swissmedic

Date: 18 January 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Columvi

International non-proprietary name: glofitamab

Pharmaceutical form: concentrate for solution for infusion

Dosage strength(s): 2.5 mg/2.5 mL, 10 mg/10 mL

Route(s) of administration: intravenous

Marketing authorisation holder: Roche Pharma (Schweiz) AG

Marketing authorisation no.: 68297

Decision and decision date: temporary authorisation in accordance with Art. 9a TPA approved on 07.11.2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
C_{max}	Maximum observed plasma/serum concentration of drug
CR	Complete response
CRS	Cytokine release syndrome
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLBCL	Diffuse large B-cell lymphoma
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
IV	Intravenous(ly)
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
NHL	Non-Hodgkin lymphoma
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
RMP	Risk management plan
r/r DLBCL	Recurrent or refractory diffuse large B-cell lymphoma
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for glofitamab in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 6 December 2021.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme for the assessment of promising cancer treatments coordinated by the FDA. It provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Glofitamab is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from follicular lymphoma, high-grade B-cell lymphoma (HGBCL), and primary mediastinal B-cell lymphoma (PMBCL).

2.2.2 Approved indication

Columvi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after 2 or more lines of systemic therapy, including an antibody that targets CD20 and an anthracycline. Furthermore, the patients must exhibit progression after prior anti-CD19-targeted CAR T-cell therapy or be ineligible for such treatment (see section "Clinical efficacy").

This indication has been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an ordinary authorisation.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Premedication with obinutuzumab 1000 mg i.v. as a single dose on day 1 of the first treatment cycle (i.e. 7 days before starting glofitamab treatment).

Prophylaxis for cytokine release syndrome (CRS) with intravenous glucocorticoid, oral antipyretic, and oral antihistamine.

Treatment with glofitamab:
Cycles of 21 days, step-up dosing to 30 mg as an intravenous infusion according to the following table:

Treatment cycle, day		Dose of Columvi	Duration of infusion
Cycle 1 (Premedication and Step-up doses)	Day 1	Premedication with obinutuzumab	
	Day 8	2.5 mg	4 hours
	Day 15	10 mg	
Cycle 2	Day 1	30 mg	
Cycles 3 to 12	Day 1	30 mg	2 hours

Treatment duration:
Max. 12 cycles or until disease progression or inacceptable toxicity.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	1 December 2022
Formal control completed	2 December 2022
Preliminary decision	14 June 2023
Response to preliminary decision	12 August 2023
Labelling corrections	19 September 2023
Response to labelling corrections	8 October 2023
Final decision	7 November 2023
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

3 Medical context

Diffuse large B-cell lymphoma (DLBCL) is the most frequent aggressive B-cell non-Hodgkin lymphoma (B-NHL) with an incidence of roughly 4/100 000/year in Europe[1].
The intent of treatment is curative in first-line therapy and in many cases in later lines of therapy as well.

First-line therapy consists of poly immune-chemotherapy and is curative in many cases. The prognosis is worse for patients with primary refractory disease or early recurrent disease. There are various treatment options for later lines of therapy, all of them with relevant toxicity and limited efficacy[2].
The main differentiation in the treatment of recurrent or refractory DLBCL (r/r DLBCL) is between patients who are eligible for high-dose chemotherapy with subsequent autologous stem cell transplantation and those who are not.

Various therapeutic options exist for r/r DLBCL patients who are not eligible for autologous stem cell transplantation. These comprise different immune-chemotherapy regimens, combination of immune-chemotherapy with antibody-drug conjugates, and the chemotherapy-free therapeutic option of a CD19 antibody in combination with an immunmodulator. For third-line treatment of r/r DLBCL, the currently preferred treatment for eligible patients is CAR T-cell therapy, if this has not been used in earlier treatment lines.

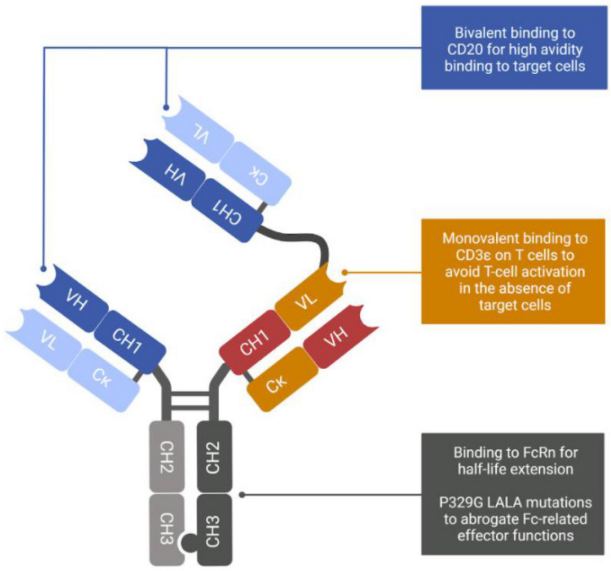
[1] Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, Walewski J, André M, Johnson PW, Pfreundschuh M, Ladetto M; ESMO Guidelines Committee. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26 Suppl 5:v116-25.

[2] Georg Lenz, Björn Chapuy, Bertram Glaß, Felix Keil, Wolfram Klapper, Maike Nickelsen, Heinz Schmidberger, Clemens A. Schmitt, Novak Urban. Onkopedia Leitlinie Diffuses grosszelliges B-Zell-Lymphom. Juli 2022.

4 Quality aspects

4.1 Drug substance

Glofitamab is a [2+1] bispecific human IgG1 monoclonal antibody produced in Chinese hamster ovary cells. Glofitamab consists of 2 different heavy chains and 2 different light chains as shown in the figure below. Two Fab domains bind to CD20 (expressed on target B cells) and 1 Fab domain binds to CD3 (expressed on effector T cells). Point mutations in the C_H3 domain promote the assembly of the 2 different heavy chains.
The molecular weight of glofitamab is approximately 194 kDa.



Note: The anti-CD20 Fabs are depicted in blue. The anti-CD3 Fab is depicted in red/orange. The heterodimeric Fc region of the human IgG1 bearing the P329G LALA mutation is depicted in grey.

The glofitamab drug substance is produced using a fed-batch production process in a production bioreactor. The cell broth is harvested and subsequently purified by several chromatographic steps. The drug substance is finally frozen down for storage.

The fermentation and purification process was validated on 4 batches and demonstrated a consistent manufacturing process that effectively reduced process-related impurities.

A few changes were implemented during the development of the glofitamab drug substance process, including changes to production scale and drug substance concentration. However, all processes used the same manufacturing cell line, and the analytical comparability studies, which considered clinical and commercial drug substance batches, demonstrated comparability between process changes. For this assessment routine analysis and extended characterisation and stability studies were evaluated.

The characterisation of the physicochemical and biological properties of the drug substance and its impurities were performed using state-of-the-art methods.

The specifications for release include relevant tests and limits, e.g. for appearance, identity, pH, several purity tests, protein concentration, and a cell-based bioassay. Specifications are based on clinical data and batch analysis (release and stability data), and are in conformance with current compendial or regulatory guidelines.

Batch analysis data of nonclinical and technical, clinical, and process performance qualification batches were provided. All batch release data comply with the drug substance specifications valid at the time of batch release. All specific analytical methods are described and were fully validated.

The drug substance is stored frozen. During storage, no changes were observed under the proposed storage conditions.

4.2 Drug product

The glofitamab drug product is provided as a sterile, colourless concentrate for solution for infusion with no preservatives; all excipients are of compendial grade. There are 2 drug configurations: a 2.5 mg/vial and 10 mg/vial. Glofitamab is intended for IV administration after dilution in 0.9% or 0.45% sodium chloride via IV bag infusion.

Changes were also implemented for the drug product, e.g. different manufacturing sites, slightly different manufacturing processes, and different protein concentrations were used. However, comparability assessments considering Phase Ib/II and commercial drug product batches were executed, and all predefined comparability acceptance criteria were met.

The drug product formulation is identical to the drug substance formulation with the exception of the concentration of glofitamab. All other formulation components remain the same between drug substance and final drug product. The drug product manufacturing process consists of thawing, pooling, (optional) and mixing of drug substance, dilution and mixing, bioburden reduction filtration, sterile filtration, filling/stoppering, capping, and visual inspection.

The validation for the drug manufacturing process was performed. The process performance qualification (PPQ) batches and representative technical batches together represent the full range of batch sizes for commercial manufacturing.

The release and stability specifications include relevant tests and limits, e.g. for appearance, identity, pH, osmolality, extractable volume, purity, protein concentration, a cell based bioassay, visible and subvisible particles, sterility, and bacterial endotoxins. All specific methods are described and validated.

Batch analysis data of nonclinical, clinical, and process performance qualification batches were provided. All batch release data comply with the drug product specifications valid at the time of batch release. All specific analytical methods are described and were fully validated.

The primary container consists of a 6 mL or 15 mL Type I borosilicate clear glass vial with fluororesin-laminated rubber stopper, and is crimped with an aluminium overseal with a flip-off cap. All product-contacting materials comply with the relevant pharmacopoeia requirements.

The drug product shelf-life acceptance criteria are fulfilled when the product is stored under the proposed long-term storage conditions at 2°C to 8°C. A shelf-life of 24 months has been accepted.

4.3 Quality conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-life of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk for adventitious agents is minimised.

