



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Gazyvaro

International non-proprietary name: obinutuzumab

Procedure No. EMEA/H/C/002799/II/0052

Note

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



Steps taken for the assessment		
Description	Planned date	Actual Date
Start of procedure	31 Dec 2022	31 Dec 2022
CHMP Rapporteur Assessment Report	24 Feb 2023	24 Feb 2023
PRAC Rapporteur Assessment Report	03 Mar 2023	03 Mar 2023
PRAC members comments	08 Mar 2023	08 Mar 2023
CHMP Co-Rapporteur Critique	08 Mar 2023	07 Mar 2023
Updated PRAC Rapporteur Assessment Report	09 Mar 2023	09 Mar 2023
PRAC endorsed relevant sections of the assessment report ³	16 Mar 2023	16 Mar 2023
CHMP members comments	20 Mar 2023	20 Mar 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 Mar 2023	23 Mar 2023
Request for Supplementary Information	30 Mar 2023	30 Mar 2023
Submission of responses	17 May 2023	17 May 2023
Re-start of procedure	22 May 2023	22 May 2023
CHMP Rapporteur Assessment Report	20 Jun 2023	21 Jun 2023
PRAC Rapporteur Assessment Report	23 Jun 2023	22 Jun 2023
Withdrawal letter received	n/a	04 Jul 2023
PRAC members comments	28 Jun 2023	n/a
Updated PRAC Rapporteur Assessment Report	29 Jun 2023	n/a
PRAC endorsed relevant sections of the assessment report ³	06 Jul 2023	n/a
CHMP members comments	10 Jul 2023	n/a
Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 Jul 2023	n/a
Request for Supplementary Information / Opinion	20 Jul 2023	n/a

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List of abbreviations

ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
ASTCT	American Society for Transplantation and Cellular Therapy
AvRO%D1	average RO% over the first 24 hours
CAR	chimeric antigen receptor (T cells)
C1D1	Cycle 1 Day 1
C1D8	Cycle 1 Day 8
CCOD	clinical cutoff date
CDC	complement-dependent cytotoxicity
CHMP	Committee for Medicinal Products for Human Use
CLL	chronic lymphocytic leukemia
CRS	cytokine release syndrome
CSR	Clinical Study Report
DIBD	Development International Birth Date
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EC ₅₀	half-maximal effective concentration
ER	exposure-response
EU	European Union
Fab	fragment antigen binding
Fc	fragment crystallizable
FL	follicular lymphoma
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage-colony stimulating factor
Gpt	obinutuzumab (Gazyvaro/Gazyva) pretreatment
Fc _γ R	Fc gamma receptor
HGBCL	high-grade B-cell lymphoma
HSC	hematopoietic stem cell
IBD	International Birth Date
ICU	Intensive Care Unit
IFN	interferon
IgG1	immunoglobulin G1
IIV	inter-individual variability
IL	interleukin
IRC	Independent Review Committee
IRR	infusion related reaction

IV	intravenous
K _d	dissociation constant
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MCL	mantle cell lymphoma
MoA	mechanism of action
MTD	maximum tolerated dose
NHL	non-Hodgkin's lymphoma
NK	natural killer
NOG	NOD/Shi scid/IL-2R ^y null
NOS	not otherwise specified
OBD	optimal biological dose
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PMBCL	primary mediastinal B-cell lymphoma
PMN	polymorphonuclear neutrophils
PT	Preferred Term
R	receptor
RO	receptor occupancy
R/R	relapsed/refractory
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
TCB	T cell bispecific antibody
TCE	T cell-engaging
TLS	tumor lysis syndrome
TMDD	target-mediated drug disposition
TNF	tumor necrosis factor
trFL	DLBCL arising from FL; transformed FL
US	United States

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 29 November 2022 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the pre-treatment to reduce the risk of cytokine release syndrome (CRS) induced by glofitamab for Gazyvaro, based on results from study NP30179; this is a multicenter, open-label, Phase I/II study evaluating the safety, efficacy, tolerability 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 Gazyvaro in patients with relapsed/refractory B-cell NHL. As a consequence, sections 4.1, 4.2, 4.4, 5.1, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

The new indication, which is the subject of this application, does not fall within any orphan designation. According to Article 7 of Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products, it is not possible to combine an orphan indication and a non-orphan indication in the same marketing authorisation. Consequently, the MAH has committed to request the withdrawal of the orphan designation from the Community Register of Orphan Medicinal Products within 2 days after the receipt of the CHMP opinion. Should the MAH not request the withdrawal of the orphan designation within the said deadline, nor request re-examination in accordance with Article 16(4) of Commission Regulation (EC) No. 1234/2008, the validation of this variation application becomes automatically null and void with retroactive effect.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) (EMA-001207-PIP06-22) on the granting of a (product-specific) waiver and on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised

orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the pre-treatment to reduce the risk of cytokine release syndrome (CRS) induced by glofitamab for Gazyvaro, based on results from study NP30179; this is a multicenter, open-label, Phase I/II study evaluating the safety, efficacy, tolerability 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 Gazyvaro in patients with relapsed/refractory B-cell NHL. As a consequence, sections 4.1, 4.2, 4.4, 5.1, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version.

☐ is recommended for approval.

☐ is not recommended for approval.

☒ is subject to a request for supplementary information (please refer to the RSI section <and the proposed Changes to the Product Information in a separate document>) before a recommendation can be made.

The responses timetable to the Request for Supplementary Information will be^{1 2}:

- ☐ 30 days (15 days to assess with clock-stop, 8 days to assess with immediate responses)
- ☒ 60 days (36 days to assess)

¹ Instructions to assessor: please select one of the two options. If no option is selected, a default 30-day assessment timetable will be applied.

² Note to MAH: this timetable refers to the assessment of the responses to the RSI and is determined by the Rapporteur/assessor; it does not refer to the clock-stop necessary for the preparation and submission of the responses which is determined by the MAH and communicated to the Procedure Assistant upon receipt of the assessment report.

3. Scientific discussion

3.1. Introduction

3.1.1. Problem statement

Disease or condition

The MAH is seeking marketing authorization for:

Obinutuzumab is indicated as a pretreatment to reduce the risk of cytokine release syndrome (CRS) induced by glofitamab.

The target patient population is dependent on the target patient population of glofitamab. Currently, glofitamab is under assessment for the proposed indication:

Glofitamab 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.

Based on the glofitamab documents attached to the current obinutuzumab application, glofitamab is also being investigated in other lymphoma types apart from DLBCL (such as FL).

Cytokine release syndrome (CRS) is a manageable but clinically significant and occasionally life-threatening inflammatory toxicity syndrome in the setting of immunotherapy. It is characterized by a supraphysiological response to immunotherapy that results in the activation of endogenous or infused T cells and/or other immune effector cells (e.g., macrophages, dendritic cells, monocytes, endothelial cells) leading to cytokine release and subsequent clinical toxicity (Lee et al. 2019). T-cell activation results in downstream release of cytokines (Neelapu et al. 2018).

Epidemiology and risk factors, screening tools/prevention

The epidemiology and risk factors of CRS are poorly described. The most well-described risk factor seems to be treatment with immunotherapeutic agents, especially, but not limited to, T-cell activating therapies. Screening tools do not seem to be employed in routine clinical practice but a high level of surveillance is required in patients treated with treatments at risk of triggering CRS. In terms of prevention, most bi-specific antibodies seem to employ a strategy of careful, incremental step-up dosing combined with anti-inflammatory premedication such as corticosteroids, anti-histamines and anti-pyretics. The current application is the focus of a prevention strategy, namely, pretreatment with obinutuzumab before treating with a bispecific antibody.

Assessor's comment

The MAH is asked to provide information on the epidemiology and risk factors of CRS as well as any relevant screening tools and prevention strategies they consider pertinent. In particular, evidence that high b-cell counts and/or tumour burden translate to a higher risk of CRS would be welcomed (**OC**).

Biologic features, Aetiology and pathogenesis

CRS occurs with varying frequency, severity, and presentation among immunotherapeutic agents that utilize or directly activate T cells, such as T cell-engaging (TCE) bispecific antibodies and chimeric antigen receptor (CAR) T cells (Murthy et al. 2019, Shimabukuro-Vornhagen et al. 2018). In the case of TCE bispecific antibodies that target B-cell targets, rapid T cell bispecific antibody (TCB)-mediated T-cell activation via interaction with B-cell targets in the circulation leads to CRS.

Clinical presentation, diagnosis and stage/prognosis

Symptoms and severity of CRS can range from mild, flu-like symptoms or fever (most commonly) to severe or life-threatening manifestations of systemic inflammation (e.g., hypotension, hypoxia, capillary leak, coagulopathy, and multi-organ failure). Early recognition and treatment of symptoms is important to reduce the severity of CRS. Interventions can mitigate and/or manage CRS in most patients and enable continued treatment with these highly effective anti-cancer drugs.

Different scales for grading of severity (and treatment paradigms) of CRS exist. The grading scheme employed in this AR is the ASTCT CRS grading scale (Lee et al Biol Blood Marrow Transplant 2019).

Management

Management of TCE bispecific antibody–induced CRS includes interrupting or discontinuing the infusion of study drug, symptomatic management of constitutional symptoms, management of hypotension with intravenous (IV) fluids and vasopressors, management of hypoxia with supplemental oxygen or mechanical ventilation, as well as corticosteroids, anti-IL-6 therapy (i.e., tocilizumab), and intensive care unit (ICU) admission, if warranted.

Despite improvements in CRS management, medical intervention is still required for a substantial proportion of patients with CRS, and some patients still require intensive care and escalation of anti-cytokine therapy beyond tocilizumab. Optimizing CRS management thus requires improved prevention. For some TCE bispecific antibodies, such as glofitamab, the risk of CRS is greatest with the first infusion while for others the risk is greatest at the target dose. This risk has been partially mitigated by the use of step-up or fractionated dosing schedules; using lower initial doses to reduce CRS risk at first infusion.

Pharmaceutical prophylaxis that fully abrogates the risk of CRS has not been developed. Several strategies targeting cytokine production and T-cell activation are under evaluation (Xiao et al. 2021; Leclercq et al. 2022), but no definitive prophylaxis paradigm has yet been identified:

- **Use of glucocorticoids:** Glucocorticoids are employed in low doses for a short term prior to the administration of TCE bispecific antibodies, similar to their use prior to blinatumomab. Extrapolating from patients treated with CAR-Ts, their use as CRS prophylaxis appears to reduce the risk of severe (Grade ≥ 3) CRS but does not eliminate CRS requiring medical intervention. In a cohort of 40 patients treated with dexamethasone 10 mg daily for 3 days as CRS prophylaxis with administration of axicabtagene ciloleucel, 32 patients (80%) experienced CRS with 18 patients (45%) having Grade 2 CRS (Oluwole et al. 2021). Use at higher doses or for longer duration potentially increases the risk of abrogating their anti-tumor T-cell function.
- **Use of anti-cytokine agents:** While tocilizumab is commonly used as CRS treatment, its use as prophylaxis has not been established. The appropriate dose and schedule of tocilizumab prophylaxis remain unknown. Comprehensive studies of other anti-cytokine agents, including adalimumab, have not been conducted.

- Use of kinase inhibitors: Kinase inhibitors show promise given their ability to inhibit cytokine production and T-cell proliferation. A number of kinase inhibitors, including inhibitors of BTK, JAK/STAT, and mTOR, have been evaluated in small clinical trials without definitive implementation (reviewed in Leclercq et al. 2022).

A complementary, alternative approach to direct pharmacologic targeting of cytokines or their mechanisms of production is to mask the therapeutic target of the TCE bispecific antibody to reduce T-cell activation with the first infusion. Obinutuzumab's ability to bind CD20 thus makes it a candidate for evaluation as a CRS prophylaxis agent for TCE bispecific antibodies that target CD20 and CD3.

3.1.2. About the product

Obinutuzumab is a glycoengineered, humanized, type II anti-CD20 monoclonal antibody (mAb) of the immunoglobulin (Ig) IgG1 subclass. Obinutuzumab recognizes a specific epitope of the CD20 molecule expressed on B-cells and was developed to enhance both cell-mediated killing of tumor cells and direct cell death.

Gazyvaro is currently approved for the following indications:

- Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated Chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy
- Gazyvaro in combination with chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced Follicular Lymphoma (FL).
- Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

3.1.3. General comments on compliance with GCP

Study NP30179, which is the single study submitted as a part of the glofitamab MAA and cross referred to in this submission, was conducted in accordance with the principles of Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and applicable local, state, and federal laws, as well as other applicable national legal requirements. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved this study.

The Roche Clinical Quality Assurance group or designee conducted audits at three investigator sites as well as three study specific audits.

No critical audit findings were observed. For all audit findings appropriate corrective and preventive actions were undertaken (see Update Interim CSR NP30179, Report 1114923, Section 3.10).

3.2. Non-clinical aspects

3.2.1. Introduction

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. To reduce the incidence and severity of cytokine-release syndrome (CRS) following glofitamab treatment, the effect of pre-treatment with a B-cell depleting agent such as obinutuzumab (anti-CD20 monoclonal antibody) prior to glofitamab treatment, in order to debulk the peripheral and tissue-resident B cells, has been investigated.

3.2.2. Pharmacology

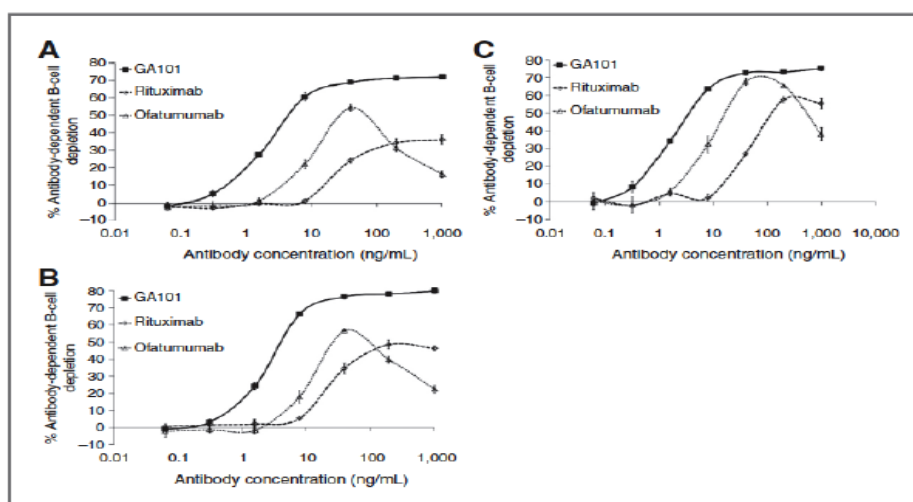
Primary pharmacodynamic studies

Obinutuzumab as pre-treatment to glofitamab ex vivo and in vivo

Obinutuzumab, as an anti CD20 pre-treatment to glofitamab, was chosen over e.g. rituximab due to a number of studies demonstrating superiority on certain parameters in ex vivo and in vivo studies.

Obinutuzumab was shown ex vivo to efficiently deplete CD19+ B cells in autologous B-cell depletion assays with whole blood from healthy donors (Reports 1025239, 1025330, 1027582, 1049394; assessment included in initial Gazyvaro EPAR). In comparison to rituximab and ofatumumab, obinutuzumab was more potent in terms of half-maximal effective concentration (EC₅₀) values and more efficacious in terms of absolute B-cell depletion in whole blood from healthy donors (Reports 1025239, 1049394, Herter et al. 2013) (Figure 1). The MAH furthermore provided literature which supports a superior B-CLL cell depletion in whole blood (Rafiq et al. 2013; Patz et al. 2011; Laprevotte et al. 2013a; Laprevotte et al. 2013b), or shows that obinutuzumab treatment depleted B cells in whole blood from patients with CLL to a similar extent to rituximab, but at a much faster rate (Bologna et al. 2011).

Figure 1 Whole Blood B-cell Depletion Mediated by Obinutuzumab, Rituximab and Ofatumumab in Heparin-Treated Human Whole Blood Samples



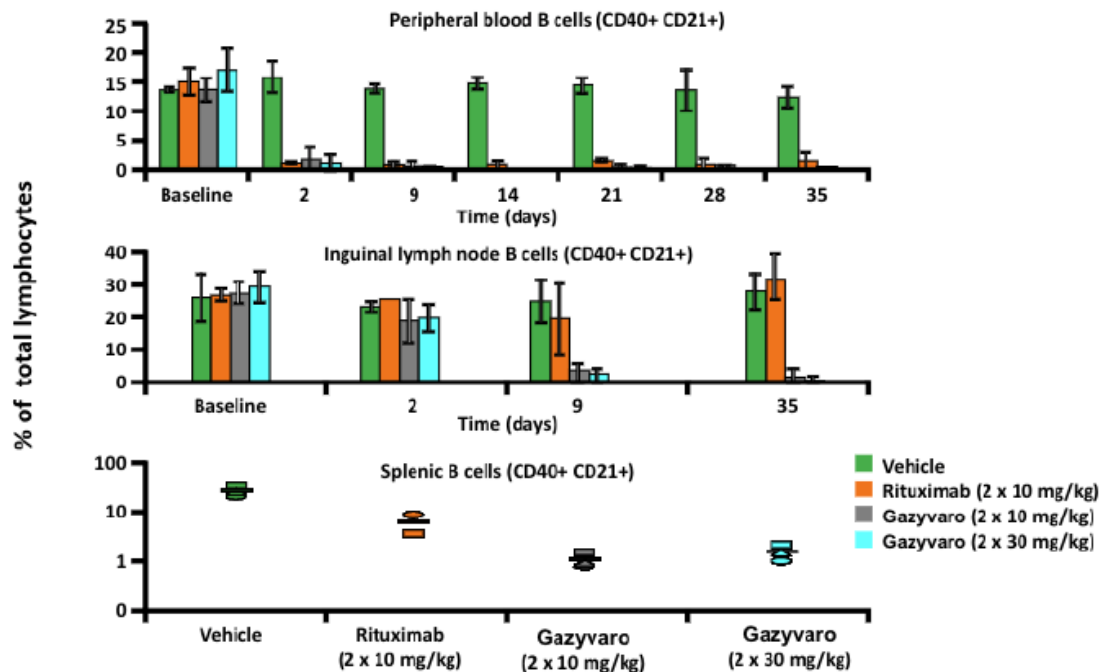
GA101=obinutuzumab.

Whole blood B-cell depletion mediated by obinutuzumab (black squares), rituximab (open diamonds) and ofatumumab (open triangles) in heparin-treated whole blood samples from healthy volunteers, representing each of the three FcγRIIIa genotypes: low-affinity receptor (158F/158F) donor (A), intermediate-affinity receptor (158F/158V) donor (B), and high-affinity receptor (158V/158V) donor (C). The average B-cell depletion and SDs were calculated from the triplicates of each experiment. The data from one of three independent experiments for each genotype are shown. Average values of triplicates corresponding to EC₅₀ values, percentage maximal killing and statistical analysis conducted for each donor and genotypes (3 donors/genotype, total of 9 experiments) are included in the Supplementary Table S1 of Herter et al 2013.

Source: [Herter et al. 2013](#).

In vivo, obinutuzumab (10 mg/kg and 30 mg/kg) induced superior depletion of B cells in the lymph nodes of cynomolgus monkeys compared to rituximab (10 mg/kg) following two IV doses administered on Days 0 and 7 (Mössner et al. 2010). In addition, there was a trend for better efficacy of obinutuzumab in depleting peripheral and spleen B cells at the early timepoints (Mössner et al. 2010; Report 1030198; Figure 2).

Figure 2 Superior B-cell Depletion in Cynomolgus Monkeys with Obinutuzumab Treatment Compared with Rituximab



Source: Modified from Mössner et al. 2010.

In another study, the efficacy of obinutuzumab at depleting B cells was compared with that of non-glycoengineered obinutuzumab and rituximab at a dose of 30 mg/kg following two IV doses administered on Days 0 and 7. The results demonstrated that obinutuzumab and non-glycoengineered obinutuzumab possess a greater capacity and durability for depleting B cells from both peripheral blood and lymph nodes of cynomolgus monkeys compared to rituximab (Reports 1030198, 1030199). These data indicate that the superior activity of obinutuzumab is not only due to the glycoengineering, but also due to the direct Type II CD20 antibody-related mechanisms.

An additional in vivo study in human CD20-expressing transgenic mice demonstrated superior depth of B-cell depletion in lymph nodes and spleen from obinutuzumab compared to rituximab and the murine anti-human CD20 antibody 2H7 (Report 1030200). Furthermore, these studies show the ability of obinutuzumab to target and deplete the marginal zone B-cell subsets at least 7 days after single-dose administration (Report 1053638).

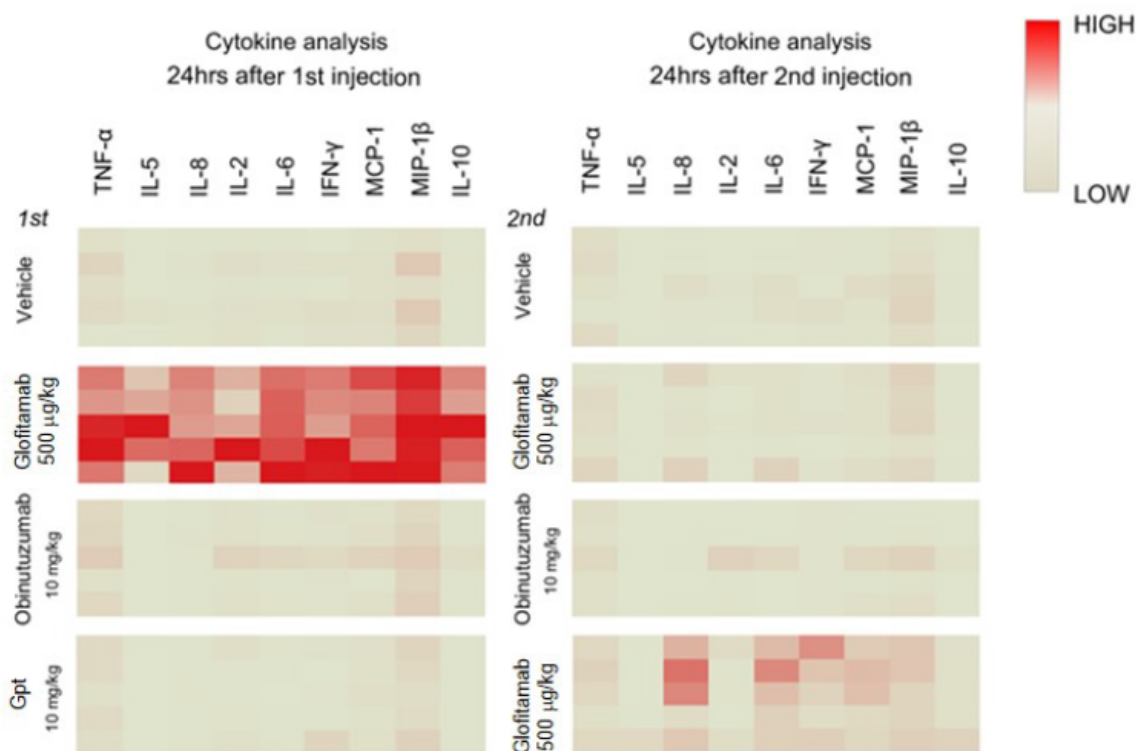
In conclusion, though no significant difference is observed between obinutuzumab and rituximab in depleting B cells in the peripheral blood in cynomolgus monkeys according to Moessner et al, 2010, obinutuzumab was 10-25 times more potent and 1.5-2.5 times more effective [$p < 0.001$] than rituximab in depleting B cells in lymph nodes, spleen and human whole blood in the same study. Additional literature

supports this observation, and a faster depletion of B cells and greater direct cytotoxicity in CLL cells of obinutuzumab compared with rituximab is also reported.

Obinutuzumab alleviates CRS effects of glofitamab in HSC-NOG mice and cynomolgus monkeys

A single administration of obinutuzumab (10 mg/kg) 7 days prior to glofitamab treatment (500 µg/kg) in tumor-bearing HSC-NOG mice, was shown to strongly reduce glofitamab-mediated cytokine release in the peripheral blood (Figure 3) and thus to prevent transient glofitamab-mediated (cytokine-dependent) T-cell decrease in the peripheral blood. Importantly, obinutuzumab pre-treatment (Gpt) was shown not to interfere with glofitamab-mediated B-cell depletion and long-term anti-tumor activity (Report 1067021).

Figure 3 Cytokines Released in the Peripheral Blood of Tumor-Bearing HSC-NSG Mice upon Glofitamab and Gpt + Glofitamab Treatments



Gpt=obinutuzumab (Gazyvaro) pretreatment; HSC-NSG=human hematopoietic stem cell-engrafted NOD.Cg Prkdc^{scid}Il2rg^{tm1Wjl}/SzJ mice; IFN-γ = interferon-gamma; IL = interleukin; MCP-1 = monocyte chemoattractant protein-1; MIP-1β = macrophage inflammatory protein 1 beta; TNF-α = tumor necrosis factor alpha.

Note: Cytokine upregulation is indicated by the increase in the intensity of the signal.

Tumor model: WSU-DLCL2 (human DLBCL tumor cell line model) injected subcutaneously.

Source: [Bacac et al 2018](#).

The capacity of Gpt and step-up dosing regimen to mitigate the cytokine release in tumor-bearing NSG mice (WSU-DLCL2, a DLBCL tumor cell line model injected subcutaneously) was compared. Gpt was found to overall provide a more efficacious mitigation approach compared with the step-up dosing regimen

(consisting of 15, 50, or 150 µg/kg in the first cycle followed by 500 µg/kg glofitamab in the second cycle) and increased the safety of glofitamab administration (Report 1071691; Bacac et al. 2018).

A mechanistic study (non-GLP) in male cynomolgus monkeys was performed to investigate the effects of Gpt on the response to glofitamab (Report 1066284). Following dosing with glofitamab (only) at 100 µg/kg (identified as the glofitamab monotherapy maximum tolerated dose (MTD) in a previous MTD/dose range-finding study (Report 1063381)), the glofitamab-related clinical signs were decreased activity, hunched posture, pale skin, and evidence of vomiting, which were considered adverse. Gpt ameliorated these clinical signs and allowed for the administration of higher doses of glofitamab. When a single dose of obinutuzumab 50 mg/kg pretreatment was given four days prior to glofitamab doses that were 3 or 10 times higher than the MTD for glofitamab without Gpt, less severe glofitamab-related clinical signs were observed compared to animals dosed with lower doses of glofitamab alone.

