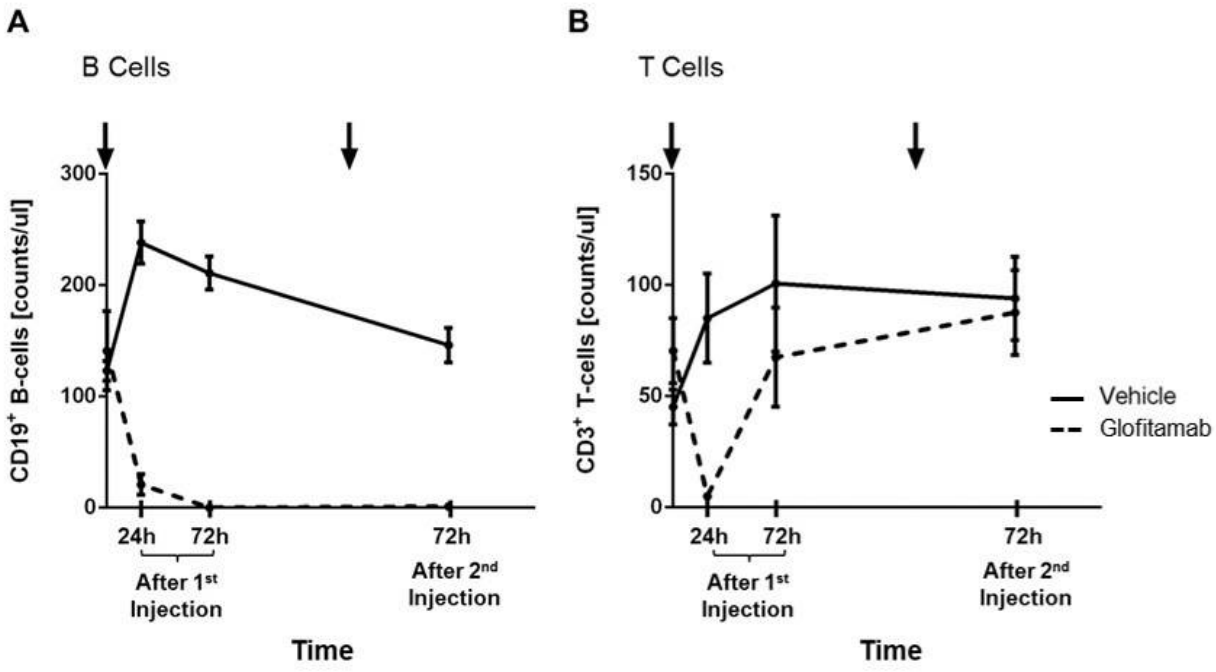
Glofitamab-induced tumor cell lysis in in vitro assays was shown to be dose-dependent in a broad panel of DLBCL tumor cell lines, and not to correlate with CD20 expression levels, indicating that glofitamab is highly efficacious in low CD20-expressing tumor cell lines. Glofitamab-mediated tumor cell lysis was shown to occur even at low CD20 receptor occupancy, as <0.5% of CD20 receptor occupancy resulted in the lysis of 50% of tumor cells. In vitro, glofitamab was shown to deplete B cells in human and cynomolgus monkey whole blood leading to mean EC50 values of 50.0 pM and 806 pM for human and cynomolgus monkey, respectively. When investigated ex vivo in primary tumor samples (i.e. whole bone marrow aspirates), which retains the native tumor environment, from patients with different types of non-Hodgkin's lymphoma (NHL, e.g. mantle cell lymphoma (MCL), splenic marginal zone lymphoma (SMZL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL)), glofitamab displayed strong anti-tumor activity and led to high overall killing of target cells, paralleled by T-cell activation and expansion in all samples. The activity of glofitamab was also compared to other CD20- and CD19-targeting TCB antibodies. Glofitamab's "2:1" bivalent binding mode was demonstrated as superior with an average of 40-fold (range: 12-95-fold) stronger potency compared to other "1:1" monovalently binding TCB antibodies with the same anti-CD20 and anti-CD3 binders, supporting the relevance of CD20 avidity/bivalency and the close spatial proximity via a flexible linker of the CD3 and CD20 binders (head-to-tail orientation) in glofitamab. Also, against a CD20-targeting "1:1 IgG-like" format TCB antibody with alternative anti-CD20, anti-CD3, and Fc sequences as well as other CD19 and CD20 targeted TCBs (e.g. blinatumomab), glofitamab demonstrated more potent activity.

The activity of glofitamab was investigated in vitro in the presence of obinutuzumab, which can be co-administered to potentially reduce the cytokine release in connection with treatment with glofitamab as well as the development of anti-drug antibodies. Glofitamab and obinutuzumab both bind to the CD20 antigen via the same CD20-binding antibody variable regions, thus competing with each other by bivalent binding to CD20-expressing target cells. At saturating concentrations of obinutuzumab (thus occupying all CD20 receptors) a transient reduction of CD20 occupancy by glofitamab is achieved, which was observed as a ~30-fold reduction in glofitamab potency. Due to the "2:1" TCB molecular format of glofitamab, the molecule has the capacity to displace obinutuzumab from the CD20 antigen and initiate T-cell redirected cytotoxicity, thus adding to the activity of obinutuzumab in vitro. Adding increasing concentrations of glofitamab to saturating concentrations of obinutuzumab (inducing approximately 70% cell lysis in itself) resulted in almost complete elimination of tumor cells. Though glofitamab was able to induce direct cell death in selected cell lines, this occurred at very high doses, which the applicant pointed out is significantly above the concentrations used for T-cell redirected cell cytotoxicity, which is identified as the primary mode of action of glofitamab.

In vivo pharmacology

Glofitamab was investigated in vivo in two different strains of mice, HSC-NSG and HSC-NOG mice. Both mice strains lack functional T and B cells and have defects in NK-cell activity, macrophage function, complement activity, and dendritic cell function, and the immunodeficiency mechanism is very similar. The results between the two strains appeared to be similar. In vivo activity was investigated in both non-tumor bearing HSC-NOG mice and in tumor-bearing HSG-NOG and HSG-NSG mice. In non-tumor bearing mice, it was demonstrated that 500 µg/kg weekly (QW) dosing efficiently depleted circulating B cells within 24 hours of first administration, leaving their numbers undetectable for up to 240 h.

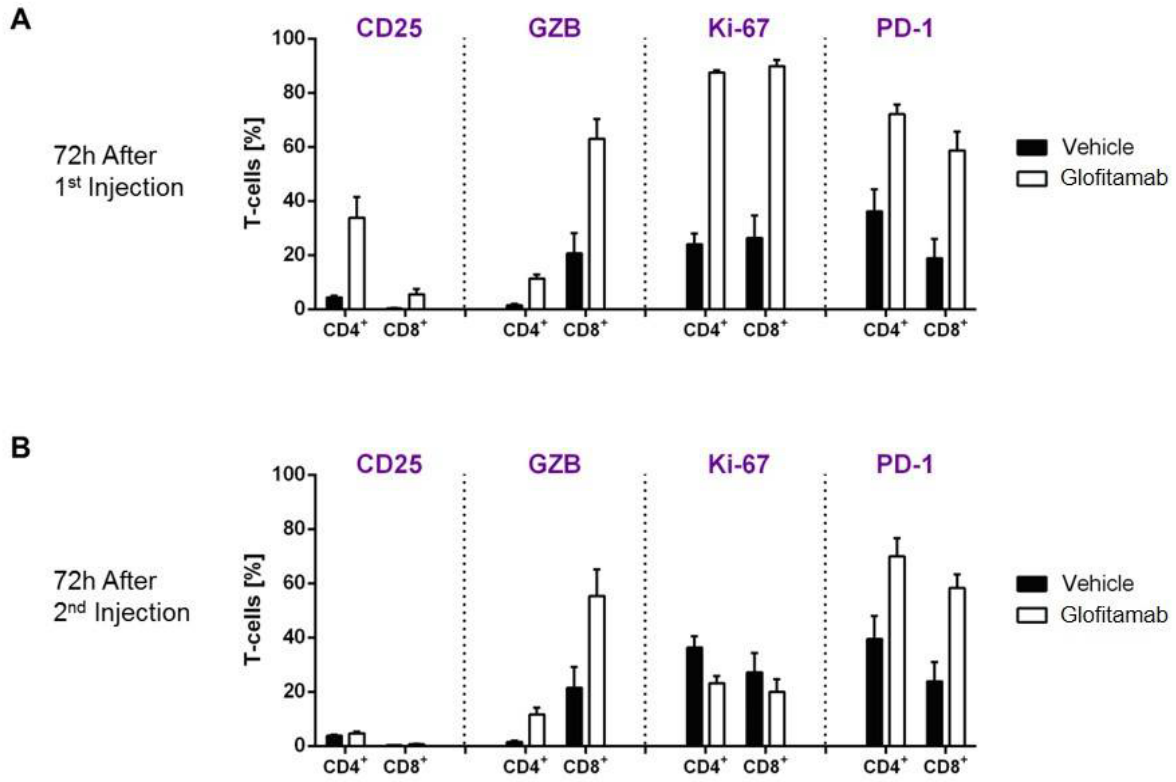
Figure 1 **Kinetics of B-Cell Depletion and T-Cell Trafficking following Glofitamab Administration in Non-Tumor-Bearing HSC-NOG Mice**



HSC-NOG=human hematopoietic stem cell-engrafted NOD/Shi scid/IL-2Rγ^{null} mice; IV=intravenous; QW=weekly.
Notes: Kinetics of CD19^{+} B-cell (A) and CD3^{+} T-cell (B) frequency in peripheral blood of vehicle-(solid line; n=7) and glofitamab-treated (dashed line; n=6) HSC-NOG mice, as assessed by ex vivo flow cytometry. Black arrows indicate vehicle/glofitamab injection (500 µg/kg IV, QW).

Peripheral blood T cells showed a transient decrease 24 hours after the first glofitamab injection, then returned to baseline levels within 72 hours, and remained stable for the rest of the study. This was observed in parallel to transient increases in multiple cytokines and chemokines 24 h after first injection, which subsequently decreased after 72 h and returned to baseline levels 72 hours after the second glofitamab injection. Also, T cell activation was observed 72 h after first injection, of which only 2 of 4 markers returned to baseline 72 h after the second injection.

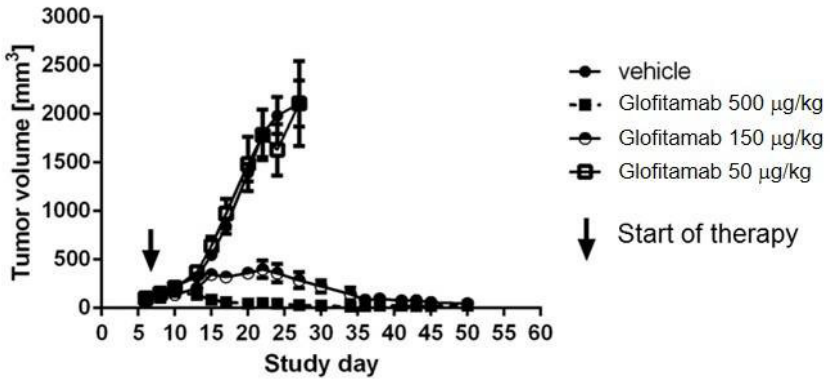
Figure 2 **Glofitamab-Mediated Transient Up-Regulation of Circulating T-Cell Markers in Non-Tumor-Bearing HSC-NOG Mice**



HSC-NOG=human hematopoietic stem cell-engrafted NOD/Shi scid/IL-2Rγnull mice. Notes: Analysis of surface markers expression on peripheral blood T cells 72 h after the 1st (**A**) and 2nd (**B**) treatment with either vehicle (black bars) or glofitamab (white bars) in HSC-NOG mice, as assessed by ex vivo flow cytometry.

Glofitamab-induced B cell depletion was furthermore observed in spleen and lymph node at 72 h after second injection of 500 µg/kg QW dose of glofitamab, however, T-cell counts showed levels comparable to vehicle control. The T cell activation profile was similar in spleen and lymph node as in blood. When given to HSC-NOG tumor bearing mice at three different doses (50, 150 and 500 µg/kg QW), glofitamab induced similar results within the first 24 as observed in non-tumor bearing mice for B- and T-cell depletion. Increases of multiple cytokines and chemokines were observed in the peripheral blood in HSC-NSG tumor-bearing mice 24 h after first dosing. Only the two highest doses (i.e. 150 and 500 µg/kg QW) were able to induce regression of established subcutaneous (SC) tumors in HSG-NOG mice, and not the lowest, though B-cell depletion was already observed at this dose level. Beside reduction in tumor size, histological examinations of tumor tissue following treatment with 500 µg/kg QW glofitamab showed a strong increase in the frequency of intra-tumor T-cell infiltration and an up-regulation of PD-1 receptors on T cells as well as of its ligand, PD-L1. As observed in blood, glofitamab-mediated B-cell depletion was seen in the spleen, as well as in lymph nodes at study termination (72 hours after the second injection) whereas T-cell counts showed levels comparable to vehicle control (Figure 2-6B). The T-cell activation status was similar to that observed in blood, with higher expression of granzyme B and PD-1 in splenic T cells of glofitamab-treated mice as compared to vehicle control.

Figure 3 **Dose-Dependent Anti-Tumor Activity of Glofitamab in Tumor-Bearing HSC-NOG Mice**



HSC-NOG=human hematopoietic stem cell-engrafted NOD/Shi scid/IL-2Rγ^{null} mice; IV=intravenous; QW=weekly.
Notes: Anti-tumor activity of glofitamab at different doses (50, 150, or 500 µg/kg IV QW for 7 cycles) in HSC-NOG mice bearing the human DLBCL tumor cell line model (WSU-DLCL2) injected subcutaneously. Black arrow indicates start of therapy (9≤n≤10).

Role of Obinutuzumab

Treatment with glofitamab is associated with severe safety issues when given alone, due to significant cytokine release as a part of its mode of action. Cytokine release is related to the load of circulating and tissue-resident B cells, as the higher the load, the higher the T-cell engagement, activation, and cytokine release in the peripheral blood. In an attempt to alleviate the extent of cytokine release and associated safety issues, the applicant conducted studies to investigate the effect of obinutuzumab given prior to glofitamab treatment in order to debulk the peripheral and tissue-resident B cells. Obinutuzumab is considered relevant as pretreatment for glofitamab (gpt) as it shares the same CD20-binding antibody variable regions as glofitamab, and leads to an efficient pre-depletion of mainly normal B cells in the peripheral blood and tissues (B-cell de-bulking). Obinutuzumab was chosen over rituximab as gpt, as the applicant claims that obinutuzumab showed superior tissue B-cell depletion compared to e.g. rituximab in cynomolgus monkeys. The applicant has sufficiently shown the superiority of obinutuzumab over rituximab in depleting B cells in lymph nodes, spleen and human whole blood according to Moessner et al 2010, leading to a faster depletion of B cells and greater direct cytotoxicity in CLL cells, as well as a well-tolerated safety profile in patients. The choice to use obinutuzumab over rituximab for B-cell debulking and mitigation of glofitamab-mediated CRS is supported.

When given once 7 days prior to glofitamab treatment (500 µg/kg) to HSC-NOG tumor bearing mice, obinutuzumab strongly reduced the glofitamab-mediated cytokine release and thereby the cytokine-dependent T-cell decrease in peripheral blood. It was also shown that obinutuzumab does not interfere with glofitamab-mediated B-cell depletion and anti-tumor activity. Obinutuzumab in itself mediates anti-tumor effects via B-cell depletion (but no effect on T-cells or upregulation of cytokines) when given by repeated dosing at saturating concentrations, though with slower kinetics than glofitamab. The applicant however argues that obinutuzumab used as gpt with a single dose is not sufficient to induce anti-tumor effect and will not contribute to the anti-tumor effect of repeated dosing of glofitamab. Though not demonstrated in non-clinical studies, this rationale can be accepted and it has also been demonstrated in the clinic that a single dose of obinutuzumab in conjunction with a low non-efficacious dose of glofitamab did not show any relevant anti-tumor activity. Step-up dosing was investigated as an

alternative to gpt. While gpt showed superior effects on minimizing cytokine release, the long-term anti-tumour effect was comparable between the groups receiving gpt and step-up dosing. Dexamethasone was also investigated as pre-medication and led to a reduction in the glofitamab-mediated cytokine release. In the animal model, it was shown that the administration of both dexamethasone and obinutuzumab in connection with a step-up dosing of glofitamab did not affect the anti-tumor effect of glofitamab, confirming the potency of glofitamab treatment and the lack of pharmacodynamic interactions with pre-treatment/pre-medication agents.

2.5.2.2. Secondary pharmacodynamic studies

The Fc region of glofitamab was engineered to abolish interactions with effector function relevant Fc-receptors, due to the "P329G LALA" mutation introduced in the Fc binding region. The lack of binding to the Fcγ receptors was demonstrated in an in vitro study using FcγRI, FcγRIIa, FcγRIIb and FcγRIIIa as well as human C1q. Thus, it has been demonstrated that glofitamab has a low potential for Fcγ receptor cross-linking and C1q complement binding on immune cells leading to induction of nontargeted immune cell activation (e.g. ADCC, ADCP and CDC).

2.5.2.3. Safety pharmacology programme

No stand-alone safety pharmacology studies were conducted with glofitamab. Safety pharmacology end-points were included as part of the 2- and 4-week repeat dose studies with glofitamab in cynomolgus monkeys, where effects related to the cardiovascular system, respiration and CNS were monitored. Glofitamab was associated with sustained, dose-dependent increases in heart rate after the first dosing (30-70 bpm higher than in control animals). Effects were less pronounced after second dosing. Further, administration of glofitamab also resulted in increases in body temperature. These observations are considered related to the pharmacological action of glofitamab and secondary to increases in cytokine levels induced by T-cell activation. No glofitamab-related changes were observed in respiration or CNS related endpoints.

2.5.2.4. Pharmacodynamic drug interactions

An assessment of the potential interactions between glofitamab and obinutuzumab as well as with steroid premedication was part of the primary pharmacology.

2.5.3. Pharmacokinetics

The PK/TK of glofitamab was investigated in C57BL/6 mice, huFcRn transgenic mice, Göttingen minipigs (all species without target binding) and in cynomolgus monkeys (cross-reactive species) in a series of IV and SC single- and repeat dose studies. Cynomolgus monkeys exhibit similar binding to CD3 and CD20 as in humans, and were selected for pivotal repeat-dose toxicology studies. Pre-treatment with obinutuzumab (clinical pre-treatment) was also investigated in this species. Due to a high incidence of ADA in cynomolgus monkeys with associated loss of exposure and loss of pharmacological effect, repeat-dose toxicology studies of more than 4 weeks were not conducted. Waivers for omission of a 13-week study were granted by both FDA (REF ID: 4362929) and EMA (Procedure No.: EMEA/H/SA/4023/1/2018/I and EMEA/H/SA/4023/2/2019/III). Further, PK/PD modelling based on in vivo studies involving tumor growth inhibition in humanized tumour-bearing mice or cytokine release in cynomolgus monkeys was performed, and plasma protein binding and blood/plasma partitioning was investigated in mouse, cynomolgus monkey, and human blood.

Table 2. An overview of pharmacokinetic/toxicokinetic studies conducted with glofitamab

Study type	Test system/Duration of study	Method of administration (test article)/Dose	GLP status
Absorption			
Single-dose PK/TK	C57BL/6J mice 35 days (840 h)	IV (glofitamab) 1 mg/kg	**Non-GLP**
	Göttingen SPF minipigs 35 days (840 h)	IV and SC (glofitamab) 200 µg/kg (IV) µg/animal (SC)	**Non-GLP**
	Cynomolgus monkeys All phase animals: 168 h post dose Recovery animals: 1344 h post dose	IV (glofitamab ± Gpt) Gpt/glofitamab: 0/0, 0/100, Gpt/100, Gpt/300, Gpt/1000 µg/kg (Dosing with glofitamab on Day 5 after Gpt)	**Non-GLP**
Repeat-dose PK/TK*	Cynomolgus monkeys MTD (single dose) + DRF study (QW for 2 weeks)	IV (glofitamab) MTD: 0.3, 1.0, 3.0, 10, 30, 100, 300 µg/kg DRF: 0, 10, 30, 100 µg/kg	**Non-GLP**
	Cynomolgus monkeys QW for 2 weeks + 4 or 12 weeks recovery	IV (glofitamab) Day1/Day 8: 0/0, 10/10, 30/30, 100/100[a], 100/NA[a], 30/100[a] µg/kg	**GLP**
	Cynomolgus monkeys Dosing Day 1/Day2/Day 3 and EOD until Day 27 + 4 weeks recovery	IV and SC (glofitamab) SC/IV: 0/0/0 IV: µg/kg SC: µg/kg SC: µg/kg	**GLP**
Distribution			
Plasma protein binding Blood plasma partitioning	Mouse, cynomolgus monkey and human whole blood	-	

Other pharmacokinetic studies		
PK/PD modelling (TGI)	Software systems: MatLab, R2013b Berkeley Madonna, v8.3.18	-
PK/PD modelling (EIH dose)	Software systems: Matlab, R2013b Berkeley Madonna, v8.3.18	-
Single-dose PK comparability study of the Ph1 and Ph3 material	huFcRn Tg mice 35 days (840 h)	IV (glofitamab Ph1 or Ph3 material) 200 µg/kg

Abbreviations: DRF: dose range finding; EIH=entry into human; EOD: every other day; Gpt=obinutuzumab (Gazyva®, Gazyvaro®, GA101, RO5072759) pretreatment; huFcRn=human neonatal Fc receptor; MTD: maximum tolerable dose; Ph1=Phase 1; Ph3=Phase 3; Tg=transgenic; TGI=tumor growth inhibition; QW: once weekly

*The study with report no. 1063381 comprised both a single-dose study (MTD) and a repeat-dose study (DRF)

[a] Three males dosed on Day 1 with 100 µg/kg were prematurely euthanized (1 Main Study animal, 2 Recovery animals). These animals were replaced, and the replacement animals and all Group 4 females received a Day 1 dose of 30 µg/kg (i.e. first dose reduced to 30 µg/kg during study). All Group 4 animals received 100 µg/kg on Day 8, as toxicity due to the release of cytokines was only expected on Day 1

Method validation

The ligand-binding assays (ELISAs) developed to measure glofitamab and anti-glofitamab antibodies in cynomolgus monkey serum in support of the GLP pivotal toxicology studies have been suitably validated in line with relevant guidance documents (EMEA/CHMP/EWP/192217/2009 Rev 1 Corr 2). Further, the ligand-binding assays used to quantify glofitamab in mouse serum (in support of 2 non-GLP studies) and obinutuzumab in monkey serum (in support of a non-GLP study) were suitably validated. The bioanalytical methods used in remaining PK and non-GLP studies were qualified and considered suitable for their intended use.

Single-dose PK/TK studies

PK parameters of glofitamab in the non-target binding species mice and mini-pigs following IV dosing were within expected range for a human IgG, and displayed similar half-lives (8.5 and 6 days, respectively) and clearance (8 ml/day/kg in both species). Volume of distribution was close to plasma volume in both species, indicating an initial propensity for glofitamab to remain in the vascular compartment.

Following IV single-dosing of glofitamab at doses from 1.0-100 µg/kg (a 0.3 µg/kg dose group was omitted due to negligible exposure, and the highest dose at 300 µg/kg was not tolerated) in male and female cynomolgus monkeys (MTD-study), $AUC_{0\text{-last}}$ increased in a greater than dose-proportional manner across the dose range tested. C_{max} increased in a greater than dose-proportional manner from 1.0-10.0 µg/kg and less than dose-proportional from 10.0 through 100.0 µg/kg. No significant sex differences were noted for the evaluated PK parameters. Glofitamab displayed dose-dependent kinetics with an overall tendency for clearance and volume of distribution to decrease with increasing doses, consistent with TMDD. Even at the HNSTD (100.0 µg/kg), CL values were markedly higher than in the non-responder species mouse and minipig and apparent $t_{1/2}$ values were shorter (CL≈200-900 ml/day/kg; $t_{1/2}$≈3-5 hours). All animals tested positive for ADA at 336 hours (14 days) post-dosing

which did, however, not impact exposure due to the rapid clearance of glofitamab before ADA presence.

In monkeys, pre-treatment with obinutuzumab (Gpt) increased exposure ($AUC_{0\text{-last}}$) of glofitamab approximately 4.5-fold following IV dosing compared to exposure in animals not receiving Gpt. Clearance of glofitamab decreased markedly with Gpt (81.2 vs 384 ml/day/kg without Gpt), and $t_{1/2}$ increased from 7.5 to 67.7 hours, illustrating the effect of initial $CD20^+$ B cell depletion by Gpt and associated decrease in TMDD. However, even after Gpt, the clearance of glofitamab remained high compared to the typical value for mAbs in this species (5-12 ml/day/kg; Deng et al. 2011). The applicant considered plasma protein binding as potential root cause for the short half-life of glofitamab. This hypothesis was addressed in a study that evaluated the partitioning of radiolabelled glofitamab from whole blood into plasma or the cellular fraction. The study showed that partitioning into plasma occurred at a comparable rate in cynomolgus and human plasma; by SE-HPLC of plasma a single radioactive peak was detected, with a retention time similar to that of the radiolabelled glofitamab. Thus, the study did not provide evidence to support plasma protein binding as cause for the increased clearance in cynomolgus monkeys. The applicant adequately justified that binding to CD3 is not assumed to contribute to TMDD due to the stronger binding to CD20 compared to CD3. Also, it was shown in the 2-week toxicity study that the total number of T cells increased after glofitamab dosing, while CL was not increased, demonstrating a lack of correlation between CD3 binding and CL. Data from other species (mice, minipigs) as well as humans, suggest the rapid clearance to be species-specific and of limited clinical relevance. Gpt did not prevent ADA-formation in the study.

Repeat-dose TK studies

Overall, observations from single dose PK studies were generally confirmed in IV repeat-dose studies of 2- and 4 weeks duration in monkeys (conducted without Gpt), i.e. no sex differences were noted, CL and V_d decreased with dose (in agreement with depletion of endogenous B-cell levels) and AUC increased in a greater-than dose-proportional manner when multiple dose levels were tested (2-week study).

In the 2-week IV repeat-dose study, CL on Day 8 was reduced compared with CL on Day 1, and $AUC_{0\text{-last}}$ values were approximately 2-fold higher, in line with a decrease in TMDD after initial depletion of B cell on Day 1. All treated cynomolgus monkeys in the 2-week study became ADA-positive at 48 or 96 hours after the second dose on Day 8. It is not expected that the presence of ADA impacted exposure significantly, as elimination of glofitamab was near complete at these time-points.

In order to mitigate the high prevalence of ADA and account for the rapid clearance of glofitamab observed in monkeys, a step-up dosing regimen combined with every-other-day (EOD) dosing was implemented in the 4-week GLP toxicology study. Animals were dosed IV or SC at ascending doses of µg/kg (IV and SC) or (SC) at Day 1, Day 2 and EOD from Day 3 to 27, respectively. Mean C_{max} and $AUC_{0\text{-48h}}$ values after IV administration were 2.68 µg/mL and 20.30 µg*h/mL on Day 3 and 2.76 µg/mL and 29.55 µg*h/mL on Day 11, respectively; the latter being the overall highest exposure achieved via the IV-route across toxicology studies. Only negligible accumulation occurred with IV-dosing from Day 3 to Day 11 (1.4-1.5 fold), likely due to ADA formation, as 4/10 glofitamab-treated animals were ADA-positive 48 hours post dosing on Day 11. levels. The SC bioavailability was % and % in male and female animals on Day 11. The bioavailability is not expected to translate to the clinical setting, due to previously described atypical PK of glofitamab in monkeys. Overall, there was no mitigation of ADA-formation with the step-up dosing regimen as 27/30 animals were ADA-positive by Day 27 with associated loss of exposure.

In summary, glofitamab was shown to be highly immunogenic in cynomolgus monkeys and to lead to loss of exposure and pharmacological effect in repeat-dose studies. Consequently, no further/longer toxicology studies were conducted, which is accepted. The presence of ADA in preclinical species are

often not predictive of immunogenicity in humans; accordingly, the occurrence of ADA was low in the clinical setting.

Due to the absence of Gpt combined with the high species-specific clearance of glofitamab observed in cynomolgus monkeys as well as immunogenicity in the toxicology studies, exposures obtained in repeat-dose studies did not exceed those obtained in the clinical setting.

Distribution

The applicant did not submit specific studies on *in vivo* distribution. This is acceptable, as in accordance with regulatory guidelines for biotechnology-derived pharmaceuticals (ICH S6), no tissue distribution studies are considered necessary. Volumes of distribution for glofitamab are reported from PK/TK studies under section 3.3. "Absorption" and approximates serum volume in mice and cynomolgus monkeys, which indicates an initial distribution within the vascular space after IV administration.

An *in vitro* binding assay, indicated that glofitamab is mostly contained in plasma, and does not distribute to red blood cells to any appreciable extent. There were no species- or concentration-dependent differences. Further, glofitamab did not bind to plasma proteins under the conditions tested.

Metabolism

No dedicated metabolism studies were provided for glofitamab. This is acceptable, in line with ICH S6(R1), as the expected consequence of metabolism of glofitamab is degradation to small peptides and individual amino acids, and as such the metabolic pathway is generally understood.

Excretion

No dedicated excretion studies were performed with glofitamab, which is acceptable in line with ICH S6 (R1). IgG antibodies are expected to undergo catabolism by proteolysis in lysosomes, and the resulting amino acids may subsequently be excreted or added to the endogenous amino acid pool. Excretion into milk was not investigated, but is assumed to be similar to that of other IgG antibodies, which are present in milk, although to a limited extent compared to e.g. secretory IgA (Van de Perre, 2003).

Pharmacokinetic drug interactions

No dedicated PK drug-drug interaction (DDI) studies were performed with glofitamab. This is considered acceptable, as there is minimal involvement of the cytochrome P450 (CYP) system in the metabolism of monoclonal antibodies.

Other pharmacokinetic studies

Three additional PK studies were submitted by the applicant. These included a PK comparability study of glofitamab Phase 1 and Phase 3 material in huFcRn mice, where bioequivalence based on $AUC_{0\text{-}inf}$ and C_{max} after IV administration was confirmed between Phase 1 and Phase 3 material in mice expressing the human FcRn; and two supportive PK/PD modelling studies, used to derive glofitamab doses for the first-in-human administration of glofitamab. Efficacious glofitamab doses in humans were predicted based on tumour growth inhibition in humanised NSG mice. In a second model, cytokine release after glofitamab treatment was predicted based on PK parameters derived from 3 toxicity studies in cynomolgus monkeys and in vitro cytokine release data from human and cynomolgus whole blood.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

All findings following single dosing in the non-GLP studies in cynomolgus monkeys were reversible and were associated with the pharmacological action of glofitamab, specifically related to acute phase reaction due to cytokine release. It was observed that pre-treatment with obinutuzumab generally resulted in less severe findings, however, increased levels of cytokines were observed nonetheless, resulting in associated clinical findings as well as changes in hematology and clinical chemistry parameters. Furthermore, pre-treatment was not sufficient to alleviate the development of anti-drug antibodies, as immunogenic reactions were observed in all recovery animals, thus affecting the achieved exposure.

2.5.4.2. Repeat dose toxicity

Observations in the two GLP repeat dose studies in cynomolgus monkeys of 2 and 4-weeks duration, respectively, were all generally mild and reversible in nature, and were assessed as indicators of acute phase reaction associated with cytokine release after glofitamab-induced T cell activation. 3 animals in the 2-week GLP study were however prematurely euthanized due to severe clinical findings (vomiting, lethargia, hunched posture, and hypothermia), erosions in the GI tract, and mixed cell infiltrates in several organs, which correlated with very high cytokine peaks 4 h after dosing. Most of the findings in the surviving animals were observed within 24 h after first treatment, correlating with reduction in B cells, T cell activation and subsequent cytokine release, which were observed as clinical signs, acute phase reactions, changes in leukocytes, and increase in HR and body temperature. After the recovery period observations generally returned to baseline levels corresponding to levels of the control group. Only short-term studies up to 4 weeks for repeated dosing of glofitamab are available, as predominant ADA development and consequently diminished exposure and PD effect were observed in almost all of the animals of all tested dose groups. Though both step-up dosing and pre-treatment with obinutuzumab was investigated, only limited differences in exposure were observed, and it was not sufficient to avoid ADA development. Thus, there is no rationale for conducting a 13-week repeat dose study in cynomolgus monkeys as limited exposure is anticipated after a short time due to ADA development. The waiver for omitting the 13-week study is therefore accepted, also as the observed effects of glofitamab is similar to that observed for other B-cell depleting agents, and no unexpected findings have been observed. It is also agreed that use of other in vivo models in e.g. rhesus monkeys or mice, is not warranted based on the available data for glofitamab. SC administration of glofitamab resulted in the attenuation of cytokine release. When glofitamab treatment was investigated with or without pre-treatment with obinutuzumab, it was shown that pre-treatment attenuated cytokine release, which allowed a dosing of 10x the dose resulting in severe CRS-related findings in non-pre-treatment animals, thus justifying the clinical treatment strategy of using obinutuzumab pre-treatment.

2.5.4.3. Genotoxicity

In accordance with ICH S6 (R1) and ICH S9 guideline no information has been submitted for the mutagenic or carcinogenic potential of glofitamab, which is acceptable.

2.5.4.4. Carcinogenicity

No carcinogenicity studies have been conducted with glofitamab. This is consistent with the current ICH guidance on the preclinical safety evaluation of biotechnology-derived pharmaceuticals ICH S6 (R1) and ICH S9.

2.5.4.5. Reproductive and developmental toxicity

Male and female fertility was investigated as part of the 4-week GLP study in sexually mature cynomolgus monkeys. No glofitamab-related findings were observed in male and female reproductive endpoints up to the highest dose tested (100 µg/kg), which corresponds to exposure multiples of 0.36 and 0.28 in relation to C_{max} and $AUC_{0\text{-}48h}$, respectively. However, due to severe ADA formation, loss of PD effect and exposure was observed during the short-term study.

In line with the ICH S9 guideline, no dedicated studies investigating the effect of glofitamab on fertility and early embryonic development (FEED) or pre- and postnatal toxicology (PPND) were performed. The applicant submitted a waiver for not performing the embryofetal (EFD)/ enhanced (e)PPND study with glofitamab, providing an extensive discussion of known class effects on pregnancy of anti-CD20 monoclonal antibodies (i.e. rituximab, obinutuzumab and ocrelizumab), which has been investigated in (e)PPND or EFD studies as well as the observed effects of glofitamab in nonclinical and clinical studies. Common for the anti-CD20 monoclonal antibodies is the pharmacologic effect of B-cell depletion in dams and the offspring observed consistently across programs in animal studies, which was reversible upon drug washout. Investigations of anti-CD20 monoclonal antibodies have shown the following:

i) Opportunistic infections and immune complex mediated hypersensitivity reactions in pregnant dams, presumably due to B-cell depletion and immunogenicity responses of cynomolgus monkeys to human proteins, respectively. No teratogenicity observed (obinutuzumab).

ii) Perinatal mortality (some associated with bacterial infections), renal toxicity (glomerulopathy and inflammation), and lymphoid follicle formation in the bone marrow in pregnant monkeys. No teratogenicity observed (ocrelizumab).

iii) A murine surrogate molecule of blinatumomab crossed the placental barrier in pregnant mice but did not cause embryo-fetal toxicity or teratogenicity.

iiii) Full-length IgG antibodies (<5,000 Da) have low placental transfer during the first trimester, the period of organogenesis, in NHP and humans and thus have low teratogenicity potential (refer to ICH S6(R1)).

While it has been shown that glofitamab also depletes B cells as part of the pharmacological action, increasing the incidence of opportunistic infection secondary to B-cell depletion following dosing, glofitamab also exerts its pharmacological action via transient T cell activation and cytokine release primarily following the first dose. The cytokine release results in acute adverse reactions such as vomiting, diarrhea, hypoactivity/hunched posture, hypotension, tachycardia, fever, acute phase protein reactions and leukocyte margination in cynomolgus monkeys, which may have a negative impact during pregnancy. Further, it appears that cytokines may be involved in establishing and maintaining pregnancy, thus potentially resulting in foetal loss when the cytokine levels are affected during the early period of pregnancy. Taken together, the toxicities associated with T cell activation and cytokine release as well as B cell depletion may pose a risk to the maintenance of early pregnancy.

Based on the provided justification, it is assumed that infections secondary to glofitamab-induced B-cell depletion as well as acute toxicities following cytokine release may result in increased risk of neonatal loss in cynomolgus monkeys, though no teratogenic effects are expected due to the low

placental transfer during the first trimester. Similar adverse toxicities following glofitamab administration have been identified in the clinic and includes cytokine release syndrome, neutropenia and infections, in line with what has been observed in repeat dose studies in monkeys. Based on the justification provided, and in accordance with ICH S6 (R1) it is agreed that no further testing is required in order to elucidate the reproductive toxicity of glofitamab in cynomolgus monkeys, as it is not likely it will add further information to the current non-clinical and clinical knowledge to support the mitigation of this risk in humans. It is considered that glofitamab should not be used during pregnancy in humans due to the identified risks, which has been adequately reflected in the SmPC section 4.6 and 5.3.

2.5.4.6. Toxicokinetic data

A high overall incidence of ADAs was observed in all toxicology studies in monkeys, leading to loss of exposure and PD effects over time. Higher exposure levels were obtained with Gpt, however, ADA formation was not prevented. In summary, obtained exposure levels in toxicology studies conducted without Gpt did not exceed those obtained in the clinical setting, as estimations of exposure multiples resulted in values of 0.03 to 0.28 (based on AUC), implying that CRS-related effects occur at clinically relevant dose levels. The same results are approximately achieved when comparing Cmax in cynomolgus monkeys with humans (i.e. exposure multiples of 0.27 to 0.36). The low exposure multiples are considered acceptable, taking into account the indication (advanced cancer), that the expected adverse effects of glofitamab occurs mainly due to exaggerated pharmacology or secondary to it, and that no obvious alternative animal species besides the monkey are available for toxicology studies. When glofitamab was administered after pre-treatment with obinutuzumab, higher doses could be administered resulting in an exposure multiple to the human dose of 3.74 based on C_{max}.

Cytokine Release Syndrome is an identified risk in the clinic and is primarily observed after the first dosing with glofitamab with signs of CRS including pyrexia, tachycardia, hypotension, chills, hypoxia, headache, and nausea. Potentially secondary effects to CRS observed in the clinic includes hepatotoxicity, neurological adverse events, cardiovascular effects and neutropenia. Thus, findings in cynomolgus monkeys are well described in humans and correlate with findings in the single and repeat-dose toxicity studies in animals. A sufficient overview of the identified risks has been included in the SmPC and discussed in the RMP covering the effects observed in cynomolgus monkeys. Both pre-treatment and step-up dosing has been used in the clinic to manage the effects of CRS, in line with what has been investigated in animals.

2.5.4.7. Local Tolerance

Local tolerance was evaluated as part of the single or repeat dose GLP studies following IV or SC administration in cynomolgus monkeys. No changes were observed that indicated local intolerance.

2.5.4.8. Other toxicity studies

The formation of anti-drug antibodies (ADA) has been investigated as part of the toxicological studies and has been thoroughly discussed in the sections above. Overall, ADA formation has been observed to severely influence the results in both the single dose and repeat dose toxicity studies in cynomolgus monkeys, as decreased exposure was observed in all the studies, thus not reaching the exposure level in humans at clinically relevant dose levels. No ADA formation has been observed in patients in the clinical studies.

The applicant conducted an in vitro binding assay for human Fcγ receptors, where glofitamab showed no detectable binding to the Fcγ receptors tested, and further, no binding to C1q was demonstrated. This is expected due to the "P329G LALA" mutation introduced in the Fc binding region which results in minimal capability of binding to effector cells via this region. It is assessed that glofitamab has a low potential for Fcγ receptor cross-linking and C1q complement binding on immune cells leading to induction of nontargeted immune cell activation (e.g. ADCC, ADCP and CDC).

Further, the applicant investigated the in vitro potential of glofitamab to induce cytokine release and T-cell activation in human and cynomolgus monkey whole blood. EC50-values for interspecies comparison were available for a subset of the cytokines tested (IL-6, TNFα and IFNγ), and indicated a marked difference in potency of glofitamab to induce IL-6 release; i.e. EC50-values for glofitamab-induced IL-6 release were 67-fold higher in cynomolgus monkeys compared to humans. Glofitamab was also more potent in inducing TNFα and IFNγ-release in human whole blood compared to cynomolgus monkey, however, this difference was more modest (within 4-fold). Glofitamab induced T cell activation in whole blood from both species, evident by an upregulation of CD25+ and CD69+ on both CD8+ and CD4+ T cells, and EC50 values indicated that glofitamab induced T cell activation with a 2-4-fold higher potency in human whole blood compared to monkeys.

Monoclonal antibodies have limited penetration across the blood-brain barrier due to the size of the molecule. Further, no evidence of off-target binding related to CNS effects have been observed for glofitamab and no evidence to suggest affected behaviour or activity patterns have been observed in general toxicity studies in cynomolgus monkeys. The weight of evidence indicates that glofitamab has a low likelihood for abuse potential.

The active substance and drug product are generally well controlled at production level and potential process derived impurities are cleared to low levels. Thus, no impurities have been identified that are of toxicological concern.

A GLP tissue cross-reactivity IHC study was conducted with biotinylated glofitamab in normal human tissues from three donors. Staining with glofitamab was observed in plasma membranes and cytoplasm of mononuclear cells in several lymphoid and non-lymphoid tissues. This is expected, considering the glofitamab target expression of CD3 on T cells and CD20 on B cells, respectively. A biotinylated untargeted control antibody with the same CD3 binder (untargeted control antibody) also stained mononuclear cells in a subset of the same tissues, in agreement with CD3 being the only target antigen for the untargeted control antibody. However, glofitamab did not stain blood cells (evaluated on peripheral blood smears) or bone marrow (evaluated on bone marrow smears). This is unexpected, since T and B lymphocytes should be present in the blood samples and at least B cells should be present in bone marrow. The applicant argues that the absence of staining in blood smears and bone marrow is most likely due to technical limitations of the immunohistochemistry method used in TCR studies, which is accepted.

Unexpected cross-reactivity was observed for both glofitamab and the untargeted control antibody, and included for both test articles cytoplasmic staining of mast cells and/or macrophages (in most tissues for glofitamab, in fewer for the untargeted control antibody); of smooth myocytes in most tissues; and of striated (skeletal and cardiac) myocytes. CD20 and CD3 are not known to be expressed in these tissues, however, as the binding was cytoplasmic in nature, and as both glofitamab and the untargeted control antibodyare expected not to have cytoplasmic access in vivo, this is not considered of specific toxicological concern. The applicant supplied relevant literature to support this claim (Leach et al, 2010), in which it is also stated that biotinylation of a test article may increase off-target cross-reactivity with cytoplasmic structures. In addition, ICH S6 (R1) states that tissue binding to areas not typically accessible to the antibody in vivo (i.e. cytoplasm) is generally not relevant.

Glofitamab was tested for hemolytic potential and blood compatibility. In vitro, glofitamab did not induce hemolysis, turbidity or precipitation in human whole blood when tested at concentrations up to 2.5 mg/mL.

2.5.5. Ecotoxicity/environmental risk assessment

The active substance is a monoclonal antibody which will be broken down by proteolysis, the use of which will not alter the concentration or distribution of the substance in the environment. Supportive documentation was provided, showing that monoclonal antibodies in general can be expected to be readily biodegradable and of low ecotoxicity. Based on these considerations, glofitamab is not expected to pose a risk to the environment.

Considering the submitted data, glofitamab is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

The pharmacology of glofitamab was thoroughly described in the provided non-clinical package and the mode of action and pharmacological effect has been demonstrated sufficiently via in vitro, ex vivo and in vivo studies. To alleviate the extent of cytokine release and associated safety issues as well as ADA formation, obinutuzumab was given prior to glofitamab treatment in order to debulk the peripheral and tissue-resident B cells. Obinutuzumab was chosen over rituximab as pre-treatment agent, as the applicant claims that obinutuzumab showed superior tissue B-cell depletion compared to e.g. rituximab in cynomolgus monkeys. Based on data provided by the applicant, the choice of obinutuzumab over rituximab seems to be supported in animal models, as a more efficient and faster depletion of B cells has been observed. It should however be noted that the animal models are not considered to completely reflect the clinical context where prior anti-CD20 treatment has been given before glofitamab treatment, as this is intended for treatment in 3L+ DLBCL, resulting in depletion of B cells before initiating pre-treatment with obinutuzumab. Hence, this limits the ability to infer superiority of obinutuzumab over rituximab in the intended clinical setting. Glofitamab showed no binding to the Fcγ receptors tested, which is expected due to the "P329G LALA" mutation introduced in the Fc binding region, resulting in minimal capability of binding to effector cells via this region. As such, it appears there is a low potential for glofitamab to induce non-targeted immune cell activation (e.g. ADCC, ADCP and CDC), via Fcγ receptor cross-linking and C1q complement binding on immune cells.

Overall, the pharmacokinetics of glofitamab was adequately described in the nonclinical package. In cynomolgus monkeys, glofitamab kinetics were dose-dependent and consistent with target-mediated drug disposition. Cl decreased with increasing dose and was approx. 240 ml/day/kg at the 100 µg/kg dose level; AUC0-last values increased with dose. Vc ranged between 25 and 40 ml/kg, i.e. in the range of the reported plasma volume in cynomolgus (33-37 ml/kg). Vss values are slightly higher, indicating some distribution of glofitamab into tissues. Of note, t1/2 was rather short, less than 5 hrs. Prior B cell depletion by obinutuzumab (4 days prior to administration of glofitamab), reduced glofitamab clearance (approx. 4.7x) and prolonged the half-life (9x) when compared to glofitamab treatment without prior B cell depletion. Nevertheless, even in B cell-depleted cynomolgus, the glofitamab t1/2 ranged from 53.4 to 67.7 hrs (2.2 to 2.8 days) which is rather short for a mAb.

The toxicity findings based on the single- and repeat dose studies in cynomolgus monkeys for up to 4 weeks showed extensive CRS-related effects, which was expected based on the mode of action of glofitamab. Some of the CRS-related effects were diminished using pre-treatment and step-up dosing, and higher dosing was allowed using these approaches, but CRS-related toxicity findings and ADA formation could not be alleviated completely. Studies of longer duration could not be completed, due to ADA formation leading to low exposures and affecting the PD effect in animals. This is considered

acceptable as no unexpected findings were observed in the toxicity studies for up to 4 weeks. The repeat-dose toxicity studies were GLP-compliant, while the single-dose studies were not. This is acceptable. Reproductive and developmental toxicity studies were waived due to the known effect on B-cell depletion and potential infections as well as acute toxicities following cytokine release, which may result in increased risk of neonatal loss. No further studies are considered warranted to inform on the safety issues during pregnancy.

The potential of glofitamab for off-target binding was evaluated in a tissue cross-reactivity study. The observed membrane staining of mononuclear cells in lymphoid and non-lymphoid tissues was as expected. Due to technical limitations of immunohistochemistry methods used in TCR studies the lack of staining of blood and bone marrow samples in the assay is acceptable.

Lastly, in a PD study in humanised NSG mice, glofitamab was administered in combination with a second bi-specific mAb (not relevant for the present submission) with and without obinutuzumab pre-treatment. The study was reported in the toxicology section due to histological findings in bone marrow (necrosis/atrophy) which had not been observed in cynomolgus monkey studies. The applicant considers the bone marrow findings largely related to the murine/human chimerism. An additional study in tumour-bearing humanised NSG mice treated with glofitamab or glofitamab plus another compound in presence or absence of obinutuzumab pre-treatment conducted by the applicant supported this conclusion. Importantly, no effects on bone marrow were observed in cynomolgus monkey toxicity studies with glofitamab nor in humans.

Overall, the non-clinical safety and efficacy profile seems well documented in the submitted non-clinical dossier, which supports the findings in the clinic. The identified non-clinical risks have been discussed regarding human relevance and follow-up measures in patients have been proposed as relevant.

The pharmacokinetics of glofitamab was overall adequately characterized in the provided nonclinical package. However, a high incidence of ADA was observed in both single-dose and repeat-dose studies conducted with and without Gpt in monkeys. For the pivotal repeat-dose toxicology studies, the presence of ADA compromised the ability to maintain exposure levels above (or at) those obtained in the clinical setting. Waivers for omission of additional toxicological studies of longer duration in monkeys were granted by the EMA and FDA, and no other relevant animal species were available. This was considered acceptable taking into account the indication (advanced cancer); and that the expected adverse effects of glofitamab consist of pharmacology, which is well-known for other antibodies in this class.

Toxicology was investigated sufficiently in cynomolgus monkey. In brief, several signals were detected that were considered relevant for translation to human administration, i.e. toxicities observed secondary to B-cell depletion and cytokine-release syndrome. The effects observed in the nonclinical studies are known in the clinic and guidance has been included in the RMP for addressing the findings.

A justification for not submitting ERA studies, due to the nature of the active substance – is acceptable in accordance with EMEA/CHMP/SWP/4447 as glofitamab is unlikely to result in a significant risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The in vitro and in vivo pharmacology programme, including in disease models, supporting the intended clinical use of glofitamab – is sufficient. Nonclinical proof of concept as an anti-CD20/CD3 T-cell-dependent bispecific (TDB) antibody mediating target B-cell lymphoma killing appears well-

established. Relevant information has been included in SmPC sections 5.3. and appropriate warnings in section 4.6.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Union were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 3 Tabular overview of clinical studies

Study ID	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Population	Duration of Treatment	Countries	Study Status; Type of Report
NP30179 FIH	To evaluate the efficacy, safety, tolerability, and pharmacokinetics of a novel T cell-bispecific antibody, glofitamab, administered by IV infusion as a single agent and in combination with obinutuzumab following pre-treatment with a fixed dose of obinutuzumab in patients with relapsed/ refractory (R/R) B-cell non–Hodgkin's lymphoma (NHL).	A multicenter, open-label, Phase I/II study to evaluate the safety, efficacy, terability and pharmacokinetics of escalating doses of glofitamab as a single agent and in combination with obinutuzumab administered after a fixed, single dose pre-treatment of obinutuzumab in pts with R/R B-cell non-Hodgkin´s lymphoma	Part I and II: Dose escalation in cohorts of R/R NHL patients who received 1 prior line of systemic therapy Fixed dosing: Glofitamab 0.005 mg – 25 mg IV, Q2W or Q3W. Step-up-dosing: Glofitamab 2.5/10/16 mg, 2.5/10/30 mg, 0.5/2.5/10/30 mg IV, Q3W. Part III: Dose expansion in cohorts of R/R DLBCL and R/R FL patients who received □2 prior lines of systemic therapy Fixed dosing: Glofitamab 10/16 mg IV, Q3W Step-up-dosing: Glofitamab 2.5/10/30 mg IV, Q3W.	458 treated patients	Patients with R/R B-cell NHL Planned: Up to 300 patients during dose escalation (Part I-II), approx. 560 patients across expansion cohorts (Part III) Enrolled: 458 patients treated in Parts I–III (Part I and II: 222 patients; Part III: 236 patients)	Initial and retreatment 12 cycles Q2W or Q3W dosing	EU: BE, CZ, DK, FI, FR, IT, PL, ES Non-EU: AU, CA, NZ, Taiwan, US	Full Interim CSR*

2.6.2. Clinical pharmacology

The PK, pharmacodynamics (PD), and immunogenicity results were all derived from Study NP30179.

Study NP30179 is an ongoing Phase I/II, multicenter, open-label, dose-escalation study designed to evaluate the efficacy, safety, tolerability, and pharmacokinetics of a novel TCB antibody, glofitamab, administered by IV infusion as a single agent and in combination with obinutuzumab following pre-treatment with a fixed dose of obinutuzumab in patients with R/R NHL.

The study is divided in three parts (i.e., dose escalation (Parts I [single patient cohorts] and II [multiple patient cohorts]) and dose expansion [Part III]).