5 Nonclinical aspects

5.1 Pharmacology

Glofitamab bound in a bivalent binding mode to CD20 on tumour and healthy B cells and cross-reacted with the CD3 epsilon (CD3ε) subunit of the T-cell receptor complex on effector T cells. The binding to CD3 is monovalent. For the activation of the effector T cells, simultaneous binding to CD20 on tumour target cells and CD3ε crosslinking is needed. Binding affinity to human and cynomolgus monkey CD20 on B cells and binding kinetics to tthe CD3ε subunit on T cells of both species were similar. There was no cross-reactivity of glofitamab to rodent or minipig CD20 or CD3. The data support the use of cynomolgus monkeys for the toxicity studies. Glofitamab induced tumour cell lysis of various CD20-expressing tumour targets in the presence of peripheral mononuclear cells (PBMCs) as effector cells. The potency of glofitamab was dependent on concentration and effector-to-target (E:T) cell ratio, but did not correlate with CD20 expression level.
Glofitamab was shown to deplete B cells in human and cynomolgus monkey whole blood *in vitro.*
In whole bone marrow aspirates or in the whole blood of different lymphoma patients (including DLBCL), glofitamab induced tumour cell lysis that was patient- and concentration-dependent (EC_{50} 0.0002-2.7 nM). No correlation with E:T ratio was found and there was no difference between B cell depletion in bone marrow and blood of the same patient. Notably, glofitamab displayed strong anti-tumour potency and led to high overall killing of target cells that paralleled T-cell activation and expansion in all patient samples with EC_{50} values considerably lower than clinical C_{max} (39.5 nM).
In HSC-NOG mice, glofitamab (500 µg/kg intravenously (IV) once weekly) mediated sustained B cell depletion and transient T cell depletion, followed by T cell activation, proliferation, and cytokine release. Depletion of B cells and activation of T cells were also noted in the spleen and lymph nodes.
In tumour-bearing mice (DLBCL tumours), glofitamab treatment (50, 150, and 500 µg/kg) led to dose-dependent shrinkage of tumour volume.
In vitro, Glofitamab was more potent in tumour cell lysis than the anti-CD20 antibodies obinutuzumab and ocrelizumab ((EC_{50} 0.6; 5.7 and 47.4 pM, respectively), and was superior in terms of inducing T-cell activation and proliferation.
The rationale for pretreatment with obinutuzumab to deplete B cells before the first glofitamab administration and to mitigate the risk of cytokine release syndrome (CRS) in clinics was supported by *in vitro* and *in vivo* nonclinical data.
Due to mutations in the Fc region, glofitamab is unable to induce Fc-mediated effector functions.
Glofitamab induced a sustained but reversible dose-dependent increase in heart rate in monkeys, likely secondary to cytokine release and body temperature increase. There were no glofitamab-related changes in the QRS duration or QT interval. Cardiovascular events were recorded in the clinical studies. There were no effects on the central nervous system and respiratory parameters in monkeys. Neurological adverse events are considered a potential risk for glofitamab based on clinical data.

5.2 Pharmacokinetics

The pharmacokinetics of glofitamab is characterised by linear pharmacokinetics in the species that do not express the target. In cynomolgus monkeys after single IV dose administration of 0.3 to 100 µg/kg, the increase in exposure (AUC) was dose-dependent and consistent with target-mediated drug deposition (TMDD). In contrast to humans, the clearance in monkeys was very high, resulting in a short $t_{1/2}$ (less than 5 h; humans 6 days). The reason for the high clearance in monkeys was not identified. The volume of distribution was in range of the plasma volume in monkeys. Pretreatment with obinutuzumab (50 mg/kg IV 4 days before treatment with glofitamab at 100, 300, or 1000 µg/kg) slightly reduced clearance, which is consistent with the obinutuzumab-induced B cell depletion and the resulting reduction of TMDD from B-cell binding. Obinutuzumab increased glofitamab exposure ($AUC_{(0\text{-last})}$) by approx. 4.5-fold and mean $t_{1/2}$ by approx. 9-fold compared to single dosing at 100 µg/kg glofitamab alone. Adequate exposure was not achieved after repeated dosing due to fast anti-drug antibody (ADA)

development. There were no gender-related differences in PK parameters. In line with ICH S6(R1), the applicant did not conduct studies on distribution, metabolism, and excretion.

5.3 Toxicology

The safety profile of glofitamab was investigated in single (with and without obinutuzumab pretreatment) and repeated-dose IV toxicity studies with a duration of up to 4 weeks in cynomolgus monkeys. Studies with longer duration were considered not to be meaningful due to high clearance, marked immunogenicity, and low exposure cytokine release. The applicant tried different set ups (step-up dosing, dosing every other day, combination with obinutuzumab, and subcutaneous administration) to overcome this problem, however without success. Therefore, long-term safety data for glofitamab are not available. This is accepted considering that the key findings were related to the pharmacology. Repeated-dose toxicity studies were conducted without pretreatment with obinutuzumab to achieve a "worst case scenario" in terms of CRS syndrome. The exposure achieved in nonclinical studies was lower than in clinics, meaning there are no safety margins.
In the single-dose study, glofitamab was administrated up to 300 µg/kg without pretreatment and up to 1000 µg/kg following pretreatment with obinutuzumab (50 mg/kg).
Toxicity findings are consistent with glofitamab-induced B cell depletion, T-cell activation, and cytokine release. Acute phase reactions starting 4 hours post-dose were characterised by clinical signs (decreased activity, hunched posture) and decreased blood pressure. Monkeys receiving >100 µg/kg were euthanised after 1 day. The morbidity was attributed to cytokine release followed by a decrease in haematology parameters, cell infiltrates in different organs (lung, liver), and epithelial cell degeneration or necrosis (pancreas, stomach mucosa, and gastrointestinal tract). Obinutuzumab pretreatment resulted in less severe glofitamab-related acute effects.
Acute inflammatory response (increased C-reactive protein, fibrinogen, triglycerides, and bilirubin; and mildly decreased albumin and cholesterol) and dose-dependent cytokine release were also observed after repeated dosing (up to 100 µg/kg). Maximum increases in cytokines and chemokines (G-CSF, IFN-γ, IL-10, IL-8, IL-6, IL-1RA, and MCP-1, Granzyme B, IL-2, TNF-α, and MIP-1β) were measured 4 hours after the first dose. CRS is an important identified risk for glofitamab. Reductions in white blood cell count are consistent with the expected pharmacological activity of glofitamab and correlated with the microscopic finding of decreased cellularity of lymphoid tissues and decreases in B-lymphocytes and T-lymphocyte subsets. Neutropenia is a known class effect with other CD20-targeted therapies and was reported as an adverse drug reaction in clinical trials. A transient activation of the coagulation system and increases in urea nitrogen and creatinine may have been secondary to haemodynamic changes induced by cytokine release.
Microscopic findings were observed in some organs (heart, salivary glands, kidneys, perivascular spaces of meninges, choroid plexus, and parenchyma of the brain). These findings were considered resolved after the 4-week dose-free interval.
Reproductive and developmental toxicity studies have not been conducted with glofitamab. There is no information on the effect of glofitamab on fertility parameters or reproductive organs in animals. Based on the weight-of-evidence risk assessment that considered the available nonclinical and clinical data for glofitamab and the known risks associated with B cell depletion, glofitamab indicates an overall risk to pregnancy and may lead to fetal B cell depletion.
The lack of genotoxicity and carcinogenicity studies is in line with ICH S6.
The description of the safety findings from the nonclinical studies and their evaluation in the risk management plan (RMP) are considered adequate.
Since glofitamab is a monoclonal antibody, there is no risk for the environment.

5.4 Nonclinical conclusions

Overall, the pharmacology and toxicological profile of glofitamab were adequately characterised in the nonclinical studies. No unexpected safety concerns were identified in toxicity studies in a pharmacologically relevant animal species. From a nonclinical point of view, the application is approvable.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Glofitamab PK data from 460 patients have been collected in the ongoing Phase I/II, multicentre, open-label, dose-escalation study NP30179.

Absorption
Following IV administration, maximum glofitamab concentrations were reached after the end of the infusion. Based on graphical exploration, glofitamab exposures increased approximately dose-proportionally between 0.005 mg and 30 mg.

Distribution
Based on the population PK analysis, the volume of distribution of glofitamab is 5.58 L.

Metabolism and elimination
No studies regarding the metabolism of glofitamab have been conducted considering the biological nature of the molecule.

The serum concentration-time profiles indicated a biphasic disposition with an initial rapid distribution phase followed by a slower elimination phase.
Based on the population PK analysis, the clearance was estimated at 0.617 L/day with a steady state terminal elimination half-life of 7.6 days.

Special populations / Intrinsic factors

Renal and hepatic impairment are not expected to have an impact on the PK behaviour of monoclonal antibodies; therefore, no dedicated studies in these populations were carried out.
Of the patients enrolled in study NP30179, 168 patients (36.5%) had mild renal impairment, 75 patients (16.3%) had moderate renal impairment, 1 patient (0.217%) had severe renal impairment, 72 patients (15.7%) had mild hepatic impairment, 2 patients (0.435%) had moderate hepatic impairment, and 1 patient (0.217%) had severe hepatic impairment. Based on the population PK analysis, neither mild to moderate renal impairment nor mild hepatic impairment had an impact on the pharmacokinetics of glofitamab.

Due to the lack of data, the impact of race could not be assessed.

Using data from 460 patients including 11,049 glofitamab concentration measurements, a population PK analysis was conducted to identify factors that account for variability of the glofitamab PK. The PK of glofitamab was well described by a 2-compartment model with parallel linear (CL_L) and time-varying clearance (CL_T). Body weight was included using allometric scaling on clearance and volume parameters. Additionally, the final model included the following covariates: C-reactive protein (CRP) on CL_L, CL_T and central volume of distribution (V1), baseline obinutuzumab concentration on CL_T, baseline tumour burden on CL_L and V1, follicular lymphoma Grades 1-3A histology on CL_L and decay coefficient (k_{des}), and mantle cell lymphoma on k_{des}.
In summary, glofitamab exposure was predicted to decrease with increasing baseline body weight, increasing baseline CRP, and increasing baseline tumour burden, and to increase with increasing baseline observed obinutuzumab concentration. Furthermore, glofitamab exposure was lower in patients with mantle cell lymphoma and follicular lymphoma of Grades 1-3A. However, these changes are not deemed clinically relevant. Only baseline weight could have a potentially relevant impact; however, the exposure-response analyses suggested the absence of an impact on efficacy or safety. Overall, no dose adjustments are recommended based on any of the evaluated covariates including

gender, age, and body weight. Due to low incidence, ADA status was not formally tested as a covariate in the population PK; however, graphical exploration suggested no impact on the PK of glofitamab.

Interactions

No direct PK-based drug-drug interactions (DDIs) are anticipated for monoclonal antibodies. However, transient elevations of cytokines including IL-6 may be associated with CYP enzyme suppression. Therapeutic monitoring should be considered when patients are being treated with CYP450 substrates with a narrow therapeutic index.

