PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]COLUMVI®

glofitamab for injection

Concentrate for solution for intravenous infusion

1 mg/mL

Professed Standard

Antineoplastic agent, monoclonal antibody (recombinant humanized immunoglobulin G1)
ATC code: L01FA80

COLUMVI, indicated for:

- the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from follicular lymphoma (trFL), or primary mediastinal B-cell lymphoma (PMBCL), who have received two or more lines of systemic therapy and are ineligible to receive or cannot receive CAR-T cell therapy or have previously received CAR-T cell therapy.

has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for COLUMVI please refer to Health Canada's Notice of Compliance with conditions – drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

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Date of Initial Approval:
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Submission Control No: 265517

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

N/A

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

COLUMVI (glofitamab for injection) is indicated for:

- the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from follicular lymphoma (trFL), or primary mediastinal B-cell lymphoma (PMBCL), who have received two or more lines of systemic therapy and are ineligible to receive or cannot receive CAR-T cell therapy or have previously received CAR-T cell therapy.

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of COLUMVI in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 4.2 Recommended Dose and Dosage Adjustment; 0

CLINICAL TRIALS; and 10.3 Pharmacokinetics, Special Populations and Conditions).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No differences in safety or efficacy of COLUMVI were observed between patients ≥ 65 years of age and those under 65 years (see 7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics; and 10.3 Pharmacokinetics, Special Populations and Conditions).

2 CONTRAINDICATIONS

COLUMVI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 0
DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Cytokine Release Syndrome - Cytokine release syndrome (CRS), which may be serious or life-threatening occurred in patients receiving COLUMVI. Pretreat with obinutuzumab 7 days prior to COLUMVI and initiate treatment with COLUMVI step-up dosing schedule to reduce the risk of CRS. Monitor for at least 10 hours following the first infusion and then as clinically indicated for subsequent infusions. Treat severe or life-threatening CRS with tocilizumab, or tocilizumab and corticosteroids. Withhold COLUMVI until CRS resolves or permanently discontinue based on severity (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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.

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 7 WARNINGS AND PRECAUTIONS).

COLUMVI must not be administered to patients with an active infection.

For information on dosing and timing of tocilizumab administration, refer to Table 3.

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 4.5 Missed Dose. The purpose of obinutuzumab pre-treatment is to deplete circulating and lymphoid tissue B cells and minimize 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 Product Monograph for complete information on premedication, preparation, administration, warnings and precautions, 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 7 WARNINGS AND PRECAUTIONS) should be administered according to the guidance 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.

4.2 Recommended Dose and Dosage Adjustment

COLUMVI dosing begins with a step-up dosing schedule to minimize the risk of CRS. The recommended dose after step-up is 30 mg.

COLUMVI Dose Step-up Schedule

Seven days after obinutuzumab pre-treatment (i.e., on Day 8), COLUMVI 2.5 mg is administered as an intravenous infusion. Subsequent doses are administered according to the step-up schedule, shown in Table 2, leading to the recommended dose of 30 mg. Each treatment 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 7 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.

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.

Pediatric Use: Health Canada has not authorized an indication for pediatric use (see INDICATIONS, 1.1 Pediatrics).

Duration of Treatment

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

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 7 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 °C	If CRS occurs during infusion: • Interrupt infusion and treat symptoms • Restart infusion at slower rate[b] 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[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 °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[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[a]	CRS Management	For Next Scheduled COLUMVI Infusion
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	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 °C and/or hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)	If CRS occurs during infusion or post-infusion: • Permanently discontinue COLUMVI and treat symptoms • 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) consensus grading criteria.

b Duration of infusion may be extended up to 8 hours (up to 50% slower infusion), 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 5.6% of patients, with a median time to onset of 27.2 hours (range: 7.7 to 145.2 hours).

Grade[a]	CRS Management	For Next Scheduled COLUMVI Infusion

f Grade ≥ 2 CRS following COLUMVI 30 mg dose at Cycle 2 Day 1 occurred in one patient (0.9%), with time to onset of 16.0 hours

4.3 Reconstitution

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 colourless, clear solution. Do not use COLUMVI if the solution is cloudy, discoloured, or contains visible particles.
- Withdraw and discard the required volume of 0.9% or 0.45% sodium chloride solution from the appropriately sized infusion bag (see Table 4) using a sterile needle and syringe.
- 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 4). 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 brought to room temperature, not exceeding the 4 hours hold time outside refrigerated conditions (see Section 11 STORAGE, STABILITY AND DISPOSAL).

