Columvi®

GLOFITAMAB 1 mg/mL

Concentrate for Solution for Infusion

1. NAME OF THE MEDICINAL PRODUCT

Columvi

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Columvi concentrate for solution for infusion

Each vial of 2.5 mL of concentrate contains 2.5 mg of glofitamab at a concentration of 1 mg/mL.

Each vial of 10 mL of concentrate contains 10 mg of glofitamab at a concentration of 1 mg/mL.

Glofitamab is a humanised anti-CD20/anti-CD3 bispecific monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipients with known effects

Each 2.5 mL vial of Columvi contains 1.25 mg (0.5 mg/mL) of polysorbate 20.
Each 10 mL vial of Columvi contains 5 mg (0.5 mg/mL) of polysorbate 20.

For the full list of excipients, see section 6.1.

Patient safety information card
The marketing of Columvi is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Colourless, clear solution with a pH of 5.5 and osmolality of 270-350 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Columvi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B cell lymphoma after two or more lines of systemic therapy.

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

4.2 Posology and method of administration

Columvi must only be administered under the supervision of a healthcare professional experienced in the diagnosis and 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 4.4).

Pre-treatment with obinutuzumab
All patients in study NP30179 and in study GO41944 (STARGLO) received a single 1 000 mg dose of obinutuzumab as pre-treatment on Cycle 1 Day 1 (7 days prior to initiation of Columvi treatment) to lower the circulating and lymphoid B cells (see Table 2, *Delayed or Missed Doses*, and section 5.1).

Obinutuzumab was administered as an intravenous infusion at 50 mg/h. The rate of infusion was 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 prophylaxis

Cytokine release syndrome prophylaxis
Columvi should be administered to well-hydrated patients. Recommended premedication for CRS (see section 4.4) 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	20 mg intravenous dexamethasone[1]	Completed at least 1 hour prior to Columvi infusion
		Oral analgesic / anti-pyretic[2]	At least 30 minutes before Columvi infusion
		Anti-histamine[3]	
All subsequent infusions	All patients	Oral analgesic / anti-pyretic[2]	At least 30 minutes before Columvi infusion
		Anti-histamine[3]	
	Patients who experienced CRS with the previous dose	20 mg intravenous dexamethasone[1, 4]	Completed at least 1 hour prior to Columvi infusion

[1] If patient has an intolerance to dexamethasone or dexamethasone is unavailable, administer 100 mg prednisone/prednisolone or 80 mg methylprednisolone.
[2] For example, 1 000 mg paracetamol.
[3] For example, 50 mg diphenhydramine.
[4] To be administered in addition to the premedication required for all patients.

Posology

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 monotherapy dose step-up schedule
Columvi must be administered as an intravenous infusion according to the dose step-up schedule leading to the recommended dose 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		**Dose of Columvi**	**Duration of infusion**
Cycle 1 (Pre-treatment and step-up dose)	Day 1	Pre-treatment with obinutuzumab 1000 mg[1]	
	Day 8	2.5 mg	4 hours[2]
	Day 15	10 mg	
Cycle 2	Day 1	30 mg	
Cycle 3 to 12	Day 1	30 mg	2 hours[3]

[1] Refer to "*Pre-treatment with obinutuzumab*" described above.
[2] For patients who experience CRS with their previous dose of Columvi, the duration of infusion may be extended up to 8 hours (see section 4.4).
[3] 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.

Columvi dose step-up schedule in combination with gemcitabine and oxaliplatin
Columvi must be administered as an intravenous infusion according to the dose step-up schedule leading to the recommended dose of 30 mg (as shown in Table 3), after completion of pre-treatment with obinutuzumab on Cycle 1 Day 1.

Columvi is given in combination with gemcitabine and oxaliplatin at Cycles 1-8 and as monotherapy at Cycles 9-12. Each cycle is 21 days.

Table 3. Columvi dose step-up schedule in combination with gemcitabine and oxaliplatin for patients with relapsed or refractory DLBCL

Treatment cycle, Day		Dose of Columvi (duration of infusion)	Dose of gemcitabine	Dose of oxaliplatin
Cycle 1 (Pre-treatment and step-up dose)	Day 1	Pre-treatment with obinutuzumab 1000 mg[a]		
	Day 2	–	1000 mg/m^{2} [b]	100 mg/m^{2} [b]
	Day 8	2.5 mg (4 hours)[c]	–	–
	Day 15	10 mg (4 hours)[c]		
Cycle 2	Day 1	30 mg (4 hours)[c,d]	1000 mg/m^{2} [b,d]	100 mg/m^{2} [b,d]
Cycle 3 to 8	Day 1	30 mg (2 hours)[d,e]	1000 mg/m^{2} [b,d]	100 mg/m^{2} [b,d]
Cycle 9 to 12	Day 1	30 mg (2 hours)[e]	–	–

[a] Refer to "*Pre-treatment with obinutuzumab*" described above.
[b] Cycles 1-8: Administer gemcitabine before oxaliplatin.
[c] For patients who experience CRS with their previous dose of Columvi, the time of infusion may be extended up to 8 hours (see section 4.4).
[d] Cycles 2-8: Administer Columvi before gemcitabine and oxaliplatin. Gemcitabine and oxaliplatin may be given on Day 1 or 2.
[e] Infusion time may be shortened to 2 hours 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.

Patient monitoring

- When Columvi is given as monotherapy, patients must be monitored for signs and symptoms of potential CRS during all Columvi infusions and for at least 10 hours after completion of the infusion of the first Columvi dose (2.5 mg on Cycle 1 Day 8) (see section 4.8).
- When Columvi is given in combination with gemcitabine and oxaliplatin, patients must be monitored for signs and symptoms of potential CRS during all Columvi infusions and for 4 hours after completion of the first Columvi dose (2.5 mg on Cycle 1 Day 8) (see section 4.8).

Patients who experienced Grade ≥ 2 CRS with their previous infusion should be monitored after completion of the infusion (see Table 4 in section 4.2).

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 (see section 4.4).

Duration of treatment

Treatment with Columvi monotherapy is recommended for a maximum of 12 cycles or until disease progression or unmanageable toxicity, whichever occurs first. Each cycle is 21 days.

Treatment with Columvi in combination with gemcitabine and oxaliplatin is recommended for 8 cycles, followed by 4 cycles of Columvi monotherapy for a maximum of 12 cycles of Columvi in total or until disease progression or unmanageable toxicity, whichever occurs first. Each cycle is 21 days.

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 or 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 2.5 mg dose or 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 and Table 3).

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 Table 3), and then resume the planned treatment cycle (30 mg dose).

Dose modifications
No dose reductions of Columvi are recommended.

Management of cytokine release syndrome
CRS should be identified based on the clinical presentation (see sections 4.4 and 4.8). 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 4.