Mechanism of action and primary pharmacology

Glofitamab is a “2:1” T-cell bispecific humanised monoclonal antibody that binds to human CD20 on tumour cells and to the human CD3ε subunit of the T-cell receptor complex (TCR) on T cells. Simultaneous binding of glofitamab to CD20 expressed on target B cells and CD3 expressed on effector T cells brings these cells into direct contact, leading to strong T-cell activation and target cell lysis as well as to recruitment of additional T cells to tumours.
Based on graphical analyses, the relationships between exposure and aplasia, B-cells, CD4 and CD8 T-cells, T-cell activation, NK cells as well as the key cytokines TNF-α, IFN-γ, IL-2, IL-6, and IL-10 were explored. B cell aplasia was observed in almost all patients after dosing initiation. There were no clear dose-dependent changes in the number of B cells, NK cells, CD4 T cells, and CD8 T cells, whereas T cell activation appeared to increase proportionally to the dose. The concentrations of the key cytokines increased after initial glofitamab dosing and appeared to return to baseline by cycle 3.

Secondary pharmacology (safety)

No tQT study was conducted. Usually, QT prolongation in monoclonal antibodies is rare, as they are not expected to interact directly with the hERG channel. In study NP30179, 16/145 of patients had post-baseline QTcF values >450 ms. One of these cases was deemed clinically significant by the investigator. Overall, no patient was withdrawn due to QT prolongation.

Exposure efficacy/safety relationship

The exposure-efficacy relationships were investigated using logistic regression based on the clinical response data (complete response (CR) rate and objective response rate (ORR)) from 285 patients with r/r DLBCL (Population 2) and 138 patients who received the proposed 2.5/10/30 mg step-up dosing regimen from Cohorts D_2 [Sub. 2] +D_3 +D_5 (Population 1). CRR and ORR increased significantly with increasing glofitamab exposure (AUC_{C1+C2}) in Population 2, whereas the relationship for CRR was less pronounced in Population 1. In contrast to Population 2, no clear relationship between clinical response and glofitamab average CD20 receptor occupancy ($AvRO\%_{C1+C2}$) was observed in Population 1. In Population 1, CRR increased with increasing time since last prior anti-CD20 therapy and decreased with increasing tumour burden. Furthermore, ORR significantly increased with increasing glofitamab exposure, increasing time since last prior anti-CD20 therapy, and decreasing baseline lactate dehydrogenase (LDH) in Population 1, whereas ORR decreased with increasing baseline tumour burden.
Based on data from 460 patients, the exposure-safety relationship for cytokine release syndrome (CRS) and Grade ≥2 neutropenia was assessed. Most CRS events of Grade ≥2 occurred following the first 2.5 mg dose. Increasing $AvgRO\%_{D1}$, increasing baseline sum of products of diameters (tumour burden), mantle cell lymphoma histology type, and Ann Arbor stage >3 were significantly associated with increased risk of CRS. Extended step-up dosing (0.5/2.5/10/30 mg) did not show an improvement in cytokine release syndrome (CRS) mitigation. No exposure-safety relationship for the incidence of Grade ≥2 neutropenia was observed.

6.2 Dose finding and dose recommendation

The step-up-dose regimen of 2.5/10/30 mg was selected based on clinical data from part I and II of study NP30179. Preliminary population PK and exposure response analyses from the glofitamab fixed dosing were used to determine a suitable starting dose which would seek to mitigate the occurrence of CRS while allowing escalation to a higher target dose to maximise efficacy.

All patients in the monotherapy cohorts received obinutuzumab as premedication for risk mitigation of CRS. The rationale for treatment with glofitamab combined with obinutuzumab in relapsed/refractory (r/r) Non-Hodgkin Lymphoma (NHL) is based on nonclinical data. No clinical data were submitted evaluating glofitamab without obinutuzumab premedication in patients with r/r NHL, and the rationale and contribution of obinutuzumab to CRS mitigation is not sufficiently justified. Therefore, the single dose of obinutuzumab in cycle 1 was only accepted as part of the dosing regimen. For details, please refer to the attached information for healthcare professionals.

6.3 Efficacy

The applicant submitted results of 1 pivotal phase 1/2 study NP30179, evaluating glofitamab as a single agent administered after a fixed, single dose pretreatment of obinutuzumab in patients with r/r B-cell NHL. The single-arm design does not fulfil the requirements for a confirmatory study according to ICH E9. Furthermore, the median follow-up time was short, limiting the evaluation of efficacy and safety.

Patients ≥18 years with a history or status of histologically confirmed haematological malignancy that was expected to express CD20, or relapse after or failure to respond to at least 1 prior treatment regimen, and no available treatment options that were expected to prolong survival (e.g. standard chemotherapy or autologous stem cell transplant) were included.

The primary analysis populations comprise patients with r/r DLBCL who had received at least 2 prior systemic therapies, including patients with DLBCL, transformed follicular lymphoma (trFL), high grade B-cell lymphoma (HGBCL), and primary mediastinal B-cell lymphoma (PMBCL) who received the proposed registrational glofitamab dosage of 2.5/10/30 mg every 3 weeks (Q3W). The primary efficacy population reflects a heavily-pretreated r/r DLBCL patient population that has exhausted several available treatment options including post-CAR-T population, and includes high-risk patients with a poor prognosis.

The primary efficacy outcome was independent review committee (IRC)-assessed complete response (CR) rate determined according to standard NHL response criteria (Lugano classification, Cheson et al. 2014[3]).

For details of study design, administration, and study population please refer to the attached information for healthcare professionals.

Overall, 47 patients in the primary efficacy population had a prior CAR-T therapy. In these heavily pre-treated patients, ORR was 55% with a CR rate of 40.4%. The median progression-free survival (PFS) was 6.8 months and median overall survival (OS) 9.8 months. These results are encouraging in heavily pretreated patients with no approved therapies available yet.

6.4 Safety

For evaluation of safety, the primary safety population (n=145, study NP30179) and the pooled safety population (n=469, including experimental combinations) were evaluated. The most common adverse events (AEs) in the pooled safety population (≥20%) were CRS, haematological adverse events,

[3] Cheson et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68.

hyperuricaemia, rash, and pyrexia. For details, please refer to the attached information for healthcare professionals.

The evaluation of safety in the primary safety population of r/r DLBCL was limited due to the single-arm design of study NP30179 and the small patient population (n=145) including different histology and different dosing schemes.

Glofitamab was associated with relevant safety concerns such as CRS and neurological AEs.

CRS was the most common AE in the primary safety population, observed in 67.6 % of patients. Overall, 22% had a serious adverse event (SAE) but no Grade 5 events were observed. Most events occurred in Cycle 1. However, CRS of all grades were also observed thereafter, with 26.8% in Cycle C2, Day 1. The incidence of CRS of any grade and serious CRS was lower in additional cohort D5 with dexamethasone premedication compared to the patient population who received methylprednisolone, prednisone, or prednisolone as premedication. Therefore, dexamethasone is proposed as the preferred premedication in the Information for healthcare professionals.

Glofitamab can cause serious and fatal neurological toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS). The majority of patients in the primary safety population experienced Grade 1-2 neurological AEs. The most commonly reported neurological preferred terms (PTs, any grade) were headache (10%), peripheral neuropathy (8%), dizziness or vertigo (7%), and mental status changes (4.8%, including confusional state, cognitive disorder, disorientation, somnolence, and delirium). Overall, 4.8% of neurological AEs were identified as ICANS.

Further relevant safety concerns, such as serious infections, tumour lysis syndrome, reactivation of hepatitis B, hyper-progression, and hepatotoxicity, are described in the information for healthcare professionals.

6.5 Final clinical benefit-risk assessment

The submitted single-arm trial NP30179 with ORR/CR as the primary endpoint does not fulfil the criteria for a confirmatory study according to ICH-E9. Furthermore, evaluation of safety in patients with r/r DLBCL was limited due to the single-arm design and small patient population including different histology. Therefore, the benefit-risk assessment was negative for a regular authorisation.

However, for patients who are not eligible for CAR T-cells or progress after CAR T-cell therapy, the results of study NP30179 are encouraging and a major therapeutic benefit can be expected from use of glofitamab in patients with r/r DLBCL after ≥ 2 prior systemic therapies and progression after an anti-CD19-CAR T-cell therapy. A temporary authorisation was therefore granted for patients that received prior therapy with anti-CD20, an anthracycline therapy, and CAR T-cell therapy. Controlled data from the Phase 3 study STARGLO were accepted as confirmatory results. STARGLO is a randomised phase 3 study evaluating glofitamab in combination with gemcitabine + oxaliplatin in comparison to rituximab in combination with gemcitabine + oxaliplatin in patients with r/r DLBCL with at least 1 prior therapy (CAR T-cell eligible). Results are expected within the timeframe of temporary authorisation.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Columvi was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Glofitamab has been authorised temporarily, see "Indications/Uses" section.

Columvi®

Composition

Active substances

Glofitamabum (genetically engineered using CHO [Chinese Hamster Ovary] cells).

Excipients

L-histidinum, L-histidini hydrochloridum monohydricum, L-methioninum, saccharum (produced from genetically engineered sugar beet), polysorbatum 20 (produced from genetically engineered maize), aqua ad iniectabile.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion

Colourless, clear solution in single-dose vial with:
- 2.5 mg of glofitamab/2.5 mL at a concentration of 1 mg/mL
- 10 mg of glofitamab/10 mL at a concentration of 1 mg/mL

Indications/Uses

Columvi 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, including an antibody that targets CD20 and an anthracycline. Furthermore, the patients must exhibit progression after prior anti-CD19-targeted CAR T-cell therapy or be ineligible for such treatment (see section "Clinical efficacy").

This indication has been granted temporary authorisation as the clinical data were incomplete at the time of the application was assessed (Art. 9a Therapeutic Product Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an ordinary authorisation.

Dosage/Administration

General

Columvi must only be used under the supervision of a healthcare professional qualified in the use of cancer treatments and in a medical facility with immediate access to medical support to manage severe reactions, such as cytokine release syndrome (CRS) and neurological toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS) (see section “Warnings and precautions”).

