Summary Report of Benefit-Risk Assessment

COLUMVI CONCENTRATE FOR SOLUTION FOR INFUSION 1MG/ML

NEW DRUG APPLICATION

Active Ingredient(s)	Glofitamab
Product Registrant	Roche Singapore Pte. Ltd.
Product Registration Number	SIN16968P
Application Route	Full evaluation
Date of Approval	05 March 2024

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A INTRODUCTION

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.

The active substance, glofitamab, is a full-length, fully humanised, immunoglobulin G1 (IgG1), T-cell-engaging bispecific antibody (TCB). As a TCB targeting CD20-expressing B cells, glofitamab binds to CD20 expressed on target B cells and CD3 epsilon chain (CD3ε) present on effector T cells. By simultaneously binding to human CD20-expressing tumour cells and to the CD3ε of the T-cell receptor (TCR) complex on T cells, it induces tumour cell lysis, in addition to T-cell activation, proliferation and cytokine release.

Columvi is available as concentrate for solution for infusion containing 1 mg/ml of glofitamab. Other ingredients in the vial are D-sucrose, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20 and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

INTRODUCTION

The drug substance, glofitamab, is manufactured at Roche Diagnostics GmbH, Penzberg, Germany. The drug product, Columvi, is manufactured at Genentech, Inc. South San Francisco, United States.

Drug substance:

Adequate controls have been presented for the starting materials, reagents, and cell bank. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities have been appropriately performed. Potential and actual impurities are adequately controlled in the specifications.

The drug substance specifications were established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2, with information on the reference standards used for identity, assay and impurities testing presented.

The packaging is ethylene vinyl acetate (EVA) copolymer single used bags. The stability data presented was adequate to support the storage of the drug substance at -40ºC with a shelf life of 48 months.

Drug product:

The manufacturing process involves pooling and homogenisation of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

The manufacturing site is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICHQ2, with information on the reference standards used for identity, assay and impurities testing presented.

The container closure system is type I glass vial with fluororesin-laminated rubber stopper. The stability data submitted was adequate to support the approved shelf-life of 30 months when stored at 2-8ºC.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of glofitamab in the treatment of relapsed or refractory DLBCL was based primarily on one pivotal Phase I/II study NP30179. This was a single-arm, open-label, multicentre, multi-cohort, dose escalation and dose expansion study of glofitamab in patients with relapsed or refractory DLBCL after at least two prior lines of systemic therapy including an anti-CD20 monoclonal antibody and an anthracycline agent.

Following pre-treatment with obinutuzumab at Cycle 1 Day 1 to reduce the risk of cytokine release syndrome (CRS), patients in the efficacy populations received 2.5 mg of glofitamab at Cycle 1 Day 8, 10 mg of glofitamab at Cycle 1 Day 15, and 30 mg of glofitamab at Cycle 2 Day 1 as per the step-up dosing schedule (2.5 mg/10 mg/30 mg). Patients continued to receive 30 mg of glofitamab on Day 1 of Cycles 3 to 12. Patients received premedication including an anti-pyretic, an antihistamine and a glucocorticoid (methylprednisolone or equivalent dose of prednisolone in Cohorts D2 (Sub cohort 2 [Sub. 2]) and D3; dexamethasone in Cohort D5). The duration of each cycle was 21 days.

The primary efficacy endpoint was complete response (CR) rate as assessed by an Independent Review Committee (IRC) using the 2014 Lugano Classification Criteria. The secondary efficacy outcome measures included Investigator (INV)-assessed CR, and overall response rate (ORR), duration of complete response (DOCR), duration of response (DOR), time to first complete response (TFCR), time to first overall response (TFOR), progression-free survival (PFS) and overall survival (OS), as assessed by IRC and INV. Tumour response was assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and positron emission tomography (PET) scan at baseline and then every 3 cycles starting at the end of cycle 2 until end of therapy (EOT) and after every 6 months until disease progression. Comparison of CR rates between the intent-to-treat (ITT) population in the pre-specified Cohort D3 and an historical control was conducted using an exact binomial test with a two-sided alpha level of 5%. The historical CR rate for patients in the relapsed or refractory DLBCL cohort was assumed to be 20%, based on a systematic literature review of regimens including chimeric antigen receptor (CAR) T-cell therapies, anti-CD20 therapy plus chemotherapy, lenalidomide, polatuzumab vedotin, and other regimens. The review identified 19 studies that together included 1373 patients, the majority of whom had received at least two prior systemic therapy regimens. The primary endpoint of CR rate is acceptable as a surrogate endpoint that is considered reasonably likely to be predictive of clinical benefit in relapsed or refractory DLBCL.

A total of 108 patients were enrolled in the pre-specified efficacy population, Cohort D3 (cut-off date 14 September 2021). In the updated interim report (cut-off date 15 June 2022), the primary efficacy population was expanded to include all patients with relapsed or refractory DLBCL who were treated with glofitamab 2.5/10/30 mg, pooling data from the dose escalation Cohort D2 [Sub. 2] and the dose expansion Cohorts D3 and D5. This expanded efficacy population consisted of 155 patients. One patient did not receive study treatment and was excluded from the primary safety population, which included 154 patients.

In the safety population (N=154), the median age was 66 years (range 21 to 90 years), the majority of subjects were male (64.9%) and White (76.6%), and 4.5% of subjects were Asian. Most patients (71.4%) had DLBCL not otherwise specified (NOS), 18.2% had DLBCL transformed from follicular lymphoma (trFL), 6.5% had high-grade B-cell lymphoma (HGBCL), and 3.9% had primary mediastinal B-cell lymphoma (PMBCL). The median number of prior lines of therapy was 3 (range 2 to 7), with 39.6% of patients having received 2 prior lines and 60.4% having received 3 or more prior lines of therapy. All patients had received prior chemotherapy and anti-CD20 monoclonal antibody therapy; 33.1% of patients had received prior CAR T-cell therapy, and 18.2% had received autologous stem cell transplant (ASCT). Most patients (89.6%) had refractory disease, 58.4% of patients had primary refractory disease, 85.1% were refractory to their last prior therapy, and 90.2% (46 out of 51) of patients who received prior CAR T-cell therapy were refractory to CAR T-cell therapy.

The primary endpoint, IRC-assessed CR rate in Cohort D3 was 35.2% (95% CI: 26.2, 45.0), which was statistically higher compared to the pre-specified historical control CR rate ($p < 0.001$). The IRC-assessed CR rate in the expanded efficacy population was 40.0% (95% CI: 32.2, 48.2), which was generally consistent with Cohort D3 and within the range of other available third-line therapies for DLBCL. The median time from first treatment to CR occurred early at the first post-baseline tumour assessment visit of 42 days. The relatively short interval to CR observed with glofitamab was desirable in the treatment of aggressive lymphoma. In the expanded efficacy population, an estimated 88.4%, 73.1%, and 63.9% of complete responders remained in remission after 6, 12, and 18 months, respectively. The median duration of complete response had not been reached.

Glofitamab demonstrated consistent efficacy based on IRC-assessed CR rates in patients who previously failed CAR T-cell therapy (37%) and those who were refractory to their last line of treatment (35%). However, a lower IRC-assessed CR rate (23%) was observed in the subgroup of patients who received recent (3 months or less) anti-CD20 therapy compared to those with >3 months since last prior anti-CD20 therapy (53%). The IRC-assessed CR rates based on histological subtype in the expanded efficacy population were as follows: 40.0% (DLBCL NOS), 10.0% (HGBCL), 50.0% (PMBCL) and 48.3% (trFL). Given the very small subgroups of patients with PMBCL (N=6), HGBCL (N=10) and trFL (N=29), the results were inconclusive in the context of a single-arm study.