Note that for statistical and PK analyses purposes presented in this document, obinutuzumab pre-treatment (Gpt) administered 7 days prior to the initial dose of glofitamab (i.e., Day 7) as described in the study protocol corresponds to Cycle 1 Day 1 (C1D1). Consequently, in the analyses, the first dose of glofitamab corresponds to C1D8 and for patients receiving the step-up dosing regimen, administration of the initial low dose of glofitamab (2.5 mg) 7 days after Gpt corresponds to C1D8 (Day 8) and administration of the intermediate 10 mg glofitamab dose 7 days after the first glofitamab

dose corresponds to C1D15 (Day 15). Thus, the cycles and days of administration of Gpt and glofitamab presented henceforth in this document follows the convention noted above.

The proposed registrational dose of glofitamab treatment is 2.5 mg C1D8, 10 mg C1D15 and 30 mg Day 1 of Cycle 2-12, with obinutuzumab 1000 mg pre-treatment on Cycle 1 Day 1.

Pharmacokinetics

Analytical methods

In study NP30179, glofitamab (RO7082859) was administered either alone or concomitantly with obinutuzumab (RO5072759). Both analytes were quantified by validated ELISA assay. Immunogenicity of glofitamab was evaluated by validated ADA assay using a rabbit polyclonal IgG directed against the CD20 binding domain of glofitamab as positive control. An ELISA method was also validated for determination of tocilizumab. Commercially available immunoassay kits were used for determination of IL-6 and IL-6sR levels in human serum samples from Study NP30179.

Pharmacokinetic data analysis

Non-compartmental analysis was used to estimate glofitamab PK parameters using Phoenix WinNonlin 8.2 software. Population PK/PD model fitting and Bayesian feedback were performed using the non-linear mixed effect modelling software NONMEM, version 7.4.3 and FOCEI. R version 4.0.5 was used for data processing, data visualization and reporting. Simulations were performed using a combination of NONMEM and R. PBPK modelling of cytokine release kinetics was performed using the Simcyp Population-Based Simulator (Version 20).

Glofitamab Population PK

The glofitamab population PK analysis was based on a dataset from Study NP30179 in which doses of glofitamab monotherapy cohorts ranged from 5 µg to 30 mg. The final population PK model for glofitamab was two-compartmental with parallel linear and time varying clearance. Inter-individual variability was included on all structural parameters, and a proportional residual variability model was used. The following covariates were identified as statistically significant and included in the final model: body weight on clearances and volumes, baseline CRP on clearances and V1, baseline obinutuzumab pre-treatment concentration on time-dependent CL and transformed follicular lymphoma histology (trFL) on decay constant (Kdes). The effect of body weight was allometrically scaled with fixed exponents of 0.75 for clearances and 1 for V2 while the exponent of V1 was estimated to 0.505, indicating that the effect of body weight was less than proportional.

Parameter estimates of the final model for glofitamab and selected diagnostic plots are shown in Table 1 and Figures 19 and 21.

Table 4 Parameter estimates for the final model for glofitamab PK

Parameter	Estimate (%RSE)	95% CI (Asymptotic)	95% CI (Bootstrap)	Shrinkage (%)
Linear CL (mL/d)	602 (0.0388)	601-602	579 ; 630	-
V1 (mL)	3330 (0.0299)	3330-3330	3190 ; 3400	-
V2 (mL)	2180 (0.0409)	2180-2180	2040 ; 2410	-
Q (mL/d)	674 (0.0372)	674-675	613 ; 794	-
Decay constant (/d)	0.445 (0.0397)	0.445-0.445	0.368 ; 0.595	-
Time-varying CL (mL/d)	396 (0.0385)	396-396	329 ; 475	-
Weight on linear CL	0.750 (Fixed)	-	-	-
Weight on V1	0.505 (0.145)	0.504-0.507	0.393 ; 0.681	-
Weight on V2	1.00 (Fixed)	-	-	-
Weight on Q	0.750 (Fixed)	-	-	-
Weight on time-varying CL	0.750 (Fixed)	-	-	-
Baseline CRP on linear CL	0.0596 (0.450)	0.059-0.0601	0.0324 ; 0.0845	-
Baseline CRP on time-varying CL	0.157 (0.205)	0.156-0.157	0.0613 ; 0.401	-
Baseline obinutuzumab on time-varying CL	-1.11 (0.0764)	-1.11--1.11	-1.39 ; -0.782	-
Baseline CRP on V1	0.0428 (0.758)	0.0422-0.0434	0.0179 ; 0.0652	-
trFL on decay constant	3.76 (0.184)	3.74-3.77	1.49 ; 5.09	-
IIV on linear CL (variance)	0.0688 (8.03)	0.0579-0.0796	0.0617 ; 0.0934	7.55
IIV on V1 (variance)	0.0582 (6.75)	0.0505-0.0659	0.0445 ; 0.0734	7.13
IIV on V2 (variance)	0.135 (14.1)	0.0975-0.172	0.110 ; 0.229	34.8
IIV on Q (variance)	0.581 (10.2)	0.465-0.696	0.263 ; 0.743	27.1
IIV on decay constant (variance)	2.52 (11.7)	1.95-3.1	1.89 ; 3.11	33.2
IIV on time-varying CL (variance)	3.61 (6.45)	3.16-4.07	2.04 ; 5.57	24.1
Proportional residual error (SD)	0.228 (0.0331)	0.228-0.228	0.216 ; 0.239	7.31

CI = confidence interval; CL = clearance; CRP = C-reactive protein; IIV = interindividual variability; Q = inter-compartmental clearance ; SD = standard deviation; trFL = transformed follicular lymphoma; V1 = central volume of distribution; V2 = first peripheral volume of distribution.

Figure 4 Goodness of fit plots for the final population PK model for glofitamab **(Run 271).**

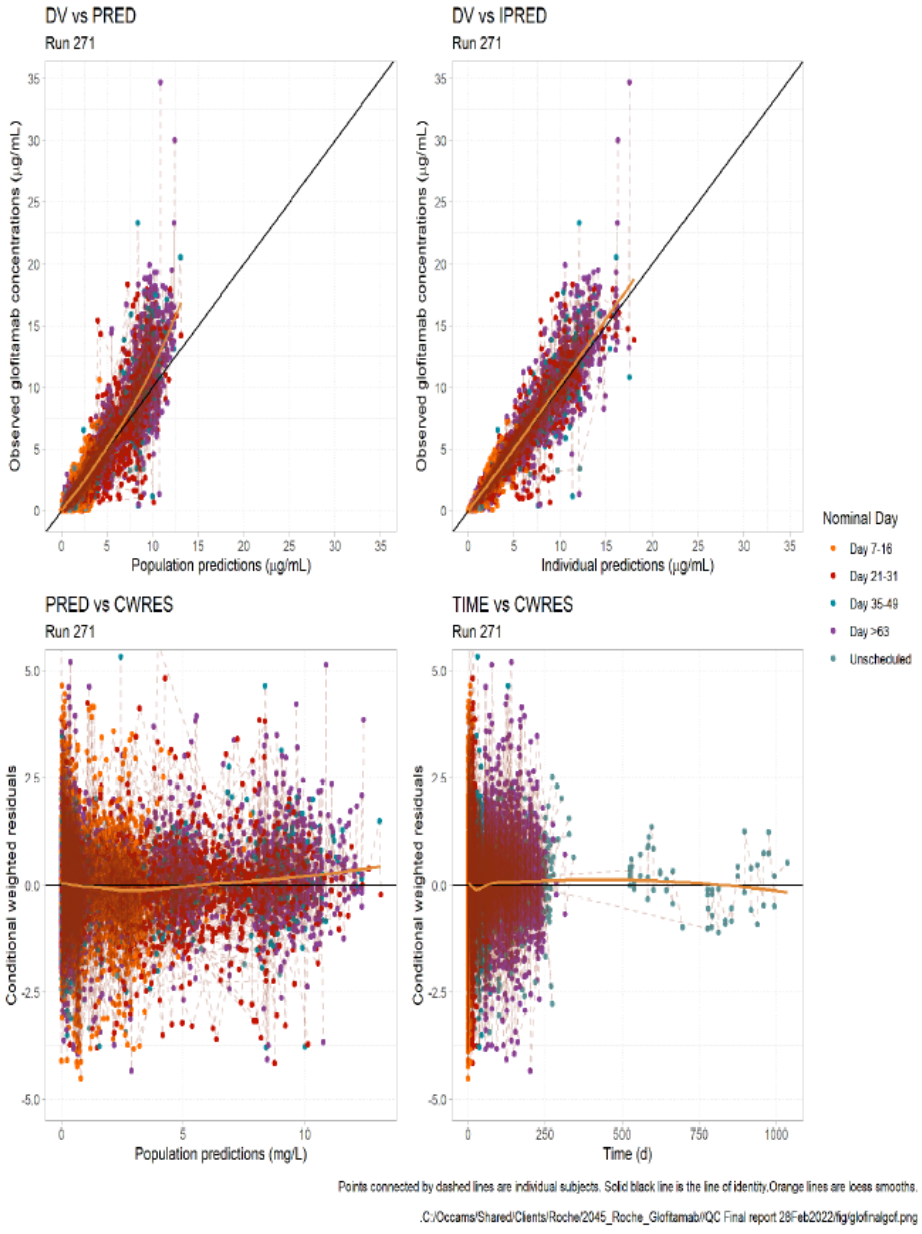
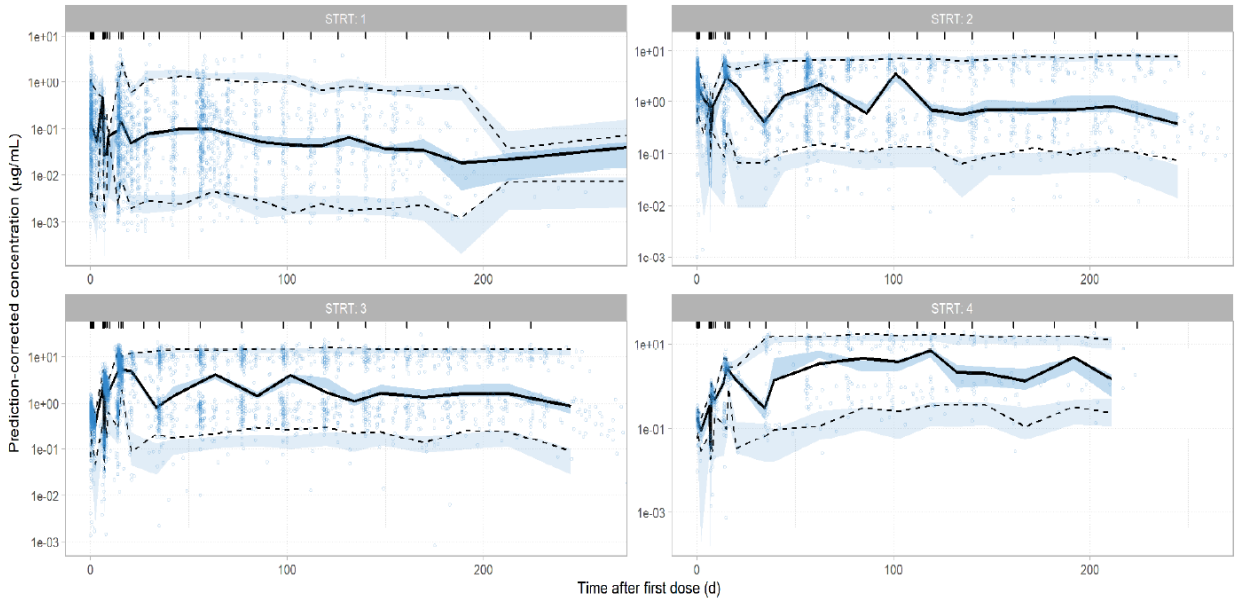


Figure 5 Prediction corrected visual predictive checks for the final population PK model (Run 271)



Glofitamab Logistic Regression analysis

Exposure-response relationships of glofitamab for efficacy and safety were characterized by logistic regression modelling, including an assessment of covariate effects. For efficacy, patients were split into two populations from Study NP30179: (1) the 2.5/10/30 mg glofitamab step-up dosing of DLBCL/trFL patients enrolled in Cohort D_3 (n = 95) and (2) patients with DLBCL/HGBCL/PMBCL/trFL administered a wider range of glofitamab doses (n = 259). No exposure-efficacy relationship was found for the 2.5/10/30 mg step-up dosing regimen of Cohort D_3 but in the DLBCL/HGBCL/PMBCL/trFL population a significant relationship was found for AUC_{C1+C2} for both CRR and ORR. In both populations, CRR was significantly associated with decreasing baseline sum of product diameters and increasing time since last prior anti-CD20 treatment. ORR was significantly associated with decreasing baseline lactate dehydrogenase and increasing time since last prior anti-CD20 treatment. An exposure-safety relationship was found for CRS (Grade ≥2) as the incidence was significantly associated with increasing $AvgRO\%_{D1}$ but no significant effect of glofitamab exposure was found for neutropenia (Grade ≥2).

QTc modelling analysis

The glofitamab concentration-QT interval relationship was characterized by mixed-effects modelling. The QT prolongation signal associated with glofitamab concentration was best described by an Emax model in which maximal prolongation was estimated to be 10.6 ms (95% CI 9.29-11.8%), with an associated glofitamab concentration to give the half-maximal effect (EC50) of 1.25 µg/mL (95% CI 1.11-1.39 µg/mL). Based on this model, the upper limit of the 90% confidence interval of the mean concentration change in individually-corrected QT interval from baseline (ΔQTcI) relationship was estimated to reach the 10 ms threshold of concern at a glofitamab concentration of 7.27 µg/mL and in the observed population receiving 2.5/10/30 mg glofitamab the upper limit of the 90% confidence interval was reached in 71.6% of patients.

PBPK modelling of IL-6 release

The MoA of glofitamab results in a transient elevation of cytokines, mainly IL-6, IL-10 and IFN-c. IL-6 is a potent suppressor of CYP-mediated metabolism in-vitro. A literature based PBPK model was used to reflect the IL-6 kinetics induced by glofitamab following the 2.5/10/30mg step-up dosing applied in

the NP30179 study. The IL-6 PBPK model was used to assess the level of suppression of CYP3A4, CYP1A2 and CYP2C9 caused by the transient IL-6 release and assess the potential impact on substrates of these CYPs.

A minimal PBPK model using the Simcyp population-based simulator was applied in simulations of plasma concentrations of IL-6. A number of simulations were run to achieve different profiles of plasma IL-6 concentrations (i.e. high, median and low IL-6 increase profiles) which encompass the observed IL-6 levels in the patients in NP30179. Based on the observed profiles in the 163 glofitamab step-up dosing patients with IL-6 peak at approximately 12h post-glofitamab dose, IL-6 was introduced as a 12-h i.v. infusion at a dose of 0.0002, 0.004 and 0.04 mg to capture the low, medium and high IL-6 increase profiles. The parameters used for the IL-6 compound file for simulation of IL-6 pharmacokinetics are shown below.

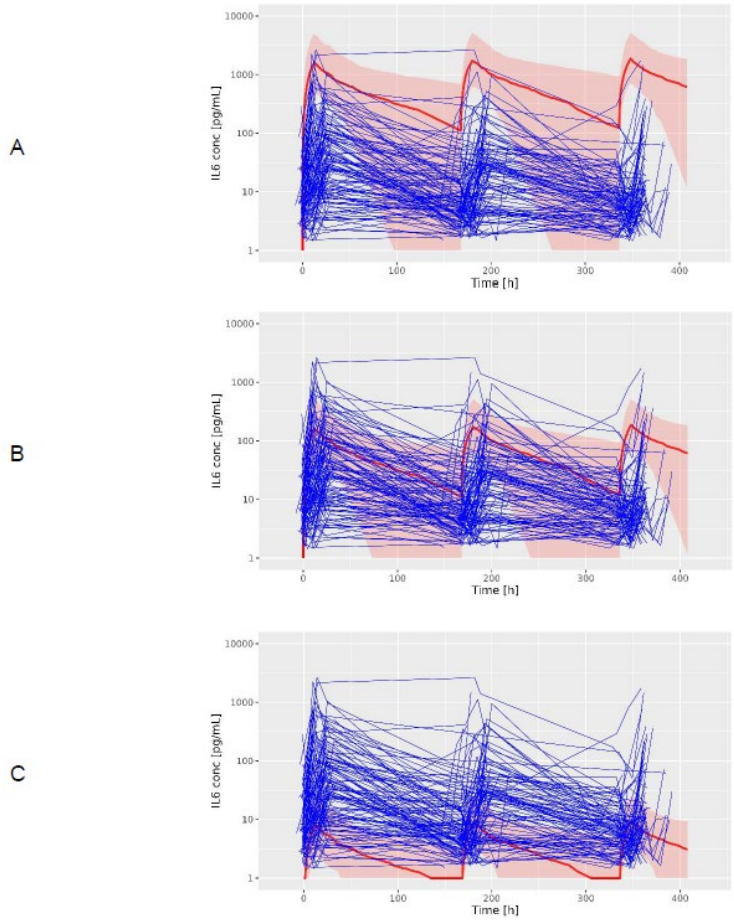
Table 5 Input parameter values used for IL-6

Parameter	Value	Method/Reference
Molecular weight (g/mol)	21000	www.invivogen.com
log P	0.01	Assumed
Compound type	Neutral	
B/P	1	Assumed
fu	1	Assumed
Main plasma binding protein	Human serum albumin	
Distribution Model	Minimal PBPK Model	
V_{SS} (L/kg)	0.43	Machavaram et al. 2013 Machavaram et al. 2019
CL_{iv} (L/h)	0.5	Xu et al. 2015
CL_R (L/h)	0	Assumed
Enzyme	CYP1A2	
E_{min}	0.23	Dickman et al. 2011
$IndC_{50}$ (µM)	5.96E-05	Dickman et al. 2011
Enzyme	CYP2C9	
E_{min}	0.053	Dickman et al. 2011
$IndC_{50}$ (µM)	5.76E-06	Dickman et al. 2011
Enzyme	CYP3A4	
E_{min}	0.24	Dickman et al. 2011
$IndC_{50}$ (µM)	3.48E-06	Dickman et al. 2011
Enzyme	CYP3A5	
E_{min}	0.24	Same values used as CYP3A4; Dickman et al. 2011
$IndC_{50}$ (µM)	3.48E-06	Same values used as CYP3A4; Dickman et al. 2011

CYP = cytochrome; CL_{iv} = clearance following an intravenous infusion dose CL_R = Renal clearance; E_{min} = minimum amount of active enzyme observed in the in vitro system (i.e. the maximum amount of suppression) expressed as a fraction of the vehicle control value; $IndC_{50}$ = concentration of inducer that supports the half maximal induction/suppression; IL-6 = interleukin 6; V_{ss} = volume of distribution at steady state.

PBPK predictions were performed using the virtual North European Caucasian population with age, body weight and gender characteristics matching the 163 patients from the NP30179 study with available IL-6 concentrations (6th July PK cut-off). The median (5th -95th percentiles) predicted plasma concentration-time profiles for IL-6 following administration of intravenous infusion doses of IL-6 at 0.0002, 0.004 and 0.04 mg weekly were overlaid to the observed IL-6 concentrations from the patients who did not receive tocilizumab (n=124) (Figure 2).

Figure 6 Overlay of spaghetti plots of observations and predicted plasma concentration-time profiles of IL-6



Overlay of spaghetti plots of observations in the patients with glofitamab step-up dosing regimen and median [5th – 95th] predicted plasma concentration-time profiles of IL-6 (bold solid red line is median and red area is 5th – 95th percentiles) during the first 17 days of glofitamab treatment representing high (A), medium (B) and low (C) increased IL-6 profiles. Curves in blue represent observations for patients not treated with tocilizumab. This selection was done as tocilizumab is reversing back the CYP-suppressing effect of IL-6 as described in Schmitt et al. (2011).

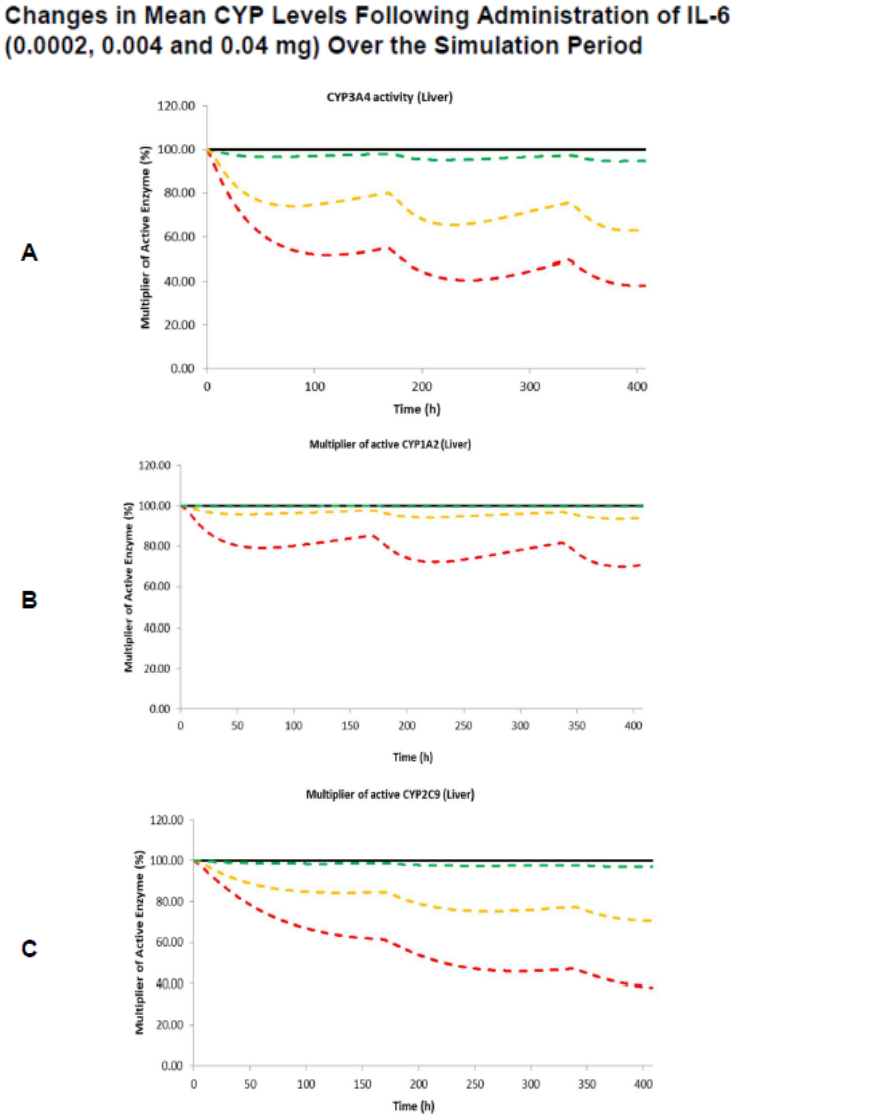
Table 6 Predicted and Observed IL-6 Concentrations in the 163 Patients with 2.5/10/30 mg Step-Up Dosing Regimen

Administration	Predictions Median [min – max]			Observations Median [min – max]
	Low dose (n=163)	**Medium dose (n=163)**	**High dose (n=163)**	**Without Toci (n=124)**
First administration (Day 1)	5.03 [0.00-42.9]	101 [0.00-858]	1010 [0.00-8580]	30.2 [1.45-2670]
Second administration (Day 8)	6.00 [0.00-42.9]	120 [0.00-857]	1200 [0.00-8570]	16 [1.62-2620]
Third administration (Day 15)	6.32 [0.00-43.0]	126 [0.00-860]	1260 [0.00-8600]	7.32 [1.45-1740]

IL-6=interleukin-6; Toci= tocilizumab.

Note: Median [min – max] of predicted IL-6 concentrations (pg/mL) achieved over the 24h following the first, second and third administration of 0.0002 (low), 0.004 (medium) and 0.04 mg (high) of IL-6 and observed IL-6 concentrations (pg/mL) after first (2.5 mg), second (10 mg) and third (30 mg) glofitamab administration in the patients with 2.5/10/30 mg step-up dosing regimen

Figure 7 changes in the mean CYP enzyme levels following iv infusion of IL-6 (0.0002, 0.004 and 0.04 mg) over the simulation period of 17 days



Changes in mean CYP levels following administration of IL-6 (0.0002, 0.004 and 0.04 mg) over the simulation period of 17 days to virtual North European Caucasian subjects (A) CYP3A4, (B) CYP1A2 and (C) CYP2C9. Data are for simulations without IL-6 (solid black line), and with low 0.0002 mg (dashed green line), medium 0.004 mg (dashed orange line) and high 0.04 mg (dashed red line) IL-6.

ADME

Mean glofitamab concentrations increased rapidly with the median time to maximum concentration (t_{max}) reached shortly after end of infusion as expected for a monoclonal antibody. The geometric means of volume of distribution from NCA (Vz) ranged from 3.49 to 9.91 L. Due to the sampling schedule, it was not possible to report pharmacokinetic parameters for all cohorts by NCA and population PK modelling has been used to further characterize the PK properties of glofitamab.

The central volume of distribution (V1) was 3.33 L and peripheral volume of distribution (V2) was 2.18 L. The central volume of distribution of 3.33 L is close to total serum volume.

The glofitamab serum concentration-time data are described by a population pharmacokinetic model with two compartments, and both time-independent clearance and time-varying clearance.

The time-independent clearance pathway was estimated as 0.602 L/day and the initial time-varying clearance pathway as 0.396 L/day, with an exponential decay over time (Kdes ~ 0.445/day). The estimated decay half-life from the initial total clearance value to the time-independent clearance only was estimated as 1.56 days.

The effective half-life in the linear phase (i.e., after the contribution of time-varying clearance has collapsed to a negligible amount) can be approximated to a typical linear effective half-life of 6.54 days (95% CI: 3.74 - 9.41) based on the population pharmacokinetic analysis.

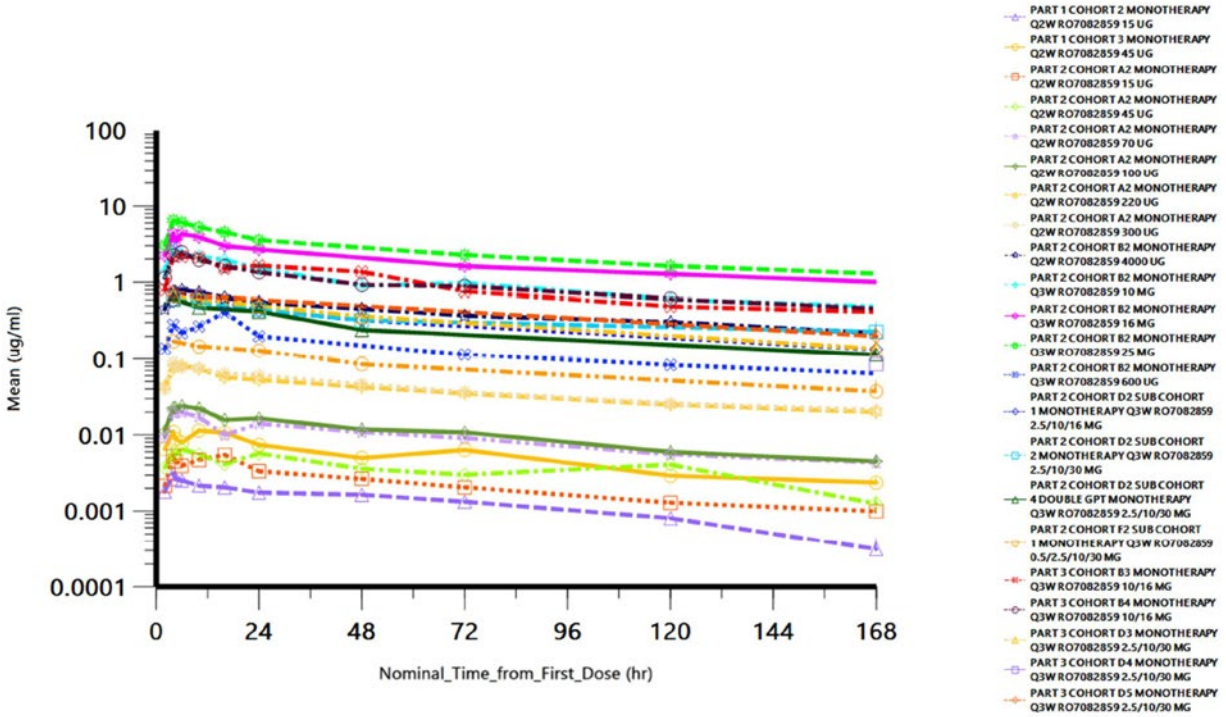
The expected consequence of metabolism of biological products is degradation to small peptides and amino acids. Glofitamab is as a MAB not cleared renally due to its large molecular weight. The primary elimination pathways are protein catabolism via the reticuloendothelial system (RES) or target-mediated disposition.

Dose proportionality and time dependencies

The mean Cycle 1 C_{max} values following first administration were dose proportional from 0.015 to 25 mg. All Cycle 1 concentrations in the single patient who received 0.005 mg were below the limit of quantification

Figure 8

Mean Serum Concentration-Time Profiles for Glofitamab Following First Dose (Cycle 1 Day 8) Administration across doses (log-lin)



Q2W=every 2 weeks; Q3W=every 3 weeks.
Note: Concentrations for the 5 µg dose (n=1) are below BLQ and not shown.

Special populations

The effect of renal impairment on glofitamab PK was investigated in the Population PK model based on creatinine clearance (CrCL) values in PK-evaluable monotherapy patients from Study NP30179. Among the 399 patients, 195 patients (48.9%) had normal renal function at baseline, 141 patients (35.3%) had mild renal impairment, 62 patients (15.5%) had moderate renal impairment, and 1 patient (0.25%) had severe renal impairment. The results indicate that CrCL did not affect glofitamab PK.

The effect of hepatic impairment on glofitamab PK was investigated in the Population PK model. From the 399 PK-evaluable patients, 347 had normal hepatic function, 48 had mild impaired function, 2 had moderate impaired function, 1 has strong hepatic impaired function and the information about hepatic function was unavailable for 1 patient.

Despite very limited data with moderate to strong hepatic impairment, no relationships were observed between hepatic impairment and clearances in the final reduced population PK model for glofitamab.

The effect of NHL histology on glofitamab PK was investigated as a categorical covariate in the population PK model based on monotherapy patients in Study NP30179. The results indicate a significant relationship between trFL versus other histologies and the decay constant Kdes of the time-varying clearance. Kdes was 4.76-fold higher in trFL versus non-trFL patients, reflecting a 4.76-fold shorter half-life of the transition from the initial total clearance value (i.e., sum of CLL and CLT0) to the linear clearance only CLL.

When considering the population PK model estimates, the estimated AUC_{D1} and AUC_{C1+C2} were very close in a trFL patient as compared to a non-trFL patient (i.e., 1.91% and 0.807% higher, respectively), suggesting that despite a statistically significant improvement of the population PK model fit when including the histology-Kdes relationship, there was a minor impact on the estimated exposures.

Gender was assessed during the covariate screening step on all the population PK model parameters. However, gender was not retained in the final reduced population PK model following the backward elimination process.

The ER analysis of both efficacy and safety of glofitamab did not suggest any significant relationship between CRR, ORR or the occurrence of Grade ≥2 CRS and gender.

The glofitamab population PK analysis dataset included 320 (80.2%) White, 3 (0.752%) Black or African American, 16 (4.04%) Asian and 60 (15%) other/unknown race patients. Differences relating to Black/African American or Asian race could not be tested in the covariate screening steps for both population PK and ER analyses owing to a lack of data.

The effect of body weight on glofitamab PK was investigated in the population PK model based on monotherapy patients in Study NP30179. Among the 399 patients included in the analysis, the median body weight is 74.3 kg with range of 31 kg to 148 kg.

The variation in body weight resulted in a -18.7% up to +28.0% of the AUC_{D1} and in a -24.4% up to +39.5% of the AUC_{C1+C2} in the higher (i.e., 107 kg) and lower (i.e., 47.5 kg) limits of the 2.5th to 97.5th body weight range, respectively, as compared to the median value (74.0 kg), when considering the PopPK model estimates.

The population PK model estimated PK exposures over the first day (AUC_{D1}) or over the first 2 cycles (AUC_{C1+C2}) following administration of the intended registration dose and schedule of 2.5/10/30 mg, across the body weight quartiles for all patients in the population PK analysis (Q1 to Q4) showed that heavier patients had lower exposure due to fixed dosing. However, the 2.5th to 97.5th percentiles of exposures are greatly overlapping across the body weight quantiles. At the intended registration dose

and schedule of 2.5/10/30 mg step-up dosing regimen, the simulated glofitamab PK exposure (median [95%CI]) over the first 2 cycles (AUCC1+C2) were 75.3 µg/mL•day (5.16-119), 57.0 µg/mL•day (3.59-97.7), 55.2 µg/mL•day (3.32-82.5) and 48.7 µg/mL•day (2.96-71.2) for the body weight group of (44.4, 67.0) (N=43), (67.0, 75.0) (N=47), (75.0, 85.0) (N=37) and (85.0,133) (N=42), respectively.

The effect of age on glofitamab PK was investigated as a potential continuous covariate in the population PK model based on monotherapy patients of Study NP30179. The results showed that age had no statistically significant impact on the glofitamab PK parameters. The associated p-value when assessing the baseline age on CLL, CLTL0, V1, V2 and Q were 0.469, 0.842, 0.780, 0.523 and 0.888, respectively.

Table 7 Older patients in glofitamab clinical trials

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials NP30179 (N=399)	134 (33.6%)	62 (15.5%)	4 (1.00%)

The ER analysis of CRS of glofitamab did not suggest any significant relationship between occurrence of Grade ≥2 CRS and the baseline age used as a continuous covariate (from 21 to 90 years). Similarly, in the ER analyses of efficacy, the covariate screening did not reveal a significant relationship between CRR or ORR and baseline age used as a continuous covariate.

Immunogenicity

As of the PK and ADA data cutoff date of the 18 April 2022, a total of 442 patients were evaluable for immunogenicity assessment with a baseline sample and at least one post dose sample. The majority (94.6%) of 418 ADA-evaluable patients who received glofitamab monotherapy were negative for ADAs at baseline and remained negative on treatment in Study NP30179. Two patients (0.5%) that were negative at baseline, developed ADAs while on study, one at the end of treatment visit, and the other at a follow up visit of 12 months. Both patients had a complete remission and continued to be in complete response beyond the timepoint of positive ADAs.

Therefore, there is no evidence to indicate formation of neutralizing antibodies as a theoretical mode of tolerance or resistance to therapy.

Pharmacokinetic interaction studies

No DDI study was performed.

PBPK modeling was performed to estimate the magnitude of potential drug interactions caused by the transient increase in interleukin-6 (IL-6) levels during the first cycle of glofitamab treatment with step-up dosing.

Data suggests that the main impact of the highest observed transient increase in IL-6 levels (>1000 pg/mL) following glofitamab administration would be to increase by a factor up to two fold the exposure of drugs predominantly metabolized by CYP3A4 enzyme (i.e., simvastatin and midazolam). This level of IL-6 increase was observed in a very limited number of patients in Study NP30179. This predicted impact was expected as among all the CYP, CYP3A4 had in vitro the highest susceptibility to the CYP activity reduction by IL-6 (Dickmann et al. 2011). Since simvastatin and midazolam are

sensitive substrates of CYP3A4, the effect of IL-6 on less-sensitive CYP3A4 substrates is expected to be lower.

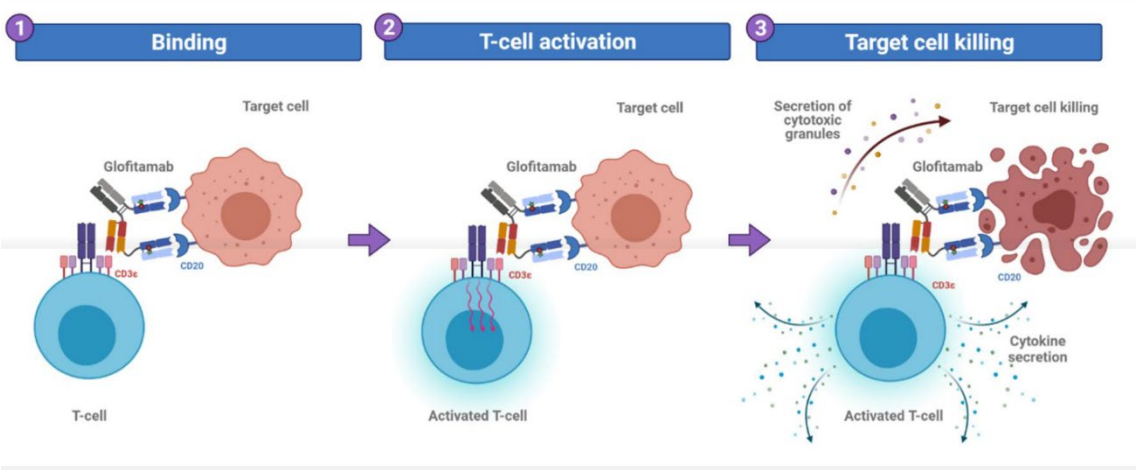
This suggests that the magnitude of the suppressive effect of transient IL-6 increase on hepatic CYP enzyme activities is <50%. In addition, the changes in exposures to substrates of CYP3A4, CYP1A2, and CYP2C9 are expected to be lower than or equal to twofold in the worst-case scenario and the magnitude of CYP suppression is dependent on the duration of cytokine elevation.

Pharmacodynamics

Mechanism 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 a 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.

Figure 9 **Schematic Representation of Glofitamab Mode of Action**



2:1="2:1" molecular format denoting 2 Fab domains binding to CD20 and 1 Fab domain binding to CD3; CD3ε=CD3 epsilon subunit; Fab=fragment antigen-binding; TCB=T-cell bispecific.
Notes: Glofitamab (CD20-TCB) simultaneously binds to CD3ε expressed on T cells and CD20 expressed on B cells. CD3 cross-linking results in T-cell activation and cytokine and cytotoxic granule release, and ultimately leads to tumor cell killing.

Primary and Secondary pharmacology

Obinutuzumab is an anti-CD20 monoclonal antibody which is approved for the treatment of untreated chronic lymphocytic leaukemia, R/R FL and untreated FL. All patients were pre-treated with obinutuzumab 1000 mg 7 days prior to treatment with glofitamab.

Glofitamab and obinutuzumab both bind to CD20 on the same epitope, and the high concentrations of circulating obinutuzumab will compete with glofitamab. Interim ER analysis prior to the 6th July 2021

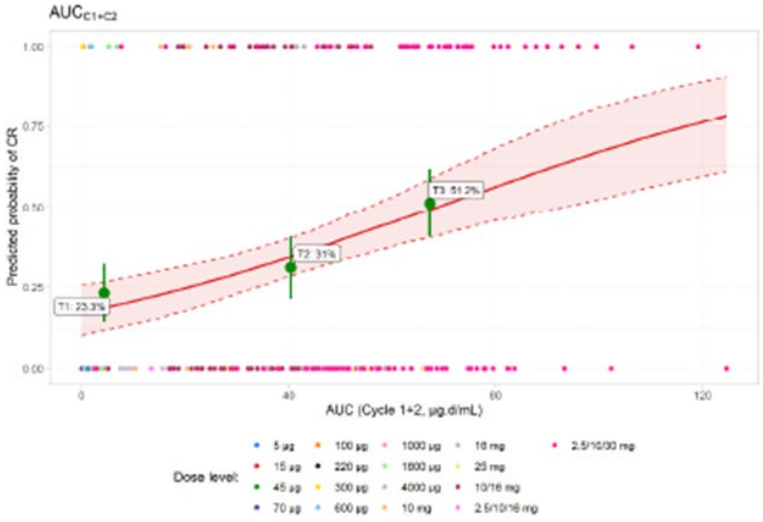
PK cut off have been conducted, and were used to identify suitable dosing regimens for Part III (Djebli et al 2019, Djebli et al 2020). The PK exposure parameter utilized in these analyses was glofitamab receptor occupancy (RO).

The relationship between IRC-assessed clinical objective response (CRR or ORR) and the population PK estimated cumulative glofitamab AUC over the first and second cycles (AUC_{C1+C2}) was determined by a logistic regression model. The results of the final ER efficacy modeling are shown below.

Figure 10

AUC_{C1+C2} – Response Analyses for IRC-CRR and IRC ORR Following IV Administrations of Glofitamab Monotherapy (Study NP30179 - R/R DLBCL patients Monotherapy Cohorts)

a) Complete Response Rate (CRR)



p-value = 3.59×10^{-6} for CRR

b) Overall Response Rate (ORR)

p-value = 1.40×10^{-6} for ORR

AUC_{C1+C2}=area under the concentration-time curve to the end of cycle 2 of glofitamab treatment; CR=complete response; DLBCL=diffuse large B-cell lymphoma; overall response; IV=intravenous; IRC=independent review committee; R/R=relapsed/refractory.

From the exposure-QTc modeling analysis, a Maximum Effect (E_{max}) model fitted the data well for predicted glofitamab concentrations (obtained from the population PK model) versus the observed QT prolongation.

The model estimated an E_{max} value of 10.6 ms. Based on this model, the upper limit of the 90%CI around the QT prolongation effect crosses the 10 ms boundary at a concentration of 7.27 µg/mL of gloftamab). Given the nature of the Emax model, the QTc prolongation will tend to reach the value of 10.6 ms at higher concentrations (i.e., typical value of QTc prolongation is not expected to be higher than 10.6 ms at highest concentrations based on the E_{max} model).

The model shows that median [95%CI] predicted C_{max} following the target 30 mg dose is 9.17 [0.637;15.9] µg/mL suggesting that 71.6% of the patient receiving 2.5/10/30 mg step-up dosing crossed the 7.27 µg/mL value following the first 30 mg dose (i.e., 121/169 patients) however, without translating in an association with cardiac events.

Simulations suggested that 23.0% of subjects might be expected to exceed 20 ms on this regimen. A total of 12.8% of simulated patients were predicted to exceed an absolute QTc level of 450 msec, but less than 1% were predicted to exceed 480 msec.

Although the model suggested a potential relationship between a QT prolongation and glofitamab exposures, this prolongation was estimated to plateau at just above 10 ms in the typical patient. The analysis had however several limitations.

Based on the updated cut-off date (15 June 2022), the applicant reviewed all cases of 16 patients where a prolongation Fredericia-corrected QT interval (QTcF)> 450 msec was reported in the primary safety population. Of the patients who experienced a prolonged QTcF, six of these were observed at the 30mg dose.

2 patients (1.4%) had post-baseline QTcF values ≥ 500 ms.

The ER analyses indicate that clinical responses including complete response rate (CRR) and overall response rate (ORR) significantly increase (p-value $3.59x10^{-6}$ and $1.40\ x10^{-6}$, respectively) with increasing glofitamab exposure for all histologies.

Glofitamab exposure was defined as the total AUC for cycles 1 and 2 (AUC_{C1+C2}) when the total NP30179 R/R DLBCL population including the complete dose range explored in the study (0.005 – 30 mg) was analyzed. This observation was confirmed when considering the glofitamab exposure (AUCC1+C2) in tertiles with 23.3%, 31.0% and 51.2% of CRR in AUCC1+C2 in tertiles 1, 2 and 3, respectively.

Similarly, the observed ORR was 38.4%, 44.8% and 67.4% in tertiles 1, 2 and 3, respectively.

When focusing only on the exposure response analysis using the efficacy from Cohort D3, which utilized step-up dosing (2.5/10/30 mg), results demonstrated a shallower relationship between glofitamab exposure and the clinical response (p-value =0.0327 for CRR and 5.33 x10-4 for ORR) in patients with R/R DLBCL.

The ER relationships for safety were assessed on 399 PK-evaluable patients with R/R NHL receiving IV administration of glofitamab from Study NP30179.

Dosing of glofitamab following the 2.5/10/30 mg step-up dosing regimen is associated with an incidence of Grade ≥2 CRS (by American Society for Transplantation and Cellular Therapy [ASTCT]) of 16.4% across all cycles in the safety population (n=152) and an incidence of 12.7% following the first dose of 2.5 mg.

The exposure-CRS analysis on the total PK-evaluable population of 399 patients (covering a wide range of exposures and dosing regimens), with starting doses over a 5,000-fold range from 0.005 mg to 25 mg, indicates that the risk of experiencing CRS Grade ≥2 significantly increases (p-value = 0.00380) with increasing glofitamab average RO% over the first 24 hours after the first dose (AvRO%D1). This observation was confirmed when looking at the AvRO%D1 quartiles with 20.6%, 24.8%, 18.8% and 35.6% in quartiles 1, 2, 3 and 4, respectively.

The exposure-neutropenia analysis on the total PK-evaluable patient population, indicates the absence of any relationship between glofitamab exposure and the incidence of Grade ≥2 neutropenia (p-value of 0.711 for AUC_{C1+C2} and 0.364 for $AvRO\%_{C1+C2}$).

2.6.3. Discussion on clinical pharmacology

The PK, pharmacodynamics (PD), and immunogenicity results were all derived from Study NP30179 which was conducted in patients with R/R NHL, R/R DLBCL and R/R FL. Hence PK data are expected to represent the target population.

A total of 399 patients (221 in Part I and II, and 178 in Part III) who had at least 1 post dose quantifiable glofitamab PK sample were included in the PK analysis. The data base with 399 patients is rather small but is considered to be sufficient. The clinical pharmacology characterization is based on various dose steps, dosing regimens, pre-treatments and subgroups of disease (Cohorts A1 and A2 (Fixed dosing 0.005-10 mg, Q2W, N=75); Cohorts B2, B3, and B4 (Fixed dosing 0.6-25 mg, Q3W, N=109) and Cohorts D2 [Sub. 1] (step-up dosing 2.5/10/16 mg, Q3W, N=16), D2 [Sub. 2 and Sub. 4], D3, D4 and D5 (2.5/10/30 mg, Q3W, N=169) and F2 (extended step-up dosing 0.5/2.5/10/30 mg, Q3W, N=30)).

Bioanalysis of glofitamab, obinutuzumab and tocilizumab were conducted using validated ELISA assays. ADAs against glofitamab were detected using validated ELISA assays, with appropriate level of drug tolerance. No NAb analyses were conducted. However, in case that nAbs are suspected in future/during the study, i.e. reduced drug exposure detected for ADA-positive individuals, the development of a separate NAb assay should be considered. Glofitamab can undergo post-translational modifications by deamidation and/or Fab glycosylation and thus escape detection by the quantitative assay. The extent could potentially be up to 45% of the drug still in circulation within a treatment cycle of 21 days with the biologically active N106 deamidation contributing about 30%. Commercially available immunoassay kits were validated for determination of IL-6 and IL-6sR levels in human serum samples from Study NP30179. Final reports covering bioanalysis in Study NP30179 should be provided, as recommended by the CHMP.

Glofitamab concentration-QT interval relationship was investigated using mixed-effects modelling and the results suggested the upper limit of the 90% confidence interval of the mean concentration-ΔQTcI relationship was estimated to reach the 10 ms threshold of concern at a glofitamab concentration of 7.27 µg/mL. However, severe deficiencies in the underlying data significantly limited the analysis of the concentration-QT relationship and its conclusions should be interpreted with caution. It is possible that the actual concentration-QT relationship for glofitamab may be stronger or weaker than estimated.

A literature based PBPK model was used to reflect the IL-6 kinetics induced by glofitamab and predict the worst-case scenarios for drug interactions mediated by the transient increase in IL-6 during Cycle 1. A dedicated drug interaction study in patients was not conducted. The PBPK model for IL-6 is not considered qualified according to the EMA PBPK Guideline. The predictions were used to support a recommendation for close observation of patients being treated with medications with a narrow therapeutic index during Cycle 1.

No plasma protein binding or tissue distribution study was performed and the metabolic pathways of glofitamab have not been investigated. This is acceptable for an IgG antibody (see SmPC section 5.2). Glofitamab exhibits linear and dose-proportional pharmacokinetics in the dose range studied (0.005 to 30 mg) and is independent of time. As a monoclonal antibody its pharmacokinetics are not expected to be impacted by renal or hepatic impairment which was supported by the population PK model.

Although, population PK modeling based on Study NP30179 in 253 men (63.4%) and 146 women (36.6%) indicates no clinically meaningful effect of gender on glofitamab pharmacokinetics, comparing male patients with female patients in the primary safety population, a slightly higher incidence of deaths (41.0% vs. 34.6%), fatal AEs (6.0% vs. 1.9%), AEs leading to withdrawal from study drug (10.0% vs. 3.8%), and CRS (by ASTCT 2019) (64.0% vs. 57.7%) were reported. A significant relationship between trFL versus other histologies and Kdes was seen (~5-fold higher Kdes in trFL versus non-trFL patients). However, glofitamab exposures were similar between all histologies. Body weight impacted PK, AUCD1 was -18.7% to +28.0% and AUC_{C1+2} -24.4% to +39.5% of the AUC_{C1+C2} for a 107 and 47.5 kg patient respectively compared to the median 74.0 kg subject. However, as exposures overlap greatly across body weight quartiles, and coupled with the absence of impact of body weight in exposure-response models of efficacy and safety, it can be agreed that no dose adjustments may be needed based on body weight. No dedicated DDI studies were conducted, PBPK modeling was used to generate estimations on IL-6 caused CYP suppression. This is acceptable, as no other CYP or transporter mediated DD is expected for monoclonal antibodies. However, a warning has been introduced in section 4.4 of the SmPC to raise clinicians' awareness on the possibility of IL-6 caused CYP suppression derived interactions.

The mechanism of action is sufficiently described and plausible. Primary pharmacology was shown by receptor occupancy.

There is no substance specific or class effect suspected to cause QTc prolongation. However, based on the updated data (CCOD: 15 June 2022) a prolongation of the Fredericia-corrected QT interval (QTcF)> 450 ms was reported in 16 subjects and over ≥ 500 ms in 2 subjects. The applicant reviewed all and considers no association has been observed between adverse clinical outcomes and QTcF over 450 msecs. The occurred QTc prolongation/results on cardiac electrophysiology are reflected in section 5.1 "Pharmacodynamic effects" of the SmPC to inform prescribers and patients. Currently, there is no clear clinical evidence that the mechanism of action of glofitamab results in QT prolongation with a cardiac event, but 16 patients in the primary safety population experienced a prolonged QTcF > 450 msec. Fifteen of the 16 patients experiencing these QT prolongations were noted to have concomitant medications that are potential confounding factors for post-baseline QTcF values > 450 ms and no recurrence of QTcF prolongation were noted after subsequent doses of glofitamab. Therefore, it is considered to be acceptable, that concomitant medication restrictions are not warranted with glofitamab administration. Efficacy-Response relationship was shown by clinical responses including complete response rate (CRR) and overall response rate (ORR) significantly increasing with increasing glofitamab exposure for all histologies. Given the lack of a dose-finding study and the limitations of the applied simulations, there remains some uncertainty that the chosen 2.5/10/30mg dose is the optimal one with regards to both, efficacy and safety. However, the 2.5/10/30mg dose regimen is the only one with an adequate size of efficacy and safety data base and based on the provided efficacy and safety data it seems that 2.5/10/30 mg is appropriate to treat patients with R/R DLBCL with ≥2 prior lines of therapy, as the risks seems to be manageable and efficacy has been demonstrated. Therefore, the proposed dosing regimen of 2.5/10/30 mg may be acceptable. Safety-Response relationship was shown for CRS, significantly increasing with increasing glofitamab average RO% over the first 24 hours after the first dose. No Safety-response relationship was seen for neutropenia.

Based on the original presentation of the ER-Analysis for safety the risk of experiencing CRS Grade ≥2 for patients treated with the dosing regimen 2.5/10/30 mg was mostly between the AvRO%D1 quartile

1 and 3. However, because the individual dose regimens could not be clearly identified based on the original presentation, the applicant was requested to provide the percentage of patients for each dosing regimen per each quartile and additionally per starting dose. Based on this representation of the ER-Analysis data for safety provided the risk of experiencing CRS Grade≥2 for patients treated with the dosing regimen 2.5/10/30 mg were mostly within the AvRO%D1 quartile 2 (n=77 [76.2%]) and quartile 3 (n=80 [79.2%]). The highest dose studied during the dose escalation studies was 25mg; step-up dosing was selected to start at a low dose and increase with subsequent dose to mitigate the risk of CRS at early doses and to enable a higher target dose to be reached. The 30 mg dose was selected based on the ER modelling to maximise the potential for efficacy. Glofitmab is a bispecific antibody and thus binding to CD3 and CD20; it has only a monovalent binding to CD3 with low affinity and will bind with considerably more efficiency to B cells compared to T cells when administered to patients. However, receptor occupancy of CD3 has not been estimated.