Monitoring

- Patients must be monitored in hospital during the infusion of titration dose 1 (2.5 mg on Day 8 of Cycle 1) and for 24 hours afterwards (see section “Warnings and Precautions”).
- Patients in whom any grade of CRS occurs during titration dose 1 must be monitored in hospital during the infusion of titration dose 2 (10 mg on Day 15 of Cycle 1) and for 24 hours afterwards. CRS can also occur during administration of titration dose 2 in patients in whom CRS did not occur during titration dose 1 (see section “Warnings and Precautions”).
- During subsequent doses (30 mg on Day 1 of Cycle 2 or subsequent cycles), patients in whom a grade ≥ 2 CRS occurred during the previous infusion must be monitored in hospital during the next infusion of Columvi and for 24 hours afterwards.

In addition, patients should be monitored on a daily basis for signs and symptoms of CRS, as well as neurological and other toxicities, over a period of up to 7 days after the administration of Columvi (see “*Dosage/Administration - Measures in the event of adverse reactions”* and *“Warnings and precautions”*). Furthermore, patients are to be instructed to remain close to a treatment centre during this period. Any potential continued monitoring is at the discretion of the physician.

All patients must be counselled on the risk, signs, and symptoms of CRS and advised to contact the treating healthcare provider immediately should they experience signs and symptoms of CRS.

In order to improve traceability of biological medicinal products, it is recommended to document the trade name and the batch number at each administration.

Pre-treatment with Obinutuzumab

All patients must receive a single 1000 mg dose of obinutuzumab on Cycle 1 Day 1 (7 days prior to initiation of Columvi treatment) (see Table 2 and "Delayed or Missed Doses"). This is to deplete

circulating and lymphoid tissue B cells. The recommendations on pre-treatment with obinutuzumab are based on non-clinical data and there are no data for Columvi without pre-treatment with obinutuzumab.
Obinutuzumab should be administered as an intravenous infusion at 50 mg/h. The rate of infusion can be escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h.

Please also refer to the full Information for Healthcare Professionals for obinutuzumab.

Premedication and Prophylactic Medications

Cytokine release syndrome prophylaxis

Columvi should be administered to well-hydrated patients. Premedication to reduce the risk of CRS (see section "Warnings and Precautions") is outlined in Table 1.

Table 1: Premedication before Columvi Infusion

Treatment Cycle (Day)	**Patients requiring premedication**	**Premedication**	**Administration**
Cycle 1 (Day 8, Day 15); **Cycle 2 (Day 1);** **Cycle 3 (Day 1)**	All patients	Intravenous dexamethasone, 20 mg[b]	Completed at least 1 hour prior to Columvi infusion.
		Oral paracetamol, 500 mg - 1000 mg	At least 30 minutes before Columvi infusion.
		Antihistamine[a]	
All subsequent infusions	All patients	Oral paracetamol, 500 mg – 1000 mg	At least 30 minutes before Columvi infusion.
		Antihistamine[a]	
	Patients who experienced CRS with previous dose	Intravenous dexamethasone, 20 mg[b]	Completed at least 1 hour prior to Columvi infusion.

[a] For example50 mg diphenhydramine.
[b] Administer 100 mg prednisone, 100 mg prednisolone or 80 mg methylprednisolone intravenously if dexamethasone is unavailable.

Tumour lysis syndrome prophylaxis

Prophylaxis with an antihyperuricaemic drug is required before starting to use Columvi in patients who are at risk of tumour lysis syndrome. In addition, patients must be adequately hydrated and monitored as necessary (see section "Warnings and Precautions").

Antiviral prophylaxis

Before starting to use Columvi, initiation of antiviral prophylaxis should be considered to prevent a reactivation of herpes viruses. Cytomegalovirus prophylaxis should be considered in patients who are at increased risk (see section "Warnings and Precautions").

Pneumocystis jirovecii pneumonia (PJP)

Prophylaxis against PJP should be considered in patients who are at increased risk before starting to use Columvi (see section "Warnings and Precautions").

Recommended Dosage

Columvi dosing begins with a titration schedule.

Columvi titration schedule

Columvi must be administered as an intravenous infusion according to the titration schedule until the recommended dosage of 30 mg is attained (as shown in Table 2), after completion of pre-treatment with obinutuzumab on Cycle 1 Day 1. Each cycle is 21 days.

Table 2: Columvi Monotherapy Titration Schedule for Patients with Relapsed or Refractory DLBCL

Treatment Cycle, Day[a]		Dose of Columvi	Duration of infusion
Cycle 1 (Pre-treatment and step-up dose)	Day 1	obinutuzumab[b]	
	Day 8	Titration dose 1 2.5 mg	4 hours[c]
	Day 15	Titration dose 2 10 mg	
Cycle 2	Day 1	30 mg	
Cycle 3 to 12	Day 1	30 mg	2 hours[d]

[a] Each treatment cycle is 21 days.

[b] Refer to *Pre-treatment with obinutuzumab* described above.

[c] For patients who experience CRS with their previous dose of Columvi, the duration of infusion may be extended up to 8 hours (see Table 4 and section "Warnings and Precautions").

[d] If the patient experienced CRS with a previous dose, the duration of infusion should be maintained at 4 hours.

Duration of Treatment

Treatment with Columvi should be administered until disease progression or the occurrence of unmanageable toxicity for a maximum of 12 cycles (including cycle 1 of the titration schedule).

Delayed or Missed Doses

Table 3: Recommendation for continuing Columvi after delayed doses

Last dose used	Time since last dose	Procedure for the next dose/next doses[a]
Obinutuzumab pre-treatment (Cycle 1, Day 1)	≤ 2 weeks	• Administration of the 2.5 mg dose of Columvi (Cycle 1, Day 8)[b], then continue with the planned treatment schedule.
	> 2 weeks	• Repeat pre-treatment with 1000 mg obinutuzumab (Cycle 1, Day 1). • Then administer the 2.5 mg dose of Columvi (Cycle 1, Day 8)[b] and continue with the planned treatment schedule.
Columvi 2,5 mg (Cycle 1, Day 8)	≤ 2 weeks	• Administration of the 10 mg dose of Columvi (Cycle 1, Day 15)[c], then continue with the planned treatment schedule.
	> 2 to ≤ 4 weeks	• Repeat administration of the 2.5 mg dose of Columvi (Cycle 1, Day 8)[b]. • Then administer the 10 mg dose of Columvi (Cycle 1, Day 15)[c] and continue with the planned treatment schedule.
	> 4 weeks	• Repeat pre-treatment with 1000 mg obinutuzumab (Cycle 1, Day 1) and administration of the 2.5 mg dose of Columvi (Cycle 1, Day 8)[b]. • Then administer the 10 mg dose of Columvi (Cycle 1, Day 15)[c] and continue with the planned treatment schedule.
Columvi 10 mg (Cycle 1, Day 15)	≤ 2 weeks	• Administration of the 30 mg dose of Columvi (Cycle 2, Day 1), then continue with the planned treatment schedule.
	> 2 to ≤ 6 weeks	• Repeat administration of the 10 mg dose of Columvi (Cycle 1, Day 15)[c]. • Then administer the 30 mg dose of Columvi (Cycle 2, Day 1) and continue with the planned treatment schedule.
	> 6 weeks	• Repeat pre-treatment with 1000 mg obinutuzumab (Cycle 1, Day 1), administration of the 2.5 mg dose of Columvi (Cycle 1, Day 8)[b] and administration of the 10 mg dose of Columvi (Cycle 1, Day 15)[c]. • Then administer the 30 mg dose of Columvi (Cycle 2, Day 1) and continue with the planned treatment schedule.
Columvi 30 mg (from Cycle 2 onwards)	≤ 6 weeks	• Administration of the 30 mg dose of Columvi, then continue with the planned treatment schedule.
	> 6 weeks	• Repeat the Cycle 1 regimen described in Table 2: pre-treatment with 1000 mg obinutuzumab (Day 1), 2.5 mg dose of Columvi (Day 8)[b] and 10 mg dose of Columvi (Day 15)[c]. • Then administer the 30 mg dose of Columvi (Day 1 of the next cycle) and continue with the planned treatment schedule.

[a] Carry out pre-treatment in all patients based on Table 1.

[b] The patients should be in hospital during the infusion of the 2.5 mg dose and for 24 hours afterwards.

[c] The patients should be in hospital during the infusion of the 10 mg dose and for 24 hours afterwards if CRS occurred during administration of the last 2.5 mg dose.

A Columvi dose reduction is not recommended.

Measures after adverse reactions

Treatment of Cytokine Release Syndrome

Cytokine release syndrome should be identified based on the clinical presentation (see section "Warnings and Precautions"). Patients should be evaluated for other causes of fever, hypoxia, and hypotension, for example infections or sepsis. If CRS is suspected, patients should be treated based on the recommendations given in Table 4 and also in accordance with the applicable practice guidelines.

Table 4: CRS Grading and Treatment recommendations

Grade[a]	CRS Treatment	Measures for Next Scheduled Columvi Infusion
Grade 1 Fever ≥ 38 °C	If CRS occurs during infusion: • Interrupt infusion and treat symptoms • Restart infusion at slower rate when symptoms resolve • If symptoms recur, discontinue current infusion If CRS occurs post-infusion: • Treat symptoms If CRS lasts more than 48 h after symptomatic management: • Treat CRS in accordance with applicable guidelines for practice	• Ensure symptoms are resolved for at least 72 hours prior to next infusion* • Consider slower infusion rate[b]
Grade 2 Fever ≥ 38 °C and/or hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen[c] by nasal cannula or blow-by	If CRS occurs during infusion: • Discontinue current infusion and treat symptoms • Treat CRS in accordance with applicable guidelines for practice If CRS occurs post-infusion: • Treat symptoms • Treat CRS in accordance with applicable guidelines for practice	• Ensure symptoms are resolved for at least 72 hours prior to next infusion* • Consider slower infusion rate[b] • Inpatient monitoring should be carried out over at least 24 hours for the next infusion (see section “Dosage/Administration, Monitoring”) • Premedication should be maximised as appropriate[d] • in the event of a recurrence of Grade 2 CRS, take measures in accordance with Grade 3 CRS
Grade 3 Fever ≥ 38 °C and/or hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow oxygen[e] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	If CRS occurs during infusion: • Discontinue current infusion and treat symptoms • Treat CRS in accordance with applicable guidelines for practice If CRS occurs post-infusion: • Treat symptoms • Treat CRS in accordance with applicable guidelines for practice	• Ensure symptoms are resolved for at least 72 hours prior to next infusion* • Consider slower infusion rate[b] • Inpatient monitoring should be carried out over at least 24 hours for the next infusion (see section “Dosage/Administration, Monitoring”) • Premedication should be maximised as appropriate[d] • If Grade ≥ 3 CRS recurs at subsequent infusion, stop infusion immediately and permanently and discontinue Columvi

Grade[a]	CRS Treatment	Measures for Next Scheduled Columvi Infusion
Grade 4 Fever ≥ 38 °C and/or hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)	If CRS occurs during infusion or post-infusion: • Permanently discontinue Columvi and treat symptoms • Treat CRS in accordance with applicable guidelines for practice	

[a] American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria.
[b] Duration of infusion may be extended up to 8 hours, as appropriate for that cycle (see Table 2).
[c] Low-flow oxygen is defined as oxygen delivered at < 6 l/minute.
[d] Refer to Table 1 for additional information.
[e] High-flow oxygen is defined as oxygen delivered at ≥ 6 l/minute.
* See Table 3 (Recommendations on continuing Columvi after delayed dosing).