Table 4. ASTCT CRS grading and CRS management guidance

Grade[1]	**CRS management**	**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: • Consider corticosteroids[3] • Consider tocilizumab[4]	• Ensure symptoms are resolved for at least 72 hours prior to next infusion • Consider slower infusion rate[2]
Grade 2 Fever ≥ 38 °C 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[3] • Consider tocilizumab[4] If CRS occurs post-infusion: • Treat symptoms • Administer corticosteroids[3] • Consider tocilizumab[4]	• Ensure symptoms are resolved for at least 72 hours prior to next infusion • Consider slower infusion rate[2] • Monitor patients post-infusion[5]
For Grade 2: Tocilizumab use Do not exceed 3 doses of tocilizumab 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[4] • If no improvement within 8 hours, administer second dose of tocilizumab[4] • After 2 doses of tocilizumab, consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy If 2 doses of tocilizumab were used within the last 6 weeks: • Administer only one dose of tocilizumab[4] • If no improvement within 8 hours, consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy		

<table>
<tr><th>Grade[1]</th><th>CRS management</th><th>For next scheduled Columvi infusion</th></tr>
<tr><td>Grade 3
Fever ≥ 38 °C 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</td><td>If CRS occurs during infusion:
Discontinue current infusion and treat symptoms
Administer corticosteroids[3]
Administer tocilizumab[4]
If CRS occurs post-infusion:
Treat symptoms
Administer corticosteroids[3]
Administer tocilizumab[4]</td><td>Ensure symptoms are resolved for at least 72 hours prior to next infusion
Consider slower infusion rate[2]
Monitor patients post-infusion[5]
If Grade ≥ 3 CRS recurs at subsequent infusion, stop infusion immediately and permanently discontinue Columvi</td></tr>
<tr><td>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)</td><td colspan="2">If CRS occurs during infusion or post-infusion:
Permanently discontinue Columvi and treat symptoms
Administer corticosteroids[3]
Administer tocilizumab[4]</td></tr>
<tr><td colspan="3">For Grade 3 and Grade 4: Tocilizumab use
Do not exceed 3 doses of tocilizumab 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[4]
If no improvement within 8 hours or rapid progression of CRS, administer second dose of tocilizumab[4]
After 2 doses of tocilizumab, consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy
If 2 doses of tocilizumab were used within the last 6 weeks:
Administer only one dose of tocilizumab[4]
If no improvement within 8 hours or rapid progression of CRS, consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy</td></tr>
</table>

[1] ASTCT consensus grading criteria (Lee 2019).

[2] Duration of infusion may be extended up to 8 hours, as appropriate for that cycle (see Table 2).

[3] Corticosteroids (e.g., 10 mg intravenous dexamethasone, 100 mg intravenous prednisolone, 1-2 mg/kg intravenous methylprednisolone per day, or equivalent).

[4] Tocilizumab 8 mg/kg intravenously (not to exceed 800 mg), as administered in Study NP30179.

[5] See section 4.8 for frequency and time to onset of Grade ≥ 2 CRS following Columvi 10 mg and 30 mg doses.

Neurologic Toxicity, Including ICANS (Immune Effector Cell-Associated Neurotoxicity Syndrome)

Management recommendations for neurologic toxicity, including ICANS, is summarized in Table 5.

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 5: Recommended Dosage Modification for Neurologic Toxicity (Including ICANS)

Adverse Reaction	Severity[1,2]	Actions
Neurologic Toxicity[1] (including ICANS[2])	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.[3, 4] 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.[4, 5] 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.

[1] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
[2] Based on ASTCT 2019 grading for ICANS.
[3] Consider the type of neurologic toxicity before deciding to withhold Columvi.
[4] See *Dosage and Administration (2.2)* on restarting Columvi after dose delays.
[5] Evaluate benefit-risk before restarting Columvi.

Special populations

Elderly
No dose adjustment is required in patients 65 years of age and older (see section 5.2).

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). Columvi has not been studied in patients with moderate or severe hepatic impairment (see section 5.2).

Renal impairment
No dose adjustment 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 5.2).

Paediatric population
The safety and efficacy of Columvi in children below 18 years of age have not been established. No data are available.

Method of administration

Columvi is for intravenous use only.

Columvi must be diluted by a healthcare professional using aseptic technique, prior to intravenous administration. It must be administered as an intravenous infusion through a dedicated infusion line.

Columvi must not be administered as an intravenous push or bolus.

For instructions on dilution of Columvi before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to obinutuzumab, or to any of the excipients listed in section 6.1.

For specific contraindications on obinutuzumab, please refer to the obinutuzumab prescribing information.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 (see section 4.8).

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

Most CRS events occurred following the first dose of Columvi. 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 (see section 4.8).

Patients in studies NP30179 and GO41944 (STARGLO) were pre-treated with obinutuzumab to lower the circulating and lymphoid B cells, 7 days prior to initiation of Columvi therapy. All patients should be premedicated with an anti-pyretic, antihistamine, and a glucocorticoid (see Table 1).

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.

When Columvi is given as monotherapy, patients must be monitored during all Columvi infusions and for at least 10 hours after completion of the first infusion.

When Columvi is given in combination with gemcitabine and oxaliplatin, patients must be monitored during all Columvi infusions and for 4 hours after completion of the first infusion.

For complete information on monitoring, see section 4.2. Patients must be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time. *(See Patient information card)*.

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 4 (section 4.2).

Immune effector cell-associated neurotoxicity syndrome

Serious cases of immune effector cell-associated neurotoxicity syndrome (ICANS) which could be life-threatening or fatal have occurred following treatment with Columvi (see section 4.8).

The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Clinical signs and symptoms of ICANS may include but are not limited to confusion, depressed level of consciousness, disorientation, seizure, aphasia, and dysgraphia.

Patients should be monitored for signs and symptoms of ICANS following Columvi administration and treated promptly. Patients must be counselled to seek immediate medical attention should signs or symptoms occur at any time (*see* Patient card).

At the first signs or symptoms of ICANS, manage according to the ICANS guidance provided in Table 5. Treatment with Columvi should be withheld or discontinued permanently as recommended.

Interaction with CYP450 substrates

The initial release of cytokines associated with the start of Columvi treatment could suppress CYP450 enzymes and lead to fluctuations in concentrations of concomitantly administered drugs. On initiation of Columvi therapy, patients being treated with CYP450 substrates with a narrow therapeutic index should be monitored as fluctuations in the concentration of concomitant drugs may lead to toxicity, loss of effect or adverse events (see section 4.5).

Serious infections

Serious infections, including opportunistic infections, have occurred in patients treated with Columvi (see section 4.8).

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. Administer prophylactic antimicrobials, as appropriate. 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 or 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.

Tumour flare

Tumour flare has been reported in patients receiving Columvi (see section 4.8). Manifestations included localised pain and swelling.

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

Specific risk factors for tumour flare have not been identified, however, 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 for tumour flare at critical anatomical sites is recommended in patients treated with Columvi and managed as clinically indicated. Corticosteroids and analgesics should be considered to treat tumour flare.

Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been reported in patients receiving Columvi (see section 4.8). Patients with high tumour burden, rapidly proliferative tumours, renal dysfunction or dehydration are at greater risk of tumour lysis syndrome.

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

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

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.

Polysorbates

This medicinal product contains 1.25 mg of polysorbate 20 in each 2.5 mL vial and 5 mg of polysorbate 20 in each 10 mL vial, which is equivalent to 0.5 mg/mL.

Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. No interactions with Columvi are expected via the cytochrome P450 enzymes, other metabolising enzymes or transporters.

The initial release of cytokines associated with the start of Columvi treatment could suppress CYP450 enzymes. The highest drug-drug interaction risk is during the period of one week following each of the first 2 doses of Columvi (i.e., Cycle 1 Day 8 and 15) in patients who are receiving concomitant CYP450 substrates with a narrow therapeutic index (e.g., warfarin, cyclosporine). On initiation of Columvi therapy, patients being treated with CYP450 substrates with a narrow therapeutic index should be monitored.

The pharmacokinetics (PK) of glofitamab are not affected by co-administration with gemcitabine or oxaliplatin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

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

Pregnancy

There are no data on the use of Columvi in pregnant women. No reproductive toxicity studies have been performed in animals (see section 5.3).

Glofitamab is an immunoglobulin G (IgG). IgG is known to cross the placenta. Based on its mechanism of action, glofitamab is likely to cause foetal B-cell depletion when administered to a pregnant woman.

Columvi is not recommended during pregnancy and in women of childbearing potential not using contraception. Female patients receiving Columvi should be advised of the potential harm to the foetus. Female patients should be advised to contact the treating physician, should pregnancy occur.

Breast-feeding

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 breast 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 breast-feeding child is unknown. Women should be advised to discontinue breast-feeding during treatment with Columvi and for 2 months after the final dose of Columvi.

Fertility

No human data on fertility are available. No fertility assessments in animals have been performed to evaluate the effect of glofitamab on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Columvi has major influence on the ability to drive and use machines.

Due to the potential for ICANS, patients receiving Columvi are at risk of depressed level of consciousness (see section 4.4). Patients should be instructed to avoid driving or operating machines for 48 hours after each of the first two doses during the step-up dosing and in the event of new onset of any symptoms of ICANS (confusion, disorientation, depressed level of consciousness) and/or CRS (pyrexia, tachycardia, hypotension, chills, hypoxia) until symptoms resolve (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of the safety profile

Columvi monotherapy
The most common adverse reactions (≥ 20%) were cytokine release syndrome, neutropenia, anaemia, thrombocytopenia, and rash.

The most common serious adverse reactions reported in ≥ 2% of patients were cytokine release syndrome (22.1%), sepsis (4.1%), COVID-19 (3.4%), tumour flare (3.4%), COVID-19 pneumonia (2.8%), febrile neutropenia (2.1%), neutropenia (2.1%), and pleural effusion (2.1%).

Permanent discontinuation of Columvi due to an adverse reaction occurred in 5.5% of patients. The most common adverse reactions leading to permanent discontinuation of Columvi were COVID-19 (1.4%) and neutropenia (1.4%).

Columvi in combination with gemcitabine and oxaliplatin
The most common adverse reactions (≥ 20%) were thrombocytopenia, cytokine release syndrome, neutropenia, anaemia, nausea, peripheral neuropathy, diarrhoea, aspartate aminotransferase increased, alanine aminotransferase increased, rash, lymphopenia, pyrexia, and vomiting.

The most common serious adverse reactions reported in ≥ 2% of patients were cytokine release syndrome (20.3%), pyrexia (6.4%), pneumonia (5.8%), COVID-19 (5.8%), thrombocytopenia (4.7%), respiratory tract infection (3.5%), sepsis (2.3%), febrile neutropenia (2.3%), and diarrhoea (2.3%).

Permanent discontinuation of Columvi due to an adverse reaction occurred in 20.9% of patients. The most common adverse reactions leading to permanent discontinuation of Columvi were COVID-19 (11.6%), sepsis (1.2%), and pneumonitis (1.2%).

Tabulated list of adverse reactions

Adverse reactions occurring in relapsed or refractory DLBCL patients treated with Columvi monotherapy (n=145) in study NP30179 are listed in Table 6. Patients received a median of 5 cycles of Columvi treatment (range: 1 to 13 cycles).

Adverse reactions occurring in relapsed or refractory DLBCL patients treated with Columvi in combination with gemcitabine and oxaliplatin (n=172) in study GO41944 (STARGLO) are listed in Table 7. Patients received a median of 11 cycles of Columvi treatment (range: 1 to 13 cycles).

The adverse reactions are listed by MedDRA system organ class and categories of frequency. The following categories of frequency have been used: 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 6. Adverse reactions reported in patients with relapsed or refractory DLBCL treated with Columvi monotherapy

System organ class	Adverse reaction	All grades	Grade 3–4
Infections and infestations	Viral infections[1]	Very common	Common*
	Bacterial infections[2]	Common	Common
	Upper respiratory tract infections[3]	Common	Very rare**
	Sepsis[4]	Common	Common*
	Lower respiratory tract infections[5]	Common	Very rare**
	Pneumonia	Common	Uncommon
	Urinary tract infection[6]	Common	Uncommon
	Fungal infections[7]	Common	Very rare**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Tumour flare	Very common	Common
Blood and lymphatic system disorders	Neutropenia	Very common	Very Common
	Anaemia	Very common	Common
	Thrombocytopenia	Very common	Common
	Lymphopenia	Common	Common
	Febrile neutropenia[8]	Common	Common
Immune system disorders	Cytokine release syndrome[9]	Very common	Common
	Hypophosphataemia	Very common	Common

System organ class	Adverse reaction	All grades	Grade 3–4
Metabolism and nutrition disorders	Hypomagnesaemia	Very common	Very rare**
	Hypocalcaemia	Very common	Very rare**
	Hypokalaemia	Very common	Uncommon
	Hyponatraemia	Common	Common
	Tumour lysis syndrome	Common	Common
Psychiatric disorders	Confusional state	Common	Very rare**
Nervous system disorders	Headache	Very common	Very rare**
	Immune effector cell-associated neurotoxicity syndrome[10]	Common	Uncommon*
	Somnolence	Common	Uncommon
	Tremor	Common	Very rare**
	Myelitis[11]	Uncommon	Uncommon
Gastrointestinal disorders	Constipation	Very common	Very rare**
	Diarrhoea	Very common	Very rare**
	Nausea	Very common	Very rare**
	Gastrointestinal haemorrhage[12]	Common	Common
	Vomiting	Common	Very rare**
	Colitis	Uncommon	Uncommon
Skin and subcutaneous tissue disorders	Rash[13]	Very common	Common
General disorders and administration site conditions	Pyrexia	Very common	Very rare**
Investigations	Alanine aminotransferase increased	Common	Common
	Aspartate aminotransferase increased	Common	Common
	Blood alkaline phosphatase increased	Common	Common
	Gamma-glutamyltransferase increased	Common	Common
	Blood bilirubin increased	Common	Uncommon
	Hepatic enzyme increased	Common	Common

* Grade 5 reactions reported. See *Description of selected adverse reactions.*

** No Grade 3-4 events were reported.

[1] Includes COVID-19, COVID-19 pneumonia, herpes zoster, influenza, and ophthalmic herpes zoster.

[2] Includes vascular device infection, bacterial infection, Campylobacter infection, biliary tract infection bacterial, urinary tract infection bacterial, *Clostridium difficile* infection, Escherichia infection, and peritonitis.