The administration of Gpt prior to glofitamab resulted in increased B-cell depletion, as well as attenuation of cytokine release and lymphocyte activation, as demonstrated by reductions in activation marker upregulation and reductions in the margination of lymphocyte and monocyte populations after glofitamab with Gpt administration, relative to changes present for animals that were treated with glofitamab alone. Thus, dosing with Gpt allowed the administration of glofitamab at doses higher than previously tolerated.

Assessor's Comment

A single administration of obinutuzumab (10 mg/kg) 7 days prior to glofitamab treatment in tumor-bearing HSC-NOG mice was shown to reduce glofitamab-mediated cytokine release in the peripheral blood thus preventing glofitamab-mediated (cytokine-dependent) T-cell decrease in the peripheral blood. In male cynomolgus monkeys, pre-treatment 4 days prior to glofitamab treatment was shown to ameliorate glofitamab-induced clinical signs and allowed for the administration of glofitamab at doses higher than previously tolerated.

The MAH argues that obinutuzumab used as pre-treatment 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. This has not been demonstrated in non-clinical studies. A clinical OC is raised on this issue (see discussion for further details). Step-up dosing was investigated as an alternative to pre-treatment. While pre-treatment showed superior effects on minimizing cytokine release, the long-term anti-tumour effect was comparable between the groups receiving pre-treatment and step-up dosing.

In conclusion, the MAH's decision to use obinutuzumab over rituximab for B-cell debulking and mitigation of glofitamab-mediated CRS is supported as well as the conclusion that obinutuzumab alleviates CRS-related symptoms in naïve animal models. There are however some concerns regarding the clinical applicability of the data, see the discussion for further reflection on the translatability of the non-clinical results to the clinical treatment situation.

3.2.3. Discussion on non-clinical aspects

It should be noted that all patients in the NP30179 study have been treated with anti-CD20 therapy prior to obinutuzumab pre-treatment. Given that glofitamab is intended for treatment in 3L+ DLBCL, all patients will have been previously exposed to anti-CD20 treatment. A large proportion of trial patients (44%) were treated with glofitamab within 3 months of last anti-CD20 therapy and an even greater proportion were B-cell depleted (73.2% of the overall safety population) before treatment with obinutuzumab, suggesting residual functional effects of prior anti-CD20 therapy. As such, the comparison between rituximab and obinutuzumab given above does not completely reflect the clinical context in which glofitamab (and obinutuzumab pre-treatment) is intended and hence limits the ability to infer superiority of obinutuzumab over rituximab in the intended setting. These reflections have also been included in section 5.3 in the

SmPC. An OC has been raised in the clinical efficacy part of the assessment for the MAH to discuss the discrepancy between the non-clinical and clinical treatment context and how this will affect the translatability to clinical relevance. While not demonstrated in non-clinical studies, the Applicant states that a single dose of obinutuzumab will not have a pharmacological anti-lymphoma effect when given as pre-treatment to glofitamab. The Applicant refers to investigations in the clinical study (Study NP30179) which according to the Applicant demonstrates that a single dose of obinutuzumab in conjunction with a low non-efficacious dose of glofitamab did not show any relevant anti-tumor activity. This is however not accepted to be conclusively shown.

3.2.4. Conclusion on the non-clinical aspects

The extension of indication to use obinutuzumab as pre-treatment to glofitamab to alleviate symptoms of CRS seems to be supported from a non-clinical perspective. The translatability of the non-clinical data to the clinical situation, where previous anti-CD20 treatment has already been administered in 1st or 2nd line treatment before glofitamab, should however be taken into account in the benefit-risk assessment and the clinical issue raised in the LoQ should be resolved before market authorisation can be recommended.

3.3. Clinical aspects

3.3.1. Introduction

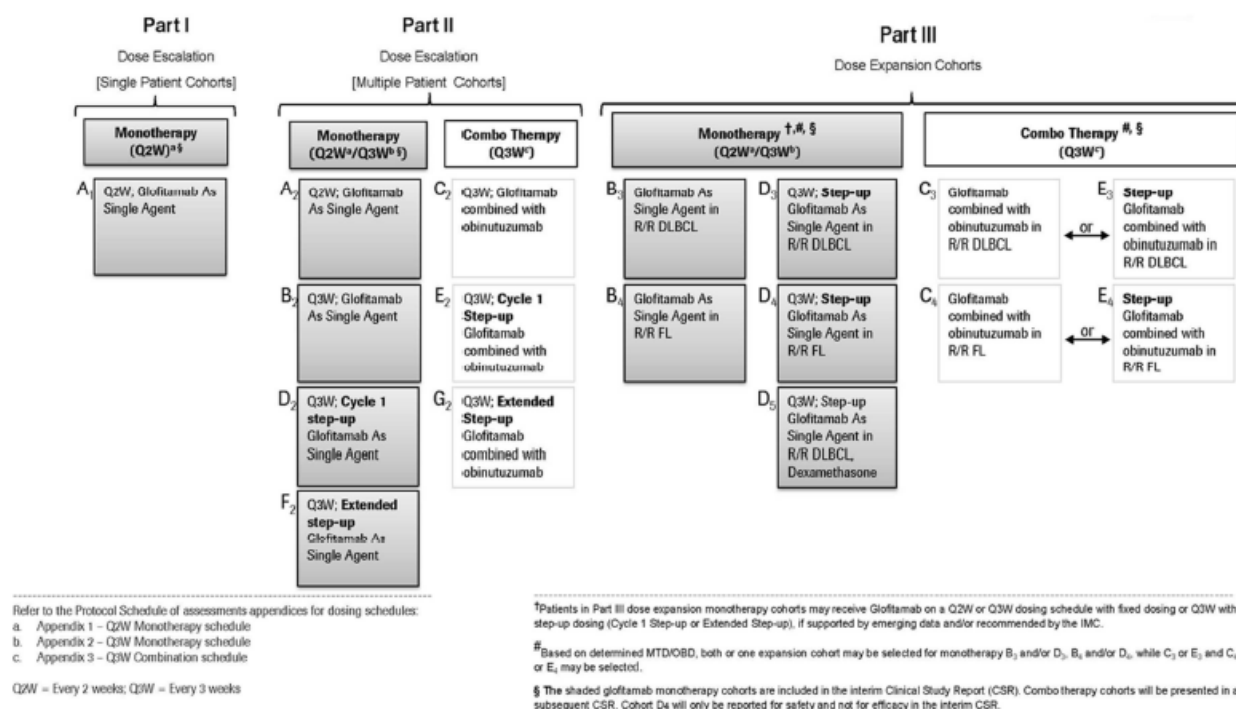
GCP

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

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

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 (Gazyvaro®, Gazyva®: Gpt) 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]). The study design is shown in Figure 5 and Table 7. The glofitamab monotherapy dosing cohorts reported in this document are shaded grey in the study design diagram.

Figure 5 Overview of the Design of Study NP30179 for Glofitamab as Monotherapy in Patients with R/R B-Cell NHL



DLBCL=diffuse large B cell lymphoma; FL=follicular lymphoma; Q2W=every 2 weeks; Q3W=every 3 weeks; R/R=relapsed or refractory.

Table 7 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 (PK cut off 6 July 2021, clinical cutoff date: 14 September 2021)	Open-label, multicenter, Phase I/II, dose-escalation and expansion study	Patients with R/R B-cell NHL <u>Planned:</u> Up to 300 patients during dose escalation (Part I-II), approx. 560 patients across expansion cohorts (Part III) <u>Enrolled:</u> 458 patients treated in Parts I-III (Part I and II: 222 patients; Part III: 236 patients)	<u>Part I and II: Dose escalation in R/R NHL patients who received 1 prior line of therapy</u> Fixed dosing: Glofitamab 0.005 mg – 25 mg IV, Q2W or Q3W. Step-up-dosing: Glofitamab 2.5/10/16 ^a mg, 2.5/10/30 ^b mg, 0.5/2.5/10/30 ^c mg IV, Q3W. <u>Part III: Dose expansion cohorts in patients who received ≥2 prior lines of therapy</u> Fixed dosing: Glofitamab 10/16mg IV, Q3W • R/R DLBCL • R/R FL Planned registrational dose: Step-up-dosing: Glofitamab 2.5/10/30 mg IV, Q3W. • R/R DLBCL • R/R FL

DLBCL=diffuse large B-cell lymphoma; Fixed dosing = a fixed dose of glofitamab administered on Day 1 in each cycle (C) from C1 onward; FL=follicular lymphoma; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory; PK=pharmacokinetic; Q2W=every 2 weeks; Q3W=every 3 weeks; IV=intravenous.

^a 2.5/10/16 mg Q3W : Glofitamab step-up dosing: 2.5 mg administered on Day 8 and 10 mg administered on Day 15 at Cycle 1, followed by 16 mg on Day 1 at Cycles 2-12 (21-day cycles [every 3 weeks, Q3W])

^b 2.5/10/30 mg Q3W : Glofitamab step-up dosing: 2.5 mg administered on Day 8 and 10 mg administered on Day 15 at Cycle 1, followed by 30 mg on Day 1 at Cycles 2-12 (21-day cycles [every 3 weeks, Q3W])

^c 0.5/2.5/10/30 mg Q3W : glofitamab extended step-up dosing (0.5 mg administered on Day 8, 2.5 mg administered on Day 15 at Cycle 1, followed by 10 mg on Day 1 at Cycle 2 followed by 30 mg on Day 1 at Cycles 3-12 [every 3 weeks, Q3W])

3.3.2. Pharmacokinetics

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

Population PK analyses

The aim of this investigation was to assess whether a second dose of obinutuzumab prior to the first dose of glofitamab could further reduce the occurrence and severity of CRS.

R version 4.0.5 was used for data processing, data visualization and reporting, supported by a range of additional packages. PK/PD model fitting and Bayesian feedback were performed using the non-linear mixed effect modelling software NONMEM, version 7.4.3. Obinutuzumab models were fitted using importance sampling assisted by mode a posteriori (IMPMAP), whereas glofitamab models were fitted using the first-order conditional estimation method with interaction (FOCEI).

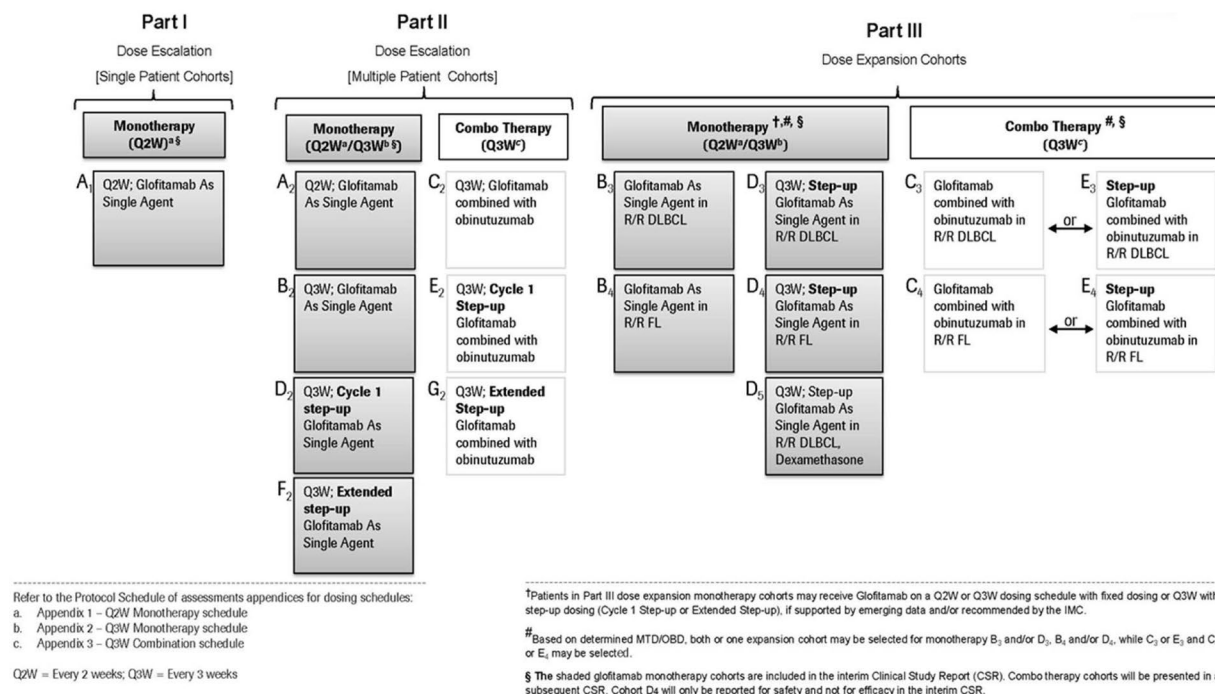
In the population PK analysis, a previously-published model (Gibiansky et al. 2014) for obinutuzumab population PK was used as the starting point to estimate the individual PK parameters and to derive the individual predicted obinutuzumab concentrations at glofitamab observation times in order matched pairs for the calculation of receptor occupancy. To improve the quality of the population PK model predictive performance with the present data set, the covariate effect coefficients and interindividual variability parameters were re-estimated using the NP30179 obinutuzumab data (while keeping the model's structural parameters fixed and parameter-covariate relationships).

Pre-treatment obinutuzumab (Gpt) was administered 7 days before the first dose of glofitamab (Cycle 1, Day 1 / C1D1) in the monotherapy and combination therapy cohorts and step-up cohorts. A double pre-treatment with obinutuzumab (DGpt) prior to first dose of glofitamab was tested in some patients in Part II. Two dosing alternatives for DGpt were available:

- Administration of two doses of Gpt 7 days before the first dose of glofitamab (2 x 1000 mg on Cycle 1 Day -7)
- Administration of two doses of Gpt, first Gpt dose (1000 mg) on Cycle 1 Day -7 followed by a second dose of Gpt (1000 mg) on Cycle 1 Day -1

An increment-based escalation was utilized in Part I (single patient cohorts) with dosing initiated at 5 µg (flat dose). Increments were 3-fold until a dose of 405 µg was reached, at which time the increment was planned to be changed to 2-fold. Thus, the 5 µg starting dose was to be followed by doses of 15 µg, 45 µg, 135 µg, 405 µg and 810 µg. The study design was to be switched to Part II (multiple patient cohorts) when either a flat dose of 810 µg was reached or a glofitamab-related Grade >2 adverse event (or DLT) occurred, whichever came first. An overview of the study design is provided in Figure 1.

Figure 1 Overall Design Schematic for Study NP30179.

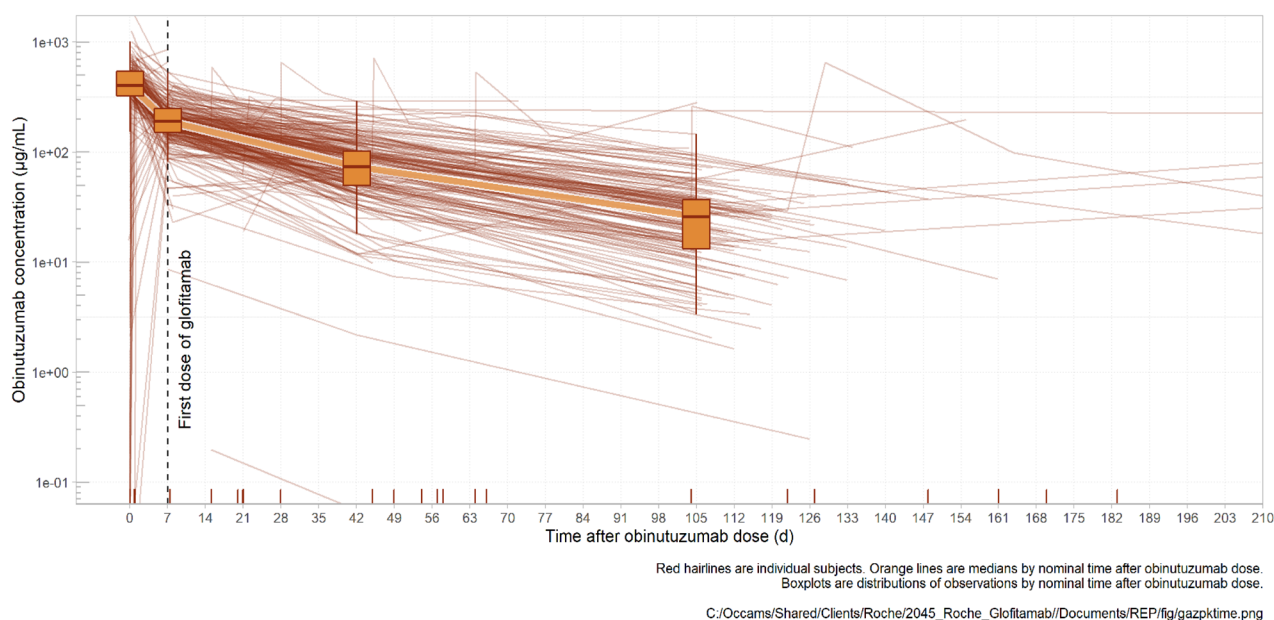


DLBCL=diffuse large B cell lymphoma; FL=follicular lymphoma; Q2W=every 2 weeks; Q3W=every 3 weeks; R/R=relapsed or refractory.

The available obinutuzumab data represented 425 unique patients, and comprised 1819 rows, including 1371 serum PK observations and 448 dosing records. Of the observations, 373 (27.2%) were flagged as below the limit of quantification (BLQ) excluded in the unmodified dataset. Of these, however, only 5 (1.34%) of the excluded BLQ observations were recorded after the first dose of obinutuzumab (the remainder were collected pre-dose). A total of 971 evaluable obinutuzumab concentration measurements were available from 406 patients.

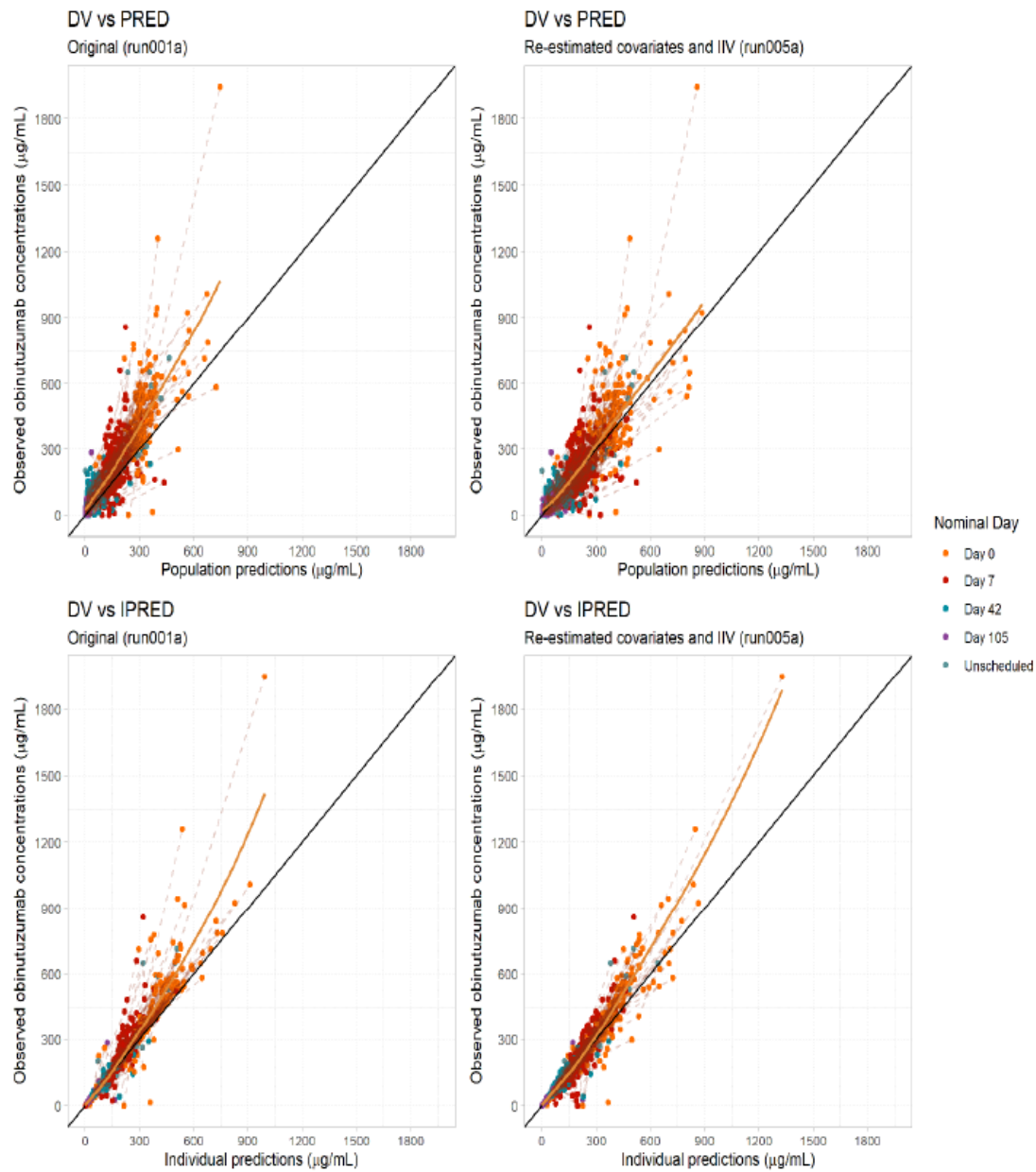
Figure 6 provides a summary of observed concentration-time profiles.

Figure 6 Observed Obinutuzumab Concentration Over Time.



The original obinutuzumab model, after modification to be compatible with the Study NP30179 obinutuzumab data (run001a), produced unsatisfactory predicted concentration-time profiles in comparison with the observations (detected primarily using goodness-of-fit plots). In order to improve the model predictions to a level at which they would be suitable for use in calculating glofitamab receptor occupancy, the covariate effect coefficients and IIV parameters in the model were re-estimated based on the Study NP30179 data, while keeping the structural parameters fixed to their published values in order to minimize the chances of introducing bias owing to the sparseness of the current obinutuzumab data (run005a, and in order to ensure a stable fit, $\Delta\text{OFV} = -835.136$). Population and individual predictions plotted against observations are provided for both model variants in Figure 7. Plots comparing variability distributions are found in Figure 9. Comparisons of individual predictions by nominal study day, of particular relevance to calculation of glofitamab receptor occupancy, are provided in Figure 10. Parameter estimates for the original and adapted models appear in Table 4.

Figure 7 Observations Plotted Against Predictions for the Original And Adapted PK Models for Obinutuzumab.



Points connected by dashed lines are individual subjects. Solid black line is the line of identity. Orange lines are loess smooths.

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Figure 9 Random-Effects Distributions for the Original and Adapted PK Models for Obinutuzumab.

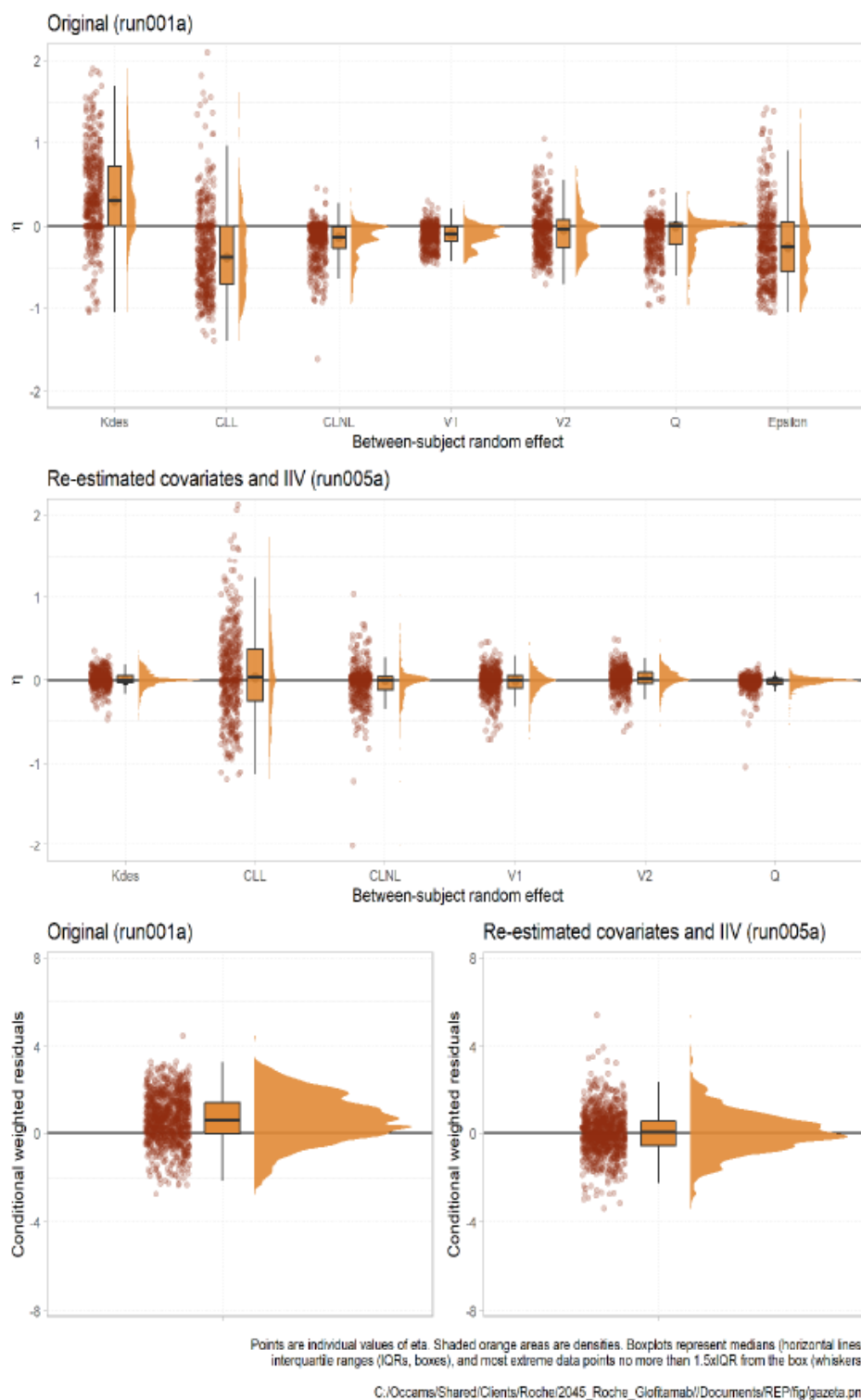


Figure 10 Individual Predictions by Nominal Day Using the Adapted Model for Obinutuzumab.