The population pharmacokinetic analysis of glofitamab showed that creatinine clearance does not affect the pharmacokinetics of glofitamab. The pharmacokinetics of glofitamab in patients with mild or moderate renal impairment (CrCL 30 to < 90 mL/min) were similar to those in patients with normal renal function. Columvi has not been studied in patients with severe renal impairment.

Population pharmacokinetic analyses showed mild hepatic impairment does not affect the pharmacokinetics of glofitamab. The pharmacokinetics of glofitamab in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 × ULN or AST > ULN) were similar to those with normal hepatic functions. Columvi has not been studied in patients with moderate or severe hepatic impairment.

No clinically significant differences in the pharmacokinetics of glofitamab were observed based on age (21 years to 90 years), gender and body weight (31 kg to 148 kg).

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology of glofitamab was overall sufficiently described. Relevant information has been included in section 5.2 of the SmPC.

In accordance with the CHMP recommendations, the applicant commits to submitting the final CSR for StudyNP30179 at the end of the study (LPLV per protocol) together with the final incremental BARs. For any additional interim CSRs/BARs produced prior to the final CSR that may not have been submitted to the EMA, these will be sent at the time of the final CSR.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

No stand-alone dose-finding study was conducted. Exposure-response analyses on basis of the dose escalation cohorts of Study NP30179 were used to find the highest possible efficacious and simultaneously most safe dose, resulting in a step-up approach.

Initial exposure-response analyses indicated that a dose of 30 mg glofitamab was required to maximize clinical response. However, administration of 25 mg as a fixed dose resulted in high rates of CRS, making this an unsuitable dose to administer at treatment initiation.

Consequently, there was a decoupling of the exposure-CRS and exposure-efficacy relationships, and a step-up dosing regimen was recommended with an initial starting dose of 2.5 mg glofitamab to

mitigate CRS, with a rapid step up to the required target dose of 30 mg to maximize the potential for efficacy.

Although 2.5/10/30 mg Q3W with single obinutuzumab administration is sought for approval, it is noted that still, double dose obinutuzumab pre-treatment as well as three-step dose ascending regimen is being investigated. In response to the possible risk that the pretreatment/dosing/schedule is not considered final, the applicant has confirmed that no further investigations of the glofitamab dose, dosing regimen, or the steroid pre-medication or Gpt are ongoing for patients with R/R DLBCL who have received ≥ 2 prior lines of therapy.

Moreover, the applicant claims that the 4-step-up dosing is problematic, because it appears not to have reduced the overall Grade 2 and more CRS incidence and prolongs the timespan to final dose.

As to pretreatment with double dose obinutuzumab in MCL the rationale is disease –specific. Patients with MCL have an initial 2-fold higher clearance of obinutuzumab than patients with DLBCL and other histologies (Gibiansky et al. 2014). This translates to a higher glofitamab receptor occupancy with 1000 mg Gpt. Therefore, 2000 mg Gpt is being tested as pretreatment for R/R MCL patients only.

Finally, CHMP confirms that the 4 step up and double obinutuzumab pretreatment was triggered by specific histology of entities other than DLBCL. Therefore, it is agreed that the requested dose and regimen may be considered final for the target population and mature enough for approval.

Drug exposure

Additionally, an issue for drug exposure has been identified: Per Study Protocol, glofitamab monotherapy was initially given as 8 cycles, with the option to give another 4 cycles (a total of 12) if this was considered in the best interest of the patient. From Study Protocol, Version 9, the treatment period was fixed at 12 cycles. All patients in Cohort D3 were enrolled to have the fixed treatment period of 12 cycles.

With a fixed treatment duration of 12 cycles (approximately 8.3 months) and the majority of CRs achieved early on during the treatment (median 42 days), up to approximately 7 months CR follow-up occurs while a patient receives glofitamab treatment. Therefore, the current median DOCR follow up of 12.8 months in Cohort D3 and a 12-month event free rate of 74.6% clearly demonstrate that glofitamab responses are maintained beyond the end of treatment. The longest CR follow-up in Cohort D3 was 20 months which is at least 12 months while being off treatment. Additionally, patient convenience and safety are important considerations for limiting treatment to 12 cycles in the target population, given the durable responses observed.

Study Design

Study NP30179 is an ongoing Phase I/II, multicenter, open-label, dose expansion and dose escalation study of glofitamab administered as monotherapy and in combination with obinutuzumab administered after a fixed, single dose pre-treatment with obinutuzumab in patients with R/R B-cell NHL.

This entry into human study consists of three parts (see Figure 1).

- Part I, dose escalation (single-patient cohorts: glofitamab fixed doses 0.005 – 0.045 mg) and
- Part II dose escalation (multiple patient cohorts: glofitamab fixed doses of 0.015 - 25 mg and step-up-doses up to 30 mg) in patients with R/R NHL (mixed histologies), and
- Part III dose expansion cohorts in patients with R/R DLBCL or R/R FL treated with glofitamab at 10/16 mg or 2.5/10/30 mg step-up dosing.

MTD

The dose-escalation cohorts (Parts I and II) were designed to ensure patient safety while minimizing the number of patients exposed to sub-therapeutic doses of glofitamab.

Single-patient dose-escalation cohorts were used in Part I, followed by multiple-patient dose-escalation cohorts in Part II to define a tentative maximum tolerated dose (MTD) or optimal biological dose (OBD). The modified data-augmentation continual reassessment method of escalation with overdose control (mDA CRM EWOC) was used to guide dose-escalation to determine the MTD. In addition, Part II dose escalation explored step-up-dosing regimens.

The dose expansion cohorts (Part III) were initiated when the MTD/OBD was defined to further evaluate the safety, pharmacokinetics and therapeutic activity of glofitamab when given as a single agent.

The final MTD/OBD was estimated based on an analysis of the data for all patients evaluable for dose-limiting toxicities (DLTs) in parts I and II of the study. Dosing regimen of glofitamab 10 mg on Cycle (C)1Day (D)8 (2-week cycle) and glofitamab 16 mg on C2D1 and subsequent three-week cycles (10/16 mg, Q3W) was chosen for the Part III expansion cohorts. Although 10/16 mg has been suggested for Part III, following a Grade 4 CRS event in a patient enrolled to receive 10/16 mg glofitamab in combination with obinutuzumab in the Part II dose escalation multiple patient cohorts (data from obinutuzumab combination cohorts are not reported in this CSR), a step-up dosing regimen was introduced with Protocol NP30179 v8 to reduce the incidence and severity of CRS.

Following evaluation of the observed CRS frequency and severity and initial efficacy data, step-up dosing with 2.5/10/30 mg was considered to be safe and tolerable and was selected as the recommended Phase II dose. This dosing regimen was subsequently investigated in the dose expansion cohorts, in Part III of the study.

For statistical and PK analyses purposes presented in this SCE, obinutuzumab pre-treatment (Gpt) administered 7 days prior to the initial dose of glofitamab (i.e. Cycle 1 Day -7) as described in the study protocol corresponds to Cycle 1 Day 1 (C1D1 = baseline). Consequently, in the analyses, the first dose of glofitamab corresponds to C1D8 and for patients receiving the step-up dosing regimen, administration of the initial low dose of glofitamab (2.5 mg) 7 days after Gpt corresponds to C1D8 and administration of the intermediate 10 mg glofitamab dose 7 days after the first glofitamab dose corresponds to C1D15. Thus, the cycles and days of administration of Gpt and glofitamab presented henceforth in this SCE follows the conventions noted above.

Response based on dose and regimen

Table 8 Summary of IRC-assessed response rate (OR and CR): glofitamab doses ≥ 0.60 mg in dose escalation and dose expansion cohorts (ITT population)

Res-ponse	Glofitamab Dose								
	Mixed R/R NHL Histologies[a]							R/R DLBCL[b]	R/R FL[b]
	0.6 mg N = 15	1.0 mg N = 8	1.8 mg N = 9	4.0 mg N = 10	10 mg N = 15	16 mg N = 23	25 mg N = 8	10/16 mg Cohort B_3 N = 56	10/16 mg Cohort B_4 N = 14
OR, n (%)	5 (33.3)	1 (12.5)	6 (66.7)	4 (40.0)	9 (60.0)	15 (65.2)	3 (37.5)	27 (48.2)	10 (71.4)
CR, n (%)	3 (20.0)	1 (12.5)	4 (44.4)	1 (10.0)	7 (46.7)	13 (56.5)	3 (37.5)	17 (30.0)	8 (57.1)

[a] dose escalation cohorts

[b] dose expansion cohorts

CR = complete response; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; OR = overall response

Table 9 Summary of IRC-assessed response rate (OR and CR): dose escalation and dose expansion cohorts – step up dosing (ITT population)

Response	Glofitamab Dose					
	2.5/10/16 mg Cohort D_2 [Sub. 1] N = 17	2.5/10/30 mg Cohort D_2 [Sub. 2] N = 47	0.5/2.5/10/30 mg Cohort F_2 N = 30	2.5/10/30 mg, Cohort D_2[a] [Sub. 4] N = 31	2.5/10/30 mg Cohort D_3[b] N = 109	2.5/10/30 mg Cohort D_5[b, c] N = 41
OR, n (%)	10 (58.8)	30 (63.8)	24 (80.0)	18 (58.1)	55 (50.5)	22 (53.7)
CR, n (%)	7 (41.2)	27 (57.4)	24 (80.0)	18 (58.1)	39 (35.8)	20 (48.8)

[a] Double Gpt

[b] Includes 1 patient with FL

[c] Dexamethasone pre-medication

CR = complete response; OR = overall response

Four-step dosing in Cohort F2 and double Gpt D2 Sub 4 have higher CR rates than the registrational dose and schedule in the target indication. R/R NHL have been treated in these cohorts.

2.6.5.2. Main study(ies)

Title of study

NP30179 A Multicenter, Open-Label, Phase I/II Study to Evaluate the Safety, Efficacy, Tolerability and Pharmacokinetics of Escalating Doses of Glofitamab (RO7082859) as a Single Agent and in Combination with Obinutuzumab Administered after a Fixed, Single Dose Pre-treatment of Obinutuzumab (Gazyva®/Gazyvaro®) in Patients with Relapsed/ Refractory B-Cell Non-Hodgkin's Lymphoma

Methods

Table 10

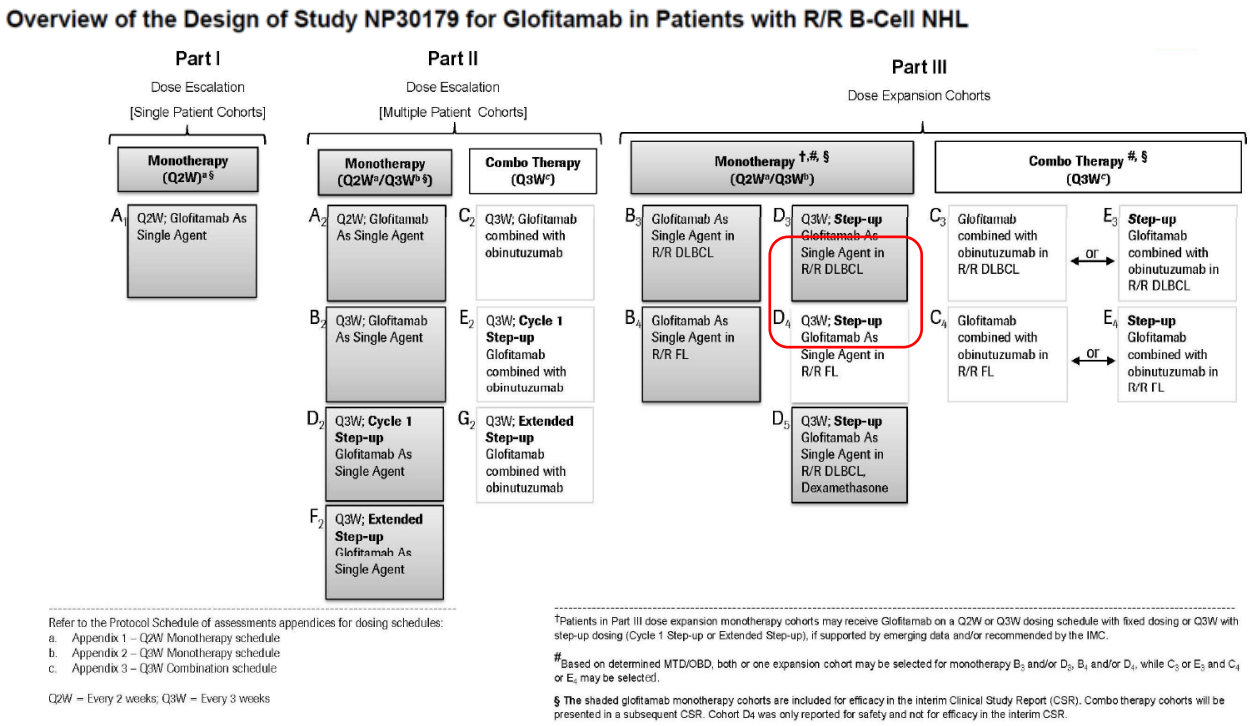
Summary of Study NP30179 in R/R NHL Patients Treated With Glofitamab

Study Number	Overall Design	Patient Population/ Number of Patients	Dose, Route, Regimen
NP30179 Ongoing (clinical cutoff date: 14 September 2021)	Open-label, multicenter, Phase I/II, dose escalation and expansion study	Patients with R/R B-cell NHL Planned: Up to 300 patients during dose escalation (Part I-II), approx. 560 patients across expansion cohorts (Part III) Enrolled: 458 patients treated in Parts I–III (Part I and II: 222 patients; Part III: 236 patients)	Part I and II: Dose escalation in cohorts of R/R NHL patients who received 1 prior line of systemic therapy Fixed dosing: Glofitamab 0.005 mg – 25 mg IV, Q2W or Q3W. Step-up-dosing: Glofitamab 2.5/10/16 mg, 2.5/10/30 mg, 0.5/2.5/10/30 mg IV, Q3W. Part III: Dose expansion in cohorts of R/R DLBCL and R/R FL patients who received ≥2 prior lines of systemic therapy Fixed dosing: Glofitamab 10/16 mg IV, Q3W Step-up-dosing: Glofitamab 2.5/10/30 mg IV, Q3W.

DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; IV = intravenous; NHL = non-Hodgkin's lymphoma; Q2W = every two weeks; Q3W = every three weeks; R/R = relapsed or refractory

Fixed dosing = a fixed dose of glofitamab administered on Cycle 1 Day 8 (C1D8) (C1D15 and C2D1 for doses of 10/16 mg) of each cycle; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory; Step-up-Dosing = dosing with glofitamab on C1D8 and C1D15 followed by dosing on Day 1 in each subsequent cycle.

Figure 11



Study Participants

The inclusion and exclusion criteria are generally in line with standard criteria for clinical trials in this setting:

Key Efficacy Inclusion Criteria

- Age ≥ 18 years.
- Depending upon study part, a history or status of: 1) a histologically-confirmed hematological malignancy that was expected to express CD20; 2) relapse after or failure to respond to at least one prior treatment regimen; and 3) no available treatment options that were expected to prolong survival (e.g., standard chemotherapy or autologous stem cell transplant [ASCT]). Eligible R/R NHL patients included:

  Parts I and II dose escalation cohorts:

  – Grades 1–3b FL; MZL (splenic; nodal; extra-nodal); MCL; DLBCL; PMBCL; Richter's transformation; and trFL

  Part III DLBCL expansion cohorts:

  – DLBCL cohort (DLBCL NOS, HGBCL), PMBCL and trFL. Patients must have relapsed after or failed to respond to at least two prior systemic treatment regimens (including at least one prior regimen containing anthracycline, and at least one containing an anti CD20-directed therapy). Cohorts D3 and D5
- Measurable disease, defined as at least one bi-dimensionally measurable nodal lesion, defined as > 1.5 cm in its longest dimension, or at least one bi-dimensionally measurable extranodal lesion, defined as >1.0 cm in its longest dimension

- Able to provide a fresh biopsy from a safely accessible site, per investigator determination, providing the patient had more than one measurable target lesion
    - In the absence of a fresh biopsy, the most recent archival tumor tissue samples.
- ECOG Performance Status of 0 or 1
- Life expectancy (in the opinion of the investigator) of ≥12 weeks

Adequate liver function: total bilirubin ≤1.5 x ULN. Patients with documented history of Gilbert's Syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible; AST/ALT ≤3 x ULN.

Adequate hematological function: Neutrophil count of ≥1.5 x 10^9 cells/L; platelet count of ≥75,000/µL (and platelet transfusion free within 14 days prior to administration of Gpt); Hemoglobin (Hb) ≥10.0 g/dL (6.2 mmol/L); transfusion free within 21 days prior to administration of Gpt.

Adequate renal function: serum creatinine ≤1.5 x ULN or a creatinine clearance (CrCl) calculated by Cockcroft-Gault formula of ≥50 mL/min for patients in whom, in the investigator's judgment, serum creatinine levels did not adequately reflect renal function

Negative serologic or polymerase chain reaction (PCR) test results for acute or chronic HBV infection. Note: Patients whose HBV infection status could be determined by serologic test results were to be negative for HBV by PCR to be eligible for study participation.

Key Efficacy Exclusion Criteria

- Inability to comply with protocol mandated hospitalizations and restrictions
- Patients with a known or suspected history of HLH
- Patients with acute bacterial, viral, or fungal infection at baseline
- Patients with known active infection, or reactivation of a latent infection, whether bacterial, viral (including, but not limited to, EBV, cytomegalovirus (CMV), hepatitis B, hepatitis C, and HIV), fungal, mycobacterial, or other pathogens (excluding fungal infections of nail beds) or 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
- Prior treatment with systemic immunotherapeutic agents, including but not limited to radio-immunoconjugates, antibody-drug conjugates, immune/cytokines and monoclonal antibodies within 4 weeks or five half-lives of the drug, whichever was shorter, before Gpt infusion
- Treatment with standard radiotherapy, any chemotherapeutic agent, or treatment with any other investigational anti-cancer agent, including CAR-T therapy (within 4 weeks prior to Gpt infusion
- Prior allogeneic stem cell transplantation (SCT)
- Autologous SCT within 100 days prior to Gpt infusion
- Current or past history of CNS lymphoma
- Significant cardiovascular disease
- History of autoimmune disease
- 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 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)
- Received systemic immunosuppressive medications within 2 weeks prior to Gpt infusion. Treatment with corticosteroid ≤25 mg/day prednisone or equivalent is allowed. Inhaled and topical steroids were permitted.

This study was conducted at 41 center(s) that enrolled patients in: Spain (8 centers), France (7 centers), USA (6 centers), Australia (3 centers), Belgium (3 centers), Italy (3 centers), Poland (3 centers), Denmark (2 centers), Taiwan (2 centers), Canada (1 center), Czech Republic (1 center), Finland (1 center), and New Zealand (1 center).

Two populations have been recruited, which are relevant for the current submission. First of all, a population with different NHLs has been recruited in Parts I and II, which were utilized for dose escalation: Grades 1-3b FL; MZL (splenic; nodal; extra-nodal); MCL; DLBCL; PMBCL; Richter's transformation; and trFL.

In the second stage, cohorts with DLBCL, PMBCL and HGBCL were opened to test the dosing for efficacy (Part III). The population utilized for this submission was defined as: DLBCL cohort (DLBCL NOS, HGBCL), PMBCL and trFL. Patients must have relapsed after or failed to respond to at least two prior systemic treatment regimens (including at least one prior regimen containing anthracycline, and at least one containing an anti CD20-directed therapy).

Treatments

An initial low dose of **glofitamab** was administered on C1D8 followed by an intermediate dose of glofitamab one week later on C1D15. The target dose of glofitamab was administered in the following cycle (C2D1) and subsequent three-week cycles.

Obinutuzumab pre-treatment (i.e., Gazyva/Gazyvaro pre-treatment [Gpt]) was given as a safety measure to deplete B-cells both in the peripheral blood and in the secondary lymphoid organs, in an attempt toreduce the risk of sudden cytokine release associated with the first glofitamab administration. All cohorts received Gpt pre-treatment on C1D1, seven days prior to starting glofitamab administration on C1D8. Gpt is a fixed dose of Gazyva/Gazyvaro (obinutuzumab; 1000 mg IV).

Tocilizumab was included to manage a potential safety risk in the treatment of patients with severe CRS and was also classified as an IMP. **Corticosteroid premedication** was given to help reduce the glofitamab-induced cytokine levels.

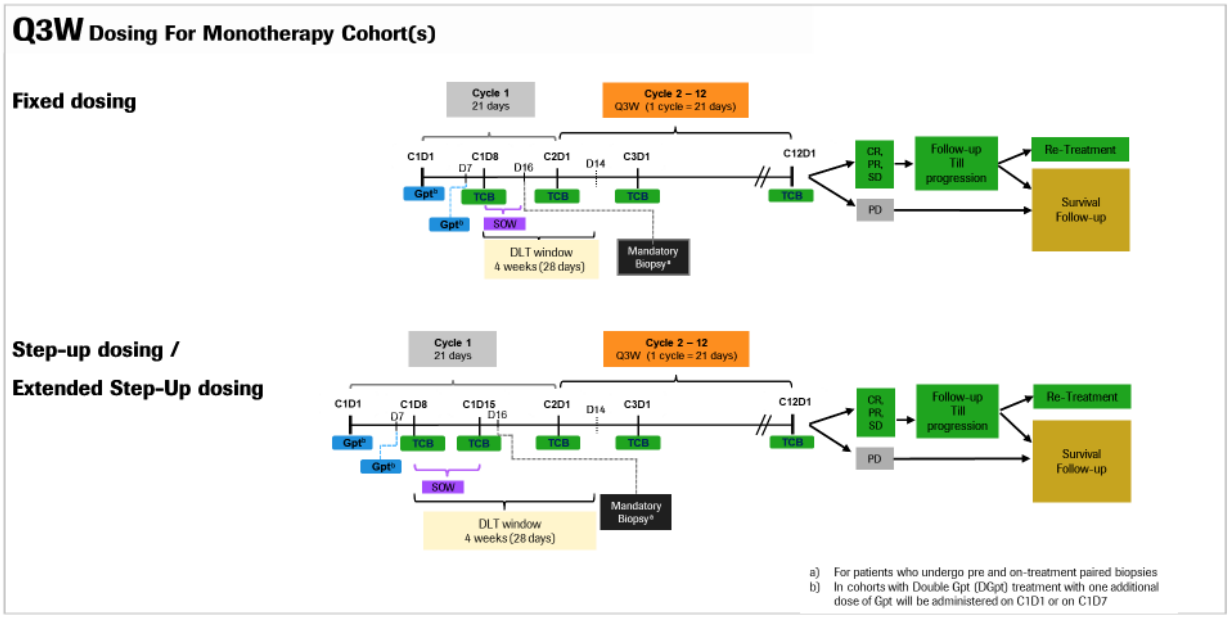
Following evaluation of the observed CRS frequency and severity and initial efficacy data, step-up dosing with 2.5/10/30 mg was considered to be safe and tolerable and was selected as the recommended Phase II dose. This dosing regimen was subsequently investigated in the dose expansion cohorts, initially in Cohort D3, in Part III of the study.

Treatment with glofitamab was for 12 cycles (3-week cycles).

Retreatment with glofitamab (following a new pre-treatment with obinutuzumab) was offered to eligible patients based on their clinical responses after completion of the initial glofitamab treatment.

Figure 12

NP30179: Q3W Dosing Schematic for Glofitamab Monotherapy in Part II or Part III*



TCB=Glofitamab (RO7082859); Gpt = Obinutuzumab pre-treatment; G = Obinutuzumab; Q3W = Every 3 weeks; DLT = Dose Limiting Toxicity; CR = Complete response; PR = Partial Response; SD = Stable Disease; SOW = Safety Observation Window (i.e. 8 days); PD = Progressive Disease

*Adapted from Protocol NP30179 version 10, Figure 4. Cycle 1 study day numbering reflects Gpt administration on Cycle 1 Day 1 per statistical analysis (instead of Cycle 1 Day -7 as described in the protocol).

Objectives

Table 11 Objectives and endpoints

Primary objectives	Endpoints/Outcome Measures
• To evaluate the safety, tolerability, and pharmacokinetics of glofitamab as single agent (*and in combination with obinutuzumab*) following obinutuzumab pre-treatment (Gpt) in patients with relapsed/refractory CD20+ B-cell Non-Hodgkin's Lymphoma (R/R NHL). • To determine the maximum tolerated dose (MTD) or optimal–biologic dose (OBD) and DLTs of glofitamab as single agent (*and in combination with obinutuzumab*) following Gpt in patients with R/R NHL. • To determine a recommended dose and schedule of glofitamab as a single agent (*and in combination with obinutuzumab*) following Gpt.	**Primary safety and tolerability outcome measures:** • The safety and tolerability of glofitamab was assessed using the following primary safety outcome measures: – Incidence and nature of DLTs (Parts I and II) when glofitamab was given as a single agent IV. – (*Incidence and nature of DLTs when glofitamab was given in combination with obinutuzumab*). • Safety and tolerability were additionally assessed using the following safety outcome measures: – Incidence, nature, and severity of all adverse events – Incidence of anti-drug antibody (ADA) formation and events related to immune complex deposition and activation – Incidence of cytokine-release related events (cytokine-release syndrome [CRS] and infusion-related reactions [IRRs]) according to the grading criteria in Lee (2014) – Changes in clinical laboratory values: hematology and biochemistry test results – Changes in vital signs, including systolic and diastolic blood pressure, respiratory rate, pulse rate, and body temperature – Incidence of ECG abnormality **Primary pharmacokinetic outcome measures:** • The following PK parameters were derived from the serum concentration–time profiles of glofitamab following administration, when appropriate as data allowed: – Total exposure (area under the concentration-time curve [AUC]) – Maximum serum concentration (C_{max}) – Minimum serum concentration (C_{min}) – Clearance (CL) – Volume of distribution (V_z)

Primary objectives (Cont.)	Endpoints/Outcome Measures
• To evaluate the efficacy of glofitamab as single agent following Gpt in patients diagnosed with DLBCL (R/R DLBCL not otherwise specified [NOS], high-grade B–cell lymphoma [*HGBCL*], primary mediastinal B-cell lymphoma [PMBCL], DLBCL arising from FL [transformed FL; trFL]) (*and R/R FL*) as measured by Independent Review Committee (IRC)–assessed complete response rate according to standard NHL response criteria (Lugano Classification, Cheson et al. 2014).	**Primary efficacy outcome measure** • IRC-assessed complete response (CR) rate determined according to standard NHL response criteria (Lugano classification, Cheson et al. 2014).
Secondary objectives	**Endpoints/Outcome Measures**
• To establish the safety, tolerability, and pharmacokinetics of Gpt. • To make a preliminary assessment of the anti-tumor activity of glofitamab as a single agent (*and in combination with obinutuzumab*) following Gpt in patients with R/R NHL. • To assess the incidence of ADAs to glofitamab. • *To assess pharmacodynamic (PD) biomarkers, including but not limited to tumor tissue B- and T–cell content and T–cell activation status in a subset of patients.*	**Secondary efficacy outcome measures** • INV-assessed CR rate (Lugano classification: Cheson et al. 2014) • (*IRC- assessed CR rate [Cheson et al. 2007]*) • IRC-assessed overall response rate (ORR) (Lugano classification: Cheson et al. 2014) • INV-assessed ORR (Lugano classification: Cheson et al. 2014) • *(IRC-assessed ORR [Cheson et al. 2007]*) • IRC - and INV-assessed duration of complete response (DOCR) (Lugano classification: Cheson et al. 2014) • IRC- and INV-assessed duration of response (DOR) (Lugano classification: Cheson et al. 2014) • IRC-assessed progression-free survival (PFS) INV-assessed PFS • Overall survival • IRC-assessed time to first complete response (TFCR) (Lugano classification: Cheson et al. 2014) • INV-assessed TFCR (Lugano classification: Cheson et al. 2014) • IRC-assessed time to first overall response (TFOR) (Lugano classification: Cheson et al. 2014) • INV-assessed TFOR (Lugano classification: Cheson et al. 2014)

Secondary objectives (Cont.)	Endpoints/Outcome Measures
	• Incidence of anti-drug antibody (ADA) formation and events related to immune complex deposition and activation
• In Part III of the study, to assess disease-related symptoms, function, and health–related quality of life (HRQoL) according to the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) Lymphoma scale.	• Change from baseline in physical function, role function, and health-related quality of life (HRQoL) according to responses on the EORTC Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) • Change from baseline in disease-related symptoms according to responses on the FACT–Lymphoma Subscale (FACT-Lym LymS)
Exploratory objectives	**Endpoints/Outcome Measures**
• *To evaluate the relationship between glofitamab, as a single agent (and in combination with obinutuzumab) (following Gpt) exposure and PD biomarkers, including, but not limited to, soluble mediators, peripheral B– and T–cell number and T–cell activation status, as appropriate.*	• *Soluble mediators* • *Peripheral B– and T–cell number* • *T–cell activation status*
• *To make a preliminary assessment of tumor burden and/or biologic markers that might act as predictors of the safety or anti-tumor activity of glofitamab as single agent (and in combination with obinutuzumab) including, but not limited to minimal residual disease status (MRD), immune-modulatory phenotypic markers, and soluble mediators.*	• *Tumor subtype (e.g., activated B-cell vs. germinal center B-cell) assessed at baseline in archived material.*
• *To assess the anti-tumor activity of retreatment with glofitamab as single agent (and in combination with obinutuzumab) of patients who achieved an objective response (CR or partial response (PR) or stable disease (SD) and who subsequently show disease progression or relapse.*	• *CR* • *ORR* • *DOR* • *PFS* • *OS* • *Safety*

Exploratory objectives (Cont.)	Endpoints/Outcome Measures
• To make a preliminary assessment of the efficacy of tocilizumab in ameliorating the symptoms of severe CRS following glofitamab treatment as single agent (*and in combination with obinutuzumab*).	• Change in the nature and severity of severe CRS/HLH following administration of tocilizumab for severe CRS/HLH
• In Part III, to assess treatment-related symptoms using the Patient-Reported Outcome Common Terminology Criteria for Adverse Events (PRO-CTCAE).	• Change from baseline in patient-reported treatment-related symptoms based on items from the PRO-CTCAE (Part III only)
• In Part III DLBCL dexamethasone cohort, assess CRS incidence and severity after pre-medication using dexamethasone.	• Incidence and severity of CRS

CR = complete response; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; DOCR = duration of complete response; DOR = duration of response; EORTC QLQ-C30 = EORTC Quality of Life Questionnaire–Core 30; FACT-Lym LymS = FACT–Lymphoma Lymphoma Subscale ; Gpt = obinutuzumab pre-treatment; HLH = hemophagocytic lymphohistiocytosis; INV = investigator; IRC = Independent Review Committee; MTD = maximum tolerated dose; NHL = non-Hodgkin's lymphoma; OBD = optimum biologic dose; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PRO-CTCAE = Patient-Reported Outcome Common Terminology Criteria for Adverse Events; SD = stable disease; R/R = relapsed/refractory; TFCR = time to first complete response; TFOR = time to first overall response;

Objectives and endpoints not included in this interim CSR are noted in italics

Outcomes/endpoints

Primary efficacy endpoint – IRC assed CR rate is acceptable as per Lugano criteria (Cheson et al. 2014) and adequate for determining response in DLBCL and other B-cell non-Hodgkin lymphoma.

Tumor and response evaluations were determined by the IRC and INV on the basis of radiological assessments and bone marrow examinations (if appropriate), using the Lugano classification (Cheson et al. 2014).

Bone marrow examinations (if appropriate) were to include biopsy and/or aspirate for morphology and flow cytometry and were required at screening for staging purposes unless a bone marrow examination had been performed within 3 months prior to study

If positive for tumor cells at screening, a subsequent bone marrow examination was required to confirm a CR. For patients with DLBCL, PET/CT scans could be utilized to assess bone marrow involvement; bone marrow examinations were not required unless clinically indicated

The clinical response assessment was to include an evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly by physical examination.

The IRC, composed of board-certified radiologists and an oncologist with experience in malignant lymphoma, assessed all patients for response and progression on the basis of imaging results, bone marrow biopsy sample results, and relevant clinical data, and were blinded to INV-assessed data and guided by a charter specific to the independent review.

Radiographic Assessments

PET CT is considered mandatory at the diagnosis of DLBCL. FDG PET/CT imaging was the preferred radiologic modality for assessing FDG-avid lymphomas and was recommended to assess baseline tumor burden in this study. Following the baseline PET/CT scan, PET/CT scans could be limited to areas of disease involvement if required by local Health Authorities.

PROs

PROs were measured with validated questionnaires like EORTC QLQ-C30 and FACT-Lym.

Sample size

This is a phase I/II study. The sample size changed during the course of the study. In protocol version 1 (21 Jul 2016) the sample size for the expansion cohort for R/R DLBCL was 40 patients. The expected

width for the confidence interval for the response rate was calculating assuming an observed response of 50% and 65%. In protocol version 6 (8 Aug 2018) the sample size for the R/R DBLCL patients was increased to 100. The expected confidence interval for CR was calculated based on a CR rate of 30% and 35%.

The sample size considerations seem minimalistic, but acceptable and adequate for an exploratory Phase 2 trial. They do not align with standards for a confirmatory trial and does not provide the power to reject a specific CR and have quite different assumptions as planning scenarios.

Randomisation and Blinding (masking)

The study is a single arm multi-cohort study. No randomisation was used. No measures to blind the study team were in place. An internal monitoring committee was used.

Statistical methods

The determination of sample size, planned analyses and statistical tests are described in detail in the NP30179 Statistical Analysis Plan (SAP) v3, and superseded the statistical analyses specified in Protocol NP30179 v10.

Efficacy analysis population

The efficacy evaluable population includes all patients who had at least one response assessment at any time during the study (earliest time point for R/R DLBCL is 49 days since the first dose of glofitamab or 56 days from the first dose of obinutuzumab). The ITT population contains all enrolled patients.

The definition of the ITT-population is endorsed (All patients enrolled in the study will be included in the ITT population used for efficacy analyses). The definition of the efficacy analysis population has changed over time (changes were made in protocol version 6, 7, and 8). In the protocol version 10 (24 Dec 2020), the efficacy analysis population is defined as "*Efficacy Analysis Population: The efficacy-evaluable population will include all patients who have been assessed for response at any time on study, who have withdrawn from treatment or study prior to reaching their first response assessment, or who have been on-study long enough to have reached their first scheduled response assessment, defined as having a minimum of **37** days since the first dose of glofitamab, **or 44** days since the first dose of obinutuzumab pre-treatment, at the time of data cut-off*". It is stated in the CSR that the analysis specified in the SAP superseded those described in the protocol v 10. The applicant presented the IRC-CR rate for the ITT, which includes all enrolled patients.

Primary efficacy endpoint IRC-CR

The applicant aimed to investigate the treatment effect, defined as the number of complete responses, in patients who at least had one scan assessment. Patients with missing assessments are considered non-responders. The applicant performed an indirect comparison of the proportion of observed complete responses against a historical responder rate of 20% using an exact binomial test. Clopper-Pearson confidence intervals were presented.

Participants with missing data included in the efficacy population are considered non-responders. The applicant presented the results for IRC-CR obtained with the ITT as supplementary analysis. The results are comparable to those obtained with the efficacy population.

Estimand framework for the primary endpoint

Variable: Number of patients who achieve a CR according to the IRC assessment of PET-CT scans with use of Lugano criteria.

Population: The study population is defined in Protocol Section 4.2. The primary endpoint analysis will be conducted on the efficacy population.

Treatment: Patients will first receive Gpt and then glofitamab for up to 12 cycles. Tocilizumab will be used to manage any severe CRS that may result.

Intercurrent Event: Missing response assessment because of early study withdrawal or study discontinuation for any reason.

Composite Strategy: Patients included in the efficacy-evaluable population with missing or no response assessments will be included as non-responders.

Population Level Summary: The proportion of patients in the efficacy-evaluable population whose best overall response is a CR based on IRC assessment of PET-CT scans with use of Lugano criteria: Comparisons of CR between the efficacy-evaluable population and historical controls will be conducted by using an exact binomial test with a two-sided alpha level of 5%.

Sensitivity analysis COVID-19

If more than 5% of patients experienced a confirmed/suspected COVID-19 diagnosis, a sensitivity analysis was planned to be performed for the primary endpoint, IRC-assessed CR rate, by removing any patients who experienced a confirmed/suspected COVID-19 diagnosis. An analysis of the safety profile for patients with confirmed/suspected COVID-19 was planned to be performed, and key safety summaries for these patients produced separately.

Secondary efficacy endpoints INV-CR, INV-ORR and IRC-ORR

These were analysed using the same statistical methods as described for IRC-CR.

Secondary time-to-event endpoints DOCR and DOR
The applicant aimed to investigate the duration of response in patients who at least had one scan assessment and achieved a response/complete response. Patients who discontinue the study while responding or start a new anti-cancer therapy before declared PD are censored. Thus, the applicant assumed that the duration of response in those patients would have been similar to that observed in the responders who did not discontinue the study. Kaplan-Meier curves and timepoint estimates were presented for DOR and DOCR.

Estimand Framework for Duration of Response Endpoints

Variable: Duration of patients' response

Population: The study population is defined in Protocol Section 4.2. Duration of response will be calculated for patients who achieve an IRC- or investigator-assessed CR (and PR for DOR) by PET-CT according to Lugano criteria.

Treatment: Patients will first receive Gpt and then glofitamab for up to 12 cycles. Tocilizumab will be used to manage any severe CRS that may result.

Intercurrent Event: Patients who discontinue or withdraw from the study while responding; patients who discontinue treatment when starting a new anti-lymphoma therapy (NALT)

Hypothetical Strategy: Patients who continue to respond will have their data censored at the date of the last response assessment by CT, or PET-CT.

Population Level Summary: Kaplan-Meier estimates will be provided at 3, 6, 9, 12, 18, and 24 months. The median will be presented if reached. The Brookmeyer-Crowley method will be used to construct the 95% CI for the median DOR/DOCR.

Sensitivity analyses

If more than 5% of patients discontinued the study because they were starting a new anti-lymphoma treatment (NALT), an event-free survival analysis was planned to be done with progression, NALT, and death counted as events.

The applicant also planned to perform a sensitivity analysis to assess the impact of COVID-19 for DOR, DOCR, and PFS.

Interim analyses

According to the SAP, the applicant could perform a nonbinding interim analysis for safety and futility for each expansion cohort in Part III of the study. According to the applicant, no interim analysis for efficacy was performed for the D3 cohort. The results from an analysis performed in the D2 cohort were used to inform the decision to continue with the trial in the D3 cohort.

Multiplicity control

The trial has been conducted as an exploratory trial without the usual rigour as seen in a confirmatory trial, e.g. lack of control of type 1 error across hypotheses being tested statistically or insufficient predefinition of hypotheses. Thus, all results should be seen as the basis for the generation of hypotheses on treatment effects, with less or strong belief on the chance of confirming these, based on the individual results only.

Results

Participant flow

The primary efficacy population (N=108) comprises those patients with R/R DLBCL (71.3%), HGBCL (7.4%), PMBCL (5.6%), and transformed FL (15.7%) who have received ≥2 prior systemic therapies treated at the proposed registrational dose of glofitamab of 2.5/10/30 mg in Cohort D3. The clinical cut-off date for the latest update for both patient disposition, efficacy data and safety data is 15 June 2022. In this update, 2 patients have had their diagnosis revised from DLBCL to HGBCL.

Table 12

Summary of Patient Disposition: Patients with R/R DLBCL Who Have Received ≥2 Prior Lines of Systemic Therapy (ITT Population)

	Glofitamab 2.5/10/30 mg Cohort D3 (N=108)	Glofitamab 2.5/10/30 mg Cohort D5 (a) (N=40)	Glofitamab Doses >=10 mg (b) (N=101)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=115)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=155)
Ongoing Study	37 (34.3%)	23 (57.5%)	36 (35.6%)	41 (35.7%)	64 (41.3%)
Discontinued Study	71 (65.7%)	17 (42.5%)	65 (64.4%)	74 (64.3%)	91 (58.7%)
Reason for Study Discontinuation					
Adverse Event	0	1 (2.5%)	0	0	1 (0.6%)
Death	63 (58.3%)	16 (40.0%)	39 (38.6%)	65 (56.5%)	81 (52.3%)
Lost To Follow-Up	2 (1.9%)	0	1 (1.0%)	2 (1.7%)	2 (1.3%)
New Anti-Cancer Therapy	0	0	4 (4.0%)	0	0
Other	0	0	2 (2.0%)	0	0
Physician Decision	0	0	4 (4.0%)	0	0
Progressive Disease	0	0	10 (9.9%)	0	0
Protocol Deviation	0	0	0	1 (0.9%)	1 (0.6%)
Withdrawal By Subject	6 (5.6%)	0	5 (5.0%)	6 (5.2%)	6 (3.9%)
Not Started Treatment	1 (0.9%)	0	1 (1.0%)	1 (0.9%)	1 (0.6%)
Active on Treatment	0	4 (10.0%)	0	0	4 (2.6%)
Completed Treatment	25 (23.1%)	10 (25.0%)	23 (22.8%)	28 (24.3%)	38 (24.5%)
Discontinued Treatment	80 (74.1%)	26 (65.0%)	76 (75.2%)	83 (72.2%)	109 (70.3%)
Reason for Treatment Discontinuation					
Adverse Event	6 (5.6%)	4 (10.0%)	0	7 (6.1%)	11 (7.1%)
Death	8 (7.4%)	3 (7.5%)	3 (3.0%)	8 (7.0%)	11 (7.1%)
Lack Of Efficacy	2 (1.9%)	1 (2.5%)	0	2 (1.7%)	3 (1.9%)
New Anti-Cancer Therapy	0	0	1 (1.0%)	0	0
Other	2 (1.9%)	1 (2.5%)	1 (1.0%)	2 (1.7%)	3 (1.9%)
Physician Decision	6 (5.6%)	3 (7.5%)	5 (5.0%)	6 (5.2%)	9 (5.8%)
Progressive Disease	49 (45.4%)	13 (32.5%)	59 (58.4%)	50 (43.5%)	63 (40.6%)
Protocol Deviation	0	0	0	1 (0.9%)	1 (0.6%)
Symptomatic Deterioration	2 (1.9%)	1 (2.5%)	3 (3.0%)	2 (1.7%)	3 (1.9%)
Withdrawal By Subject	5 (4.6%)	0	4 (4.0%)	5 (4.3%)	5 (3.2%)
Not Started Initial Treatment	1 (0.9%)	0	1 (1.0%)	1 (0.9%)	1 (0.6%)
Active on Initial Treatment	0	4 (10.0%)	0	0	4 (2.6%)
Completed Initial Treatment	27 (25.0%)	10 (25.0%)	24 (23.8%)	31 (27.0%)	41 (26.5%)
Discontinued Initial Treatment	80 (74.1%)	26 (65.0%)	76 (75.2%)	83 (72.2%)	109 (70.3%)
Reason for Initial Treatment Discontinuation					
Adverse Event	6 (5.6%)	4 (10.0%)	0	7 (6.1%)	11 (7.1%)
Death	8 (7.4%)	3 (7.5%)	3 (3.0%)	8 (7.0%)	11 (7.1%)
Lack Of Efficacy	2 (1.9%)	1 (2.5%)	0	2 (1.7%)	3 (1.9%)
New Anti-Cancer Therapy	0	0	1 (1.0%)	0	0
Other	2 (1.9%)	1 (2.5%)	1 (1.0%)	2 (1.7%)	3 (1.9%)
Physician Decision	6 (5.6%)	3 (7.5%)	5 (5.0%)	6 (5.2%)	9 (5.8%)
Progressive Disease	49 (45.4%)	13 (32.5%)	59 (58.4%)	50 (43.5%)	63 (40.6%)
Protocol Deviation	0	0	0	1 (0.9%)	1 (0.6%)
Symptomatic Deterioration	2 (1.9%)	1 (2.5%)	3 (3.0%)	2 (1.7%)	3 (1.9%)
Withdrawal By Subject	5 (4.6%)	0	4 (4.0%)	5 (4.3%)	5 (3.2%)
Active on Retreatment	0	0	0	0	0
Completed Retreatment	0	0	0	0	0
Discontinued Retreatment	2 (1.9%)	0	1 (1.0%)	3 (2.6%)	3 (1.9%)
Reason for Retreatment Discontinuation					
Adverse Event	1 (0.9%)	0	0	1 (0.9%)	1 (0.6%)
Progressive Disease	1 (0.9%)	0	1 (1.0%)	2 (1.7%)	2 (1.3%)

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Patients can not technically complete the study until the study itself finishes.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ds.sas
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23AUG2022 19:52

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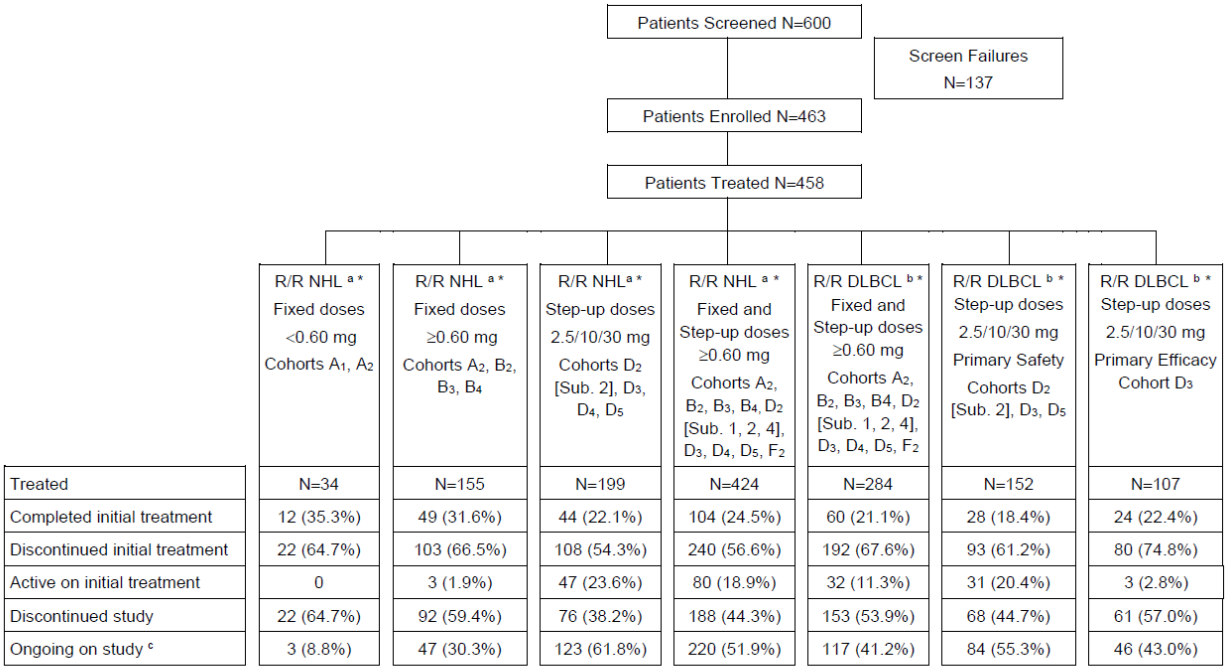
Figure 13

Disposition of Patients Treated with Glofitamab Monotherapy in Study NP30179



	R/R NHL [a] * Fixed doses <0.60 mg Cohorts A_1, A_2	R/R NHL [a] * Fixed doses ≥0.60 mg Cohorts A_2, B_2, B_3, B_4	R/R NHL [a] * Step-up doses 2.5/10/30 mg Cohorts D_2 [Sub. 2], D_3, D_4, D_5	R/R NHL [a] * Fixed and Step-up doses ≥0.60 mg Cohorts A_2, B_2, B_3, B_4, D_2 [Sub. 1, 2, 4], D_3, D_4, D_5, F_2	R/R DLBCL [b] * Fixed and Step-up doses ≥0.60 mg Cohorts A_2, B_2, B_3, B4, D_2 [Sub. 1, 2, 4], D_3, D_4, D_5, F_2	R/R DLBCL [b] * Step-up doses 2.5/10/30 mg Primary Safety Cohorts D_2 [Sub. 2], D_3, D_5	R/R DLBCL [b] * Step-up doses 2.5/10/30 mg Primary Efficacy Cohort D_3
Treated	N=34	N=155	N=199	N=424	N=284	N=152	N=107
Completed initial treatment	12 (35.3%)	49 (31.6%)	44 (22.1%)	104 (24.5%)	60 (21.1%)	28 (18.4%)	24 (22.4%)
Discontinued initial treatment	22 (64.7%)	103 (66.5%)	108 (54.3%)	240 (56.6%)	192 (67.6%)	93 (61.2%)	80 (74.8%)
Active on initial treatment	0	3 (1.9%)	47 (23.6%)	80 (18.9%)	32 (11.3%)	31 (20.4%)	3 (2.8%)
Discontinued study	22 (64.7%)	92 (59.4%)	76 (38.2%)	188 (44.3%)	153 (53.9%)	68 (44.7%)	61 (57.0%)
Ongoing on study [c]	3 (8.8%)	47 (30.3%)	123 (61.8%)	220 (51.9%)	117 (41.2%)	84 (55.3%)	46 (43.0%)

[a] Patients with mixed R/R NHL histologies: ≥1 prior lines of systemic therapy; [b] Patients with R/R DLBCL: ≥2 prior lines of systemic therapy; [c] As of the CCOD (14 September 2021)

* Note that the numbers in the cohort columns are the number of patients in that analysis group so as to match the presentation of the data in the text. They cannot be accumulated to match the number of patients treated, as a particular cohort may appear in more than one analysis group and therefore counted more than once.

Data source: t_ds_LT600_CSR_SE_14SEP2021_30179; t_ds_GE600_CSR_SE_14SEP2021_30179; t_ds_PIV_SCS_SE_14SEP2021_30179

Recruitment

First Patient Enrolled: 14 February 2017

First Patient Enrolled in Cohort D3: 24 March 2020

Last Patient Enrolled: The study is ongoing.

Last Patient Enrolled in Cohort D3: 16 February 2021

Clinical Cutoff Date: 15 June 2022.

The overall median duration of follow-up for Cohort D3 was 15 months (range: 0 to 21 months).

Conduct of the study

Table 13 Summary of key changes to the protocol NP 30179

Protocol Version 1 (21 July 2016) Initial version
Protocol Version 2 (05 October 2016) A dose threshold of 810 μg (flat dose) in Part I was added to ensure that the multiple-patient cohorts (Part II) would begin enrolling close to the start of the estimated therapeutic dose range of 1-10 mg. Part II was to initiate when either a flat dose of 810 (405 μg x2) μg was reached or a glofitamab-related ≥Grade 2 toxicity occurred, whichever came first.
Protocol Version 3 (24 May 2017) Tumor assessment(s) (FDG PET and Diagnostic CT scans) at week 6 (Cycle 3) were incorporated. This additional assessment was supported by data indicating a strong potential for positive responses that occur prior to week 12 of treatment.
Protocol Version 4 (29 September 2017) Removal of Inclusion Criteria 10: "Patient must have a peripheral B-cell count at or below 500 cells/μL at screening". Removal of Cycle 1/Day 8 RO7082859 (glofitamab) dose/infusion.
Protocol Version 5 (8 March 2018) Dose-escalation and expansion cohorts were added to the study to assess the safety, pharmacokinetics (PK), and preliminary anti-tumor activity of glofitamab in combination with obinutuzumab, following pre-treatment with obinutuzumab (Gpt). A Q3W schedule was to be explored for newly enrolled patients assigned to escalation and expansion cohorts receiving glofitamab either as a single agent or in combination with obinutuzumab.