[3] Includes upper respiratory tract infection, sinusitis, nasopharyngitis, chronic sinusitis, and rhinitis.

[4] Includes sepsis and septic shock.

[5] Includes lower respiratory tract infection and bronchitis.

[6] Includes urinary tract infection and Escherichia urinary tract infection.

[7] Includes oesophageal candidiasis and oral candidiasis.

[8] Includes febrile neutropenia and neutropenic infection.

[9] Based on ASTCT consensus grading (Lee 2019).

[10] ICANS based on Lee 2019 and includes somnolence, cognitive disorder, confusional state, delirium, and disorientation.

[11] Myelitis occurred concurrently with CRS.

[12] Includes gastrointestinal haemorrhage, large intestinal haemorrhage, and gastric haemorrhage.

[13] Includes rash, rash pruritic, rash maculo-papular, dermatitis, dermatitis acneiform, dermatitis exfoliative, erythema, palmar erythema, pruritis, and rash erythematous.

Table 7. Adverse reactions reported in patients with relapsed or refractory DLBCL treated with Columvi in combination with gemcitabine and oxaliplatin

System organ class	Adverse reaction	All grades	Grade 3–4
Infections and infestations	COVID-19[1]	Very common	Common*
	Respiratory tract infections[2]	Very common	Common*
	Pneumonia[3]	Very common	Common*
	Cytomegalovirus infections[4]	Common	Uncommon
	Herpes viral infections[5]	Common	Uncommon
	Urinary tract infection[6]	Common	Common
	Sepsis[7]	Common	Common*
	Candida infections[8]	Common	Very rare**
	Pneumocystis jirovecii pneumonia	Uncommon	Uncommon
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Tumour flare[9]	Common	Very rare**
Blood and lymphatic system disorders	Thrombocytopenia	Very common	Very common
	Neutropenia	Very common	Very common
	Anaemia	Very common	Very common
	Lymphopenia	Very common	Very common
	Febrile neutropenia	Common	Common
Immune system disorders	Cytokine release syndrome[10]	Very common	Common
Metabolism and nutrition disorders	Hypokalaemia	Very common	Common
	Hyponatraemia	Very common	Uncommon
	Hypomagnesaemia	Common	Very rare**
	Hypocalcaemia	Common	Uncommon
	Hypophosphataemia	Common	Common
	Tumour lysis syndrome	Common	Common
Nervous system disorders	Peripheral neuropathy[11]	Very common	Common
	Immune effector cell-associated neurotoxicity syndrome[12]	Common	Uncommon
	Headache	Common	Very rare**
	Tremor	Uncommon	Very rare**
Respiratory, thoracic and mediastinal disorders	Pneumonitis	Common	Very rare*,**
Gastrointestinal disorders	Nausea	Very common	Uncommon
	Diarrhoea	Very common	Common
	Vomiting	Very common	Uncommon
	Abdominal pain[13]	Very common	Common
	Constipation	Very common	Very rare**
	Colitis[14]	Common	Common
	Pancreatitis[15]	Common	Common
Skin and subcutaneous tissue disorders	Rash[16]	Very common	Uncommon
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[17]	Very common	Common

System organ class	Adverse reaction	All grades	Grade 3–4
General disorders and administration site conditions	Pyrexia	Very common	Uncommon
Investigations	Aspartate aminotransferase increased	Very common	Common
	Alanine aminotransferase increased	Very common	Common
	Blood alkaline phosphatase increased	Very common	Uncommon
	Gamma-glutamyltransferase increased	Very common	Common
	Blood lactate dehydrogenase increased	Very common	Very rare**
	Blood bilirubin increased[18]	Common	Very rare**
	Hepatic enzyme increased	Uncommon	Very rare**

* Grade 5 reactions reported. See *Description of selected adverse reactions*.

** No Grade 3-4 events were reported.

[1] Includes COVID-19, COVID-19 pneumonia, and SARS-CoV-2 test positive.

[2] Includes upper respiratory tract infection, lower respiratory tract infection, respiratory tract infection, and respiratory tract infection bacterial.

[3] Includes pneumonia, pneumonia bacterial, and pneumonia pneumococcal.

[4] New onset or reactivation. Includes cytomegalovirus infection, cytomegalovirus test positive, cytomegalovirus infection reactivation and cytomegalovirus viraemia.

[5] New onset or reactivation. Includes herpes zoster and herpes virus infection.

[6] Includes urinary tract infection and urosepsis.

[7] Includes sepsis, streptococcal sepsis, septic shock, and enterococcal sepsis.

[8] Includes oral candidiasis and candida infection.

[9] Includes tumour flare and tumour pain.

[10] Based on ASTCT consensus grading (Lee 2019).

[11] Includes neuropathy peripheral, peripheral sensory neuropathy, dysaesthesia, paraesthesia, hypoaesthesia, peripheral motor neuropathy, and polyneuropathy.

[12] Includes confusional state, delirium, and ICANS.

[13] Includes abdominal pain, abdominal discomfort, abdominal pain upper, abdominal pain lower, and gastrointestinal pain.

[14] Includes colitis, colitis ischaemic, and enterocolitis.

[15] Includes pancreatitis and pancreatitis acute.

[16] Includes rash, rash pruritic, rash maculo-papular, erythema, pruritus, rash erythematous, urticaria, and erythema multiforme.

[17] Includes arthralgia, musculoskeletal pain, back pain, bone pain, myalgia, neck pain, pain in extremity, musculoskeletal chest pain, and non-cardiac chest pain.

[18] Includes blood bilirubin increased and hyperbilirubinaemia.

Description of selected adverse reactions

The descriptions below reflect information for significant adverse reactions for Columvi monotherapy and/or combination therapy. Details for the significant adverse reactions for Columvi when given in combination are presented separately if clinically relevant differences were noted in comparison to Columvi monotherapy.

Cytokine release syndrome

Columvi monotherapy

Any grade CRS (by ASTCT criteria) occurred in 67.6% of patients who received Columvi monotherapy, with Grade 1 CRS reported in 50.3% of patients, Grade 2 CRS in 13.1% of patients, Grade 3 CRS in 2.8% of patients and Grade 4 CRS in 1.4% of patients. CRS occurred more than once in 32.4% (47/145) 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 treatment 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%).

CRS of any grade occurred in 54.5% of patients following the first 2.5 mg dose of Columvi at Cycle 1 Day 8 with median time to onset (from 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 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.

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.

In 145 patients, 7 patients (4.8%) 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).

Among the 25 patients who experienced Grade ≥ 2 CRS after Columvi, 22 (88.0%) received tocilizumab, 15 (60.0%) received corticosteroids and 14 (56.0%) received both tocilizumab and corticosteroids. Ten patients (40.0%) received oxygen. All 6 patients (24.0%) with Grade 3 or 4 CRS received a single vasopressor.

Hospitalisations due to patients experiencing CRS following Columvi administration occurred in 22.1% of patients and the reported median duration of hospitalisation was 4 days (range: 2 to 15 days).