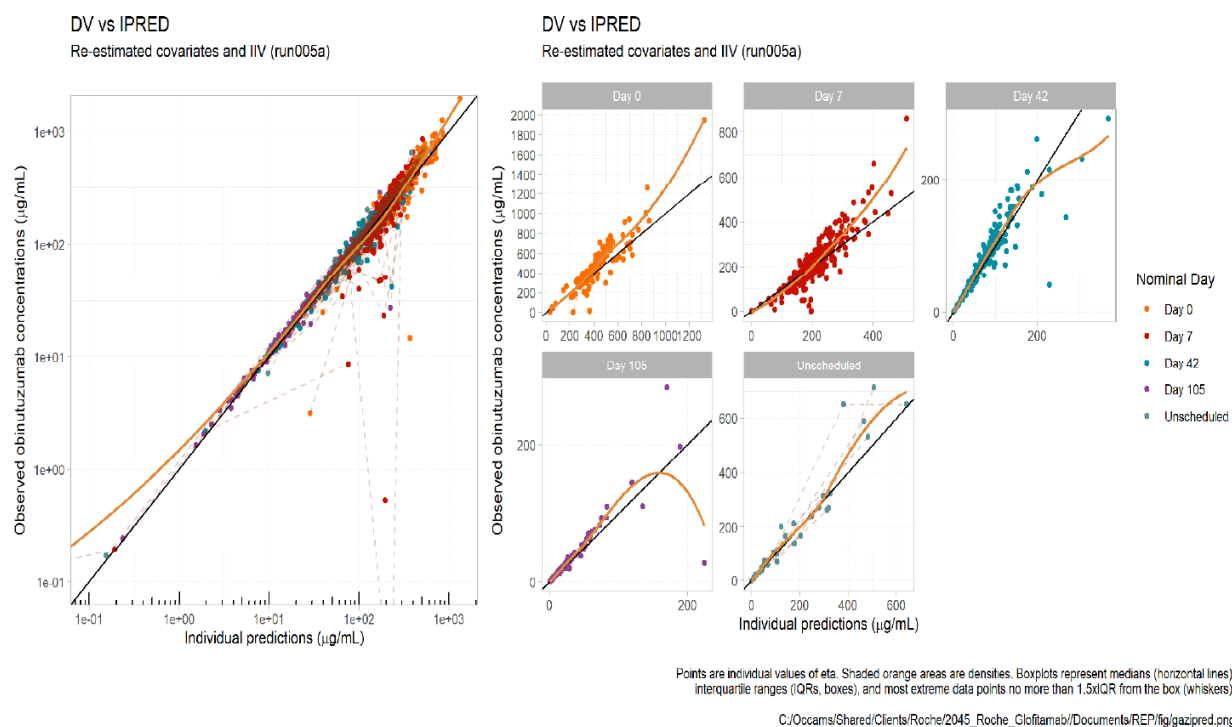


Table 4 Obinutuzumab Population PK Model Parameter Estimates for the Original and Adapted Models.

Parameter	Original (run 001a)	Re-estimated (run 005a)
OFV	9792.736	8957.600
Decay constant (/d)	0.0359 (Fixed)	0.0359 (Fixed)
Time-dependent CL (L/d)	0.231 (Fixed)	0.231 (Fixed)
Linear CL (L/d)	0.0828 (Fixed)	0.0828 (Fixed)
V1 (L)	2.76 (Fixed)	2.76 (Fixed)
V2 (L)	1.01 (Fixed)	1.01 (Fixed)
Q (L/d)	1.29 (Fixed)	1.29 (Fixed)
Weight on CL	0.615 (Fixed)	0.917 (15.4)
Weight on V1	0.383 (Fixed)	0.880 (15.7)
Sex on time-dependent CL	1.49 (Fixed)	0.845 (8.91)
Sex on linear CL	1.22 (Fixed)	0.768 (7.81)
Sex on V1	1.18 (Fixed)	0.855 (3.59)
DLBCL and BCL on decay coefficient	2.08 (Fixed)	1.44 (25.1)
DLBCL and BCL on clearance	0.834 (Fixed)	0.708 (7.27)
Tumor size on decay coefficient	1.75 (Fixed)	5.04 (32.9)
MCL on clearance	2.65 (Fixed)	1.08 (10.9)
IIV on decay coefficient (variance)	1.62 (Fixed)	0.176 (162)
IIV on time-dependent CL (variance)	0.907 (Fixed)	0.584 (23.3)
IIV on linear CL (variance)	0.159 (Fixed)	0.195 (56.1)
IIV on V1 (variance)	0.0340 (Fixed)	0.0804 (21.3)
IIV on V2 (variance)	0.361 (Fixed)	0.198 (20.1)
IIV on Q (variance)	0.890 (Fixed)	0.472 (80.8)
IIV on residual error (variance)	0.274 (Fixed)	0.00 (Fixed)
Additive residual error (variance)	0.0318 (Fixed)	0.0742 (11.7)
Proportional residual error (variance)	0.0271 (Fixed)	0.000762 (70.9)

OFV=objective function value; CL=clearance; V1=volume of distribution; DLBCL=diffuse large B-cell lymphoma; BCL=B-cell lymphoma; MCL=mantle cell lymphoma.

Assessor's comment

Population PK analysis of obinutuzumab comprised of 425 unique patients with 1371 PK samples. 373 were BLQ and of these only 5 were recorded after the first dose of obinutuzumab. A total of 971 evaluable obinutuzumab concentration measurements were available from 406 patients. As the majority of BLQ samples were pre-dose, and post-dose BLQ PK samples only amounted to 1.34%, exclusion of BLQ PK samples is considered acceptable. An explanation for the exclusion of the remaining PK samples was not found/provided. A tabulated summary of excluded observations in the population PK analysis for obinutuzumab should be provided **(OC)**.

A previously published model for the population PK of obinutuzumab was adapted to provide predicted obinutuzumab concentrations at the available glofitamab observation times to facilitate calculation of glofitamab receptor occupancy, necessary for subsequent ER analyses. Study NP30179 data was used to re-estimate covariate effect coefficients and IIV parameters in the model. Structural model parameters were fixed to their published values and not re-estimated due to the sparseness of the obinutuzumab data, which could potentially introduce model bias. Methods are considered acceptable.

GOF-plots (e.g. Figure 7, 9 and 10) suggested no major trends indicative of model-misspecifications. Covariate effects were estimated with adequate precision (%RSE range: 3.59%-32.9%). However,

covariate effects were in some cases significantly different in the re-estimated model when compared to the original model, e.g. tumour size on decay coefficient. IIV on decay constant, IIV on linear CL, IIV on Q and the proportional residual error were estimated with poor precision. No pcVPCs were found/provided, shrinkage was not presented and the model was not validated by bootstrap analysis. To complete the model evaluation, these diagnostics should be provided **(OC)**.

Exposure-safety modelling

The ER relationships for safety were assessed on 399 PK-evaluable patients with R/R NHL receiving IV administration of glofitamab from Study NP30179 with data from all cohorts where glofitamab was administered as monotherapy.

Average receptor occupancy values over the first 24 hours after glofitamab dosing (AvgRO%D1) and over the first two cycles of glofitamab treatment (AvgRO%C1+C2) were calculated using individual predicted obinutuzumab concentrations and individual predicted glofitamab concentrations based on the final models for these two drugs. The simulation tool RxODE in R was used to simulate complete glofitamab and obinutuzumab concentration-time profiles for every patient, using individualized dosing information, over the period of interest (24 hours after the first dose, or the first two cycles of glofitamab treatment). Predictions were calculated at intervals of 30 minutes, and matched to ensure concentrations for both drugs were available at every time point. The metrics of interest were obtained from these individual simulated profiles. Individually-predicted percentage receptor occupancy (RO%) was calculated at each time point in each individual using the following mass action equation:

$$RO\%_{i,t} = 100 \cdot \frac{[GLO_{i,t}]}{[GLO_{i,t}] + kd_{GLO} \cdot \left(1 + \frac{[OBIN_{i,t}]}{kd_{OBIN}}\right)}$$

where $RO\%_{i,t}$ is receptor occupancy for glofitamab in individual i at time t , $[GLO_{i,t}]$ is the predicted concentration of glofitamab in individual i at time t in nM, kd_{GLO} is the dissociation constant for glofitamab (4 nM), $[OBIN_{i,t}]$ is the predicted concentration of obinutuzumab in individual i at time t in nM, and kd_{OBIN} is the dissociation constant for obinutuzumab (4 nM). The molar mass of glofitamab used in conversions to molar concentration was 194341.70 Da, and for obinutuzumab, it was 146064.72 Da.

Most CRS events of Grade ≥ 2 took place within the first day of treatment. A strong exposure-response signal was seen in the highest exposure quartiles when comparing CRS (Grade ≥ 2) incidence by quartiles of AvgRO%D1, AUCD1 and CmaxD1 (Figure 81 and Figure 82).

Figure 81 Kaplan-Meier plots of CRS (Grade ≥2) Incidence by Quartiles of Exposure.

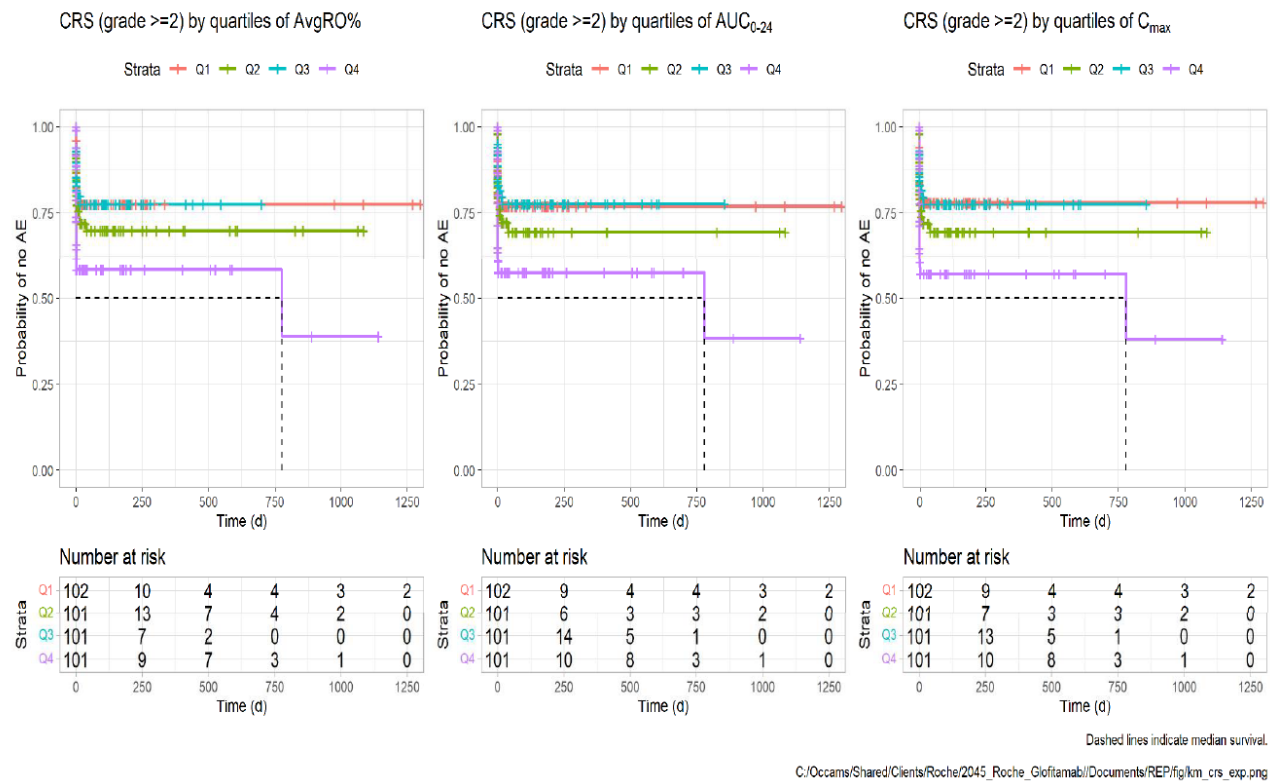
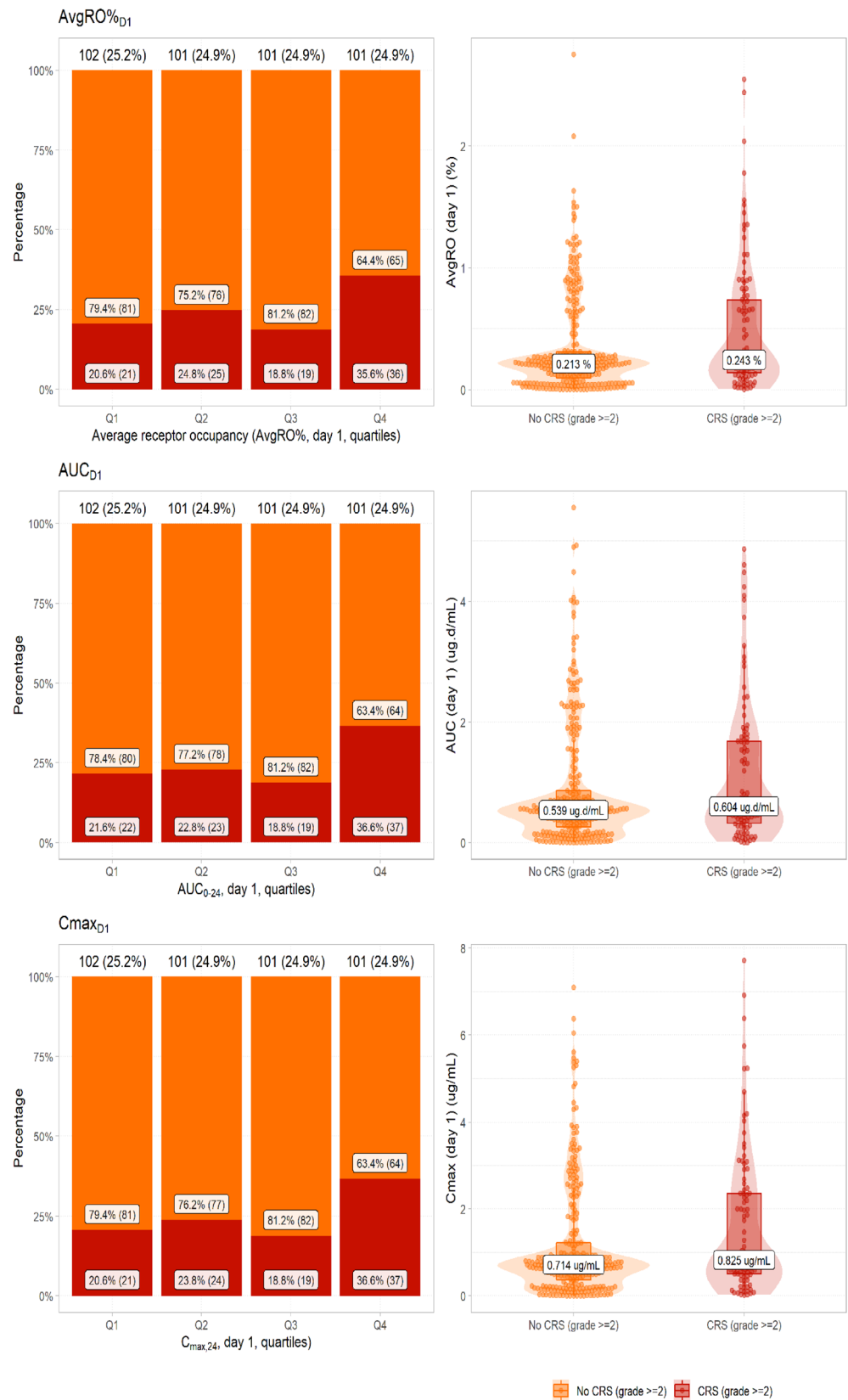


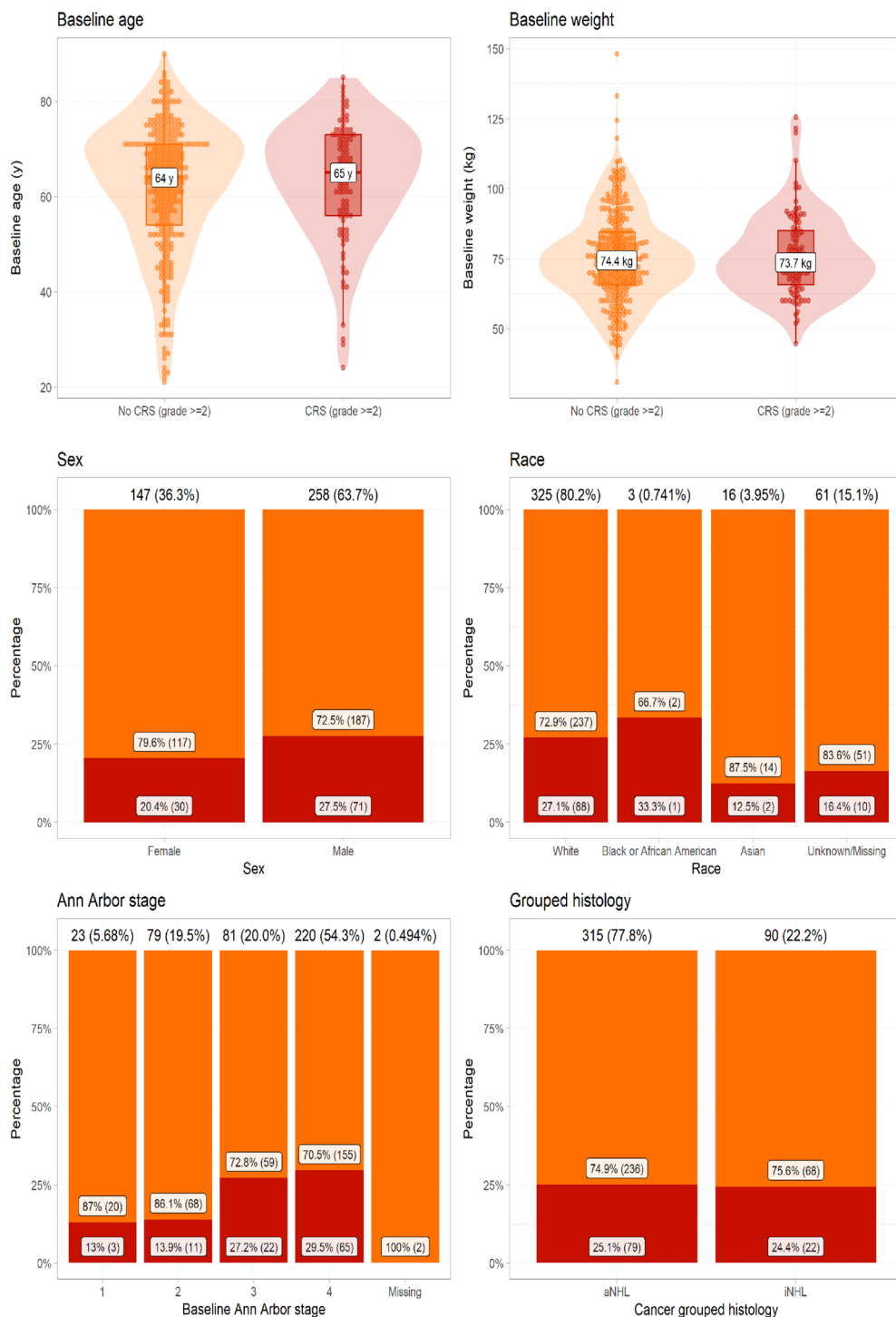
Figure 82 Plots of CRS (Grade ≥2) incidence by Quartiles of Exposure.



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From graphical exploration, trends in CRS (Grade ≥ 2) in other covariates were seen for male sex, Ann Arbor stage >2 , increasing baseline SPD and decreasing baseline obinutuzumab concentration; a trend towards decreasing incidence was seen in patients with trFL (Figure 168 and 169).

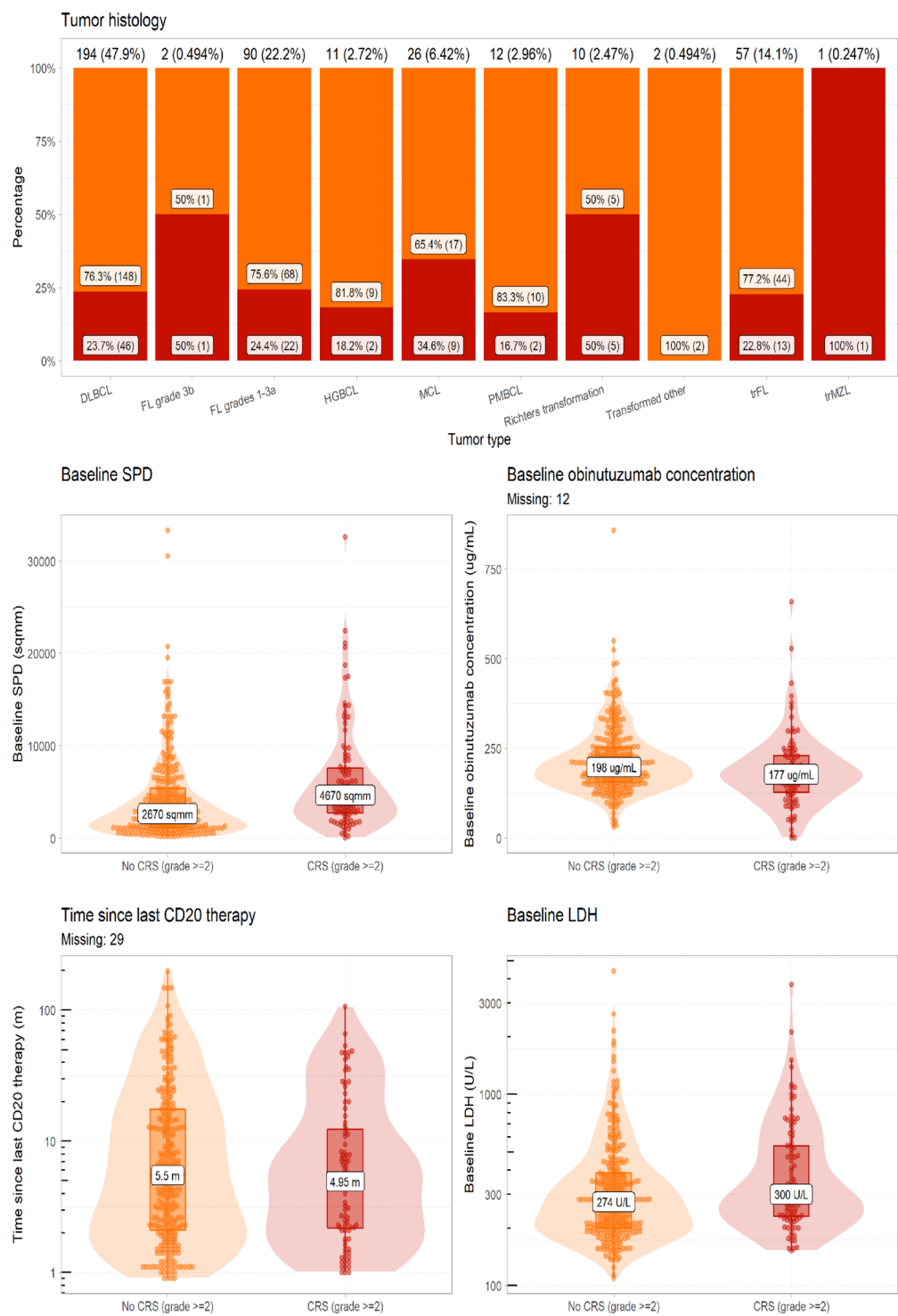
Figure 168 Plots of CRS (Grade ≥ 2) Incidence by Covariates of Interest (1).



Numbers are counts (percentages).

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Figure 169 Plots of CRS (Grade ≥2) Incidence by Covariates of Interest (2).