Neurological toxicity and ICANS

At the first sign of neurological toxicity, including ICANS, consider a neurology evaluation and withholding Columvi based on the type and severity of neurotoxicity. Other causes of neurological symptoms must be excluded. Intensive care treatment and supportive treatment are required in cases of severe or life-threatening neurological toxicity (see “Warnings and precautions - Neurological events”). The recommendations given in Table 5 are to be considered with reference to the measures that are taken.

Table 5: Recommendations for the treatment of neurological events (including ICANS)

Adverse reaction	Severity[1, 2]	Measures
Neurological side effect[1] (including ICANS[2]) (see section "Warnings and Precautions")	Grade 1	• Continue treatment with Columvi and monitor the symptoms of the neurological side effect. • In the event of ICANS occurring, treat this in accordance with the applicable guidelines for practice.
	Grade 2	• Interrupt treatment with Columvi until the symptoms of the neurological side effect have returned to Grade 1 or the initial state.[3, 4] • Carry out supportive therapeutic measures and consider a neurological assessment. • In the event of ICANS occurring, treat this in accordance with the applicable guidelines for practice.
	Grade 3	• Interrupt treatment with Columvi until the symptoms of the neurological side effect have returned to Grade 1 or the initial state over a period of at least 7 days.[4, 5] • In the event of Grade 3 neurological side effects that persist for longer than 7 days, consider permanent discontinuation of Columvi. • Discontinue Columvi permanently in the event of a recurrence.

Grade[a]	CRS Treatment	Measures for Next Scheduled Columvi Infusion
		• Carry out supportive therapeutic measures and consider a neurological assessment. • In the event of ICANS occurring, treat this in accordance with the applicable guidelines for practice.
	Grade 4	• Discontinue Columvi permanently. • Carry out supportive therapeutic measures, if necessary with intensive care treatment, and consider a neurological assessment. • In the event of ICANS occurring, treat this in accordance with the applicable guidelines for practice.

[1] Based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03.
[2] Based on the ICANS consensus grading system pursuant to ASTCT 2019.
[3] Consider the type of neurological side effect before taking the decision to interrupt Columvi.
[4] See section "Dosage/Administration" in relation to continuing treatment with Columvi after a delayed dose.
[5] Assess the benefit-risk ratio before continuing treatment with Columvi.

Other adverse reactions

Table 6: Recommendations for the treatment of other adverse reactions (including ICANS)

Adverse Reaction[1]	Severity[1]	Actions
Infections *[see section "Warnings and Precautions"]*	Grades 1 – 4	• Withhold Columvi in patients with active infection until the infection resolves.[2] • For Grade 4, consider permanent discontinuation of Columvi.
Hyperprogression (tumour flare reaction) *[see section "Warnings and Precautions"]*	Grade 1	• Monitor for signs and symptoms of compression or obstruction due to mass effect secondary to tumour flare.
	Grades 2 – 4	• Monitor for signs and symptoms of compression or obstruction due to mass effect secondary to tumour flare, and institute appropriate treatment with an antihistamine and corticosteroids. • Withhold Columvi until tumour flare resolves.[2]
Neutropenia	Absolute neutrophil count less than 0.5 x 10^9/l	• Withhold Columvi until absolute neutrophil count is 0.5 x 10^9/l or higher.[2]
Thrombocytopenia	Platelet count less than 50 x 10^9/l	• Withhold Columvi until platelet count is 50 x 10^9/L or higher.[2]
Other adverse reactions *[see section "Undesirable effects"]*	Grade 3 or higher	• Withhold Columvi until the toxicity resolves to Grade 1 or baseline.[2]

[1] Based on NCI CTCAE, version 4.03.
[2] See Table 3 (Recommendations on continuing Columvi after delayed dosing).

Special dosage instructions

Patients with hepatic disorders

No dose adjustment is required in patients with mild hepatic impairment (total bilirubin > upper limit of normal [ULN] to ≤ 1.5 × ULN or aspartate transaminase [AST] > ULN). No specific studies in patients with moderate or severe hepatic impairment have been conducted with Columvi (see paragraphs “Dosage/Administration, special dosage instructions” and “Pharmacokinetics, Kinetics in special populations”).

Patients with renal disorders

No dose adjustment of Columvi is required in patients with mild or moderate renal impairment (CrCL 30 to < 90 mL/min). The safety and efficacy of Columvi has not been studied in patients with severe renal impairment (see paragraphs “Dosage/Administration, special dosage instructions” and “Pharmacokinetics, Kinetics in special populations”).

Elderly patients

No differences in safety or efficacy of Columvi were observed between patients ≥ 65 years of age and those under 65 years. No dose adjustment of Columvi is required in patients ≥ 65 years of age (see paragraphs “Dosage/Administration, special dosage instructions” and “Pharmacokinetics, Kinetics in special populations”).

Children and adolescents

The safety and efficacy of Columvi in children and adolescents have not been established.

Preparation and administration of Columvi

Preparation

Columvi must be diluted by a healthcare professional using aseptic technique prior to intravenous administration (see paragraph “Other information, Instructions for handling”).

Administration

- Columvi must be administered as an intravenous infusion through a dedicated infusion line.
- Columvi must not be administered as an intravenous push or bolus.
- Columvi must not be mixed with other drugs.

Contraindications

Columvi is contraindicated in patients with a known hypersensitivity to glofitamab or any of the excipients.

Warnings and precautions

General

Refer to obinutuzumab-specific warnings and precautions in the Information for Healthcare Professionals for obinutuzumab.

Cytokine Release Syndrome

CRS, including reactions with a fatal outcome, may occur in patients receiving Columvi (see section "Undesirable effects").

The most frequent manifestations of CRS were pyrexia, tachycardia, hypotension, chills, and hypoxia. Infusion-related reactions may be clinically indistinguishable from manifestations of CRS.

CRS of any grade (ASTCT criteria) occurred in 67.6% of patients in study NP30179. Grade 3 or 4 CRS occurred in 4.1% of patients. (see paragraph "Undesirable effects, Description of specific adverse reactions and additional information"). Recurrent CRS occurred in 32.4% of patients.

CRS of any grade occurred in 54.5% of patients after receiving the 2.5 mg dose of Columvi on Day 8 of Cycle 1, with a median time to occurrence (calculated from the start of the infusion) of 12.6 hours (range: 5.2 to 50.8 hours), in 33.3% of patients after receiving the 10 mg dose on Day 15 of Cycle 1, with a median time to occurrence of 26.8 hours (range: 6.7 to 125.0 hours), and in 26.8% of patients after receiving the 30 mg dose on Day 1 of Cycle 2, with a median time to occurrence of 28.2 hours (range: 15.0 to 44.2 hours). CRS was reported in 0.9% of patients in Cycle 3 and in 2% of patients after Cycle 3.

Treatment must be started based on the titration schedule for Columvi to reduce the risk of CRS occurring (see Table 2 in section “Dosage/Administration”). The frequency and severity of adverse events may be increased due to the mechanism of action if the recommended dosage or dosage schedule is not adhered to at the start of therapy or when therapy is resumed after delayed doses. Patients should be given pre-treatment with corticosteroids, antipyretics and antihistamines and adequate fluids before receiving Columvi (see Table 1 in section “Dosage/Administration”). Patients are to be monitored for signs and symptoms of CRS (see Recommendations on monitoring in section “Dosage/Administration”).

The prescriber must counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. The patient must be assessed immediately for possible admission to

hospital at the first signs of CRS. CRS is to be treated in accordance with the applicable guidelines for practice. Supportive measures are to be taken by the physician based on the severity of the CRS (this may also include intensive care treatment in cases of serious or life-threatening CRS), or administration of Columvi is to be interrupted or permanently discontinued (see section “Dosage/Administration” Table 4).

Patients should be evaluated for other causes of fever, hypoxia, and hypotension, for example infections or sepsis. Other causes must be considered in cases of treatment-refractory CRS, including haemophagocytic lymphohistiocytosis or capillary leak syndrome.

CRS should be managed based on the patient’s clinical presentation and according to the CRS management guidance provided in Table 4 (see section "Dosage/Administration").

Neurological Events

Columvi can cause serious or life-threatening adverse neurological reactions, including immune effector cell-associated neurotoxicity syndrome (ICANS). Adverse neurological reactions ≥ grade 3 occurred in 2.1% of the 145 patients treated with Columvi. ICANS of any grade was observed in 4.8% of the patients (see section “Undesirable effects”).

Concomitant treatment with Columvi and other medicines that can cause dizziness or alter the state of consciousness may increase the risk of adverse neurological reactions.

Patients should be monitored for signs and symptoms of neurotoxicity during treatment. The patient must be examined immediately at the first signs of neurotoxicity (including ICANS), a neurological examination should potentially be considered and, depending on severity, supportive therapeutic measures should be taken. Columvi is to be interrupted or permanently discontinued, depending on the severity, and the recommendations for treatment are to be adhered to (see section "Dosage/Administration").

Serious Infections

Serious infections (such as sepsis and pneumonia) have occurred in patients treated with Columvi, including infections that took a fatal course (see paragraph "Description of specific adverse reactions and additional information").

Columvi must not be administered to patients with an active infection. Patients should be monitored before and during Columvi treatment for the emergence of possible bacterial, fungal, and new or reactivated viral infections and treated appropriately (see Table 6, section "Dosage/Administration").