Columvi in combination with gemcitabine and oxaliplatin

Any grade CRS (by ASTCT criteria) occurred in 44.2% of patients who received Columvi with gemcitabine and oxaliplatin, with Grade 1 CRS reported in 31.4% of patients, Grade 2 CRS in 10.5% of patients, and Grade 3 CRS in 2.3% of patients. CRS occurred more than once in 21.5% (37/172) of patients; 30/37 patients experienced multiple Grade 1 CRS events only. There were no Grade 4 or fatal cases of CRS. CRS resolved in all patients except one. One patient discontinued treatment due to CRS.

In patients with CRS, the most common manifestations of CRS included pyrexia (98.7%), hypotension (22.4%), chills (17.1%) and hypoxia (14.5%). Grade 3 or higher events associated with CRS included hypotension (6.6%), hypoxia (5.3%), pyrexia (3.9%), chills (1.3%) and diarrhoea (1.3%).

CRS of any grade occurred in 34.9% of patients following the first 2.5 mg dose of Columvi at Cycle 1 Day 8 with median time to onset (from start of infusion) of 12.6 hours (range: 4.4 to 54.7 hours) and median duration of 19.8 hours (range: 2.0 to 168.0 hours); in 14.4% of patients following the 10 mg

dose at Cycle 1 Day 15 with median time to onset of 22.8 hours (range: 7.4 to 81.2 hours) and median duration of 10.6 hours (range: 1.0 to 248.5 hours); and in 9.3% of patients following the 30 mg dose at Cycle 2 with median time to onset of 23.5 hours (range: 14.7 to 33.4 hours) and median duration of 18.4 hours (range: 8.3 to 137.0 hours). CRS was reported in 6.7% of patients at Cycle 3 and in 11.0% of patients beyond Cycle 3.

Grade ≥ 2 CRS occurred in 10.5% of patients following the first Columvi dose (2.5 mg) with median time to onset of 12.0 hours (range: 4.4 to 30.5 hours) and median duration of 42.3 hours (range: 3.5 to 143.7 hours). The majority (14/18) of patients who experienced Grade ≥ 2 CRS had onset of CRS within 8 hours of the start of the first Columvi dose (2.5 mg) or presented with a fever ≥ 1.5 hours before the onset of other symptoms of a Grade ≥ 2 CRS. Following Columvi 10 mg dose at Cycle 1 Day 15, the incidence of Grade ≥ 2 CRS decreased to 1.8% of patients with median time to onset of 22.3 hours (range: 7.4 to 22.8 hours) and median duration of 37.0 hours (range: 34.8 to 248.5 hours). There were no Grade ≥ 2 CRS events following Columvi 30 mg dose at Cycle 2 Day 1. Three patients (2.0%) had Grade ≥ 2 CRS beyond Cycle 2 (all Grade 2 events).

Of the 172 patients, 2 patients (1.2%) experienced elevated liver function tests (AST and ALT > 3 × ULN) reported concurrently with CRS.

Out of the 76 patients with any grade CRS, 28 patients (36.8%) were treated with tocilizumab, 39 patients (51.3%) were treated with corticosteroids, and 18 patients (23.7%) received both tocilizumab and corticosteroids.

Among the 22 patients who experienced Grade ≥ 2 CRS after Columvi, 16 (72.7%) received tocilizumab, 15 (68.2%) received corticosteroids, and 12 (54.5%) received both tocilizumab and corticosteroids. Eleven patients (50.0%) received oxygen. All 4 patients (18.2%) with Grade 3 CRS received a single vasopressor.

Hospitalisations due to patients experiencing CRS following Columvi administration occurred in 19.8% of patients and the reported median duration of hospitalisation was 5 days (range: 2 to 85 days).

Immune effector cell-associated neurotoxicity syndrome
ICANS, including Grade 3 and higher, was reported in clinical trials and with post-marketing experience. The most frequent clinical manifestations of ICANS were confusion, depressed level of consciousness, disorientation, seizure, aphasia, and dysgraphia. Based on the available data, the onset of neurologic toxicity was concurrent with CRS in the majority of cases.

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

Serious infections
Serious infections were reported in 15.9% of patients who received Columvi monotherapy. The most frequent serious infections reported in ≥ 2% of 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 or 4 neutropenia.

Serious infections were reported in 22.7% of patients who received Columvi with gemcitabine and oxaliplatin. The most frequent serious infections reported in ≥ 2% of patients were pneumonia (5.8%), COVID-19 (4.7%), and lower respiratory tract infection (2.9%). Infection-related deaths were reported in 3.5% of patients (due to COVID-19, pneumonia, respiratory tract infection, and septic

shock). One patient (0.6%) experienced a serious infection (pneumonia) concurrently with Grade 3 neutropenia.

Pneumonitis
Pneumonitis events (excluding pneumonia of infectious aetiology) were reported in 2 patients (1.2%) who received Columvi with gemcitabine and oxaliplatin, both of which were fatal events. The median time to onset of pneumonitis from the first Columvi dose was 168 days (range: 102 to 255 days).

Colitis
Colitis (Grade 4) was reported in 1 patient (0.7%) who received Columvi monotherapy, with time to onset from the first Columvi dose of 104 days.

Colitis events (excluding infectious aetiology) were reported in 4/172 patients (2.3%) who received Columvi with gemcitabine and oxaliplatin. Two patients (1.2%) had Grade 3 events. The median time to onset of colitis from the first Columvi dose was 154 days (range: 115 to 187 days).

Opportunistic infections
CMV events were reported in 6/467 patients (1.3%) who received Columvi monotherapy, with 1 patient (0.2%) experiencing Grade 3 CMV chorioretinitis. Pneumocystis jirovecii pneumonia was reported in 4/467 patients (0.9%), 3 of whom (0.6%) had Grade 3 events.

CMV events were reported in 11 patients (6.4%) who received Columvi with gemcitabine and oxaliplatin, with 1 patient (0.6%) experiencing Grade 3 CMV viraemia. Oral candidiasis was reported in 3 patients (1.7%) all of which were Grade 1-2 events. Pneumocystis jirovecii pneumonia (Grade 3) was reported in 1 patient (0.6%), the same patient with Grade 3 CMV viraemia. Borellia meningitis (Grade 2) was reported in 1 patient (0.6%).

Neutropenia
Neutropenia (including neutrophil count decreased) was reported in 40.0% of patients and severe neutropenia (Grade 3 or 4) was reported in 29.0% of patients who received Columvi monotherapy. 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.

Tumour flare
Tumour flare was reported in 11.7% of patients who received Columvi monotherapy, 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).

Among the 11 patients who experienced Grade $\geq$ 2 tumour flare, 2 patients (18.2%) received analgesics, 6 patients (54.5%) received corticosteroids and analgesics including morphine derivatives, 1 patient (9.1%) received corticosteroids and anti-emetics, and 2 patients (18.2%) did not require treatment. All tumour flare events resolved except in one patient with a Grade $\geq$ 2 event. No patients discontinued treatment due to tumour flare.