Protocol Version 6 (8 August 2018) The protocol was amended to modify the study design to obtain additional safety, tolerability, pharmacokinetic, and clinical activity data. Based on the clinical activity observed in this study, including complete responses (4/45 patients as of 18 May 2018) and partial responses (14/45 patients as of 18 May 2018) in indolent as well as aggressive R/R NHL, the expansion phase was modified to further assess and confirm clinical activity of glofitamab in a R/R follicular NHL and a R/R DLBCL cohort. In addition, patient reported outcome (PRO) assessments were added to the expansion cohorts.
Protocol Version 7 (2 April 2019) The protocol was amended to update the safety management guidelines for glofitamab and to add a single-arm monotherapy cohort to evaluate the safety, tolerability and PK of glofitamab when administered using the Phase III formulation in a subset of patients with R/R NHL.
Protocol Version 8 (6 August 2019) Protocol v6 was amended to v7 on 02 April 2019; however, v7 was only released to the health authority in the United States. Version 7 was subsequently amended to v8 for global release; therefore, this amendment included all revisions made in v7 and v8. The cytokine release syndrome (CRS) risk description was updated to include factors that may increase risk of severe CRS, updated CRS management guidelines, including guidance regarding glofitamab infusion, usage of tocilizumab and dexamethasone. Investigation of step-up dosing in Cycle 1 was introduced as a possible additional safety measure for CRS. Response Criteria for Malignant Lymphoma was updated to the standard Lugano Classification (rather than the modified Lugano Classification).
Protocol Version 9 (22 May 2020) Protocol v8 was amended to update the initial treatment period to 12 cycles of glofitamab with an additional response assessment in Cycle 9, incorporate new treatment cohorts with extended step-up dosing and double pre-treatment with obinutuzumab (dGpt) prior to first dose of glofitamab, reduce the mandatory hospitalization to 24 hours in Cycle 1, and to update the corticosteroid premedication in later cycles.
Protocol Version 9 France (19 May 2020) The protocol was amended to provide the planned doses for step-up dosing in Cycle 1 as well as dose ranges planned for extended step-up.
Protocol Version 10 (24 December 2020) The protocol was amended to reduce mandatory hospitalization with step-up dosing, re-classify the study to Phase I/II to reflect the overall size of the study and the purpose of Part III of the study, incorporate a new expansion cohort in patients with R/R DLBCL receiving dexamethasone as premedication and include dexamethasone as an option for premedication for all patients.
Protocol Version 10 USA (10 March 2021) Protocol NP30179 was amended as requested by the FDA review to update the mandatory hospitalization required for patients receiving step-up dosing.
Protocol Version 10 France (5 January 2021) Protocol NP30179 (France) was amended to align with the Study NP30179 global protocol amendment v10.
Protocol Version 11 (27 May 2021) The protocol was amended to align with the glofitamab Investigator's Brochure v6, including the incorporation of new adverse event of special interest (AESI) categories, and updating identified and potential risks associated with glofitamab. Furthermore, recommendations regarding SARS-CoV-2 vaccines were added, and the cytokine release syndrome (CRS) management guidelines were consolidated into a single table. Note that as this protocol version was only partly implemented globally as of the CCOD, this CSR is based on Protocol v10.
Protocol Version 11 France (3 June 2021) Protocol NP30179 (France) was amended to align with the Study NP30179 global protocol amendment v11.

Changes following interim database snapshot

There were no changes made to the planned endpoints or analyses following the study database snapshot extract.

Changes to the planned analyses and SAP

There are 3 versions of the SAP. The current version of the SAP was dated 23 Nov 2021. According to the applicant, no changes in the planned analyses were made after the interim database snapshot (19 November 2021). The applicant clarified that the database lock was one day after the finalization of the relevant SAP version 3 and only the database snapshot was taken already on 19 November, i.e. 4 days prior to finalization of the SAP. It is further stated that "Therefore, the applicant's statistical team had no access to the study data and outputs until after SAP version 3 was approved." It is also acknowledged that already in SAP version 2, dated 16 June 2020, it was clarified that the cohort of primary interest (of that SAP) was Cohort D3 and that hypothesis testing was to be conducted for the primary endpoint in that cohort only.

The impact of the COVID-19 specific sensitivity analyses, censoring rules for time to response and duration of response and additional details related to the historical control are indeed not considered critical for the overall outcome of the trial (regardless of whether these decisions had been informed by the data or not). It is also agreed that the key analysis methods for cohort D3 were specified already in the initial SAP, i.e., a binomial test for r/r DLBCL patients against a CR rate of 20% was already defined with SAP version 1. However, the decision to consider cohort D3 as pivotal is – to the best of our knowledge – only documented within SAP version 3 and there only in the list of changes. Given the complexity of the study and its exploratory nature, this is still considered a flaw in the conduct of study which cannot be ruled out by the provided response.

No GCP inspections have taken place for Study NP30179.

Baseline data

In the primary efficacy cohort D3 (N=108) 43.5% were still on study at the CCOD. 24/108 patients (22.2%) had completed initial treatment, 80 patients had discontinued initial study treatment and 3 (2.8%) were still on treatment.

All patients in the primary efficacy cohort D3 have received at least 2 prior lines of therapy, which is in line with the indication sought.

The study population includes a number of different diagnoses (DLBCL NOS, HGBCL, PMBCL) as well as the clinically distinct group of transformed FL.

Table 14

Summary of Demographic Data: Patients with R/R DLBCL Who Have Received ≥2 Prior Lines of Systemic Therapy (ITT Population)

	Glofitamab 2.5/10/30 mg Cohort D3 (N=108)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=40)	Glofitamab Doses >=10 mg(b) (N=101)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=115)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=155)
Age (yr)					
n	108	40	101	115	155
Mean (SD)	61.8 (14.9)	66.2 (14.2)	60.0 (14.5)	62.0 (14.7)	63.1 (14.7)
Median	66.0	73.0	63.0	66.0	66.0
Min - Max	21 - 90	27 - 86	22 - 84	21 - 90	21 - 90
Age group (yr)					
n	108	40	101	115	155
<65	50 (46.3%)	16 (40.0%)	52 (51.5%)	55 (47.8%)	71 (45.8%)
>=65	58 (53.7%)	24 (60.0%)	49 (48.5%)	60 (52.2%)	84 (54.2%)
Sex					
n	108	40	101	115	155
Male	75 (69.4%)	23 (57.5%)	67 (66.3%)	78 (67.8%)	101 (65.2%)
Female	33 (30.6%)	17 (42.5%)	34 (33.7%)	37 (32.2%)	54 (34.8%)
Ethnicity					
n	108	40	101	115	155
Hispanic or Latino	6 (5.6%)	3 (7.5%)	1 (1.0%)	6 (5.2%)	9 (5.8%)
Not Hispanic or Latino	83 (76.9%)	34 (85.0%)	86 (85.1%)	87 (75.7%)	121 (78.1%)
Not Stated	17 (15.7%)	3 (7.5%)	7 (6.9%)	18 (15.7%)	21 (13.5%)
Unknown	2 (1.9%)	0	7 (6.9%)	4 (3.5%)	4 (2.6%)

Race					
n	108	40	101	115	155
Asian	6 (5.6%)	1 (2.5%)	6 (5.9%)	6 (5.2%)	7 (4.5%)
Black or African American	1 (0.9%)	2 (5.0%)	1 (1.0%)	1 (0.9%)	3 (1.9%)
White	80 (74.1%)	34 (85.0%)	86 (85.1%)	85 (73.9%)	119 (76.8%)
Unknown	21 (19.4%)	3 (7.5%)	8 (7.9%)	23 (20.0%)	26 (16.8%)
Weight (kg)					
n	106	39	100	113	152
Mean (SD)	75.56 (15.74)	74.41 (18.79)	75.38 (16.80)	75.13 (15.55)	74.95 (16.38)
Median	74.15	71.00	75.60	73.70	73.65
Min - Max	45.0 - 151.1	44.4 - 118.9	31.0 - 148.2	45.0 - 151.1	44.4 - 151.1
Height (cm)					
n	106	39	100	113	152
Mean (SD)	171.58 (9.84)	168.00 (10.38)	171.03 (9.38)	171.39 (9.94)	170.52 (10.13)
Median	173.00	170.00	172.00	173.00	171.00
Min - Max	144.0 - 193.0	141.0 - 185.4	147.0 - 196.0	144.0 - 193.0	141.0 - 193.0
Body Mass Index (kg/m2) at Baseline					
n	106	39	100	113	152
Mean (SD)	25.64 (4.82)	26.24 (5.69)	25.67 (4.83)	25.56 (4.78)	25.73 (5.02)
Median	24.81	25.97	25.34	24.76	24.81
Min - Max	17.6 - 45.1	17.6 - 44.5	11.8 - 41.9	17.6 - 45.1	17.6 - 45.1
ECOG Status at Baseline					
0	50 (46.3%)	14 (35.0%)	38 (37.6%)	55 (47.8%)	69 (44.5%)
1	57 (52.8%)	25 (62.5%)	61 (60.4%)	59 (51.3%)	84 (54.2%)
2	0	1 (2.5%)	1 (1.0%)	0	1 (0.6%)
Missing/Unknown	1 (0.9%)	0	1 (1.0%)	1 (0.9%)	1 (0.6%)
Cancer Hist. Subtype II at Study Entry					
Diffuse Large B-Cell Lymphoma	77 (71.3%)	29 (72.5%)	70 (69.3%)	81 (70.4%)	110 (71.0%)
High Grade B Cell Lymphoma	8 (7.4%)	2 (5.0%)	8 (7.9%)	8 (7.0%)	10 (6.5%)
Primary Mediastinal B Cell Lymphoma	6 (5.6%)	0	4 (4.0%)	6 (5.2%)	6 (3.9%)
Transformed Follicular Lymphoma	17 (15.7%)	9 (22.5%)	19 (18.8%)	20 (17.4%)	29 (18.7%)

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Data Cutoff Date: 15JUN2022

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Table 15

Summary of Baseline Disease Characteristics: Patients with R/R DLBCL Who Have Received ≥2 Prior Lines of Systemic Therapy (ITT Population)

	Glofitamab 2.5/10/30 mg Cohort D3 (N=108)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=40)	Glofitamab Doses >=10 mg(b) (N=101)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=115)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=155)
Ann Arbor Staging at Study Entry					
n	108	40	101	115	155
STAGE I	10 (9.3%)	0	4 (4.0%)	10 (8.7%)	10 (6.5%)
STAGE II	16 (14.8%)	9 (22.5%)	18 (17.8%)	16 (13.9%)	25 (16.1%)
STAGE III	18 (16.7%)	10 (25.0%)	21 (20.8%)	21 (18.3%)	31 (20.0%)
STAGE IV	61 (56.5%)	20 (50.0%)	58 (57.4%)	65 (56.5%)	85 (54.8%)
UNKNOWN	3 (2.8%)	1 (2.5%)	0	3 (2.6%)	4 (2.6%)
Risk factors for IPI (non-FL patients only)					
n	108	40	101	115	155
0	5 (4.6%)	0	3 (3.0%)	5 (4.3%)	5 (3.2%)
1	15 (13.9%)	7 (17.5%)	21 (20.8%)	17 (14.8%)	24 (15.5%)
2	32 (29.6%)	12 (30.0%)	31 (30.7%)	33 (28.7%)	45 (29.0%)
3	37 (34.3%)	16 (40.0%)	35 (34.7%)	39 (33.9%)	55 (35.5%)
4	19 (17.6%)	5 (12.5%)	11 (10.9%)	21 (18.3%)	26 (16.8%)
Extranodal Disease					
n	108	40	101	115	155
No	38 (35.2%)	21 (52.5%)	45 (44.6%)	39 (33.9%)	60 (38.7%)
Yes	70 (64.8%)	19 (47.5%)	56 (55.4%)	76 (66.1%)	95 (61.3%)
Bulky Disease > 6cm					
n	107	40	101	114	154
No	63 (58.3%)	23 (57.5%)	50 (49.5%)	67 (58.3%)	90 (58.1%)
Yes	44 (40.7%)	17 (42.5%)	51 (50.5%)	47 (40.9%)	64 (41.3%)
Bulky Disease > 10cm					
n	107	40	101	114	154
No	92 (85.2%)	36 (90.0%)	85 (84.2%)	99 (86.1%)	135 (87.1%)
Yes	15 (13.9%)	4 (10.0%)	16 (15.8%)	15 (13.0%)	19 (12.3%)

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
All baseline statistics refer to the initial treatment phase.
Data Cutoff Date: 15JUN2022

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Table 16

Summary of Prior Cancer Therapies: Patients with R/R DLBCL Who Have Received ≥2 Prior Lines of Systemic Therapy (ITT Population)

	Glofitamab 2.5/10/30 mg Cohort D3 (N=108)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=40)	Glofitamab Doses >=10 mg(b) (N=101)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=115)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=155)
Prior Cancer-related Surgery	36 (33.3%)	15 (37.5%)	39 (38.6%)	40 (34.8%)	55 (35.5%)
Prior Radiotherapy	33 (30.6%)	13 (32.5%)	35 (34.7%)	36 (31.3%)	49 (31.6%)
Prior Cancer Therapy	108 (100%)	40 (100%)	101 (100%)	115 (100%)	155 (100%)
Chemotherapy	108 (100%)	40 (100%)	101 (100%)	115 (100%)	155 (100%)
Anti-CD20 Monoclonal Antibody	108 (100%)	40 (100%)	101 (100%)	115 (100%)	155 (100%)
Non Anti-CD20 Monoclonal Antibody	18 (16.7%)	7 (17.5%)	21 (20.8%)	18 (15.7%)	25 (16.1%)
Conditioning Regimen For Stem Cell Transplant	21 (19.4%)	6 (15.0%)	17 (16.8%)	25 (21.7%)	31 (20.0%)
Signaling Pathway Inhibitor	11 (10.2%)	3 (7.5%)	12 (11.9%)	14 (12.2%)	17 (11.0%)
Immunotherapy Non Stem Cell Transplant	10 (9.3%)	4 (10.0%)	7 (6.9%)	10 (8.7%)	14 (9.0%)
PI3K Inhibitor	3 (2.8%)	0	0	3 (2.6%)	3 (1.9%)
Car-T Therapy	38 (35.2%)	13 (32.5%)	10 (9.9%)	39 (33.9%)	52 (33.5%)
Anthracycline	106 (98.1%)	39 (97.5%)	101 (100%)	113 (98.3%)	152 (98.1%)
Alkylator	108 (100%)	40 (100%)	50 (49.5%)	115 (100%)	155 (100%)
Immunomodulatory Imide	16 (14.8%)	5 (12.5%)	7 (6.9%)	17 (14.8%)	22 (14.2%)
Autologous Stem Cell Transplant	18 (16.7%)	6 (15.0%)	16 (15.8%)	22 (19.1%)	28 (18.1%)
Other	26 (24.1%)	9 (22.5%)	19 (18.8%)	27 (23.5%)	36 (23.2%)
Number of Prior Lines of Cancer Therapy per Subject					
n	108	40	101	115	155
Mean (SD)	3.1 (1.2)	3.0 (1.1)	3.2 (1.6)	3.1 (1.2)	3.1 (1.2)
Median	3.0	3.0	3.0	3.0	3.0
Min - Max	2 - 7	2 - 7	2 - 9	2 - 7	2 - 7
Prior Lines of Cancer Therapy per Subject (Cat)					
2	43 (39.8%)	17 (42.5%)	46 (45.5%)	44 (38.3%)	61 (39.4%)
3	34 (31.5%)	12 (30.0%)	27 (26.7%)	37 (32.2%)	49 (31.6%)
>3	31 (28.7%)	11 (27.5%)	28 (27.7%)	34 (29.6%)	45 (29.0%)
Numbers of Prior Lines of Cancer Therapy (N)					
2	43 (39.8%)	17 (42.5%)	46 (45.5%)	44 (38.3%)	61 (39.4%)
3	34 (31.5%)	12 (30.0%)	27 (26.7%)	37 (32.2%)	49 (31.6%)
4	18 (16.7%)	8 (20.0%)	13 (12.9%)	19 (16.5%)	27 (17.4%)
5	7 (6.5%)	2 (5.0%)	5 (5.0%)	8 (7.0%)	10 (6.5%)
6	4 (3.7%)	0	4 (4.0%)	5 (4.3%)	5 (3.2%)
7	2 (1.9%)	1 (2.5%)	4 (4.0%)	2 (1.7%)	3 (1.9%)
9	0	0	2 (2.0%)	0	0
Category Time from Last Prior Therapy to First Study Treatment (0-3 vs. 3+) (Months)					
<3	56 (51.9%)	19 (47.5%)	60 (59.4%)	60 (52.2%)	79 (51.0%)
>=3	49 (45.4%)	19 (47.5%)	34 (33.7%)	52 (45.2%)	71 (45.8%)
Category Time from Last Prior CD20 Therapy to First Study Treatment (0-3 vs. 3+) (Months)					
<3	38 (35.2%)	10 (25.0%)	44 (43.6%)	39 (33.9%)	49 (31.6%)
>=3	65 (60.2%)	30 (75.0%)	48 (47.5%)	71 (61.7%)	101 (65.2%)
Time from Last Prior Therapy to First Study Treatment (Months)					
n	105	38	94	112	150
Mean (SD)	7.52 (17.81)	4.76 (6.66)	5.30 (10.07)	7.38 (17.29)	6.71 (15.33)
Median	2.60	3.10	2.05	2.60	2.70
Min - Max	0.3 - 147.3	0.8 - 33.3	0.8 - 66.2	0.3 - 147.3	0.3 - 147.3
Time from Last Anti-CD20 Therapy to First Study Treatment (Months)					
n	103	40	92	110	150
Mean (SD)	12.67 (26.91)	10.00 (12.27)	8.11 (12.43)	13.01 (26.43)	12.21 (23.50)
Median	4.20	5.00	3.10	4.75	4.75
Min - Max	0.9 - 198.9	0.9 - 58.7	1.0 - 67.5	0.9 - 198.9	0.9 - 198.9

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Category Time from Last Prior Prior Therapy, or Last Prior CD20 Therapy, is not available where Medication End date is missing the month or First Study Treatment is missing.
Only ASCT records containing "AUTO STEM CELL TRANSPLANTATION" or "AUTOLOGOUS STEM CELL TRANSPLANT" or "AUTOLOGUS STEM CELL TRANSPLANTATION" are included as actual transplants.
Data Cutoff Date: 15JUN2022

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Page 3 of 3

Only 14.8% in the D3 population received autologous SCT. Most subjects have been pre-treated with 2-4 lines of therapies.

Table 17

Summary of Non-Hodgkin's Lymphoma Refractory and Relapse Status to Prior Lines of Therapy: Patients with R/R DLBCL Who Have Received ≥2 Prior Lines of Systemic Therapy (ITT Population)

	Glofitamab 2.5/10/30 mg Cohort D3 (N=108)	Glofitamab 2.5/10/30 mg Cohort D5 (a) (N=40)	Glofitamab Doses >=10 mg(b) (N=101)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=115)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=155)
Relapse or Refractory to Any Prior Therapy					
n	108	40	101	115	155
Refractory	97 (89.8%)	36 (90.0%)	93 (92.1%)	103 (89.6%)	139 (89.7%)
Relapse (No Refractory)	11 (10.2%)	4 (10.0%)	8 (7.9%)	12 (10.4%)	16 (10.3%)
Relapse or Refractory to Last Line of Prior Therapy					
n	108	40	101	115	155
Refractory	90 (83.3%)	35 (87.5%)	91 (90.1%)	96 (83.5%)	131 (84.5%)
Relapse	18 (16.7%)	5 (12.5%)	10 (9.9%)	19 (16.5%)	24 (15.5%)
Relapse or Refractory to First Line of Prior Therapy					
n	108	40	101	115	155
Refractory	65 (60.2%)	22 (55.0%)	54 (53.5%)	69 (60.0%)	91 (58.7%)
Relapse	43 (39.8%)	18 (45.0%)	47 (46.5%)	46 (40.0%)	64 (41.3%)
Relapse or Refractory to Any Prior Anti-CD20 Therapy					
n	108	40	101	115	155
Refractory	92 (85.2%)	32 (80.0%)	90 (89.1%)	97 (84.3%)	129 (83.2%)
Relapse (No Refractory)	16 (14.8%)	8 (20.0%)	11 (10.9%)	18 (15.7%)	26 (16.8%)
Relapse or Refractory to Any Prior Alkylator Therapy					
n	108	40	101	115	155
Refractory	91 (84.3%)	33 (82.5%)	40 (39.6%)	95 (82.6%)	128 (82.6%)
Relapse (No Refractory)	17 (15.7%)	7 (17.5%)	10 (9.9%)	20 (17.4%)	27 (17.4%)
Unknown	0	0	51 (50.5%)	0	0
Relapse or Refractory to Any Prior CAR-T Therapy					
n	108	40	101	115	155
Refractory	34 (31.5%)	11 (27.5%)	10 (9.9%)	35 (30.4%)	46 (29.7%)
Relapse (No Refractory)	4 (3.7%)	2 (5.0%)	0	4 (3.5%)	6 (3.9%)
Unknown	70 (64.8%)	27 (67.5%)	91 (90.1%)	76 (66.1%)	103 (66.5%)
Relapse or Refractory to Any Prior Pi3K Therapy					
n	108	40	101	115	155
Refractory	2 (1.9%)	0	0	2 (1.7%)	2 (1.3%)
Relapse (No Refractory)	1 (0.9%)	0	0	1 (0.9%)	1 (0.6%)
Unknown	105 (97.2%)	40 (100%)	101 (100%)	112 (97.4%)	152 (98.1%)

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Only ASCT records containing "AUTO STEM CELL TRANSPLANTATION" or "AUTOLOGOUS STEM CELL TRANSPLANT" or "AUTOLOGUS STEM CELL TRANSPLANTATION" are included as actual transplants.
Data Cutoff Date: 15JUN2022

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Modified by PDRD
Source: t_cm_rrstat_PIV_I_SCE_IT_15JUN2022_30179.out
01SEP2022 19:54

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Only 3 subjects have been pre-treated with PI3K Inhibitors and no statement as to efficacy in such subjects can be made in this study.

38 subjects received CAR-Ts in the previous therapies, of which 34/38 were considered refractory.

Numbers analysed

This application is based on Cohort D3 from Study NP30179. The complexity of the trial and the very variable number of subjects enrolled to the various cohorts at the time of the data cutoff is illustrated in table 1, figure 1 and table 3 above. The justification for choosing cohort D3 as the primary efficacy cohort was initially not completely obvious (data-driven or arbitrarily chosen), however, upon clarification from the applicant justification is acceptable. All arms, where single or double Gpt dose is used are referred to as "monotherapy".

Table 18 Analyses of Efficacy for Patients with R/R DLBCL Who Have Received ≥2 Prior Systemic Therapies

	Supportive Efficacy Populations		Primary Efficacy Population
	≥10 mg Target Dose	Pooled Cohort D_2 [Sub. 2] and Cohort D_3	Cohort D_3
Cohorts	Cohorts B_2 (Part II, dose escalation), Cohort B_3 (Part III, fixed dosing) and Cohort D_2 Sub. 1 (Part II, dose escalation)	Cohort D_2 [Sub. 2], Part II dose escalation, and Cohort D_3, Part III dose expansion	Cohort D_3, Part III dose expansion
No. of patients	N=100	N=115[d]	N=108[d]
Dose (mg)	Fixed dosing, 10 mg, 16 mg, 25 mg or 10/16 mg[a] glofitamab Step-up dosing, 2.5/10/16 mg[b] glofitamab	Step-up dosing, 2.5/10/30 mg[c] glofitamab	Step-up dosing, 2.5/10/30[c] mg glofitamab
Patient population	R/R DLBCL with ≥2 prior therapies in dose escalation/expansion cohorts (fixed and step-up dosing)	R/R DLBCL with ≥2 prior therapies at the proposed registrational dose	R/R DLBCL with ≥2 prior therapies at the proposed registrational dose
Histologies included	DLBCL NOS, HGBCL, trFL and PMBCL	DLBCL NOS, HGBCL, trFL and PMBCL	DLBCL NOS, HGBCL, trFL and PMBCL

DLBCL = diffuse large B-cell lymphoma, DLBCL NOS = diffuse large B-cell lymphoma, not otherwise specified; HGBCL = high-grade B-cell lymphoma; PMBCL = primary mediastinal B-cell lymphoma; R/R = relapsed/refractory; trFL = DLBCL arising from follicular lymphoma

[a] 10 mg on C1D8, 16 mg on C2D1 and subsequent Q3W cycles.

[b] 2.5 mg on C1D8, 10 mg on C1D15, 16 mg C2D1 and subsequent Q3W cycles.

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

[d] Note, one FL patient was enrolled in error in Cohort D_3 and is excluded from the primary efficacy population.

For assessment purposes, the n=108 (ITT) will be used through assessment report and SmPC.

Results from Supportive Efficacy populations include patients who have received glofitamab doses ≥10 mg (cohorts B2, B3 and D2-Sub1 = 100 patients, with no overlap with cohort D3) and pooled results from cohorts treated with the proposed registrational step up dosing (cohorts D2-Sub2 + D3 = 115 patients).

All patients in the pivotal cohort and supportive efficacy populations had received at least two prior lines of therapy before enrolment.

Primary Efficacy Population:

- Patients with R/R DLBCL treated with ≥2 prior systemic therapies enrolled in primary efficacy Cohort D3 treated at the proposed registrational step-up dosing of 2.5/10/30 mg IV Q3W glofitamab (N=108). This population is comprised of patients who had received at least two prior systemic therapies, including patients with DLBCL not otherwise specified (DLBCL-NOS), DLBCL arising from follicular lymphoma (trFL), high-grade B-cell lymphoma (HGBCL), and primary mediastinal B-cell lymphoma (PMBCL) and have received the proposed registrational dose of 2.5/10/30 mg.

Supportive Efficacy Population:

- Glofitamab doses ≥10 mg: Patients with R/R DLBCL enrolled to receive doses of 10 mg-25 mg glofitamab (Cohorts B2, B3 [Study Part II and Part III: 10 mg, 16 mg, 25 mg or 10/16 mg fixed dosing] and Cohort D2 [Sub. 1] [Study Part II, 2.5/10/16 mg step-up dosing]) (N=100).
- Glofitamab 2.5/10/30 mg: Patients with R/R DLBCL treated with ≥2 prior systemic therapies in Cohort D2 [Sub. 2] + Cohort D3 + D5 treated at the proposed registrational dose of 2.5/10/30 mg IV Q3W glofitamab (N=155).
- Supportively, 115 patients with R/R DLBCL treated with step-up-doses of 2.5/10/30 mg glofitamab in the supportive efficacy cohorts D2 [Sub. 2] + D3.

For efficacy analysis 108 patients from D3 were included in the ITT population and includes a patient that received no study drug (enrolled by error).

Table 19

Analysis Populations: Part III Dose Expansion Cohorts in Study NP30179

Analysis Populations	Glofitamab 10/16 mg Cohort B3 (N=56)	Glofitamab 10/16 mg Cohort B4 (N=14)	Glofitamab 2.5/10/30 mg Cohort D3 (N=109)	Glofitamab 2.5/10/30 mg Cohort D3 (3L+ DLBCL) (N=108)	Glofitamab 2.5/10/30 mg Cohort D4 (N=41)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=41)
Intent-to-treat Population (IT)						
Inclusion	56 (100%)	14 (100%)	109 (100%)	108 (100%)	41 (100%)	41 (100%)
Safety Population (SE)						
Exclusions	1 (1.8%)	2 (14.3%)	1 (0.9%)	1 (0.9%)	0	0
Inclusion	55 (98.2%)	12 (85.7%)	108 (99.1%)	107 (99.1%)	41 (100%)	41 (100%)
Glofitamab Treated Safety Evaluable Population (SERO)						
Exclusions	4 (7.1%)	2 (14.3%)	7 (6.4%)	7 (6.5%)	1 (2.4%)	3 (7.3%)
Inclusion	52 (92.9%)	12 (85.7%)	102 (93.6%)	101 (93.5%)	40 (97.6%)	38 (92.7%)
Primary Efficacy Population (EFP)						
Exclusions	1 (1.8%)	2 (14.3%)	1 (0.9%)	1 (0.9%)	4 (9.8%)	0
Inclusion	55 (98.2%)	12 (85.7%)	108 (99.1%)	107 (99.1%)	37 (90.2%)	41 (100%)
FACT-LYM v4 Population (QS1)						
Exclusions	8 (14.3%)	3 (21.4%)	17 (15.6%)	16 (14.8%)	5 (12.2%)	6 (14.6%)
Inclusion	48 (85.7%)	11 (78.6%)	92 (84.4%)	92 (85.2%)	36 (87.8%)	35 (85.4%)
EORTC QLQ-C30 Population (QS3)						
Exclusions	8 (14.3%)	3 (21.4%)	17 (15.6%)	16 (14.8%)	5 (12.2%)	5 (12.2%)
Inclusion	48 (85.7%)	11 (78.6%)	92 (84.4%)	92 (85.2%)	36 (87.8%)	36 (87.8%)

(a) Dexamethasone pretreated.
Primary efficacy population includes all patients who have a response assessment performed, who withdrew early from treatment or study, or who are on still on treatment at the time of their first scheduled response assessment, in addition to receiving a dose of any study treatment.
The FACT-LYM v4 and EORTC QLQ-C30 populations include patients with at least one valid pre & post baseline assessment.
Data Cutoff Date: 15JUN2022

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15SEP2022 11:50 Page 1 of 1

Outcomes and estimation

Table 20

Overview of the Efficacy of Glofitamab in R/R DLBCL Patients (≥2 Prior Lines of Systemic Therapy)

	Glofitamab 2.5/10/30 mg Cohort D_3 N = 108	Glofitamab 2.5/10/30 mg Cohort D_5[a] N = 40	Glofitamab doses ≥10 mg[b] N = 101	Glofitamab 2.5/10/30 mg Cohorts D_2 [Sub. 2] + D_3 N = 115	Glofitamab 2.5/10/30 mg Cohorts D_2 [Sub. 2] + D_3 + D_5[a] N = 155
		Primary Efficacy Endpoint (14 September 2021 CCOD)			
		IRC-Assessed Complete Response Rate[c]			
CR - % [95% CI]	35.2 [26.2, 45.0]	ND	34.0 [24.8, 44.2]	37.4 [28.6, 46.9]	ND
CR rate vs. Historical Control[d]	p-value <0.0001	-	-	-	-
		Primary Efficacy Endpoint (15 June 2022 CCOD)			
		IRC-Assessed Complete Response Rate[c]			
CR - % [95% CI]	35.2 [26.2, 45.0]	47.5 [31.5, 63.9]	34.7 [25.5, 44.8]	37.4 [28.6, 46.9]	40.0 [32.2, 48.2]
		Secondary Efficacy Endpoints (15 June 2022 CCOD)			
		INV-Assessed Complete Response Rate[c]			
CR - % [95% CI]	33.3 [24.6, 43.1]	45.0 [29.3, 61.5]	37.6 [28.2, 47.8]	35.7 [26.9, 45.1]	38.1 [30.4, 46.2]
		IRC-Assessed Overall Response Rate[c]			
ORR - % [95% CI]	50.0 [40.2, 59.8]	52.5 [36.1, 68.5]	49.5 [39.4, 59.6]	51.3 [41.8, 60.7]	51.6 [43.5, 59.7]
		INV-Assessed Overall Response Rate[b]			
ORR - % [95% CI]	56.5 [46.6, 66.0]	60.0 [43.3, 75.1]	50.5 [40.4, 60.6]	58.3 [48.7, 67.4]	58.7 [50.5, 66.6]
		IRC-Assessed Duration of Complete Response[c]			
Median DOCR - months [95% CI]	NE [18.4, NE]	8.4 [NE, NE]	NE [17.9, NE]	NE [16.8, NE]	NE [16.8, NE]
		INV-Assessed Duration of Complete Response[c]			
Median DOCR - months [95% CI]	NE [18.2, NE]	NE [4.2, NE]	30.1 [5.5, NE]	NE [19.8, NE]	NE [19.8, NE]
		IRC-Assessed Duration of Response[c]			
Median DOR - months [95% CI]	14.4 [8.6, NE]	8.4 [NE, NE]*	24.7 [6.0, NE]	16.8 [9.3, NE]	16.8 [10.4, NE]
		INV-Assessed Duration of Response[c]			
Median DOR - months) [95% CI]	7.8 [3.8, NE]	NE [5.4, NE]	7.5 [4.7, NE]	10.0 [4.1, NE]	10.4 [5.4, NE]
		IRC-Assessed Time to First Complete Response[c]			
Median TFCR - days [95% CI]	42.0 [41.0, 47.0]	43.0 [40.0, 50.0]	44.0 [41.0, 51.0]	42.0 [42.0, 45.0]	42.0 [42.0, 44.0]
		INV-Assessed Time to First Complete Response[c]			
Median TFCR - days [95% CI]	42.0 [42.0, 48.0]	52.0 [42.0, 104.0]	43.0 [41.0, 50.0]	42.0 [42.0, 45.0]	43.0 [42.0, 48.0]
		IRC-Assessed Time to First Overall Response[c]			
Median TFOR - days [95% CI]	42.0 [41.0, 42.0]	42.0 [40.0, 43.0]	43.0 [41.0, 44.0]	42.0 [41.0, 42.0]	42.0 [41.0, 42.0]
		INV-Assessed Time to First Overall Response[c]			
Median TFOR - days [95% CI]	41.0 [40.0, 42.0]	42.0 [40.0, 43.0]	41.0 [39.0, 42.0]	41.0 [40.0, 42.0]	42.0 (40.0, 42.0]
		IRC-Assessed Progression-Free Survival			
Median PFS - months [95% CI]	3.7 [3.3, 6.8]	8.1 [3.4, NE]	3.8 [2.6, 6.4]	3.8 [3.3, 7.6]	4.9 [3.4, 8.1]
Event-free rate at 1 year - % [95% CI]	33.0 [23.5, 42.4]	NE [NE, NE]	35.1 [24.9, 45.3]	34.8 [25.5, 44.1]	34.9 [26.5, 43.3]
		INV-Assessed Progression-Free Survival			
Median PFS - months) - % [95% CI]	3.4 [2.8, 5.0]	5.2 [3.1, NE]	3.3 (1.8, 5.5]	3.4 [3.2, 5.4]	3.8 [3.3, 5.4]
Event-free rate at 1 year - % [95% CI]	27.9 [18.8, 36.9]	NE [NE, NE]	26.5 [17.4, 35.6]	30.0 [21.0, 39.0]	30.6 [22.6, 38.7]
		Overall Survival			
Median OS - months [95% CI]	8.9 [7.1, 15.3]	NE [8.1, NE]	ND	10.2 [7.5, 15.7]	12.0 [8.0, 16.1]
Event-free rate at 1 year - % [95% CI]	45.6 [35.9, 55.4]	54.2 [35.6, 72.8]	ND	48.7 [39.2, 58.2]	50.4 [42.1, 58.7]

Table 13 Overview of the Efficacy of Glofitamab in R/R DLBCL Patients (≥2 Prior Lines of Systemic Therapy) (cont.)

CI = confidence interval; CR = complete response; DOCR = duration of complete response; DOR = duration of response; INV = Investigator; IRC = Independent Review Committee; ND = not done; NE = not evaluable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TFCR = time to first complete response; TFOR = time to first overall response

[a] Dexamethasone premedication

[b] Includes patients treated with glofitamab doses of 10 mg, 16 mg, 25 mg, 10/16 mg and step-up doses of 2.5/10/16 mg

[c] Lugano classification (Cheson 2014)

[d] Historical control CR rate = 20%

[e] The median has been estimated due to the fact the last patient had an event and is expected to change with longer follow-up. The Kaplan-Meier estimated event-free rate among complete responders after the first CR was 93.8% at 6 months, and at the time of the CCOD was not estimable at later time points.

Source: t_rsp_IRC_PIV_I_SCE_IT_15JUN2022_30179, t_rsp_INV_PIV_I_SCE_IT_15JUN2022_30179, t_ef_dor_IRCCR_PIV_I_SCE_EFPCRO_15JUN2022_30179, t_ef_dor_CR_PIV_I_SCE_EFPCR_15JUN2022_30179, t_ef_dor_IRCOVR_PIV_I_SCE_EFPORO_15JUN2022_30179, t_ef_dor_OVR_PIV_I_SCE_EFPOR_15JUN2022_30179 t_ef_tte_IRCPFS_PIV_I_SCE_IT_15JUN2022_30179, t_ef_tte_IRCFCRSP_PIV_I_SCE_EFPCRO_15JUN2022_30179, t_ef_tte_OS_PIV_RP2D_I_SCE_IT_15JUN2022_30179

Primary efficacy endpoint: CR by IRC (CCOD 15 JUNE 2022):

There was a 35.2% IRC-assessed CR-rate (CI 26.2-45.0) in the primary efficacy cohort D3, unchanged with the update with longer follow-up. The median duration of CR was not reached ([95% CI: 18.4, NE]).

Different CR-rates were noted in the application. The applicant has explained that the discrepancy in CR-rates is due to one being based on the ITT population (CR-rate=35.2%) while the other is based on the efficacy evaluable population (CR-rate=36.1%). For the purposes of this assessment, data from the ITT population will be utilized.

Secondary endpoints (CCOD 15 JUNE 2022)**:**

DOCR:

Table 21

Summary of Follow-Up for IRC-Assessed Duration of Complete Response: Glofitamab Dose Escalation and Dose Expansion Cohorts (R/R DLBCL Patients, ≥2 Prior Lines of Systemic Therapy) (Complete Responder Population)

	Glofitamab 2.5/10/30 mg Cohort D3 (N=38)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=19)	Glofitamab Doses >=10 mg(b) (N=35)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=43)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=62)
Patients with event (%)	28 (73.7%)	16 (84.2%)	22 (62.9%)	31 (72.1%)	47 (75.8%)
Earliest contributing event					
Last Tumor Assessment	28	16	22	31	47
Patients without event (%)	10 (26.3%)	3 (15.8%)	13 (37.1%)	12 (27.9%)	15 (24.2%)
Time to event (months)					
Median	12.8	7.3	26.0	15.9	11.6
95% CI	(11.6, 18.2)	(2.9, 7.4)	(24.2, 35.9)	(12.0, 18.3)	(7.6, 15.9)
25% and 75%-ile	8.3 - 18.3	2.6 - 7.5	22.0 - 36.1	10.1 - 18.4	5.4 - 18.3
Range	0 - 20	0 - 8*	0 - 42	0 - 27	0 - 27

Primary efficacy population includes all patients who have a response assessment performed, who withdrew early from treatment or study, or who are still on treatment at the time of their first scheduled response assessment.
(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
* Censored observation. NE = Not estimable.
Median and percentiles are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ef_tte_fup.sas
Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/FDA_Sub2_EU_RTQ_Aug2022/prod/output/t_ef_tte_fup_IRCCR_PIV_I_SCE_EFPCRO_15JUN2022_30179.out
23AUG2022 19:56

Page 1 of 1

Table 22

Duration of IRC-Assessed Complete Response: Glofitamab Dose Escalation and Dose Expansion Cohorts (R/R DLBCL Patients, ≥2 Prior Lines of Systemic Therapy) (Complete Responder Population)

	Glofitamab 2.5/10/30 mg Cohort D3 (N=38)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=19)	Glofitamab Doses >=10 mg(b) (N=35)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=43)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=62)
Responders	38	19	35	43	62
Responders with subsequent event (%)	10 (26.3%)	3 (15.8%)	13 (37.1%)	12 (27.9%)	15 (24.2%)
Earliest contributing event					
Death	2	0	2	2	2
Disease Progression	8	3	11	10	13
Responders without subsequent event (%)	28 (73.7%)	16 (84.2%)	22 (62.9%)	31 (72.1%)	47 (75.8%)
Duration of response (months)					
Median	NE	8.4	NE	NE	NE
95% CI	(18.4, NE)	NE	(17.9, NE)	(16.8, NE)	(16.8, NE)
25% and 75%-ile	9.3 - NE	8.4 - 8.4	4.7 - NE	14.4 - NE	9.3 - NE
Range	0* - 20*	0* - 8	0* - 42*	0* - 27*	0* - 27*

Primary efficacy population includes all patients who have a response assessment performed, who withdrew early from treatment or study, or who are still on treatment at the time of their first scheduled response assessment.
(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
* = Censored observation. NE = Not estimable.
The median and percentiles for duration of response are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ef_dor.sas
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23AUG2022 19:52 Page 1 of 1

Based on updated data, in the primary efficacy Cohort D3, the median duration of follow-up for IRC-assessed DOCR was 12.8 months (95% CI: 11.6, 18.2) (see Table above), while median follow-up for INV-assessed DOCR was 15.9 months. The median IRC-assessed DOCR was not reached ([95% CI: 18.4, NE]). The K-M estimated event-free rates among complete responders at 3, 6, 9, 12 months were 94.4%, 88.1%, 78.1%, and 74.6%, respectively.

Table 23

Kaplan-Meier Event-Free Rates for the IRC-Assessed Duration of Complete Response Over Time: Glofitamab Dose Escalation and Dose Expansion Cohorts (R/R DLBCL Patients, ≥2 Prior Lines of Systemic Therapy) (Complete Responder Population)

Duration of Complete Response by IRC (CR)

Treatment	Time Point	Patients at Risk	Number of Events	Patients Censored	Event-free Rate (%) KM-Estimate	95% CI
Glofitamab 2.5/10/30 mg Cohort D3 (N=38)	3 Months	31	2	5	94.36	(86.77, 100.00)
	6 Months	28	4	6	88.07	(77.07, 99.08)
	9 Months	22	7	9	78.11	(63.66, 92.56)
	12 Months	17	8	13	74.56	(59.19, 89.93)
	15 Months	12	9	17	68.82	(50.99, 86.66)
	18 Months	10	9	19	68.82	(50.99, 86.66)
	21 Months	NE	NE	NE	NE	NE
	24 Months	NE	NE	NE	NE	NE
Glofitamab 2.5/10/30 mg Cohort D5(a) (N=19)	3 Months	12	1	6	93.75	(81.89, 100.00)
	6 Months	9	1	9	93.75	(81.89, 100.00)
	9 Months	NE	NE	NE	NE	NE
	12 Months	NE	NE	NE	NE	NE
	15 Months	NE	NE	NE	NE	NE
	18 Months	NE	NE	NE	NE	NE
	21 Months	NE	NE	NE	NE	NE
	24 Months	NE	NE	NE	NE	NE
Glofitamab Doses >=10 mg(b) (N=35)	3 Months	23	6	6	80.50	(66.44, 94.56)
	6 Months	20	9	6	70.00	(53.50, 86.50)
	9 Months	20	9	6	70.00	(53.50, 86.50)
	12 Months	19	9	7	70.00	(53.50, 86.50)
	15 Months	19	9	7	70.00	(53.50, 86.50)
	18 Months	18	10	7	66.32	(49.18, 83.46)
	21 Months	18	10	7	66.32	(49.18, 83.46)
	24 Months	15	11	9	62.41	(44.66, 80.17)
Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=43)	3 Months	36	2	5	95.06	(88.38, 100.00)
	6 Months	32	5	6	86.91	(76.19, 97.64)
	9 Months	26	8	9	78.37	(65.03, 91.72)
	12 Months	21	9	13	75.36	(61.28, 89.44)
	15 Months	16	10	17	70.93	(55.22, 86.63)
	18 Months	13	11	19	65.86	(48.42, 83.30)
	21 Months	3	12	28	57.63	(36.16, 79.09)
	24 Months	3	12	28	57.63	(36.16, 79.09)
Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=62)	3 Months	48	3	11	94.67	(88.80, 100.00)
	6 Months	41	6	15	88.35	(79.53, 97.17)
	9 Months	26	11	25	75.99	(63.26, 88.71)
	12 Months	21	12	29	73.06	(59.60, 86.53)
	15 Months	16	13	33	60.77	(53.69, 83.84)
	18 Months	13	14	35	63.85	(47.06, 80.65)
	21 Months	3	15	44	55.87	(35.13, 76.61)
	24 Months	3	15	44	55.87	(35.13, 76.61)

Primary efficacy population includes all patients who have a response assessment performed, who withdrew early from treatment or study, or who are still on treatment at the time of their first scheduled response assessment.
(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Data Cutoff Date: 15JUN2022

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Table 24

Kaplan-Meier Event-Free Rates for the IRC-Assessed Duration of Complete Response Over Time: Glofitamab Dose Escalation and Dose Expansion Cohorts (R/R DLBCL Patients, ≥2 Prior Lines of Systemic Therapy) (Complete Responder Population)

Duration of Complete Response by IRC (CR)

Treatment	Time Point	Patients at Risk	Number of Events	Patients Censored	Event-free Rate (%) KM-Estimate	95% CI
Glofitamab 2.5/10/30 mg Cohort D3 (N=38)	3 Months	31	2	5	94.36	(86.77, 100.00)
	6 Months	28	4	6	88.07	(77.07, 99.08)
	9 Months	22	7	9	78.11	(63.66, 92.56)
	12 Months	17	8	13	74.56	(59.19, 89.93)
	15 Months	12	9	17	68.82	(50.99, 86.66)
	18 Months	10	9	19	68.82	(50.99, 86.66)
	21 Months	NE	NE	NE	NE	NE
	24 Months	NE	NE	NE	NE	NE
Glofitamab 2.5/10/30 mg Cohort D5(a) (N=19)	3 Months	12	1	6	93.75	(81.89, 100.00)
	6 Months	9	1	9	93.75	(81.89, 100.00)
	9 Months	NE	NE	NE	NE	NE
	12 Months	NE	NE	NE	NE	NE
	15 Months	NE	NE	NE	NE	NE
	18 Months	NE	NE	NE	NE	NE
	21 Months	NE	NE	NE	NE	NE
	24 Months	NE	NE	NE	NE	NE
Glofitamab Doses >=10 mg(b) (N=35)	3 Months	23	6	6	80.50	(66.44, 94.56)
	6 Months	20	9	6	70.00	(53.50, 86.50)
	9 Months	20	9	6	70.00	(53.50, 86.50)
	12 Months	19	9	7	70.00	(53.50, 86.50)
	15 Months	19	9	7	70.00	(53.50, 86.50)
	18 Months	18	10	7	66.32	(49.18, 83.46)
	21 Months	18	10	7	66.32	(49.18, 83.46)
	24 Months	15	11	9	62.41	(44.66, 80.17)
Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=43)	3 Months	36	2	5	95.06	(88.38, 100.00)
	6 Months	32	5	6	86.91	(76.19, 97.64)
	9 Months	26	8	9	78.37	(65.03, 91.72)
	12 Months	21	9	13	75.36	(61.28, 89.44)
	15 Months	16	10	17	70.93	(55.22, 86.63)
	18 Months	13	11	19	65.86	(48.42, 83.30)
	21 Months	3	12	28	57.63	(36.16, 79.09)
	24 Months	3	12	28	57.63	(36.16, 79.09)

Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=62)	3 Months	48	3	11	94.67	(88.80, 100.00)
	6 Months	41	6	15	88.35	(79.53, 97.17)
	9 Months	26	11	25	75.99	(63.26, 88.71)
	12 Months	21	12	29	73.06	(59.60, 86.53)
	15 Months	16	13	33	68.77	(53.69, 83.84)
	18 Months	13	14	35	63.85	(47.06, 80.65)
	21 Months	3	15	44	55.87	(35.13, 76.61)
	24 Months	3	15	44	55.87	(35.13, 76.61)

DOR:

Of the 54 patients with R/R DLBCL treated with glofitamab step-up doses of 2.5/10/30 mg in primary efficacy Cohort D3 who achieved a response (CR or PR) as determined by the IRC, 30 patients (55.6%) remained in remission and 24 patients (44.4%) subsequently had disease progression or died at the updated cut-off date of 15 June 2022.

Table 25

Duration of IRC-Assessed Response: Glofitamab Dose Escalation and Dose Expansion Cohorts (R/R DLBCL Patients, ≥2 Prior Lines of Systemic Therapy) (Responder Population)

	Glofitamab 2.5/10/30 mg Cohort D3 (N=54)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=21)	Glofitamab Doses >=10 mg(b) (N=50)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=59)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=80)
Responders	54	21	50	59	80
Responders with subsequent event (%)	24 (44.4%)	4 (19.0%)	23 (46.0%)	26 (44.1%)	30 (37.5%)
Earliest contributing event					
Death	3	0	5	3	3
Disease Progression	21	4	18	23	27
Responders without subsequent event (%)	30 (55.6%)	17 (81.0%)	27 (54.0%)	33 (55.9%)	50 (62.5%)
Duration of response (months)					
Median	14.4	8.4	24.7	16.8	16.8
95% CI	(8.6, NE)	NE	(6.0, NE)	(9.3, NE)	(10.4, NE)
25% and 75%-ile	2.6 - NE	8.4 - 8.4	2.8 - NE	3.5 - NE	6.5 - NE
Range	0* - 20*	0* - 8	0* - 42*	0* - 27*	0* - 27*

Primary efficacy population includes all patients who have a response assessment performed, who withdrew early from treatment or study, or who are still on treatment at the time of their first scheduled response assessment.
(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
* = Censored observation. NE = Not estimable.
The median and percentiles for duration of response are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Data Cutoff Date: 15JUN2022

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Source: uCSR

Table 26

Kaplan-Meier Event-Free Rates for the IRC-Assessed Duration of Overall Response Over Time: Glofitamab Dose Escalation and Dose Expansion Cohorts (R/R DLBCL Patients, ≥2 Prior Lines of Systemic Therapy) (Complete Responder Population)

Duration of Any Response by IRC (PR/CR)

Treatment	Time Point	Patients at Risk	Number of Events	Patients Censored	Event-free Rate (%) KM-Estimate	95% CI
Glofitamab 2.5/10/30 mg Cohort D3 (N=54)	3 Months	37	13	4	74.29	(62.23, 86.35)
	6 Months	34	15	5	70.22	(57.57, 82.87)
	9 Months	25	19	10	61.43	(47.71, 75.15)
	12 Months	19	21	14	56.29	(41.99, 70.60)
	15 Months	12	23	19	48.50	(32.60, 64.40)
	18 Months	11	23	20	48.50	(32.60, 64.40)
	21 Months	NE	NE	NE	NE	NE
	24 Months	NE	NE	NE	NE	NE
Glofitamab 2.5/10/30 mg Cohort D5(a) (N=21)	3 Months	15	2	4	89.72	(76.22, 100.00)
	6 Months	13	2	6	89.72	(76.22, 100.00)
	9 Months	NE	NE	NE	NE	NE
	12 Months	NE	NE	NE	NE	NE
	15 Months	NE	NE	NE	NE	NE
	18 Months	NE	NE	NE	NE	NE
	21 Months	NE	NE	NE	NE	NE
	24 Months	NE	NE	NE	NE	NE
Glofitamab Doses >=10 mg(b) (N=50)	3 Months	31	12	7	73.58	(60.69, 86.46)
	6 Months	25	16	9	63.43	(48.98, 77.87)
	9 Months	24	16	10	63.43	(48.98, 77.87)
	12 Months	23	17	10	60.79	(46.04, 75.53)
	15 Months	22	18	10	58.14	(43.16, 73.13)
	18 Months	21	19	10	55.50	(40.33, 70.67)
	21 Months	20	20	10	52.86	(37.55, 68.16)
	24 Months	18	21	11	50.07	(34.63, 65.52)
Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=59)	3 Months	42	13	4	76.61	(65.47, 87.75)
	6 Months	39	15	5	72.92	(61.20, 84.64)
	9 Months	30	19	10	65.03	(52.27, 77.80)
	12 Months	23	22	14	58.29	(44.75, 71.83)
	15 Months	16	24	19	51.97	(37.34, 66.61)
	18 Months	14	25	20	48.51	(33.36, 63.66)
	21 Months	3	26	30	42.45	(25.14, 59.75)
	24 Months	3	26	30	42.45	(25.14, 59.75)
Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=80)	3 Months	57	15	8	79.82	(70.69, 88.96)
	6 Months	52	17	11	76.97	(67.34, 86.60)
	9 Months	30	23	27	66.46	(54.91, 78.00)
	12 Months	23	26	31	59.57	(46.85, 72.28)
	15 Months	16	28	36	53.11	(38.97, 67.26)
	18 Months	14	29	37	49.57	(34.76, 64.38)
	21 Months	3	30	47	43.37	(26.14, 60.61)
	24 Months	3	30	47	43.37	(26.14, 60.61)

Primary efficacy population includes all patients who have a response assessment performed, who withdrew early from treatment or study, or who are still on treatment at the time of their first scheduled response assessment.
(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Data Cutoff Date: 15JUN2022

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The median DOR was 14.4 months (95% CI; 8.6, NE). Among responders, the event-free rates at 3, 6, 9, and 12 months after the first response were 74.3%, 70.2%, 61.4%, and 56.3%, respectively (Table 38/uCSR above).