Patients should be instructed to seek medical advice if signs and symptoms suggestive of an infection occur.

Febrile neutropenia has been reported during treatment with Columvi. Patients with febrile neutropenia should be evaluated for infection and treated promptly.

Cytopenia

Columvi may cause serious or severe cytopenia, including neutropenia, anaemia and thrombocytopenia (see section "Undesirable effects").

Blood parameters must be monitored throughout treatment with Columvi. Columvi must be interrupted or permanently discontinued depending on the severity of the cytopenia (see "Dosage/Administration").

Hepatitis B Reactivation

Reactivation of the hepatitis B virus (HBV) may occur in patients who are undergoing treatment with medicines that target B cells, which can result in a fulminant course of hepatitis and liver failure, including death. Patients with a positive HBV serology should be monitored for clinical symptoms, which may be signs of HBV reactivation, and laboratory tests must be carried out during treatment with Columvi and for at least six months after completion of treatment.

Tumour Flare

Tumour flare has been reported in patients receiving Columvi. Manifestations included localized pain and swelling (see section “Undesirable effects”).

Consistent with the mechanism of action for Columvi, tumour flare can probably be attributed to the influx of T cells into the tumour lesions after the administration of Columvi.

There is a heightened risk of compromise and morbidity due to mass effect secondary to tumour flare in patients with bulky tumours located in close proximity to airways and/or a vital organ. Monitoring and evaluation of tumour flare at critical anatomical sites is recommended in patients treated with Columvi and managed as clinically indicated.

Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) has been reported in patients receiving Columvi (see section "Undesirable effects"). Patients with high tumour burden, rapidly proliferative tumours, renal dysfunction, or dehydration are at greater risk of TLS.

Patients at risk should be monitored closely by appropriate clinical and laboratory tests for electrolyte status, hydration, and renal function. Appropriate prophylactic measures with anti-hyperuricemics (e.g., allopurinol or rasburicase) and adequate hydration should be considered prior to Columvi infusion.

Management of TLS may include aggressive hydration, correction of electrolyte abnormalities, anti-hyperuricemic therapy, and supportive care.

Hepatotoxicity

Columvi can cause hepatotoxicity that may take a fatal course.

Elevated liver enzymes have been reported in patients undergoing treatment with Columvi (see section "Undesirable effects"). Liver enzymes and bilirubin are to be monitored at the start and during treatment if clinically indicated. The approach to treatment should be in line with the standard local protocols/guidelines. Columvi is to be interrupted or permanently discontinued, depending on severity (see section "Dosage/Administration").

Immunisation

Live vaccines and/or live-attenuated vaccines should not be used at the same time as Columvi. There are no data on patients shortly after they have been given live vaccines.

Interactions

No clinical drug-drug interaction studies have been performed.

The initial release of cytokines associated with the start of treatment with Columvi may inhibit CYP450 enzymes. The highest drug-drug interaction risk is during the period of one week following each of the first two doses of Columvi (i.e., Cycle 1 Day 8 and Day 15) in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index (e.g., warfarin, cyclosporine). On initiation of Columvi therapy, close monitoring of patients being treated with CYP450 substrates with a narrow therapeutic index should be considered.

Pregnancy, lactation

Contraception
Female patients of reproductive potential must use highly effective contraceptive methods *while receiving Columvi* and for at least 2 months following the last dose of Columvi.

Pregnancy

There are no available data on the use of Columvi in pregnant women. No animal experiments have been conducted on reproductive toxicity. Glofitamab is an immunoglobulin G (IgG). IgG is known to cross the placenta. Based on its mechanism of action, glofitamab is likely to cause fetal B-cell depletion when administered to a pregnant woman.

Glofitamab is not recommended during pregnancy and in women of child-bearing age who are not using any contraception.

Female patients receiving Columvi should be advised of the potential harm to the fetus. Female patients should be advised to contact the treating physician, should pregnancy occur.

Lactation

It is not known whether glofitamab is excreted in human milk. No studies have been conducted to assess the impact of glofitamab on milk production or its presence in human milk. Human IgG is known to be present in human milk. A risk to the neonates/infants cannot be excluded. Breastfeeding is to be interrupted during treatment with glofitamab. The potential for absorption of glofitamab and the potential for adverse reactions in the nursing infant is unknown. Women should be advised to discontinue breastfeeding during treatment with Columvi and for 2 months after the last dose of Columvi.

Fertility

There are no data on the effects of glofitamab on fertility. No animal experiments have been conducted on the effects of glofitamab on male or female fertility.

Effects on ability to drive and use machines

Patients experiencing CRS or adverse neurological reactions, such as tremor, dizziness, insomnia, severe neurotoxicity or other side effects that have an adverse impact on awareness should be examined accordingly, potentially in particular, a neurological examination. These patients should be advised not to drive or use heavy or potentially dangerous machines until the undesirable symptoms resolve.

Undesirable effects

Summary of the safety profile

The adverse reactions described in this section were identified in 145 patients with relapsed or refractory DLBCL, including DLBCL in the context of follicular lymphoma, high-grade B-cell lymphoma (HGBCL) and PMBCL, who had received at least two prior lines of systemic therapy and were being given Columvi monotherapy in the study NP30179, an open-label, multi-centre clinical study. A

median 5 (range: 1 to 13) cycles of Columvi were used, with 38.6% of patients receiving at least 8 cycles and 29.7% all 12 cycles of the Columvi treatment.

The most common adverse reactions (≥ 20%) in the 145 patients were cytokine release syndrome, neutropenia, anaemia and thrombocytopenia, as well as skin rash. The most common serious adverse events (≥ 2%) included cytokine release syndrome (CRS) (22.1%, based on the ASTCT consensus grading system), sepsis (4.1%), COVID-19 (3.4%), tumour flare (3.4%) and COVID-19 pneumonia (2.8%). Treatment was discontinued in eight of the 145 patients (5.5%) due to an adverse event. Adverse reactions that resulted in Columvi being discontinued in more than one patient were COVID-19 (1.3%), delirium (1.4%) and neutropenia (1.4%).

List of adverse reactions

The adverse reactions of all grades of severity that are listed below are based on pooled data from patients from Study NP30179 (n = 469) in which Columvi was used as a monotherapy.

The adverse reactions should be arranged according to MedDRA system organ classes and the conventional frequencies as follows:
"very common" (≥1/10)
"common" (≥1/100, <1/10),
"uncommon" (≥1/1000, <1/100)
"rare" (≥1/10,000, <1/1000)
"very rare" (<1/10000)

Table 7: Adverse drug reactions under treatment with Columvi monotherapy

	Columvi N = 469[+]
Infections and infestations	
Very common	Viral infections[a] (all grades 11.0%, Grade 3-4 3.4%)
Common	Upper respiratory tract infections[b] (all grades 8.1%, Grade 3-4 0.6%), pneumonia (all grades 4.9%, Grade 3-4 2.3%), urinary tract infection[c] (all grades 3.6%, Grade 3-4 0.9%), lower respiratory tract infections[d] (all grades 3.4%, Grade 3-4 0.9%), bacterial infections[e+] (all grades 6.2%, Grade 3-4 1.4%), sepsis[f+] (all grades 4.1%, Grade 3-4 2.8%), fungal infections[g] (all grades 1.4%, Grade 3-4 0%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	
Very Common	Hyperprogression (Tumour flare) (all grades 11.7%, Grade 3-4 2.8%)
Blood and lymphatic system disorders	
Very common	Lymphocytes reduced (all grades 90.2%, Grade 3-4 83.2%), leukocytes reduced (all grades 71.0%, Grade 3-4 18.5%), neutrophils reduced (all grades 57.8%, Grade 3-4 30.9%), Neutropenia[h+] (all grades 40.0%, Grade 3-4 29.0%), anaemia[i+] (all grades 30.3%, Grade 3-4 8.5%), thrombocytopenia[j+] (all grades 24.1%, Grade 3-4 7.9%)

Common	Lymphopenia[k+] (all grades 4.8%, Grade 3-4 4.8%), febrile neutropenia[l+] (all grades 3.4%, Grade 3-4 3.4%)
Immune system disorders	
Very common	Cytokine release syndrome[m+] (all grades 64%, Grade 3-4 5.1%)
Metabolism and nutrition disorders	
Very common	Hyperuricaemia (all grades 22.6%, Grade 3-4 22.6%), hyperglycaemia (all grades 14.2%, Grade 3-4 14.2%), hypomagnesaemia[+] (all grades 15.2%, Grade 3-4 0%), hypophosphataemia (all grades 18.6%, Grade 3-4 6.2%), hypokalaemia (all grades 11.1%, Grade 3-4 1.3%), hypocalcaemia[+] (all grades 10.3%, Grade 3-4 0.7%)
Common	Hyponatraemia+ (all grades 8.3%, Grade 3-4 1.4%), tumour lysis syndrome (all grades 2.1%, Grade 3-4 2.1%)
Psychiatric disorders	
Common	Confusion (all grades 1.7%, Grade 3-4 0%)
Nervous system disorders	
Very common	Headache (all grades 11.7%, Grade 3-4 0%)
Common	Somnolence (all grades 1.4%, Grade 3-4 0.7%), tremor (all grades 1.4%, Grade 3-4 0%)
Uncommon	Myelitis[n]
Gastrointestinal disorders	
Very common	Diarrhoea (all grades 15.6%, Grade 3-4 0.4%), constipation (all grades 14.5%, grade 3-4 0%), nausea (all grades 13.2%, Grade 3-4 0%)
Common	Vomiting (all grades 5.8%, Grade 3-4 0%), Gastrointestinal haemorrhage[o] (all grades 2.8%, Grade 3-4 2.8%)
Hepatobiliary disorders	
Very common	Alanine aminotransferase increased (all grades 10.0%, Grade 3-4 2.8%)
Common	Aspartate aminotransferase increased (all grades 8.5%, Grade 3-4 2.8%), blood alkaline phosphatase increased (all grades 9.0%, Grade 3-4 1.4%), gamma-glutamyltransferase increased (all grades 7.5%, Grade 3-4 2.8%) blood bilirubin increased (all grades 4.1%, Grade 3-4 0.9%), liver enzymes increased*** (all grades 1.4%, Grade 3-4 1.4%)
Skin and subcutaneous tissue disorders	
Very common	Rash[p] (all grades 20.0%, Grade 3-4 1.4%)
General disorders and administration site conditions	
Very common	Pyrexia (all grades 23.5%, Grade 3-4 0.2%)