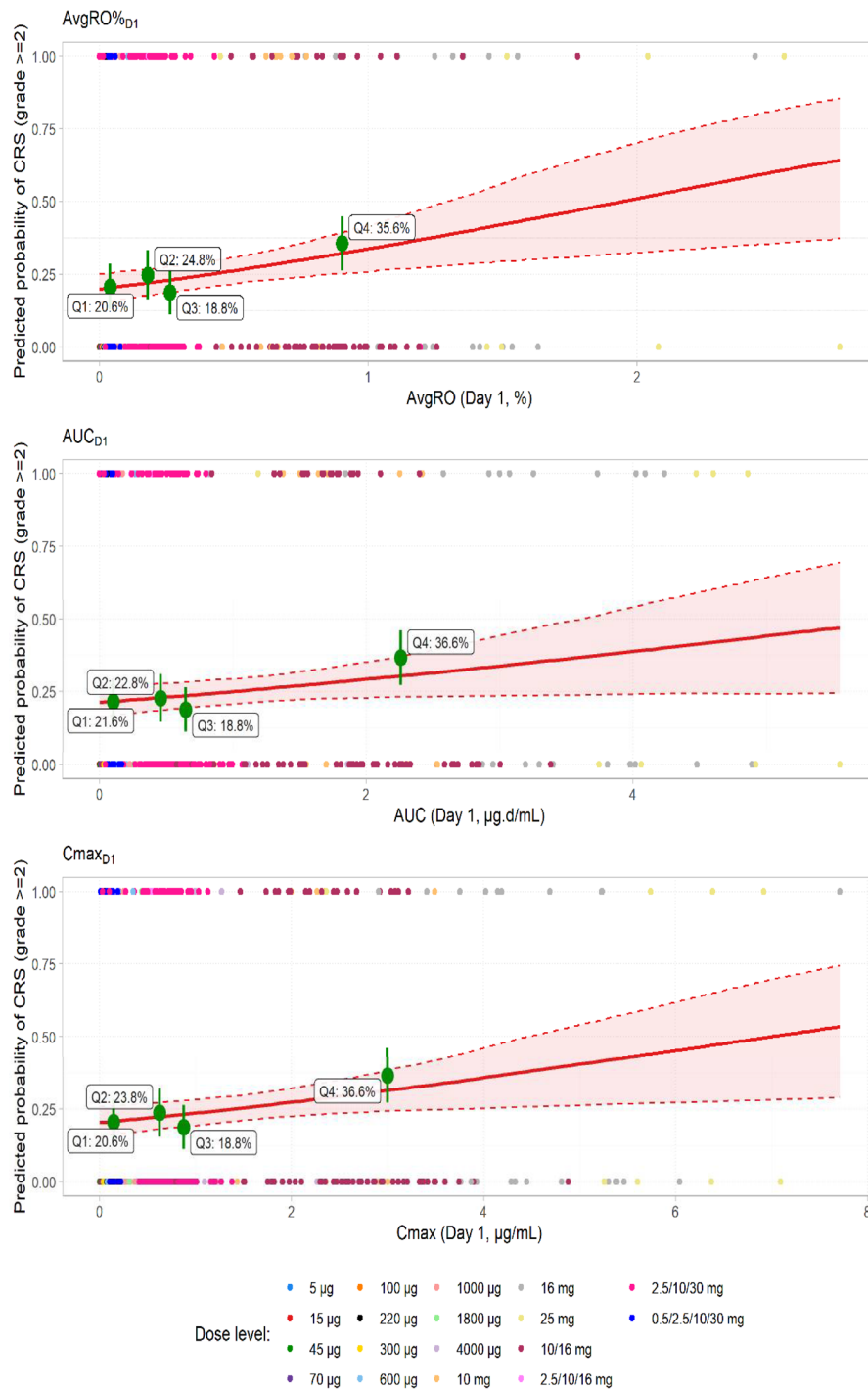


Numbers are counts (percentages).

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AvgROD1, AUCD1 and CmaxD1 were tested as univariable glofitamab exposure predictors of CRS (Grade ≥ 2). Clear exposure-response relationships were seen for all three metrics - in AvgRO%D1, ($p=0.00380$), in AUCD1 ($p=0.0426$) and in CmaxD1 ($p=0.0119$). Figure 83 provides a graphical comparison of the models.

Figure 83 Comparison of Univariable Exposure Models for CRS (Grade ≥ 2) by Glofitamab Exposure in the Safety Population.



Bootstrapped model predictions ($n=1000$). Red line is probability of CRS (grade ≥ 2) by unit exposure. Labelled green points and error bars are observed incidence by exposure quartile and associated 95% CI. Shaded area represents 95% prediction interval. Blue points are observations.

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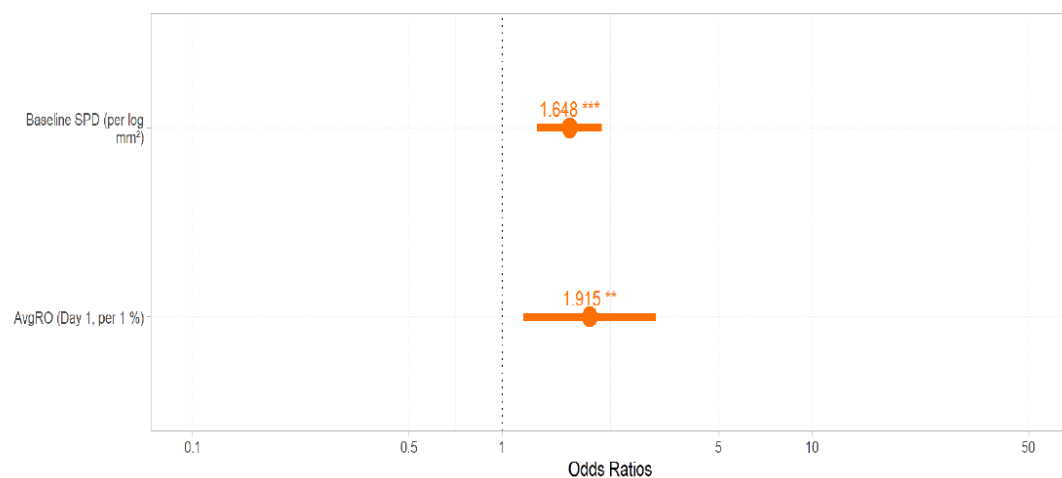
A full model was constructed using AvgRO%D1 and all covariate predictors of interest. Stepwise model reduction was then performed. The final reduced model for CRS (Grade ≥ 2) in the safety population is described in Table 45 and Figure 85 and 86. Increasing AvgRO%D1 (although it very narrowly did not meet the inclusion criterion of $p < 0.01$, it was included nonetheless on the basis of pre-existing knowledge and scientific judgment) and increasing baseline SPD were retained in the reduced model.

Table 45 Parameter Estimates and Odds Ratios for the Final Reduced Model for CRS (Grade ≥ 2) in the Safety Population.

Parameter	Estimate			Odds ratio		
	Estimate	Lower 95%	Upper 95%	OR	Lower 95%	Upper 95%
Intercept	-5.41	-7.47	-3.48			
Baseline SPD (per log mm ²)	0.499	0.265	0.745	1.65	1.30	2.11
AvgRO (Day 1, per 1 %)	0.650	0.156	1.15	1.92	1.17	3.14

AvgRO%D1=average receptor occupancy for 24h after the first glofitamab dose; CRS=cytokine release syndrome; OR=odds ratio.

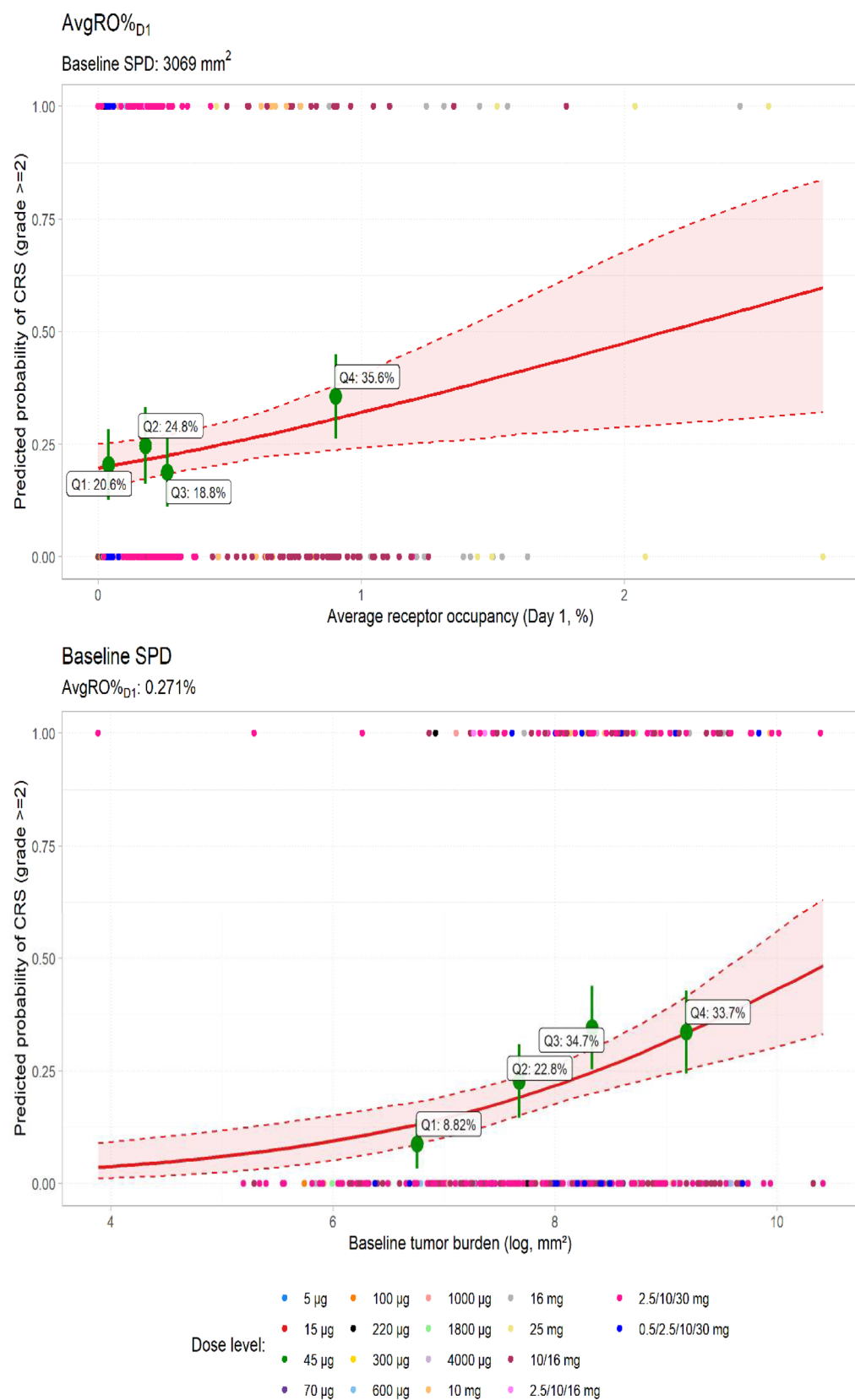
Figure 85 Comparison of Odds Ratios for Covariates in the Final Reduced Model for CRS (Grade ≥ 2) in the Safety Population.



**** p < 0.001, *** p < 0.01, ** p < 0.05.
Labels are odds ratios. Bars are 95% confidence intervals.

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Figure 86 Predictors of CRS (Grade ≥ 2) in the Final Reduced Model.

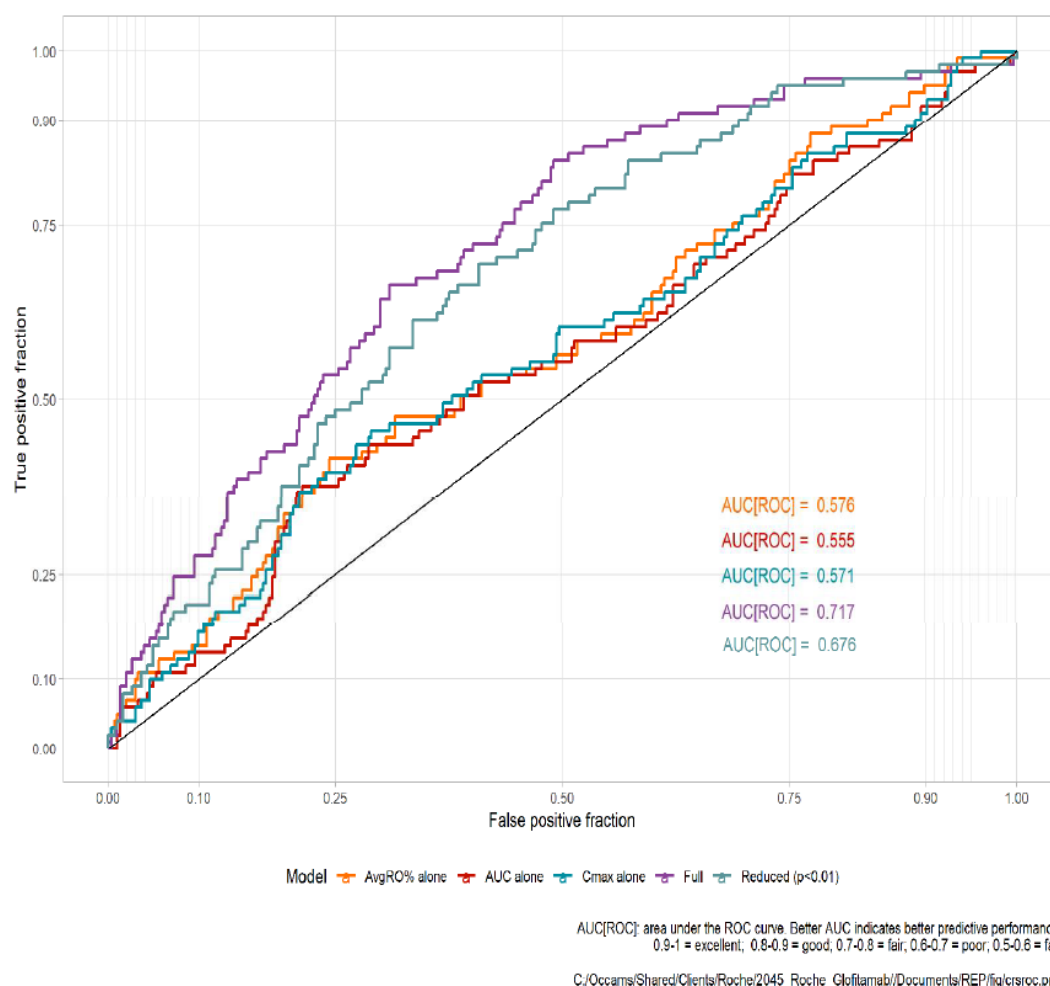


Bootstrapped model predictions (n=1000). Red line is probability of CRS (grade ≥ 2) by unit predictor. Labeled green points and error bars are observed incidence by predictor quartile and associated 95% CI. Shaded area represents 95% prediction interval. Blue points are observations.

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A comparison of the predictive power of the models evaluated appears in Figure 87. The univariable models all performed poorly as predictors of CRS (Grade ≥ 2), being classified as “fail” (ROC_{AUC} between 0.5 and 0.6). The full model was classified as “fair” (ROC_{AUC} between 0.7 and 0.8), whereas the final reduced model was classified as “poor” (ROC_{AUC} between 0.6 and 0.7). This implies that glofitamab exposure and baseline SPD, while playing a role in CRS incidence, were not the only or most important predictors - and that the covariates tested only explain some of the CRS (Grade ≥ 2) in this population.

Figure 87 Comparison of ROC Curves for the Models for CRS (Grade ≥ 2) in the Safety Population.



Assessor's comment

CRS occurred relatively frequently with Grade ≥ 2 incidence rates of 24.9% in the analysis population. In the majority of patients experiencing CRS (Grade ≥ 2), events were observed within the first days of glofitamab treatment. Graphical exploration indicated an exposure-response signal in the highest exposure quartiles when comparing CRS (Grade ≥ 2) to quartiles of AvgRO%_{D1}, AUC_{D1} and Cmax_{D1}. Logistic regression was applied to explore exposure-safety relationships for CRS (Grade ≥ 2). After stepwise model reduction, baseline SPD (tumour size) was retained as a highly statistically significant predictor of CRS (Grade ≥ 2). AvgRO%_{D1} was also retained as predictor of CRS (Grade ≥ 2) incidence even though it narrowly did not meet the retainment criteria (p-value: 0.0101>0.01). Evaluation of the final logistic regression model was based on ROC curves. The final reduced model was classified as poor (ROC_{AUC} between 0.6 and 0.7). The predictive performance of the logistic regression models on CRS (Grade ≥ 2) is questionable.

Absorption

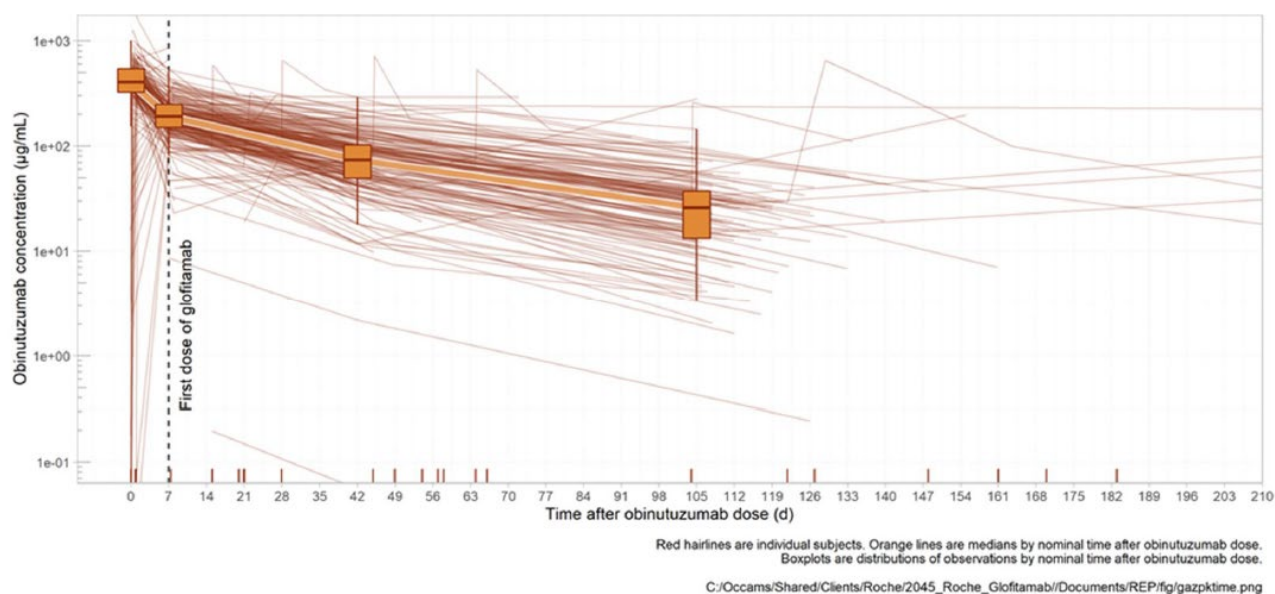
The proposed registrational dosing regimen is a single dose of obinutuzumab 1000 mg pre-treatment (Gpt) administered via IV infusion, on Cycle 1 Day 1, 7 days before initial dosing of glofitamab.

Consequently obinutuzumab was administered as a single dose 1000 mg 7 days prior to the first dose of glofitamab. Patients in Cohort D2 [Sub. 4] also received an additional 1000 mg dose of obinutuzumab 7 days prior to the first dose of glofitamab.

Observed obinutuzumab concentration over time are shown in Figure 7, summary concentration data are provided in Appendix 3.

The maximum mean obinutuzumab concentrations were achieved at the first sample timepoint (6 or 168 hours from first dose). In the cohorts with further PK sampling the mean concentrations decreased with measurable concentrations 2520 hours (105 days) after the first administration (Appendix 3). There was no observed trend for a difference in obinutuzumab concentrations across cohorts.

Figure 7 Observed Obinutuzumab Concentration Over Time



**Appendix 3 Summary of Serum Obinutuzumab Concentrations
Following Administration of a Single Dose IV in Study NP30179:
PK-Evaluable Patients**

		Nominal Time from First Dose (hr)			
		6	168	1008	2520
Cohort and Dose		Obinutuzumab Concentration (µg/ml)			
Part 1 Cohort A ₁ Q2W 0.005 mg	N		1		
	Geo Mean		224		
	Geo CV%				
Part 1 Cohort A ₁ Q2W 0.015 mg	N		1		
	Geo Mean		226		
	Geo CV%				
Part 1 Cohort A ₁ Q2W 0.045 mg	N		1		
	Geo Mean		181		
	Geo CV%				
Part 2 Cohort A ₂ Q2W 10 mg	N		3		
	Geo Mean		224		
	Geo CV%		26.9		
Part 2 Cohort A ₂ Q2W 0.015 mg	N		5		
	Geo Mean		235		
	Geo CV%		43.7		
Part 2 Cohort A ₂ Q2W 0.045 mg	N		3		
	Geo Mean		179		
	Geo CV%		55.5		
Part 2 Cohort A ₂ Q2W 0.07 mg	N		5		
	Geo Mean		327		
	Geo CV%		61.9		
Part 2 Cohort A ₂ Q2W 0.1 mg	N		6	1	1
	Geo Mean		186	57.1	10.6
	Geo CV%		25.7		
Part 2 Cohort A ₂ Q2W 0.22 mg	N		7		
	Geo Mean		302		
	Geo CV%		44.7		
Part 2 Cohort A ₂ Q2W 0.3 mg	N		6		
	Geo Mean		256		
	Geo CV%		33.0		

**Appendix 3 Summary of Serum Obinutuzumab Concentrations
Following Administration of a Single Dose IV in Study NP30179:
PK-Evaluable Patients (cont.)**

		Nominal Time from First Dose (hr)			
		6	168	1008	2520
Part 2 Cohort A ₂ Q2W 0.6 mg	N		12		
	Geo Mean		300		
	Geo CV%		24.9		
Part 2 Cohort A ₂ Q2W 1 mg	N		8		
	Geo Mean		309		
	Geo CV%		22.6		
Part 2 Cohort A ₂ Q2W 1.8 mg	N		9		
	Geo Mean		238		
	Geo CV%		29.7		
Part 2 Cohort A ₂ Q2W 4 mg	N		8		
	Geo Mean		284		
	Geo CV%		22.8		
Part 2 Cohort B ₂ Q2W 4 mg	N		1		
	Geo Mean		233		
	Geo CV%				
Part 2 Cohort B ₂ Q3W 10 mg	N		11		
	Geo Mean		229		
	Geo CV%		25.1		
Part 2 Cohort B ₂ Q3W 18 mg	N		23	1	8
	Geo Mean			261	53.6
	Geo CV%				91.5
Part 2 Cohort B ₂ Q3W 25 mg	N		8	2	1
	Geo Mean		144	90.4	26.9
	Geo CV%		63.3	54.9	
Part 2 Cohort B ₂ Q3W 0.6 mg	N		2		
	Geo Mean		248		
	Geo CV%		16.0		
Part 2 Cohort D ₂ Sub Cohort 1 Q3W 2.5/10/18 mg	N	11	14	13	8
	Geo Mean	594	183	55.8	17.8
	Geo CV%	14.8	53.7	105	297
Part 2 Cohort D ₂ Sub Cohort 2 Q3W 2.5/10/30 mg	N	30	33	29	25
	Geo Mean	463	149	53.7	14.2
	Geo CV%	36.4	52.6	79.3	76.0

**Appendix 3 Summary of Serum Obinutuzumab Concentrations
Following Administration of a Single Dose IV in Study NP30179:
PK-Evaluable Patients (cont.)**

	Nominal Time from First Dose (hr)				
		6	168	1008	2520
Part 2 Cohort D2 Sub Cohort 4 Double Gpt Q3W 2.5/10/30 mg	N	17	20	17	8
	Geo Mean	644	225	82.7	23.2
	Geo CV%	49.1	282	71.9	141
Part 2 Cohort F2 Sub Cohort 1 Q3W 0.5/2.5/10/30 mg	N	25	29	26	23
	Geo Mean	388	141	48.0	16.0
	Geo CV%	21.8	211	359	148
Part 3 Cohort B3 Q3W 10/16 mg	N		52	38	25
	Geo Mean		148	62.1	21.2
	Geo CV%		57.1	95.4	217
Part 3 Cohort B4 Q3W 10/16 mg	N	1	12	11	9
	Geo Mean	271	161	55.1	18.7
	Geo CV%		40.1	91.0	62.8
Part 3 Cohort D3 Q3W 2.5/10/30 mg	N	82	100	72	43
	Geo Mean	363	171	82.7	28.9
	Geo CV%	63.5	45.8	50.1	62.6
Part 3 Cohort D4 Q3W 2.5/10/30 mg	N	1	1		
	Geo Mean	350	177		
	Geo CV%				
Part 3 Cohort D5 Q3W 2.5/10/30 mg	N	10	10	2	
	Geo Mean	329	141	51.2	
	Geo CV%	25.4	24.4	1.24	

Geo Mean = Geometric mean; Geo CV% = Percentage coefficient of variation of the geometric mean.

Where more than 50% of concentrations were below limit of quantification the mean data is not reported

For more details, please refer to Interim CSR NP30179, Report 1111323, Table 61.

The above described PopPK model was used to estimate the individual PK parameters and to derive the individual predicted obinutuzumab concentrations at glofitamab observation times in order matched pairs for the calculation of receptor occupancy.

3.3.3. Pharmacodynamics

Mechanism of action

Obinutuzumab is an anti-CD20 monoclonal antibody, proposed as a pretreatment to mitigate CRS by reducing peripheral and lymphoid associated B cells (Mossner et al. 2010).

The rationale is that Glofitamab and obinutuzumab both bind to CD20 on the same epitope, and the high concentrations of circulating obinutuzumab will compete with glofitamab.

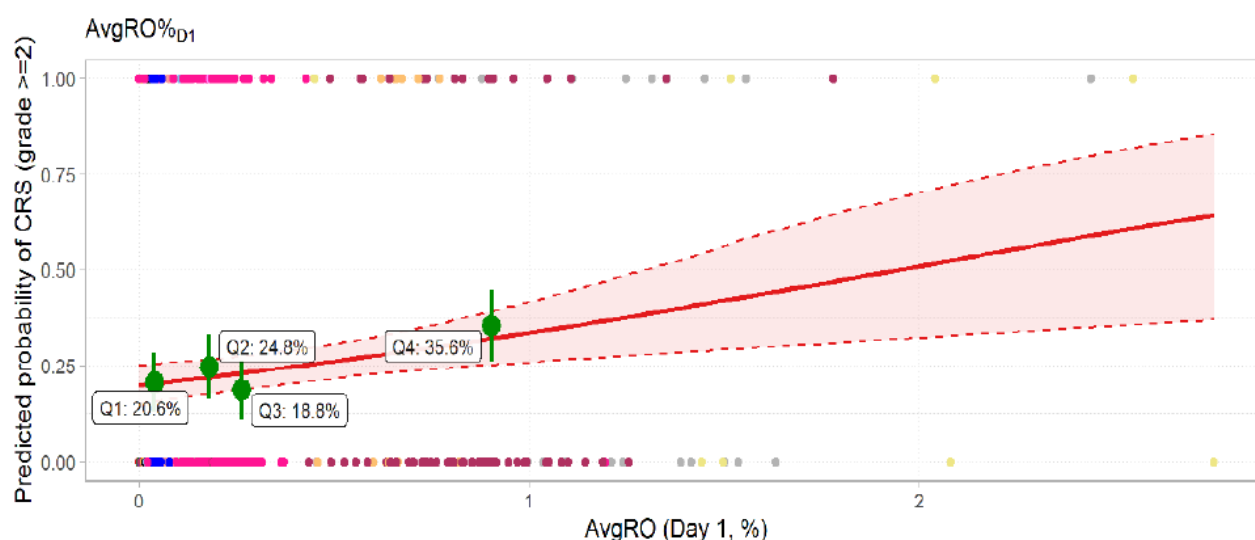
Assessor's comment:

The proposed mechanism of action for the indication is plausible.