Tumour lysis syndrome
TLS was reported in 2 patients (1.4%) who received Columvi monotherapy and was Grade 3 in severity in both cases. The median time to onset of TLS onset was 2 days, and the median duration was 4 days (range: 3 to 5 days).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form sideeffects.health.gov.il/

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX28

Mechanism of action

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

Pharmacodynamics

In study NP30179, 84% (84/100) of patients were already B-cell depleted (< 70 cells/µL) before pre-treatment with obinutuzumab. The proportion of patients with B-cell depletion increased to 100% (94/94) after obinutuzumab pre-treatment prior to Columvi treatment initiation, and B-cell counts 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.

In study GO41944 (STARGLO), 63.9% (115/180) of patients were already B-cell depleted (< 70 cells/µL) before pre-treatment with obinutuzumab. The proportion of patients with B-cell depletion increased to 79.4% (143/180) after obinutuzumab pre-treatment prior to Columvi treatment initiation, and B-cell counts remained low during Columvi treatment.

Cardiac electrophysiology
In study NP30179, 16/145 patients who were exposed to Columvi experienced a post-baseline QTc value > 450 ms. One of these cases was assessed to be of clinical significance by the investigator. No patients discontinued treatment due to QTc prolongation.

In study GO41944 (STARGLO), 16/172 patients who were exposed to Columvi experienced a post-baseline QTc value > 450 ms. No patients discontinued treatment due to QTc prolongation.

Clinical efficacy and safety

Relapsed or refractory DLBCL

Columvi monotherapy

An open-label multicentre, multi-cohort trial (NP30179) was conducted to evaluate Columvi in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. In the single-arm monotherapy DLBCL cohort (n=108), patients with relapsed or refractory DLBCL were required to have received at least two prior lines of systemic therapy, including an anti-CD20 monoclonal antibody and an anthracycline agent. Patients with FL3b and Richter transformation were not eligible. Patients were expected to present CD20-positive DLBCL, but biomarker eligibility was not a requirement for inclusion (see section 4.4).

The study excluded patients with ECOG performance status ≥ 2, significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina), significant active pulmonary disease, impaired renal functions (CrCL < 50 mL/min with elevated serum creatinine level), active autoimmune disease requiring immunosuppressive therapy, active infections (i.e., chronic active EBV, acute or chronic hepatitis C, hepatitis B, HIV), progressive multifocal leukoencephalopathy, current or a history of CNS lymphoma or CNS disease, a history of macrophage activation syndrome / hemophagocytic lymphohistiocytosis, prior allogeneic stem cell transplant, prior organ transplantation, or hepatic transaminases ≥ 3 × ULN.

All patients received 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. The duration of each cycle was 21 days. Patients received a median of 5 cycles of Columvi treatment (range: 1 to 13 cycles); 34.7% received 8 or more cycles and 25.7% received 12 cycles of Columvi treatment.

The baseline demographic and disease characteristics were: median age 66 years (range: 21 to 90 years) with 53.7% aged 65 years or older and 15.7% aged 75 years or older; 69.4% males; 74.1% white, 5.6% Asian and 0.9% Black or African American; 5.6% Hispanic or Latino; and ECOG performance status of 0 (46.3%) or 1 (52.8%). Most patients (71.3%) had DLBCL not otherwise specified, 7.4% had DLBCL transformed from follicular lymphoma, 8.3% had high-grade B-cell lymphoma (HGBCL) or another histology transformed from follicular lymphoma, 7.4% had HGBCL, and 5.6% had primary mediastinal large B-cell lymphoma (PMBCL). The median number of prior lines of therapy was 3 (range: 2 to 7); 39.8% of patients received 2 prior lines and 60.2% received 3 or more prior lines of therapy. All patients had received prior chemotherapy (all patients received alkylator therapy and 98.1% of patients received anthracycline therapy) and all patients had received prior anti-CD20 monoclonal antibody therapy; 35.2% of patients had received prior CAR T-cell therapy, and 16.7% of patients had received autologous stem cell transplant. Most patients (89.8%) had refractory disease, 60.2% of patients had primary refractory disease and 83.3% of patients were refractory to their last prior therapy.

The primary efficacy outcome measure was complete response (CR) rate as assessed by an independent review committee (IRC) using 2014 Lugano criteria. The overall median duration of follow-up was 15 months (range: 0 to 21 months). The secondary efficacy outcome measures included overall response rate (ORR), duration of response (DOR), duration of complete response (DOCR), and time to first complete response (TFCR) as assessed by IRC.

Efficacy results are summarised in Table 8.

Table 8. Summary of efficacy in patients with relapsed or refractory DLBCL

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

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

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

Columvi in combination with gemcitabine and oxaliplatin

The efficacy of Columvi in combination with gemcitabine and oxaliplatin (Columvi+GemOx) was evaluated in study GO41944 (STARGLO), an open-label multicentre, randomised clinical trial in 274 patients with relapsed or refractory DLBCL not otherwise specified (DLBCL NOS).

The study included patients with DLBCL NOS who received only one prior line of therapy who were not candidates for autologous stem cell transplant (ASCT), or who had received ≥ 2 prior therapies. Patients were required to have ECOG performance status ≤ 2, CrCL ≥ 30 mL/min, hepatic transaminases ≤ 2.5 × ULN, no significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 3 months, unstable arrhythmias, or unstable angina) and no current or prior CNS lymphoma or CNS disease, no active autoimmune disease requiring immunosuppressive therapy, no active infections (i.e., chronic active EBV, active hepatitis B, hepatitis C), and no history of any of the following: HIV, progressive multifocal leukoencephalopathy, hemophagocytic lymphohistiocytosis, prior allogeneic stem cell transplant, or prior organ transplantation. Patients with HGBCL, PMBCL, or history of transformation of indolent disease to DLBCL were excluded.

Patients who received only one prior line of therapy were not considered candidates for transplant if they met at least one of the following criteria: age ≥ 70 years, ECOG performance status 2, left ventricular ejection fraction ≤ 40%, insufficient response to salvage therapy prior to ASCT, CrCL ≤ 45 mL/min, other comorbidities or criteria that preclude use of transplant based on local practice standards or in the investigator's opinion, or patient refusal of high-dose chemotherapy and/or transplant.

Patients were randomised 2:1 to receive Columvi+GemOx (N=183) or rituximab in combination with gemcitabine plus oxaliplatin (R-GemOx; N=91) for 8 cycles, followed by 4 additional cycles of Columvi monotherapy for patients in the Columvi+GemOx arm. Randomisation was stratified by number of previous lines of systemic therapy for DLBCL (1 vs. ≥ 2) and outcome of last systemic therapy (relapsed vs. refractory).

In the Columvi+GemOx arm, patients received pre-treatment with obinutuzumab at Cycle 1 Day 1 followed by 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. Gemcitabine (1000 mg/m^2) and oxaliplatin (100 mg/m^2) were administered intravenously on Day 2 of Cycle 1 and then on Day 1 of subsequent cycles, up to Cycle 8. The duration of each cycle was 21 days in both arms. Patients received a median of 11 cycles of Columvi treatment (range: 1 to 13 cycles); 64.5% received 8 or more cycles and 44.8% received 12 cycles of Columvi treatment.