The primary endpoint was supported by the secondary endpoints of ORR (51.6%) and median DOR (16.8 months) in the expanded efficacy population. The time-to-event endpoints, including median OS (12 months) and median PFS (4.9 months), have limited interpretability in single-arm studies and were considered exploratory.

Overview of Efficacy Results (Study NP30179, Efficacy-evaluable population)

Population	Pre-specified		Expanded	
	Cohort D3 (Glofitamab 2.5/10/30 mg) (N=108)		Cohort D2 [Sub.2], D3 and D5 (Glofitamab 2.5/10/30 mg) (N=155)	
Endpoint	**INV-assessed**	**IRC-assessed**	**INV-assessed**	**IRC-assessed**

Complete response rate n (%) (95% CI) CR rate vs historical control	36 (33.3%) (24.6, 43.1)	**Primary efficacy endpoint** 38 (35.2%) (26.2, 45.0) p < 0.0001	59 (38.1%) (30.4, 46.2)	62 (40.0%) (32.2, 48.2)
Secondary efficacy endpoints				
Overall response rate (CR+PR) n (%) (95% CI)	61 (56.5%) (46.6, 66.0)	54 (50.0%) (40.2, 59.8)	91 (58.7%) (50.5, 66.6)	80 (51.6%) (43.5, 59.7)
Duration of complete response Patients without event, n (%) Median (months) (95% CI) K-M event-free proportion, % (95% CI) at: 6 months 12 months 18 months	27/36 (75.0%) NE (18.2, NE) 81.6% (68.3, 94.9) 74.3% (58.8, 89.8) 74.3% (58.8, 89.8)	28/38 (73.7%) NE (18.4, NE) 88.1% (77.1, 99.1) 74.6% (59.2, 89.9) 68.8% (51.0, 86.7)	44/59 (74.6%) NE (19.8, NE) 81.1% (70.5, 91.7) 72.5% (59.3, 85.7) 72.5% (59.3, 85.7)	47/62 (75.8%) NE (16.8, NE) 88.4% (79.5, 97.2) 73.1% (59.6, 86.5) 63.9% (47.1, 80.7)
Duration of response Patients without event, n (%) Median (months) (95% CI) K-M event-free proportion, % (95% CI) at: 6 months 12 months 18 months	29/61 (47.5%) 7.8 (3.8, NE) 54.6% (41.6, 67.5) 44.8% (31.6, 58.0) 44.8% (31.6, 58.0)	30/54 (55.6%) 14.4 (8.6, NE) 70.2% (57.6, 82.9) 56.3% (42.0, 70.6) 48.5% (32.6, 64.4)	48/91 (52.7%) 10.4 (5.4, NE) 59.7% (49.2, 70.2) 48.4% (36.9, 59.9) 48.4% (36.9, 59.9)	50/80 (62.5%) 16.8 (10.4, NE) 77.0% (67.3, 86.6) 59.6% (46.9, 72.3) 49.6% (34.8, 64.4)
Time to first complete response Median, days (95% CI)	42.0 (42.0, 48.0)	42.0 (41.0, 47.0)	43.0 (42.0, 48.0)	42.0 (42.0, 44.0)
Time to first overall response Median, days (95% CI)	41.0 (40.0, 42.0)	42.0 (41.0, 42.0)	42.0 (40.0, 42.0)	42.0 (41.0, 42.0)
Progression-free survival Patients with event, n (%) Median, months (95% CI) K-M event-free proportion, % at: 12 months (95% CI)	72 (66.7%) 3.4 (2.8, 5.0) 27.8% (18.8, 36.9)	71 (65.7%) 3.7 (3.3, 6.8) 33.0% (23.5, 42.4)	98 (63.2%) 3.8 (3.3, 5.4) 30.6% (22.6, 38.7)	95 (61.3%) 4.9 (3.4, 8.1) 34.9% (26.5, 43.3)
Overall survival Patients with event, n (%) Median, months (95% CI) K-M event-free proportion, % at: 12 months (95% CI)	63 (58.3%) 8.9 (7.1, 15.3) 45.6% (35.9, 55.4)		81 (52.3%) 12.0 (8.0, 16.1) 50.4% (42.1, 58.7)	

The overall evidence on efficacy as demonstrated by CR rate and supported by the secondary endpoints (ORR, DOR, PFS and OS) was deemed reasonable in a population with relapsed or refractory DLBCL after two or more lines of systemic therapy. Nonetheless, given the limitations of the early phase study and the small sample size, results from the ongoing confirmatory Phase III study, GO41944, evaluating glofitamab in combination with gemcitabine and oxaliplatin versus rituximab in combination with gemcitabine and oxaliplatin in participants with relapsed/refractory DLBCL NOS, would be required to be provided to confirm the clinical benefit of glofitamab.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of glofitamab was based on safety data derived from the pivotal study NP30179, comprising a total of 154 patients in the primary safety population who received at least one dose of study treatment (obinutuzumab and/or glofitamab), of which 145 patients received glofitamab treatment. The median duration of exposure was 79.0 days (range 1 to 326).

Overview of Safety Profile (Study NP30179)

Adverse Event (AE)	Primary Safety Population (Cohorts D2 [Sub. 2], D3 and D5) (N=154)
Any AE	152 (98.7%)
Treatment-related AE	144 (93.5%)
SAE	75 (48.7%)
Discontinuations due to AE	14 (9.1%)
Deaths	81 (52.6%)
AE with fatal outcome	9 (5.8%)

In the primary safety population, almost all subjects experienced an adverse event (AE; 98.7%). Commonly reported treatment-emergent AEs included CRS by American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading (64.3%), neutropenia (35.7%), anaemia (30.5%), thrombocytopenia (21.4%), hypophosphatemia (17.5%) and pyrexia (16.2%).

The most frequent cause of the 81 reported deaths was progressive disease (75.3%). A total of 9 deaths were due to fatal AEs, including COVID-19 pneumonia (3 patients), COVID-19 (3 patients), sepsis (2 patients) and delirium (1 patient). While none of the fatal AEs were assessed by investigators as related to glofitamab, there was a higher rate of fatal AEs, primarily from COVID-19, in patients 65 years of age or older (8/84 patients, 9.5%) compared to younger patients below 65 years (1/70 patients, 1.4%).

The most common serious AEs (SAEs) reported in ≥ 2% of patients were CRS by ASTCT 2019 (20.8%), sepsis (3.9%), COVID-19 (3.2%), COVID-19 pneumonia (3.2%) and tumour flare (3.2%). A total of 14 patients (9.1%) reported an AE leading to discontinuation of glofitamab treatment. Of these, 5 patients reported Grade 4 AEs (neutropenia [2 patients], gastrointestinal haemorrhage, myelitis, and CRS [1 patient each]) leading to discontinuation that were assessed as related to glofitamab.

The AEs of special interest (AESIs) reported with glofitamab were Grade ≥ 2 CRS, Grade ≥ 2 tumour flare, Grade ≥ 2 neurological AEs and serious infections. The most commonly reported AESI was Grade ≥ 2 CRS by ASTCT 2019 (25 patients, 16.2%). Regardless of CRS grade, 47 (30.5%) and 32 (20.8%) patients experienced multiple CRS and serious CRS AEs, respectively. CRS events occurred predominantly in Cycle 1 and were mainly associated with Day 8 and Day 15 glofitamab dose administrations. Among the 25 patients who experienced ≥ Grade 2 CRS after glofitamab, 22 (88%) received tocilizumab, 15 (60%) received corticosteroids, and 14 (56%) received both tocilizumab and corticosteroids. All CRS events except one Grade 4 event had resolved. A CRS management guidance has been provided under the dosage and administration section of the package insert. As CRS may quickly become life-threatening, prompt recognition of the signs and symptoms and immediate medical attention is crucial. To ensure adequate risk mitigation, the risk management plan (RMP) has included a patient card for educating patients about CRS.