3.3.4. PK/PD modelling

The ER analysis for CRS focused on the relationship between model-derived glofitamab average CD20 RO% over the first 24 hours following the first glofitamab administration and the occurrence of Grade ≥ 2 CRS. 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, see figure 2.

Figure 2 Exposure-Response Analysis Relating the Glofitamab Average CD20 RO% Over The First 24h To The Risk of Grade ≥ 2 CRS



p-value = 0.00380

AvgRO%D1=average receptor occupancy for 24h after the first glofitamab dose; CRS=cytokine release syndrome.

Assessor's comment:

The PK exposure parameter utilized in these analyses was glofitamab receptor occupancy (RO).

The Risk for 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). The AvRO%D1 quartiles with 20.6%, 24.8%, 18.8% and 35.6% in quartiles 1, 2, 3 and 4, respectively, supported this.

The evidence generated here is that there is a higher risk for CRS with higher receptor binding of glofitamab.

Although the proposed mechanism of action for the indication is plausible and the PD endpoint glofitamab receptor occupancy (RO) does seem meaningful in the setting, The data provided, namely the exposure-response analysis, does not allow conclusions on a causal relationship to obinutuzumab

receptor binding which has not been measured. It is unknown whether all receptors are bound, thus it is not possible to conclude that the ones not bound by glofitamab are bound by obinutuzumab. Furthermore, even if all receptors were bound, they could be blocked by former administered drugs from earlier treatments.

As there is no comparison without obinutuzumab, neither at least a comparison with only non-pretreated (with other possible binders of the receptor in question) it is not possible to conclude definitely on the action of obinutuzumab. The MAH should justify how the design of the study does allow certain conclusions on the PD of obinutuzumab **(MO)**.

3.3.5. Discussion on clinical pharmacology

A previously published model for the population PK of obinutuzumab was adapted to provide predicted obinutuzumab concentrations at the available glofitamab observation times to facilitate calculation of glofitamab receptor occupancy, necessary for subsequent ER analyses. Study NP30179 data was used to re-estimate covariate effect coefficients and IIV parameters in the model. Additional model diagnostics have been requested **(OC)**.

Logistic regression was applied to explore exposure-safety relationships for CRS (Grade ≥ 2). Increasing CRS (Grade ≥ 2) incidence was associated with increasing average glofitamab receptor occupancy over the first 24 hours (AvgROD1) and with increasing baseline SPD. Increasing AvgRO%D1 was retained in the final reduced model even though it narrowly did not meet the inclusion criteria of $p\text{-value} < 0.01$. No significant effects of baseline age, baseline weight, sex, tumour histology, baseline obinutuzumab concentration, Ann Arbor stage, baseline LDH or time since last prior anti-CD20 treatment were detected. Race could not be assessed owing to a lack of data. Evaluation of logistic regression models was based on ROC curves and the final reduced model was classified as poor (ROCAUC between 0.6 and 0.7). The predictive performance of the logistic regression models on CRS (Grade ≥ 2) is questionable.

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 proposed registrational dosing regimen is consequently a single dose of obinutuzumab 1000 mg pre-treatment (Gpt) administered via IV infusion, on Cycle 1 Day 1, 7 days before initial dosing of glofitamab.

Overall the information on obinutuzumab PK is sparse. The only given information is the concentration at sample time, which does not represent T_{max} . As PK/PD of obinutuzumab has been assessed during the initial MAA for the currently approved indications this is acceptable.

Although the proposed mechanism of action for the indication is plausible and the PD endpoint glofitamab receptor occupancy (RO) does seem meaningful in the setting, it does not allow conclusions on a causal relationship to obinutuzumab receptor binding which has not been measured. It is unknown whether all receptors are bound, thus it is not possible to conclude that the ones not bound by glofitamab are bound by obinutuzumab. Furthermore even if all receptors were bound, they could be blocked by former administered drugs from earlier treatments.

As there is no comparison without obinutuzumab, neither at least a comparison with only non-pretreated (with other possible binders of the receptor in question) it is not possible to conclude definitely on the action of obinutuzumab. In the opinion of the assessor the design of the study does not allow any certain conclusions on the PD of obinutuzumab.

No Exposure-response relationships of obinutuzumab for efficacy or safety has been provided.

Besides, exposure-response relationships of glofitamab for incidence rates of Cytokine release syndrome (CRS) of Grade ≥ 2 were characterized by logistic regression modelling. Even graphical analysis indicated a trend towards increasing incidence of CRS with decreasing baseline obinutuzumab concentration, this predictor was not retained in the final model. Overall, the analysis retained that occurrence of CRS (Grade ≥ 2) was essentially associated with increasing average glofitamab receptor occupancy over the first 24 hours (AvgROD1) and with increasing baseline SPD. However, this does not answer / support any potential relationship between obinutuzumab concentration and PD / clinical effect under the scope of the claimed indication. This appears to be essentially due to the design of NP30179 study in which no data without obinutuzumab and with an alternative obinutuzumab dosage regimen are available / provided.

Overall, even though obinutuzumab has been used under such level of dose (1g), the adequacy of the selected dose in the claimed indication (pre-treatment to reduce the risk of CRS events associated to glofitamab) is not known. No justification or PK/PD rationale for the chosen single 1 g dose has been discussed. Therefore the effectiveness of the claimed dose should be supported by clinical (efficacy/safety) data.

3.3.6. Conclusions on clinical pharmacology

The following measures are considered necessary to address issues related to clinical pharmacology:

A major objection on the exposure-response analysis provided has been raised and needs to be addressed by the MAH.

3.4. Clinical efficacy

This application, for an extension of indication of Gazyvaro (obinutuzumab) to be used as pre-treatment in order to reduce the risk of CRS in conjunction with glofitamab treatment, is based on Study NP30179, a Phase I/II (Phase I prior to Protocol NP30179 v10), multicenter, open-label study to evaluate the safety, efficacy, tolerability 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 (gazyvaro pre-treatment (Gpt)) in patients with relapsed/refractory (R/R) B-cell non-Hodgkin's lymphoma. The clinical cutoff date (CCOD) for the data presented in this submission is 15 June 2022.

The sought indication for **glofitamab** only concerns DLBCL patients treated with glofitamab monotherapy and receiving single-dose obinutuzumab pre-treatment (but not combination treatment): *Glofitamab 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.* Note that glofitamab is not yet approved for this indication and as such, the indication text may yet change.

The indication sought for **obinutuzumab** is: *Obinutuzumab is indicated as a pre-treatment to reduce the risk of cytokine release syndrome (CRS) induced by glofitamab.*

The stated rationale for Gpt is:

- Preclinical data identified Gpt as a strategy for mitigating the risk of glofitamab-associated CRS and, accordingly, has been implemented in clinical studies of glofitamab monotherapy.
- Obinutuzumab has been shown *ex vivo* and *in vivo* to have superior ability to deplete peripheral and lymphoid B cells relative to rituximab or other anti-CD20 monoclonal antibodies.

- Gpt has a two-fold MoA in reducing glofitamab's engagement with its B-cell target, CD20, and thus mitigating CRS risk. Gpt depletes non-malignant B cells both in the peripheral blood and in the secondary lymphoid organs resulting in attenuation of the risk of CRS, which can result from rapid glofitamab-mediated T-cell activation via interaction with B cell targets in the circulation. Additionally, Gpt reduces CD20 receptor occupancy (RO) by glofitamab on non-malignant and malignant B cells based on its shared target with glofitamab, thus limiting glofitamab binding and subsequent T-cell activation induced by glofitamab.
- Nonclinical data in tumor-bearing hematopoietic stem cell (HSC)-engrafted NOD/Shi scid/IL-2R γ null (NOG) mice and cynomolgus monkeys demonstrated the ability of Gpt to reduce cytokine release and facilitate the tolerable administration of log-fold higher doses of glofitamab.
- Due to the high potency of glofitamab in killing non-malignant and malignant CD20+ B cells, dosing without an initial peripheral B-cell pre-depletion and without the initial presence of competing anti-CD20 antibody would be anticipated to result in T-cell activation associated with frequent $\geq$ Grade 2 CRS. There would be a reduced likelihood of achieving clinically relevant target doses in a timely manner, which is critical in the setting of an aggressive malignancy, such as DLBCL.
- Every patient dosed with glofitamab monotherapy in clinical trials so far has received Gpt. There is no patient experience with glofitamab in the monotherapy setting that does not include Gpt.

Assessor's comment

According to the MAH, Gpt is an integral component of the CRS risk mitigation strategy for treatment with glofitamab. All patients in Study NP30179 received Gpt, so a comparison with and without Gpt cannot be made. The absence of a comparator cohort of patients who have not received pre-treatment with obinutuzumab constitutes a serious impediment to assessing the efficacy of obinutuzumab in mitigating glofitamab-induced CRS in a meaningful way. The only parameter of efficacy available from the clinical cohort will be the absolute rate of CRS. This can be compared to CRS-rates reported for other CD20 x CD3 bispecific TCEs but such comparisons are fraught with uncertainty given the unique structure of glofitamab with double CD20 binding-domains, as well as the usual caveats associated with comparisons among single-arm studies.

The MAH has not explicitly defined an efficacy cohort in which to evaluate the present obinutuzumab type II variation. Since no efficacy analysis was planned for Gpt per protocol, the Applicant should at least define the efficacy analysis population for Gpt that would support this submission since it was agreed during the pre-submission meetings that no cross-references to glofitamab dossier nor "glofitamab-only" data could be acceptable. Data from cohorts investigating other dosing escalation regimens than the one selected as the RP2D should not be overlooked since no comparison is possible at this stage and that it is quite difficult to settle a causal relationship between Gpt and CRS risk reduction. Every available data from every cohort should be cautiously analysed even though, any interpretation will be very difficult since the retrospective results' analysis will only be of exploratory nature with non-compellingly and unreasonably low scientific evidence. The MAH is requested to define an efficacy cohort to evaluate Gpt's ability to prevent CRS. The MAH is then requested to provide data on CRS-rate for the chosen Gpt efficacy cohort. The cohorts from study NP30179 that contribute patients to this efficacy cohort are requested (including numbers of patients from each cohort). Data from cohorts investigating other dosing escalation regimens than the one selected as the RP2D should not be overlooked and the corresponding results should be presented separately. (**OC**).

The proposed mechanism of action of obinutuzumab pre-treatment, reducing CD20 receptor occupancy by glofitamab, gives cause for concern that obinutuzumab pre-treatment could negatively impact the anti-lymphoma effect of glofitamab. An OC requesting further information on this has been raised in the section on Outcomes and estimation.

Given the inadequacy of clinical data to shed light on the effect of obinutuzumab pre-treatment on CRS risk, due to the lack of a comparator, much of the “burden-of-proof” will be on pre-clinical data. Such data are associated with issues concerning their translatability to the clinic, as well as, in this instance, the clinical context from which they are derived. Translation of pre-clinical data as evidence of clinical effect is discussed further under Supportive Studies below.

According to the MAH, the reason why no comparator cohort has been provided seems to be primarily ethical. The ethical reasons underlying why patients cannot receive glofitamab without obinutuzumab pre-treatment mentioned above, are not very clearly communicated, however, it is broadly stated that the risk of CRS would be “substantial and unacceptable”, both in terms of frequency and severity. The MAH is requested to discuss in greater detail what constitutes the mentioned ethical reason(s) and to provide data to support the position that glofitamab cannot be given without obinutuzumab pre-treatment in the intended clinical setting, namely 3L+ DLBCL patients (all of whom will have been previously exposed to other anti-CD20 targeting therapy, many of them within months of starting glofitamab). This discussion should include specific mention of why glofitamab therapy necessitates pre-treatment when other CD20xCD3 targeting bispecific antibodies (mosunetuzumab, epcoritamab, odronextamab, among others) do not seem to have such a requirement **(OC)**.

The wording “There is no patient experience with glofitamab in the monotherapy setting without Gpt”, repeated twice on p. 10 in the Clinical Overview, seems to suggest that there could be experience with glofitamab without Gpt in patients in the combination therapy setting. The MAH is requested to provide such data, if they exist, including a comparison of the rates and severity of CRS in Gpt pre-treated and non-pre-treated cohorts, respectively. A clear description (preferably a figure) of when treatments (obinutuzumab, glofitamab and any other treatments such as steroids, which might impact CRS) are given in the respective cohorts is also requested. Furthermore, the MAH is requested to provide any data on glofitamab treatment without Gpt that may be available from other trials **(OC)**.

The MAH is asked to discuss whether other means of minimizing risk of CRS might be feasible in the patient population for which glofitamab is intended **(OC)**. It seems glofitamab is the only bispecific CD20xCD3 targeting treatment thus far, where anti-CD20 prophylaxis is employed. For other drugs in this class, including mosunetuzumab (in FL) and epcoritamab (in DLBCL), CRS-minimization was done by step-up dosing. Specifically, the MAH is asked whether a lower initial dose of glofitamab might have potential for further CRS-mitigation? Concerning this, it must be noted that the glofitamab doses from start of step up to maintenance dose range from 2.5 mg to 30 mg (12-fold increase) while the range in epcoritamab is from 0.16 mg to 48 mg (300-fold increase) according to Thieblemont et al JCO 2022. In this publication, the reported CRS-rate of epcoritamab was 49.7% (all-grade) while 4/157 = 2.5% patients had grade 3 CRS (and no grade 4 events reported). A comment from the MAH on how the addition of another step-up dose will impact the overall delivery of anti-lymphoma treatment in this population is also requested (IE what is the MAH’s perception of the balance between the extra 1 week of treatment before target dose glofitamab is reached contra the potential for lower CRS risk?) **(OC)**.

A concerning uncertainty within this application is dose selection. While Gazyvaro is administered at its MA dose with no dose-finding studies conducted (see OC under the section “Treatments” below), the choice of glofitamab step-up dosing scheme could also be critical for this application given the unclear dose selection and rationale raised within glofitamab application. In addition, the Applicant continues to investigate combination therapies (with obinutuzumab) in the same indication. The Applicant should

elaborate on lower dose levels of glofitamab and Gpt that could provide more comprehensive efficacy and safety results. (OC)

3.4.1. Dose response study(ies)

Assessor's comment

No specific dose-finding studies for obinutuzumab pre-treatment were performed. The choice of pre-treatment with a single dose of 1000 mg obinutuzumab given 7 days prior to start of glofitamab seems to be based on what has been approved in follicular lymphoma as well as theoretical considerations on target-mediated drug disposition.

The majority of patients enrolled, were refractory to any anti-CD20 treatment (85% of glofitamab pivotal cohort D3 and 83% in supportive efficacy pop cohorts D3+D2sub2+D5) and refractory to last prior therapy (D3= 83% and D3+D2sub2+D5= 85%). As such, a large proportion of patients will have been refractory to last therapy and have received anti-CD20 treatment as part of this last prior therapy. Recently anti-CD20 treated, refractory patients are likely to retain effective concentrations of anti-CD20 treatment for many months. Indeed, the Gazyvaro clinical overview mentions that 73.2% of the overall safety population had low b-cell counts, "likely reflective of prior anti-CD20 therapy". This increased to 94.3% of patients being b-cell depleted after Gpt. It is overwhelmingly likely that it is normal b-cells being depleted but depletion is, nevertheless, indicative of lingering functional effects of anti-CD20 treatment. Given that a large proportion of patients have recently failed CD20-targeting treatment and that 73% of enrolled patients are already b-cell depleted before Gpt, the MAH is asked to justify how Gpt contributes to lowering the risk of CRS in this patient population (OC). Specifically, the answer should include a discussion on whether or not rituximab also blocks CD20, and thereby hinders glofitamab binding and a discussion on whether any residual rituximab will compete with obinutuzumab for binding to CD20. If part of the MAH's proposed answer includes a suggestion that Gpt "debulks" the lymphoma burden, thereby reducing the CRS risk, the MAH is further requested to provide evidence that obinutuzumab retains efficacy in patients who have recently failed rituximab (OC).

Source: Proportions of refractory patients from cohort D3 are taken from EMA response 86 of the glofitamab application while proportions of cohorts D3+D2sub2+D5 are taken from the CSR accompanying the Gazyvaro type II variation (table 55).

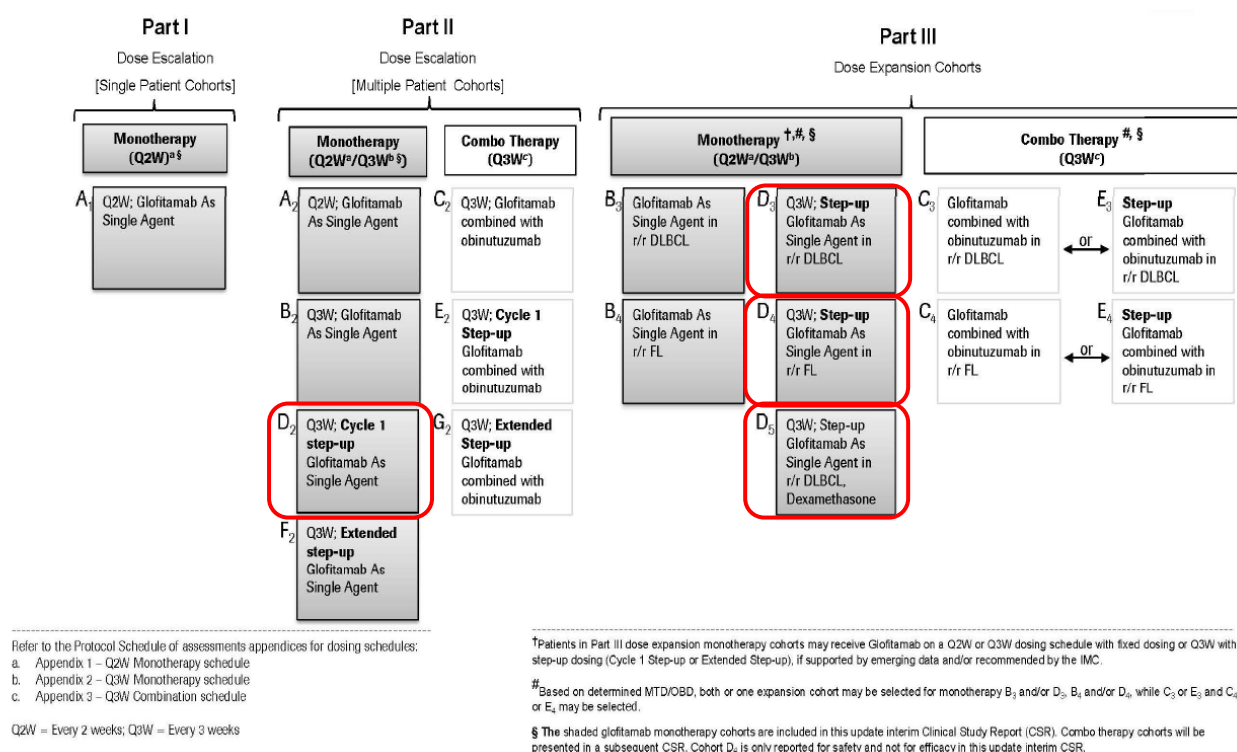
One subcohort in trial NP30179 was pre-treated with 2 doses of obinutuzumab (cohort D2sub4). For this cohort, 10/31 (32.3%) patients had CRS grade ≥ 2 . The corresponding rate of CRS ≥ 2 in cohorts D2sub2, D3, D5 was 41/195 (21%) (source: CSR body1 p 1382+1383). The MAH is asked to discuss the significance of these results in terms of the claimed effect of CRS-mitigation (it seems odd to have greater CRS-rate with greater Gpt) (OC).

3.4.2. Main study: NP30179

Title of the 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

Figure 1 Study Design Overview – Protocol NP30179: Glofitamab Monotherapy and Combination Therapy in R/R NHL Dose-Escalation and Dose Expansion Cohorts



The glofitamab application in R/R DLBCL is based on the pivotal cohort D3 (one of 17 different cohorts included in the trial NP30179). Supportive data including patients with DLBCL and treated with the same step-up regimen of glofitamab come from cohorts D2sub2 and D5. Furthermore, FL patients in cohort D4 are treated with the proposed registrational step-up and Gpt and could be informative in terms of Gpt ability to prevent CRS.

Methods

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 $\leq 1.5 \times$ 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 $\leq 3 \times$ ULN.
- Adequate hematological function: Neutrophil count of $\geq 1.5 \times 10^9$ cells/L; platelet count of $\geq 75,000/\mu\text{L}$ (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 $\leq 1.5 \times$ 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).

Assessor's comment

If the MAH's proposed efficacy cohort for Gpt consists of lymphoma patients not included under the in-/exclusion criteria above, the in-/exclusion criteria for these patients should be provided, along with data on the risk of CRS etc as requested elsewhere. It should be specified if these patients, in line with the DLBCL extension cohorts, have received ≥ 2 prior systemic lines of therapy and single-dose Gpt as well as the proposed registrational step-up dosing of glofitamab (**OC**).

Treatments

Glofitamab and **obinutuzumab** (given to reduce the risk of CRS) were considered as the main investigational medicinal products (IMPs). **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.

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 to reduce 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).

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.

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.

Additionally, patients with a response at end of initial treatment phase with glofitamab who had subsequent progression of disease were potentially eligible for re-treatment (including Gpt).

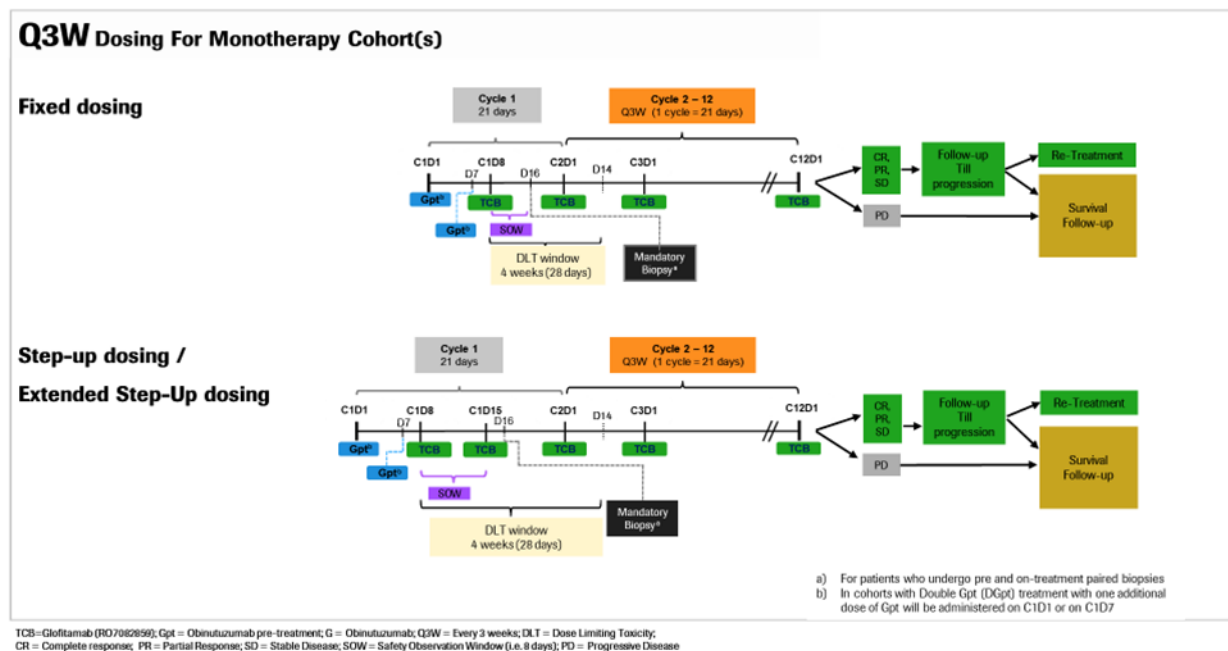
Tocilizumab is a recombinant, humanized, anti-human monoclonal antibody directed against soluble and membrane-bound IL-6R, which inhibits IL-6 mediated signalling. Blocking the inflammatory action of IL-6 using tocilizumab could therefore represent a novel approach for the treatment of CRS and tocilizumab has been approved for the treatment of CAR-T cell-induced severe or life-threatening CRS. CRS is observed with T-cell recruiting therapies, including CAR-T-cell therapy and bispecific molecules, such as blinatumomab (Nagorsen et al. 2012). There have been multiple reports in the literature of tocilizumab being used off-label to successfully treat severe or life-threatening CRS (Lee et al. 2014; National Institutes of Health 2015, Teachey et al. 2013), and it is rapidly becoming the SoC in some settings, particularly in the treatment of CRS following cancer immunotherapy.

Corticosteroid premedication was given in this study to reduce the frequency and severity of CRS. Starting from Protocol NP30179 v10, dexamethasone (20 mg IV prior to the obinutuzumab and glofitamab infusion) was included as an option for corticosteroid premedication (in addition to prednisolone and methylprednisolone) for all patients, and in addition, a R/R DLBCL expansion cohort (D5) was introduced to investigate (exploratory objective) if dexamethasone could further help to reduce the occurrence and severity of CRS.

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

Retreatment with glofitamab (including repeated pre-treatment with obinutuzumab) was offered to eligible patients based on their clinical responses after completion of the initial glofitamab treatment, such as those who initially achieved a CR but subsequently progressed.