* The reported Grade 5 reactions were sepsis (1.3%), COVID-19 pneumonia (1.9%) and COVID-19 (1.9%).
+ The ADR table presents the highest frequency in pooled data with N = 469 (all patients who received Columvi as monotherapy in Study NP30179) and pooled data with N = 145 (patients with relapsed or refractory DLBCL in Study NP30179).
[a] Including COVID-19, COVID-19 pneumonia, herpes zoster, influenza and ophthalmic herpes zoster.
[b] Including upper respiratory tract infection, sinusitis, nasopharyngitis, chronic sinusitis and rhinitis.
[c] Including urinary tract infection and urinary tract infection caused by Escherichia.
[d] Including lower respiratory tract infection and bronchitis.
[e] Including infection associated with a vascular device, bacterial infection, Campylobacter infection, bacterial biliary tract infection, bacterial urinary tract infection, *Clostridium difficile* infection, infection caused by Escherichia and peritonitis.
[f] Including sepsis and septic shock.
[g] Including oesophageal candidiasis and oral candidiasis.
[h] Including neutropenia and reduced neutrophil count.
[i] Including anaemia and reduced haemoglobin.
[j] Including thrombocytopenia and reduced thrombocyte count.
[k] Including lymphopenia and reduced lymphocyte count.
[l] Including febrile neutropenia and neutropenic infection.
[m] Based on the ASTCT consensus grading recommendations.
[n] Myelitis occurring simultaneously with CRS.
[o] Including gastrointestinal haemorrhage, colon haemorrhage and gastric bleeding.
[p] Including skin rash, itchy skin rash, maculopapular skin rash, dermatitis, acneiform dermatitis, exfoliative dermatitis, erythema, palmar erythema, pruritus and erythematous skin rash.
*** Liver enzymes increased; includes non-specific increase in transaminase values.

Description of specific adverse reactions and additional information

Description of selected adverse drug reactions from clinical trials

Cytokine Release Syndrome

In study NP30179 (n = 145), any grade CRS (by ASTCT criteria) occurred in 67.6% (98/145) of patients, with Grade 1 CRS being reported in 50.3% of patients, Grade 2 CRS in 13.1% patients, Grade 3 CRS in 2.8% of patients, and Grade 4 CRS in 1.4% of patients. CRS resolved in all patients except one. One patient discontinued Columvi due to CRS.

In patients with CRS, the most common manifestations of CRS included pyrexia (99.0%), tachycardia (25.5%), hypotension (23.5%), chills (14.3%), and hypoxia (12.2%). Grade 3 or higher events associated with CRS included hypotension (3.1%), hypoxia (3.1%), pyrexia (2.0%), and tachycardia (2.0%).
Grade ≥ 2 CRS occurred in 12.4% of patients following the first Columvi dose (2.5 mg), with median time to onset of 9.7 hours (range: 5.2 to 19.1 hours) and median duration of 50.4 hours (range: 6.5 to 316.7 hours). Following Columvi 10 mg dose at Cycle 1 Day 15, the incidence of Grade ≥ 2 CRS decreased to 5.2% of patients, with median time to onset of 26.2 hours (range: 6.7 to 144.2 hours) and median duration of 30.9 hours (range: 3.7 to 227.2 hours). Grade ≥ 2 CRS following Columvi 30 mg dose at Cycle 2 Day 1 occurred in one patient (0.8%) with time to onset of 15.0 hours and duration of 44.8 hours. No Grade ≥ 2 CRS was reported beyond Cycle 2.
Hospitalisation was required in 22.1% of patients due to CRS after receiving Columvi, with a median duration of hospitalisation of 4 days (range: 2 to 15 days) being given.

Neurotoxicity

The most common adverse neurological reactions of any grade in 145 patients treated with Columvi were headache (10.3%), peripheral neuropathy (7.6%), dizziness or vertigo (6.9%) and alterations to the mental state (4.8%, including confusion, cognitive disorder, disorientation, somnolence and delirium). Grade 3 or higher adverse neurological reactions occurred in 2.1% of the patients and included somnolence, delirium and myelitis. Cases of ICANS of any grade occurred in 4.8% of the patients. Median duration to the first occurrence of neurological events was 12 days (range: 1–181 days), median duration of the events was 2 days (range: 1 – 114 days).

Serious Infections

In study NP30179, serious infections were reported in 15.9% (23/145) of patients. The most frequent serious infections reported in ≥ 2% patients were sepsis (4.1%), COVID-19 (3.4%) and COVID-19 pneumonia (2.8%). Infection-related deaths were reported in 4.8% of patients (due to sepsis, COVID-19 pneumonia, and COVID-19). Four patients (2.8%) experienced serious infections concurrently with Grade 3–4 neutropenia.

Cytopenias

Severe neutropenia (Grade 3–4) was reported in 29.0% (42/145) of patients. The median time to onset of the first neutropenia event was 29 days (range: 1 to 203 days). Prolonged neutropenia (lasting longer than 30 days) occurred in 11.7% of patients. The majority of patients with neutropenia (79.3%) were treated with G-CSF. Febrile neutropenia was reported in 3.4% of patients. Grade 3-4 anaemia was reported in 7.6% of patients and Grade 3-4 thrombocytopenia in 5.5% of patients (including reduced thrombocyte counts).

Tumour Flare

Tumour flare was reported in 11.7% of patients, including Grade 2 tumour flare in 4.8% of patients and Grade 3 tumour flare in 2.8% of patients. Tumour flare was reported involving lymph nodes in the head and neck presenting with pain, and involving lymph nodes in the thorax with symptoms of breathlessness due to development of pleural effusion. Most tumour flare events (16/17) occurred during Cycle 1, and no tumour flare events were reported beyond Cycle 2. The median time to onset of tumour flare of any grade was 2 days (range: 1 to 16 days), and the median duration was 3.5 days (range: 1 to 35 days). No patients discontinued Columvi due to tumour flare.

Tumour Lysis Syndrome

TLS was reported in 2 out of 145 patients (1.4%) and was Grade 3 in severity in both cases. The median time to TLS onset was 2 days, and the median duration was 4 days (range: 3 to 5 days).

Hepatotoxicity

An increase in liver enzymes has been reported in patients undergoing treatment with Columvi, including the following adverse reactions: alanine aminotransferase (ALT) increased (9.0%), aspartate aminotransferase (AST) increased (8.3%), blood bilirubin increased (4.1%) and liver enzymes increased (1.4%).

Out of a total of 145 patients, 10 (6.9%) exhibited a Grade ≥ 2 increase in ALT, in AST or in total bilirubin (Grade 2: 4 patients and Grade 3: 6 patients). Median time to occurrence from the first glofitamab dose was 10.0 days (range: 1.0 – 92.0 days), median duration was 9.0 days (range: 5.0 – 43.0 days). None of the patients fulfilled all the Hy's Law criteria for drug-induced liver injury.

Immunogenicity

The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to glofitamab with the incidence of antibodies to other products may be misleading.

As with all therapeutic proteins, there is the potential for immunogenicity.

The majority of patients (94.6%, n = 418) who received glofitamab monotherapy in study NP30179 were negative for ADAs at baseline and remained negative throughout treatment with Columvi. Two (0.5%) patients were negative for ADAs at baseline and became positive for ADAs during treatment. Three patients (0.7%) were ADA-positive at baseline and at one or more post-dose timepoints. Due to the limited number of patients with antibodies against glofitamab, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no experience with overdosage of Columvi in clinical trials.

Properties/Effects

ATC code

Unknown.

Mechanism of action

Glofitamab is a bispecific monoclonal antibody that binds bivalently (with high avidity) to CD20 expressed on the surface of B cells, and monovalently to CD3 in the T-cell receptor (TCR) complex expressed on the surface of T cells. By simultaneous binding to CD20 on the B cell and CD3 on the T cell, glofitamab mediates the formation of an immunological synapse with subsequent potent T-cell activation and proliferation, secretion of cytokines, and release of cytolytic proteins that results in the lysis of CD20-expressing B cells.

Pharmacodynamics

Number of circulating B cells

In Study NP30179, 84% (84/100) patients were already B cell depleted (< 70 cells/µl) before pre-treatment with obinutuzumab. B cell depletion increased to 100% (94/94) after obinutuzumab pre-treatment prior to the initiation of treatment with Columvi and remained low during Columvi treatment.

Cytokine concentrations

A transient increase in cytokines was observed in the measurements of plasma cytokine concentrations (IL-2, IL-6, IL-10, TNF-α and IFN-γ) at doses of 0.045 mg and above. After the recommended dosage of Columvi was administered, the highest increase in cytokines was generally observed within 6 hours after the first 2.5 mg dose of glofitamab on Day 8 of Cycle 1. The elevated cytokine levels generally returned to baseline within 48 hours after the first 30 mg dose on Day 1 of Cycle 2.

Effects on the QT/QTc interval and on cardiac electrophysiology
No studies have been conducted to investigate the effect of glofitamab on the QT/QTc interval and on cardiac electrophysiology.
In Study NP30179, 16/145 patients who were exposed to glofitamab experienced a post-baseline QTc value > 450ms. One of these cases was assessed to be of clinical significance by the investigator. No patients discontinued treatment due to QTc prolongation.

Clinical efficacy

Relapsed or Refractory DLBCL

The efficacy of Columvi monotherapy was evaluated in study NP30179, a single-arm, open-label, multicenter, multi-cohort trial, which included patients with relapsed or refractory DLBCL after at least

two prior lines of systemic therapy. The study excluded patients with prior allogeneic hematopoietic stem cell transplant, previous or active central nervous system lymphoma, ECOG performance status ≥ 2, creatinine clearance (CrCL) < 50 mL/min, or hepatic transaminases $> 3 \times$ ULN.
The patients were given pre-treatment with obinutuzumab on Day 1 of Cycle 1 before treatment with Columvi. Following pre-treatment with obinutuzumab, patients received 2.5 mg of Columvi at Cycle 1 Day 8, 10 mg of Columvi at Cycle 1 Day 15, and 30 mg of Columvi at Cycle 2 Day 1 as per the titration schedule. Patients continued to receive 30 mg of Columvi on Day 1 of Cycles 3 to 12. Patients received premedication including an anti-pyretic, an anti-histamine and a glucocorticoid (see section "Dosage/Administration"). The duration of each cycle was 21 days.