Table 4 Dilution of COLUMVI for Infusion

Vial Size (concentration)	Dose of COLUMVI to be administered	Number of vials to achieve required dose	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/2.5 mL (1 mg/mL)	2.5 mg	1	50 mL	27.5 mL	2.5 mL
		1	100 mL	77.5 mL	2.5 mL
10 mg/10 mL (1 mg/mL)	10 mg	1	50 mL	10 mL	10 mL
		1	100 mL	10 mL	10 mL
10 mg/10 mL (1 mg/mL)	30 mg	3	50 mL	30 mL	30 mL
		3	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.

4.4 Administration

- COLUMVI must be administered as an intravenous infusion through a dedicated infusion line, typically over a period of 2 hours – 4 hours.
- COLUMVI must not be administered as an intravenous push or bolus.
- COLUMVI must not be mixed with other drugs.

4.5 Missed Dose

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).

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).

5 OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 5 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Concentrate for solution for infusion, 2.5 mg/2.5 mL vial and 10 mg/10 mL vial	L-histidine; L-histidine hydrochloride, monohydrate; L-methionine; polysorbate 20; D-sucrose; water for injection

COLUMVI is a preservative-free, colourless, clear solution supplied in single-dose vials containing:

- 2.5 mg of glofitamab in 2.5 mL solution in a 6 mL single-use glass vial at a concentration of 1 mg/mL
- 10 mg of glofitamab in 10 mL solution in a 15 mL single-use glass vial at a concentration of 1 mg/mL

7 WARNINGS AND PRECAUTIONS

General

Driving and Operating Machinery

COLUMVI may have an influence on the ability to drive and use machines. Patients experiencing symptoms that might affect their ability to drive or use machines (e.g., symptoms of CRS, such as pyrexia, tachycardia, hypotension, chills, hypoxia) should be advised not to drive or use machines until symptoms resolve.

Endocrine and Metabolism

Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) has been reported in patients receiving COLUMVI (see 8.2 Clinical Trial Adverse Reactions). Patients with high tumour burden, rapidly proliferative tumours, renal dysfunction, or dehydration are at greater risk of TLS.

Patients at risk should be monitored closely by appropriate clinical and laboratory tests for electrolyte status, hydration, and renal function. Appropriate prophylactic measures with anti-

hyperuricemics (e.g., allopurinol or rasburicase) and adequate hydration should be considered prior to COLUMVI infusion.

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

Hepatic/Biliary/Pancreatic

The safety and efficacy of COLUMVI in patients with moderate and severe hepatic impairment has not been studied (see 10.3 Pharmacokinetics, Special Populations and Conditions).

Immune

Cytokine Release Syndrome

CRS, including life-threatening reactions, has occurred 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 and vice versa. Elevated liver function tests (AST and ALT ≥3x ULN and/or total bilirubin ≥2x ULN) concurrent with CRS have been reported after COLUMVI use.

In relapsed or refractory DLBCL patients who had received at least 2 prior systemic treatment regimens and were administered obinutuzumab pre-treatment followed by COLUMVI step-dosing (2.5/10/30 mg) (n=152), CRS of any grade (ASTCT criteria) occurred in 61.8% of patients. Grade 3 or 4 CRS occurred in 3.9% of patients. There were no fatal cases of CRS. CRS events were most common following the first dose of COLUMVI, but were also frequently observed after the second and third doses (see 8.2 Clinical Trial Adverse Reactions).

To reduce the occurrence and/or severity of CRS, patients must be pre-treated with obinutuzumab, 7 days prior to initiation of COLUMVI, and should be premedicated with an anti-pyretic, anti-histamine, and a glucocorticoid (see 4.2 Recommended Dose and Dosage Adjustment, Management of Cytokine Release Syndrome).

In the event of CRS, treatment with supportive care, tocilizumab and/or corticosteroids should be instituted as indicated (see 4.2 Recommended Dose and Dosage Adjustment, Management of Cytokine Release Syndrome). 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. In case CRS is not adequately controlled after 1 dose of tocilizumab, an additional dose of tocilizumab must be accessible for use within 8 hours of the first.

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 4.2 Recommended Dose and Dosage Adjustment. The healthcare professional 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 4.2 Recommended Dose and Dosage Adjustment, Management of Cytokine Release Syndrome).