Tumour flare was reported in 11.0% of patients and occurred most frequently in Cycle 1 (16/17 patients). Among patients who experienced Grade ≥ 2 tumour flare, most (9/11 patients) received treatment with corticosteroids and/or pain medication.
Grade ≥ 3 neurologic AEs occurred in 2.6% of patients and included somnolence, delirium, and myelitis. Cases of immune effector cell-associated neurotoxicity syndrome (ICANS) of any grade occurred in 7.1% of patients treated with glofitamab. Recommendations for monitoring of neurological toxicity including dose modifications have been included in the package insert as neurological toxicity can be potentially serious and fatal. Serious infections were reported in 18.2% of patients, including 4 patients (2.6%) who reported a serious infection concurrent with Grade 3−4 neutropenia. The AESIs have been adequately described in the warnings and precautions section of the package insert.

Overall, the treatment was associated with significant toxicities. Nevertheless, considering the advanced and aggressive nature of the disease, the safety profile of glofitamab in relapsed or refractory DLBCL was assessed to be acceptable.

E ASSESSMENT OF BENEFIT-RISK PROFILE

DLBCL is a life-threatening disease with an aggressive natural history. In patients with relapsed or refractory DLBCL having failed at least two prior lines of therapy, available therapeutic options are limited with reported CR rates in the range of approximately 12 - 54%.

The pivotal study NP30179 was designed as a Phase I, single-arm, dose-finding and dose escalation study. The results demonstrated an IRC-assessed CR rate of 35.2% (95% CI: 26.2, 45.0) in the pre-specified efficacy population (Cohort D3: N=108) and 40.0% (95% CI: 32.2, 48.2) in the expanded efficacy population (Cohort D2 [Sub.2], D3 and D5: N= 155), with 63.9% of complete responders remaining in remission at 18 months. The onset of efficacy was rapid as could be seen from the short median time from first treatment to CR of 42 days. Patients previously having failed CAR T-cell treatment and those who were refractory to their last line of treatment achieved consistent CR rates of 37% and 35%, respectively.

The safety profile of glofitamab is characterised by the immune-related AE, CRS, which occurred in approximately two-thirds of subjects in the primary safety population. The important safety concerns of CRS, tumour flare, neurological AEs and serious infections have been adequately described in the package insert, with relevant warnings and precautions, as well as management guidance and dose modification recommendations in the event of toxicities. A patient card for educating patients about CRS has also been included as part of the RMP. Notwithstanding the toxicity profile, overall, the adverse events were considered acceptable in this disease population with unfavourable prognosis and limited treatment options.

Taken in totality the magnitude of the observed CR rates, the early and durable responses after treatment initiation, as well as the comprehensive risk mitigation measures for managing adverse events associated with the treatment, the overall benefit-risk profile of glofitamab was considered favourable for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy. Data from the ongoing Phase III study GO41944 would be required to provide confirmatory evidence on the efficacy and safety profiles.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of glofitamab for the treatment of relapsed or refractory DLBCL after two or more lines of systemic therapy was deemed favourable and approval of the product registration was granted on 05 March 2024. The approval of this application is subject to the submission of the final study report of the ongoing Phase III Study GO41944 (STARGLO) to confirm the clinical benefit and favourable overall risk-benefit profile.

APPROVED PACKAGE INSERT AT REGISTRATION

Please visit www.roche.com.sg/pharma/columvi for a printable version of this leaflet.

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Columvi®

Glofitamab

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Antineoplastic agent, monoclonal antibody (recombinant humanized immunoglobulin G1)
ATC code: L01FX28

1.2 TYPE OF DOSAGE FORM

Concentrate for solution for Infusion

1.3 ROUTE OF ADMINISTRATION

Intravenous (IV) Infusion

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile Product

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: glofitamab

Columvi is a preservative-free, colorless, clear solution supplied in colorless type I borosilicate glass single-dose vials with fluororesin-laminated rubber stopper and aluminium seal with plastic flip-off cap containing:

- 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

Excipients: D-Sucrose; L-Histidine; L-Histidine Hydrochloride, Monohydrate; L-Methionine; Polysorbate 20; Water for Injection.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

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. (See 3.1.2 Clinical / Efficacy Studies)

2.2 DOSAGE AND ADMINISTRATION

General

Columvi therapy should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients and who has access to appropriate medical support to manage severe reactions associated with cytokine release syndrome (CRS). At least 1 dose of tocilizumab for use in the event of CRS must be available prior to Columvi infusion at Cycles 1 and 2. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose must be ensured. See Section 2.4.1 *Warnings and Precautions.*

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 and thereby reduce the risk of CRS.

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.

Refer to the obinutuzumab prescribing information for complete information on premedication, preparation, administration, and management of adverse reactions of 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 2.4.1 *Warnings and Precautions*) is outlined in Table 1.

Table 1 Premedication Before Columvi Infusion To Reduce the Risk of Cytokine Release Syndrome

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 glucocorticoid[a]	Completed at least 1 hour prior to Columvi infusion.
		Oral analgesic / anti-pyretic[b]	At least 30 minutes before Columvi infusion.
		Anti-histamine[c]	
All subsequent infusions	All patients	Oral analgesic / anti-pyretic[b]	At least 30 minutes before Columvi infusion.
		Anti-histamine[c]	
	Patients who experienced CRS with previous dose	Intravenous glucocorticoid[a]	Completed at least 1 hour prior to Columvi infusion.

a. 20 mg dexamethasone or 100 mg prednisone/prednisolone or 80 mg methylprednisolone.
b. For example, 1000 mg acetaminophen/paracetamol.
c. For example, 50 mg diphenhydramine.

Recommended Dosage

Columvi dosing begins with a step-up dosing schedule (which is designed to decrease the risk of CRS), leading to the recommended dose of 30 mg.

Columvi Dose Step-Up Schedule

Columvi must be administered as an intravenous infusion according to the dose step-up schedule leading to the recommended dosage of 30 mg (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 Dose Step-Up 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	Pre-treatment with obinutuzumab[b]	
	Day 8	2.5 mg	4 hours[c]
	Day 15	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 3 and Section 2.4.1 *Warnings and Precautions*).
d. At the discretion of the treating physician, if the previous infusion was well tolerated. If the patient experienced CRS with a previous dose, the duration of infusion should be maintained at 4 hours.

Monitoring after infusion

- All patients must be monitored for signs and symptoms of potential CRS during infusion and for at least 10 hours after completion of the infusion of the first Columvi dose (2.5 mg on Cycle 1 Day 8).
- Patients who experienced Grade ≥ 2 CRS with their previous infusion should be monitored after completion of the infusion. See Table 3.
- Refer to section 2.6.1. *Description of selected adverse drug reactions from clinical trials, Cytokine Release Syndrome.*

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

Duration of Treatment

Treatment with Columvi is recommended for a maximum of 12 cycles or until disease progression or unmanageable toxicity.

Delayed or Missed Doses

During step-up dosing (weekly dosing):

- Following pre-treatment with obinutuzumab, if the Columvi 2.5 mg dose is delayed by more than 1 week, then repeat pre-treatment with obinutuzumab.
- Following Columvi 2.5 mg dose, if there is a Columvi treatment-free interval of 2 to 4 weeks, then repeat glofitamab 2.5 mg dose and resume the planned step-up dosing.
- Following Columvi 2.5mg dose, if there is a Columvi treatment-free interval of more than 4 weeks, then repeat pretreatment with obinutuzumab and Columvi step-up dosing (see Cycle 1 in Table 2).
- Following Columvi 10 mg dose, if there is a Columvi treatment-free interval of 2 weeks to 6 weeks, then repeat the last tolerated Columvi dose and resume the planned step-up dosing.
- Following Columvi 10 mg dose, if there is a Columvi treatment-free interval of more than 6 weeks, then repeat pre-treatment with obinutuzumab and Columvi step-up dosing (see Cycle 1 in Table 2).