Time to First CR (TFCR) and Time to First OR (TFOR):

The median TFCR and TFOR were 42 days.

Table 27

Time to First IRC-Assessed Complete Response: Glofitamab Dose Escalation and Dose Expansion Cohorts (R/R DLBCL Patients, ≥2 Prior Lines of Systemic Therapy) (Complete Responder Population)

	Glofitamab 2.5/10/30 mg Cohort D3 (N=38)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=19)	Glofitamab Doses >=10 mg(b) (N=35)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=43)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=62)
Patients with event (%)	38 (100%)	19 (100%)	35 (100%)	43 (100%)	62 (100%)
Earliest contributing event					
CR	38	19	35	43	62
Patients without event (%)	0	0	0	0	0
Time to event (days)					
Median	42.0	43.0	44.0	42.0	42.0
95% CI	(41.0, 47.0)	(40.0, 50.0)	(41.0, 51.0)	(42.0, 45.0)	(42.0, 44.0)
25% and 75%-ile	40.0 - 101.0	40.0 - 104.0	39.0 - 92.0	40.0 - 101.0	40.0 - 101.0
Range	31 - 308	36 - 265	31 - 466	31 - 308	31 - 308

Primary efficacy population includes all patients who have a response assessment performed, who withdrew early from treatment or study, or who are still on treatment at the time of their first scheduled response assessment.
(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
* Censored observation. NE = Not estimable.
Median and percentiles are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Data Cutoff Date: 15JUN2022

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Among the 54 patients with R/R DLBCL treated with glofitamab step-up doses of 2.5/10/30 mg in primary efficacy Cohort D3 who achieved an overall response (CR or PR) by IRC-assessment in Cohort D3, the median time to first overall response was 42.0 days (range: 31 - 178 days).

PFS and OS:

Median PFS was 3.7 (95% CI: 3.3, 6.8) months in patients in Cohort D3. The median duration of follow-up for IRC Assessed PFS was 9.0 months (95% CI: 8.5, 9.6) for patients in Cohort D3.

At the CCOD 15 JUNE 2022, 63 of the 108 patients (58.3%) with R/R DLBCL in the primary efficacy Cohort D3 had died, with a median survival of 8.9 (95% CI: 7.1, 15.3) months.

Patient-Reported Outcomes (PROs)

Patients reported moderate to moderate-high levels at baseline of Physical Functioning, Role Functioning, and global health status/quality of life (GHS/QoL) and low levels of Fatigue (weakness, tiredness) at baseline; which were maintained during treatment. Most patients indicated that symptoms commonly associated with treatment (nausea, constipation, diarrhea, and vomiting) were not present or were of low severity if present, and maintained during treatment. Patients reported low levels of lymphoma symptoms at baseline as measured by the FACT-Lym Lymphoma scale which were maintained during treatment.

Improvement for EORTC QLQ C-30 physical function, role function and GHS/QOL and FACT-Lym LymS is defined as an increase in the subscale score. Improvement for EORTC QLQ-30 fatigue is defined as a decrease in the subscale score.

Although PRO results are inconsistent and based on small numbers of patients filling out the questionnaires properly and considering the fact that patients died during the study, very slight beneficial effect may be seen in patients that filled the questionnaires and continued treatment.

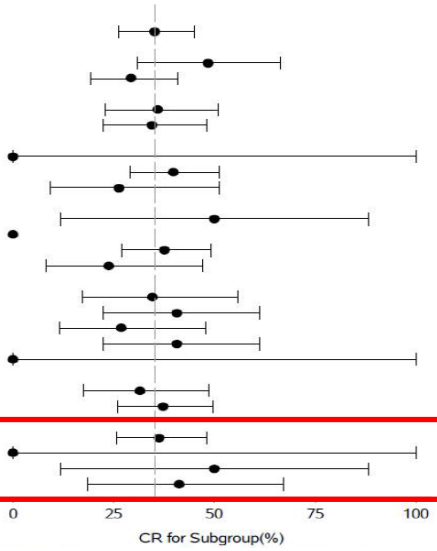
Ancillary analyses

Figure 14 Subgroup Analysis of Complete Response Rate by IRC Assessment

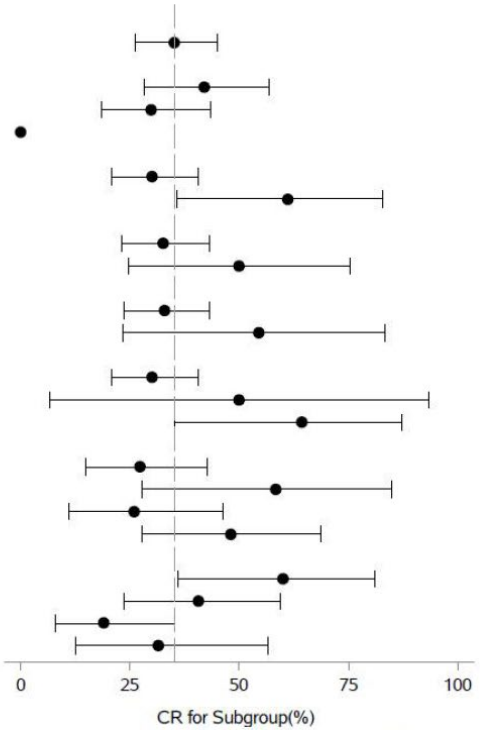
Figure 1 Subgroup Analysis of IRC-Assessed Complete Response Rate: Glofitamab 2.5/10/30 mg in Cohort D_3 (R/R DLBCL Patients, ≥2 Prior Lines of Systemic Therapy) (ITT Population)

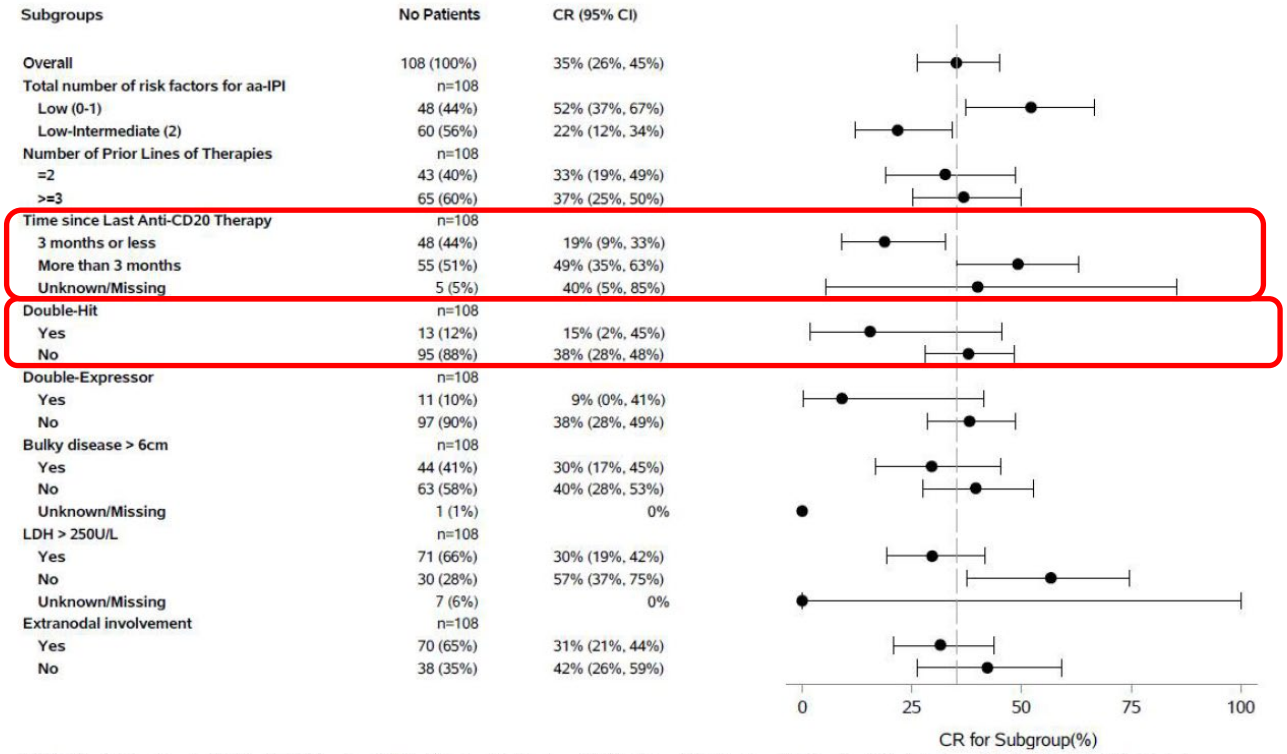
Forest Plot for Response by Subgroup, IRC Assessed Complete Response, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Glofitamab 2.5/10/30 mg D3 Cohort, Intent-to-Treat Monotherapy Patients
Protocol: NP30179

Subgroups	No Patients	CR (95% CI)
Overall	108 (100%)	35% (26%, 45%)
Sex	n=108	
Female	33 (31%)	48% (31%, 66%)
Male	75 (69%)	29% (19%, 41%)
Age Group	n=108	
<65	50 (46%)	36% (23%, 51%)
>=65	58 (54%)	34% (22%, 48%)
Ethnicity	n=108	
Hispanic or Latino	6 (6%)	0%
Not Hispanic or Latino	83 (77%)	40% (29%, 51%)
Not Stated or Unknown	19 (18%)	26% (9%, 51%)
Race	n=108	
Asian	6 (6%)	50% (12%, 88%)
Black or African American	1 (1%)	0%
White	80 (74%)	38% (27%, 49%)
Unknown	21 (19%)	24% (8%, 47%)
Baseline BMI (kg/m2)	n=108	
<25%	26 (24%)	35% (17%, 56%)
25-50%	27 (25%)	41% (22%, 61%)
50-75%	26 (24%)	27% (12%, 48%)
75-100%	27 (25%)	41% (22%, 61%)
Unknown/Missing	2 (2%)	0%
Prior CAR-T Therapy	n=108	
Yes	38 (35%)	32% (18%, 49%)
No	70 (65%)	37% (26%, 50%)
NHL Subtype	n=108	
DLBCL	77 (71%)	36% (26%, 48%)
HGBCL	8 (7%)	0%
PMBCL	6 (6%)	50% (12%, 88%)
trFL	17 (16%)	41% (18%, 67%)



Subgroups	No Patients	CR (95% CI)
Overall	108 (100%)	35% (26%, 45%)
Baseline ECOG	n=108	
0	50 (46%)	42% (28%, 57%)
>=1	57 (53%)	30% (18%, 43%)
Unknown/Missing	1 (1%)	0%
Relapse or Refractory to Last Prior Therapy	n=108	
Refractory	90 (83%)	30% (21%, 41%)
Non-Refractory	18 (17%)	61% (36%, 83%)
Relapse or Refr. to Any Prior Anti-CD20 Therapy	n=108	
Refractory	92 (85%)	33% (23%, 43%)
Non-Refractory	16 (15%)	50% (25%, 75%)
Relapse or Refr. to Any Prior Therapy	n=108	
Refractory	97 (90%)	33% (24%, 43%)
Non-Refractory	11 (10%)	55% (23%, 83%)
Prior Autologous Stem Cell Transplant Therapy	n=108	
Unknown	90 (83%)	30% (21%, 41%)
Refractory	4 (4%)	50% (7%, 93%)
Non-Refractory	14 (13%)	64% (35%, 87%)
Cell of Origin	n=108	
GCB	44 (41%)	27% (15%, 43%)
ABC	12 (11%)	58% (28%, 85%)
non-GCB	27 (25%)	26% (11%, 46%)
Missing/Unclassified	25 (23%)	48% (28%, 69%)
Total number of risk factors for IPI	n=108	
Low (0-1)	20 (19%)	60% (36%, 81%)
Low-Intermediate (2)	32 (30%)	41% (24%, 59%)
High-Intermediate (3)	37 (34%)	19% (8%, 35%)
High (4-5)	19 (18%)	32% (13%, 57%)





CAR-T = Chimeric Antigen Receptor, NHL = Non-Hodgkin's lymphoma, DLBCL = Diffuse large B-cell lymphoma, HGBCL = High-grade B-cell lymphoma, trFl = Transformed follicular lymphoma, BMI = Body Mass Index, GCB = Germinal center B-cell, ABC = Activated Bcell, IPI = International Prognostic Index, CD = Cluster of differentiation, aa-IPI = Age adjusted International Prognostic Index, LDH = Lactate dehydrogenase.
Data Cutoff Date: 15JUN2022

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The majority of patients characterized as double-hit without a HGBCL diagnosis were trFL with the relevant translocations. The group of 17 patients labelled trFL encompasses 8 DLBCL, 5 HGBCL and 4 "trFL" histologies. The latter indicate patients whose transformation occurred at an earlier line of treatment. Of the whole trFL group, 7/17 (41%) patients achieved a CR. CRs could be further subdivided based on histology: 4/8 DLBCL (50%), 2/5 HGBCL (40%) and 1/4 (25%) "trFL" achieved a CR. In total, Study NP30179 includes 79 DLBCL patients + 6 HGBCL patients + 6 PMBCL patients + 17 trFL patients = 108 patients; in the latest update, two DLBCL patients have been reclassified as HGBCL, the total number of patients remains at 108.

Table 28

Summary of IRC-Assessed Complete Responses Lasting Greater Than 3, 6 and 12 Months by Histology Subtype (Complete Responder Population)

Response	Cohort D_2 [Sub. 2] + D_3 + D_5				
	DLBCL (NOS) (N=44)	trFL (N=14)	HGBCL (N=1)	PMBCL (N=3)	All (N=62)
CR > 3 months	33 (75.0%)	13 (92.9%)	0	2 (66.7%)	48 (77.4%)
CR > 6 months	26 (59.1%)	13 (92.9%)	0	2 (66.7%)	41 (66.1%)
CR > 12 months	13 (29.5%)	7 (50.0%)	0	1 (33.3%)	21 (33.9%)
	Cohort D_3				
	DLBCL (NOS (N=28)	trFL (N=7)	HGBCL (N=0)	PMBCL (N=3)	All (N=38)
CR > 3 months	22 (78.6%)	7 (100%)	0	2 (66.7%)	31 (81.6%)
CR > 6 months	19 (67.9%)	7 (100%)	0	2 (66.7%)	28 (73.7%)
CR > 12 months	12 (42.9%)	4 (57.1%)	0	1 (33.3%)	17 (44.7%)
	Cohort D_5				
	DLBCL (NOS) (N=14)	trFL (N=4)	HGBCL (N=1)	PMBCL (N=0)	All (N=19)
CR > 3 months	9 (64.3%)	3 (75.0%)	0	0	12 (63.2%)
CR > 6 months	6 (42.9%)	3 (75.0%)	0	0	9 (47.4%)
CR > 12 months	0	0	0	0	0
	Cohort D_2 [Sub. 2] + D_3				
	DLBCL (NOS) (N=30)	trFL (N=10)	HGBCL (N=0)	PMBCL (N=3)	All (N=43)
CR > 3 months	24 (80.0%)	10 (100%)	0	2 (66.7%)	36 (83.7%)
CR > 6 months	20 (66.7%)	10 (100%)	0	2 (66.7%)	32 (74.4%)
CR > 12 months	13 (43.3%)	7 (70.0%)	0	1 (33.3%)	21 (48.8%)
	≥10 mg glofitamab				
	DLBCL (NOS) (N=23)	trFL (N=11)	HGBCL (N=1)	PMBCL (N=0)	All (N=35)
CR > 3 months	16 (69.6%)	7 (63.6%)	0	0	23 (65.7%)
CR > 6 months	14 (60.9%)	6 (54.5%)	0	0	20 (57.1%)
CR > 12 months	13 (56.5%)	6 (54.5%)	0	0	19 (54.3%)

Four-step dosing in Cohort F2 (follicular lymphoma grade 1-3a) and double Gpt D2 Sub 4 (mostly mantle cell lymphoma) have higher CR than the registrational dose and schedule:

Table 29 Summary of IRC assessed Response rate (OR and CR): Dose escalation and dose expansion cohorts- step up dosing (ITT population)

Response	Glofitamab Dose					
	2.5/10/16 mg Cohort D_2 [Sub. 1] N = 17	2.5/10/30 mg Cohort D_2 [Sub. 2] N = 47	0.5/2.5/10/30 mg Cohort F_2 N = 30	2.5/10/30 mg, Cohort D_2[a] [Sub. 4] N = 31	2.5/10/30 mg Cohort D_3[b] N = 109	2.5/10/30 mg Cohort D_5[b, c] N = 41
OR, n (%)	10 (58.8)	30 (63.8)	24 (80.0)	18 (58.1)	55 (50.5)	22 (53.7)
CR, n (%)	7 (41.2)	27 (57.4)	24 (80.0)	18 (58.1)	39 (35.8)	20 (48.8)

[a] Double Gpt
[b] Includes 1 patient with FL
[c] Dexamethasone pre-medication
CR = complete response; OR = overall response

Table 30. Summary of efficacy in patients with relapsed or refractory DLBCL

Efficacy endpoints	**Columvi N=108**
Complete response	
Patients with CR, n (%)	38 (35.2)
95% CI	[26.24, 44.96]
Overall response rate	
Patients with CR or PR, n (%)	54 (50.0)
95% CI	[40.22, 59.78]
Duration of complete response[1]	
Median DOCR, months [95% CI]	NE [18.4, NE]
Range, months	0[2]–20[2]
12-month DOCR, % [95% CI][3]	74.6 [59.19, 89.93]
Duration of response[4]	
Median duration, months [95% CI]	14.4 [8.6, NE]
Range, months	0[2]–20[2]
Time to first complete response	
Median TFCR, days [95% CI]	42 [41, 47]
Range, days	31–308

CI=confidence interval; NE=not estimable; PR=partial response.
Hypothesis testing was conducted on the primary endpoint of IRC-assessed CR rate.
[1] DOCR is defined as the date of first complete response until disease progression or death due to any cause.
[2] Censored observations.
[3] Event-free rates based on Kaplan-Meier estimates.
[4] DOR is defined as the date of first response (PR or CR) until disease progression or death due to any cause.

The median follow-up for DOR was 12.8 months (range: 0 to 20 months).

Immunogenicity

Of 418 patients in study NP30179, only two (0.5%) patients were negative for anti-glofitamab antibodies at baseline and became positive following treatment. Due to the limited number of patients with antibodies against glofitamab, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.

Summary of main efficacy results

The following table summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 31 Summary of efficacy for trial NP30179

Title: A multicenter, open-label, Phase I/II study to evaluate the safety, efficacy, tolerability and pharmacokinetics of escalating doses of glofitamab (RO7082859) as a single agent and in combination with obinutuzumab administered after a fixed, single dose pre-treatment of obinutuzumab in patients with relapsed/refractory B-cell non-Hodgkin's lymphoma.			
Study identifier	NP30179 EudraCT number: 2016-0011845-28 NCT03075696		
Design	A Phase I/II, multicenter, multicohort, open-label, dose-escalation and expansion study designed to evaluate the efficacy, safety, tolerability, and pharmacokinetics of glofitamab, administered by IV infusion as monotherapy and in combination with obinutuzumab following pre-treatment with a fixed dose of obinutuzumab (Gpt) in patients with relapsed/refractory (R/R) non-Hodgkin's lymphoma (NHL).		
	Duration of main phase:		Approx. 5 years (ongoing)
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis (DLBCL patients)	The null hypothesis (H_o) that the complete response (CR) rate in R/R diffuse large B-cell lymphoma (DLBCL) patients (including R/R DLBCL not otherwise specified [NOS], high-grade B-cell lymphoma [HGBCL], primary mediastinal B-cell lymphoma [PMBCL], DLBCL arising from follicular lymphoma (FL) [transformed FL; trFL]) in Cohort D_3 was equivalent to an historical control CR rate of 20% was tested using an exact binomial test at the 0.05 level of significance.		
Treatments groups	R/R DLBCL patients (≥2 prior lines of systemic therapy) treated with glofitamab monotherapy in Cohort D_3		Fixed dose of Gpt (1000 mg) on C1D1 followed by glofitamab IV monotherapy 2.5 mg on C1D8, 10 mg on C1D15 and 30 mg on C2D1, Q3W.
Endpoints and definitions	Primary efficacy endpoint	IRC-assessed CR rate	Proportion of patients who had a best overall response of CR using the Lugano response criteria for NHL (Cheson et al. 2014).
	Secondary efficacy endpoint	IRC- assessed DOCR	Time from the initial occurrence of a documented CR until documented disease progression or death due to any cause, whichever occurs first using the Lugano response criteria for NHL (Cheson et al. 2014).
	Secondary efficacy endpoint	IRC- assessed DOR	Time from the initial occurrence of a documented CR or PR until documented disease progression or death due to any cause, whichever occurs first using the Lugano response criteria for NHL (Cheson et al. 2014).
	Secondary efficacy endpoint	IRC- assessed TFCR	Time from first study treatment to the first documented CR using the Lugano response criteria for NHL (Cheson et al. 2014).

Database lock	Database lock has not yet occurred; study is ongoing. This summary is based on an updated clinical cut-off date of 15 June 2022 with a database snapshot date of 09 August 2022.		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary efficacy population comprised 108 R/R DLBCL patients in Cohort D_3 who had received ≥2 prior lines of systemic therapy treated with glofitamab step-up dosing at the intended registrational dose (2.5/10/30 mg) and schedule (Q3W). Efficacy was evaluated by scheduled tumor assessments at Cycles 3, 6, 9 and end of treatment, and every 6 months until progression. The primary analysis in the glofitamab monotherapy R/R DLBCL Cohort D_3 was to occur when the following condition was met: • The efficacy-evaluable population (Cohort D_3) has approximately a median of 10 months of follow-up since the first response recorded, unless the patient has withdrawn before this time point.		
Descriptive statistics and estimate variability	Treatment group	R/R DLBCL patients (≥2 prior lines of systemic therapy) Cohort D_3 – Glofitamab 2.5/10/30 mg	
	Number of patients	108	
		IRC-assessed	
	CR rate (95% CI)	35.2% (26.2, 45.0) (primary efficacy endpoint)	
	DOCR: median – months* (95% CI)	NE (18.4, NE)	
	DOR: median - months (95% CI)	14.4 (8.6, NE)	
	TFCR: median - days (95% CI)	42.0 (41.0, 47.0)	
Notes	Patients enrolled in the study with R/R FL treated with glofitamab monotherapy and patients with R/R NHL (all histologies) treated with glofitamab in combination with obinutuzumab will be reported separately at a later time. Concordance between the IRC- and INV-assessment on whether a patient achieved a CR was high (94.5%). The CR rate and ORR for relevant subpopulations in Cohort D_3 defined by demographic, baseline disease, prior treatment, prognostic factors, and prior CAR-T therapy were similar to the response rate for Cohort D_3 overall.		

C = cycle; CI = confidence interval; CR = complete response; D = day; DOCR = duration of complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; Gpt = obinutuzumab pre-treatment; INV = investigator; IRC = Independent Review Committee; NHL = non-Hodgkin's lymphoma; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PR = partial response; Q3W = every three weeks; R/R = relapsed /refractory; SD = standard deviation; Sub. = subcohort; TFCR = time to complete response; TFOR = time to overall response

*Median follow-up for DOCR is 12.8 months.

Clinical studies in special populations

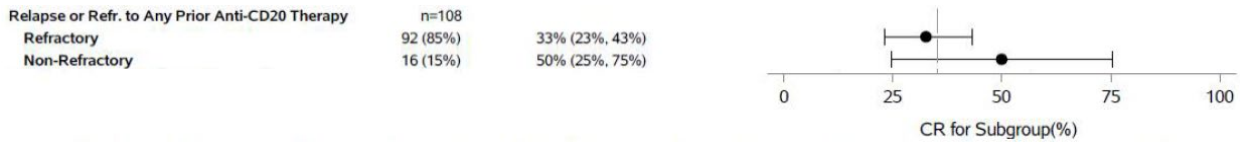
Table 32 Clinical Studies in Special Populations (CCOD: 15 June 2022)

	Age 65–74 (Older subjects number/ total number)	Age 75–84 (Older subjects number/ total number)	Age 85+ (Older subjects number/ total number)
Controlled trials	N/A	N/A	N/A
Non-controlled trials NP30179, Cohort D_3 (N = 108)	41/108	15/108	2/108

N/A = not applicable

From the table above, 58/108 (54%) patients in this trial were aged 65 years or older. The following complete responses by age bracket were noted (source document: ema-responses-support-data1.pdf - linked via response to Q89): Age < 65: 18/50 (36%), Age 65 – 74: 14/41 (34%), Age 75-84: 6/15 (40%) and Age 85+: 1/2 (50%).

Figure 15 Complete response in patients refractory to anti -CD20 vs patients not refractory to prior anti-CD20 treatment*



(not statistically significant)

Figure 16 Time since last anti-CD20 therapy and CR (non-overlapping 95% CI at 3 months cut-off):

2.6.5.3. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.6.5.5. Supportive study(ies)

Supportive cohorts D2sub2 and D5 include R/R DLBCL patients treated with the proposed registrational step-up dosing as cohort D3. Cohort D5 received mandatory dexamethasone pre-treatment.

Immunogenicity

No patients developed anti-drug antibodies while on glofitamab treatment.

Table 33 Summary of anti-drug antibody incidence

Baseline ADA Status	Post Dose ADA Status	n (%)
Negative	All negative	355 (95.9)
Negative	At least one positive sample	0 (0)
Positive	All negative	12 (3.3)
Positive	At least one positive sample	3 (0.8)

Including patients with at least one baseline and one post-dose ADA sample

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The Application is based on preliminary results from the phase I/II study NP30179. A confirmatory randomised phase 3 study has commenced as part of the conditions for granting CMA (*A Phase III Study Evaluating Glofitamab in Combination with Gemcitabine + Oxaliplatin vs Rituximab in Combination With Gemcitabine + Oxaliplatin in Participants With Relapsed/Refractory Diffuse Large B-Cell Lymphoma,* ClinicalTrials.gov Identifier: NCT04408638).

NP30179 is an ongoing single-arm, first-in-human, multicenter, open-label, Phase I/II dose-escalation and cohort-expansion study evaluating the efficacy, safety and tolerability, and pharmacokinetics of glofitamab. The study investigates glofitamab in various dose regimens (fixed dose, step-up dose regimen, extended step-up dose regimen; Q2W/Q3W) as a single agent with one or two 1000 mg doses of obinutuzumab/Gazyvaro given as pre-treatment (Gpt), and/or as combination therapy of glofitamab and obinutuzumab in patients with R/R NHL. All patients received Gpt so there is no way to differentiate the effect of Gpt from glofitamab, and it is not feasible to determine the CRS-mitigating effect of Gpt.

Different cohorts for R/R DLBCL and R/R FL are included. The study currently consists of 17 cohorts, 9 of which are dose expansion cohorts in study part III. The primary efficacy cohort for this application was defined as D3 and includes 108 patients with various aggressive histologies, treated with step-up dosing of glofitamab (to reduce risk of cytokine release syndrome). The study was initiated as a Phase 1 study and was subsequently amended 10 times. Only with Protocol Amendment 9 (= Protocol Version 10) was the study title upgraded to call the study a Phase 1/2 study.

The confirmatory cohort was only defined in the SAP, which was finalized on 23. Nov 2021. The clinical data cut-off date was before that on 14 Sept 2021, i.e., the decision on the primary analysis cohort was made after all data had been accrued, and thus open to bias due to choices related to specifications on the analyses. The choice of a single cohort out of many is problematic as there is no multiplicity control over cohorts, despite the highly flexible and data-driven nature of the study. This was also considered critical given the lack of a clear dose rationale and given that the applicant continues to investigate combination therapies (with obinutuzumab) in the same indication and within

the same study. Moreover, the study was open-label and guided by an internal review committee with the risk of upward biased results.

Overall, it is noted that the response data seems comparable within comparable populations (i.e., within r/r NHL or within r/r DLBCL but not across these populations). However, no data for the combination therapy arms in the DLBCL cohorts was provided and hence this information and a potential type 1 error in relation to this data cannot be ascertained. Since the other cohorts do not concern this application, this issue will not be further pursued. It is also noted that no documentation of the decision to consider the study a confirmatory study and Cohort D3 as confirmatory cohort was provided. The type 1 error concern and related possibilities of selection bias were thus substantially alleviated.

It is obvious that the study was designed as an exploratory early-phase study. For this purpose, the study design itself (open-label single-arm trial without independent DMC), the flexibility in the study design, the lack of type-1-error control (or the lack of a pre-specified pivotal cohort), and the many substantial amendments are considered acceptable. All these issues are, however, considered very critical for a confirmatory trial considered to provide pivotal evidence of efficacy and safety.

The histological cancer subtypes enrolled included DLBCL (73.1% patients), trFL (15.7% patients), and HGBCL and PMBCL (5.6% patients each). The median number of prior cancer therapies was 3 (range: 2-7). 34.3% patients had failed prior CAR-T therapy. The majority of the patients were refractory to any prior therapy (90.7% patients). As such, the patients enrolled in the study have a poor prognosis and are reflective of the inclusion and exclusion criteria and of the indication sought. Patients with autoimmune disease, prior allogeneic transplant, follicular lymphoma (FL) grade 3B and those with HIV and hepatitis were excluded. PET CT is considered mandatory at the diagnosis of DLBCL. FDG PET/CT imaging was the preferred radiologic modality for assessing FDG-avid lymphomas and was recommended to assess baseline tumor burden in this study.

With a fixed treatment duration of 12 cycles (approximately 8.3 months) and the majority of CRs achieved early on during the treatment (median 42 days), up to approximately 7 months CR follow-up occurs while a patient receives glofitamab treatment. Therefore, the current median DOCR follow up of 12.8 months in Cohort D3 and a 12-month event free rate of 74.6% suggest that glofitamab responses are maintained beyond the end of treatment. The longest CR follow-up in Cohort D3 was 20 months, which is at least 12 months while being off treatment. Additionally, patient convenience and safety are important considerations for limiting treatment to 12 cycles in the target population, given the durable responses observed. CR rate and duration of CR /duration of response are acceptable and meaningful endpoints in the setting of R/R DLBCL.

Due to the design of the trial, the question as to whether efficacy was a primary or secondary endpoint could impact the power of the trial. In addition, the size of the primary efficacy cohort was increased – from ~40 to ~100 patients– while the study was ongoing, which was discussed and found acceptable. The primary endpoint for the main efficacy cohort was CR-rate as assessed by independent review committee (IRC). CR-rate as assessed by investigator (INV) and duration of complete response (DOCR) assessed by IRC and INV were the key secondary endpoints. The primary and secondary endpoints are considered relevant and appropriate for a single-arm trial in R/R DLBCL. Concordance between the IRC- and INV-assessment on whether a patient achieved a CR was high (94.4%). The applicant also compared the CR-rate of glofitamab to the CR-rate of a historical cohort of R/R DLBCL compiled from a number of published trials in R/R DLBCL dating back to 2008, but this indirect comparison was not deemed very useful for B/R assessment.

Considering the limitations of an open-label nature of the trial, PROs measured with validated questionnaires like EORTC QLQ-C30 and FACT-Lym are considered only supportive in assessment of efficacy.

Supportive efficacy data are provided from patients in the dose-expansion part of the study who received the proposed registrational dose of glofitamab and a cohort of patients treated with the proposed registrational dose including mandatory pre-treatment with dexamethasone (whereas the primary efficacy cohort was pre-treated with physician's choice of corticosteroid). Since both obinutuzumab and corticosteroids have anti-lymphoma activity, these differences are considered to be non-negligible and preclude pooling of results with the primary efficacy cohort.

Overall, data on duration of CR presented in the supportive efficacy populations are consistent with data in the primary efficacy population. Because of the longer follow up time (26.0 months; Table 29/uCSR), DOCR data from patients treated with doses of glofitamab ≥10mg provide further indication of the durability of CR responses.

Searching the Clinicaltrials.gov database, 13 additional studies for glofitamab (excluding the pivotal NP30179 and GO41944 which is intended to be used as SOB) have been identified. None of these additional studies has been considered supportive by the applicant. Obinutuzumab pretreatment, corticosteroid premedication as well as step-up dosing as submitted within the MAA have a rationale in the pivotal NP30179 study. Moreover, the doses and premedication investigated by the applicant and in investigator-initiated studies seem to oscillate around what is currently sought to be approved and will possibly not be changed very much in the future due to similar efficacy and similar incidence of related AEs across studies. The applicant provided additional data from study YO42610 which seem to confirm efficacy and safety results of the pivotal NP30179 study.

Study NP30179 includes 79 DLBCL patients + 6 HGBCL patients + 6 PMBCL patients + 17 trFL patients = 108 patients -note that in the latest update, two DLBCL patients have been reclassified as HGBCL, so that the ITT denominator is 108 including all patients with correct histologies (IE, including the trFL patient who did not receive treatment but excluding the FL gr 1-3A patient who was treated). The patient with FL gr 1-3A who was enrolled in error and treated had a CR. As such, it does not make sense to include a single patient with an indolent lymphoma in a trial of aggressive histologies and given the above, it is accepted that the applicant's proposition of an ITT population of n=108 is the most pragmatic.

The majority of patients characterized as double-hit without a HGBCL diagnosis were trFL with the relevant translocations. This explains the discrepancy between the HGBCL and double-/triple-hit populations. Since the wording used was slightly ambiguous, the applicant was requested to verify that all patients counted as double-hit have a MYC translocation. The applicant was only able to substantiate that 5 of the original 13 claimed double-/triple-hit patients did in fact have this diagnosis. The diagnosis was conclusively disproven in 4 patients (3 had their diagnoses revised while 1 was found to be MYC-translocation negative). For 3 patients, no biopsy was available for ascertainment of MYC-translocation and these have been reported as major protocol deviations. The designation of double-/triple-hit diagnosis is not possible in the absence of a MYC-translocation and so the applicant should not claim double/triple-hit status in any lymphomas where such a translocation is not demonstrated. Given that this will not have an impact on whether glofitamab can be approved, it is not pursued further.

Efficacy data and additional analyses

At the updated data cut-off (15 JUNE 2022), with a median follow-up for DOCR of 12.8 months, the primary efficacy endpoint in the main efficacy dataset (D3, n=108), CR-rate by IRC, was 35.2% (95% CI 26.2, 45.0) with a median DOCR not yet reached. Overall, these results are clinically meaningful in the R/R DLBCL setting. The comparison to a historical control cohort with a CR rate of 20% is not deemed useful for B/R assessment in this context. It is agreed, though, that the totality of evidence

suggests that the studied treatment (and the studied dosing regimen) is efficacious in the targeted population. It is particularly noteworthy that the duration of CR extends beyond the duration of fixed glofitamab treatment.

Overall, baseline characteristics of the disease itself seems well distributed as to Ann Arbor, IPI, extranodal disease and bulky disease. The age distribution of subjects enrolled in this trial is considered reasonably representative of the R/R DLBCL population (3rd line and higher). Responses were noted in all age brackets and for age cohorts with more than 2 patients enrolled, matched the response rate of the entire cohort well.

The median time to CR was 42 days, meaning that responses were evident after patients had received the step-up dosing and one full maintenance dose of glofitamab. This is of clinical relevance as quick responses are of benefit in aggressive diseases such as R/R DLBCL and also as it means that patients who do not respond will be able to discontinue treatment relatively quickly.

The efficacy cohort included a number of different histologies. In the updated data package, two patients have had their diagnosis changed from DLBCL to HGBCL. Updated subtype analysis on the different lymphoma types now demonstrate the following CR-rates: DLBCL = 36% (CI 26-48%), HGBCL = 0%, PMBCL = 50% (CI 12-88%) and trFL 41% (18-67%). While these results are, with the exception of DLBCL, based on very small numbers of patients (DLBCL=77 pts, HGBCL=8 pts, PMBCL=6 pts and trFL=17 pts), it is notable that not a single patient with HGBCL had a CR.

The treatment effect was in general consistent across relevant subpopulations defined by e.g., demographic (gender, age range categories, race/ethnicity, ECOG PS), prior CAR-T therapy, NHL subtype at study entry, relapse and refractory status and risk factors for IPI. Encouragingly, patients previously having failed CAR-T treatment, patients receiving glofitamab post autologous stem cell transplant therapy and those who were refractory to their last line of treatment (all of which represent difficult-to-treat patient categories) achieved 32%, 56% and 29% CR-rates, respectively.

The applicant has clarified that the group of 17 patients labelled trFL encompasses 8 DLBCL, 5 HGBCL and 4 "trFL" histologies. The latter indicate patients whose transformation occurred at an earlier line of treatment. Of the whole trFL group, 7/17 (41%) patients achieved a CR. CRs could be further subdivided based on histology: 4/8 DLBCL (50%), 2/5 HGBCL (40%) and 1/4 (25%) "trFL" achieved a CR.

Regarding the MoA of glofitamab (targeting CD20 on malignant B-cells and recruiting host T-cells): CD20 expression on tumour cells was assumed but not tested for prior to enrolment. This is considered problematic in a patient population where all participants have failed prior anti-CD20 targeting therapy as part of the eligibility criteria. The applicant has ascertained CD20 status for participants and correlated this with glofitamab response. Overall, concern remains that previous anti-CD20 treatment could negatively impact the efficacy of glofitamab in the intended patient population. Sequencing of drugs with the same target in subsequent treatment lines is controversial and, for example, recent CD19-targeting CAR-T lymphoma trials had either exclusion criteria to limit prior CD19 targeted therapy and/or required verification of continued CD19 expression for eligibility. All patients in the intended population for glofitamab treatment (3L+ R/R DLBCL) will have been exposed to prior anti-CD20 treatment. This is well reflected in the study population where 100% of patients were previously exposed to anti-CD20 therapy. No effort to ascertain CD20 status prior to enrollment was reported, despite this being a routine test in lymphoma (relapse) diagnosis. 85% of enrolled patients were refractory to any prior anti-CD20 therapy. This has important implications. It is perhaps not surprising that early relapses/refractory disease have an inferior prognosis, however, an alternative explanation could be that recent anti-CD20 treatment negatively impacts glofitamab activity.

The applicant has provided evidence that some patients enrolled in the study were in fact CD20-negative. All 3 patients with CD20-negative disease (less than 5% of CD20-positive cells in the tumor area) had progressive disease as their best response to glofitamab and died during follow-up. One of the 3 patients had CD20-negativity demonstrated on an archival biopsy meaning that the result likely was available before enrolment and that the applicant and investigator in charge of enrolment therefore potentially knowingly included this patient in a trial of a CD20-targeting therapy (this might also be true of the other 2 CD20-negative patients). The applicant acknowledges that prior exposure to CD20-targeting agents may predispose to the development of CD20-related mechanisms of resistance. Subgroup analyses requested could also be interpreted to indicate some deleterious effect of (recent) prior anti-CD20 treatment. Overall, concern still remains that the clinical context in which glofitamab is given (in patients, all of whom have been exposed to prior CD20-targeted therapy) predisposes to development of resistance to CD20-targeted agents. Such resistance may be due to several mechanisms but the one that is possible thus far is low (less than 5%) CD20-expression. The relevant inclusion criterion defining the CD20-expression for the pivotal study was "a histologically-confirmed hematological malignancy that was expected to express CD20". Such a wording suggests the expectation that glofitamab is only efficacious against CD20-positive lymphomas. This in turn translates to an uncertainty as to whether glofitamab provides any benefit in CD20-negative cases. Based on the responses provided by the applicant, it does not seem that glofitamab retains anti-lymphoma activity in CD20-negative lymphomas. This casts doubt on whether benefit of glofitamab has been established for the entire patient population encompassed by the applicant's proposed indication text. This uncertainty, is reflected as a warning at 4.4 in the SmPC: There are limited data available on patients with CD20-negative DLBCL treated with Columvi, and it is possible that patients with CD20-negative DLBCL may have less benefit compared to patients with CD20-positive DLBCL. The potential risks and benefits associated with treatment of patients with CD20-negative DLBCL with Columvi should be considered. The efficacy of Columvi has not been established in patients with CD20-negative disease who have relapsed from prior anti-CD20 therapy.

The approved therapeutic indication is *Columvi as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.*

Additional expert consultation

Not applicable

Assessment of paediatric data on clinical efficacy

Not applicable

Additional efficacy data needed in the context of a conditional MA

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

Glofitamab is currently being investigated as monotherapy and in combination with other therapies in multiple Phase I/II studies and one Phase III open label, randomized (2:1) study in patients with R/R DLBCL. The confirmatory study agreed as an SOB for the CMA was discussed during a scientific advice procedure in Dec 2019 (EMEA/H/SA/4023/2/2019/III))is: A Phase III Study Evaluating Glofitamab in Combination with Gemcitabine + Oxaliplatin vs Rituximab in Combination with Gemcitabine + Oxaliplatin in Participants with Relapsed/Refractory Diffuse Large B-Cell Lymphoma, ClinicalTrials.gov

Identifier: NCT04408638/ Study GO41944. The study is ongoing and the applicant intends to submit the Type II variation to fulfil this SOB approximately Q3 2024. Of 270 patients to be included, the number of patients enrolled as of 08 November 2022 has been provided. It should be noted that patients are eligible for this study as second-line treatment (as opposed to the current application which is third-line or higher). In addition, the only LBCL subtype that is eligible is DLBCL NOS (meaning that no further data on the efficacy of glofitamab in trFL, HGBCL and PMBCL will be provided by this study).

2.6.7. Conclusions on the clinical efficacy

In terms of complete response rate and duration of complete response, the efficacy of glofitamab in R/R DLBCL is considered promising. The need to further improve treatment outcomes and overcome resistance to other therapies with a manageable safety reflects the unmet need.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- Submission of 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
- In order to provide further evidence of efficacy and safety of glofitamab in DLBCL, the MAH will provide the results of Study GO41944, a phase III open-label, multicentre, randomised study evaluating the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin versus rituximab in combination with gemcitabine and oxaliplatin in patients with relapsed or refractory DLBCL. The study is ongoing.

In addition, following the recommendations of the CHMP,

- the applicant will provide the final list of CD20 expression in Study NP30179 for the entire Cohort D3 with evaluable CD20 and to correlate expression with response to glofitamab at the time of the 2 years follow-up from the end of treatment of the last patient enrolled in the primary safety population.
- The applicant will measure CD20 expression and correlate this to response and risk of CRS in the ongoing SOB phase III trial NCT04408638/ Study GO41944 (R-GemOx vs Glofit-GemOx in 2L+ DLBCL NOS).

2.6.8. Clinical safety

Primary safety population: Data from safety-evaluable patients (i.e. patients who have received at least one dose of study medication [obinutuzumab pre-treatment, glofitamab]) treated with 2.5/10/30 mg step-up doses of glofitamab in the proposed indication (patients with R/R DLBCL who have received ≥2 prior lines of systemic therapy) pooled from cohorts D2 subcohort 2 ([Sub.2], Part II), D3 (Part III) and Cohort D5 (Part III) (N=154 patients). The safety population has later been amended to exclude patients who did not receive glofitamab but only obinutuzumab (N=9).

Table 34 Summary of Studies Contributing to Safety Evaluation

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

Gpt=obinutuzumab (Gazyvaro®/ Gazyva®) pre-treatment; IV=intravenous; NHL=non-Hodgkin's lymphoma; Q3W=every 3 weeks; R/R=relapsed or refractory.

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

[b] Overall safety population includes all enrolled patients in Study NP30179 glofitamab monotherapy ≥0.6 mg dosing cohorts who have received at least one dose of study medication (obinutuzumab pre-treatment, glofitamab), irrespective of histology.

Table 35 Current Primary and Supportive Safety Populations and Proposed Alternatives

	Current primary safety population		Current supportive population in SCS **(Extended Safety Population 1)**		Extended population 1 + Cohort D_4 **(Extended Safety Population 2)**[a]		Extended safety population 2 + Cohort D_2 [Sub.4] **(Extended Safety Population 3)**	
Definition	**R/R DLBCL**[b] patients with ≥2 prior lines of systemic therapy, treated with 2.5/10/30 mg glofitamab		**R/R NHL** patients with ≥1 prior lines of systemic therapy, treated with 2.5/10/30 mg glofitamab		**R/R NHL** patients with ≥1 prior lines of systemic therapy, treated with 2.5/10/30 mg glofitamab		**R/R NHL** patients who have received ≥1 prior lines of systemic therapy, treated with 2.5/10/30 mg glofitamab	
Obinutuzumab pretreatment	Gpt		Gpt		Gpt		Gpt or double Gpt	
Histologies	R/R DLBCL[b]		R/R DLBCL[b], R/R FL, R/R MCL, Richter's transformation		R/R DLBCL[b], R/R FL, R/R MCL, Richter's transformation		R/R DLBCL[b], R/R FL, R/R MCL, Richter's transformation	
Cohorts	D_2 Subcohort 2 + D_3 + D_5		D_2 Subcohort 2 + D_3 + D_5		D_2 Subcohort 2 + D_3 + D_5 + D_4		D_2 Subcohort 2 + D_3 + D_5 + D_4 + D_2 Subcohort 4	
CCOD	14 Sep 2021	15 June 2022[c]	14 Sep 2021	15 June 2022 [c]	14 Sep 2021	15 June 2022 [c]	14 Sep 2021	15 June 2022 [c]
N	152	154	191	195	199	236	222	267

[a] Extended step-up dosing 0.5/2.5/10/30 mg, Cohort F_2 and patients treated with two doses of Gpt (double Gpt) in Cohort D_2 [Sub. 4] are excluded.

[b] R/R DLBCL: includes DLBCL NOS, trFL, PMBCL, HGBCL.

[c] Cohorts D_2 [Sub. 2], D_2 [Sub. 4], D_4, and D_5 continued to enroll patients between the 14 September 2021 and 15 June 2022 CCODs, hence the Ns have changed for the primary safety population and SCS supportive population as well as the two new extended safety population proposals.

With the additional 9 months updated safety data it is considered pertinent, that the primary safety population is the DLBCL-population having received at least two prior treatments and treated with the recommended dose.

The number of patients receiving the recommended dose of 2.5/10/30 mg in cohort D2, subcohorts 2 and 4 by diagnosis (FL, DLBCL etc.) is presented below.

Table 36 Cancer Histological Subtypes in Cohort D_2, Subcohorts 2 and 4 (Safety-Evaluable Population, 15 June 2022 CCOD)

Cohort (Diagnosis)	Dose of Glofitamab [a]	Number of Patients Treated	Cancer histological subtype
D_2 (R/R NHL, ≥ 1 prior line of therapy)	Subcohort 2: 2.5/10/30 mg	46	DLBCL: 5 (10.9%) FL 3B: 1 (2.2%) FL 1-3A: 21 (45.7%) MCL : 14 (30.4%) Richter's: 2 (4.3%) trFL: 3 (6.5%)
	Subcohort 4: 2.5/10/30 mg (after dGpt)	31	HGBCL: 1 (3.2%) MCL : 29 (93.5%) Richter's: 1 (3.2%)

FL 1-3A = follicular lymphoma grade 1-3A; FL 3B = follicular lymphoma grade 3B; HGBCL = high-grade B-cell lymphoma; MCL = mantle cell lymphoma; Richter's = Richter's transformation; trFL = DLBCL transformed from follicular lymphoma.

[a] All patients received a single fixed dose of obinutuzumab (Gpt: 1000 mg IV) pre-treatment, given 7 days (C1D1) prior to the initial dose of glofitamab, except for patients in Cohort D_2 Subcohort 4 who received two doses of Gpt (dGpt [2 × 1000mg IV]).

Source: Update Interim CSR NP30179, Report 1114923 (t_mh_char_GE600_CSR_SE_15JUN2022_30179).

2.6.8.1. Patient exposure

For the primary safety population (N = 154) at the 15 June 2022 CCOD, the median number of cycles of glofitamab received was 5.0 (range: 1-13 cycles), with 61.4% of patients receiving less than 8 cycles and 29.7% of patients receiving 12 cycles of treatment, and median treatment duration was 79.0 days (range: 1-326 days). Patients achieving a complete response (n=62 in the corresponding efficacy population) received a median of 12 cycles of glofitamab treatment whereas non-responders received fewer cycles largely due to study treatment discontinuation (Update SCS, Section 1.2.1).

Exposure to treatment in Cohorts D3 and D5 was as follows:

- Cohort D3: median of 5.0 cycles of glofitamab (range: 1-13 cycles) and median 78.0 days treatment duration (range: 1-326 days).
- Cohort D5: median of 6.0 cycles of glofitamab (range: 1-12 cycles) and median 98.0 days treatment duration (range: 1-245 days).

Table 37: Exposure to Study Treatment (Glofitamab, Tocilizumab): Patients with R/R DLBCL, ⩾2 Previous Lines of Systemic Therapy, Fixed Dosing and Step-up Dosing (Safety-Evaluable Population)

Name of Treatment	Glofitamab 2.5/10/30 mg Cohort D3 (N=107)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=40)	Glofitamab Doses >=10 mg(b) (N=100)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=114)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=154)
Glofitamab					
Number of Infusions					
n	101	37	97	108	145
Mean (SD)	7.1 (4.2)	7.8 (4.5)	6.3 (3.8)	7.3 (4.2)	7.4 (4.3)
Median	6.0	7.0	6.0	6.0	6.0
Min - Max	1 - 14	1 - 13	1 - 13	1 - 14	1 - 14
Total Cumulative Dose(mg)					
n	101	37	97	108	145
Mean (SD)	164.78 (123.45)	187.67 (134.19)	94.42 (65.00)	170.65 (124.99)	175.00 (127.14)
Median	132.50	135.00	80.00	132.50	132.50
Min - Max	2.5 - 345.0	2.5 - 342.5	10.0 - 300.0	2.5 - 345.0	2.5 - 345.0
Total Duration (Days)					
n	101	37	97	108	145
Mean (SD)	108.4 (89.3)	124.6 (94.5)	109.0 (83.5)	112.2 (89.7)	115.4 (90.8)
Median	78.0	98.0	91.0	78.5	79.0
Min - Max	1 - 326	1 - 245	1 - 315	1 - 326	1 - 326
Glofitamab					
Number of Treatment Cycles					
n	101	37	97	108	145
Mean (SD)	6.1 (4.1)	6.9 (4.4)	6.2 (3.8)	6.3 (4.1)	6.5 (4.2)
Median	5.0	6.0	5.0	5.0	5.0
Min - Max	1 - 13	1 - 12	1 - 12	1 - 13	1 - 13
Categorized Number of Cycles					
Less than 8 cycles	66 (65.3%)	21 (56.8%)	59 (60.8%)	68 (63.0%)	89 (61.4%)
8 cycles	7 (6.9%)	1 (2.7%)	11 (11.3%)	7 (6.5%)	8 (5.5%)
9-11 cycles	1 (1.0%)	1 (2.7%)	7 (7.2%)	3 (2.8%)	4 (2.8%)
12 cycles	26 (25.7%)	14 (37.8%)	20 (20.6%)	29 (26.9%)	43 (29.7%)
>12 cycles	1 (1.0%)	0	0	1 (0.9%)	1 (0.7%)
Dose Intensity(%)					
n	101	37	97	108	145
Mean (SD)	99.93 (0.51)	99.82 (1.05)	99.80 (3.13)	99.94 (0.49)	99.91 (0.68)
Median	100.00	100.00	100.00	100.00	100.00
Min - Max	95.0 - 100.0	93.6 - 100.0	72.0 - 112.5	95.0 - 100.0	93.6 - 100.0
Categorized Dose Intensity(%)					
<90%	0	0	1 (1.0%)	0	0
>=90%	101 (100%)	37 (100%)	96 (99.0%)	108 (100%)	145 (100%)
Tocilizumab					
Number of Infusions					
n	26	5	18	27	32
Mean (SD)	1.4 (0.9)	1.8 (0.8)	1.3 (0.6)	1.4 (0.8)	1.5 (0.8)
Median	1.0	2.0	1.0	1.0	1.0
Min - Max	1 - 4	1 - 3	1 - 3	1 - 4	1 - 4
Total Cumulative Dose(mg)					
n	26	5	18	27	32
Mean (SD)	813.12 (399.63)	899.12 (419.23)	714.13 (342.69)	824.48 (396.30)	836.14 (393.90)
Median	678.00	980.00	650.00	680.00	690.00
Min - Max	450.0 - 1920.0	470.0 - 1440.0	200.0 - 1800.0	450.0 - 1920.0	450.0 - 1920.0
Total Duration (Days)					
n	26	5	18	27	32
Mean (SD)	3.3 (8.2)	59.4 (126.1)	1.2 (0.5)	3.3 (8.0)	12.1 (50.3)
Median	1.0	2.0	1.0	1.0	1.0
Min - Max	1 - 42	1 - 285	1 - 3	1 - 42	1 - 285

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Dose intensity is the number of doses actually received divided by the expected number of doses.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ex.sas
Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/FDA_Sub2_EU_RTQ_Aug2022/prod/output/
t ex PIV I SCE SE 15JUN2022 30179.out

2.6.8.2. Adverse events

A summary of safety results for the 145 patients who received at least one dose of obinutuzumab and glofitamab based on the 15 June 2022 CCOD alongside the results for the initial primary safety population (N = 154 patients who received at least one dose of obinutuzumab and potentially

glofitamab), for ease of comparison – is given in the table below. Differences of 2% or more in frequencies of AEs has been underlined.