Infusion Related Reaction (IRR)

Infusion related reactions (IRRs) were reported with COLUMVI. IRRs may be clinically indistinguishable from manifestations of CRS. For all events with clinical presentation of IRR/CRS with onset during infusion or after from the end of COLUMVI infusion (e.g., fever, nausea, chills, headache, hypotension, hypoxia or organ toxicity), these events should be treated as signs or symptoms of CRS.

Serious Infections

Serious infections (such as sepsis and pneumonia), sometimes leading to death, have occurred in patients treated with COLUMVI (see 4.2 Recommended Dose and Dosage Adjustment).

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.

Tumour Flare

Tumour flare has been reported in patients receiving COLUMVI. Manifestations included localized pain and swelling at the sites of lymphoma lesions and tumour inflammation (see 8.2 Clinical Trial Adverse Reactions).

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 of tumour flare at critical anatomical sites is recommended in patients treated with COLUMVI and managed as clinically indicated.

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.

Neurological Adverse Events (NAEs)

Neurological adverse events (NAEs) were reported in 55/152 patients (36.2%) with the majority of events reported as the highest grade of Grade 1-2. The most commonly reported adverse events (>3.0%) were headache (9.2%), dizziness (3.9%), anxiety (6 patients, 3.9%) and paraesthesia (3.3%). Only 3 patients had a Grade 3-4 NAEs (1 patient had grade 3 agitation, 1 patient had grade 3 somnolence and 1 patient grade 4 myelitis) and one patient had a Grade 5 NAE (delirium).

Renal

The safety and efficacy of COLUMVI in patients with severe renal impairment has not been studied (see 10.3 Pharmacokinetics, Special Populations and Conditions).

Reproductive Health: Female and Male Potential

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 (see 7.1.1 **Pregnant Women**).

Fertility

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

7.1 Special Populations

7.1.1 Pregnant Women

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. COLUMVI is an immunoglobulin G (IgG). IgG is known to cross the placenta. Based on its mechanism of action, COLUMVI 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.

7.1.2 Breast-feeding

It is not known whether COLUMVI is excreted in human milk. No studies have been conducted to assess the impact of COLUMVI on milk production or its presence in human milk. Human IgG is known to be present in human milk. The potential for absorption of COLUMVI 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.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of COLUMVI in pediatric patients have not been established.

7.1.4 Geriatrics

No differences in safety or efficacy of COLUMVI were observed between patients ≥ 65 years of age and those under 65 years. No dose adjustment of COLUMVI is required in patients ≥ 65 years of age (see 10.3 Pharmacokinetics, Special Populations and Conditions).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Approximately 424 patients with relapsed or refractory non-Hodgkin's lymphoma have received various dosing regimens of COLUMVI as monotherapy in the clinical development program of COLUMVI.

The adverse drug reactions described below were identified from 152 patients with relapsed or refractory DLBCL, who had received at least two prior lines of systemic therapy, including DLBCL NOS (73.0%), DLBCL arising from follicular lymphoma (18.4%), high-grade B-cell lymphoma (HGBCL) (4.6%), and PMBCL (3.9%), treated with COLUMVI monotherapy in Study NP30179, an open-label multicenter clinical trial. The most common serious adverse reactions (occurred in more than 5%) are Cytokine release syndrome and viral infections. All 152 patients received a single infusion of obinutuzumab 7 days prior to the first administration of glofitimab. Patients must have had an ECOG performance status of 0 or 1, and must not have had an ongoing infection or current or past CNS disease.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 6 Adverse Drug Reactions Occurring in ≥5% of Patients with Relapsed or Refractory DLBCL Treated with COLUMVI Monotherapy

System Organ Class (SOC) Adverse Drug Reaction	COLUMVI N=152	
	All Grades n (%)	Grade 3–4 n (%)
Blood and lymphatic system disorders		
Neutropenia[a]	52 (34.2)	36 (23.7)
Anaemia[b]	43 (28.3)	10 (6.6)
Thrombocytopenia[c]	36 (23.7)	9 (5.9)
Gastrointestinal disorders		
Abdominal pain[d]	15 (9.9)	0
Constipation	18 (11.8)	0
Diarrhoea	15 (9.9)	0
Nausea	14 (9.2)	0
General disorders and administration site conditions		
Fatigue[e]	27 (17.8)	2 (1.3)
Pyrexia	28 (18.4)	0
Oedema[f]	16 (10.5)	1 (0.7)
Immune system disorders		
Cytokine release syndrome[g]	94 (61.8)	6 (3.9)
Infections and infestations		
Viral infections[h]	16 (10.5)	4 (2.6[*])
Bacterial infections[i]	14 (9.2)	4 (2.6)
Upper respiratory tract infections[j]	8 (5.3)	0
Investigations[†]		
Alanine aminotransferase increased	12 (7.9)	4 (2.6)
Aspartate aminotransferase increased	11 (7.2)	4 (2.6)
Blood alkaline phosphatase increased	11 (7.2)	2 (1.3)
Gamma-glutamyltransferase increased	9 (5.9)	4 (2.6)
Metabolism and nutrition disorders		
Hypophosphataemia	27 (17.8)	9 (5.9)
Hypomagnesaemia	20 (13.2)	0
Hypocalcaemia	19 (12.5)	0
Hypochloraemia	9 (5.9)	0
Hypokalaemia	16 (10.5)	1 (0.7)
Hyponatraemia	12 (7.9)	1 (0.7)
Musculoskeletal and Connective Tissue Disorders SOC		