After Cycle 2 (30 mg dose):

- If there is a Columvi treatment-free interval of more than 6 weeks between cycles, then repeat pre-treatment with obinutuzumab and Columvi step-up dosing (see Cycle 1 in Table 2), and then resume the planned treatment cycle (30 mg dose).

Preparation and Administration of Columvi

Preparation

Columvi must be diluted by a healthcare professional using aseptic technique, prior to intravenous administration. See Section 4.2 *Special Instructions for Use, Handling, and Disposal*.

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.

Dose Modifications

No dose reductions of Columvi are recommended.

Management of Cytokine Release Syndrome

Cytokine release syndrome should be identified based on the clinical presentation (see Section *2.4 Warnings and Precautions*). Patients should be evaluated for other causes of fever, hypoxia, and hypotension, such as infections or sepsis. If CRS is suspected, it should be managed according to the CRS management recommendations based on American Society for Transplantation and Cellular Therapy [ASTCT] consensus grading in Table 3.

Table 3 ASTCT CRS Grading and CRS Management Guidance

Grade[a]	CRS Management	For Next Scheduled Columvi Infusion
Grade 1 Fever ≥38 ºC	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 48h after symptomatic management: • Consider corticosteroids[c] • Consider tocilizumab[d]	• Ensure symptoms are resolved for at least 72 hours prior to next infusion • Consider slower infusion rate[b]
Grade 2 Fever ≥38 ºC and/or hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen by nasal cannula or blow-by	If CRS occurs during infusion: • Discontinue current infusion and treat symptoms • Administer corticosteroids[c] • Consider tocilizumab[d] If CRS occurs post-infusion: • Treat symptoms • Administer corticosteroids[c] • Consider tocilizumab[d]	• Ensure symptoms are resolved for at least 72 hours prior to next infusion • Consider slower infusion rate[b] • Monitor patients post-infusion[e,f]
For Grade 2: Tocilizumab use Do not exceed 3 doses of tocilizumab[d] in a period of 6 weeks. If no prior use of tocilizumab or if 1 dose of tocilizumab was used within the last 6 weeks: • Administer first dose of tocilizumab[d] • If no improvement within 8 hours administer second dose of tocilizumab[d] • After 2 doses of tocilizumab, consider alternative anti-cytokine and/or alternative immunosuppressant therapy If 2 doses of tocilizumab were used within the last 6 weeks: • Administer only one dose of tocilizumab • If no improvement within 8 hours consider alternative anti-cytokine and/or alternative immunosuppressant therapy		
Grade 3 Fever ≥38 ºC and/or hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow oxygen by nasal cannula, face mask, non-rebreather mask, or Venturi mask	If CRS occurs during infusion: • Discontinue current infusion and treat symptoms • Administer corticosteroids[c] • Administer tocilizumab[d] If CRS occurs post-infusion: • Treat symptoms • Administer corticosteroids[c] • Administer tocilizumab[d]	• Ensure symptoms are resolved for at least 72 hours prior to next infusion • Consider slower infusion rate[b] • Monitor patients post-infusion[e,f] • If Grade ≥ 3 CRS recurs at subsequent infusion, stop infusion immediately and permanently discontinue Columvi
Grade 4 Fever ≥38 ºC 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 • Administer corticosteroids[c] • Administer tocilizumab[d]	
For Grade 3 and Grade 4: Tocilizumab use Do not exceed 3 doses of tocilizumab[d] in a period of 6 weeks. If no prior use of tocilizumab or if 1 dose of tocilizumab was used within the last 6 weeks: • Administer first dose of tocilizumab[d] • If no improvement within 8 hours or rapid progression of CRS, administer second dose of tocilizumab[d] • After 2 doses of tocilizumab, consider alternative anti-cytokine and/or alternative immunosuppressant therapy If 2 doses of tocilizumab were used within the last 6 weeks: • Administer only one dose of tocilizumab • If no improvement within 8 hours or rapid progression of CRS, consider alternative anti-cytokine and/or alternative immunosuppressant therapy		

a. American Society for Transplantation and Cellular Therapy (ASTCT) 2019 consensus grading criteria.
b. Duration of infusion may be extended up to 8 hours, as appropriate for that cycle (see Table 2).
c. Corticosteroids (e.g., 10 mg IV dexamethasone, 100 mg IV prednisolone, 1-2 mg/kg IV methylprednisolone per day, or equivalent).
d. Tocilizumab 8 mg/kg IV (not to exceed 800 mg).
e. Grade ≥ 2 CRS following Columvi 10 mg dose at Cycle 1 Day 15 occurred in 5.2% of patients, with a median time to onset (from start of infusion) of 26.2 hours (range: 6.7 to 144.2 hours).
f. 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.

Management of Neurologic Toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Management recommendations for neurologic toxicity, including ICANS, are summarized in Table 4. At the first sign of neurologic toxicity, including ICANS, consider neurology evaluation and withholding Columvi based on the type and severity of neurotoxicity. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care.

Table 4 Recommended Dosage Modification for Neurologic Toxicity (including ICANS)

Adverse Reaction	Severity[a,b]	Actions
Neurologic Toxicity[a] (including ICANS[b]) (see Section 2.4 *Warnings and Precautions*)	Grade 1	• Continue Columvi and monitor neurologic toxicity symptoms. • If ICANS, manage per current practice guidelines.
	Grade 2	• Withhold Columvi until neurologic toxicity symptoms improve to Grade 1 or baseline.[c,d] • Provide supportive therapy and consider neurologic evaluation. • If ICANS, manage per current practice guidelines.
	Grade 3	• Withhold Columvi until neurologic toxicity symptoms improve to Grade 1 or baseline for at least 7 days.[d,e] • For Grade 3 neurologic events lasting more than 7 days, consider permanently discontinuing Columvi. • Provide supportive therapy and consider neurology evaluation. • If ICANS, manage per current practice guidelines.
	Grade 4	• Permanently discontinue Columvi. • Provide supportive therapy, which may include intensive care, and consider neurology evaluation. • If ICANS, manage per current practice guidelines.

a. Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
b. Based on ASTCT 2019 grading for ICANS.
c. Consider the type of neurologic toxicity before deciding to withhold Columvi.
d. See *Delayed or Missed doses section* on restarting Columvi after dose delays.
e. Evaluate benefit-risk before restarting Columvi.

2.2.1 Special Dosage Instructions

Pediatric use

The safety and efficacy of Columvi in pediatric patients have not been established.

Geriatric use

No dose adjustment of Columvi is required in patients ≥ 65 years of age. (See Section 2.5 *Use in Special Populations* and Section 3.2.5 *Pharmacokinetics in Special Populations.*)

Renal Impairment

No dose adjustment of Columvi is required in patients with mild or moderate renal impairment (CrCL 30 to < 90 mL/min). Columvi has not been studied in patients with severe renal impairment. (See Section 2.5 *Use in Special Populations* and Section 3.2.5 *Pharmacokinetics in Special Populations.*)

Hepatic Impairment

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 Section 2.5 *Use in Special Populations* and Section 3.2.5 *Pharmacokinetics in Special Populations.*)

2.3 CONTRAINDICATIONS

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

Refer to obinutuzumab-specific contraindications in the obinutuzumab prescribing information.