Table 38 Overview of Safety in the Primary Safety Population (Gpt or Glofitamab) and in Those Patients Who Received Gpt and Glofitamab (R/R DLBCL ≥2 Prior Lines,[a] 15 June 2022 CCOD)

Total number of patients with:	Gpt +/- Glofitamab, Primary Safety Population[b] N=154	Gpt and Glofitamab, Primary Safety Population[c] N=145
Common AEs (any grade), Severe (Grade ≥3) AEs and Serious AEs[e]		
Common AEs (≥ 20% of patients), n (%)	CRS (ASTCT): 99 (64.3%) Neutropenia/neutrophil count decreased: 58 (37.7%) Anemia: 47 (30.5%) Thrombocytopenia/platelet count decreased: 38 (24.7%)	CRS (ASTCT): 98 (67.6%) Neutropenia/neutrophil count decreased: 58 (40.0%) Anemia: 44 (30.3%) Thrombocytopenia/platelet count decreased: 35 (24.1%)
Common SAEs (≥ 3% of patients), n (%)	CRS (ASTCT): 32 (20.8%) Sepsis: 6 (3.9%) COVID-19 pneumonia: 5 (3.2%) COVID-19: 5 (3.2%) Tumor flare: 5 (3.2%)	CRS (ASTCT): 32 (22.1%) Sepsis: 6 (4.1%) COVID-19: 5 (3.4%) Tumor flare: 5 (3.4%) *COVID-19 pneumonia: 4 (2.8%)*
Common Grade ≥3 AEs (≥ 5% of patients), n (%)	Neutropenia/neutrophil count decreased: 42 (27.3%) Anemia: 12 (7.8%) Thrombocytopenia/platelet count decreased: 12 (7.8%) Hypophosphatemia: 9 (5.8%)	Neutropenia/neutrophil count decreased: 42 (29.0%) Anemia: 11 (7.6%) Thrombocytopenia/platelet count decreased: 10 (6.9%) Hypophosphatemia: 9 (6.2%)
Common AEs (≥2 patients) leading to glofitamab treatment discontinuation, n (%)	COVID-19: 2 (1.3%) Neutropenia: 2 (1.3%) Delirium: 2 (1.3%)	COVID-19: 2 (1.4%) Neutropenia: 2 (1.4%) Delirium: 1 (0.7%)
Common AEs (≥2% of patients) leading to glofitamab dose modification / interruption, n (%)	Neutropenia: 13 (8.4%) Thrombocytopenia: 4 (2.6%)	Neutropenia: 13 (9.0%) Thrombocytopenia 3 (2.1%) COVID-19: 3 (2.1%)

AE = adverse event; ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; COVID-19 = coronavirus disease; DLBCL = diffuse large B-cell lymphoma; Gpt = obinutuzumab pretreatment; R/R=relapsed or refractory; SAE = serious adverse event.

a Patients with R/R DLBCL (includes DLBCL NOS, trFL, PMBCL, HGBCL; ≥2 prior lines) from Cohorts D2 [Sub. 2], D3, and D5.

b Patients who received one dose of obinutuzumab. 145/154 subsequently received glofitamab.

c Patients who received at least one dose of obinutuzumab and glofitamab. Differences of 2% or more in frequencies of AEs between N=154 and N=145 populations are underlined.

d AEs within the SOCs of Nervous System Disorders and Psychiatric Disorders.

e Events that met the selected threshold for the primary population but were reported with lower incidence in the N=145 population are included for completeness (italicized).

Source: *Primary safety population (N=154)*: Update SCS Table 12 (safety overview), Table 14 (common AEs), Table 15 (SAEs), Table 17 (CRS), Table 18 (Grade ≥ 2 CRS), Table 27 (tumor flare), Table 29 (Grade ≥ 2 NAEs), Table 31 (TLS), and Table 33 (febrile neutropenia); and Update Interim CSR, Report No. 1114923, Section 5.4.4.3 (severe AEs), Section 5.4.7.3 (SAEs by SOC and PT), Section 5.4.10.3 (all-grade NAEs), Section 5.4.12.1 (neutropenia AEs), Section 5.4.12.2 (thrombocytopenia AEs), Section 5.4.8 (glofitamab discontinuation), and Section 5.4.9.3 (glofitamab dose modifications/interruptions).

Table 39

Overview of Safety: Patients with R/R DLBCL, ≥ 2 Prior Lines of Systemic Therapy, Fixed Dosing and Step-up Dosing

Overview of Adverse Events, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Glofitamab Doses >= 0.6 mg, Safety-Evaluable Monotherapy Patients
Protocol: NP30179

	Glofitamab 2.5/10/30 mg Cohort D3 (N=107)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=40)	Glofitamab Doses >=0.60 mg (N=287)	Glofitamab Doses >=10 mg(b) (N=100)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=114)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=154)
Total number of patients with at least one AE	106 (99.1%)	39 (97.5%)	281 (97.9%)	97 (97.0%)	113 (99.1%)	152 (98.7%)
Total number of patients with a graded AE	106 (99.1%)	39 (97.5%)	281 (97.9%)	97 (97.0%)	113 (99.1%)	152 (98.7%)
Total number of AEs	899	353	2799	1100	996	1349
Total number of graded AEs	893	351	2785	1094	990	1341
Total number of deaths	63 (58.9%)	16 (40.0%)	132 (46.0%)	42 (42.0%)	65 (57.0%)	81 (52.6%)
Total number of patients withdrawn from treatment due to an AE	9 (8.4%)	4 (10.0%)	17 (5.9%)	2 (2.0%)	10 (8.8%)	14 (9.1%)
Total number of patients with at least one adverse event related to study drug	100 (93.5%)	37 (92.5%)	255 (88.9%)	86 (86.0%)	107 (93.9%)	144 (93.5%)
Total number of patients with at least one AE with fatal outcome	7 (6.5%)	2 (5.0%)	13 (4.5%)	4 (4.0%)	7 (6.1%)	9 (5.8%)
Total number of patients with at least one AE leading to withdrawal from Glofitamab	9 (8.4%)	4 (10.0%)	16 (5.6%)	1 (1.0%)	10 (8.8%)	14 (9.1%)
AE leading to withdrawal from Obinutuzumab	0	0	1 (0.3%)	1 (1.0%)	0	0
AE leading to dose modification/ interruption of Glofitamab	17 (15.9%)	9 (22.5%)	62 (21.6%)	24 (24.0%)	19 (16.7%)	28 (18.2%)
Serious AE	57 (53.3%)	15 (37.5%)	153 (53.3%)	61 (61.0%)	60 (52.6%)	75 (48.7%)
Serious AE leading to withdrawal from Glofitamab	9 (8.4%)	1 (2.5%)	12 (4.2%)	1 (1.0%)	9 (7.9%)	10 (6.5%)
Serious AE leading to dose modification/interruption of Glofitamab	4 (3.7%)	4 (10.0%)	23 (8.0%)	11 (11.0%)	5 (4.4%)	9 (5.8%)
AE Related to Glofitamab	98 (91.6%)	35 (87.5%)	246 (85.7%)	83 (83.0%)	105 (92.1%)	140 (90.9%)
AE Related to Obinutuzumab	27 (25.2%)	13 (32.5%)	81 (28.2%)	26 (26.0%)	30 (26.3%)	43 (27.9%)
Total number of patients with at least one Serious AE Related to Glofitamab	36 (33.6%)	7 (17.5%)	107 (37.3%)	51 (51.0%)	39 (34.2%)	46 (29.9%)
Serious AE Related to Obinutuzumab	2 (1.9%)	1 (2.5%)	7 (2.4%)	1 (1.0%)	3 (2.6%)	4 (2.6%)
AEs Grade 3-5 (NCI-CTCAE/ASTCT)	71 (66.4%)	23 (57.5%)	182 (63.4%)	61 (61.0%)	75 (65.8%)	98 (63.6%)
Grade 3-5 (NCI-CTCAE/ASTCT) AE Related to Glofitamab	48 (44.9%)	16 (40.0%)	113 (39.4%)	35 (35.0%)	51 (44.7%)	67 (43.5%)
Grade 3-5 (NCI-CTCAE/ASTCT) AE Related to Obinutuzumab	8 (7.5%)	3 (7.5%)	27 (9.4%)	6 (6.0%)	9 (7.9%)	12 (7.8%)
AE Related to Glofitamab leading to withdrawal from Glofitamab	3 (2.8%)	1 (2.5%)	5 (1.7%)	0	4 (3.5%)	5 (3.2%)
AE Related to Glofitamab leading to dose modification/interruption	11 (10.3%)	4 (10.0%)	33 (11.5%)	13 (13.0%)	12 (10.5%)	16 (10.4%)
AE with Dose limiting toxicity	0	0	6 (2.1%)	5 (5.0%)	0	0
CRS by LEE grade	78 (72.9%)	20 (50.0%)	179 (62.4%)	66 (66.0%)	83 (72.8%)	103 (66.9%)
Total number of patients with at least one CRS by ASTCT grade	75 (70.1%)	19 (47.5%)	173 (60.3%)	64 (64.0%)	80 (70.2%)	99 (64.3%)
CRS by LEE with grade 3-4	4 (3.7%)	1 (2.5%)	10 (3.5%)	4 (4.0%)	4 (3.5%)	5 (3.2%)
CRS by ASTCT with grade 3-4	5 (4.7%)	1 (2.5%)	13 (4.5%)	5 (5.0%)	5 (4.4%)	6 (3.9%)
Outcome of Adverse Events						
Recovered / Resolved	698	223	2158	886	787	1010
Recovering / Resolving	4	10	40	2	5	15
Recovered / Resolved with Sequelae	4	0	22	17	4	4
Not Recovered / Resolved	186	118	564	189	193	311
Fatal	7	2	13	4	7	9
Unknown / Missing	0	0	2	2	0	0

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Investigator text for AEs encoded using MedDRA version 25.0. Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" and "Outcome of Adverse Events" rows in which multiple occurrences of the same AE are counted separately.
AEs with missing toxicity grades are included as a result of either missing Lee/NCI CTCAE or ungraded by ASTCT.
Tocilizumab not included as a study drug.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ae_oview.sas
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t ae oview PIV I SCS SE 15JUN2022 30179.out

Table 40

Overview of Safety: Glofitamab Doses ≥ 0.60 mg Fixed Dosing and Step-up Dosing (Patients with R/R NHL, All Histologies)

Overview of Adverse Events, Initial Treatment Phase, Glofitamab Doses >= 0.6 mg, Safety-Evaluable Monotherapy Patients
Protocol: NP30179

	Glofitamab Doses >=0.60 mg (N=469)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=195)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D4, D5 (N=236)
Total number of patients with at least one AE	460 (98.1%)	192 (98.5%)	232 (98.3%)
Total number of patients with a graded AE	460 (98.1%)	192 (98.5%)	232 (98.3%)
Total number of AEs	4943	1968	2307
Total number of graded AEs	4921	1958	2294
Total number of deaths	170 (36.2%)	91 (46.7%)	92 (39.0%)
Total number of patients withdrawn from treatment due to an AE	20 (4.3%)	16 (8.2%)	16 (6.8%)
Total number of patients with at least one adverse event related to study drug	421 (89.8%)	184 (94.4%)	217 (91.9%)
Total number of patients with at least one AE with fatal outcome	22 (4.7%)	11 (5.6%)	11 (4.7%)
AE leading to withdrawal from Glofitamab	18 (3.8%)	16 (8.2%)	16 (6.8%)
AE leading to withdrawal from Obinutuzumab	2 (0.4%)	0	0
AE leading to dose modification/ interruption of Glofitamab	119 (25.4%)	46 (23.6%)	56 (23.7%)
Serious AE	259 (55.2%)	105 (53.8%)	120 (50.8%)
Serious AE leading to withdrawal from Glofitamab	14 (3.0%)	12 (6.2%)	12 (5.1%)
Serious AE leading to dose modification/interruption of Glofitamab	50 (10.7%)	17 (8.7%)	22 (9.3%)
AE Related to Glofitamab	406 (86.6%)	178 (91.3%)	210 (89.0%)
AE Related to Obinutuzumab	160 (34.1%)	61 (31.3%)	75 (31.8%)
Serious AE Related to Glofitamab	192 (40.9%)	71 (36.4%)	82 (34.7%)
Serious AE Related to Obinutuzumab	23 (4.9%)	7 (3.6%)	9 (3.8%)

Table 26 (cont'd)

Overview of Adverse Events, Initial Treatment Phase, Glofitamab Doses >= 0.6 mg, Safety-Evaluable Monotherapy Patients
Protocol: NP30179

	Glofitamab Doses >=0.60 mg (N=469)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=195)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D4, D5 (N=236)
Total number of patients with at least one AEs Grade 3-5 (NCI-CTCAE/ASTCT)	290 (61.8%)	127 (65.1%)	148 (62.7%)
Grade 3-5 (NCI-CTCAE/ASTCT) AE Related to Glofitamab	188 (40.1%)	93 (47.7%)	108 (45.8%)
Grade 3-5 (NCI-CTCAE/ASTCT) AE Related to Obinutuzumab	53 (11.3%)	17 (8.7%)	22 (9.3%)
AE Related to Glofitamab leading to withdrawal from Glofitamab	5 (1.1%)	5 (2.6%)	5 (2.1%)
AE Related to Glofitamab leading to dose modification/interruption	75 (16.0%)	30 (15.4%)	37 (15.7%)
AE with Dose limiting toxicity	13 (2.8%)	3 (1.5%)	3 (1.3%)
CRS by LEE grade	310 (66.1%)	138 (70.8%)	162 (68.6%)
CRS by ASTCT grade	300 (64.0%)	133 (68.2%)	156 (66.1%)
CRS by LEE with grade 3-4	18 (3.8%)	9 (4.6%)	10 (4.2%)
CRS by ASTCT with grade 3-4	24 (5.1%)	11 (5.6%)	11 (4.7%)
Outcome of Adverse Events			
Recovered / Resolved	3965	1535	1812
Recovering / Resolving	53	18	22
Recovered / Resolved with Sequelae	34	6	8
Not Recovered / Resolved	867	398	454
Fatal	22	11	11
Unknown / Missing	2	0	0

Investigator text for AEs encoded using MedDRA version 25.0. Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" and "Outcome of Adverse Events" rows in which multiple occurrences of the same AE are counted separately.
AEs with missing toxicity grades are included as a result of either missing Lee/NCI CTCAE or ungraded by ASTCT.
Tocilizumab not included as a study drug.
Data Cutoff Date: 15JUN2022

Table 41 Summary of Adverse Events with an Incidence Rate of at Least 10%: Patients with R/R DLBCL; ≥2 Prior Lines of Systemic Therapy, Fixed Dosing and Step-up Dosing

MedDRA System Organ Class MedRA Preferred Term	Glofitamab 2.5/10/30 mg Cohort D3 (N=107)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=40)	Glofitamab Doses >=0.60 mg (N=287)	Glofitamab Doses >=10 mg(b) (N=100)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=114)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=154)
Total number of patients with at least one adverse event	100 (93.5%)	39 (97.5%)	264 (92.0%)	93 (93.0%)	106 (93.0%)	145 (94.2%)
Overall total number of events	518	189	1497	563	563	752
Immune system disorders						
Total number of patients with at least one adverse event	78 (72.9%)	20 (50.0%)	179 (62.4%)	66 (66.0%)	83 (72.8%)	103 (66.9%)
Total number of events	141	27	287	97	149	176
Cytokine release syndrome	78 (72.9%)	20 (50.0%)	179 (62.4%)	66 (66.0%)	83 (72.8%)	103 (66.9%)
Blood and lymphatic system disorders						
Total number of patients with at least one adverse event	56 (52.3%)	25 (62.5%)	156 (54.4%)	48 (48.0%)	61 (53.5%)	86 (55.8%)
Total number of events	134	43	387	134	145	188
Neutropenia	39 (36.4%)	12 (30.0%)	100 (34.8%)	31 (31.0%)	43 (37.7%)	55 (35.7%)
Anaemia	32 (29.9%)	12 (30.0%)	85 (29.6%)	27 (27.0%)	35 (30.7%)	47 (30.5%)
Thrombocytopenia	23 (21.5%)	8 (20.0%)	60 (20.9%)	16 (16.0%)	25 (21.9%)	33 (21.4%)
Gastrointestinal disorders						
Total number of patients with at least one adverse event	38 (35.5%)	15 (37.5%)	106 (36.9%)	36 (36.0%)	41 (36.0%)	56 (36.4%)
Total number of events	51	28	164	59	56	84
Diarrhoea	13 (12.1%)	6 (15.0%)	39 (13.6%)	13 (13.0%)	14 (12.3%)	20 (13.0%)
Constipation	11 (10.3%)	8 (20.0%)	36 (12.5%)	10 (10.0%)	13 (11.4%)	21 (13.6%)
Nausea	11 (10.3%)	4 (10.0%)	35 (12.2%)	15 (15.0%)	12 (10.5%)	16 (10.4%)
Abdominal pain	9 (8.4%)	3 (7.5%)	27 (9.4%)	11 (11.0%)	10 (8.8%)	13 (8.4%)
General disorders and administration site conditions						
Total number of patients with at least one adverse event	35 (32.7%)	11 (27.5%)	105 (36.6%)	45 (45.0%)	37 (32.5%)	48 (31.2%)
Total number of events	51	19	192	94	53	72
Pyrexia	18 (16.8%)	6 (15.0%)	64 (22.3%)	30 (30.0%)	19 (16.7%)	25 (16.2%)
Fatigue	12 (11.2%)	5 (12.5%)	40 (13.9%)	19 (19.0%)	13 (11.4%)	18 (11.7%)
Asthenia	8 (7.5%)	5 (12.5%)	25 (8.7%)	8 (8.0%)	8 (7.0%)	13 (8.4%)
Metabolism and nutrition disorders						
Total number of patients with at least one adverse event	33 (30.8%)	15 (37.5%)	94 (32.8%)	30 (30.0%)	37 (32.5%)	52 (33.8%)
Total number of events	66	23	179	59	78	101
Hypophosphataemia	17 (15.9%)	7 (17.5%)	42 (14.6%)	12 (12.0%)	20 (17.5%)	27 (17.5%)
Hypomagnesaemia	17 (15.9%)	3 (7.5%)	44 (15.3%)	17 (17.0%)	19 (16.7%)	22 (14.3%)
Hypocalcaemia	12 (11.2%)	6 (15.0%)	29 (10.1%)	7 (7.0%)	13 (11.4%)	19 (12.3%)
Hypokalaemia	9 (8.4%)	5 (12.5%)	33 (11.5%)	10 (10.0%)	12 (10.5%)	17 (11.0%)
Investigations						
Total number of patients with at least one adverse event	13 (12.1%)	9 (22.5%)	51 (17.8%)	20 (20.0%)	15 (13.2%)	24 (15.6%)
Total number of events	34	18	130	53	38	56
Alanine aminotransferase increased	7 (6.5%)	6 (15.0%)	31 (10.8%)	13 (13.0%)	7 (6.1%)	13 (8.4%)
Gamma-glutamyltransferase increased	7 (6.5%)	2 (5.0%)	26 (9.1%)	15 (15.0%)	8 (7.0%)	10 (6.5%)
Aspartate aminotransferase increased	7 (6.5%)	4 (10.0%)	24 (8.4%)	8 (8.0%)	8 (7.0%)	12 (7.8%)
Blood alkaline phosphatase increased	6 (5.6%)	6 (15.0%)	24 (8.4%)	6 (6.0%)	7 (6.1%)	13 (8.4%)
Nervous system disorders						
Total number of patients with at least one adverse event	13 (12.1%)	8 (20.0%)	40 (13.9%)	16 (16.0%)	14 (12.3%)	22 (14.3%)
Total number of events	13	14	50	20	14	28
Headache	11 (10.3%)	4 (10.0%)	29 (10.1%)	13 (13.0%)	11 (9.6%)	15 (9.7%)
Dizziness	2 (1.9%)	5 (12.5%)	12 (4.2%)	3 (3.0%)	3 (2.6%)	8 (5.2%)
Musculoskeletal and connective tissue disorders						
Total number of patients with at least one adverse event	10 (9.3%)	5 (12.5%)	32 (11.1%)	9 (9.0%)	11 (9.6%)	16 (10.4%)
Total number of events	10	6	36	12	11	17
Back pain	10 (9.3%)	5 (12.5%)	32 (11.1%)	9 (9.0%)	11 (9.6%)	16 (10.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Total number of patients with at least one adverse event	13 (12.1%)	3 (7.5%)	27 (9.4%)	8 (8.0%)	14 (12.3%)	17 (11.0%)
Total number of events	15	3	31	10	16	19
Tumour flare	13 (12.1%)	3 (7.5%)	27 (9.4%)	8 (8.0%)	14 (12.3%)	17 (11.0%)
Respiratory, thoracic and mediastinal disorders						
Total number of patients with at least one adverse event	3 (2.8%)	3 (7.5%)	27 (9.4%)	17 (17.0%)	3 (2.6%)	6 (3.9%)
Total number of events	3	8	41	25	3	11
Cough	3 (2.8%)	3 (7.5%)	27 (9.4%)	17 (17.0%)	3 (2.6%)	6 (3.9%)

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Investigator text for AEs encoded using MedDRA version 25.0. Percentages are based on N in the column headings.
Only treatment emergent AEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Data Cutoff Date: 15JUN2022

a No PT within this SOC was reported at a frequency of ≥ 10%.

SOCs Renal and urinary disorders (5.5%), Eye disorders (3.4%), Ear and labyrinth disorders (2.8%), Reproductive system and breast disorders (3.4%), Hepatobiliary disorders (1.4%), and Endocrine disorders (0.7%) did not meet the 10% frequency threshold for inclusion.

Treatment-related adverse events (TRAEs)

The ADRs presented in Table 48/uSCS correspond to the adverse reactions presented in section 4.8 of the SmPC. Figure 2/uSCS is a graphic presentation of all AEs as well as those considered related in the applicant's primary safety population.

Figure 17

Figure 2 Tornado Plot of AEs with ≥10% Incidence or NCI CTCAE Grade 5 (Patients with R/R DLBCL, ≥ 2 Prior Lines of Systemic Therapy, Glofitamab 2.5/10/30 mg Step-up Dosing, Cohorts D_2 [Sub2], D_3, D_5)

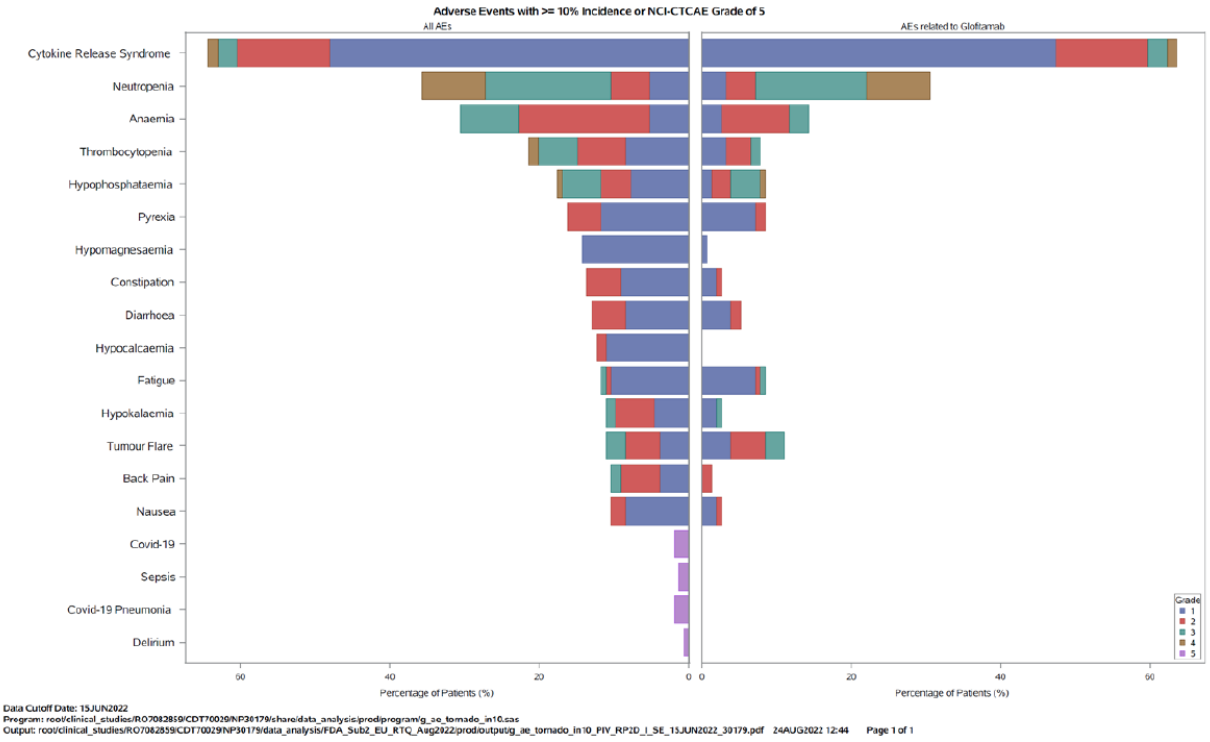

Table 42

Adverse Drug Reactions in the Primary Safety Population (Gpt or Glofitamab) and in Those Patients Who Received Gpt and Glofitamab (R/R DLBCL ≥2 Prior Lines, 15 June 2022 CCOD)

System Organ Class / Adverse Reaction	Gpt +/- Glofitamab,[£] Primary Safety Population N=154			Gpt and Glofitamab, Primary Safety Population N=145		
	All grades (frequency category)	All grades (%)	Grade 3-4 (%)	All grades (frequency category)	All grades (%)	Grade 3-4 (%)
Immune system disorders						
Cytokine release syndrome [a]	Very common	64.3	3.9	Very common	67.6	4.1
Blood and lymphatic system disorders						
Neutropenia [b]	Very common	37.7	27.3	Very common	40.0	29.0
Anemia [c]	Very common	30.5	7.8	Very common	30.3	7.6
Thrombocytopenia [d]	Very common	24.7	7.8	Very common	24.1	6.9
Lymphopenia [e]	Common	4.5	4.5	Common	4.8	4.8
Febrile neutropenia [f]	Common	3.2	3.2	Common	3.4	3.4
General disorders and administration site conditions						
Pyrexia	Very common	16.2	0	Very common	15.9	0
Metabolism and nutrition disorders						
Hypophosphatemia	Very common	17.5	5.8	Very common	18.6	6.2
Hypomagnesemia	Very common	14.3	0	Very common	15.2	0
Hypocalcemia	Very common	12.3	0	Very common	12.4	0
Hypokalemia	Very common	11.0	1.3	Very common	10.3	0.7
Hyponatremia	Common	7.8	1.3	Common	8.3	1.4
Tumor lysis syndrome	Common	1.3	1.3	Common	1.4	1.4
Skin and subcutaneous tissue disorders						
Rash [g]	Very common	18.8	1.3	Very common	20.0	1.4
Gastrointestinal disorders						
Constipation	Very common	13.6	0	Very common	14.5	0
Diarrhea	Very common	13.0	0	Very common	13.8	0
Nausea	Very common	10.4	0	Very common	10.3	0
Gastrointestinal hemorrhage [h]	Common	2.6	2.6	Common	2.8	2.8
Vomiting	Common	4.5	0	Common	4.1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Tumor flare	Very common	11.0	2.6	Very common	11.7	2.8

System Organ Class / Adverse Reaction	Gpt +/- Glofitamab,[£] Primary Safety Population N=154			Gpt and Glofitamab, Primary Safety Population N=145		
	All grades (frequency category)	All grades (%)	Grade 3-4 (%)	All grades (frequency category)	All grades (%)	Grade 3-4 (%)
Nervous system disorders						
Headache	Common	9.7	0	Very common	10.3	0
Somnolence	Common	1.3	0.6	Common	1.4	0.7
Tremor	Common	1.3	0	Common	1.4	0
Myelitis [i]	Uncommon	0.6	0.6	Uncommon	0.7	0.7
Infections and infestations						
Viral infections [j]	Very common	11.0	3.2*	Very common	11.0	3.4#
Bacterial infections [k]	Common	6.5	1.9	Common	6.2	1.4
Upper respiratory tract infections [l]	Common	5.2	0	Common	5.5	0
Sepsis [m]	Common	3.9	2.6*	Common	4.1	2.8#
Lower respiratory tract infections [n]	Common	1.9	0	Common	2.1	0
Pneumonia	Common	4.5	1.3	Common	4.1	0.7
Urinary tract infection [o]	Common	2.6	0.6	Common	2.8	0.7
Fungal Infections [p]	Common	1.3	0	Common	1.4	0
Investigations						
Alanine amino-transferase increased	Common	8.4	2.6	Common	9.0	2.8
Aspartate amino-transferase increased	Common	7.8	2.6	Common	8.3	2.8
Blood alkaline phosphatase increased	Common	8.4	1.3	Common	9.0	1.4
Gamma-glutamyl-transferase increased	Common	6.5	2.6	Common	6.9	2.8
Blood bilirubin increased	Common	3.9	0.6	Common	4.1	0.7
Hepatic enzyme increased	Common	1.3	1.3	Common	1.4	1.4
Psychiatric disorders						
Confusional state	Common	1.9	0	Common	1.4	0

Patients who received one dose of obinutuzumab. 145/154 subsequently received glofitamab.

Grade 3-4 adverse events

Table 43

Summary of Grade 3-4 Adverse Events with ≥5% Incidence (15 June 2022 CCOD)

MedDRA SOC PT	Primary Safety Population [a] (D_2 [Sub. 2] + D_3 + D_5) (N=154)	Cohort D_3 [a] (N=108)	Extended Safety Population R/R NHL ≥1 prior line Pooled D_2 [Sub. 2] + D_3 + D_4 + D_5 [b] (N=236)	Overall Safety Population (Glofitamab doses ≥0.6 mg) [c] (N=469)
Any adverse events Grade 3-4	89 (57.8%)	64 (59.3%)	137 (58.1%)	268 (57.1%)
Blood and lymphatic system disorders	54 (35.1%)	37 (34.3%)	79 (33.5%)	167 (35.6%)
Neutropenia	39 (25.3%)	28 (25.9%)	58 (24.6%)	116 (24.7%)
Anemia	12 (7.8%)	9 (8.3%)	16 (6.8%)	39 (8.3%)
Thrombocytopenia	10 (6.5%)	7 (6.5%)	14 (5.9%)	29 (6.2%)
Infections and infestations [d]	18 (11.7%)	12 (11.1%)	32 (13.6%)	64 (13.6%)
Investigations [d]	18 (11.7%)	12 (11.1%)	32 (13.6%)	54 (11.5%)
Metabolism and nutrition disorders	17 (11.0%)	10 (9.3%)	21 (8.9%)	42 (9.0%)
Hypophosphataemia	9 (5.8%)	4 (3.7%)*	9 (3.8%)	15 (3.2%)*
Immune System Disorders	6 (3.9%)*	5 (4.6%)*	11 (4.7%)*	24 (5.1%)
Cytokine release syndrome	6 (3.9%)*	5 (4.6%)*	11 (4.7%)*	24 (5.1%)

[a] Patients with R/R DLBCL (includes DLBCL NOS, trFL, PMBCL, HGBCL) with ≥2 prior lines of systemic therapy treated with glofitamab 2.5/10/30mg.

[b] Patients with R/R NHL with ≥1 prior lines of systemic therapy, treated with 2.5/10/30 mg glofitamab.

[c] Patients with R/R NHL treated with glofitamab doses ≥0.6 mg who have received at least one dose of study medication (obinutuzumab pre-treatment, glofitamab), irrespective of histology.

[d] No PTs with ≥5% incidence.

* Indicates SOCs and PTs that occur with <5% frequency, which are included in the table for completeness.

Adverse events of special interest (AESI)

In accordance with the NP30179 study Protocol version 11, AESIs specific for glofitamab include the following:

- Grade ≥ 2 CRS

- Grade ≥ 2 neurologic adverse events
- Any suspected hemophagocytic lymphohistiocytosis (HLH)
- Tumor Lysis Syndrome (TLS) (minimum Grade 3 by definition)
- Febrile neutropenia (minimum Grade 3 by definition)
- Grade ≥ 2 aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation
- Any grade disseminated intravascular coagulation (minimum Grade 2 by definition)
- Grade ≥ 2 tumor inflammation/flare (e.g., manifestation of signs/symptoms associated with an increase in size of known nodal or extranodal lesions by clinical or radiographic assessment)
- Any grade pneumonitis or interstitial lung disease (ILD) (excluding pneumonia of infectious etiology)*
- Colitis of any grade (excluding infectious etiology)*

Cytokine Release Syndrome

For the primary safety population (n=154) CRS AEs of any grade were reported in 99 patients (64.3%) by ASTCT 2019. The corresponding number for the extended safety population 2 (n=236; see table in the introduction to Safety) was 156 (66.1%). An OC has been raised regarding the inclusion of patients having only received Gpt (obinutuzumab) and not glofitamab. In particular CRS is not expected to occur in these patients and thus lowering the CRS frequency (when glofitamab untreated patients are included).

In the primary safety population (n=154) a total of 47/154 patients (30.5%; based on ASTCT 2019) experienced multiple CRS AEs (Table 17/uSCS), and the corresponding number for the extended safety population 2 was 72/236 (30.5%).

CRS SAEs:

In the primary safety population (n=154) serious CRS AEs were experienced by 22.1% (Table 17/uSCS) and for the extended safety population 1 (n=195), it was 28.7% (Table 20/uSCS).

Hospitalisation or prolonged hospitalisation was the main reason for the SAEs events. No Grade 5 CRS AEs were reported, although there was one case of delirium leading to death in the setting of Grade 1 CRS, but it is considered that this most likely was related to pain (potentially due to PD) and pain medication based on the narrative as signs of overdose was already apparent before treatment with glofitamab.

Table 44

Overview of Cytokine Release Syndrome AEs Patients with R/R DLBCL, ≥ 2 Prior Lines of Systemic Therapy, Fixed Dosing and Step-up Dosing

Overview of Adverse Events, Cytokine Release Syndrome AEs, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Glofitamab Doses >= 0.6 mg, Safety-Evaluable Monotherapy Patients
Protocol: NP30179

	Glofitamab 2.5/10/30 mg Cohort D3 (N=107)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=40)	Glofitamab Doses >=0.60 mg (N=287)	Glofitamab Doses >=10 mg(b) (N=100)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=114)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=154)
Total number of patients with at least one AE	78 (72.9%)	20 (50.0%)	179 (62.4%)	66 (66.0%)	83 (72.8%)	103 (66.9%)
Total number of patients with a graded AE	75 (70.1%)	19 (47.5%)	173 (60.3%)	64 (64.0%)	80 (70.2%)	99 (64.3%)
Total number of AEs	141	27	287	97	149	176
Total number of graded AEs	136	25	275	92	144	169
Total number of patients with at least one AE with fatal outcome	0	0	0	0	0	0
AE leading to withdrawal from Glofitamab	1 (0.9%)	0	1 (0.3%)	0	1 (0.9%)	1 (0.6%)
AE leading to withdrawal from Obinutuzumab	0	0	0	0	0	0
AE leading to dose modification/ interruption of Glofitamab	1 (0.9%)	0	3 (1.0%)	1 (1.0%)	1 (0.9%)	1 (0.6%)
Total number of patients with at least one Serious AE	27 (25.2%)	6 (15.0%)	84 (29.3%)	41 (41.0%)	28 (24.6%)	34 (22.1%)
Serious AE leading to withdrawal from Glofitamab	1 (0.9%)	0	1 (0.3%)	0	1 (0.9%)	1 (0.6%)
Serious AE leading to dose modification/interruption of Glofitamab	1 (0.9%)	0	3 (1.0%)	1 (1.0%)	1 (0.9%)	1 (0.6%)
AE Related to Glofitamab	77 (72.0%)	20 (50.0%)	177 (61.7%)	65 (65.0%)	82 (71.9%)	102 (66.2%)
AE Related to Obinutuzumab	1 (0.9%)	0	1 (0.3%)	0	1 (0.9%)	1 (0.6%)
Serious AE Related to Glofitamab	27 (25.2%)	6 (15.0%)	84 (29.3%)	41 (41.0%)	28 (24.6%)	34 (22.1%)
Serious AE Related to Obinutuzumab	0	0	0	0	0	0
AEs Grade 3-5 (NCI-CTCAE/ASTCT)	5 (4.7%)	1 (2.5%)	13 (4.5%)	5 (5.0%)	5 (4.4%)	6 (3.9%)
Grade 3-5 (NCI-CTCAE/ASTCT) AE Related to Glofitamab	5 (4.7%)	1 (2.5%)	13 (4.5%)	5 (5.0%)	5 (4.4%)	6 (3.9%)
Total number of patients with at least one Grade 3-5 (NCI-CTCAE/ASTCT) AE Related to Obinutuzumab	0	0	0	0	0	0
AE Related to Glofitamab leading to withdrawal from Glofitamab	1 (0.9%)	0	1 (0.3%)	0	1 (0.9%)	1 (0.6%)
AE Related to Glofitamab leading to dose modification/interruption	1 (0.9%)	0	3 (1.0%)	1 (1.0%)	1 (0.9%)	1 (0.6%)
AE with Dose limiting toxicity	0	0	3 (1.0%)	3 (3.0%)	0	0
CRS by LEE grade	78 (72.9%)	20 (50.0%)	179 (62.4%)	66 (66.0%)	83 (72.8%)	103 (66.9%)
CRS by ASTCT grade	75 (70.1%)	19 (47.5%)	173 (60.3%)	64 (64.0%)	80 (70.2%)	99 (64.3%)
CRS by LEE with grade 3-4	4 (3.7%)	1 (2.5%)	10 (3.5%)	4 (4.0%)	4 (3.5%)	5 (3.2%)
CRS by ASTCT with grade 3-4	5 (4.7%)	1 (2.5%)	13 (4.5%)	5 (5.0%)	5 (4.4%)	6 (3.9%)
Total number of patients with more than one CRS by LEE grade	40 (37.4%)	7 (17.5%)	76 (26.5%)	24 (24.0%)	42 (36.8%)	49 (31.8%)
CRS by ASTCT grade	39 (36.4%)	6 (15.0%)	74 (25.8%)	24 (24.0%)	41 (36.0%)	47 (30.5%)
Outcome of Adverse Events						
Recovered / Resolved	139	27	283	95	147	174
Recovering / Resolving	0	0	0	0	0	0
Recovered / Resolved with Sequelae	0	0	1	1	0	0
Not Recovered / Resolved	2	0	3	1	2	2
Fatal	0	0	0	0	0	0
Unknown / Missing	0	0	0	0	0	0

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Investigator text for AEs encoded using MedDRA version 25.0. Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" and "Outcome of Adverse Events" rows in which multiple occurrences of the same AE are counted separately.
AEs with missing toxicity grades are included as a result of either missing Lee/NCI CTCAE or ungraded by ASTCT.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ae_oview.sas
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t ae oview CRSAE PIV I SCS SE 15JUN2022 30179.out

Grade ≥ 2 CRS AEs:

Grade ≥ 2 CRS AEs for glofitamab were reported as an AESI per the study protocol. In the primary safety population, 25/154 patients (16.2%) experienced a total of 27 Grade ≥ 2 CRS AEs by ASTCT 2019 grading, and for the extended safety population 1 41/195 experienced a total of 51 Grade ≥ 2 CRS AEs by ASTCT 2019 grading.

In all patients with CRS AEs, the CRS was assessed as related to glofitamab treatment by the investigator and all patients received treatment for CRS.

Table 45

Summary of Grade ≥ 2 CRS (ASTCT Grade) (Adverse Events of Special Interest), Patients with R/R DLBCL, ≥ 2 Prior Lines of Systemic Therapy, Fixed Dosing and Step-up Dosing

	Glofitamab 2.5/10/30 mg Cohort D3 (N=107)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=40)	Glofitamab Doses >=0.60 mg (N=287)	Glofitamab Doses >=10 mg(b) (N=100)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=114)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=154)
Total number of pts with at least one AE	19 (17.8%)	4 (10.0%)	62 (21.6%)	32 (32.0%)	21 (18.4%)	25 (16.2%)
Total number of AEs	21	4	66	33	23	27
Total number of pts with at least one AE by worst grade						
Grade 2	14 (13.1%)	3 (7.5%)	49 (17.1%)	27 (27.0%)	16 (14.0%)	19 (12.3%)
Grade 3	3 (2.8%)	1 (2.5%)	9 (3.1%)	4 (4.0%)	3 (2.6%)	4 (2.6%)
Grade 4	2 (1.9%)	0	4 (1.4%)	1 (1.0%)	2 (1.8%)	2 (1.3%)
Grade 5 (fatal outcome)	0	0	0	0	0	0
Total number of pts with dose modified/interrupted due to AE	1 (0.9%)	0	3 (1.0%)	1 (1.0%)	1 (0.9%)	1 (0.6%)
Total number of pts with treatment received for AE	19 (17.8%)	4 (10.0%)	62 (21.6%)	32 (32.0%)	21 (18.4%)	25 (16.2%)
Total number of pts with all AEs resolved	18 (16.8%)	4 (10.0%)	61 (21.3%)	32 (32.0%)	20 (17.5%)	24 (15.6%)
Total number of pts with at least one unresolved or ongoing AE	1 (0.9%)	0	1 (0.3%)	0	1 (0.9%)	1 (0.6%)
Total number of pts with at least one serious AE	13 (12.1%)	2 (5.0%)	42 (14.6%)	21 (21.0%)	14 (12.3%)	16 (10.4%)
Total number of pts with at least one related AE	19 (17.8%)	4 (10.0%)	62 (21.6%)	32 (32.0%)	21 (18.4%)	25 (16.2%)
Duration of AE (days)						
n	20	4	65	33	22	26
Mean (SD)	3.00 (2.05)	5.50 (5.69)	3.55 (2.65)	3.67 (2.10)	3.00 (1.95)	3.38 (2.82)
Median	2.50	3.00	3.00	3.00	3.00	3.00
Min - Max	1.0 - 10.0	2.0 - 14.0	1.0 - 14.0	1.0 - 11.0	1.0 - 10.0	1.0 - 14.0
Time to Onset (days)						
n	21	4	66	33	23	27
Mean (SD)	16.38 (12.67)	10.25 (3.30)	13.21 (8.99)	11.82 (6.54)	15.65 (12.32)	14.85 (11.56)
Median	14.00	10.00	9.00	8.00	9.00	9.00
Min - Max	8.0 - 63.0	7.0 - 14.0	7.0 - 63.0	7.0 - 30.0	8.0 - 63.0	7.0 - 63.0
Time to Onset from first Glofit dose (days)						
n	21	4	66	33	23	27
Mean (SD)	7.76 (12.51)	1.25 (0.50)	5.20 (8.73)	4.06 (6.28)	7.17 (12.09)	6.30 (11.33)
Median	2.00	1.00	1.00	1.00	1.00	1.00
Min - Max	1.0 - 56.0	1.0 - 2.0	1.0 - 56.0	1.0 - 23.0	1.0 - 56.0	1.0 - 56.0

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Treatment related AEs includes Glofitamab, Obinutuzumab or Tocilizumab. Dose modified/interrupted due to AE refers to Glofitamab and Obinutuzumab only.
Investigator text for AEs encoded using MedDRA version 25.0. AESIs not experienced by any patients are excluded. Multiple occurrences of the same AE in one individual are counted only once except for the Time to Onset, Duration and 'Total number of AEs' rows in which multiple occurrences of the same AE are counted separately. Percentages are based on N in the column headings. The count of 'Patients with treatment received for AE' is based on the AE CRF question 'Was Medication Given For AE?'
Data Cutoff Date: 15JUN2022
Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_aesi_bysmq.sas
Output:root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/FDA_Sub2_EU_RTQ_Aug2022/prod/output/t_aesi_bysmq_PIV_I_SCS_SE_15JUN2022_30179.out
13SEP2022 18:13 (Modified by PDRD)
Page 1 of 1
Note: time to onset from first glofit dose (days) includes patients who may have had a Grade ≥2 CRS AE with other glofitamab doses or unscheduled doses due to a dose delay.

In the primary safety population 16/154 patients (10.4%) experienced CRS SAEs ≥ 2 by ASTCT 2019 and in the extended safety population 1 this was observed in 29/195 (14.9%; Table 21 /uSCS).

At the time of CCOD (15Jun2022) the CRS in 24/25 patients in the primary safety population with Grade ≥ 2 CRS had resolved.

Table 46

Summary of Grade ≥ 2 CRS (ASTCT Grade) (Adverse Events of Special Interest): Glofitamab Doses ≥ 0.60 mg Fixed Dosing and Step-up Dosing (Patients with R/R NHL, All Histologies)

	Glofitamab Doses >=0.60 mg (N=469)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=195)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D4, D5 (N=236)
Total number of pts with at least one AE	122 (26.0%)	41 (21.0%)	52 (22.0%)
Total number of AEs	149	51	67
Total number of pts with at least one AE by worst grade			
Grade 2	98 (20.9%)	30 (15.4%)	41 (17.4%)
Grade 3	17 (3.6%)	7 (3.6%)	7 (3.0%)
Grade 4	7 (1.5%)	4 (2.1%)	4 (1.7%)
Grade 5 (fatal outcome)	0	0	0
Total number of pts with dose modified/interrupted due to AE	10 (2.1%)	4 (2.1%)	5 (2.1%)
Total number of pts with treatment received for AE	122 (26.0%)	41 (21.0%)	52 (22.0%)
Total number of pts with all AEs resolved	120 (25.6%)	39 (20.0%)	50 (21.2%)
Total number of pts with at least one unresolved or ongoing AE	2 (0.4%)	2 (1.0%)	2 (0.8%)
Total number of pts with at least one serious AE	81 (17.3%)	29 (14.9%)	34 (14.4%)
Total number of pts with at least one related AE	122 (26.0%)	41 (21.0%)	52 (22.0%)
Duration of AE (days)			
n	147	49	65
Mean (SD)	3.54 (2.67)	3.47 (2.49)	3.52 (2.57)
Median	3.00	3.00	3.00
Min - Max	1.0 - 19.0	1.0 - 14.0	1.0 - 14.0
Time to Onset (days)			
n	149	51	67
Mean (SD)	20.57 (29.35)	17.24 (14.65)	24.19 (31.47)
Median	9.00	9.00	14.00
Min - Max	7.0 - 241.0	7.0 - 71.0	7.0 - 160.0
Time to Onset from first Glofit dose (days)			
n	149	51	67
Mean (SD)	12.28 (28.91)	8.43 (13.94)	15.72 (31.57)
Median	1.00	1.00	1.00
Min - Max	1.0 - 227.0	1.0 - 58.0	1.0 - 153.0

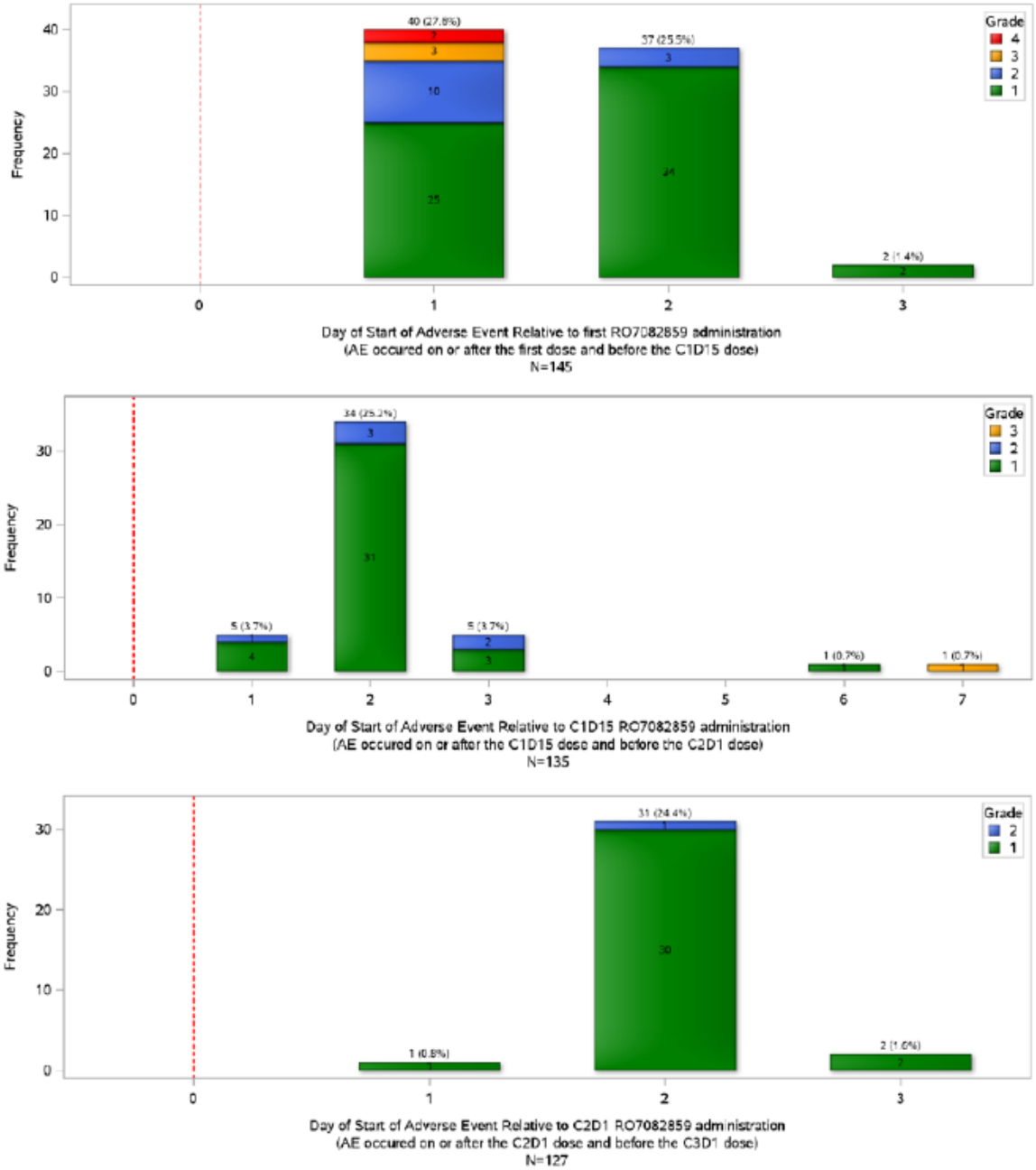
Treatment related AEs includes Glofitamab, Obinutuzumab or Tocilizumab. Dose modified/interrupted due to AE refers to Glofitamab and Obinutuzumab only. Investigator text for AEs encoded using MedDRA version 25.0. AESIs not experienced by any patients are excluded. Multiple occurrences of the same AE in one individual are counted only once except for the Time to Onset, Duration and 'Total number of AEs' rows in which multiple occurrences of the same AE are counted separately. Percentages are based on N in the column headings. The count of 'Patients with treatment received for AE' is based on the AE CRF question 'Was Medication Given For AE?'
Data Cutoff Date: 15JUN2022
Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_aesi_bysmq.sas
Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/FDA_Sub2_EU_RTQ_Aug2022/prod/output/t_aesi_bysmq_I_SCS2_SE_15JUN2022_30179.out
13SEP2022 18:14 (Modified by PDRD) Page 1 of 1
Note: time to onset from first glofit dose (days) includes patients who may have had a Grade ≥2 CRS AE with other glofitamab doses or unscheduled doses due to a dose delay.