System Organ Class (SOC) Adverse Drug Reaction	COLUMVI N=152	
	All Grades n (%)	**Grade 3–4 n (%)**
Back Pain[k]	13 (8.6)	2 (1.3)
Arthralgia	9 (5.9)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Tumour flare	17 (11.2)	4 (2.6)
Nervous system disorders		
Headache	14 (9.2)	0
Skin and subcutaneous tissue disorders		
Rash[l]	21 (13.8)	2 (1.3)

* Grade 5 reactions reported include sepsis (1.3%), COVID-19 pneumonia (2.0%), COVID-19 (0.7%) and delirium (0.7%).

† The frequency of ADRs under Investigations are based on reported AEs by investigators and not based on evaluation of all reported laboratory results.

a Includes neutropenia and neutrophil count decreased.

b Includes anaemia, haemoglobin decreased, iron deficiency anaemia and anaemia of malignant disease.

c Includes thrombocytopenia and platelet count decreased.

d includes abdominal pain, abdominal discomfort and abdominal pain upper.

e includes fatigue, asthenia and malaise.

f includes oedema peripheral, oedema, localized oedema, face oedema, swelling, swelling face and peripheral swelling.

g Based on ASTCT consensus grading.

h Includes COVID-19, COVID-19 pneumonia, herpes zoster, ophthalmic herpes zoster, SARS-CoV-2 test positive and polymerase chain reaction positive.

i Includes vascular device infection, bacterial infection, Campylobacter infection, biliary tract infection bacterial, urinary tract infection bacterial, *Clostridium difficile* infection, Escherichia infection, peritonitis, infection, localized infection, clostridium difficile colitis and pneumococcal infection.

j Includes upper respiratory tract infection, sinusitis, nasopharyngitis, chronic sinusitis, and rhinitis.

k includes back pain and spinal pain.

l Includes rash, rash pruritic, rash maculo-papular, dermatitis, dermatitis acneiform, dermatitis exfoliative, erythema, and palmar erythema.

Description of selected adverse drug reactions from clinical trials

Cytokine Release Syndrome

In Study NP30179, any grade CRS (by ASTCT criteria) occurred in 61.8% of patients, with Grade 1 CRS being reported in 45.4% of patients, Grade 2 CRS in 12.5% patients, Grade 3 CRS in 2.6% of patients, and Grade 4 CRS in 1.3% of patients. 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 (98.9%), tachycardia (27.7%), hypotension (25.5%), chills (13.8%), and hypoxia (12.8%). Grade 3 or higher events associated with CRS included hypotension (3.2%), hypoxia (3.2%), pyrexia (3.2%), and tachycardia (2.1%).

CRS of any grade occurred in 53.9% of patients following the 2.5 mg dose of COLUMVI at Cycle 1 Day 8 with median time to onset of 13.4 hours (range: 2.5 to 51.8 hours); in 32.5% of patients following the 10 mg dose at Cycle 1 Day 15 with median time to onset of 28.7 hours (range: 7.7 to 126.0 hours); and in 28.4% of patients following the 30 mg dose at Cycle 2 Day 1 with median time to onset of 29.1 hours (range: 15.9 to 45.1 hours). CRS was reported in 1.1% of patients at Cycle 3 and in 2.4% of patients beyond Cycle 3.