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

Refer to obinutuzumab-specific warnings and precautions in the obinutuzumab prescribing information.

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

CD20-negative disease

There are limited data available on patients with CD20-negative DLBCL treated with Columvi, and it is possible that patients with CD20-negative DLBCL may have less benefit compared to patients with CD20-positive DLBCL. The potential risks and benefits associated with treatment of patients with CD20-negative DLBCL with Columvi should be considered.

Cytokine Release Syndrome

CRS, including life-threatening reactions, has been reported in patients receiving Columvi.

The most common 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 64.3% of patients in study NP30179. Grade 3 or 4 CRS occurred in 3.9% of patients. There were no fatal cases of CRS. Most CRS events occurred following the first dose of Columvi. See Section 2.6.1 *Description of selected adverse reactions.*

To reduce the occurrence of CRS, patients must be pre-treated with obinutuzumab, 7 days prior to initiation of Columvi, and should be premedicated with an antipyretic, anti-histamine, and a glucocorticoid. See Section 2.2 *Dosage and Administration*.

At least 1 dose of tocilizumab for use in the event of CRS must be available prior to Columvi infusion at Cycles 1 and 2. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose must be ensured.

Patients must be monitored during all Columvi infusions and for at least 10 hours after completion of the first infusion. For complete information on monitoring, see Section 2.2 *Dosage and Administration*. The prescriber must counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.

Patients should be evaluated for other causes of fever, hypoxia, and hypotension, such as infections or sepsis. CRS should be managed based on the patient's clinical presentation and according to the CRS management guidance provided in Table 3 (see Section 2.2 *Dosage and Administration*).

Elevated liver function tests (AST and alanine transaminase [ALT] > 3 × ULN and/or total bilirubin > 2 × ULN) concurrent with CRS have been reported after Columvi use.

Immunisation
The safety of immunisation with live vaccines during or following Columvi therapy has not been studied. Immunisation with live vaccines is not recommended during Columvi therapy.

Neurologic Toxicity
Columvi can cause serious and fatal neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) (see Section 2.6.1 *Description of selected adverse events*). Grade 3 or higher neurologic adverse reactions occurred in 2.6% of patients. Cases of ICANS of any grade occurred in 7.1% of patients (see Section 2.6.1 *Description of selected adverse events*).

Co-administration of Columvi with other products that cause dizziness or mental status changes may increase the risk of neurologic toxicity. Optimize concomitant medications and hydration to avoid dizziness or mental status changes. Institute fall precautions as appropriate.

Monitor patients for signs and symptoms of neurologic toxicity, evaluate, and provide supportive therapy; withhold or permanently discontinue Columvi based on severity (see Section 2.2 *Dosage and Administration*).

Evaluate patients who experience neurologic toxicity such as tremors, dizziness, or adverse reactions that may impair cognition or consciousness promptly, including potential neurology evaluation. Advise affected patients to refrain from driving and/or engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until the neurologic toxicity fully resolves.

Serious Infections
Serious infections (such as sepsis and pneumonia) have occurred in patients treated with Columvi (see Section 2.6.1 *Description of selected adverse events*).

Columvi must not be administered to patients with an active infection. Caution should be exercised when considering the use of Columvi in patients with a history of chronic or recurrent infection, those with underlying conditions that may predispose them to infections, or those who have had significant prior immunosuppressive treatment. 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.

Columvi should be temporarily withheld in the presence of an active infection until the infection has resolved. 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.

Tumor Flare
Tumor flare has been reported in patients receiving Columvi. Manifestations included localized pain and swelling (see Section 2.6.1 *Description of selected adverse events*).

Consistent with the mechanism of action of Columvi, tumor flare is likely due to the influx of T cells into tumor sites following Columvi administration and may mimic progression of disease. Tumor flare does not imply treatment failure or represent tumor progression.

Specific risk factors for tumor flare have not been identified, however, there is a heightened risk of compromise and morbidity due to mass effect secondary to tumor flare in patients with bulky tumors located in close proximity to airways and/or a vital organ. Monitoring and evaluation of tumor flare at critical anatomical sites is recommended in patients treated with Columvi and managed as clinically indicated.

Tumor Lysis Syndrome
Tumor lysis syndrome (TLS) has been reported in patients receiving Columvi (see Section 2.6.1 *Description of selected adverse events*). Patients with high tumor burden, rapidly proliferative tumors, 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.

2.4.2 Drug Abuse and Dependence
Columvi does not have the potential for abuse and dependence.

2.4.3 Ability to Drive and Use Machines
Columvi has no or negligible influence on the ability to drive and use machines. Patients experiencing symptoms of CRS (pyrexia, tachycardia, hypotension, chills, hypoxia) should be advised not to drive or use machines until symptoms resolve.

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential
Fertility
See Section 3.3.3 *Impairment of fertility*.

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

2.5.2 Pregnancy
Columvi is not recommended during pregnancy and in women of childbearing potential not using contraception. Female patients of reproductive potential must be advised to avoid pregnancy while receiving Columvi. There are no available data on the use of Columvi in pregnant women. 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. 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.

Labor and Delivery
The safe use of Columvi during labor and delivery has not been established.

2.5.3 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. 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.

2.5.4 Pediatric Use
The safety and efficacy of Columvi in pediatric patients have not been established.

2.5.5 Geriatric Use
Of the 154 patients with relapsed or refractory DLBCL who were evaluable for safety, 55% were 65 years of age or older. There was a higher rate of fatal adverse events, primarily from COVID-19, in patients 65 years of age or older compared to younger patients. No differences in 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 Section 2.2.1 *Special Dosage Instructions* and Section 3.2.5 *Pharmacokinetics in Special Populations*.

2.5.6 Renal Impairment
No dose adjustment is required in patients with mild or moderate renal impairment (CrCL 30 to < 90 mL/min) based on population pharmacokinetic analysis. The safety and efficacy of Columvi in patients with severe renal impairment has not been studied. See Section 2.2.1 *Special Dosage Instructions* and Section 3.2.5 *Pharmacokinetics in Special Populations*.

2.5.7 Hepatic Impairment
No dose adjustment is required in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 × ULN or AST > ULN) based on population pharmacokinetic analysis. The safety and efficacy of Columvi in patients with moderate or severe hepatic impairment has not been studied. See Section 2.2.1 *Special Dosage Instructions* and Section 3.2.5 *Pharmacokinetics in Special Populations*.

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials
Summary of the safety profile

Columvi monotherapy
Approximately 469 patients with relapsed or refractory non-Hodgkin's lymphoma have received Columvi as monotherapy in the clinical development program of Columvi.

The adverse drug reactions described below were identified from 154 patients with relapsed or refractory DLBCL, who had received at least two prior lines of systemic therapy, including DLBCL arising from follicular lymphoma, high-grade B-cell lymphoma (HGBCL), and PMBCL, treated with Columvi monotherapy in study NP30179, an open-label multicenter clinical trial.