Severity, onset, and duration of CRS:

In the primary safety population, the severity of CRS was reduced by each glofitamab dose and only Grade 1 CRS was seen from Cycle 3 onwards (see Figure 9/uSCS).

The time to onset and duration in cycle 1 and 2 varies considerably between patients. A patient card stating that the patients should contact their doctor if specified signs and symptoms for CRS occur, has been drafted, which is satisfactory. In the SmPC the median time to onset and duration including range has been included.

Figure 9 Frequency of CRS Events by Glofitamab Dose Cycle (Patients with R/R DLBCL, ≥ 2 Prior Lines of Systemic Therapy, Glofitamab 2.5/10/30 mg, Cohorts D_2 [Sub2], D_3, D_5)



Only adverse events which are treatment emergent with valid start dates are shown. The output displays ASTCT grade for CRS events and AE study days >1 year are shown as 1 year.
Relative day of start of Adverse event is calculated as the start date of AE - start date of Glofitamab dose + 1.
Only events occurring between this dose and the following are displayed.
N corresponds to the number of subjects that received the respective Glofitamab dose.
Data Cutoff Date: 15JUN2022
Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/g_ae_hist2_dose.sas
Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/FDA_Sub2_EU_RTQ_Aug2022/prod/output/g_ae_hist2_dose_CRSAE_PIV_RP2D_I_SE_15JUN2022_30179.pdf 23AUG2022 19:24 Page 3 of 3

Source: g_ae_hist2_dose_CRSAE_PIV_RP2D_I_SE_15JUN2022_30179 (modified by PDRD)

Source: uSCS

Management:

In the primary safety population (N=154) ICU admission was required for 7/99 patients (7.1%) and 31.3% required tocilizumab, 28 patients (28.3%) used corticosteroids, and 16 patients (16.2%) used both tocilizumab and corticosteroids to treat CRS (Table 25/uSCS).

Table 47

Summary of CRS Management: Patients with R/R DLBCL, ≥ 2 Prior Lines of Systemic Therapy, Fixed Dosing and Step-up Dosing

Summary of Tocilizumab Use and CRS Management, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), (ASTCT) CRS Patients,
Glofitamab Doses >= 0.6 mg, Safety-Evaluable Monotherapy Patients
Protocol: NP30179

	Glofitamab 2.5/10/30 mg Cohort D3 (N=75)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=19)	Glofitamab Doses >=0.60 mg (N=173)	Glofitamab Doses >=10 mg(b) (N=64)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=80)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=99)
Patients who used Tocilizumab	25 (33.3%)	5 (26.3%)	48 (27.7%)	16 (25.0%)	26 (32.5%)	31 (31.3%)
Patients who used Corticosteroids	19 (25.3%)	9 (47.4%)	56 (32.4%)	26 (40.6%)	19 (23.8%)	28 (28.3%)
Patients who used Tocilizumab and Corticosteroids together	12 (16.0%)	4 (21.1%)	25 (14.5%)	9 (14.1%)	12 (15.0%)	16 (16.2%)
Patients who used ICU	6 (8.0%)	1 (5.3%)	17 (9.8%)	9 (14.1%)	6 (7.5%)	7 (7.1%)
Patients who used fluids	10 (13.3%)	2 (10.5%)	41 (23.7%)	23 (35.9%)	12 (15.0%)	14 (14.1%)
Patients who used a single pressor	5 (6.7%)	1 (5.3%)	12 (6.9%)	5 (7.8%)	5 (6.3%)	6 (6.1%)
Patients who used multiple pressors	0	0	1 (0.6%)	0	0	0
Patients who used low flow oxygen	7 (9.3%)	1 (5.3%)	20 (11.6%)	11 (17.2%)	8 (10.0%)	9 (9.1%)
Patients who used high flow oxygen	0	1 (5.3%)	2 (1.2%)	1 (1.6%)	0	1 (1.0%)
Patients who used mechanical ventilation	2 (2.7%)	0	3 (1.7%)	1 (1.6%)	2 (2.5%)	2 (2.0%)

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Same CRS event has been considered to display 'Patients who used Tocilizumab and Corticosteroids together'.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_crs_mngmnt.sas
Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/FDA_Sub2_EU_RTQ_Aug2022/prod/output/t_crs_mngmnt_FIV_CRSPT2_I_SCS_SE_15JUN2022_30179.out
23AUG2022 21:53 Page 1 of 1

In the subgroup of patients with R/R NHL treated with 2.5/10/30 mg glofitamab (Cohort D3, Cohort D2 [Sub. 2] and Cohort D5) (N=195) the use of the various treatments was generally comparable (Table 26/uSCS

The median number of tocilizumab infusions in the primary safety population was 1.0 (range 1 – 4) with a median total cumulative dose of 678.0 mg (range 450.0 – 1920.0), and a median dose intensity of 100.0% (range 100.0-100.0) underscoring the importance of the availability of this product when administering glofitamab.

Information regarding hospitalisation and the length of hospitalisation is presented in the SmPC, section 4.8, for the primary safety population.

Table 48

Summary of CRS Management: Glofitamab ≥ 0.6 mg (Patients with R/R NHL, All Histologies)

Summary of Tocilizumab Use and CRS Management, Initial Treatment Phase, (ASTCT) CRS Patients, Glofitamab Doses >= 0.6 mg, Safety-Evaluable Monotherapy Patients
Protocol: NP30179

	Glofitamab Doses >=0.60 mg (N=300)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=133)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D4, D5 (N=156)
Patients who used Tocilizumab	98 (32.7%)	44 (33.1%)	54 (34.6%)
Patients who used Corticosteroids	98 (32.7%)	41 (30.8%)	45 (28.8%)
Patients who used Tocilizumab and Corticosteroids together	46 (15.3%)	23 (17.3%)	27 (17.3%)
Patients who used ICU	32 (10.7%)	13 (9.8%)	14 (9.0%)
Patients who used fluids	81 (27.0%)	21 (15.8%)	31 (19.9%)
Patients who used a single pressor	21 (7.0%)	10 (7.5%)	10 (6.4%)
Patients who used multiple pressors	4 (1.3%)	2 (1.5%)	2 (1.3%)
Patients who used low flow oxygen	46 (15.3%)	19 (14.3%)	22 (14.1%)
Patients who used high flow oxygen	4 (1.3%)	2 (1.5%)	2 (1.3%)
Patients who used mechanical ventilation	4 (1.3%)	3 (2.3%)	3 (1.9%)

Same CRS event has been considered to display 'Patients who used Tocilizumab and Corticosteroids together'.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_crs_mngmnt.sas
Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/FDA_Sub2_EU_RTQ_Aug2022/prod/output/t_crs_mngmnt_CRSPT2_I_SCS2_SE_15JUN2022_30179.out
23AUG2022 21:I1 (Modified by PDRD) Page 1 of 1
Note: Patients can be counted in more than one category of CRS management.

Source: uSCS

CRS with NAEs:

PTs consistent with immune effector cell-associated neurotoxicity syndrome (ICANS; Lee et al. 2019) were also identified through the list of PTs presented in Appendix 2 of the SCS. NAEs consistent with ICANS event rates (non-concurrent and concurrent with CRS) were 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 (2.6%) mainly in the first cycle of glofitamab treatment. Considering the low frequency of NAEs consistent with ICANS events, it is agreed, that the NAEs section represents a more appropriate characterization of the neurological adverse events.

Liver function test (LFT) AEs are discussed in the clinical chemistry section and below.

Dexamethasone pre-treatment (Cohort D5)

The applicant states that: "*The differences in baseline characteristics between patients enrolled in Cohort D5 and those enrolled in Cohort D3 as well as the ongoing enrolment may, in part along with dexamethasone premedication, explain the lower incidence of all-grade CRS, serious CRS and Grade ≥ 2 CRS in Cohort D5 compared with Cohort D3.*" Based on the small number of patients, the difference in baseline characteristics, and the updated data, where the difference between D5 and D3 is less, the role of dexamethasone cannot be assessed.

Cytokine release syndrome is included in the RMP Summary of safety concerns as an Important identified risk.

Grade ≥ 2 Tumour Flare

Tumour flare of any grade was reported in 17/154 patients (11.0%) and for ≥ Grade 2 in 11/154 patients (7.1%) in the primary safety population. Tumour flare occurred most frequently in Cycle 1 (16/17 patients) and 1/17 in Cycle 2 with a median time to onset of 2.00 days (range: 1.0-16.0 days). The median duration of Grade ≥ 2 tumour flare was 5.50 days (range: 1.0 – 27.0).

Nine of 11 patients (in the primary safety population, N=154) received treatment for tumour flare, which consisted of steroids and/or pain medication. This information including a warning to observe the patients for tumour flare is presented in section 4.4 and 4.8 of the SmPC.

Table 49

Summary of Grade ≥ 2 Tumor Flare Events (Adverse Events of Special Interest), Patients with R/R DLBCL, ≥ 2 Prior Lines of Systemic Therapy, Fixed Dosing and Step-up Dosing

	Glofitamab 2.5/10/30 mg Cohort D3 (N=107)	Glofitamab 2.5/10/30 mg Cohort D5 (a) (N=40)	Glofitamab Doses >=0.60 mg (N=287)	Glofitamab Doses >=10 mg (b) (N=100)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=114)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=154)
Total number of pts with at least one AE	7 (6.5%)	3 (7.5%)	20 (7.0%)	7 (7.0%)	8 (7.0%)	11 (7.1%)
Total number of AEs	7	3	22	9	8	11
Total number of pts with at least one AE by worst grade						
Grade 2	5 (4.7%)	1 (2.5%)	11 (3.8%)	3 (3.0%)	6 (5.3%)	7 (4.5%)
Grade 3	2 (1.9%)	2 (5.0%)	9 (3.1%)	4 (4.0%)	2 (1.8%)	4 (2.6%)
Grade 4	0	0	0	0	0	0
Grade 5 (fatal outcome)	0	0	0	0	0	0
Total number of pts with dose modified/interrupted due to AE	1 (0.9%)	0	1 (0.3%)	0	1 (0.9%)	1 (0.6%)
Total number of pts with treatment received for AE	5 (4.7%)	3 (7.5%)	16 (5.6%)	7 (7.0%)	6 (5.3%)	9 (5.8%)
Total number of pts with all AEs resolved	6 (5.6%)	3 (7.5%)	18 (6.3%)	6 (6.0%)	7 (6.1%)	10 (6.5%)
Total number of pts with at least one unresolved or ongoing AE	1 (0.9%)	0	2 (0.7%)	1 (1.0%)	1 (0.9%)	1 (0.6%)
Total number of pts with at least one serious AE	3 (2.8%)	0	6 (2.1%)	2 (2.0%)	4 (3.5%)	4 (2.6%)
Total number of pts with at least one related AE	7 (6.5%)	3 (7.5%)	20 (7.0%)	7 (7.0%)	8 (7.0%)	11 (7.1%)
Duration of AE (days)						
n	6	3	20	8	7	10
Mean (SD)	9.67 (9.81)	5.67 (2.31)	6.30 (6.30)	5.50 (4.41)	8.43 (9.54)	7.60 (7.97)
Median	6.00	7.00	4.00	3.50	4.00	5.50
Min - Max	2.0 - 27.0	3.0 - 7.0	1.0 - 27.0	2.0 - 14.0	1.0 - 27.0	1.0 - 27.0
Time to Onset (days)						
n	7	3	22	9	8	11
Mean (SD)	14.00 (5.97)	8.33 (0.58)	10.55 (5.46)	9.11 (5.97)	13.50 (5.71)	12.09 (5.36)
Median	16.00	8.00	8.50	8.00	13.00	9.00
Min - Max	8.0 - 24.0	8.0 - 9.0	2.0 - 24.0	2.0 - 24.0	8.0 - 24.0	8.0 - 24.0
Time to Onset from first Glofit dose (days)						
n	7	3	21	8	8	11
Mean (SD)	5.71 (5.99)	2.00 (1.00)	3.57 (4.82)	3.00 (5.26)	5.25 (5.70)	4.36 (5.03)
Median	2.00	2.00	1.00	1.00	2.00	2.00
Min - Max	1.0 - 16.0	1.0 - 3.0	1.0 - 16.0	1.0 - 16.0	1.0 - 16.0	1.0 - 16.0

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Treatment related AEs includes Glofitamab, Obinutuzumab or Tocilizumab. Dose modified/interrupted due to AE refers to Glofitamab and Obinutuzumab only. Investigator text for AEs encoded using MedDRA version 25.0. AESIs not experienced by any patients are excluded. Multiple occurrences of the same AE in one individual are counted only once except for the Time to Onset, Duration and 'Total number of AEs' rows in which multiple occurrences of the same AE are counted separately. Percentages are based on N in the column headings. The count of 'Patients with treatment received for AE' is based on the AE CRF question 'Was Medication Given For AE?'
Data Cutoff Date: 15JUN2022

Tumour flare is included in the RMP Summary of safety concerns as an Important identified risk.

≥ Grade 2 Neurologic Adverse Events

In the primary safety population, 22 of 154 patients (14.3%) treated with glofitamab step-up dosing experienced a Grade ≥ 2 neurological AE. Of these 22 patients, 18 patients reported a Grade 2 event, 2 patients reported a Grade 3 event, one patient reported Grade 4 myelitis (onset of 76.2 hours following the C1D15 10 mg glofitamab dose – see the SAE section), and one patient experienced the Grade 5 (fatal) event of delirium (onset of 56.8 hours following the C1D15 10 mg glofitamab dose – discussed in the SAE/deaths section and not assessed as related to glofitamab but to pain/pain-treatment and PD).

In the extended safety population 1 (N =195) the frequency of ≥ Grade 2 NAEs were 16.4%. With longer follow-up the incidences in both safety population had increased slightly.

Table 50

Summary of Grade ≥ 2 Neurological Events (Adverse Events of Special Interest), Patients with R/R DLBCL, ≥ 2 Prior Lines of Systemic Therapy, Fixed Dosing and Step-up Dosing

	Glofitamab 2.5/10/30 mg Cohort D3 (N=107)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=40)	Glofitamab Doses >=0.60 mg (N=287)	Glofitamab Doses >=10 mg(b) (N=100)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=114)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=154)
Total number of pts with at least one AE	15 (14.0%)	5 (12.5%)	40 (13.9%)	15 (15.0%)	17 (14.9%)	22 (14.3%)
Total number of AEs	16	7	56	26	18	25
Total number of pts with at least one AE by worst grade						
Grade 2	12 (11.2%)	4 (10.0%)	34 (11.8%)	14 (14.0%)	14 (12.3%)	18 (11.7%)
Grade 3	1 (0.9%)	1 (2.5%)	4 (1.4%)	1 (1.0%)	1 (0.9%)	2 (1.3%)
Grade 4	1 (0.9%)	0	1 (0.3%)	0	1 (0.9%)	1 (0.6%)
Grade 5 (fatal outcome)	1 (0.9%)	0	1 (0.3%)	0	1 (0.9%)	1 (0.6%)
Total number of pts with dose modified/interrupted due to AE	1 (0.9%)	0	1 (0.3%)	0	1 (0.9%)	1 (0.6%)
Total number of pts with treatment received for AE	12 (11.2%)	4 (10.0%)	31 (10.8%)	10 (10.0%)	14 (12.3%)	18 (11.7%)
Total number of pts with all AEs resolved	7 (6.5%)	2 (5.0%)	22 (7.7%)	9 (9.0%)	9 (7.9%)	11 (7.1%)
Total number of pts with at least one unresolved or ongoing AE	7 (6.5%)	3 (7.5%)	17 (5.9%)	6 (6.0%)	7 (6.1%)	10 (6.5%)
Total number of pts with at least one serious AE	2 (1.9%)	1 (2.5%)	5 (1.7%)	1 (1.0%)	2 (1.8%)	3 (1.9%)
Total number of pts with at least one related AE	5 (4.7%)	0	10 (3.5%)	3 (3.0%)	6 (5.3%)	6 (3.9%)
Duration of AE (days)						
n	9	3	36	19	11	14
Mean (SD)	8.78 (13.37)	2.00 (1.00)	25.06 (53.35)	32.21 (65.05)	10.27 (12.41)	8.50 (11.45)
Median	4.00	2.00	3.50	2.00	7.00	3.50
Min - Max	1.0 - 43.0	1.0 - 3.0	1.0 - 234.0	1.0 - 234.0	1.0 - 43.0	1.0 - 43.0
Time to Onset (days)						
n	16	7	56	26	18	25
Mean (SD)	29.13 (35.80)	52.57 (81.54)	41.55 (55.94)	42.46 (56.25)	36.78 (50.59)	41.20 (59.39)
Median	17.50	11.00	17.50	18.00	17.50	17.00
Min - Max	1.0 - 137.0	6.0 - 231.0	1.0 - 247.0	2.0 - 247.0	1.0 - 187.0	1.0 - 231.0
Time to Onset from first Glofit dose (days)						
n	15	4	48	22	17	21
Mean (SD)	23.40 (36.44)	79.00 (100.00)	40.19 (58.38)	41.95 (58.35)	31.29 (51.57)	40.38 (63.22)
Median	11.00	45.00	14.50	14.50	11.00	13.00
Min - Max	2.0 - 130.0	1.0 - 225.0	1.0 - 240.0	1.0 - 240.0	1.0 - 180.0	1.0 - 225.0

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Treatment related AEs includes Glofitamab, Obinutuzumab or Tocilizumab. Dose modified/interrupted due to AE refers to Glofitamab and Obinutuzumab only. Investigator text for AEs encoded using MedDRA version 25.0. AESIs not experienced by any patients are excluded. Multiple occurrences of the same AE in one individual are counted only once except for the Time to Onset, Duration and 'Total number of AEs' rows in which multiple occurrences of the same AE are counted separately. Percentages are based on N in the column headings. The count of 'Patients with treatment received for AE' is based on the AE CRF question 'Was Medication Given For AE?'
Data Cutoff Date: 15JUN2022

Source: uSCS

Hemophagocytic Lymphohistiocytosis

At the time of the CCOD, no events of suspected hemophagocytic lymphohistiocytosis were reported during Study NP30179.

Grade ≥ 3 Tumour Lysis Syndrome (TLS)

In the primary safety population, 2 of 154 patients (1.3%) experienced a Grade 3 TLS AE. The time to onset from the first glofitamab dose was 2.00 days for each patient, and the median duration was 4.00 days (range: 3.0-5.0). At the time of the CCOD, both events had resolved.

In patients who received glofitamab step-up dosing 2.5/10/30 mg (N=236/extended safety population 2), one additional patient experienced a Grade 4 event. The applicant states: *On Study Day 14, the patient died due to progressive disease or disease relapse (metabolic disease progression). An autopsy was not performed. The event of tumor lysis syndrome remained unresolved at the time of patient's death.* From the narrative there is no way of knowing if death was due to TLS or progressive disease in this MCL patient, highlighting the importance of the warning for TLS, which is presented in section 4.4 and 4.8 of the SmPC.

Grade ≥ 3 Febrile Neutropenia

In the primary safety population, 4 of 154 patients (2.6%) treated with glofitamab step-up dosing experienced Grade ≥ 3 febrile neutropenia. All events resolved.

Information regarding the frequency of infections (SAEs and Grade 3-4 AEs) are presented in the relevant sections.

Table 51

Summary of Grade ≥ 3 Febrile Neutropenia (Adverse Events of Special Interest): Glofitamab Doses ≥ 0.60 mg Fixed Dosing and Step-up Dosing (Patients with R/R NHL, All Histologies)

	Glofitamab Doses >=0.60 mg (N=469)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=195)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D4, D5 (N=236)
Total number of pts with at least one AE	8 (1.7%)	4 (2.1%)	4 (1.7%)
Total number of AEs	10	6	6
Total number of pts with at least one AE by worst grade			
Grade 3	6 (1.3%)	2 (1.0%)	2 (0.8%)
Grade 4	2 (0.4%)	2 (1.0%)	2 (0.8%)
Grade 5 (fatal outcome)	0	0	0
Total number of pts with dose modified/interrupted due to AE	0	0	0
Total number of pts with treatment received for AE	8 (1.7%)	4 (2.1%)	4 (1.7%)
Total number of pts with all AEs resolved	7 (1.5%)	4 (2.1%)	4 (1.7%)
Total number of pts with at least one unresolved or ongoing AE	1 (0.2%)	0	0
Total number of pts with at least one serious AE	6 (1.3%)	3 (1.5%)	3 (1.3%)
Total number of pts with at least one related AE	5 (1.1%)	3 (1.5%)	3 (1.3%)
Duration of AE (days)			
n	9	6	6
Mean (SD)	8.44 (6.23)	10.50 (6.72)	10.50 (6.72)
Median	6.00	8.50	8.50
Min - Max	2.0 - 22.0	5.0 - 22.0	5.0 - 22.0
Time to Onset (days)			
n	10	6	6
Mean (SD)	124.90 (65.87)	112.33 (64.69)	112.33 (64.69)
Median	139.50	139.50	139.50
Min - Max	25.0 - 235.0	25.0 - 182.0	25.0 - 182.0
Time to Onset from first Glofit dose (days)			
n	10	6	6
Mean (SD)	117.90 (65.87)	105.33 (64.69)	105.33 (64.69)
Median	132.50	132.50	132.50
Min - Max	18.0 - 228.0	18.0 - 175.0	18.0 - 175.0

Treatment related AEs includes Glofitamab, Obinutuzumab or Tocilizumab. Dose modified/interrupted due to AE refers to Glofitamab and Obinutuzumab only. Investigator text for AEs encoded using MedDRA version 25.0. AESIs not experienced by any patients are excluded. Multiple occurrences of the same AE in one individual are counted only once except for the Time to Onset, Duration and 'Total number of AEs' rows in which multiple occurrences of the same AE are counted separately. Percentages are based on N in the column headings. The count of 'Patients with treatment received for AE' is based on the AE CRF question 'Was Medication Given For AE?'
Data Cutoff Date: 15JUN2022

Source: uSCS

Grade ≥ 2 AST, ALT, or Total Bilirubin Elevation

In the primary safety population, 11 of 154 patients (7.1%) experienced Grade ≥ 2 ALT, AST, or total bilirubin elevation (Grade 2: 5 patients and Grade 3: 6 patients). 7 patients (4.5%) had at least one unresolved or ongoing AE at the CCOD of 15 June 2022. There is no clear indication that glofitamab was the cause of the unresolved hepatic enzyme or bilirubin increases; the reason these cases had not resolved was most likely PD.

Table 52

Summary of Grade ≥ 2 AST, ALT, or Total Bilirubin (Adverse Events of Special Interest): Glofitamab Doses ≥ 0.60 mg Fixed Dosing and Step-up Dosing (Patients with R/R NHL, All Histologies)

	Glofitamab Doses >=0.60 mg (N=469)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=195)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D4, D5 (N=236)
Total number of pts with at least one AE	39 (8.3%)	19 (9.7%)	23 (9.7%)
Total number of AEs	68	36	41
Total number of pts with at least one AE by worst grade			
Grade 2	19 (4.1%)	7 (3.6%)	8 (3.4%)
Grade 3	17 (3.6%)	11 (5.6%)	14 (5.9%)
Grade 4	3 (0.6%)	1 (0.5%)	1 (0.4%)
Grade 5 (fatal outcome)	0	0	0
Total number of pts with dose modified/interrupted due to AE	4 (0.9%)	2 (1.0%)	2 (0.8%)
Total number of pts with treatment received for AE	8 (1.7%)	4 (2.1%)	5 (2.1%)
Total number of pts with all AEs resolved	28 (6.0%)	12 (6.2%)	16 (6.8%)
Total number of pts with at least one unresolved or ongoing AE	11 (2.3%)	7 (3.6%)	7 (3.0%)
Total number of pts with at least one serious AE	1 (0.2%)	0	0
Total number of pts with at least one related AE	23 (4.9%)	11 (5.6%)	15 (6.4%)
Duration of AE (days)			
n	52	26	31
Mean (SD)	20.73 (30.86)	21.73 (40.57)	21.16 (37.35)
Median	10.50	8.00	8.00
Min - Max	1.0 - 156.0	2.0 - 156.0	2.0 - 156.0
Time to Onset (days)			
n	68	36	41
Mean (SD)	26.00 (29.62)	26.31 (29.51)	24.27 (28.19)
Median	11.00	11.00	10.00
Min - Max	2.0 - 112.0	2.0 - 112.0	2.0 - 112.0
Time to Onset from first Glofit dose (days)			
n	57	30	34
Mean (SD)	21.21 (30.25)	21.80 (30.57)	19.68 (29.27)
Median	4.00	4.00	4.00
Min - Max	1.0 - 99.0	1.0 - 99.0	1.0 - 99.0

Treatment related AEs includes Glofitamab, Obinutuzumab or Tocilizumab. Dose modified/interrupted due to AE refers to Glofitamab and Obinutuzumab only. Investigator text for AEs encoded using MedDRA version 25.0. AESIs not experienced by any patients are excluded. Multiple occurrences of the same AE in one individual are counted only once except for the Time to Onset, Duration and 'Total number of AEs' rows in which multiple occurrences of the same AE are counted separately. Percentages are based on N in the column headings. The count of 'Patients with treatment received for AE' is based on the AE CRF question 'Was Medication Given For AE?'
Data Cutoff Date: 15JUN2022

Source: uSCS

Grade ≥ 2 Disseminated Intravascular Coagulation

At the time of the CCOD, no events of disseminated intravascular coagulation were reported in Study NP30179.

Pneumonitis and Interstitial Lung Disease (Any Grade)

The investigators considered the two cases of ≥ Grade 2 pneumonitis in the population receiving the RP2D unrelated to glofitamab (and obinutuzumab), and reading the narratives it is difficult to assign causality, although both events occurred within one week of a CRS event; both resolved.

Table 53

Summary of Pneumonitis (Adverse Events of Special Interest): Glofitamab Doses ≥ 0.60 mg Fixed Dosing and Step-up Dosing (Patients with R/R NHL, All Histologies)

	Glofitamab Doses >=0.60 mg (N=469)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=195)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D4, D5 (N=236)
Total number of pts with at least one AE	7 (1.5%)	2 (1.0%)	2 (0.8%)
Total number of AEs	7	2	2
Total number of pts with at least one AE by worst grade			
Grade 1	0	0	0
Grade 2	4 (0.9%)	1 (0.5%)	1 (0.4%)
Grade 3	3 (0.6%)	1 (0.5%)	1 (0.4%)
Grade 4	0	0	0
Grade 5 (fatal outcome)	0	0	0
Total number of pts with dose modified/interrupted due to AE	4 (0.9%)	0	0
Total number of pts with treatment received for AE	7 (1.5%)	2 (1.0%)	2 (0.8%)
Total number of pts with all AEs resolved	6 (1.3%)	2 (1.0%)	2 (0.8%)
Total number of pts with at least one unresolved or ongoing AE	1 (0.2%)	0	0
Total number of pts with at least one serious AE	2 (0.4%)	0	0
Total number of pts with at least one related AE	1 (0.2%)	0	0
Duration of AE (days)			
n	6	2	2
Mean (SD)	20.00 (28.95)	7.00 (1.41)	7.00 (1.41)
Median	9.00	7.00	7.00
Min - Max	6.0 - 79.0	6.0 - 8.0	6.0 - 8.0
Time to Onset (days)			
n	7	2	2
Mean (SD)	69.86 (80.00)	32.00 (15.56)	32.00 (15.56)
Median	43.00	32.00	32.00
Min - Max	16.0 - 241.0	21.0 - 43.0	21.0 - 43.0
Time to Onset from first Glofit dose (days)			
n	7	2	2
Mean (SD)	61.86 (80.75)	22.00 (19.80)	22.00 (19.80)
Median	36.00	22.00	22.00
Min - Max	8.0 - 234.0	8.0 - 36.0	8.0 - 36.0

Treatment related AEs includes Glofitamab, Obinutuzumab or Tocilizumab. Dose modified/interrupted due to AE refers to Glofitamab and Obinutuzumab only. Investigator text for AEs encoded using MedDRA version 25.0. AESIs not experienced by any patients are excluded. Multiple occurrences of the same AE in one individual are counted only once except for the Time to Onset, Duration and 'Total number of AEs' rows in which multiple occurrences of the same AE are counted separately. Percentages are based on N in the column headings. The count of 'Patients with treatment received for AE' is based on the AE CRF question 'Was Medication Given For AE?'
Data Cutoff Date: 15JUN2022

Colitis (Any Grade)

One patient in Part II dose escalation Cohort D2 experienced severe colitis, which was considered related to glofitamab and concurrent DLBCL located abdominally. There were two episodes; the last starting on D111 and leading to a left end-ileostomy being performed on D234 with the last glofitamab dose on D175; C9D1. Treatment with infliximab was also administered. The patient died of PD D462 after palliative radiotherapy D394-420. There were no additional patients with colitis in the Overall safety population (n=469).

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

The most frequent cause of **death** in the primary safety population (n=154) irrespective of time point (i.e., >/< 30 days after last dose) was progressive disease, which accounted for 61 deaths (75.3%), followed by 9 AEs [COVID-19 pneumonia (3 deaths), sepsis (2 deaths), COVID-19 (3 patient), and delirium (1 death)]. None of the Grade 5 AEs were assessed as related to glofitamab by the investigator.

Table 54

Summary of Adverse Events, Fatal Adverse Events, Initial Treatment Phase, (R/R DLBCL Patients, >=2 Prior Lines of Systemic Therapy), Glofitamab Doses >= 0.6 mg, Safety-Evaluable Monotherapy Patients
Protocol: NP30179

MedDRA System Organ Class MedRA Preferred Term	Glofitamab 2.5/10/30 mg Cohort D3 (N=107)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=40)	Glofitamab Doses >=0.60 mg (N=287)	Glofitamab Doses >=10 mg(b) (N=100)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3 (N=114)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=154)
Total number of patients with at least one adverse event	7 (6.5%)	2 (5.0%)	13 (4.5%)	4 (4.0%)	7 (6.1%)	9 (5.8%)
Overall total number of events	7	2	13	4	7	9
Infections and infestations						
Total number of patients with at least one adverse event	6 (5.6%)	2 (5.0%)	9 (3.1%)	1 (1.0%)	6 (5.3%)	8 (5.2%)
Total number of events	6	2	9	1	6	8
COVID-19 pneumonia	3 (2.8%)	0	3 (1.0%)	0	3 (2.6%)	3 (1.9%)
COVID-19	1 (0.9%)	2 (5.0%)	3 (1.0%)	0	1 (0.9%)	3 (1.9%)
Sepsis	2 (1.9%)	0	2 (0.7%)	0	2 (1.8%)	2 (1.3%)
Pneumonia	0	0	1 (0.3%)	1 (1.0%)	0	0
Psychiatric disorders						
Total number of patients with at least one adverse event	1 (0.9%)	0	1 (0.3%)	0	1 (0.9%)	1 (0.6%)
Total number of events	1	0	1	0	1	1
Delirium	1 (0.9%)	0	1 (0.3%)	0	1 (0.9%)	1 (0.6%)
Cardiac disorders						
Total number of patients with at least one adverse event	0	0	1 (0.3%)	1 (1.0%)	0	0
Total number of events	0	0	1	1	0	0
Myocardial infarction	0	0	1 (0.3%)	1 (1.0%)	0	0

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.
Investigator text for AEs encoded using MedDRA version 25.0. Percentages are based on N in the column headings.
Only treatment emergent AEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Data Cutoff Date: 15JUN2022

Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/t_ae.sas
Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/FDA_Sub2_EU_RTQ_Aug2022/prod/output/t_ae_FATAL_PIV_I_SCS_SE_15JUN2022_30179.out
26AUG2022 12:41 Page 1 of 2

Summary of Adverse Events, Fatal Adverse Events, Initial Treatment Phase, Glofitamab Doses >= 0.6 mg, Safety-Evaluable Monotherapy Patients
Protocol: NP30179

MedDRA System Organ Class MedRA Preferred Term	Glofitamab Doses >=0.60 mg (N=469)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=195)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D4, D5 (N=236)
Total number of patients with at least one adverse event	22 (4.7%)	11 (5.6%)	11 (4.7%)
Overall total number of events	22	11	11
Infections and infestations			
Total number of patients with at least one adverse event	14 (3.0%)	10 (5.1%)	10 (4.2%)
Total number of events	14	10	10
COVID-19 pneumonia	5 (1.1%)	4 (2.1%)	4 (1.7%)
COVID-19	5 (1.1%)	3 (1.5%)	3 (1.3%)
Sepsis	2 (0.4%)	2 (1.0%)	2 (0.8%)
Septic shock	1 (0.2%)	1 (0.5%)	1 (0.4%)
Pneumonia	1 (0.2%)	0	0
Cardiac disorders			
Total number of patients with at least one adverse event	3 (0.6%)	0	0
Total number of events	3	0	0
Cardiac arrest	1 (0.2%)	0	0
Cardio-respiratory arrest	1 (0.2%)	0	0
Myocardial infarction	1 (0.2%)	0	0
Psychiatric disorders			
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.5%)	1 (0.4%)
Total number of events	1	1	1
Delirium	1 (0.2%)	1 (0.5%)	1 (0.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Total number of patients with at least one adverse event	2 (0.4%)	0	0
Total number of events	2	0	0
Acute myeloid leukaemia	1 (0.2%)	0	0
Basal cell carcinoma	1 (0.2%)	0	0
Respiratory, thoracic and mediastinal disorders			
Total number of patients with at least one adverse event	1 (0.2%)	0	0
Total number of events	1	0	0
Acute respiratory failure	1 (0.2%)	0	0
Vascular disorders			
Total number of patients with at least one adverse event	1 (0.2%)	0	0
Total number of events	1	0	0
Hypovolaemic shock	1 (0.2%)	0	0

Investigator text for AEs encoded using MedDRA version 25.0. Percentages are based on N in the column headings.
Only treatment emergent AEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in a individual are counted separately.
Data Cutoff Date: 15JUN2022

Serious Adverse Events

The most common Serious AEs by SOC were Immune system disorders, Infections and infestations, and Blood and lymphatic system disorders.

These SOCs correspond to the most common SAE PTs in the primary and extended safety populations. The most frequent was CRS. Other SAEs reported in ≥ 3 patients included sepsis, COVID-19 including pneumonia, tumor flare, anemia, febrile neutropenia, and neutropenia.

Table 55

Summary of Serious AEs by SOC in Primary and Extended Safety Populations (CCOD: 15 June 2022)

MedDRA SOC MedDRA PT	Primary Safety Population[a] N = 154	Extended Safety Population[b] N = 236
Immune system disorders	34 (22.1%)	64 (27.1%)
Cytokine release syndrome	34 (22.1%)	64 (27.1%)
Infections and Infestations	28 (18.2%)	46 (19.5%)
COVID-19	5 (3.2%)	8 (3.4%)
Pneumonia	2 (1.3%)	3 (1.3%)
COVID-19 pneumonia	5 (3.2%)	7 (3.0%)
Sepsis	6 (3.9%)	6 (2.5%)
Infection	2 (1.3%)	2 (0.8%)
Vascular device infection	2 (1.3%)	2 (0.8%)
Blood and lymphatic system disorders	10 (6.5%)	12 (5.1%)
Neutropenia	3 (1.9%)	4 (1.7%)
Febrile neutropenia	3 (1.9%)	3 (1.3%)
Anemia	3 (1.9%)	4 (1.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (5.2%)	11 (4.7%)
Tumour flare	5 (3.2%)	7 (3.0%)
Gastrointestinal disorders	7 (4.5%)	9 (3.8%)
Gastrointestinal hemorrhage	2 (1.3%)	2 (0.8%)
General disorders and administration site conditions	4 (2.6%)	8 (3.4%)
Pyrexia	2 (1.3%)	6 (2.5%)
Injury, poisoning, and procedural complications	3 (1.9%)	7 (3.0%)
Infusion-related reaction	1 (0.6%)	4 (1.7%)

MedDRA SOC MedDRA PT	Primary Safety Population[a] N = 154	Extended Safety Population[b] N = 236
Respiratory, thoracic and mediastinal disorders	4 (2.6%)	7 (3.0%)
Pleural effusion	3 (1.9%)	5 (2.1%)
Musculoskeletal and connective tissue disorders	2 (1.3%)	2 (0.8%)
Back pain	2 (1.3%)	2 (0.8%)
Cardiac disorders	2 (1.3%)	3 (1.3%)
Investigations	2 (1.3%)	4 (1.7%)
CRP increased	1 (0.6%)	3 (1.3%)
Nervous system disorders	2 (1.3%)	3 (1.3%)

CRP = C-reactive protein; DLBCL = diffuse large B-cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; NHL = non-Hodgkin's lymphoma.

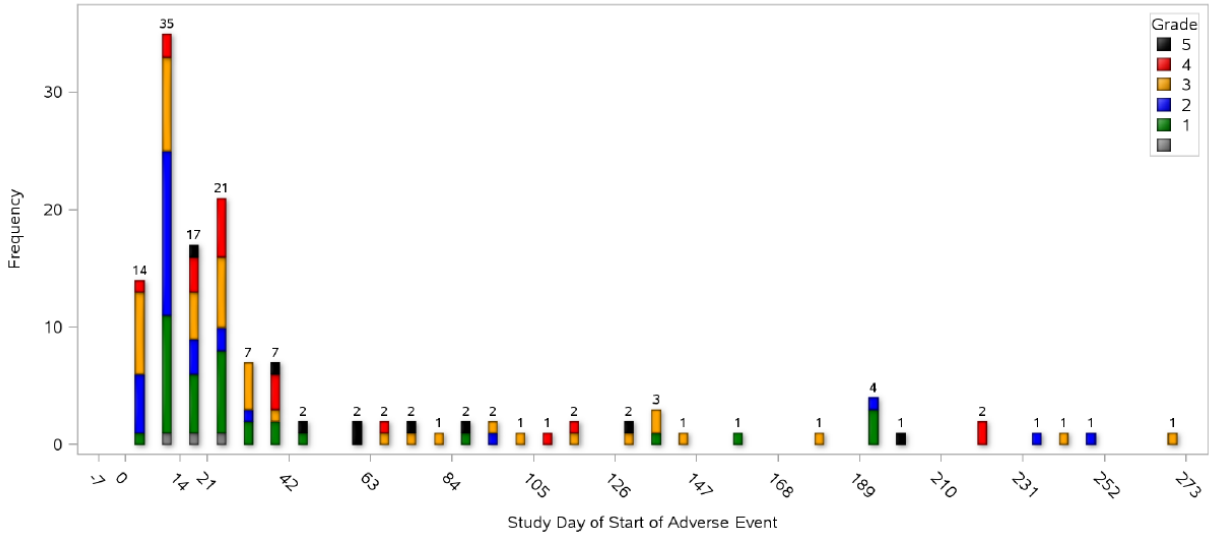
Most common SAEs by SOC or PT occurring in ≥ 1% of patients in respective population.

a Primary safety population: Patients with R/R DLBCL (includes DLBCL NOS, trFL, PMBCL, HGBCL) with ≥ 2 prior lines of systemic therapy treated with glofitamab 2.5/10/30 mg in Cohorts D_2 [Sub. 2], D_3, and D_5.

b Extended safety population: Patients with R/R NHL with ≥ 1 prior line of systemic therapy treated with glofitamab 2.5/10/30 mg in Cohorts D_2 [Sub. 2], D_3, D_4, and D_5.

Figure 18

Figure 6 Timing of SAEs by Study Day (Patients with R/R DLBCL, ≥ 2 Prior Lines of Systemic Therapy, Glofitamab 2.5/10/30 mg Step-up Dosing, Cohorts D_2 [Sub2], D_3, D_5)



Adverse Events with missing preferred term are excluded from this output. Adverse Events with missing CTC grades are shown in grey.
Data Cutoff Date: 15JUN2022
Program: root/clinical_studies/RO7082859/CDT70029/NP30179/share/data_analysis/prod/program/g_ae_hist2.sas
Output: root/clinical_studies/RO7082859/CDT70029/NP30179/data_analysis/FDA_Sub2_EU_RTQ_Aug2022/prod/output/g_ae_hist2_PIV_RP2D_I_SE_15JUN2022_30179.pdf 26AUG2022 12:27 Page 2 of 2

2.6.8.4. Laboratory findings

Haematology

In the extended safety populations, the most frequent treatment-emergent Grade ≥ 3 worsening hematological laboratory parameter (apart from decreases in lymphocytes as expected based on the MoA) were decreases in neutrophils and which were comparable to the overall safety population and the primary safety population.

Table 56

Treatment-Emergent Hematology Laboratory Abnormalities Occurring in ≥ 10% of Patients in the Primary Safety population; Patients with R/R DLBCL, ≥ 2 Prior Lines of Systemic Therapy, Fixed Dosing and Step-up Dosing

	Worsening NCI CTCAE Grade from BL to Any Grade																	
	Glofitamab 2.5/10/30 mg Cohort D_3 (N=107)			Glofitamab 2.5/10/30 mg Cohort D_5 (N=40)			Glofitamab Doses ≥ 0.60 mg (N=287)			Glofitamab Doses ≥ 10 mg (N=100)			Glofitamab 2.5/10/30 mg Cohorts D_2 [Sub. 2], D_3 (N=114)			Glofitamab 2.5/10/30 mg Cohorts D_2 [Sub. 2], D_3, and D_5 (N=154)		
	Grade			Grade			Grade			Grade			Grade			Grade		
	Any[a]	≥ 3 [b]	4	Any[a]	≥ 3 [b]	4	Any[a]	≥ 3 [b]	4	Any[a]	≥ 3 [b]	4	Any[a]	≥ 3 [b]	4	Any[a]	≥ 3 [b]	4
↓Lymphocytes	86.3%	78.4%	38.2%	92.3%	87.2%	51.3%	88.7%	81.8%	48.0%	90.6%	87.5%	64.6%	87.2%	78.9%	38.5%	88.5%	81.1%	41.9%
↓Leukocytes	69.9%	13.6%	2.9%	67.5%	33 p	0	66.9%	20.5%	4.7%	62.9%	24.7%	8.2%	70.0%	13.6%	2.7%	69.3%	13.3%	2.0%
↓Platelets	54.9%	6.9%	0	50.0%	17.5%	5.0%	55.2%	10.1%	2.5%	57.7%	13.4%	5.2%	57.8%	6.4%	0	55.7%	9.4%	1.3%
↓Neutrophils	56.9%	27.5%	8.8%	47.5%	17.5%	7.5%	55.8%	30.8%	14.1%	58.3%	35.4%	17.7%	56.9%	28.4%	10.1%	54.4%	25.5%	9.4%
↓Hemoglobin	73.8%	8.7%	0	67.5%	5.0%	0	70.1%	10.8%	0	66.0%	13.4%	0	74.5%	9.1%	0	72.7%	8.0%	0

Includes any worsening grade laboratory shifts from Baseline (BL) to 1 or higher (for High) or -1 or lower (for Low).

[a] Number of patients with a Baseline and at least one post-Baseline assessment for the lab parameter.

[b] Includes shifts from NCI CTCAE Grade <3 to Grade ≥3 and shifts from Grade 3 to Grade 4. The "Grade 4" column includes shifts from NCI CTCAE Grade <4 to Grade 4.

Source: t_lb_freqabn_HAELB_PIV_I_SCS_SE_15JUN2022_30179

Chemistry

Table 57 Treatment-emergent chemistry laboratory parameter shifts (N=236)

Occurring in ≥ 10% of Patients (Mixed R/R NHL Histologies, ≥ 1 Prior Lines of Systemic Therapy), Glofitamab Step-Up Dosing, Safety-Evaluable Monotherapy Patients

	Glofitamab 2.5/10/30 mg Cohorts D2 [Sub. 2], D3, D4, D5 (N=236)			
	N [a]	Any Grade	Grade ≥ 3 [b, c]	Grade 4
↓Albumin	228	143 (62.7%)	3 (1.3%)	0
↓Calcium	231	116 (50.2%)	5 (2.2%)	3 (1.3%)
↓Glucose	224	36 (16.1%)	2 (0.9%)	1 (0.4%)
↓Phosphorus	230	156 (67.8%)	65 (28.3%)	8 (3.5%)
↓Potassium	231	71 (30.7%)	11 (4.8%)	1 (0.4%)
↓Sodium	231	101 (43.7%)	15 (6.5%)	2 (0.9%)
↑Alkaline phosphatase	225	75 (33.3%)	3 (1.3%)	0
↑SGPT/ALT	230	86 (37.4%)	12 (5.2%)	0
↑SGOT/AST	229	93 (40.6%)	16 (7.0%)	2 (0.9%)
↑Cholesterol	168	39 (23.2%)	1 (0.6%)	1 (0.6%)
↑Creatinine	227	183 (80.6%)	4 (1.8%)	2 (0.9%)
↑Gamma glutamyl transferase	217	84 (38.7%)	24 (11.1%)	2 (0.9%)
↑Glucose	224	40 (17.9%)	40 (17.9%)	2 (0.9%)
↑Potassium	231	36 (15.6%)	4 (1.7%)	3 (1.3%)
↑Bilirubin	230	36 (15.7%)	8 (3.5%)	0
↑Triglycerides	169	81 (47.9%)	4 (2.4%)	0
↑Uric acid	221	42 (19.0%)	42 (19.0%)	15 (6.8%)

[a] Table shows any worsening grade laboratory shifts from baseline measured in ≥10% of patients with any grade worsening only.

[b] Number of patients with a baseline and at least one post-baseline assessment for lab parameter.

[c] Includes shifts from NCI CTCAE Grade < 3 to Grade ≥ ≥3, and shifts from Grade 3 to Grade 4.

Elevated liver function tests

The finding of an elevated ALT or AST (> 3 x ULN) in combination with either an elevated total bilirubin (> 2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia was considered to be an indicator of severe liver injury, as defined by Hy's law.

There were 14 potential Hy's Law cases in the "glofitamab doses ≥0.60 mg" population (=Extended safety population 3, see Table 1 in the safety introduction, N=467).

From the narratives it seems that 4 patients had PD and 10 patients had CRS as the probable cause of the elevated liver function tests fulfilling Hy's Law in the overall safety population (N=469). Of the

seven patients in the population receiving the RP2D fulfilling Hy's Law three had PD and four had CRS as the probable cause. Elevated liver function tests fulfilling Hy's Law regularly occur in conjunction with CRS events (from Grade 1).

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Safety in special populations

Age

Table 58 Safety Results by Age Cohort in Patients Who Received Gpt and Glofitamab (N=145; R/R DLBCL ≥2 Prior Lines; 15 June 2022)

MedDRA terms	Age < 65 N=66 n (%)	Age 65–74 N=46 n (%)	Age 75–84 N=28 n (%)	Age 85+ N=5 n (%)
Total number of patients with AEs	65 (98.5%)	46 (100%)	27 (96.4%)	5 (100%)
Total number of patients with:				
Serious AEs	30 (45.5%)	24 (52.2%)	14 (50.0%)	2 (40.0%)
Fatal	0 (0.0%)	3 (6.5%)	4 (14.3%)	1 (20.0%)
Hospitalization/ prolong existing hospitalization	29 (43.9%)	24 (52.2%)	13 (46.4%)	2 (40.0%)
Life-threatening	0	0	4 (14.3%)	0
Disability/ incapacity	1 (1.5%)	1 (2.2%)	0	0
Other (medically significant)	4 (6.1%)	2 (4.3%)	2 (7.1%)	0
AE leading to withdrawal from glofitamab	1 (1.5%)	5 (10.9%)	4 (14.3%)	1 (20.0%)
AE leading to withdrawal from obinutuzumab	0	0	0	0
Psychiatric disorders [b]	5 (7.6%)	6 (13.0%)	4 (14.3%)	1 (20.0%)
Nervous system disorders [b]	19 (28.8%)	9 (19.6%)	10 (35.7%)	1 (20.0%)
Accidents and Injuries [f]	NA	NA	NA	NA
Cardiac disorders [b]	6 (9.1%)	9 (19.6%)	0	0
Vascular disorders [b]	7 (10.6%)	7 (15.2%)	1 (3.6%)	0
Cerebrovascular disorders [c]	0	0	0	0
Infections and infestations [b]	26 (39.4%)	18 (39.1%)	11 (39.3%)	2 (40.0%)
Anticholinergic syndrome [c]	0	0	0	0
Quality of life decreased [c]	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [d]	3 (4.5%)	1 (2.2%)	5 (17.9%)	0
Other AEs appearing more frequently in older patients [e]:				
Hypomagnesaemia	6 (9.1%)	12 (26.1%)	4 (14.3%)	0
Hypophosphataemia	7 (10.6%)	10 (21.7%)	7 (25.0%)	3 (60.0%)
Diarrhoea	6 (9.1%)	6 (13.0%)	6 (21.4%)	2 (40.0%)
Oedema peripheral	1 (1.5%)	3 (6.5%)	4 (14.3%)	1 (20.0%)

DLBCL =diffuse large B-cell lymphoma; Gpt = obinutuzumab pretreatment; MedDRA =Medical Dictionary for Regulatory Activities; NA=not available; R/R =relapsed or refractory.

Note: Only treatment emergent AEs are displayed. Multiple occurrences of the same AE in one individual are counted only once.

a Patients with R/R DLBCL (includes DLBCL NOS, trFL, PMBCL, HGBCL; ≥ 2 prior lines) from Cohorts D2 [Sub. 2], D3, and D5.

b MedDRA SOCs were used to identify events for Psychiatric Disorders, Nervous System Disorders, Cardiac Disorders, Vascular Disorders, and Infections and Infestations.

c PTs were used to identify events for Cerebrovascular Disorders, Anticholinergic Syndrome, and Quality of life decreased.

d For Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, and fractures: events were identified using the PTs Orthostatic hypotension, Fall, Loss of consciousness, Syncope, Dizziness, Ataxia, Multiple fractures.

e Other AEs appearing more frequently in older patients were defined as treatment-emergent AEs by PT occurring with ≥ 5% higher incidence in patients aged ≥ 65 years (N=79) compared with patients < 65 years old (N=66). Hypomagnesaemia 16/79 (20.0%) vs 8.6%; Hypophosphatemia 20/79 (25%) vs 10.6% Diarrhea 14/79 (17.7%) vs 9.1%; Oedema peripheral 8/79 (10.1%) vs 1.4%.

f Information on Accidents and Injuries cannot be derived currently.

Gender

Higher AEs were seen in male patients.

The applicant has presented gender results using the new primary safety population of N=145 (removing the patients that only received obinutuzumab). No major changes in AE frequencies between the sexes were observed, and the table below (with the N=154 patients population is kept as this includes the overall safety population also.