The baseline demographic and disease characteristics were: median age 68 years (range: 20 to 88 years) with 62.8% aged 65 years or older and 23.7% aged 75 years or older; 57.7% males; 42% white, 50% Asian, and 1.1% Black or African American; 5.8% Hispanic or Latino; and ECOG performance status of 0 (43.3%), 1 (46.6%), or 2 (10.1%). The majority of patients (62.8%) had received 1 prior line of systemic therapy; 37.2% of patients received 2 or more prior lines. All patients had received prior chemotherapy and most (98.5%) had received prior anti-CD20 monoclonal antibody therapy; 7.7% of patients had received prior CAR T-cell therapy, and 4.0% of patients had received autologous stem cell transplant. The majority of patients (66.8%) had refractory disease, 55.8% of patients had primary refractory disease, and 60.6% of patients were refractory to their last prior therapy. The most common reasons why patients were not considered candidates for transplant included age (42.3%), patient refused high-dose chemotherapy and/or transplant (34.7%), and insufficient response to salvage therapy (9.9%).

The primary efficacy outcome measure was overall survival (OS). At the time of the prespecified primary analysis, a statistically significant improvement in OS was observed for patients randomised to the Columvi+GemOx arm compared to patients randomised to R-GemOx (HR 0.59, 95% CI: 0.40, 0.89; p-value=0.011). Median OS in the R-GemOx arm was 9.0 months (95% CI: 7.3, 14.4) and was not reached in the Columvi+GemOx arm (95% CI: 13.8, NE). Statistically significant improvements in progression-free survival (PFS) and CR rate, as assessed by an IRC, were also observed with Columvi+GemOx over R-GemOx. Median PFS was 12.1 months (95% CI: 6.8, 18.3) in the Columvi+GemOx arm versus 3.3 months (95% CI: 2.5, 5.6) in the R-GemOx arm (HR 0.37, 95% CI: 0.25, 0.55; p-value<0.001). The rate of complete response was 50.3% with Columvi+GemOx versus 22.0% with R-GemOx, a difference of 28.3% (p-value<0.001).

Overall survival, PFS, and CR results from an updated analysis conducted after an additional 10.5 months of follow-up continue to demonstrate benefit of Columvi+GemOx over R-GemOx. The key results are summarised in Table 9. Kaplan-Meier plots for OS and PFS from the updated analysis are presented in Figure 1 and Figure 2, respectively. Exploratory subgroup analysis at the time of the updated analysis showed an OS hazard ratio of 1.09 (95% CI: 0.54, 2.18) and PFS hazard ratio of 0.84 (95% CI: 0.44, 1.59) for patients enrolled in Europe.

Table 9. Efficacy in patients with relapsed or refractory DLBCL treated with Columvi in combination with gemcitabine and oxaliplatin (ITT)

Efficacy endpoints	Updated analysis (median observation time=20.7 months)	
	Columvi+GemOx N=183	R-GemOx N=91
Overall survival		
Number (%) of deaths	80 (43.7)	52 (57.1)
Median (95% CI), months	25.5 (18.3, NE)	12.9 (7.9, 18.5)
HR (95% CI)	0.62 (0.43, 0.88)	
Progression-free survival - IRC-assessed		
Number (%) of patients with events	90 (49.2)	54 (59.3)
Median (95% CI), months	13.8 (8.7, 20.5)	3.6 (2.5, 7.1)
HR (95% CI)	0.40 (0.28, 0.57)	
Complete response rate - IRC-assessed		
Responders (%)	107 (58.5)	23 (25.3)
Difference in response rate (95% CI), %	33.2 (20.9, 45.5)	
Objective response rate - IRC-assessed		
Responders (%) (CR, PR)	125 (68.3)	37 (40.7)
Difference in response rate (95% CI), %	27.7 (14.7, 40.6)	

CI=confidence interval; HR=hazard ratio; NE=not estimable.

Figure 1. Kaplan-Meier plot of overall survival in study GO41944 (STARGLO, updated analysis; ITT)

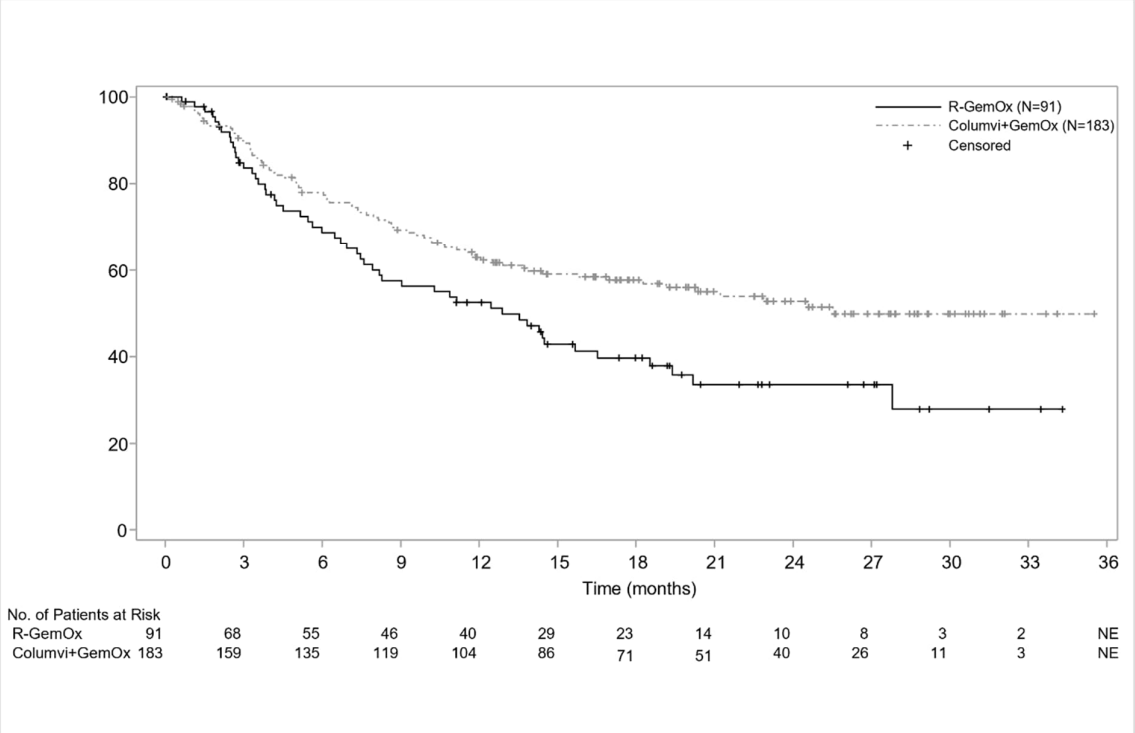
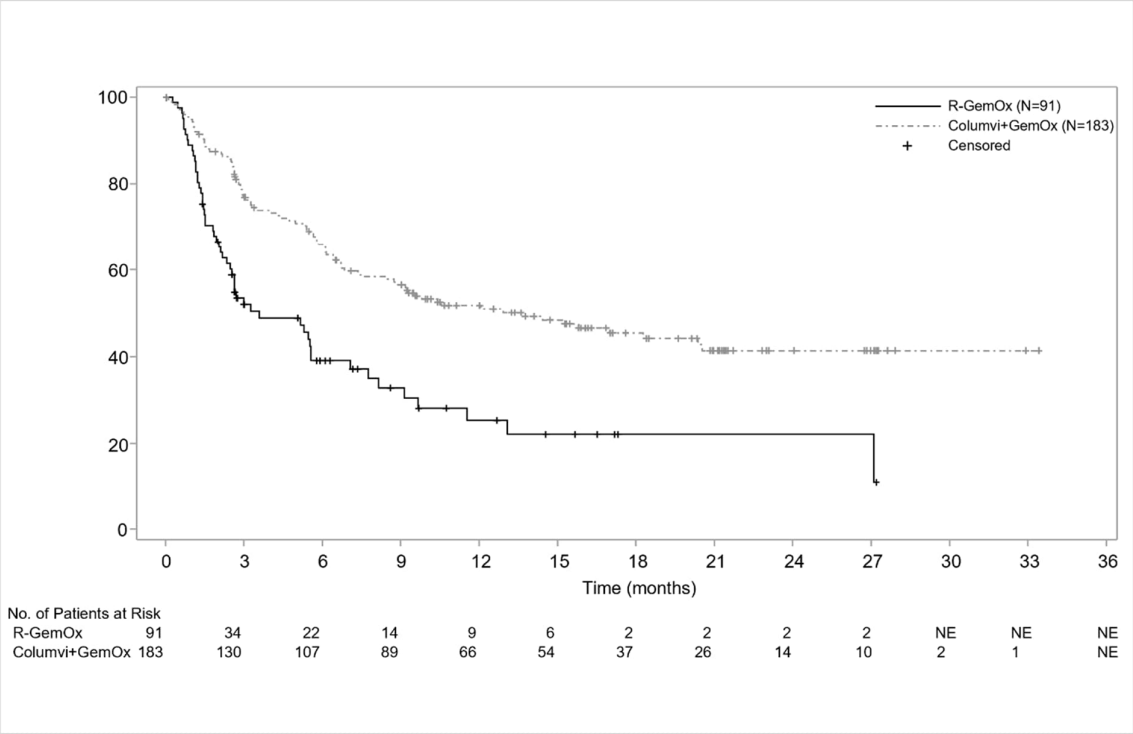