Tabulated summary of adverse drug reactions from clinical trials
Adverse drug reactions from clinical trials (Table 5) are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Table 5 Adverse Drug Reactions Occurring in Patients with Relapsed or Refractory DLBCL treated with Columvi Monotherapy

System Organ Class Adverse Reaction	Columvi N=154		
	All Grades (frequency category)	All Grades (%)	Grade 3-4 (%)
Immune system disorders			
Cytokine release syndrome[a]	Very common	64.3	3.9
Blood and lymphatic system disorders			
Neutropenia[b]	Very common	37.7	27.3
Anaemia[c]	Very common	30.5	7.8
Thrombocytopenia[d]	Very common	24.7	7.8
Lymphopenia[e]	Common	4.5	4.5
Febrile neutropenia[f]	Common	3.2	3.2
General disorders and administration site conditions			
Pyrexia	Very common	16.2	0
Metabolism and nutrition disorders			
Hypophosphataemia	Very common	17.5	5.8
Hypomagnesaemia	Very common	14.3	0
Hypocalcaemia	Very common	12.3	0
Hypokalaemia	Very common	11.0	1.3
Hyponatraemia	Common	7.8	1.3
Tumour lysis syndrome	Common	1.3	1.3
Skin and subcutaneous tissue disorders			
Rash[g]	Very common	18.8	1.3
Gastrointestinal disorders			
Constipation	Very common	13.6	0
Diarrhoea	Very common	13.0	0
Nausea	Very common	10.4	0
Gastrointestinal haemorrhage[h]	Common	2.6	2.6
Vomiting	Common	4.5	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour flare	Very common	11.0	2.6
Nervous system disorders			
Headache	Common	9.7	0
Somnolence	Common	1.3	0.6
Tremor	Common	1.3	0
Myelitis[i]	Uncommon	0.6	0.6
Infections and infestations			
Viral infections[j]	Very common	11.0	3.2*
Bacterial infections[k]	Common	6.5	1.9
Upper respiratory tract infections[l]	Common	5.2	0
Sepsis[m]	Common	3.9	2.6*
Lower respiratory tract infections[n]	Common	1.9	0
Pneumonia	Common	4.5	1.3
Urinary tract infection[o]	Common	2.6	0.6
Fungal infections[p]	Uncommon	1.3	0
Investigations			
Alanine aminotransferase increased	Common	8.4	2.6
Aspartate aminotransferase increased	Common	7.8	2.6
Blood alkaline phosphatase increased	Common	8.4	1.3
Gamma-glutamyltransferase increased	Common	6.5	2.6
Blood bilirubin increased	Common	3.9	0.6
Hepatic enzyme increased	Common	1.3	1.3
Psychiatric disorders			
Confusional state	Common	1.9	0

* Grade 5 reactions reported include sepsis (1.3%), COVID-19 pneumonia (1.9%), and COVID-19 (1.9%).
a. Based on ASTCT consensus grading.
b. Includes neutropenia and neutrophil count decreased.
c. Includes anaemia and haemoglobin decreased.
d. Includes thrombocytopenia and platelet count decreased.
e. Includes lymphopenia and lymphocyte count decreased.
f. Includes febrile neutropenia and neutropenic infection.
g. Includes rash, rash pruritic, rash maculo-papular, dermatitis, dermatitis acneiform, dermatitis exfoliative, erythema, palmar erythema, pruritus, and rash erythematous.
h. Includes gastrointestinal haemorrhage, large intestinal haemorrhage, and gastric haemorrhage.
i. Myelitis occurred concurrently with CRS.
j. Includes COVID-19, COVID-19 pneumonia, herpes zoster, influenza, and ophthalmic herpes zoster.
k. Includes vascular device infection, bacterial infection, Campylobacter infection, biliary tract infection bacterial, urinary tract infection bacterial, *Clostridium difficile* infection, Escherichia infection, and peritonitis.
l. Includes upper respiratory tract infection, sinusitis, nasopharyngitis, chronic sinusitis, and rhinitis.
m. Includes sepsis and septic shock.
n. Includes lower respiratory tract infection and bronchitis.
o. Includes urinary tract infection and Escherichia urinary tract infection.
p. Includes oesophageal candidiasis and oral candidiasis.

The most common serious adverse reactions reported in ≥ 2% of patients were cytokine release syndrome (22.1%), sepsis (3.9%), COVID-19 (3.2%), COVID-19 pneumonia (3.2%) and tumour flare (3.2%).

Description of selected adverse drug reactions from clinical trials
Cytokine Release Syndrome
In study NP30179, any grade CRS (by ASTCT criteria) occurred in 64.3% of patients, with Grade 1 CRS being reported in 48.1% of patients, Grade 2 CRS in 12.3% patients, Grade 3 CRS in 2.6% of patients, and Grade 4 CRS in 1.3% of patients. CRS occurred more than once in 30.5% (47/154) of patients; 36/47 patients experienced multiple Grade 1 CRS events only.

There were no fatal cases of CRS. 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 (26.3%), hypotension (23.2%), chills (14.1%), and hypoxia (12.1%). Grade 3 or higher events associated with CRS included hypotension (3.0%), hypoxia (3.0%), pyrexia (2.0%), and tachycardia (2.0%).

CRS of any grade occurred in 54.5% of patients following the 2.5 mg dose of Columvi at Cycle 1 Day 8 with median time to onset (from the start of infusion) of 12.6 hours (range: 5.2 to 50.8 hours) and median duration of 31.8 hours (range: 0.5 to 316.7 hours); in 33.3% of patients following the 10 mg dose at Cycle 1 Day 15 with median time to onset of 26.8 hours (range: 6.7 to 125.0 hours) and median duration of 16.5 hours (range: 0.3 to 109.2 hours); and in 26.8% of patients following the 30 mg dose at Cycle 2 Day 1 with median time to onset of 28.2 hours (range: 15.0 to 44.2 hours) and median duration of 18.9 hours (range: 1.0 to 180.5 hours). CRS was reported in 0.9% of patients at Cycle 3 and in 2% of patients beyond Cycle 3.

In 154 patients, 7 (4.5%) patients experienced elevated liver function tests (AST and ALT > 3 ULN and/or total bilirubin > 2 ULN) reported concurrently with CRS (n=6) or with disease progression (n=1).

Hospitalisations due to patients experiencing CRS following Columvi administration occurred in 20.8% of patients and the reported median duration of hospitalisation was 4 days (range: 2 to 15 days).

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.

Among the 25 patients who experienced Grade 2 or higher CRS after Columvi, 22 (88%) received tocilizumab, 15 (60%) received corticosteroids, and 14 (56%) received both tocilizumab and corticosteroids. Ten patients (40%) received oxygen. All 6 patients (24.0%) with Grade 3-4 CRS received a single vasopressor.

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

Neurologic Toxicity
The most frequent neurologic toxicities of any grade were headache (9.7%), peripheral neuropathy (1.9%), dizziness or vertigo (6.5%), and mental status changes (5.8%, including confusional state, cognitive disorder, disorientation, somnolence, and delirium). Grade 3 or higher neurologic adverse reactions occurred in 2.6% of patients and included somnolence, delirium, and myelitis. Cases of ICANS of any grade occurred in 4.8% of patients treated with Columvi.

Serious Infections
In study NP30179, serious infections were reported in 18.2% of patients. The most frequent serious infections reported in ≥ 2% patients were sepsis (3.9%), COVID-19 pneumonia (3.2%), and COVID-19 (3.2%). Infection-related deaths were reported in 5.2% of patients (due to sepsis, COVID-19 pneumonia, and COVID-19). Four patients (2.6%) experienced serious infections concurrently with Grade 3-4 neutropenia.

Neutropenia
Neutropenia (including neutrophil count decreased) was reported in 37.7% of patients and severe neutropenia (Grade 3-4) was reported in 27.3% 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 11.0% of patients. The majority of patients with neutropenia (79.3%) were treated with G-CSF. Febrile neutropenia was reported in 2.6% of patients.