Table 59 Overview of Safety by Sex (Safety-Evaluable Population, 15 June 2022 CCOD)

	Primary Safety Population[a] N=154		Extended Safety Population[b] N=236		Overall Safety Population[c] N=469	
	Male N=100	Female N=54	Male N=142	Female N=94	Male N=290	Female N=179
Total number of patients with at least one AE	99 (99.0%)	53 (98.1%)	140 (98.6%)	92 (97.9%)	284 (97.9%)	176 (98.3%)
Total number of deaths	57 (57.0%)	24 (44.4%)	63 (44.4%)	29 (30.9%)	117 (40.3%)	53 (29.6%)
Total number of patients withdrawn from treatment due to an AE	11 (11.0%)	3 (5.6%)	13 (9.2%)	3 (3.2%)	17 (5.9%)	3 (1.7%)
Total number of patients with at least one:						
adverse event related to study drug	94 (94.0%)	50 (92.6%)	132 (93.0%)	85 (90.4%)	266 (91.7%)	155 (86.6%)
AE with fatal outcome	8 (8.0%)	1 (1.9%)	9 (6.3%)	2 (2.1%)	17 (5.9%)	5 (2.8%)
AE leading to withdrawal from Glofitamab	11 (11.0%)	3 (5.6%)	13 (9.2%)	3 (3.2%)	15 (5.2%)	3 (1.7%)
AE leading to withdrawal from Obinutuzumab	0	0	0	0	2 (0.7%)	0
AE leading to dose modification/interruption of Glofitamab	17 (17.0%)	11 (20.4%)	32 (22.5%)	24 (25.5%)	76 (26.2%)	43 (24.0%)
Serious AE	50 (50.0%)	25 (46.3%)	75 (52.8%)	45 (47.9%)	170 (58.6%)	89 (49.7%)
Serious AE leading to withdrawal from Glofitamab	8 (8.0%)	2 (3.7%)	10 (7.0%)	2 (2.1%)	12 (4.1%)	2 (1.1%)
Serious AE leading to dose modification/interruption of Glofitamab	5 (5.0%)	4 (7.4%)	10 (7.0%)	12 (12.8%)	32 (11.0%)	18 (10.1%)
AE Related to Glofitamab	92 (92.0%)	48 (88.9%)	128 (90.1%)	82 (87.2%)	258 (89.0%)	148 (82.7%)
AE Related to Obinutuzumab	25 (25.0%)	18 (33.3%)	43 (30.3%)	32 (34.0%)	103 (35.5%)	57 (31.8%)
Serious AE Related to Glofitamab	30 (30.0%)	16 (29.6%)	51 (35.9%)	31 (33.0%)	125 (43.1%)	67 (37.4%)
Serious AE Related to Obinutuzumab	3 (3.0%)	1 (1.9%)	7 (4.9%)	2 (2.1%)	20 (6.9%)	3 (1.7%)

	Primary Safety Population[a] N=154		Extended Safety Population[b] N=236		Overall Safety Population[c] N=469	
	Male N=100	Female N=54	Male N=142	Female N=94	Male N=290	Female N=179
AEs Grade 3-5 (NCI-CTCAE/ASTCT)	66 (66.0%)	32 (59.3%)	93 (65.5%)	55 (58.5%)	191 (65.9%)	99 (55.3%)
Grade 3-5 (NCI-CTCAE/ASTCT) AE Related to Glofitamab	46 (46.0%)	21 (38.9%)	69 (48.6%)	39 (41.5%)	125 (43.1%)	63 (35.2%)
Grade 3-5 (NCI-CTCAE/ASTCT) AE Related to Obinutuzumab	8 (8.0%)	4 (7.4%)	15 (10.6%)	7 (7.4%)	38 (13.1%)	15 (8.4%)
AE Related to Glofitamab leading to withdrawal from Glofitamab	4 (4.0%)	1 (1.9%)	4 (2.8%)	1 (1.1%)	4 (1.4%)	1 (0.6%)
AE Related to Glofitamab leading to dose modification/interruption	12 (12.0%)	4 (7.4%)	26 (18.3%)	11 (11.7%)	52 (17.9%)	23 (12.8%)
CRS by ASTCT grade	67 (67.0%)	32 (59.3%)	97 (68.3%)	59 (62.8%)	195 (67.2%)	105 (58.7%)
CRS by ASTCT with grade 3-4	6 (6.0%)	0	10 (7.0%)	1 (1.1%)	20 (6.9%)	4 (2.2%)

a Primary safety population: Patients with R/R DLBCL (includes DLBCL NOS, trFL, PMBCL, HGBCL; ≥2 prior lines) from Cohorts D_2 Subcohort 2, D_3, and D_5.

b Extended safety population: Patients with R/R NHL with ≥1 prior lines of systemic therapy, treated with 2.5/10/30 mg glofitamab in Cohorts D_2 Subcohort 2 + D_3 + D_4 +D_5.

c Overall safety population: Patients with R/R NHL with ≥1 prior lines of systemic therapy, treated with glofitamab doses ≥0.6 mg.

Source: t_ae_oview2_subgrp_SEXC_PIV_I_SCS_SE_15JUN2022_30179, t_ae_oview2_subgrp_SEXC_I_SCS2_SE_15JUN2022_30179; Update Interim NP30179 CSR, Report 1114923: t_ae_oview_subgrp_SEXC_PIV_I_SCS_SE_15JUN2022_30179, t_ae_oview_subgrp_SEXC_I_SCS2_SE_15JUN2022_30179.

Race

In the primary safety population (N=154), the majority of patients were white (n=118) and no other racial subgroup was large enough to make any conclusion on racial differences.

Prior CAR-T Therapy

In the primary safety population, the adverse event PTs that occurred at a higher frequency among patients who had received prior CAR-T therapy were thrombocytopenia (11.8% vs. 3.9%) and lymphopenia (9.8% vs. 1.0%) (Table 2), which have been reported in other studies after CAR-T therapy (Wudhikarn et al., 2020; Strati et al. 2021). The proportion of patients experiencing an AE in the SOC Infections and infestations were comparable.

The most common SAE in the primary safety population was CRS with a higher proportion of patients who received prior CAR-T therapy experiencing serious CRS events (29.4% vs. 18.4%) compared to patients who had not received prior CAR-T therapy.

Table 60

Overview of Safety by Prior CAR-T in Patients Who Received Gpt and Glofitamab (N=145; R/
DLBCL ≥2 Prior Lines; 15 June 2022)

	Prior CAR-T N=47	No Prior CAR-T N=98
Total number of patients with at least one AE	46 (97.9%)	97 (99.0%)
Total number of deaths	25 (53.2%)	50 (51.0%)
Total number of patients withdrawn from treatment due to an AE	2 (4.3%)	8 (8.2%)
Total number of patients with at least one:		
adverse event related to study drug	46 (97.9%)	94 (95.9%)
AE with fatal outcome	1 (2.1%)	7 (7.1%)
AE leading to withdrawal from glofitamab	2 (4.3%)	8 (8.2%)
AE leading to withdrawal from obinutuzumab	0	0
AE leading to dose modification/interruption of glofitamab	6 (12.8%)	21 (21.4%)
Serious AE	26 (55.3%)	44 (44.9%)
Serious AE leading to withdrawal from glofitamab	2 (4.3%)	5 (5.1%)
Serious AE leading to dose modification/interruption of glofitamab	4 (8.5%)	4 (4.1%)
AE related to glofitamab	46 (97.9%)	94 (95.9%)
AE related to obinutuzumab	14 (29.8%)	25 (25.5%)
Serious AE related to glofitamab	20 (42.6%)	26 (26.5%)
Serious AE related to obinutuzumab	2 (4.3%)	2 (2.0%)
AEs Grade 3-5 (NCI CTCAE/ASTCT)	29 (61.7%)	64 (65.3%)
Grade 3-5 (NCI CTCAE/ASTCT) AE related to glofitamab	24 (51.1%)	43 (43.9%)
Grade 3-5 (NCI CTCAE/ASTCT) AE related to obinutuzumab	4 (8.5%)	8 (8.2%)
AE related to glofitamab leading to withdrawal from glofitamab	1 (2.1%)	4 (4.1%)
AE related to glofitamab leading to dose modification/interruption	2 (4.3%)	14 (14.3%)
CRS by ASTCT grade	34 (72.3%)	64 (65.3%)
CRS by ASTCT with Grade 3-4	1 (2.1%)	5 (5.1%)

AE= adverse event; ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; DLBCL =diffuse large B-cell lymphoma; Gpt= obinutuzumab pretreatment; NCI CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; R/R =relapsed or refractory.

NHL Sub-Histologies

Table 61 Summary of Adverse Events by Histology, Incidence Rate of at Least 5%, NCI CTCAE (or ASTCT) Grade 3 to 4 Adverse Events, Extended Safety Population [a], CCOD: 15 June 2022

MedDRA SOC PT	DLBCL (N = 111)	FL, Grade 3B (N=1)	MCL (N=14)	PMBCL (N=6)	Richter's Transformation (N=2)	trFL (N=29)	FL, Grades 1–3A (N=63)	HGBCL (N=10)
Blood and lymphatic system disorders	41 (36.9%)	0	6 (42.9%)	1 (16.7%)	1 (50.0%)	7 (24.1%)	18 (28.6%)	1 (10.0%)
Neutropenia	34 (30.6%)	0	4 (28.6%)	0	0	5 (17.2%)	15 (23.8%)	0
Anaemia	8 (7.2%)	0	2 (14.3%)	1 (16.7%)	0	2 (6.9%)	2 (3.2%)	1 (10.0%)
Thrombocytopenia	7 (6.3%)	0	1 (7.1%)	0	1 (50.0%)	2 (6.9%)	2 (3.2%)	1 (10.0%)
Immune system disorders	4 (3.6%)	0	4 (28.6%)	0	1 (50.0%)	2 (6.9%)	0	0
CRS	4 (3.6%)	0	4 (28.6%)	0	1 (50.0%)	2 (6.9%)	0	0
Metabolism and nutrition disorders	8 (7.2%)	0	0	0	0	1 (3.4%)	0	0
Hypophosphataemia	8 (7.2%)	0	0	0	0	1 (3.4%)	0	0
Investigations	2 (1.8%)	0	3 (21.4%)	0	0	0	1 (1.6%)	0
Platelet count decreased	2 (1.8%)	0	3 (21.4%)	0	0	0	1 (1.6%)	0
Infections and Infestations	1 (0.9%)	0	2 (14.3%)	0	0	0	0	1 (10.0%)
Pneumonia	1 (0.9%)	0	2 (14.3%)	0	0	0	0	1 (10.0%)
Vascular Disorders	1 (0.9%)	0	1 (7.1%)	0	0	0	2 (3.2%)	0
Hypertension	1 (0.9%)	0	1 (7.1%)	0	0	0	2 (3.2%)	0

ASTCT=American Society for Transplantation and Cellular Therapy; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HGBCL = high-grade B-cell lymphoma; MCL = mantle cell lymphoma; NCI CTCAE =National Cancer Institute Common Terminology Criteria for Adverse Events; trFL = transformed FL; SOC = System Organ Class.

Note: Only treatment-emergent AEs are displayed. Frequency counts are based on total number of patients. Multiple occurrences of the same AE in an individual patient are only counted once.

2.6.8.7. Immunological events

The main immunological events were CRS, which have been discussed in the relevant section above.

For ADA see the pharmacology section.

2.6.8.8. Safety related to drug-drug interactions and other interactions

See Clinical Pharmacology Section

2.6.8.9. Discontinuation due to adverse events

Table 62 Adverse events leading to discontinuation and dose modification/ interruption:

Total number of patients with:	Primary Safety Population[a] R/R DLBCL ≥2 prior lines, 2.5/10/30 mg glofitamab N=154	Extended Safety Population[b] R/R NHL ≥1 prior line, 2.5/10/30 mg glofitamab N=236	Overall Safety Population[c] R/R NHL ≥1 prior line, ≥0.6 mg glofitamab N=469
AE leading to glofitamab treatment discontinuation, n (%)	14 (9.1%)	16 (6.8%)	18 (3.8%)
Glofitamab-related, n (%)	5 (3.2%)	5 (2.1%)	5 (1.1%)
AE leading to glofitamab dose modification / interruption, n (%)	28 (18.2%)	56 (23.7%)	119 (25.4%)
Glofitamab-related, n (%)	16 (10.4%)	37 (15.7%)	75 (16.0%)
Common AEs (≥2 patients) leading to glofitamab treatment discontinuation, n (%)	COVID-19: 2 (1.3%) Neutropenia: 2 (1.3%) Delirium: 2 (1.3%) *COVID-19 pneumonia: 1 (0.6%)*	COVID-19: 3 (1.3%) COVID-19 pneumonia: 2 (0.8%) Neutropenia: 2 (0.8%) Delirium: 2 (0.8%)	COVID-19: 3 (0.6%) COVID-19 pneumonia: 2 (0.4%) Neutropenia: 2 (0.4%) Delirium: 2 (0.4%)
Common AEs (≥2%) leading to glofitamab dose modification / interruption, n (%)	Neutropenia: 13 (8.4%) Thrombocytopenia: 4 (2.6%) *COVID-19: 3 (1.9%)* *CRS: 1 (0.6%)* *Pyrexia: 1 (0.6%)*	Neutropenia: 19 (8.1%) COVID-19: 9 (3.8%) CRS: 8 (3.4%) *Thrombocytopenia: 4 (1.7%)* *Pyrexia: 3 (1.3%)*	Neutropenia: 42 (9.0%) CRS: 15 (3.2%) COVID-19: 11 (2.3%) Pyrexia: 10 (2.1%) *Thrombocytopenia: 5 (1.1%)*

2.6.8.10. Post marketing experience

Not applicable

2.6.9. Discussion on clinical safety

This application seeks conditional marketing authorisation for glofitamab for the treatment of adult patients with R/R diffuse large B-cell-lymphoma (DLBCL) who have received at least two prior systemic therapies based on results from Study NP30179.

The safety data for glofitamab IV for the treatment of R/R DLBCL (≥2 prior lines of systemic therapy) are from the ongoing, single-arm, uncontrolled, clinical trial NP30179 (updated data with a CCOD 15 June 2022). There is currently no post marketing experience with glofitamab and no data from other clinical trials supporting this Application.

The primary safety population after the first round was the updated results from 154 patients in the D3+D5 cohorts with R/R DLBCL (≥2 prior therapies) having received the recommended dose of 2.5/10/30 mg. The general definition of the safety population are all patients receiving at least one dose of the experimental treatment being investigated. In this case the experimental treatment is glofitamab and obinutuzumab is considered as supportive treatment (and is not included in the indication). It appears that 9/154 patients in the primary safety population did not receive any glofitamab, however it was argued that obinutuzumab pretreatment (Gpt) is an integral part of the proposed glofitamab treatment regimen and considered an essential measure for mitigating the risk of cytokine release syndrome (CRS) induced by glofitamab, thereby maintaining a positive benefit/risk balance for glofitamab. Glofitamab monotherapy without Gpt has not been evaluated in clinical studies; there is no patient experience with glofitamab in the monotherapy setting without Gpt. Despite the fact that glofitamab has not been given without obinutuzumab, the efficacy of obinutuzumab to prevent CRS is currently not considered demonstrated. Obinutuzumab has a well-known safety profile whereas glofitamab is a new medicine, and it is thus considered pertinent to focus on the adverse events of glofitamab and to avoid dilution of the AE frequencies by obinutuzumab particularly for early adverse events such as CRS.

Safety results are presented for the 145 patients who received at least one dose of obinutuzumab and glofitamab based on the 15 June 2022 CCOD alongside the results for the initial primary safety population (N = 154 patients who received at least one dose of obinutuzumab and potentially glofitamab), for ease of comparison. No major differences in the Adverse events frequencies between the two populations (N= 145 and N=154) were seen except for CRS which is considered related to glofitamab and which occurs in the first treatment cycle. Therefore, in the following the updated AE frequencies from the last round has been kept in line with the tables presented in the overview.

The main supportive safety population are the 469 R/R NHL patients having received ≥ 0.6 mg glofitamab with a subpopulation of 195 R/R NHL patients having received the recommended dose (Extended safety population 1, see table in the Safety introduction section). In this population safety was assessed in all B-NHL histologies (patients with the already mentioned DLBCL histologies, patient with Grades 1-3b follicular lymphoma, marginal zone lymphoma and mantle cell lymphoma).

In general, the proportion of patients with HGBCL and PMBCL enrolled in this study is very small. Therefore, no specific statement can be made regarding safety in these subgroups. However, in general the disease characteristics are considered representative of the proposed indication.

For the primary safety population (N = 154) at the 15 June 2022 CCOD, the median number of cycles of glofitamab received was 5.0 (range: 1-13 cycles), with 61.4% of patients receiving less than 8 cycles and 29.7% of patients receiving 12 cycles of treatment, and median treatment duration was 79.0 days (range: 1-326 days).

The demographic data and baseline characteristics are considered representative for the proposed indication in general. The safety pool is similar/balanced between the primary safety population and the overall safety population and the number of treated subjects representing the proposed indication (145 subjects) is considered sufficient for a preliminary safety profile. However, it needs to be considered that the cancer histologies varies between the cohorts and that not all cancer histologies and races are sufficiently represented in this study to make a clinical meaningful assessment in these subpopulations. For example, the proportion of patients with HGBCL and PMBCL enrolled in this study is very small. In addition, the demographic and baseline characteristics of Cohort D5, differ from the other two subgroups comprising the primary safety population. The Cohort D5 included patients with a higher median age, higher proportion of females, higher percentage of non-Hispanic patients and a higher percentage of patients with trFL and a lower percentage of patients with PMBCL and HGBCL.

In both the primary and the overall safety population, the median number of prior lines of cancer therapy per subject was 3 and all patients had received two or more prior lines of cancer therapy. Almost all patients had received chemotherapy and anti-CD-20 monoclonal antibody therapy as previous cancer therapy in the primary safety population and overall safety population respectively. Also, patients with prior CAR-T cell therapy were included in the study. The majority of the patients were refractory or relapsed to any prior therapy.

Based on the currently provided safety data by sex, a potential effect that males have a higher safety risk than females cannot be excluded and the applicant has committed to monitoring this. The applicant has also committed to provide the final safety analyses post-approval. It is very clear, though, that the main safety issue is the occurrence and management of CRS and related events followed by adverse events related to infection including neutropenia.

Key safety findings:

The SOCs in the primary safety population (N=154) in which adverse events were most frequently reported included Immune system disorders (65.8%), driven mainly by (cytokine release syndrome (CRS; 62%% although 68% by ASTCT 2019 for the smaller safety population of 145 patients, where patients only having received obinutuzumab have been removed), Blood and lymphatic system

disorders [50.7%; the most frequent PTs being neutropenia (32.9%), anemia (28.3%), and thrombocytopenia (20.4%)], and General disorders and administration site conditions [41.4%; the most frequent PTs being pyrexia (18.4%), fatigue (9.9%), and asthenia (7.2%)]. Thus, overall, the AEs mainly relate to immune-related issues and cytopenias. Infections are also of particular interest for patients with haematological malignancies, and for the SOC Infections and Infestations 40.3% (62/154) had at least one adverse event and 18.2% (28/154) experienced at least one SAE in this SOC.

The most frequent cause of **death** in the primary safety population (n=154) irrespective of time point was progressive disease, which accounted for 61 deaths (75.3%), followed by 9 AEs [COVID-19 pneumonia (3 deaths), sepsis (2 deaths), COVID-19 (3 patients), and delirium (1 death)]. None of the Grade 5 AEs were assessed as related to glofitamab by the investigator.

The incidence of **serious AEs** (SAEs) in the Extended safety population 2 (R/R NHL≥ 1 prior line who received 2.5/10/30 mg glofitamab, N=236) was 50.8%, comparable to the primary safety population; 75/154 (48.7%). Not unexpectedly, the most frequent SAE in the primary safety population was CRS [32/154 (20.8%) by ASTCT] and 64/236 (27.1%) in the Extended safety population 2. For the safety population excluding patients having only received obinutuzumab (N=145) the SAE for CRS was 32/145 (22.1% - see Table 1 in the introduction to adverse events). In the SOC Infections and infestations 28/154 (18.2%) and 46/236 (19.5%) respectively, experienced at least one SAE.

In the primary safety population (n=154), 14 patients (9.1%) reported an AE leading to any study treatment **discontinuation**, whereas in the Extended safety population 2 16/236 (6.8%) discontinued due to an AE.

Of the 236 patients who received glofitamab step-up dosing 2.5/10/30 mg, 56 patients (23.7%) reported an AE leading to dose **interruption/modification** of study treatment. Preferred terms from the SOCs Blood and lymphatic disorder, Infections and infestations, and Immune system disorders (CRS) were the most frequent events.

Adverse events of special interest

For the primary safety population (n=154) **CRS** AEs of any grade were reported in 103 patients (66.9% by Lee et al 2014). The corresponding number for the Extended safety population 2 (n=236) was 162 (68.6%). For the safety population excluding patients having only received obinutuzumab (N=145) the SAE for CRS of any grade was 102/145 (70.3% by ASCTC).

In the initial primary safety population (n=154) a total of 47/154 patients (30.5% based on ASTCT 2019) experienced multiple CRS AEs, and the corresponding number for the Extended safety population 2 was 72/236 (30.5%).

For the primary safety population (n=154) serious CRS AEs were experienced by 22.1% by Lee et al..

In the primary safety population (N=154) ICU admission was required for 7/99 patients (7.1%) and 31.5% required tocilizumab, 28 patients (28.3%) used corticosteroids, and 16 patients (16.2%) used both tocilizumab and corticosteroids to treat CRS.

Tumour flare of any grade was reported in 17/154 patients (11.0%) and for ≥ Grade 2 in 11/154 patients (7.1%) in the primary safety population. Tumour flare occurred most frequently in Cycle 1 (16/17 patients) and 1/17 in Cycle 2 with a median time to onset of 2.00 days (range: 1.0-16.0 days). The median duration of Grade ≥ 2 tumour flare was 5.50 days (range: 1.0 – 27.0). Nine of 11 patients (N=154) received treatment for tumour flare.

In the primary safety population, 22 of 154 patients (14.3%) treated with glofitamab step-up dosing experienced a **Grade ≥ 2 neurological AE**. Of these 22 patients, 18 patients reported a Grade 2

event, 2 patients reported a Grade 3 event, one patient reported Grade 4 myelitis (onset of 76.2 hours following the C1D15 10 mg glofitamab dose – see the SAE section), and one patient experienced a Grade 5 (fatal) event of delirium (which was not assessed as related to glofitamab but to pain/pain-treatment and PD).

In the primary safety population, 11 of 154 patients (7.1%) experienced **Grade ≥ 2 ALT, AST, or total bilirubin elevation** (Grade 2: 5 patients and Grade 3: 6 patients). 7 patients (4.5%) had at least one unresolved or ongoing AE at the CCOD of 15 June 2022. There is no clear indication that glofitamab was the cause of the unresolved hepatic enzyme or bilirubin increases; the reason these cases had not resolved were most likely PD.

Higher AEs were seen in male patients. Possible explanations are imbalances in baseline patient characteristics between the sex groups, the higher proportion of male patients enrolled, and the increased risk of death associated with male and advanced age lymphoma patients who contract COVID-19, may have contributed to the higher incidence of deaths, fatal AEs, severe AEs, and AEs leading to withdrawal from study drug and CRS in males compared with female patients. However, based on the currently provided safety data by sex, a potential effect that males have a higher safety risk than females cannot be excluded so far. The applicant has committed to monitoring safety in male patients versus female patients and present the data in Periodic Safety Update Reports (PSURs)/Periodic Benefit-Risk Evaluation Reports (PBRERs) and also to provide an updated analysis by gender at the time of the Study NP30179 Update Clinical Study Report due Q4 2024.

Additional expert consultation

Not applicable

Assessment of paediatric data on clinical safety

Not applicable

Additional safety data needed in the context of a conditional MA

- The applicant will provide the updated study report for study NP30179.
- Further the applicant will submit the results from a phase III study GO41944 as a specific obligation. The study is ongoing and the applicant intends to submit a filing submission in approximately Q3 2024. Information on recruitment as of 08 November 2022, has been provided.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

Overall, the preliminary safety profile of glofitamab appears to be manageable. Considering the advanced nature of the disease and the pre-treated patient population under investigation, the preliminary safety profile seems to be acceptable. Updated data has alleviated most of the concerns raised. The ongoing phase 3 study (Glofitamab-GemOx vs. R-GemOx in R/R DLBCL NOS), outlined as a specific obligation for conditional marketing authorisation, is expected to further clarify safety issues that are difficult to evaluate in a SAT.

The CHMP considers the following measures necessary to address the missing safety data in the

context of a conditional MA

- The applicant will provide the updated study report for study NP30179.
- Further the applicant will submit the results from a phase III study GO41944 as a specific obligation. The study is ongoing and the applicant intends to submit a filing submission in approximately Q3 2024.

Further, an educational programme is aimed at informing physicians to provide each patient with the patient card which includes a list of symptoms of CRS to prompt patient actions including to seek immediate medical attention in case of its occurrence.

The CHMP considers the following measures necessary to address issues related to safety:

- The applicant will submit study BO43309 on the Evaluation of the Effectiveness of the Additional Risk Minimisation Measures for Glofitamab: A Survey Among Healthcare Professionals in 10 Countries in the European Economic Area (see RMP).

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

Table 63 Summary of safety concerns

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

2.7.2. Pharmacovigilance plan

Table 64 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
NP30179 A multicenter, open-label, Phase I/II study to evaluate the safety, efficacy, tolerability and pharmacokinetics of escalating doses of glofitamab (RO7082859) as a single agent and in combination with obinutuzumab administered after a fixed, single dose pre-treatment of obinutuzumab (Gazyva®/Gazyvaro™) in patients with R/R B-cell NHL **Ongoing**	A primary objective of the study is to evaluate the safety, tolerability, and pharmacokinetics of glofitamab as single agent (and in combination with obinutuzumab) following obinutuzumab pre-treatment (Gpt) in patients with R/R CD20 + B –cell NHL. The 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.	Long-term safety Safety in patients with prior CAR-T therapy	Update CSR	Q4 2024
Category 3 - Required additional pharmacovigilance activities				
BO43309 Evaluation of the Effectiveness of the Additional Risk Minimisation Measures for Glofitamab: A Survey Among Healthcare Professionals in 10 Countries in the European Economic Area **Planned**	The primary objective of this study is to assess, by survey: • the receipt of the educational materials, i.e., HCP brochure (for the important identified risk of TF) and Patient Card (for the important identified risk of CRS), by the target population (glofitamab prescribers) and the distribution of the Patient Card by prescribers to their patients • behavioral indicators (the level of awareness, knowledge, comprehension and adherence) of prescribers with respect to TF information included in the HCP brochure.	•Cytokine release syndrome •Tumor Flare	Final report	Q2 2026

Table 65: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
none				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
GO41944 A Phase III, Open-Label, Multicenter, Randomized Study Evaluating the Efficacy and Safety of Glofitamab in Combination with Gemcitabine plus Oxaliplatin versus Rituximab in Combination with Gemcitabine and Oxaliplatin in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma Ongoing	To evaluate the efficacy of Glofit-GemOx compared with R-GemOx on the basis of OS, PFS, CR rate, ORR, duration of OR, duration of CR, and time to deterioration in physical functioning and fatigue, and lymphoma symptoms - To evaluate the safety and tolerability of Glofit-GemOx compared with R-GemOx on the basis of the following endpoints: • Incidence and severity of AEs (severity determined according to NCI CTCAE v5.0), including CRS, with severity determined according to ASTCT CRS grading criteria • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results • Tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of AEs	Overall survival benefit Safety concerns addressed: CRS; Tumor Flare; Serious Infections	Primary CSR	Q3 2024

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

2.7.3. Risk minimisation measures

Table 66: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cytokine release syndrome	**Routine risk minimisation measures:** SmPC section 4.2, 4.4, and 4.8 Recommendation for monitoring for the development of CRS is included in	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** No activities beyond routine PSUR/PBRER reporting **Additional pharmacovigilance**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.2. Package leaflet sections 2 and 4 **Additional risk minimisation measures:** Patient Card	**activities:** Study BO43309 Final report: Q2 2026
Tumour Flare	**Routine risk minimisation measures:** SmPC section 4.4 and 4.8 Package leaflet section 2 and 4 **Additional risk minimisation measures:** HCP brochure	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** No activities beyond routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** Study BO43309 Final report: Q2 2026
Serious Infections	**Routine risk minimisation measures:** SmPC section 4.4 and 4.8 Package leaflet section 2 and 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** No activities beyond routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** None
Long-term safety	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Monitoring and reporting of safety by sex in (PSURs)/PBRERs **Additional pharmacovigilance activities:** Study NP30179 Update CSR: Q4 2024
Safety in patients with prior CAR-T therapy	**Routine risk minimisation measures:** None **Additional risk minimisation**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** No activities beyond routine PSUR/PBRER

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	measures: None	reporting **Additional pharmacovigilance activities:** Study NP30179 Update CSR: Q4 2024

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 24.03.2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation (EC) No 726/2004, Columvi (glofitamab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Columvi as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.

3.1.2. Available therapies and unmet medical need

For patients with R/R DLBCL having failed at least two prior lines of therapy, the therapeutic options are somewhat limited. A steady stream of new treatments has been approved since 2018 with scant availability of evidence to support any particular treatment over the others or to aid in the rational sequencing of treatments. Regardless of treatment, the prognosis is quite poor with CR-rates between approximately 30-50%.

3.1.3. Main clinical studies

NP30179 is a single-arm, ongoing, first-in-human, multicenter, multicohort, open-label, Phase I/II dose-escalation and expansion study evaluating the efficacy, safety and tolerability, and pharmacokinetics of glofitamab as monotherapy with a single 1000 mg dose of obinutuzumab/Gazyvaro given as pre-treatment (Gpt) in patients with R/R NHL.

D3 (N=108) was the cohort that supports the therapeutic indication in R/R DLBCL after ≥2 prior treatments. The primary efficacy endpoint in this cohort was CR by independent central review (ICR). Duration of complete response (DOCR) and time from first treatment to CR (TFCR) –both by IRC– were the key secondary endpoints.

3.2. Favourable effects

The primary efficacy cohort D3 had a CR-rate (by IRC) of 35.2% (95% CI: 26.2, 45.0) (CCOD 15 June 2022). The median duration of CR was not reached. For complete responders, the median time from first treatment to CR was 42.0 days (95% CI: 41.0, 48.0). Patients previously having failed CAR-T treatment, patients receiving glofitamab post autologous stem cell transplant therapy and those who were refractory to their last line of treatment (all of which represent difficult-to-treat patient categories) achieved 32%, 56% and 29% CR-rates, respectively. The median DOCR extended beyond the duration of treatment, suggesting that some patients achieve disease control.

3.3. Uncertainties and limitations about favourable effects

The study was designed as a Phase 1 dose-finding and dose escalation study without the required rigor usually requested for confirmatory trials (adequate pre-specification of key elements, appropriate type 1 error control, blinded and independent decision making, randomized control arm, etc) and was amended 10 times changing its nature from a Phase 1 to a Phase 1/2 (and finally "confirmatory") study.

As comprehensive data on the product are not available, a conditional marketing authorisation is

agreed. In the context of the specific obligations the applicant will provide the updated study report for study NP30179. The applicant will submit the results from a phase III study GO41944 as a specific obligation. The study is ongoing and recruitment has progressed (data as of 08 November 2022). The SOB is planned to be fulfilled by Q3 2024.

All 3 patients with CD20-negative disease had progressive disease as their best response to glofitamab. Overall, concern still remains that the clinical context in which glofitamab is given (in patients, all of whom have been exposed to prior CD20-targeted therapy) predisposes to development of resistance to CD20-targeted agents and it does not seem that glofitamab retains anti-lymphoma activity in CD20-negative lymphomas. This uncertainty, is reflected as a warning at 4.4 in the SmPC: There are limited data available on patients with CD20-negative DLBCL treated with Columvi, and it is possible that patients with CD20-negative DLBCL may have less benefit compared to patients with CD20-positive DLBCL. The potential risks and benefits associated with treatment of patients with CD20-negative DLBCL with Columvi should be considered. The efficacy of Columvi has not been established in patients with CD20-negative disease who have relapsed from prior anti-CD20 therapy. Further, the applicant will provide the final list of CD20 expression in Study NP30179 for the entire Cohort D3 with evaluable CD20 and to correlate expression with response to glofitamab at the time of the 2 years follow-up from the end of treatment of the last patient enrolled in the primary safety population. The applicant will measure CD20 expression and correlate this to response and risk of CRS in the ongoing SOB phase III trial NCT04408638/ Study GO41944 (R-GemOx vs Glofit-GemOx in 2L+ DLBCL NOS).

3.4. Unfavourable effects

The SOCs in the primary safety population (N=154) in which adverse events were most frequently reported included Immune system disorders (68.2%), driven mainly by cytokine release syndrome (CRS; 62%% although 68% by ASTCT 2019 for the smaller safety population of 145 patients, where patients only having received obinutuzumab have been removed), Blood and lymphatic system disorders [55.8%; the most frequent PTs being neutropenia (35.7%), anaemia (30.5%), and thrombocytopenia (21.4). Thus, overall, the AEs mainly relate to immune-related issues and cytopenias. Infections are also of particular interest for patients with haematological malignancies, and for the SOC Infections and Infestations 40.3% (62/154) had at least one adverse event and 18.2% (28/154) experienced at least one SAE in this SOC.

The most frequent cause of **death** in the primary safety population (n=154) irrespective of time point was progressive disease, which accounted for 61 deaths (78.3%), followed by 9 AEs [COVID-19 pneumonia (3 deaths), sepsis (2 deaths), COVID-19 (3 patients), and delirium (1 death)]. None of the Grade 5 AEs were assessed as related to glofitamab by the investigator.

The incidence of **serious AEs** (SAEs) in the Extended safety population 2 (R/R NHL≥ 1 prior line who received 2.5/10/30 mg glofitamab, N=236) was 50.8%, comparable to the primary safety population; 75/154 (48.7%). Not unexpectedly, the most frequent SAE in the primary safety population was CRS [32/154 (20.8%) by ASTCT] and 64/236 (27.1%) in the Extended safety population 2. For the safety population excluding patients having only received obinutuzumab (N=145) the SAE for CRS was 32/145 (22.1% - see Table 1 in the introduction to adverse events). In the SOC Infections and infestations 28/154 (18.2%) and 46/236 (19.5%) respectively, experienced at least one SAE.

In the primary safety population (n=154), 14 patients (9.1%) reported an AE leading to any study treatment **discontinuation**, whereas in the alternative Extended safety population 2 16/236 (6.8%) discontinued due to an AE. The added 1 patient discontinued due to COVID-19 infection. Of the 236 patients who received glofitamab step-up dosing 2.5/10/30 mg, 56 patients (23.7%) reported an AE

leading to dose **interruption/modification** of study treatment. Preferred terms from the SOCs Blood and lymphatic disorder, Infections and infestations, and Immune system disorders (CRS) were the most frequent events.

For the primary safety population (n=154) **CRS** AEs of any grade were reported in 103 patients (66.9% by Lee et al 2014). The corresponding number for the Extended safety population 2 (n=236) was 162 (68.6%). For the safety population excluding patients having only received obinutuzumab (N=145) the SAE for CRS of any grade was 102/145 (70.3% by ASCTC). For the primary safety population (n=154) serious CRS AEs were experienced by 22.1% by Lee et al., ICU admission was required for 7/99 patients (7.1%) and 31.5% required tocilizumab, 28 patients (28.3%) used corticosteroids, and 16 patients (16.2%) used both tocilizumab and corticosteroids to treat CRS.

Tumour flare of any grade was reported in 17/154 patients (11.0%) and for ≥ Grade 2 in 11/154 patients (7.1%) in the primary safety population. Tumour flare occurred most frequently in Cycle 1 (16/17 patients) and 1/17 in Cycle 2 with a median time to onset of 2.00 days (range: 1.0-16.0 days). The median duration of Grade ≥ 2 tumour flare was 5.50 days (range: 1.0 – 27.0). Nine of 11 patients (N=154) received treatment for tumour flare. At the time of the CCOD, events were resolved in 10 of 11 patients.

In the primary safety population, 22 of 154 patients (14.3%) treated with glofitamab step-up dosing experienced a **Grade ≥ 2 neurological AE**. Of these 22 patients, 18 patients reported a Grade 2 event, 2 patients reported a Grade 3 event, one patient reported Grade 4 myelitis (onset of 76.2 hours following the C1D15 10 mg glofitamab dose – see the SAE section), and one patient experienced a Grade 5 (fatal) event of delirium (which was not assessed as related to glofitamab but to pain/pain-treatment and PD). In the primary safety population, 11 of 154 patients (7.1%) experienced **Grade ≥ 2 ALT, AST, or total bilirubin elevation** (Grade 2: 5 patients and Grade 3: 6 patients). 7 patients (4.5%) had at least one unresolved or ongoing AE at the CCOD of 15 June 2022. There is no clear indication that glofitamab was the cause of the unresolved hepatic enzyme or bilirubin increases; in the evaluable 6 out of 7 cases the reason these cases had not resolved were most likely PD or in 1 case tocilizumab AE.

3.5. Uncertainties and limitations about unfavourable effects

Given the single-arm trial design, the relatively small safety population (N=154), the short exposure, and known risks for other monoclonal antibodies targeting CD20 on B-cells and/or CD3 on T-cells, uncertainties remain with regards to the CRS, Tumour flare Serious infections Prior CAR-T treatment, which are reflected in the Summary of safety concerns of the RMP

More data on long-term safety are needed; the median exposure was 79 days in the primary safety population; treatment may be given for 12 cycles (á 21 days).

Risk minimisation measures are in place to mitigate the risk of CRS and tumour flare (see Annex II).

Study BO43309 on the Evaluation of the Effectiveness of the Additional Risk Minimisation Measures for Glofitamab is a Survey Among Healthcare Professionals in 10 Countries in the European Economic Area with the primary objective of this study is to assess, by survey the receipt of the educational materials, i.e., HCP brochure (for the important identified risk of TF) and Patient Card (for the important identified risk of CRS), by the target population (glofitamab prescribers) and the distribution of the Patient Card by prescribers to their patients and behavioral indicators (the level of awareness, knowledge, comprehension and adherence) of prescribers with respect to TF information included in the HCP brochure. This study will provide more information on Cytokine release syndrome and Tumor Flare (see RMP).

Further information on the safety concerns and on long term safety will be provided by the submission of the updated report of study NP30179 and from the randomised phase III trial NCT04408638/ Study GO41944 (R-GemOx vs Glofit-GemOx in 2L+ DLBCL NOS) – already ongoing, in the context of the specific obligations.

3.6. Effects Table

Table 67: Effects Table for Glofitamab for R/R DLBCL After ≥ 2 Prior Lines of Treatment (CCOD: 15 June 2022)

Effect	Short Description	Unit	Treatment Glofitamab monotherapy[1]	Uncertainties/ Strength of evidence	References[3]
Favourable Effects (Cohort D3 from study NP30179, N=108)					
Primary endpoint: **CR rate by IRC**	Complete response rate by Independent Review Committee	% (95% CI)	35.2% (26.2, 45.0)	Uncertainties: Single-arm trial, several lymphoma types included in same trial. Strengths: Efficacy in patients failing CAR-T treatment.	Table 13/uCSR
Secondary endpoints					
Median DOCR by IRC	Duration of CR	Months (95% CI)	NE (18.4, NE)	Median duration of follow-up for IRC-assessed DOCR was 12.8 months (95% CI: 11.6, 18.2)	Table 13/uCSR
Median DOR by IRC	Duration of ORR	Months (95% CI)	14.4 (8.6, NE)		Table 13/uCSR
TFCR by IRC	Time from first treatment to first CR	(95% CI)	42.0 (41.0, 47.0)		Table 13/uCSR
Unfavourable Effects: Primary safety population (N=154): R/R DLBCL (≥2 Tx)[4]					
Serious adverse events (SAE)		N, %	75/154 (48.7)		Table 12/uSCS
Discontinuations		N, %	14/154 (9.1)		Table 12/uSCS
Cytokine release syndrome (CRS)[2]	Any AE SAE	N, % N, %	99 (64.3) 34 (22.1)	1 discontinuation, 1 interruption	
Tumour flare (TF)	Any AE Grade ≥ 2 SAE	N, % N, % N, %	17 (11.0) 11 (7.1) 4 (2.6)	10/11 patients with resolved TF	Table 27/uSCS
Neutropenia (PT)	Any AE Grade 3-4	N, % N, %	58 (37.7) 42 (27.3)	Neutrophil count decreased added for the ADR included in the SmPC: 37.7% (All grades)	Table 48/uSCS

Infections (by SOC) Serious Infections	Any AE	N, %	62 (40.3)		
	SAE	N, %	28 (18.2)		

Notes:

Abbreviations: NE=not evaluable.Notes:
[1]Step-up dose 2.5/10/30 mg (C1D8/C1D15/C2D1-C12D1) preceded by obinutuzumab 1000 mg C1D1.
[2] by ASTCT 2019
[3] Refers to the updated reports
[4] SmPC reflects the glofitamab-exposed patients in the primary safety population (N=145)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There is an unmet need for patients with R/R DLBCL who have received ≥2 prior therapies, particularly for patients who are R/R to different classes of agents, as they are left with limited treatment options that may have challenging safety profiles.

Results from the single-arm trial NP30179 are encouraging, with 38/108 (35.2%) patients achieving CR. Obtaining a CR, which is the disappearance of all measurable evidence of disease, is considered relevant for this population in need and indicates a clinically meaningful effect. Results from secondary endpoints, in particular DOCR (not reached) support the primary endpoint.

The main uncertainties regarding the B/R assessment relate to the highly flexible and data-driven nature of the study without appropriate pre-specification of key elements such as the pivotal cohort and without type 1 error control over the (17) cohorts, a clear rationale for the dose and/or treatment regimen, the limited sample size, the short follow-up, and the limitations associated with the single-arm study design. The updated efficacy data provided in Round 2 assuage some of these uncertainties, in particular the demonstration of durable CRs (DOCR not reached) lasting beyond the fixed duration of treatment. The short TFCR is considered of benefit in this population of patients with aggressive lymphoma as well. Finally, the relatively high CR-rate in patients relapsing after CAR-T treatment is considered of benefit.

The most important safety concerns are CRS, neutropenia/neutrophil count decreased, infections, neurological adverse events and tumour flare. The adverse events are generally manageable and acceptable in this disease population with ominous prognosis and scarce treatment possibilities.

3.7.2. Balance of benefits and risks

Glofitamab provides a novel mechanism of action, could have potential therapeutic advantage compared to available treatments (pending resolution of the concerns raised in this AR), and provides durable complete responses, while having a clinically manageable safety profile.

3.7.3. Additional considerations on the benefit-risk balance

This being a conditional marketing authorisation the following studies will be submitted as part of the specific obligations:

- 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
- In order to provide further evidence of efficacy and safety of glofitamab in DLBCL, the MAH will provide the results of Study GO41944, a phase III open-label, multicentre, randomised study evaluating the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin versus rituximab in combination with gemcitabine and oxaliplatin in patients with relapsed or refractory DLBCL.

Conclusions

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

Glofitamab is currently being investigated as monotherapy and in combination with other therapies in multiple Phase I/II studies and one Phase III open label, randomized (2:1) study in patients with R/R DLBCL. The confirmatory study agreed as an SOB for the CMA was discussed during a scientific advice procedure in Dec 2019 (EMEA/H/SA/4023/2/2019/III) is: A Phase III Study Evaluating Glofitamab in Combination with Gemcitabine + Oxaliplatin vs Rituximab in Combination with Gemcitabine + Oxaliplatin in Participants with Relapsed/Refractory Diffuse Large B-Cell Lymphoma, ClinicalTrials.gov Identifier: NCT04408638/ Study GO41944. The study is ongoing and recruitment has progressed. It should be noted that patients are eligible for this study as second-line treatment (as opposed to the current application which is third-line or higher). In addition, the only LBCL subtype that is eligible is DLBCL NOS (meaning that no further data on the efficacy of glofitamab in trFL, HGBCL and PMBCL will be provided by this study). The update on enrolment is reassuring for the feasibility of the trial.

- Unmet medical needs will be addressed, as glofitamab has shown consistent and durable complete responses and significant overall response rate in the targeted population who were refractory to other options, while having a clinically manageable safety profile.

The current treatment landscape of R/R DLCBL contains numerous options which makes the demonstration of unmet medical need particularly important for considering granting a CMA. The applicant has satisfactorily provided evidence of MTA over polatuzumab vedotin (+BR), CAR-T therapies and pixantrone which have a full MA. In comparison to a recent CMA approval of Zynlonta, glofitamab addresses the unmet medical need to a similar extent.

The applicant has provided indirect comparisons of glofitamab against published results for other available treatments in the R/R DLBCL setting including the fully approved CAR-T treatments Yescarta, Kymriah, and Breyanzi as well as the monoclonal antibody conjugate Polivy (in combination with rituximab and bendamustine) – full approval was recently granted for Polivy in place of CMA. In

addition, the cytotoxic Pixuvri is fully approved. Furthermore, comparisons with the conditionally approved targeted treatment Minjuvi (in combination with lenalidomide) is provided. Finally, comparisons between glofitamab and rituximab-chemotherapy combinations are mentioned.

Compared to CAR-T therapies (Yescarta, Kymriah, Breyanzi), glofitamab is immediately available, whereas, due to the complex manufacturing of CAR-Ts, their distribution and the need for intense monitoring this treatment modality is currently limited to specialized tertiary centers and for patients who are well enough to withstand the delays in receiving an active treatment, as delays which are inherent in the preparation of a CAR-T product could potentially be detrimental to a R/R DLBCL patient. Columvi will present a treatment for immediate administration to the patient. Further, Columvi has demonstrated efficacy in patients who have failed CAR-T treatment.

Compared to Polivy+BR, in terms of efficacy, Polivy+BR (in 3L+) and glofitamab (also 3L+) demonstrate similar CR-rates (31% and 35%, respectively) in their respective studies in r/r DLBCL, while the DOR of glofitamab (14.4 months) was numerically longer than that of Polivy+BR (10.3 months). Such numbers, while not formally demonstrating MTA, indicate that Glofitamab will provide meaningful clinical effects in patients with R/R DLBCL NOS, and thus constitute an additional treatment option in this non-curative 3L+ setting.

The sequencing of Polivy+BR and glofitamab has not been explicitly studied. There is, however, some evidence of effect of glofitamab after CAR-T (CR 32% & ORR 45%, n = 38), while Polivy+BR has yet to demonstrate effect in this setting (CR 0% & ORR 33%, n = 6). Considering that CAR-T treatment is moving from 3L+ to 2L in R/R (D)LBCL, and as such a greater proportion of patients needing 3L+ treatment will have been previously exposed to CAR-T, this is an important advantage over the treatment management of DLBCL. Of note, although some patients in the pivotal (D3) cohort for glofitamab had previously been treated with Polivy-containing regimens, no current knowledge is available on the efficacy of glofitamab after Polivy+BR.

In terms of clinical safety it is difficult to compare the prevalence of specific adverse events in Polivy+BR treated vs glofitamab treated cohorts in a meaningful way without any direct comparative studies. However, the studies record substantially different rates of AEs associated with the particular mechanisms of action of Polivy and glofitamab. Peripheral neuropathy is characteristic of tubulin targeting agents such as the vedotin toxin of Polivy, and was seen in 31% in Polivy+BR treated patients, whereas it was only reported in 2% of those treated with glofitamab. Moreover CRS, which is characteristic of T-cell engagers, is seen in 64% of those treated glofitamab and not reported for Polivy+BR. Although it cannot be stated that one product is safer than the other, CRS is treatable and reversible, while neuropathy may be irreversible. Based on this, glofitamab has a safety advantage over Polivy+BR due to the abovementioned differential ADR profiles resulting from the respective mechanisms of action.

Based on the above, it is concluded that glofitamab provides a major therapeutic advantage over Polivy+BR due to the lack of peripheral neuropathies. Additionally, compared to Polivy+BR, glofitamab provides advantage in terms of an additional line of treatment after patients have failed CAR-T treatment.

In terms of MTA over Pixuvri; Pixantrone (in 3L+) demonstrated a CR-rate of 11% compared to glofitamab which demonstrated a CR-rate of 35%, in the R/R DLBCL setting. The DOR was 7 vs 14.4 months for Pixuvri and glofitamab, respectively. With regards to Pixuvri, it can be accepted that the activity of this compound is limited and a major therapeutic advantage of Columvi over pixantrone in terms of efficacy may be inferred.

Although the sequencing of Pixuvri and glofitamab has not been studied, it is very likely that nearly all DLBCL NOS patients eligible for 3L+ treatment will have received anthracycline drugs as part of 1st

line therapy (most commonly in the form of doxorubicin as part of R-CHOP chemo or variations thereof). The main exception would be patients with known heart failure at the time of diagnosis and these patients would not be candidates for pixantrone treatment in any case. Total (life-time) cumulative anthracycline dose is typically capped in order to minimize the risk of heart failure. That means that sequencing of Pixuvri after 1st (and potentially 2nd) line treatment containing anthracycline is problematic as it is the cumulative dose of anthracycline that determines the risk of heart failure. Therefore, it can be considered that glofitamab has a therapeutic advantage over pixantrone since it can be given to patients who have met (or are close to) their maximum allowed anthracycline limit (likely a large proportion of the 3L+ cohort).

It is difficult to compare the prevalence of specific adverse events in Pixuvri treated vs glofitamab treated cohorts in a meaningful way without any direct comparative studies. However, the studies record different rates of AEs associated with the particular mechanisms of action of Pixuvri and glofitamab. Cardiac failure, a well-described risk of anthracycline drugs, was found in 8.8% of Pixuvri-treated patients vs 1.3% of glofitamab treated patients. Moreover CRS, which is characteristic of T-cell engagers, is seen in 64% of those treated with glofitamab and not reported for Pixuvri. Although it cannot be stated that one product is safer than the other, CRS is treatable and reversible, while anthracycline-induced heart failure may be irreversible. Based on this, glofitamab has a safety advantage over Pixuvri due to the abovementioned differential ADR profiles resulting from the respective mechanisms of action.

Based on the above, glofitamab provides a major therapeutic advantage over Pixuvri due to the lack of risk of cardiac failure. Additionally, compared to Pixuvri, glofitamab provides advantage in terms of an additional line of treatment regardless of previous cumulative anthracycline dose received.

In order to shed light on the effects of sequencing of glofitamab after Pola+CHP, Pola+BR and Pixuvri, the applicant was requested to provide the number of patients in the pivotal cohort D3 having previously received one or more of the abovementioned therapies along with the responses these patients then achieved on glofitamab treatment**.** The limited number of patients available to investigate the sequencing of glofitamab after regimens containing either polatuzumab (n=6 patients) or pixantrone (n=2 patients) preclude any conclusions on glofitamab efficacy in these settings being drawn.

While clinically relevant activity has been shown for products approved in 3L+, comparing the relative impact of these medicinal products on time-dependent endpoints is fraught with uncertainty due to cross-study comparisons of relatively small studies.

Compared to the conditionally approved product Minjuvi, glofitamab offers a similar level of efficacy and exhibits a comparable safety profile, suggesting that glofitamab fulfils the unmet medical need to a similar extent.

Compared to the conditionally approved Zynlonta Based on the evidence available, glofitamab offers benefit over zynlonta in terms of a shorter duration of treatment, the advantage in the subset of patients who have previously been treated with anti-CD19 directed therapy (primarily CAR-T) and a different safety profile. Efficacy is potentially better although this is difficult to conclusively ascertain based on comparisons between two single-arm trials. It is assessed that glofitamab addresses the unmet medical need to a similar extent.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Based on the aggressiveness of, and poor prognosis associated with, R/R DLBCL as well as the fact

that the risk-benefit balance of Columvi is positive, it is agreed that the benefits to public health of immediate availability outweigh the risks.

3.8. Conclusions

The overall benefit/risk balance of Columvi is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Columvi is not similar to Kymriah, Yescarta, Minjuvi and Polivy within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Columvi is favourable in the following indication:

Columvi as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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

The educational programme is aimed at:

- Informing physicians to provide each patient with the patient card and educate the patient on its content, which includes a list of symptoms of CRS to prompt patient actions including to seek immediate medical attention in case of its occurrence.
- Prompting patient actions, including seeking immediate medical attention, in case of the occurrence of symptoms of CRS.
- Informing physicians on the risk of tumour flare and its manifestations.

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, which will contain:

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

All patients who receive Columvi shall be provided with a patient card, which will contain the following key elements:

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

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
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.	Q4 2024
In order to provide further evidence of efficacy and safety of glofitamab in DLBCL, the MAH will provide the results of Study GO41944, a phase III open-label, multicentre, randomised study evaluating the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin versus rituximab in combination with gemcitabine and oxaliplatin in patients with relapsed or refractory DLBCL.	Q3 2024

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that glofitamab is to be qualified

as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.