Figure 1 NP30179: Q3W Dosing Schematic for Glofitamab Monotherapy in Part II or Part III*



Source: Response to Q77 glofitamab application.

Assessor's comment

A single dose of obinutuzumab 1000 mg iv was administered on C1D1 to try to decrease the risk of CRS. All patients in all cohorts treated with the glofitamab regimen proposed for approval have received obinutuzumab pre-treatment, given according to the Gazyvaro SmPC. In addition, corticosteroids, which

may also impact the risk of CRS, were employed as pre-treatment. The MAH is requested to provide a comparison of CRS-rates between patients treated with the different corticosteroids permitted in the NP30179 study. Any differences in CRS-rates associated with corticosteroid choice should be discussed **(OC)**.

Gpt dose selection rationale is very limited and should be further elaborated by the applicant. In light of the absence of Gpt dose-finding studies, the applicant should elaborate on the relevance of the MA dose scheme retained for the pre-treatment setting. Pertinence of lower dose levels should be discussed **(OC)**.

It appears that too many variables could bias the response that can be imputed to Gpt on CRS rates and grades. In absence of any control or planned analysis to elaborate on a possible beneficial effect of Gpt, the effect of Glofitamab step-up dosing, prior anti-CD20 therapies and other administered corticosteroids pretreatments on the potentially observable low CRS rate cannot be ruled out. The Applicant should explain how to discriminate the effect of each compound possibly participating to the final observed effect on CRS rates and grades. **(OC)**

Objectives

Table 1 Objectives and Endpoints

Primary objectives	Endpoints/Outcome Measures
- To evaluate the safety, tolerability, and pharmacokinetics of glofitamab as single agent (<i>and in combination with obinutuzumab</i>) 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 (<i>and in combination with obinutuzumab</i>) following Gpt in patients with R/R NHL. - To determine a recommended dose and schedule of glofitamab as a single agent (<i>and in combination with obinutuzumab</i>) 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. (<i>Incidence and nature of DLTs when glofitamab was given in combination with obinutuzumab</i>). - 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)

Table 1 Objectives and Endpoints (cont.)

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)

Table 1 Objectives and Endpoints (cont.)

Secondary objectives (Cont.)	Endpoints/Outcome Measures
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.	- Incidence of anti-drug antibody (ADA) formation and events related to immune complex deposition and activation - 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, <i>soluble mediators</i>, peripheral B- and T-cell number and T-cell activation status, as appropriate. - 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. - To assess the anti-tumor activity of re-treatment 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.	<i>Soluble mediators</i> - Peripheral B- and T-cell number - T-cell activation status <i>Tumor subtype (e.g., activated B-cell vs. germinal center B-cell) assessed at baseline in archived material.</i> - CR - ORR - DOR - PFS - OS - Safety

Table 1 Objectives and Endpoints (cont.)

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 (<i>and in combination with obinutuzumab</i>). - In Part III, to assess treatment-related symptoms using the Patient Reported Outcome Common Terminology Criteria for Adverse Events (PRO-CTCAE). - In Part III DLBCL dexamethasone cohort, assess CRS incidence and severity after pre-medication using dexamethasone.	- Change in the nature and severity of severe CRS/HLH following administration of tocilizumab for severe CRS/HLH - Change from baseline in patient reported treatment-related symptoms based on items from the PRO-CTCAE (Part III only) - 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 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 Update Interim CSR are noted in italics

Source: CSR Gazyvaro application.

Assessor's comment

As is apparent from table 1 above, evaluation of the efficacy of Gpt in reducing CRS was not even an objective of this trial. A secondary objective "to establish the safety, tolerability, and pharmacokinetics of Gpt" was the only stated objective concerning Gpt. The MAH is requested to discuss how not including an objective to investigate the efficacy of Gpt in the trial impacts the ability to evaluate the efficacy of Gpt in the intended clinical setting **(OC)**.

Outcomes/endpoints

Assessor's comment

Please see Table 1 above in the Objectives section. None of the endpoints/outcome measures listed in conjunction with the only secondary objective to include Gpt seem to address the "safety, tolerability and pharmacokinetics of Gpt" directly (Listed outcome measures include: *INV-assessed CR rate, IRC-assessed CR rate, IRC-assessed overall response rate (ORR), INV-assessed ORR, IRC-assessed ORR, IRC - and INV-assessed duration of complete response (DOCR), IRC- and INV-assessed duration of response (DOR), IRC-assessed progression-free survival (PFS) INV-assessed PFS, Overall survival, IRC-assessed time to first complete response (TFCR), INV-assessed TFCR, IRC-assessed time to first overall response (TFOR), INV-assessed TFOR, Incidence of anti-drug antibody (ADA) formation and events related to immune complex deposition and activation*). As such, it does not seem like assessment of Gpt was a planned goal of the trial. The MAH is requested to comment on this. **(OC)**.

Sample size

DATA ANALYSIS PLAN:

The determination of sample size, planned analyses and statistical tests are described in detail in the NP30179 Statistical Analysis Plan (SAP v5), and superseded the statistical analyses specified in Protocol NP30179 v11, Section 6.

Assessor's comment

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 (to glofitamab) was calculating assuming an observed response of 50 % and 65 %. In protocol version 6 (8 Aug 2018) the sample size for the R/R DLBCL 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.

The sample size was calculated based on expected response rate of glofitamab effect. Gpt did not figure in these calculations.

Randomisation

Assessor's comment

This application refers to a single-arm trial. No randomization was performed. All patients received Gpt.

Blinding (masking)

Assessor's comment

This was an open-label trial without randomization or blinding.

Statistical methods

The only SAP information relating to obinutuzumab/Gpt can be found in section 6.5 (of study NP30179 – the glofitamab trial):

The safety analyses will include all patients who received any amount of obinutuzumab and all patients who also received glofitamab. Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in ECG, presence of ADAs, and changes in VS. All collected adverse event data will be listed by assigned dose level and patient number. All adverse events occurring on or after treatment on C1D-7 will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.03 toxicity grade, with the exception of grading for CRS. Among those, adverse events that are attributed to glofitamab or obinutuzumab will be summarized in two separate tables through the same mapping or grading method. Adverse events can only be attributed to Gpt if they occur between C1D -7 and before glofitamab dosing on C1D 1. In addition, all serious adverse events, including deaths, will be listed separately and summarized. DLTs and adverse events leading to treatment discontinuation will also be separately listed. Individual and mean serum glofitamab concentration versus time data will be tabulated and plotted by dose level.

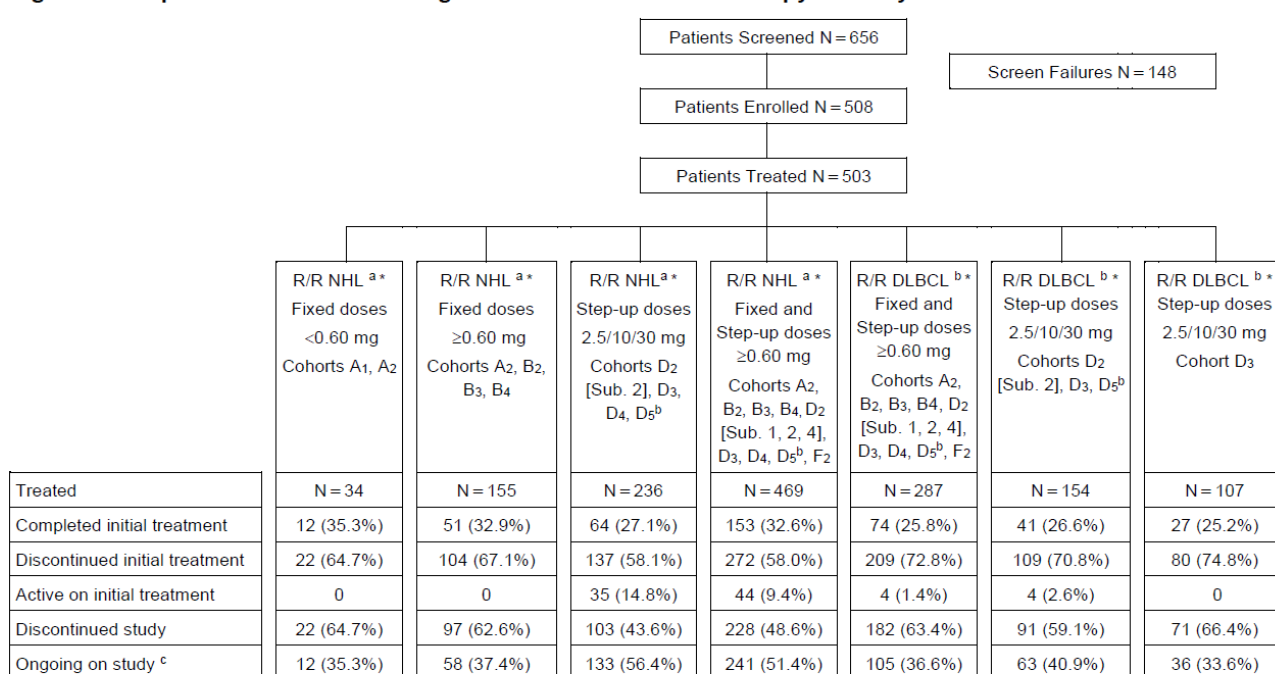
Assessor's comment

No statistical analyses for the efficacy of Gpt is actually described in the SAP and this is of concern since any interpretation of data from glofitamab application will be quite difficult.

Results

Participant flow

Figure 2 Disposition of Patients Assigned to Glofitamab Monotherapy in Study NP30179



^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 (15 June 2022)

^b 4 patients had completed all cycles but the disposition page had not been updated at the time of the analysis

* Note that the numbers in the cohort columns are the number of patients in that analysis group 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_LIT600_CSR_SE_15JUN2022_30179](#); [t_ds_GE600_CSR_SE_15JUN2022_30179](#); [t_ds_PIV_SCS_SE_15JUN2022_30179](#)

Source: CSR Gazyvaro application.

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 Cut-off Date: 15 June 2022.

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

Assessor's comment

Depending on the efficacy cohort chosen by the MAH to evaluate efficacy of Gpt, the MAH is asked to provide the dates of first and last patient enrolment to the study cohorts that form the efficacy cohort (OC).

Conduct of the study

Table 2 Summary of Key Changes to Protocol NP30179

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 µg (405 µg x2) 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.

Table 2 Summary of Key Changes to Protocol NP30179 (cont.)

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.

Table 2 Summary of Key Changes to Protocol NP30179 (cont.)

Protocol Version 10 France (5 January 2021) Protocol NP30179 (France) was amended to align with the Study NP30179 global protocol 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.
Protocol Version 11 France (3 June 2021) Protocol NP30179 (France) was amended to align with the Study NP30179 global protocol v11.

Source: CSR (CCOD 15 JUNE 2022).

Protocol version 5 from March 8th 2018 implemented obinutuzumab. All patients in all cohorts have been pre-treated with obinutuzumab. Also, Q3W schedule was started.

Protocol version 6 from August 8th 2018 implemented study cohorts explicitly for DLBCL and FL, based on observed complete responses.

Step-up dosing was introduced in Protocol version 8. Data based on the proposed registrational dose of 2.5/10/30 mg step-up are first mentioned in Protocol version 10 (Dec 2020) suggesting this dosing regimen was first implemented in Protocol version 9 (May 2020).

Protocol version 10 (Dec 2020) allowed dexamethasone (dexa) as corticosteroid pre-treatment (prior to this, dexa was not among the available options for physician's choice for pre-treatment) and added a specific cohort (D5) with mandatory dexa pre-treatment.

Protocol version 10 also updated the initial treatment period to 12 cycles of glofitamab with an additional response assessment in Cycle 9, incorporated new treatment cohorts with extended step-up dosing and double pre-treatment with obinutuzumab (DGpt) prior to first dose of glofitamab, reduced the mandatory hospitalization to 24 hours in Cycle 1. In the modified US Protocol version 10, mandatory hospitalization was modified per FDA request.

The definition of the efficacy analysis population for glofitamab has changed over time (changes were made in protocol version 6, 7, and 8).

No GCP inspections have taken place for Study NP30179.

Assessor's comment

Obinutuzumab pre-treatment was implemented in Protocol version 5, while the study was already recruiting. It is not clear how the MAH intended to assess the impact of such pre-treatment (see OC above in objectives section).

Baseline data

Assessor's comment

It is not made explicitly clear which group of patients the MAH considers to be the primary efficacy population for Gpt. Once the MAH has defined an efficacy cohort, baseline data from the chosen efficacy cohort are requested (OC).

Numbers analysed

Assessor's comment

As no well-defined efficacy population has been designated, the numbers analysed are still pending.

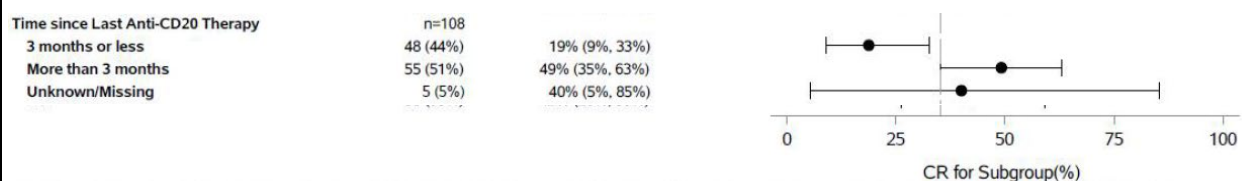
Outcomes and estimation

Assessor's comment

No well-defined efficacy population has been designated (see OC under section Clinical efficacy). Furthermore, no primary efficacy endpoint has been defined. As mentioned under Outcomes/endpoints in the Methods section, no efficacy endpoint relating to Gpt was listed under the only Objective mentioning Gpt.

The main challenge, concerning the design of this trial, is that there is no comparator at all. At this point, it is impossible to know if the absolute CRS-rate would be higher or lower than what would have been seen in a comparable population of patients treated with glofitamab without Gpt (furthermore, it is not known if Gpt affects glofitamab's anti-lymphoma effect, which poses another dilemma). The point of Gpt is to act as CRS prophylaxis to allow reasonably rapid dose step-up of glofitamab so patients can receive anti-lymphoma treatment in efficacious doses with minimal risk of dose-limiting/delaying side effects. However, the MoA of Gpt could also be somewhat antagonistic to glofitamab (blocks binding to CD20) and so the cost of preventing CRS may imply preventing some anti-cancer effects.

From the glofitamab application, recently anti-CD20-treated patients seem to fare worse than those who are further temporally removed from last anti-CD20 treatment:



Source document: ema-responses-86.pdf.

As such, mandatory pre-treatment with another CD20-targeting agent (obinutuzumab) needs to be carefully justified. The MAH is invited to provide a discussion, ideally based on evidence, on the impact of Gpt blocking CD20 on glofitamab's anti-lymphoma activity. Some reassurance on this point seems to be provided from non-clinical data in the protocol. The MAH is encouraged to include such data in the requested justification above (OC).

Ultimately, since no comparator in the form of a cohort of glofitamab-treated patients naïve to Gpt exists, it will be impossible to demonstrate whether Gpt hampers glofitamab's anti-lymphoma activity. Theoretically, it is also possible that Gpt, being a CD20-directed therapy which most patients with DLBCL will not have been previously exposed to, augments the anti-lymphoma activity of glofitamab.

Ancillary analyses

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. 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 ₀) 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 definitions and	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	CRS-rate, all grades	Proportion of patients experiencing CRS, based on Lee et al 2014 criteria.
	Secondary efficacy endpoint	CRS-rate, grade 3-4	Proportion of patients experiencing CRS grade 3-4, based on Lee et al 2014 criteria.
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 D₃ 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 D₃ was to occur when the following condition was met: The efficacy-evaluable population (Cohort D₃) 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	
	CRS-rate, all grades	XX	
	CRS-rate, grade 3-4	XX	
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%).		

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.

*Median follow-up for DOCR is 12.8 months.

Assessor's comment
The Highlighted text outlines the paucity of data from the current submission: definition of an appropriate efficacy cohort, definition of outcome(s) to assess Gpt and data on these outcomes are all missing. At present, no analysis of efficacy is possible and even when the requested data have been provided, efficacy evaluation is hampered by the lack of a comparator.

Clinical studies in special populations

	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, Efficacy cohort for Gpt			
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Assessor's comment

The MAH is asked to provide the number of patients from the Gpt efficacy cohort falling within the age brackets listed in the table above. Furthermore, the CRS rate in each age bracket is requested **(OC)**.

Supportive study(ies)

Assessor's comment

As mentioned in the Primary pharmacodynamic studies section above (5.2.2), pre-clinical studies in mice and cynomolgus monkeys indicate that obinutuzumab pre-treatment allows for the administration of higher doses of glofitamab with less severe clinical and laboratory signs of cytokine release than in animals who have not received such pre-treatment. In the absence of a clinical comparator (patients who have received glofitamab without Gpt), these pre-clinical data serve as the main argument that Gpt is efficacious in CRS prevention. However, concern that the pre-clinical studies included in this application do not accurately reflect the clinical context in which glofitamab is intended seems warranted: The sought indication for glofitamab is in 3L+ for DLBCL. All patients who are candidates for glofitamab will therefore have received prior anti-CD20 targeted therapy, often as part of several previous lines (and this is well reflected in the trial population where 100% of patients in the primary efficacy cohort D3 had received prior anti-CD20 treatment). In addition, a large proportion of patients received glofitamab in close temporal proximity to failing their most recent anti-CD20 therapy (48/108=44% of patients in cohort D3 failed last anti-CD20 therapy within 3 months or less) and an even greater proportion (73.2%) of patients (336/459) in the glofitamab overall safety population had B-cell counts < 70 cells/ μ L at study entry, likely reflective of prior anti-CD20 therapy. Given these results, it is questionable how much, if any, CRS-mitigation is afforded by the addition of a single dose of obinutuzumab pre-treatment to a group of patients where many have recently been exposed to therapeutic doses of anti-CD20 treatment and the majority have laboratory values indicative of persisting functional effects of anti-CD20 treatment. The MAH is requested to comment on whether a single dose of obinutuzumab can be expected to provide CRS-protection in a patient who has recently been exposed to anti-CD20 therapy and where residual effects of such recent treatment can be readily ascertained with a standard blood test **(OC)**. Furthermore, the MAH is asked to discuss whether the pre-clinical models included in this application (pre-treatment with a single dose of obinutuzumab) can be expected to reflect the clinical context in which glofitamab is intended (patients who have ALL received prior anti-CD20 in therapeutic doses and where the majority have received such treatment so recently that the effects can still be measured in a blood sample) **(OC)**. The reference values for the normal interval of B-cells for the assay used in this application are requested **(OC)**.

3.4.3. Discussion on clinical efficacy

Evaluation of the clinical efficacy of Gazyvaro pre-treatment to prevent/minimize the occurrence of glofitamab-associated CRS is hampered by a number of factors:

It seems like the evaluation of Gpt efficacy was not a stated objective of the trial from which data for this application is derived. Furthermore, no endpoint(s) to evaluate Gpt efficacy was directly presented and no efficacy cohort in which to evaluate efficacy was defined. The MAH has been asked to provide data to correct these omissions in order to facilitate the evaluation of efficacy of Gpt.

A severe limitation of the trial which provides data for this extension of indication application is that it does not include a control arm, meaning that no patients have received glofitamab monotherapy without Gpt pre-treatment. As such, there is no possibility of a direct comparison. The MAH has been requested to provide any data on patients who have received glofitamab as part of combination therapy who did not receive Gpt, if such data are available.

Somewhat contradictory to the argument that Gpt protects against glofitamab-induced CRS, patients receiving double-Gpt had a higher CRS-rate than those who received single-dose Gpt. A discussion on this has been requested.

In the absence of clinical data on efficacy, the MAH has presented pre-clinical data from mice and cynomolgus monkeys demonstrating that Gpt allows for the administration of higher doses of glofitamab with less severe clinical and laboratory signs of cytokine release than in animals who have not received Gpt. The pre-clinical models presented do not faithfully reflect the clinical context in which glofitamab is intended and a discussion on this has been requested.

Given the abovementioned deficiencies, it is challenging to evaluate the efficacy of Gpt in mitigating glofitamab-associated CRS. One comparison to gauge the efficacy of Gpt which is readily available is to compare the CRS-rate reported for glofitamab in this application with that reported for another bispecific antibody in a similar patient population. Such cross-study comparison is fraught with problems but is currently the only evaluation deemed possible. Epcoritamab is being tested in a similar patient population to glofitamab (R/R DLBCL who have received ≥ 2 lines of prior systemic therapy). No Gpt was employed as CRS-prophylaxis in the epcoritamab study. Results on epcoritamab, reported in Thieblemont et al JCO 2022, showed a CRS-rate of 49.7% (all-grade) and $4/157 = 2.5\%$ patients with grade 3 CRS (and no grade 4 events reported). Results from the SmPC of mosunetuzumab in FL-patients reported a CRS-rate of 39% (all-grade), grade 3 occurring in 2.3%, and grade 4 occurring in 0.5% of patients. In comparison, glofitamab (using cohorts D2sub2, D3 and D5 in order to only look at DLBCL patients to be as comparable to epcoritamab as possible) demonstrates a CRS-rate of 68.2% (all-grades) and $11/195 = 5.6\%$ with grades 3-4 CRS (including $4/195 = 2.6\%$ of glofitamab patients with grade 4 CRS). All CRS-rates were evaluated using the same grading scale (ASTCT).

Based on the above, with all the caveats associated with comparisons between studies, the CRS-rate in patients treated with Gpt+glofitamab does not seem particularly low compared to other bispecific CD20xCD3 antibodies used without pre-treatment. The MAH is invited to comment on the above comparison as a method of evaluating the efficacy of Gpt and the results described (**OC**).

Overall, no clinical evidence to suggest that Gpt protects against CRS has been presented at all. No efficacy analysis was planned for Gpt per protocol and no efficacy analysis population was defined either. Even though additional data are provided as part of responses to RSI, it is not quite clear what relevant conclusion could be made from such exploratory data. The totality of the concerns raised on evaluation of efficacy including the lack of efficacy cohort, defined outcome(s), end-point(s), the absence of a clinical comparator arm and representative pre-clinical correlates together constitute an outstanding objection: the B/R of the intended indication for Gpt cannot be ascertained (**MO**).

Design and conduct of clinical studies

OCs requesting a discussion on the lack of defined outcome(s), end-point(s) and efficacy cohort have been raised.

Efficacy data and additional analyses

OCs requesting the definition of efficacy end-points have been raised.

3.4.4. Conclusions on the clinical efficacy

The overall efficacy of Gpt in reducing glofitamab-induced CRS remains to be determined. The pivotal trial, on which this application is based, failed to specify key details such as objective(s) and end point(s) to assess Gpt efficacy and which cohort of patients is considered the efficacy cohort. It does not include a comparator arm and the pre-clinical models submitted in support of the application do not reflect the clinical context in which the treatment is supposed to be given. Furthermore, more Gpt does not translate to greater CRS-protection.

This leaves little basis for evaluation other than cross study comparison which, as is detailed above, is unconvincing in establishing a benefit of Gpt.

Based on the totality of the evidence at hand, the efficacy of Gpt in reducing glofitamab-induced CRS still remains to be determined since no efficacy data were provided in order to support the extension of indication application. An outstanding MO has been raised concerning the totality of the lack of evidence provided.

3.5. Clinical safety

Introduction

Obinutuzumab received first approval in the European Union (EU) on 23 July 2014 in combination with chlorambucil for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine-based therapy. Subsequently, additional indications have been granted:

- Obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.
- Obinutuzumab in combination with chemotherapy, followed by obinutuzumab maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced FL.

Obinutuzumab has a well-established safety profile when administered at a dose of 1000 mg (in combination with chemotherapy) for 6 treatment cycles in patients with CLL and 6 or 8 treatment cycles in patients with FL up to 2 years as monotherapy maintenance (every 2 months, or until disease progression).

Table 3 Presentation of Summary Analyses of Safety for Patients with Relapsed/Refractory NHL (All Histologies, Safety-Evaluable Population)

	Patients with R/R NHL (All Histologies)		
Group/cohort	All patients ≥ 0.6 mg	Cohort D ₂ Subcohort 2, D ₃ and D ₅ Step-up dosing, 2.5/10/30 ^a mg	Cohort D ₂ Subcohort 2, D ₃ , D ₄ and D ₅ Step-up dosing, 2.5/10/30 ^a mg
Analysis Population	Overall Safety Population ^{d, g}	Supportive Safety ^g	Supportive Safety ^{d, g}
No. of pts	N = 469	N = 195	N = 236
Dose (mg)	Fixed dosing, 0.6, 1, 1.6, 4, 10, 16, 25 mg or 10/16 ^b mg; step-up dosing, 2.5/10/16 ^c mg, 2.5/10/30 ^{a, d} mg or 0.5/2.5/10/30 ^e mg glofitamab	Step-up dosing, 2.5/10/30 ^a mg glofitamab	Step-up dosing, 2.5/10/30 ^a mg glofitamab
Patient population	Patients with R/R NHL	Patients with R/R NHL	Patients with R/R NHL
Source of patients	Cohorts A ₂ , B ₂ , D ₂ , F ₂ , B ₃ , B ₄ , D ₃ , D ₄ , D ₅	Cohort D ₂ Subcohort 2 (Part II dose-escalation) + Cohort D ₃ and Cohort D ₅ (Part III dose expansion) (Cohort D ₅ , Dex pre-medication)	Cohort D ₂ Subcohort 2 (Part II dose-escalation) + Cohort D ₃ + Cohort D ₄ and Cohort D ₅ (Part III dose expansion) (Cohort D ₅ , Dex pre-medication)
Histologies included	All NHL histologies per protocol ^f	All NHL histologies per protocol ^f	All NHL histologies per protocol ^f

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

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

^b 10 mg on C1D8, 16 mg on C2D1 and subsequent Q3W cycles.

^c 2.5 mg on C1D8, 10 mg on C1D15, 16 mg C2D1 and subsequent Q3W cycles.

^d Includes patients treated with two doses of obinutuzumab (Gazyva®, double Gpt [DGpt]) in Cohort D₂, Subcohort 4.