Figure 2. Kaplan Meier plot of IRC-assessed progression-free survival in study GO41944 (STARGLO, updated analysis; ITT)



Immunogenicity

Across studies, of 608 patients, only 4 patients (0.7%) were negative for anti-glofitamab antibodies at baseline and became positive following treatment. Due to the limited number of patients with antibodies against glofitamab, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.

5.2 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.

Absorption

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

Distribution

Following intravenous administration, the central volume of distribution was 3.34 L, which is close to total serum volume. The peripheral volume of distribution was 2.35 L.

Biotransformation

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

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 0.633 L/day and the initial time-varying clearance pathway as 0.814 L/day, with an exponential decay over time (K_{des} ~ 1.5/day). The estimated decay half-life from the initial total clearance value to the time-independent clearance only was estimated as 0.471 days.

The effective half-life in the linear phase (i.e., after the contribution of time-varying clearance has collapsed to a negligible amount) is 7.92 days (geometric mean, 95% CI: 4.69, 11.90) based on the population pharmacokinetic analysis.

Special populations

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

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

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

5.3 Preclinical safety data

No studies have been conducted to establish the carcinogenic potential and mutagenic potential of glofitamab.

Fertility

No fertility assessments in animals have been performed to evaluate the effect of glofitamab.

Reproductive toxicity

No reproductive and developmental toxicity studies in animals have been performed to evaluate the effect of glofitamab. 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 glofitamab and 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 foetal loss. Transient CRS associated with Columvi administration may also be harmful to the foetus (see section 4.6).

Systemic toxicity

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. Pre-treatment 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 3.74 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.

As all relapsed or refractory DLBCL patients to be treated have been exposed to anti-CD20 treatment before, the majority will likely have low levels of circulating B cells due to residual effects of prior anti-CD20 therapy, before treatment with obinutuzumab. Therefore, the animal model without prior rituximab (or other anti-CD20) treatment may not fully reflect the clinical context.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D-Sucrose
L-histidine hydrochloride monohydrate
L-methionine
L-histidine
Polysorbate 20
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

The expiry date of the product is indicated on the packaging materials.

Diluted solution for intravenous infusion

Chemical and physical in-use stability have been demonstrated for a maximum of 72 hours at 2 °C to 8 °C and 24 hours at 30 °C followed by a maximum infusion time of 8 hours.

From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.

Do not shake.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

- 2.5 mL concentrate for solution for infusion in a 6 mL vial (colourless Type I glass) with stopper (butyl rubber).
  Pack size of 1 vial.
- 10 mL concentrate for solution for infusion in a 15 mL vial (colourless Type I glass) with stopper (butyl rubber).
  Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Instructions for dilution

- 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 discolouration prior to administration. Columvi is a colourless, clear solution. Discard the vial if the solution is cloudy, discoloured or contains visible particles.
- Withdraw the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or sodium chloride 4.5 mg/mL (0.45%) solution for injection, as described in Table 10, from the infusion bag 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 glofitamab 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 (25 °C).

Table 10. Dilution of Columvi for infusion

Dose of Columvi to be administered	Size of infusion bag	Volume of sodium chloride 9 mg/mL (0.9%) or 4.5 mg/mL (0.45%) solution for injection 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

Administration

Only administer as an intravenous infusion.

Do not administer as an intravenous push or bolus.

Administer as an intravenous infusion through a dedicated infusion line via intravenous bag infusion using a pump, over a maximum of 8 hours.

The Columvi infusion bag may empty before the recommended duration of infusion is reached. To ensure the entire dose of Columvi is administered, clear the infusion line by replacing the emptied Columvi infusion bag with an infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection or sodium chloride 4.5 mg/mL (0.45%) solution for injection connected to the same infusion line. Continue the infusion at the same rate until the recommended infusion duration is reached according to Table 2.

Incompatibilities

Only sodium chloride 9 mg/mL (0.9%) or 4.5 mg/mL (0.45%) solution for injection should be used to dilute Columvi, since other solvents have not been tested.

When diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, Columvi is compatible with intravenous infusion bags composed of polyvinyl chloride (PVC), polyethylene (PE), polypropylene (PP) or polyolefin. When diluted with sodium chloride 4.5 mg/mL (0.45%) solution for injection, 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, PE, polybutadiene (PBD), polyetherurethane (PEU), polycarbonate (PC), silicone, polytetrafluoroethylene (PTFE) or acrylonitrile butadiene styrene (ABS), and in-line filter membranes composed of polyethersulfone (PES) or polysulfone. The use of in-line filter membranes is optional.

Disposal

Columvi vial is for single use only.

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

7. MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd., P.O.Box 6391 Hod Hasharon 4524079.

8. MARKETING AUTHORISATION NUMBER(S)

[176-69-37772-00]

9. MANUFACURER

F. Hoffmann-La Roche Ltd. Basel, Switzerland

Revised in January 2026