Grade ≥ 2 CRS occurred in 12.8% of patients following the first COLUMVI dose (2.5 mg), with median time to onset of 10.5 hours (range: 2.5 to 14 hours) and median duration of 40.8 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 5.6% of patients, with median time to onset of 27.2 hours (range: 7.7 to 145.2 hours) and median duration of 30.9 hours (range: 3.1 to 227.2 hours). Grade ≥ 2 CRS following COLUMVI 30 mg dose at Cycle 2 Day 1 occurred in one patient (0.9%) with time to onset of 16.0 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.

Neutropenia

Neutropenia (including neutrophil count decreased) was reported in 34.2% of patients and severe neutropenia (Grade 3–4) was reported in 23.7% of patients. The median time to onset of the first neutropenia event was 22.5 days (range: 1 to 183 days). Prolonged neutropenia (lasting longer than 30 days) occurred in 7.9% of patients. The majority of patients with neutropenia (82.7%) were treated with G-CSF. Febrile neutropenia was reported in 2.6% of patients.

Serious Infections

In Study NP30179, serious infections were reported in 17.1% of patients. The most frequent serious infections reported in ≥ 2% patients were sepsis (3.9%), COVID-19 pneumonia (3.3%), and COVID-19 (2%). Infection-related deaths were reported in 3.9% of patients (due to sepsis, COVID-19 pneumonia, and COVID-19). Three patients (2%) experienced serious infections concurrently with Grade 3–4 neutropenia.

Tumour Flare

Tumour flare was reported in 11.2% of patients, including Grade 2 tumour flare in 4.6% of patients and Grade 3 tumour flare in 2.6% of patients. Tumour flare involved lymph nodes in the head and neck presenting with pain and lymph nodes in the thorax with symptoms of breathlessness due to development of pleural effusion. Most tumour flare events (16/17) occurred during Cycle 1, and no tumour flare events were reported beyond Cycle 2. The

median time to onset of tumour flare of any grade was 2 days (range: 1 to 16 days), and the median duration was 3.5 days (range: 1 to 35 days). No patients discontinued COLUMVI due to tumour flare.

Tumour Lysis Syndrome

TLS was reported in 2 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).

8.3 Less Common Clinical Trial Adverse Reactions

The ADRs which occurred in Study NP30179 with a frequency of <5% were:

Blood and lymphatic system disorders: Lymphopenia, including lymphocyte count decreased (3.9%); Febrile neutropenia, including neutropenic infection (3.3%).

Gastrointestinal disorders: Gastrointestinal haemorrhage, including large intestinal haemorrhage, and gastric haemorrhage (2.6%); Vomiting (2.6%) and Intestinal Perforation (0.7%).

Infections and infestations: Sepsis (3.9%); Lower respiratory tract infections, including bronchitis (2.0%); Pneumonia (2.6%); Urinary tract infection (1.3%); Fungal infections, including oesophageal candidiasis (0.7%).

Immune system disorders: Hypogammaglobulinemia (1.3%)

Investigations: Blood bilirubin increased (3.3%); Hepatic enzyme increased (1.3%).

Metabolism and nutrition disorders: Tumour lysis syndrome (1.3%).

Nervous system disorders: Somnolence (1.3%); Tremor, Myelitis, occurred concurrently with CRS (0.7%).

Psychiatric disorders: Confusional state (2.0%).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

The following table summarizes treatment-emergent shifts from baseline in laboratory abnormalities in Study NP30179.

Table 7 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	88.1	80.4
Decreased neutrophils	50.0	23.6
Decreased leukocytes	66.2	11.7
Chemistry		
Hypophosphatemia	68.1	26.4
Hyperglycemia	12.1	12.1
Hyperuricemia	20.9	20.9

a Percentages based on patients with a baseline and at least one post-baseline assessment for the specific laboratory parameter.

b N=143 for decreased lymphocytes; N=144 for decreased neutrophils; N=145 for decreased leukocytes; N=144 for hypophosphatemia; N=141 for hyperglycemia; N=139 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.

8.5 Post-Market Adverse Reactions

Not applicable.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No clinical drug–drug interaction studies have been performed with COLUMVI.

9.3 Drug-Behavioural Interactions

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 (see 7.1.1 **Pregnant Women**).

9.4 Drug-Drug Interactions

No drug interactions with COLUMVI are expected via the cytochrome P450 (CYP) enzymes, other metabolizing enzymes, or transporters.

A minimal physiologically-based pharmacokinetic model predicted some trends in the magnitude of potential drug interactions caused by the glofitamab-induced transient increase

in interleukin-6 (IL-6) levels which may impact CYP activity. The modelling suggested it was feasible that the magnitude of the suppressive effect of transient IL-6 increase on CYP activities is < 50%. In addition, it was predicted that the changes in exposures to substrates of CYP3A4, CYP1A2, and CYP2C9 might be less than or equal to twofold.