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

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

^g Safety population (R/R DLBCL) in Cohort D₃ excludes one patient who did not receive any study treatment with Gpt or glofitamab (enrolled in error).

Source: SCS

Assessor's comment

The adverse event profile of obinutuzumab has been established in patients with CLL and FL in conjunction with chemotherapy followed by maintenance treatment (iNHL) and not as monotherapy treatment only. In study NP30179 a single dose of obinutuzumab was given ahead of glofitamab (anti-CD20/anti-CD3 bispecific antibody) treatment to potentially reduce the risk of cytokine release syndrome (CRS).

Generally, the first dose of obinutuzumab is the dose causing infusion-related reactions (IRR), hypersensitivity reactions, and tumour lysis syndrome (TLS). These are thus the most relevant adverse events related to the sought indication given that only one infusion of obinutuzumab is administered and given the subsequent adverse events that mainly are considered to be related to the glofitamab treatment.

The primary safety population for glofitamab was the DLBCL population having received ≥ 2 prior therapies, but for obinutuzumab the pivotal safety population is considered the NHL population having received one dose of Gpt i.e. the overall safety population (N=469) as this is the largest population and the subsequent glofitamab dosing does not have any bearing on the safety analysis for obinutuzumab.

As the safety pool consists of different types of lymphomas, an OC has been raised in the efficacy section regarding the possibility that there may be a difference in CRS risk between patients with a more indolent lymphoma, such as follicular lymphoma, and a more aggressive B-NHL like DLBCL-NOS.

Patient exposure

Summary of Study Treatment Exposure, Initial Treatment Phase, Glofitamab ≥ 0.6 mg, Safety-Evaluable Monotherapy Patients
Protocol: NP30179

Name of Treatment	Glofitamab 2.5/10/30 mg Cohort D4 (N=41)	Glofitamab 2.5/10/30 mg Cohort D5(a) (N=41)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D4, D5 (N=236)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub 2), D3, D5 (N=195)	Glofitamab Doses ≥ 0.60 mg (N=469)
Glofitamab Categorized Dose Intensity(%)					
<90%	1 (2.5%)	0	1 (0.4%)	0	3 (0.7%)
$\geq 90\%$	39 (97.5%)	38 (100%)	224 (99.6%)	185 (100%)	447 (99.3%)
Obinutuzumab (Gpt)					
Number of Infusions	41	41	236	195	469
n	41	41	236	195	469
Mean (SD)	1.1 (0.3)	1.0 (0.2)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)
Median	1.0	1.0	1.0	1.0	1.0
Min - Max	1 - 2	1 - 2	1 - 3	1 - 3	1 - 3
Total Cumulative Dose(mg)					
n	41	41	236	195	469
Mean (SD)	1072.46 (263.89)	1048.78 (218.08)	1080.13 (301.04)	1081.75 (308.87)	1145.56 (466.25)
Median	1000.00	1000.00	1000.00	1000.00	1000.00
Min - Max	970.8 - 2000.0	1000.0 - 2000.0	970.8 - 3000.0	1000.0 - 3000.0	100.0 - 6000.0

Obinutuzumab (Gpt)					
Total Duration (Days)					
n	41	41	236	195	469
Mean (SD)	6.1 (20.8)	5.2 (26.4)	10.9 (55.8)	11.9 (60.6)	9.2 (48.0)
Median	1.0	1.0	1.0	1.0	1.0
Min - Max	1 - 99	1 - 170	1 - 708	1 - 708	1 - 708
Number of Treatment Cycles					
n	41	41	236	195	469
Mean (SD)	1.1 (0.3)	1.0 (0.2)	1.1 (0.3)	1.1 (0.3)	1.1 (0.2)
Median	1.0	1.0	1.0	1.0	1.0
Min - Max	1 - 2	1 - 2	1 - 2	1 - 2	1 - 2
Categorized Number of Cycles					
Less than 8 cycles	41 (100%)	41 (100%)	236 (100%)	195 (100%)	469 (100%)
Dose Intensity(%)					
n	41	41	236	195	469
Mean (SD)	99.93 (0.46)	102.44 (15.62)	100.21 (7.27)	100.27 (7.99)	100.17 (9.71)
Median	100.00	100.00	100.00	100.00	100.00
Min - Max	97.1 - 100.0	100.0 - 200.0	50.9 - 200.0	50.9 - 200.0	10.0 - 200.0

dGpt = two doses of Gazyva (Obinutuzumab); Sub = subcohort.

(a) Dexamethasone pretreated. (b) Includes patients treated with Glofitamab 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

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t_ex_GE600_I_CSR_SE_15JUN2022_30179.out
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Source: CSR, p. 1931-1932

Table 6 Exposure to Study Treatment (Glofitamab, Obinutuzumab, Tocilizumab): Patients with R/R DLBCL, ≥ 2 Previous Lines of Systemic Therapy, Fixed Dosing and Step-up Dosing (Safety-Evaluable Population) (cont'd)

Summary of Study Treatment Exposure, Initial Treatment Phase, (R/R DLBCL Patients, ≥2 Prior Lines of Systemic Therapy), Glofitamab
Doses ≥ 10 mg, Safety-Evaluable Monotherapy Patients
Protocol: NP30179

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)
Obinutuzumab (Gpt)					
Number of Infusions					
n	107	40	100	114	154
Mean (SD)	1.1 (0.3)	1.0 (0.2)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)
Median	1.0	1.0	1.0	1.0	1.0
Min - Max	1 - 3	1 - 2	1 - 3	1 - 3	1 - 3
Total Cumulative Dose (mg)					
n	107	40	100	114	154
Mean (SD)	1083.18 (308.22)	1050.00 (220.72)	1041.00 (277.83)	1078.23 (299.15)	1070.90 (280.48)
Median	1000.00	1000.00	1000.00	1000.00	1000.00
Min - Max	1000.0 - 3000.0	1000.0 - 2000.0	100.0 - 3000.0	1000.0 - 3000.0	1000.0 - 3000.0
Total Duration (Days)					
n	107	40	100	114	154
Mean (SD)	7.6 (29.8)	5.3 (26.7)	5.3 (24.9)	13.4 (71.7)	11.3 (63.2)
Median	1.0	1.0	1.0	1.0	1.0
Min - Max	1 - 213	1 - 170	1 - 184	1 - 708	1 - 708
Obinutuzumab (Gpt)					
Number of Treatment Cycles					
n	107	40	100	114	154
Mean (SD)	1.1 (0.3)	1.0 (0.2)	1.1 (0.2)	1.1 (0.3)	1.1 (0.2)
Median	1.0	1.0	1.0	1.0	1.0
Min - Max	1 - 2	1 - 2	1 - 2	1 - 2	1 - 2
Categorized Number of Cycles					
Less than 8 cycles	107 (100%)	40 (100%)	100 (100%)	114 (100%)	154 (100%)
8 cycles	0	0	0	0	0
9-11 cycles	0	0	0	0	0
12 cycles	0	0	0	0	0
>12 cycles	0	0	0	0	0
Dose Intensity(%)					
n	107	40	100	114	154
Mean (SD)	100.00 (0.00)	102.50 (15.81)	99.10 (9.00)	99.57 (4.60)	100.33 (9.00)
Median	100.00	100.00	100.00	100.00	100.00
Min - Max	100.0 - 100.0	100.0 - 200.0	10.0 - 100.0	50.9 - 100.0	50.9 - 200.0
Categorized Dose Intensity(%)					
<90%	0	0	1 (1.0%)	1 (0.9%)	1 (0.6%)
≥90%	107 (100%)	40 (100%)	99 (99.0%)	113 (99.1%)	153 (99.4%)

(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

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t_ex_PIV_I_SCE_SE_15JUN2022_30179.out
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Source: SCS

Assessor's comment

The median number of obinutuzumab infusions in the overall safety population was 1.0 (range: 1-3). Median dose intensity was 100.0% (range: 10%–200%) and 464 patients (98.9%) had a dose intensity $\geq 90\%$. This includes 31 patients in Cohort D2, subcohort 4, who received two obinutuzumab pre-treatment doses.

Adverse events

In the overall safety population, during the pre-treatment with a dose of 1000 mg obinutuzumab phase (Cycle 1, Day 1 [C1D1] to Cycle 1, Day 8 [C1D8]) prior to receiving the first glofitamab dose:

- There were 233/469 patients (49.7%) that reported an AE of any grade, irrespective of causality.
- The most common AEs (Preferred Term [PT] $\geq 5\%$) during the Gpt period were thrombocytopenia (47 patients, 10.0%), infusion-related reaction (44 patients, 9.4%) and anemia (25 patients, 5.3%).
- Grade ≥ 3 AEs during the Gpt period were reported in 65 patients (13.9%) and included two Grade 5 AEs: COVID-19 pneumonia and myocardial infarction, both considered not related to obinutuzumab per the investigator.
- There were 160/469 patients (34.1%) that had reported AEs that were considered by the investigator as related to obinutuzumab.
- The most common AEs considered as related by the investigator ($\geq 2\%$ incidence by PT) were infusion-related reactions (45 patients, 9.6%), thrombocytopenia (28 patients, 6.0%) and neutropenia (25 patients, 5.3%) and anemia (13 patients, 2.8%).
- Two patients discontinued all other study treatment due to AEs occurring following Gpt (Grade 5 myocardial infarction and Grade 4 ventricular tachycardia in one patient, both events with onset during the Gpt period but considered not related to obinutuzumab per the investigator and Grade 4 thrombocytopenia in one patient, with onset during the Gpt period and considered related to obinutuzumab per the investigator). The patient with Grade 5 myocardial infarction and Grade 4 ventricular tachycardia had pre-existing medical conditions including hypercholesterolemia, multilobar pulmonary embolism, paroxysmal atrial fibrillation, and hypertension. The patient with Grade 4 thrombocytopenia had pre-existing medical conditions including ongoing hypertension, type 2 diabetes, benign prostatic hyperplasia and anemia at baseline. The patient received platelet transfusions and the event resolved.
- One patient had a Grade 3, serious event of tumor lysis syndrome (TLS) with onset during the Gpt period, which was considered related to obinutuzumab and resolved after 2 days.

Assessor's comment

The applicant presented a very condensed overview of safety data for Gpt. This is not acceptable for an extension of indication application even though the safety profile of Gazyvaro is well known. Efforts should be made in order to better and more exhaustively present safety data from Gpt setting.

In the CSR on page 283 the MAH is referring to a table (t_xae_ctc1_ph_GE600_I_CSR_SE_15JUN2022_30179, starting page 3974) that includes all AEs for Gpt treatment and glofitamab by SOC, all PTs and Grade 1-5 in all cohorts having received glofitamab ≥ 0.6 mg (=880 pages): Please present AEs for the Gpt

treatment phase (before glofitamab was given) in a table by SOC and PT (including All Grade and Grade 3-4) with a reasonable cut-off for both the glofitamab primary safety population (N=154) as well as the overall safety population (N=469). **(OC)**

It is not understood how there can be more IRR AEs related to Gpt (45) than actual events (44). This also pertains to the AE Neutropenia (14/469; p. 3973) vs Related Neutropenia (25/469; p.4844. Please clarify. **(OC)**

Serious adverse event/deaths/other significant events

Grade ≥ 3 AEs during the Gpt period were reported in 65 patients (13.9%) and included two Grade 5 AEs: COVID-19 pneumonia and myocardial infarction, both considered not related to obinutuzumab per the investigator.

Assessor's comment

No assessment can be provided at this stage. A better presentation of SAE is needed.

Please present SAEs for the Gpt treatment phase (before glofitamab was given) in a table by SOC and PT (cut-off $\geq 1\%$) for both the glofitamab primary safety population (N=154) as well as the overall safety population (N=469). **(OC)**

There were two deaths during the Gpt treatment period:

COVID-19 pneumonia: No evaluation of relatedness is possible given the general immune suppressed state of this group of patients (due to NHL, prior treatment, and PD) and the ongoing pandemic at the time, although receiving a B-cell depleting agent as well as steroid is considered to add to the risk of dying from COVID-19.

Myocardial infarction: This occurred in a patient with a history of essential hypertension and hypercholesterolemia who received the following concomitant medication on Day 1, on which he received 100 mg obinutuzumab, according to the narrative: enoxaparin, ondansetron, dutasteride, furosemide, allopurinol, metoprolol, acyclovir, oxycodone, atorvastatin and tamsulosin. In the Gazyvaro SmPC it is stated: *Hypotension, as a symptom of IRRs, may occur during Gazyvaro intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyvaro infusion and for the first hour after administration (see section 4.4).* Furthermore, the SmPC states: *Cases of arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with Gazyvaro (see section 4.4). These events may occur as part of an IRR and can be fatal.* Given that there was a drop in BP compared to Day -8 (from 124/76 to 102/68) it is considered plausible, that obinutuzumab together with the continued antihypertensive therapy led to the event of myocardial infarction on Day 2 (within 24 hrs of obinutuzumab treatment). The patient discontinued from the study and received bendamustine D12 and died of myocardial infarction on D42 in the setting of PD.

Adverse events of special interest for obinutuzumab:

In the CSR the MAH has presented a section with the headline "Adverse Events of Special Interest for Obinutuzumab": It is not understood why Infusion-related reaction (IRR) is not included. The MAH has included secondary malignancies, which is considered impossible to evaluate given prior treatments, that only one dose of obinutuzumab administered, and subsequent glofitamab treatment. The MAH has also

included tumour lysis syndrome which 10/469 patients experienced; all after glofitamab administration with a median of 2 days from first glofitamab dose (1.0 – 57.0 days).

Please present information regarding IRR, TLS, and hypersensitivity reactions in the primary and overall safety population before glofitamab treatment. **(OC)**

The MAH is also requested to present IRR by All Grade and Grade 3-4 in a table for both the glofitamab primary safety population (N=154) as well as the overall safety population (N=469) in the following subgroups of patients (before glofitamab treatment); according to B-cell count, by age group, +/- prior CAR-T treatment, time since last rituximab therapy, according to the Ki67 level, and low vs. high tumour burden. **(OC)**

Laboratory findings

No Gpt specific Lab clinical evaluation has been provided.

Assessor's comment

From the Gazyvaro SmPC: *Transient elevation in liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase) has been observed shortly after the first infusion of Gazyvaro.*

Please present the most frequent laboratory findings for the Gpt treatment phase (before glofitamab was given) in a table for both the glofitamab primary safety population (N=154) as well as the overall safety population (N=469). **(OC)**

Safety in special populations

Assessor's comment

In the CSR the MAH has presented a section with the headline "*Adverse Events of Special Interest for Obinutuzumab*": It is not understood why Infusion-related reaction (IRR) is not included. The MAH has included secondary malignancies, which is considered impossible to evaluate given prior treatments, only one dose of obinutuzumab administered, and subsequent glofitamab treatment. The MAH has also included tumour lysis syndrome which 10/469 patients experienced; all after glofitamab administration with a median of 2 days from first glofitamab dose (1.0 – 57.0 days).

The MAH is requested to present IRR by All Grade and Grade 3-4 in a table for both the glofitamab primary safety population (N=154) as well as the overall safety population (N=469) in the following subgroups of patients (before glofitamab treatment); according to B-cell count, by age group, +/- prior CAR-T treatment, time since last rituximab therapy, according to the Ki67 level, and low vs. high tumour burden. **(OC)**

Safety related to drug-drug interactions and other interactions

No new DDI data were provided for Gpt within this application.

Assessor's comment

From the Gazyvaro SmPC:

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug-drug interaction studies have been performed, although limited drug-drug interaction sub-studies have been undertaken for Gazyvaro with bendamustine, CHOP, fludarabine and cyclophosphamide (FC), and chlorambucil.

A risk for interactions with other concomitantly used medicinal products cannot be excluded.

Pharmacokinetic interactions

Obinutuzumab is not a substrate, inhibitor, or inducer of cytochrome P450 (CYP450), uridine diphosphate glucuronyltransferase (UGT) enzymes and transporters such as P-glycoprotein. Therefore, no pharmacokinetic interaction is expected with medicinal products known to be metabolised by these enzyme systems.

Co-administration with Gazyvaro had no effect on the pharmacokinetics of bendamustine, FC, chlorambucil or the individual components of CHOP. In addition, there were no apparent effects of bendamustine, FC, chlorambucil or CHOP on the pharmacokinetics of Gazyvaro.

No new concerns regarding obinutuzumab interactions are anticipated.

Discontinuation due to adverse events

Two patients discontinued all other study treatment due to AEs occurring following Gpt (Grade 5 myocardial infarction and Grade 4 ventricular tachycardia in one patient, both events with onset during the Gpt period but considered not related to obinutuzumab per the investigator and Grade 4 thrombocytopenia in one patient, with onset during the Gpt period and considered related to obinutuzumab per the investigator). The patient with Grade 5 myocardial infarction and Grade 4 ventricular tachycardia had pre-existing medical conditions including hypercholesterolemia, multilobar pulmonary embolism, paroxysmal atrial fibrillation, and hypertension. The patient with Grade 4 thrombocytopenia had pre-existing medical conditions including ongoing hypertension, type 2 diabetes, benign prostatic hyperplasia and anemia at baseline. The patient received platelet transfusions and the event resolved.

One patient had a Grade 3, serious event of tumour lysis syndrome (TLS) with onset during the Gpt period, which was considered related to obinutuzumab and resolved after 2 days.

Assessor's comment

Arrhythmias and myocardial infarction with possible fatal outcomes are known risks with Gazyvaro and a warning is included in section 4.4 as it is the case for possible severe/life threatening thrombocytopenia and TLS events.

The MAH is requested to present (in a table) the reasons why patients did not continue treatment with glofitamab after obinutuzumab treatment: in the overall safety population 450/469 patients received glofitamab, so this concerns 19 patients. Direct links to their narratives is also requested. **(OC)**

Post marketing experience

. Obinutuzumab has a well-established safety profile when administered at a dose of 1000 mg (in combination with chemotherapy) for 6 treatment cycles in patients with CLL and 6 or 8 treatment cycles in patients with FL up to 2 years as monotherapy maintenance (every 2 months, or until disease progression).

Assessor's comment

No new safety concern is anticipated to be identified in view of the administration scheme proposed and the known safety profile of Gazyvaro.

In study NP30179 in the ≥ 0.6 mg glofitamab cohorts obinutuzumab was given as one single dose (except for in the D2 subcohort 4 where 2 doses were given; N=31). Thus, safety in this study cannot be directly inferred from the SmPC for Gazyvaro as the adverse reactions are pooled (obinutuzumab + chemotherapy). The main adverse reaction of interest after the first dose of obinutuzumab is considered to be IRR and the MAH has been requested to present this for the relevant populations.

RETROSPECTIVE REVIEW OF CRS CASES IN OBINUTUZUMAB CLINICAL STUDIES

As part of the process to update the obinutuzumab product information with a new indication for a single 1000 mg dose of obinutuzumab to reduce the risk of CRS induced by glofitamab, the Marketing Authorisation Holder (MAH) investigated the basis for the CRS wording related to infusion related reactions (IRRs) in Section 4.4, Special warnings and precautions for use in the obinutuzumab EU Summary of Product Characteristics (SmPC). The currently approved EU SmPC (10 May 2022) states – “IRRs may be related to cytokine release syndrome which has also been reported in Gazyvaro treated patients.” This wording was added at the request of the Committee for Medicinal Products for Human Use (CHMP) to the initially approved EU SmPC version 1.0 (EMA/H/C/002799/0000, dated 23 July 2014) during the initial MAA for the indication of CLL and was slightly amended in the EU SmPC v3.0 during the filing of FL as a further therapeutic indication.

The MAH performed a retrospective assessment of cases reported in the clinical study reports (CSRs) for Study BO21004, which was submitted with the initial MAA for CLL indication in 2013, and Study GAO4753g/GO01297 (GADOLIN), which was submitted during the filing of FL.

IRRs are a well-known effect of anti-CD20 antibodies and a consequence of cytokine release. They are also the most frequent AE seen with obinutuzumab.

CRS is a supraphysiologic response following any immune therapy and has some overlapping features with IRRs often resulting in a lack of clarity in its consistent diagnosis, severity grading, reporting, and management (Shimabukuro-Vornhagen et al. 2018; Wang and Han, 2018). A suspected diagnosis of CRS should be made based on clinical signs and symptoms. Hallmarks of CRS are fever with hypotension and hypoxia. Elevation of plasma inflammatory cytokine(s) serve as biomarker to diagnose CRS, although the cytokine profile and dynamics could potentially differ among cancer immunotherapies. A blood sample should be collected and analyzed for cytokines when CRS is suspected. IL-6, IL-8, tumor necrosis factor (TNF)- α , and IFN- γ are recommended as a core cytokine panel (Lee et al. 2014).

Retrospective review of the CSRs for Study BO21004 (Reports 1038127, 1054798, 1057363, 1058935, 1056550, 1058936; Goede et al. 2014) showed that of the 781 patients randomized in this study, wording related to CRS was mentioned in 3 patients; detailed analysis of these cases revealed that the clinical symptoms suggestive of CRS like fever ($\geq 38^\circ$ C), hypoxia or hypotension were not reported in 2 patients whereas the third patient only reported fever (39.2° C). The second hallmark for the diagnosis of CRS is cytokine biomarkers. Per the published literature and decision tree for assessing CRS, evidence

to conclude that CRS is present includes cytokine-driven clinical signs and symptoms, increase in CRS biomarkers such as IL-6 and/or responsiveness to tocilizumab or other cytokine-directed therapies (Stewart et al. 2022). Cytokine levels were not measured in Study BO21004 per the protocol; therefore, assessment of the cases was only based on the reported cytokine-driven clinical signs and symptoms. In addition, IRR was the reported event in all 3 patients and CRS was only mentioned as a “comment” for IRR in these patients.

A review of the initial MAA Summary of Clinical Safety (SCS) showed that none of the obinutuzumab treated patients had reported CRS and no cases indicative of CRS were identified in a retrospective review of the CSR for Study GAO4753g/GO01297 (GADOLIN; Report No.1092968) supporting the follicular lymphoma filing.

Furthermore, since the Development International Birth Date (DIBD, 13 August 2007) and International Birth Date (IBD, 01 November 2013), CRS has not been identified as a safety concern associated with obinutuzumab during regular risk assessments from an estimated total of 6082 obinutuzumab-treated-patients in clinical trial participation and 108,822 obinutuzumab-treated-patients from marketing experience.

Based on the detailed retrospective assessment of cases in Study BO21004 which originally led to addition of “CRS” wording in the SmPC and considering the biological plausibility and lack of identification of CRS as a safety signal during routine pharmacovigilance activities over ten years, the current CRS wording in the SmPC is unsubstantiated and could be misleading, as the reactions reported in patients randomized to Study BO21004 were reported after obinutuzumab infusion and are with a very high likelihood, a manifestation of IRR. Therefore, the MAH deems an update to the existing CRS wording in the SmPC section 4.4 is warranted and proposes revising the text to remove the statement that CRS has been reported in Gazyvaro treated patients as follows:

“Infusion related reactions (IRRs)

*The most frequently observed adverse drug reactions in patients receiving Gazyvaro® were IRRs, which occurred predominantly during infusion of the first 1,000 mg. **IRRs may be related to cytokine release syndrome which has also been reported in Gazyvaro treated patients.** In CLL patients who received the combined measures for prevention of IRRs (adequate corticosteroid, oral analgesic/anti-histamine, omission of antihypertensive medicine in the morning of the first infusion, and the Cycle 1 Day 1 dose administered over 2 days) as described in section 4.2, a decreased incidence of IRRs of all grades was observed.”*

Assessor’s comment

The MAH is requesting to have the reference to cytokine release syndrome in the SmPC removed. To this end the MAH has looked through previous clinical study reports and reassessed the adverse events that could lead to the diagnosis CRS. No data apart from the MAHs statement/assessment (above) has been presented. CRS is also included in the rituximab SmPCs.

Regarding the CRS frequency in the initial Gazyvaro studies: CRS was not a commonly known entity at the time of the obinutuzumab studies, which readily could explain the low frequency.

It seems contradictory to claim a CRS prevention indication while the Gazyvaro SmPC report IRR linked to CR syndromes. However, according to Cheson et al., 2017: it was hypothesized that the increase in IRRs during the first infusion of obinutuzumab was potentially due to cytokine release as it was noted that peak levels of IL-6, IL-8, IL-10, TNF- α , and interferon-gamma were significantly higher during the first infusion of obinutuzumab compared with rituximab. Levels returned to baseline and did not increase

in subsequent infusions. Other literature references also report cytokine release during IRR events without formal or confirmed CRS events.

The Applicant is requested to provide a detailed review of all CRS cases reported overall with obinutuzumab in trials, post-marketing experience and literature along with any pre-clinical data that could help elucidate whether IRR could be linked to CRS. The submission of such data should be considered as a standalone procedure. **(OC)**

Given the above uncertainties, the MAH's claim is currently not considered substantiated.

3.5.1. Discussion on clinical safety

The adverse event profile of obinutuzumab has been established in patients with CLL and FL in conjunction with chemotherapy followed by maintenance treatment (iNHL) and not as monotherapy treatment only. In study NP30179 a single dose of obinutuzumab was given ahead of glofitamab (anti-CD20/anti-CD3 bispecific antibody) treatment to potentially reduce the risk of cytokine release syndrome (CRS).

The dossier for this application is the dossier for the glofitamab application and very little information specifically pertaining to the safety of obinutuzumab monotherapy has been presented: No tables of various adverse events for the Gpt period were displayed in the SCS but instead references to tables of several hundred pages that included glofitamab AEs were given, which precludes an overview of Gpt safety. Furthermore, this condensed overview is not acceptable for an extension of indication application even though the safety profile of Gazyvaro is well known. Efforts should be made in order to better and more exhaustively present safety data from Gpt setting; relevant tables have been requested.

The MAH also took the opportunity to request to have the reference to cytokine release syndrome in the SmPC amended: a detailed review of all CRS cases reported overall with obinutuzumab in trials, post-marketing experience and literature (narratives should be included) along with any pre-clinical data is awaited in order to help elucidate whether IRR could be linked to CRS. The submission of such data should be considered as a standalone procedure.