Tumor Flare
Tumor flare was reported in 11.0% of patients, including Grade 2 tumor flare in 4.5% of patients and Grade 3 tumor flare in 2.6% of patients. Tumor flare was reported involving lymph nodes in the head and neck presenting with pain, and involving lymph nodes in the thorax with symptoms of breathlessness due to development of pleural effusion. Most tumor flare events (16/17) occurred during Cycle 1, and no tumor flare events were reported beyond Cycle 2. The median time to onset of tumor 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). Among the 11 patients who experienced Grade ≥ 2 tumour flare, of which 2 (18.2%) patients received analgesics, 6 (54.5%) patients received corticosteroids and analgesics including morphine derivatives, 1 (0.9%) patient received corticosteroids and anti-emetics, and 2 (18.2%) patients did not require treatment. All tumour flare events resolved except in one patient* with a Grade ≥ 2 event. No patients discontinued Columvi due to tumor flare.

*One patient had tumour flare unresolved at the time of death due to disease progression. The treatment of tumour flare for this patients was not reported.

Tumor Lysis Syndrome
TLS was reported in 2 patients (1.3%) 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).

Laboratory Abnormalities
Table 6 summarizes treatment-emergent shifts from baseline in laboratory abnormalities in study NP30179.

Table 6 Laboratory Abnormalities Worsening from Baseline, with Grade 3 to 4 Occurring in ≥ 10% of Patients with Relapsed or Refractory DLBCL Treated with Columvi Monotherapy

Laboratory Abnormality[a]	Columvi NCI CTCAE Grade	
	All Grades (%)[b]	Grade 3 or 4 (%)[b,c]
Hematology		
Decreased lymphocytes	88.5	81.1
Decreased neutrophils	54.4	25.5
Decreased leukoctyes	69.3	13.3
Chemistry		
Hypophosphatemia	67.8	26.8
Hyperglycemia	13.7	13.7
Hyperuricemia	22.5	22.5

a. Percentages based on patients with a baseline and at least one post-baseline assessment for the specific laboratory parameter.
b. N=148 for decreased lymphocytes; N=149 for decreased neutrophils; N=150 for decreased leukocytes; N=149 for hypophosphatemia; N=146 for hyperglycemia; N=142 for hyperuricemia.
c. Includes shifts from Grade 0-2 at baseline to Grade ≥ 3 post-baseline, and shifts from Grade 3 at baseline to Grade 4 post-baseline.

2.6.2 Post marketing Experience
Not applicable.

2.7 OVERDOSE
There is no experience with overdose of Columvi in clinical trials. In case of overdose, patients should be closely monitored for signs and symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
No clinical drug-drug interaction studies have been performed.

No drug interactions with Columvi are expected via the cytochrome P450 enzymes, other metabolizing enzymes, or transporters.

For certain CYP substrates (e.g. warfarin, cyclosporine) where minimal concentration changes may lead to serious adverse reactions, monitor for toxicities or drug concentrations of such CYP substrates when coadministered with Columvi.

Glofitamab causes the release of cytokines that may suppress the activity of CYP enzymes, resulting in increased exposure of CYP substrates. Increased exposure of CYP substrates is more likely to occur after the first dose of Columvi on Cycle 1 Day 8 and up to 14 days after the first 30 mg dose on Cycle 2 Day 1 and during and after CRS.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS
3.1 PHARMACODYNAMIC PROPERTIES
3.1.1 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 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
Peripheral B-cell counts, prior to Columvi treatment initiation, in almost all patients (98.6%) with relapsed and refractory LBCL were <70 cells/µL, and remained low during Columvi treatment.

During Cycle 1 (step-up dosing), transient increases in plasma IL-6 levels were observed at 6 hours post-Columvi infusion, which remained elevated at 20 hours post-infusion and returned to baseline prior to the next infusion.

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.

3.1.2 Clinical / Efficacy Studies
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 155 patients with relapsed or refractory DLBCL after at least two prior lines of systemic therapy including an anti-CD20 monoclonal antibody and an anthracycline agent. The study excluded patients with prior allogeneic hematopoietic stem cell transplant, previous or active central nervous system lymphoma, active infection, recent infection requiring intravenous antibiotics, ECOG performance status ≥ 2, creatinine clearance (CrCL) < 50 mL/min, or hepatic transaminases > 3 × ULN.

Following pre-treatment with obinutuzumab at Cycle 1 Day 1, 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 step-up dosing 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 2.2 *Dosage and 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 Investigator (INV)-assessed CR, and 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 and by INV.

Efficacy results are summarized in Table 7.

Table 7 Efficacy in Patients with Relapsed or Refractory DLBCL Treated with Columvi Monotherapy

Efficacy Endpoints	Columvi N=155	
Primary Endpoint		
IRC-Assessed Complete Response		
Patients with CR, n (%)	62 (40.0)	
95% CI	[32.22, 48.17]	
Secondary Endpoints		
INV-Assessed Complete Response		
Patients with CR, n (%)	59 (38.1)	
95% CI	[30.39, 46.20]	
Overall Response Rate	*IRC-Assessed*	*INV-Assessed*
Patients with CR or PR, n (%)	80 (51.6)	91 (58.7)
95% CI	[43.46, 59.70]	[50.53, 66.55]
Partial Response (PR), n (%)	18 (11.6)	32 (20.6)
95% CI	[7.03, 17.73]	[14.57, 27.88]
Duration of Complete Response[a]	*IRC-Assessed*	*INV-Assessed*
Median DOCR, months [95% CI]	NE [16.8, NE]	NE [19.8, NE]
Range, months	0[b]-27[b]	0[b]-27[b]
9-month DOCR, % [95% CI][c]	76.0 [63.26, 88.71]	72.5 [59.25, 85.68]
12-month DOCR, % [95% CI][c]	73.1 [59.57, 86.53]	72.5 [59.25, 85.68]
Duration of Response[d]	*IRC-Assessed*	*INV-Assessed*
Median DOR, months [95% CI]	16.8 [10.4, NE]	10.4 [5.4, NE]
Range, months	0[b]-27[b]	0[b]-27[b]
9-month DOR, % [95% CI][c]	66.5 [54.91, 78.00]	52.2 [41.10, 63.34]
12-month DOR, % [95% CI][c]	59.6 [46.85, 72.28]	48.4 [36.93, 59.91]
Time to First Response	*IRC-Assessed*	*INV-Assessed*
Median TFOR, days [95% CI]	42 [41, 42]	42 [40, 42]
Range, days	31-178	31-178
Time to First Complete Response	*IRC-Assessed*	*INV-Assessed*
Median TFCR, days [95% CI]	42 [42, 44]	43 [42, 48]
Range, days	31-308	31-274
Progression-Free Survival	*IRC-Assessed*	*INV-Assessed*
Patients with event, n (%)	95 (61.3)	98 (63.2)
Median PFS, months [95% CI]	4.9 [3.4, 8.1]	3.8 [3.3, 5.4]
6-month PFS, % [95% CI][c]	46.7 [38.40, 54.92]	39.1 [30.98, 47.14]
9-month PFS, % [95% CI][c]	39.6 [31.34, 47.76]	35.1 [27.08, 43.03]
12-month PFS, % [95% CI][c]	34.9 [26.48, 43.31]	30.6 [22.55, 38.69]
Overall Survival	*INV-Assessed*	
Patients with event, n (%)	81 (52.3)	
Median OS, months [95% CI]	12 [8.0, 16.1]	
6-month OS, % [95% CI][c]	71.6 [64.34, 78.89]	
9-month OS, % [95% CI][c]	54.8 [46.65, 62.87]	
12-month OS, % [95% CI][c]	50.4 [42.06, 58.71]	

CI=confidence interval; INV=Investigator; IRC=Independent Review Committee; N/A=not applicable; NE=not estimable.
a. From date of first complete response until disease progression or death due to any cause.
b. Censored observations.
c. Event-free rates based on Kaplan-Meier estimates.
d. From date of first response (PR or CR) until disease progression or death due to any cause.