Based on these data, on initiation of COLUMVI therapy in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring for toxicity (e.g., warfarin) or for drug concentrations (e.g., cyclosporine) of the concomitant drug should be considered.

9.5 Drug-Food Interactions

No drug–food interaction studies have been performed with COLUMVI.

9.6 Drug-Herb Interactions

No drug–herb interaction studies have been performed with COLUMVI.

9.7 Drug-Laboratory Test Interactions

No drug–laboratory test interaction studies have been performed with COLUMVI.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

QT Prolongation: In Study NP30179, 10/152 patients who were exposed to glofitamab experienced a post-baseline QTc value > 450 ms. All but one were assessed as not of clinical significance by the investigator. No patients discontinued treatment due to QTc prolongation.

10.3 Pharmacokinetics

Non-compartmental analyses (NCA) 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).

Table 8 Summary of Glofitamab Pharmacokinetic Parameters in r/r DBLC Patients calculated by Non-Compartmental Analysis after Single Dose of 10 mg

	C_{max} (µg/ml)	T_{max} (hr)	Half-life (hr)	AUC_{inf} (hr*µg/ml)	CL (ml/hr)	Vz (ml)
Single dose (10 mg)	2.34 (46.1)	8.05 (3.92-26.2)	106 (23.9)	244 (54.8)	40.4 (54.3)	6180 (44.9)

All Parameters reported as Geometric Mean (Geo CV%) apart T_{max} reported as Median (Min-Max**)**

PK samples following the single dose of 10 mg were collected up to 336 h post dose

Absorption: COLUMVI is administered as an IV infusion. The NCA and PopPK Analysis showed a peak geometric mean concentration of 0.674 ug/mL of glofitamab (C_{max}) on Day 1 after the first infusion of 2.5 mg. The geometric mean C_{max} at the end of Cycle 2 following the step-up dosing of 2.5, 10 and 30 mg, was estimated via PopPK model to be 7.67 ug/mL.

Distribution: Following IV administration, the PopPK model estimated the central volume of distribution parameter to be 3.33 L, and the peripheral volume of distribution parameter to be 2.18 L, with an intercompartmental clearance of 0.674 L/day.

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

Elimination: The NCA analysis estimated a half-life that ranged from 4 to 8 days across the *doses tested. The glofitamab serum concentration–time data are described by a population* pharmacokinetic model with two compartments and both time-independent clearance parameter and a time-varying clearance parameter.

The time-independent clearance parameter was estimated as 0.602 L/day and the initial time-varying clearance parameter as 0.396 L/day, with an exponential decay over time (K_{des} ~ 0.445/day). The estimated transition from the non-linear phase to the linear phase was estimated as 1.56 days, after which the effective half-life in the linear phase can be approximated to a typical linear effective half-life of 6.54 days (95% CI: 3.74 - 9.41) based on the empirical Bayes estimates in the current patient population.

Special Populations and Conditions

Pediatrics: No studies have been conducted to investigate the pharmacokinetics of glofitamab in pediatric patients.

Geriatrics: 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.

Hepatic Insufficiency: No formal pharmacokinetic study has been conducted in patients with moderate and severe hepatic impairment.

Renal Insufficiency: Creatinine clearance is not associated with the linear or time varying clearance parameters in the model for glofitamab. The pharmacokinetic response of COLUMVI has not been studied in patients with severe renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

Vials

Store at 2 °C to 8 °C. Keep the vial in the outer carton in order to protect it from light. Do not freeze. Do not shake.

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 64 hours and at 25°C for up to 4 hours prior to administration, followed by a maximum infusion time of 8 hours.

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.

12 SPECIAL HANDLING INSTRUCTIONS

Do not freeze. Do not shake.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