Patients received a median of 5 cycles of Columvi treatment (range: 1 to 13 cycles).

The baseline demographic and disease characteristics were: median age 66 years (range: 21 to 90 years); 65.2% males; 76.8% white, 4.5% Asian, and 1.9% Black or African American; 5.8% Hispanic or Latino; and ECOG performance status of 0 (44.5%) or 1 (54.2%). Most patients (71.0%) had DLBCL not otherwise specified, 18.7% had DLBCL transformed from follicular lymphoma, 6.5% had HGBCL, and 3.9% had PMBCL. The median number of prior lines of therapy was 3 (range: 2 to 7), with 39.4% of patients having received 2 prior lines and 60.6% having received 3 or more prior lines of therapy. All patients had received prior chemotherapy and anti-CD20 monoclonal antibody therapy; 33.5% of patients had received prior CAR T-cell therapy, and 18.1% of patients had received autologous stem cell transplant. Most patients (89.7%) had refractory disease, 58.7% patients had primary refractory disease, 84.5% of patients were refractory to their last prior therapy, and 88.5% of patients who received prior CAR T-cell therapy were refractory to CAR T-cell therapy.

The overall median duration of follow-up was 13.4 months (range: 0 to 28 months). Median duration of follow-up from the date of first response per Independent Review Committee (IRC) assessment was 12.0 months (range: 0 to 27 months).

The primary efficacy outcome measure was complete response (CR) rate as assessed by IRC using 2014 Lugano criteria. The secondary efficacy outcome measures included overall response rate (ORR), duration of response (DOR), duration of complete response (DOCR), time to first response (TFOR), time to first complete response (TFCR), overall survival (OS), and progression-free survival (PFS), as assessed by IRC.

The efficacy results for patients who received at least one dose of Columvi and had previously also been given CAR T-cell therapy (n = 47) are summarised in Tables 8 and 9. Median TFCR was 48 days (95% CI: 41 to 105 days). Median TFOR (complete or partial remission) was 42 days (95%CI: 41 to 43 days). The estimated median follow-up on the DOR in responders was 7.3 months.

Table 8: Efficacy in Patients with Relapsed or Refractory DLBCL Treated with Columvi Monotherapy who had Previously Received CAR T-cell Therapy

Efficacy endpoints	Columvi N = 47
Complete response (CR)	
Patients with CR, n (%)	19 (40.4)
95% CI	[26.37; 55.73]
Overall response rate (ORR)	
Patients with CR or PR, n (%)	26 (55.3)
95% CI	[40.12; 69.83]
Patients with PR, n (%)	7 (14.9)
95% CI	[6.20; 28.31]
Duration of response	
Median DOR, months (95% CI)	14.4 (6.7; n. a.)
Range, months	0[b] – 18[b]
DOR over 12 months, % (95% CI)[c]	57.42 (31.28; 83.56)

CI = confidence interval; CR = complete response; n. e. = no estimate possible; PR = partial response.
[a] From the date of the first complete response to disease progression or death with any cause.
[b] Censored observations.
[c] Event-free rates based on Kaplan-Meier estimates.
[d] From the date of the first response (PR or CR) to disease progression or death with any cause.

Table 9: Efficacy in patients with relapsed or refractory DLBCL under treatment with a Columvi monotherapy who had previously received CAR T-cell therapy (according to histological subtype)

Efficacy endpoints	Columvi N = 47			
	DLBCL, NOS N = 34	trFL N = 6	PMBCL N = 3	HGBCL N = 4
Complete response (CR)				
Patients with CR, n (%)	15 (44.1)	1 (16.7)	2 (66.7)	1 (25)
95% CI	[27.19; 62.11]	[0.42; 64.12]	[9.43; 99.16]	[0.63; 80.59]
Overall response rate (ORR)				
Patients with CR or PR, n (%)	19 (55.9)	3 (50)	2 (66.7)	2 (50)
95% CI	[37.89; 72.81]	[11.81; 88.19]	[9.43; 99.16]	[6.76; 93.24]

trFL = DLBCL after transformation of follicular lymphoma.

Median progression-free survival was 6.8 months (95% CI: 3.4 – 15.7) in patients who received at least one dose of Columvi and had previously already been given CAR T-cell therapy (n = 47). Median overall survival up to the date of the clinical cut-off was 9.8 months (95% CI: 7.5 – 15.7).

Pharmacokinetics

The pharmacokinetics of glofitamab were determined after pre-treatment with 1000 mg obinutuzumab as a single dose. Non-compartmental analyses indicate that glofitamab serum concentration reaches the maximal level (C_{max}) at the end of infusion and declines in a bi-exponential fashion. Glofitamab exhibits linear and dose-proportional pharmacokinetics over the dose range studied (0.005 to 30 mg) and is independent of time.

Absorption

Columvi is administered as an IV infusion. Peak concentration of glofitamab (C_{max}) was reached at the end of the infusion.

Distribution

Based on a population pharmacokinetic analysis, the total distribution volume for glofitamab is 5.6 l (24%).

Metabolism

The metabolism of glofitamab has not been directly studied. Antibodies are cleared principally by catabolism.

Elimination

Based on a population pharmacokinetic analysis, the terminal half-life for glofitamab at steady state is 7.6 days (24%) and the clearance is 0.617 l/day (33%).

Kinetics in specific patient groups

Hepatic impairment

Population pharmacokinetic analyses showed hepatic impairment does not affect the pharmacokinetics of glofitamab. The pharmacokinetics of glofitamab in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 × ULN or AST > ULN, n = 72) were similar to those with normal hepatic functions (n = 383). No dose adjustment is required for patients with mild hepatic impairment. Columvi has not been studied in patients with moderate and severe hepatic impairment.

Renal impairment

Population pharmacokinetic analyses showed that creatinine clearance does not affect the pharmacokinetics of glofitamab. The pharmacokinetics of glofitamab in patients with mild (n = 168) or moderate (n = 75) renal impairment (CrCL 30 to < 90 mL/min) were similar to those in patients with

normal renal function (n = 213). No dose adjustment is required for patients with mild or moderate renal impairment. Columvi has not been studied in patients with severe renal impairment.

Effects of age, sex and body weight

Based on a population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of glofitamab were determined based on age (21 to 90 years), sex or body weight (31 to 148 kg).

Elderly patients

No differences in glofitamab exposure were noted in patients 65 years of age and older (n = 238) and those under 65 years (n = 222) based on population pharmacokinetic analysis.

Children and adolescents

No studies have been conducted to investigate the pharmacokinetics of glofitamab in paediatric patients.

Preclinical data

No studies lasting longer than 4 weeks were performed as glofitamab was strongly immunogenic in cynomolgus monkeys and led to a loss of exposure and pharmacokinetic effects. All results obtained for glofitamab in cynomolgus monkeys were viewed as pharmacologically mediated effects. In repeat toxicity studies, only effects were observed that also occurred in the clinical studies.

No studies have been performed to establish the genotoxicity, carcinogenicity and reproductive toxicity of Columvi.

Other information

Incompatibilities

Only 0.9% or 0.45% sodium chloride solution should be used to dilute Columvi, since other diluents have not been tested.

Columvi when diluted with 0.9% sodium chloride solution is compatible with intravenous infusion bags composed of polyvinyl chloride (PVC), polyethylene (PE), polypropylene (PP), or non-PVC polyolefin. When diluted with 0.45% sodium chloride solution, Columvi is compatible with intravenous infusion bags composed of PVC.

No incompatibilities have been observed with infusion sets with product-contacting surfaces of polyurethane (PUR), PVC, or PE, and in-line filter membranes composed of polyethersulfone (PES) or polysulfone. The use of in-line filter membranes is optional.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Diluted solution for intravenous infusion

For microbiological reasons, the ready-to-use dilute solution for infusion should be used immediately. Storage times and conditions are the responsibility of the user if the solution is not used immediately and should be no longer than 72 hours in the refrigerator at 2 °C to 8 °C or 24 hours at 30 °C, unless the solution for infusion was prepared under controlled and validated aseptic conditions.

Special precautions for storage

Keep out of the reach of children.
Store in the refrigerator (2-8 °C).
Do not shake. Do not freeze.
Keep the container in the outer carton in order to protect the contents from light.

Instructions for handling

Instructions for dilutions

- Columvi contains no preservative and is intended for single use only.
- Columvi must be diluted by a healthcare professional using aseptic technique, prior to intravenous administration.
- Visually inspect the Columvi vial for particulate matter or discoloration prior to administration. Columvi is a colorless, clear solution. Discard the vial if the solution is cloudy, discolored, or contains visible particles.
- Withdraw the required volume of 0.9% or 0.45% sodium chloride solution from the infusion bag (see Table 10) using a sterile needle and syringe and discard.
- Withdraw the required volume of Columvi concentrate for the intended dose from the vial using a sterile needle and syringe and dilute into the infusion bag (see Table 10). Discard any unused portion left in the vial.
- The final drug concentration after dilution must be 0.1 mg/mL to 0.6 mg/mL.
- Gently invert the infusion bag to mix the solution in order to avoid excessive foaming. Do not shake.
- Inspect the infusion bag for particulates and discard if present.
- Prior to the start of the intravenous infusion, the content of the infusion bag should be at room temperature.

Table 10: Dilution of Columvi for Infusion

Dose of Columvi to be administered	Size of 0.9% or 0.45% sodium chloride solution infusion bag	Volume of 0.9% or 0.45% sodium chloride solution solution to be withdrawn and discarded	Volume of Columvi concentrate to be added
2.5 mg	50 mL	27.5 mL	2.5 mL
	100 mL	77.5 mL	2.5 mL
10 mg	50 mL	10 mL	10 mL
	100 mL	10 mL	10 mL
30 mg	50 mL	30 mL	30 mL
	100 mL	30 mL	30 mL

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

68297 (Swissmedic).

Packs

Injection vials containing 2.5 mg/2.5 mL: 1 [A]
Injection vials containing 10 mg/10 mL: 1 [A]

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd., Basel.

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June 2023.