The efficacy population included a cohort of patients (N=40) where dexamethasone was mandated as the glucocorticoid premedication. In this cohort, the IRC-assessed ORR was 52.5% (95% CI: 36.1, 68.5) and the CR was 47.5% (95% CI: 31.5, 63.9).

Figure 1 Duration of IRC-Assessed Complete Response in Patients with Relapsed or Refractory DLBCL Treated with Columvi Monotherapy

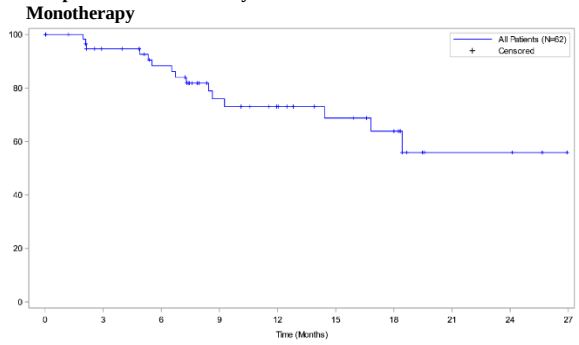
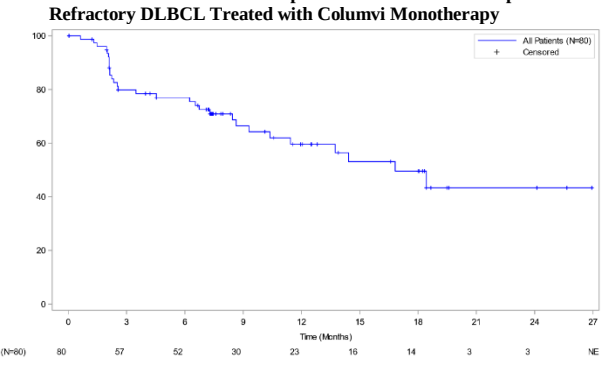


Figure 2 Duration of IRC-Assessed Response in Patients with Relapsed or Refractory DLBCL Treated with Columvi Monotherapy



The efficacy results based on the non-Hodgkin lymphoma subtype are summarized in Table 8.

Table 8 IRC-Assessed Response Rates by Histology Subtypes for Patients with Relapsed or Refractory DLBCL Treated with Columvi Monotherapy

Efficacy Endpoints	DLBCL NOS n=110	Transformed Follicular Lymphoma n=29	High Grade B-cell Lymphoma n=10	Primary mediastinal B-cell lymphoma n=6
CRR, n(%) 95% CI	44 (40.0%) [30.8, 49.8]	14 (48.3%) [29.5, 67.5]	1 (10.0%) [0.3, 44.5]	3 (50.0%) [11.8, 88.2]
ORR, n(%) 95% CI	57 (51.8%) [42.1, 61.5]	17 (58.6%) [38.9, 76.5]	2 (20.0%) [2.5, 55.6]	4 (66.7%) [22.3, 95.7]

Patient Reported Outcomes
Study NP30179 evaluated patient-reported outcomes of Columvi treatment. Patients reported moderate to moderate-high levels at baseline of Physical Functioning, Role Functioning, and Global Health Status/QoL and low levels of fatigue (weakness, tiredness) as measured by the EORTC QLQ-C30 at baseline which were maintained during treatment. Most patients indicated that symptoms commonly associated with Columvi treatment (constipation, diarrhea, and nausea) were not present or were of low severity if present, and maintained during treatment. Patients reported low levels of lymphoma symptoms at baseline as measured by the FACT-Lym scale which were maintained during treatment. The results should be interpreted with caution in the context of the open-label study design.

3.1.4 Immunogenicity
As with all therapeutic proteins, there is a potential 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.

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.

3.2 PHARMACOKINETIC PROPERTIES
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.

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

3.2.2 Distribution
Following IV administration, the central volume of distribution was 3.38 L, which is close to total serum volume. The peripheral volume of distribution was 2.13 L.

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

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

The time-independent clearance pathway was estimated as 0.627L/day and the initial time-varying clearance pathway as 0.584 L/day, with an exponential decay over time (K_{des} ~ 0.614/day). The estimated decay half-life from the initial total clearance value to the time-independent clearance only was estimated as 1.26 days.

The effective half-life in the linear phase (i.e., after the contribution of time-varying clearance has collapsed to a negligible amount) can be approximated to a typical linear effective half-life of 6.10days based on the population pharmacokinetic analysis.

3.2.5 Pharmacokinetics in Special Populations
Pediatric Population
No studies have been conducted to investigate the pharmacokinetics of glofitamab in pediatric patients.

Geriatric Population
No differences in glofitamab exposure were noted in patients 65 years of age and older and those under 65 years based on population pharmacokinetic analysis.

Renal impairment
Population pharmacokinetic analyses showed that creatinine clearance does not affect the pharmacokinetics of glofitamab. The pharmacokinetics of glofitamab in patients with mild or moderate renal impairment (CrCL 30 to < 90 mL/min) were similar to those in patients with normal renal function. No dose adjustment is required for patients with mild or moderate renal impairment. Columvi has not been studied in patients with severe renal impairment.

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

3.3 NONCLINICAL SAFETY
3.3.1 Carcinogenicity
No carcinogenicity studies have been performed to establish the carcinogenic potential of Columvi.

3.3.2 Genotoxicity
No studies have been performed to establish the mutagenic potential of Columvi.

3.3.3 Impairment of Fertility
No fertility assessments in animals have been performed to evaluate the effect of Columvi.

3.3.4 Reproductive toxicity
No reproductive toxicity studies in animals have been performed to evaluate the effect of Columvi.

Based on low placental transfer of antibodies during the first trimester, the mechanism of action of glofitamab (B-cell depletion, target-dependent T-cell activation, and cytokine release), the available safety data with Columvi, and the data on other anti CD20 antibodies, the risk for teratogenicity is low. Prolonged B-cell depletion can lead to increased risk of opportunistic infection, which may cause fetal loss. Transient CRS associated with Columvi administration may also be harmful to the fetus.

3.3.5 Other
In a study in cynomolgus monkeys, animals experiencing severe CRS after a single intravenous dose of glofitamab (0.1 mg/kg) without obinutuzumab pre-treatment had erosions in the gastrointestinal tract and inflammatory cell infiltrates in spleen and sinusoids of the liver and sporadically in some other organs. These inflammatory cell infiltrates were likely secondary to cytokine-induced immune cell activation. Pretreatment with obinutuzumab resulted in the attenuation of glofitamab-induced cytokine release and related adverse effects by depleting B cells in peripheral blood and lymphoid tissue. This allowed at least 10 times higher doses of glofitamab (1 mg/kg) in cynomolgus monkeys resulting in a C_{max} of up to 3.8 times the human C_{max} at the recommended 30 mg dose. All findings with glofitamab were considered pharmacologically mediated effects and reversible.

Studies longer than 4 weeks were not performed, as glofitamab was highly immunogenic in cynomolgus monkeys and led to loss of exposure and loss of the pharmacologic effect.

4. PHARMACEUTICAL PARTICULARS
4.1 STORAGE
Vials
Store at 2 °C to 8 °C.
Keep vial in the outer carton in order to protect from light.
Do not freeze. Do not shake.

Shelf life
As registered locally.
Columvi should not be used after the expiry date (EXP) shown on the carton.

Diluted solution for intravenous infusion
The prepared infusion solution should be used immediately. If not used immediately, the infusion solution can be stored in the refrigerator at 2 °C to 8 °C for up to 72 hours and at 30 °C for up to 24 hours, if prepared under aseptic conditions, followed by a maximum infusion time of 8 hours.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL
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 9) 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 9). 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 9 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 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

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.

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.

Medicine: keep out of reach of children

Current at Feb 2024

F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070 Basel, Switzerland