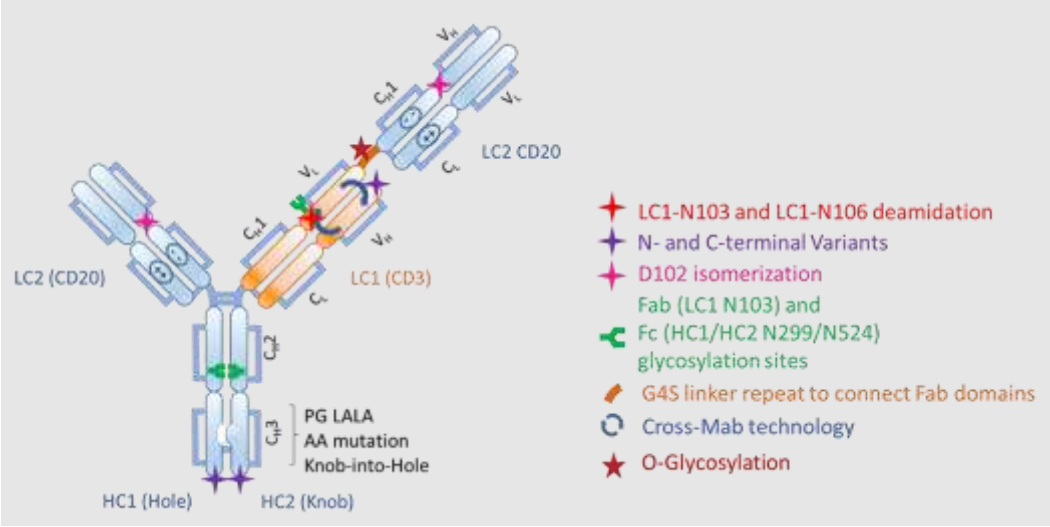
Drug Substance

Proper name: glofitamab

Chemical name: Recombinant anti-human CD20 and anti-human CD3 monoclonal antibody

Molecular formula and molecular mass: $C_{8632}H_{13326}N_{2296}O_{2701}S_{58}$; Approx. 194 kDa (peptide chains only, without heavy chain C terminal lysine residues, with N terminal glutamines converted into pyroglutamates due to cyclization)

Structural formula:



Physicochemical properties: COLUMVI is a sterile, preservative-free, colorless concentrate for solution for infusion.

Product characteristics: Glofitamab is a heterogeneous protein having the intended primary structure, post-translational modifications, and other characteristics of a recombinant IgG1 derived from CHO cells.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Relapsed or Refractory DLBCL

An open-label, phase I/II, multicenter, multi-cohort trial (NP30179) was conducted to evaluate COLUMVI monotherapy in patients with relapsed or refractory B-cell lymphoma. In the single-arm 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. Patients with FL3b and/or Richter's transformation were not eligible. The study excluded patients with prior allogeneic hematopoietic stem cell transplant, previous or active central nervous system lymphoma, active infections, previous history of active autoimmune disease requiring immunosuppressive therapy, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, creatinine clearance (CrCL) < 50 mL/min, or hepatic transaminases $> 3 \times$ ULN.

Following pre-treatment with obinutuzumab 1000 mg 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 4.1 Dosing Considerations). The duration of each cycle was 21 days. Patients received a median of 5 cycles of COLUMVI treatment (range: 1 to 12 cycles).

The baseline demographic and disease characteristics were: median age 66 years (range: 21 to 90 years); 69.4% male; 74.1% white, 5.6% Asian, and 0.9% Black or African American; 5.6% Hispanic or Latino; and ECOG performance status of 0 (47.2%) or 1 (50.0%). Most patients (73.1%) had DLBCL not otherwise specified, 15.7% had DLBCL arising from follicular lymphoma, 5.6% had high-grade B-cell lymphoma (HGBCL), and 5.6% had PMBCL.

The median number of prior lines of therapy was 3 (range: 2 to 7), with 40.7% of patients having received 2 prior lines and 59.3% having received 3 or more prior lines of therapy. Almost all patients (99.1%) had received prior chemotherapy and anti-CD20 monoclonal antibody therapy; 34.3% of patients had received prior CAR T-cell therapy; and 14.8% of patients had received autologous stem cell transplant. Most patients (90.7%) had refractory disease, 59.3% patients had primary refractory disease, and 84.3% of patients were refractory to their last prior therapy.

The overall median duration of follow-up was 9 months (range: 0 to 16 months). Median duration of follow-up from the date of first response (CR or ORR) per Independent Review Committee (IRC) assessment was 7.6 months (range: 0 to 14 months).

The primary efficacy outcome measure was complete response (CR) rate as assessed by the IRC using 2014 Lugano response criteria. The key secondary efficacy outcome measures

included IRC assessed overall response rate (ORR), duration of response (DOR), and duration of complete response (DOCR). The primary and key secondary efficacy endpoints are shown in Table 9.