Additional expert consultations

Not Applicable

Assessment of paediatric data on clinical safety

Not Applicable

3.5.2. Conclusions on clinical safety

The safety profile of Gpt is not expected to differ from the one known for Gazyvaro. However, the applicant should make all efforts in order to better present the Gpt safety data and consider amending the 4.4 Gazyvaro CRS warning within a standalone procedure.

3.5.3. PSUR cycle

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.

4. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

Section in the RMP	Summary of changes
Part I: Product Overview	The ATC code was updated. The indication and dosage information for Gazyvaro pre-treatment (Gpt) was added. The previously approved short duration infusion (SDI) was moved from 'proposed label update' to 'current'.
Part II: Module SI-Epidemiology(s) of the Indications and Target Population(s)	A new indication was added: Pre-treatment with Gazyvaro to reduce the risk of CRS induced by glofitamab.
Part II: Module SII-Nonclinical Part of the Safety Specification	Update to a subheading based on the EMA guidelines for Pregnancy and Breastfeeding Women (GVP P. III).
Part II: Module SIII-Clinical Trial Exposure	New indication of Gpt and related data was added. Patient exposure data from Study NP30179 was added to Table 2. Exposure and cut-off date for Study GAO4915g was updated to reflect the most recent data. Cut-off dates were updated for Studies BO20999/BO21003, and GAO4768g, to reflect the most recent information. Footnotes pertaining to Study NP30179 were added in Tables 4, 6, 8, 10, and 12.
Part II: Module SIV-Populations Not Studied in Clinical Trials	Updates based on the EMA guidelines for Pregnancy and Breastfeeding Women (GVP P. III) were added.
Part II: Module SV-Post-Authorization Experience	Information was updated with the latest post-authorization exposure data.
Part II: Module SVII-Identified and Potential Risks	Section was updated with a footnote for Study NP30179 as no new safety concerns were identified with Gazyvaro used as a pre-treatment. Removed footer d in Table 17 and footer c in Table 21 as the 10 Sept 2016 CCOD for Study BO21223 was outdated, and the outputs contained data from CCOD 30 July 2021. Text in the 'Nature of IRRs' was updated to remove the statement that cases of cytokine release syndrome have been reported with obintutuzmab.

Section in the RMP	Summary of changes
Part III: Pharmacovigilance Plan	Updates to headings based on EMA guidelines for Pregnancy and Breastfeeding Women (GVP P. III).
Part VI: Summary of the Risk-Management Plan	Updated to include the new indication of Gazyvaro as a pre-treatment to reduce the risk of CRS induced by glofitamab.
Annex 7	Summary tabulations of prospective and retrospective ICSRs on pregnancy have been appended.
Annex 8	Annex 8 was updated to reflect the changes to this EU RMP.

Assessor's comment:

The proposed RMP amendments based on the EMA guidelines for Pregnancy and Breastfeeding Women (GVP P.III) and updated data from the Study BO21223/GALLIUM to reflect the completed status are acceptable. The update of RMP with the information reflecting the new sought indication: Pre-treatment with Gazyvaro to reduce the risk of CRS induced by glofitamab, could be acceptable pending the CHMP conclusion on the procedure regarding extension of indication.

4.1. Overall conclusion on the RMP

The changes to the RMP could be acceptable pending the outcome of the procedure as applicable.

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

The indication sought for Gazyvaro (obinutuzumab) is: *Obinutuzumab is indicated as a pretreatment to reduce the risk of cytokine release syndrome (CRS) induced by glofitamab.*

The aim of Gpt is to reduce the frequency and severity of CRS, a well-established adverse event associated with glofitamab (and other immune-active drugs). CRS is treatable but requires close monitoring and supportive treatment, typically in the ICU-setting. Emergence of CRS will often result in delay or discontinuation of the ongoing anti-lymphoma treatment which carries a risk of worsening prognosis. Glofitamab is under evaluation for 3L+ treatment of DLBCL. The aim of therapy is to reduce the lymphoma burden as much as possible (complete response, CR, corresponding to no detectable lymphoma) and to follow patients to see how long they maintain their "lymphoma-free" status (duration of complete response, DOCR). Cure is possible but is not considered very likely given the heavily pre-treated nature of the cohort under investigation.

Patients with DLBCL who have failed at least 2 prior systemic therapies are a vulnerable patient group due to both the nature of their aggressive cancer as well as side effects from previous treatments. As such, it makes sense to try to develop companion therapeutics that will alleviate some of the risks inherent in 3L+ treatment to help ensure that efficacious doses of anti-lymphoma treatment can be reached without undue delay and with a minimum of unfavourable effects. This is particularly true for

“class-specific” adverse events related to the mechanism of action of anti-lymphoma treatment such as CRS.

5.1.2. Available therapies and unmet medical need

No other medicinal product is approved for the prophylaxis of CRS. Corticosteroids are commonly used for this end but are not approved for the precise indication.

5.1.3. 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.

No specific outcome(s), end-point(s) or efficacy cohort for the evaluation of Gpt have been defined for this study. No patients have been treated with glofitamab without Gpt meaning there is no control arm available for comparison.

5.2. Favourable effects

It is not yet possible to evaluate the efficacy of Gpt based on the dossier submitted.

5.3. Uncertainties and limitations about favourable effects

The necessary information required (defined outcome(s), end-point(s) and an efficacy cohort) to evaluate the effect of Gpt has been requested. Until such data have been provided, the benefit of Gpt is uncertain. A major additional uncertainty is that no glofitamab patient experience without Gpt is available meaning that even when the requested information has been provided, it may still not be possible to ascertain effect of Gpt. In lieu of evidence of clinical effects, the MAH has provided pre-clinical data from animal studies. However, these models also have severe limitations as they do not reliably approximate the therapeutic context in which Gpt and glofitamab are intended.

No new exposure-response relationships of obinutuzumab for PD, efficacy or safety nor studies for dose level selection have been provided. Many uncertainties are raised concerning the selection of the Gazyvaro MA dose level by default even more when considering the fact that there is no possibility to identify a potential beneficial effect of Gpt when assessing the clinical data provided.

The majority of Gazyvaro-pretreated patients were already b-cell depleted prior to Gpt. Linking a potential effect on CRS rate to Gpt will anyway be very difficult since recent anti-CD20 therapy (rituximab and/or obinutuzumab) is very likely to bias the interpretation of data.

In addition to the limitations concerning the evaluation of effect, it must be borne in mind that the mechanism of action of obinutuzumab is theoretically antagonistic to that of glofitamab. Therefore, a further uncertainty awaiting illumination is whether Gpt negatively impacts the anti-lymphoma effect of glofitamab.

Another concerning uncertainty within this application is dose selection. While Gazyvaro is administered at its MA dose with no dose-finding studies conducted, the choice of glofitamab step-up dosing scheme could also be critical for this application given the unclear dose selection and rationale raised within glofitamab application. It is not excluded that lower dose levels of glofitamab and Gpt could provide more comprehensive efficacy and safety results.

Too many variables appear to possibly bias the response that can be imputed to Gpt on CRS rates and grades. In the absence of any control arm or planned analysis to elaborate on a possible beneficial effect of Gpt, the effect of Glofitamab step-up dosing, prior anti-CD20 therapies and other administered corticosteroids pre-treatments on the potentially observable low CRS rate cannot be ruled out.

If the above issues remain remiss, it may not be possible to assess benefit of Gpt in a meaningful manner.

5.4. Unfavourable effects

The adverse event profile of obinutuzumab has been established in patients with CLL and FL in conjunction with chemotherapy followed by maintenance treatment (iNHL) and not as monotherapy treatment only. In study NP30179 a single dose of obinutuzumab was given ahead of glofitamab (anti-CD20/anti-CD3 bispecific antibody) treatment to potentially reduce the risk of cytokine release syndrome (CRS).

5.5. Uncertainties and limitations about unfavourable effects

The dossier for this application is the dossier for the glofitamab application and very little information specifically pertaining to the safety of obinutuzumab monotherapy has been presented: No tables of various adverse events for the Gpt period were displayed in the SCS but instead references to tables of several hundred pages that included glofitamab AEs were given, which precludes an overview of Gpt safety. Furthermore, this condensed overview is not acceptable for an extension of indication application even though the safety profile of Gazyvaro is well known. Efforts should be made in order to better and more exhaustively present safety data from Gpt setting; relevant tables have been requested.

Of special concern are the Adverse events of special interest for obinutuzumab: IRR, which needs to be described for subgroups of patients, and TLS and hypersensitivity reactions related to the obinutuzumab treatment only.

The MAH also took the opportunity to request to have the reference to cytokine release syndrome in the SmPC amended: a detailed review of all CRS cases reported overall with obinutuzumab in trials, post-marketing experience and literature (narratives should be included) along with any pre-clinical data is awaited in order to help elucidate whether IRR could be linked to CRS. The submission of such data should be considered as a standalone procedure.

5.6. Effects Table

Table 2. Effects Table for Gazyvaro (data cut-off: 15 JUNE 2022)

Effect	Short description	Unit	Treatment Gazyvaro ¹	Uncertainties / Strength of evidence	References
Favourable Effects[#]					
CRS-rate (ASTCT)	All grades Grade 3-4	N (%)	99/154 ³ (64.3) 11/195 ³ (5.6)	Single-arm trial, no comparator, no defined objective(s), end-point(s) or efficacy cohort.	CO p. 28 CSRbody1 p. 1383
CR-rate		N (%)		Pending definition of efficacy cohort	
DoCR				Pending definition of efficacy cohort	
Unfavourable Effects* N=469=Overall Safety Population					

Effect	Short description	Unit	Treatment Gazyvaro ¹	Uncertainties / Strength of evidence	References
All AEs	Any grade	N (%)	233 (49.7)		CO p.30
Grade ≥ 3 AEs		N (%)	65 (13.9)	2 deaths; COVID-19 and myocardial infarction	CO p.30 and/or CSR p. 283 ²
SAEs		N (%)		Not found; awaits new tables	
Immune related reactions (IRR)	All grades Grade 3-4 SAE	N (%)	45 (9.6) 5 (1.1.) 10 (2.4)		Ditto
Thrombocytopenia (AE)	All grades Grade 3-4	N (%)	47 (10.0)		Ditto CSR p.3983
Neutropenia, Related AE	All grades	N (%)	25 (5.3)	Fewer Neutropenia AEs than related Neutropenia AEs. OC raised	CSR p. 3973 and p. 4847
TLS			?		
Hyper-sensitivity reactions			?		

Abbreviations: CO; Clinical Overview,

Notes:

#Objectives, end-points and efficacy cohort concerning the efficacy of Gpt have been requested

¹1000 mg Gazyvaro IV according to the SmPC

²Tables regarding various adverse events for Gpt (and not glofitamab) has been requested

³Note the all grade and grade 3-4 CRS come from different cohorts. A defined cohort has been requested

*AEs occurring in the Gpt period (D1-D7; before the first glofitamab dose was administered)

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Even though the results of glofitamab in 3L+ patients with R/R DLBCL are encouraging, significant uncertainty is associated with the evaluation of the potential effect of Gpt on lowering the risk of CRS. No favourable effect can be claimed for Gpt in the prevention of CRS associated with glofitamab at this stage.

Regarding unfavourable effects: These are not considered to significantly affect the B/R as only one dose is given followed by treatment with glofitamab with the adverse events related to the latter dominating. Furthermore, the safety profile of Gpt is not expected to differ from the one known for Gazyvaro,

5.7.2. Balance of benefits and risks

Major uncertainties associated with the assessment of favourable effects of Gpt preclude evaluation of the balance of benefits and risks at this time.

5.7.3. Additional considerations on the benefit-risk balance

5.8. Conclusions

The overall B/R of obinutuzumab in the context of prevention of CRS is negative as efficacy is currently not considered shown in the population for which approval is sought.

Annex 1: Rapporteur Request for Supplementary Information

Major objections

Non clinical aspects

Clinical pharmacology aspects

1. Although the proposed mechanism of action for the indication is plausible and the PD endpoint glofitamab receptor occupancy (RO) does seem meaningful in the setting, the data provided, namely the exposure-response analysis of glofitamab, does not allow conclusions on a causal relationship to obinutuzumab receptor binding, which has not been measured. For instance, no Exposure-response relationships of obinutuzumab for incidence rates of CRS has been provided. It is unknown whether all receptors are bound, thus it is not possible to conclude that the ones not bound by glofitamab are bound by obinutuzumab. Furthermore, even if all receptors were bound, they could be blocked by former administrated drugs from earlier treatments.

As there is no comparison without obinutuzumab, neither at least a comparison with only non-pretreated (with other possible binders of the receptor in question) it is not possible to conclude definitely on the action of obinutuzumab. Overall, even though obinutuzumab has been used under such level of dose (1g), the adequacy of the selected dose under the scope of the claimed indication is not known. No justification or PK/PD rationale for the chosen single 1 g dose has been discussed. This is essentially due to the design of NP30179 study in which no data without obinutuzumab and with an alternative obinutuzumab dosage regimen are available / provided. The MAH should justify how the design of the study does allow certain conclusions on the PD of obinutuzumab and discuss how the proposed dose is justified from a PK/PD perspective. Alternatively, the effectiveness of the claimed dose should be supported by clinical (efficacy/safety) data.

Clinical efficacy aspects

2. No clinical evidence to suggest that Gpt protects against CRS has been at all presented. No efficacy analysis was planned for Gpt per protocol and no efficacy analysis population was defined either. Even though additional data are provided as part of responses to RSI, it is not quite clear what relevant conclusion could be made from such exploratory data. The totality of the concerns raised on evaluation of efficacy including the lack of efficacy cohort, defined outcome(s), end-point(s), the absence of a clinical comparator arm and representative pre-clinical correlatives together constitute an outstanding objection: the B/R of the intended indication for Gpt cannot be ascertained.

Clinical safety aspects

None.

RMP

Other concerns

Non clinical aspects

None.

Clinical pharmacology aspects

3. A tabulated summary of excluded observations in the population PK analysis for obinutuzumab should be provided.
4. No pcVPCs were found/provided, shrinkage was not presented and the model was not validated by bootstrap analysis. To complete the model evaluation, these diagnostics should be provided.

Clinical efficacy aspects

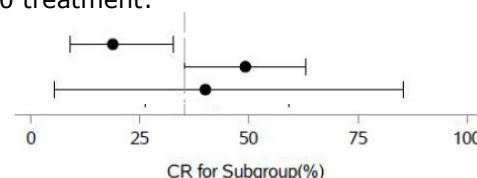
5. The MAH is asked to provide information on the epidemiology and risk factors of CRS as well as any relevant screening tools and prevention strategies they consider pertinent. In particular, evidence that high b-cell counts and/or tumour burden translate to a higher risk of CRS would be welcomed.
6. The MAH is requested to define an efficacy cohort to evaluate Gpt's ability to prevent CRS. The MAH is then requested to provide data on CRS-rate for the chosen Gpt efficacy cohort. The cohorts from study NP30179 that contribute patients to this efficacy cohort are requested (including numbers of patients from each cohort). Data from cohorts investigating other dosing escalation regimens than the one selected as the RP2D should not be overlooked and the corresponding results should be presented separately.
7. According to the MAH, the reason why no comparator cohort has been provided seems to be primarily ethical. The ethical reasons underlying why patients cannot receive glofitamab without obinutuzumab pre-treatment mentioned above, are not very clearly communicated, however, it is broadly stated that the risk of CRS would be "substantial and unacceptable", both in terms of frequency and severity. The MAH is requested to discuss in greater detail what constitutes the mentioned ethical reason(s) and to provide data to support the position that glofitamab cannot be given without obinutuzumab pre-treatment in the intended clinical setting, namely 3L+ DLBCL patients (all of whom will have been previously exposed to other anti-CD20 targeting therapy, many of them within months of starting glofitamab). This discussion should include specific mention of why glofitamab therapy necessitates pre-treatment when other CD20xCD3 targeting bispecific antibodies (mosunetuzumab, epcoritamab, odronextamab, among others) do not seem to have such a requirement.
8. The wording "There is no patient experience with glofitamab in the monotherapy setting without Gpt", repeated twice on p. 10 in the Clinical Overview, seems to suggest that there could be experience with glofitamab without Gpt in patients in the combination therapy setting. The MAH is requested to provide such data, if they exist, including a comparison of the rates and severity of CRS in Gpt pre-treated and non-pre-treated cohorts, respectively. A clear description (preferably a figure) of when treatments (obinutuzumab, glofitamab and any other treatments such as steroids, which might impact CRS) are given in the respective cohorts is also requested.

Furthermore, the MAH is requested to provide any data on glofitamab treatment without Gpt that may be available from other trials.

9. The MAH is asked to discuss whether other means of minimizing risk of CRS might be feasible in the patient population for which glofitamab is intended. It seems glofitamab is the only bispecific CD20xCD3 targeting treatment thus far, where anti-CD20 prophylaxis is employed. For other drugs in this class, including mosunetuzumab (in FL) and epcoritamab (in DLBCL), CRS-minimization was done by step-up dosing. Specifically, the MAH is asked whether a lower initial dose of glofitamab might have potential for further CRS-mitigation?
10. Gpt dose selection rationale is very limited and should be further elaborated by the applicant. In light of the absence of Gpt dose-finding studies, the applicant should elaborate on the relevance of the MA dose scheme retained for the pre-treatment setting. Pertinence of lower dose levels should be discussed.
11. A comment from the MAH on how the addition of another step-up dose will impact the overall delivery of anti-lymphoma treatment in this population is also requested (IE what is the MAH's perception of the balance between the extra 1 week of treatment before target dose glofitamab is reached contra the potential for lower CRS risk?).
12. The Applicant should elaborate on lower dose levels of glofitamab and Gpt that could provide more comprehensive efficacy and safety results.
13. Given that a large proportion of patients have recently failed CD20-targeting treatment and that 73% of enrolled patients are already b-cell depleted before Gpt, the MAH is asked to justify how Gpt contributes to lowering the risk of CRS in this patient population. Specifically, the answer should include a discussion on whether or not rituximab also blocks CD20, and thereby hinders glofitamab binding and a discussion on whether any residual rituximab will compete with obinutuzumab for binding to CD20.
14. If part of the MAH's proposed answer includes a suggestion that Gpt "debulks" the lymphoma burden, thereby reducing the CRS risk, the MAH is further requested to provide evidence that obinutuzumab retains efficacy in patients who have recently failed rituximab.
15. One subcohort in trial NP30179 was pre-treated with 2 doses of obinutuzumab (cohort D2sub4). For this cohort, 10/31 (32.3%) patients had CRS grade ≥ 2 . The corresponding rate of CRS ≥ 2 in cohorts D2sub2, D3, D5 was 41/195 (21%) (source: CSR body1 p 1382+1383). The MAH is asked to discuss the significance of these results in terms of the claimed effect of CRS-mitigation (it seems odd to have greater CRS-rate with greater Gpt).
16. If the MAH's proposed efficacy cohort for Gpt consists of lymphoma patients not included under the in-/exclusion criteria above, the in-/exclusion criteria for these patients should be provided, along with data on the risk of CRS etc as requested elsewhere. It should be specified if these patients, in line with the DLBCL extension cohorts, have received ≥ 2 prior systemic lines of therapy and single-dose Gpt as well as the proposed registrational step-up dosing of glofitamab (OC).
17. The MAH is requested to provide a comparison of CRS-rates between patients treated with the different corticosteroids permitted in the NP30179 study. Any differences in CRS-rates associated with corticosteroid choice should be discussed.

18. As is apparent from table 1 above (CSR Gazyvaro application), evaluation of the efficacy of Gpt in reducing CRS was not even an objective of this trial. A secondary objective “to establish the safety, tolerability, and pharmacokinetics of Gpt” was the only stated objective concerning Gpt. The MAH is requested to discuss how not including an objective to investigate the efficacy of Gpt in the trial impacts the ability to evaluate the efficacy of Gpt in the intended clinical setting.
19. None of the endpoints/outcome measures listed in conjunction with the only secondary objective to include Gpt seem to address the “safety, tolerability and pharmacokinetics of Gpt” directly (Listed outcome measures include: *INV-assessed CR rate*, *IRC- assessed CR rate*, *IRC-assessed overall response rate (ORR)*, *INV-assessed ORR*, *IRC-assessed ORR*, *IRC - and INV-assessed duration of complete response (DOCR)*, *IRC- and INV-assessed duration of response (DOR)*, *IRC-assessed progression-free survival (PFS)* *INV-assessed PFS*, *Overall survival*, *IRC-assessed time to first complete response (TFCR)*, *INV-assessed TFCR*, *IRC-assessed time to first overall response (TFOR)*, *INV-assessed TFOR*, *Incidence of anti-drug antibody (ADA) formation and events related to immune complex deposition and activation*). As such, it does not seem like assessment of Gpt was a planned goal of the trial. The MAH is requested to comment on this.
20. Depending on the efficacy cohort chosen by the MAH to evaluate efficacy of Gpt, the MAH is asked to provide the dates of first and last patient enrolment to the study cohorts that form the efficacy cohort.
21. Baseline data from the chosen efficacy cohort are requested
22. From the glofitamab application, recently anti-CD20-treated patients seem to fare worse than those who are further temporally removed from last anti-CD20 treatment:

Time since Last Anti-CD20 Therapy	n=108	
3 months or less	48 (44%)	19% (9%, 33%)
More than 3 months	55 (51%)	49% (35%, 63%)
Unknown/Missing	5 (5%)	40% (5%, 85%)



Source document: *ema-responses-86.pdf*.

As such, mandatory pre-treatment with another CD20-targeting agent (obinutuzumab) needs to be carefully justified. Some reassurance on this point seems to be provided from non-clinical data in the protocol. The MAH is encouraged to include such data in the requested justification above.

23. The MAH is invited to provide a discussion, ideally based on evidence, on the impact of Gpt blocking CD20 on glofitamab’s anti-lymphoma activity. Some reassurance on this point seems to be provided from non-clinical data in the protocol. The MAH is encouraged to include such data in the requested justification above.

	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, Efficacy cohort for Gpt			
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24. The MAH is asked to provide the number of patients from the Gpt efficacy cohort falling within the age brackets listed in the table above. Furthermore, the CRS rate, CR-rate and DoCR in each age bracket are requested.
25. The MAH is requested to comment on whether a single dose of obinutuzumab can be expected to provide CRS-protection in a patient who has recently been exposed to anti-CD20 therapy and where residual effects of such recent treatment can be readily ascertained with a standard blood test.
26. The MAH is asked to discuss whether the pre-clinical models included in this application (pre-treatment with a single dose of obinutuzumab) can be expected to reflect the clinical context in which glofitamab is intended (patients who have ALL received prior anti-CD20 in therapeutic doses and where the majority have received such treatment so recently that the effects can still be measured in a blood sample).
27. The reference values for the normal interval of B-cells for the assay used in this application are requested.
28. The MAH is invited to comment on the use of cross-study comparison as a method of evaluating the efficacy of Gpt and the results described.
29. It appears that too many variables could bias the response that can be imputed to Gpt on CRS rates and grades. In absence of any control or planned analysis to elaborate on a possible beneficial effect of Gpt, the effect of Glofitamab step-up dosing, prior anti-CD20 therapies and other administered corticosteroids pretreatments on the potentially observable low CRS rate cannot be ruled out. The Applicant should explain how to discriminate the effect of each compound possibly participating to the final observed effect on CRS rates and grades.

Clinical safety aspects

30. In the CSR on page 283 the MAH is referring to a table (t_xae_ctc1_ph_GE600_I_CSR_SE_15JUN2022_30179, starting page 3974) that includes all AEs for Gpt treatment and glofitamab by SOC, all PTs and Grade 1-5 in all cohorts having received glofitamab ≥ 0.6 mg (=880 pages): Please present AEs for the Gpt treatment phase (before glofitamab was given) in a table by SOC and PT (including All Grade and Grade 3-4) with a reasonable cut-off for both the glofitamab primary safety population (N=154) as well as the overall safety population (N=469).
31. It is not understood how there can be more IRR AEs related to Gpt (45) than actual events (44). This also pertains to the AE Neutropenia (14/469; p. 3973) vs Related Neutropenia (25/469; p.4844). Please clarify.
32. Please present SAEs for the Gpt treatment phase (before glofitamab was given) in a table by SOC and PT (cut-off $\geq 1\%$) for both the glofitamab primary safety population (N=154) as well as the overall safety population (N=469).

33. Adverse events of special interest for obinutuzumab: Please present information regarding IRR, TLS, and hypersensitivity reactions in the primary and overall safety population before glofitamab treatment.
34. Please present the most frequent laboratory findings for the Gpt treatment phase (before glofitamab was given) in a table for both the glofitamab primary safety population (N=154) as well as the overall safety population (N=469).
35. The MAH is requested to present IRR by All Grade and Grade 3-4 in a table for both the glofitamab primary safety population (N=154) as well as the overall safety population (N=469) in the following subgroups of patients (before glofitamab treatment); according to B-cell count, by age group, +/- prior CAR-T treatment, time since last rituximab therapy, according to the Ki67 level, and low vs. high tumour burden.
36. The MAH is requested to present (in a table) the reasons why patients did not continue treatment with glofitamab after obinutuzumab treatment: in the overall safety population 450/469 patients received glofitamab, so this concerns 19 patients. Direct links to their narratives is also requested.
37. The MAH took the opportunity to request to have the reference to cytokine release syndrome in the SmPC amended. It seems indeed contradictory to claim a CRS prevention indication while the Gazyvaro SmPC reports IRR linked to CR syndromes. According to Cheson et al., 2017: it was hypothesized that the increase in IRRs during the first infusion of obinutuzumab was potentially due to cytokine release as it was noted that peak levels of IL-6, IL-8, IL-10, TNF- α , and interferon-gamma were significantly higher during the first infusion of obinutuzumab compared with rituximab. Levels returned to baseline and did not increase in subsequent infusions. Other literature references also report cytokine release during IRR events without formal or confirmed CRS events. In light of the preceding, a detailed review of all CRS cases reported overall with obinutuzumab in trials, post-marketing experience and literature (narratives should be included) along with any pre-clinical data is awaited in order to help elucidate whether IRR could be linked to CRS. The submission of such data should be considered as a standalone procedure.

RMP

None.