Table 9 Summary of efficacy in patients with relapsed or refractory DLBCL as assessed by an independent review committee (Study NP30179, Cohort D3)

Efficacy Endpoints	COLUMVI N=108
Primary Endpoint	
IRC-Assessed Complete Response	
Patients with CR, n (%)	38 (35.2)
95% CI	[26.24, 44.96]
Secondary Endpoints	
Overall Response Rate	
Patients with CR or PR, n (%)	54 (50.0)
95% CI	[40.22, 59.78]
Partial Response (PR), n (%)	16 (14.8)
95% CI	[8.71, 22.94]
Duration of Complete Response	
Median DOCR†, months [95% CI]	14.4 [NE] [a]
Range, months	0[b]-14
9-month DOCR, % [95% CI][c]	83.8 [68.92, 98.65]
Duration of Response	
Median DOR‡, months [95% CI]	14.4 [7.3, NE] [a]
Range, months	0[b]-14
9-month DOR, % [95% CI][c]	60.9 [46.49, 75.38]

CI=confidence interval; INV=Investigator; IRC=Independent Review Committee; N/A=not applicable; NE=not estimable.
†DOCR is defined as the date of first complete response until disease progression or death due to any cause.
‡DOR is defined as the date of first response (PR or CR) until disease progression or death due to any cause.
a IRC-assessed median DOCR and median DOR were immature at the time of analysis but were reached at 14.4 months when the last patient at risk experienced an event.
b Censored observations.
c Event-free rates based on Kaplan-Meier estimates
Note: 95% CI for response rates computed using the Clopper-Pearson method; 95% CI for median computed using the Brookmeyer and Crowley method

The time to first complete response was 42 days (95% CI: 41, 42).

Post CAR-T Subgroup

Among patients who have previously received CAR-T cell therapy, the complete response rate was 31.6% (12/38) and the overall response rate was 44.7% (17/38).

14.3 Immunogenicity

As with all therapeutic proteins, there is a potential immunogenicity.

No patients developed treatment-emergent anti-drug antibodies (ADA) against COLUMVI. The majority of patients (95.9%, N=370) who received COLUMVI monotherapy in Study NP30179 were negative for ADAs at baseline and remained negative throughout treatment with COLUMVI. Three patients (0.8%) were ADA-positive at baseline and at one or more post-dose timepoints.

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 COLUMVI with the incidence of antibodies to other products may be misleading.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicity: A 2-week GLP repeat-dose toxicity study was conducted in cynomolgus monkeys to evaluate the toxicity of IV administration of glofitamab (0.01, 0.03 and 0.1 mg/kg/dose). 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.

In a 4-week repeat-dose toxicity study with step-up dosing 0.03/0.1/0.1 or 0.3 mg/kg and then dosing every other day, acute phase reactions (increased CRP, fibrinogen, triglycerides, and bilirubin; and mildly decreased albumin and cholesterol) and changes in leukocytes occurred and were considered secondary to cytokine release and activation-induced margination. Minimal to mild mononuclear cell infiltrates in some organs (heart, salivary gland, kidney, perivascular spaces of meninges, choroid plexus, and parenchyma of the brain - some with minimal gliosis) were increased in incidence among glofitamab-dosed animals as compared to controls.

Administration of glofitamab was also associated with sustained (beginning as early as 30 minutes post-dose up to 20 hours post-dose), dose-dependent increases in heart rate (decreased RR interval), with similar and rate-related decreases in PR and QT intervals. Effects were less pronounced after the second glofitamab dose. There were glofitamab-related increases in average body temperature 6 hours post-dose on Day 1 and 24 hours post-dose on

Day 15 of the 4-week study. Increases in heart rate and body temperature are considered to be related to increases in cytokine levels following dosing. No test article-related findings on respiration, and no clinical signs specifically related to effects on CNS were identified.

In the absence of obinutuzumab, the maximum tolerated IV doses were 0.03 mg/kg on Day 1 followed by 0.1 mg/kg on Day 8 (step-up dosing). In the absence of obinutuzumab pretreatment and because of high clearance in monkeys, lower glofitamab exposures were achieved in repeat-dose toxicity studies compared to the clinical setting. Pre-treatment with obinutuzumab resulted in the attenuation of 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.

Carcinogenicity: No carcinogenicity studies have been performed to establish the carcinogenic potential of COLUMVI.

Genotoxicity: No studies have been performed to establish the mutagenic potential of COLUMVI.

Reproductive and Developmental Toxicology: 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.

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

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]COLUMVI®
glofitamab for injection
Concentrate for solution for intravenous infusion

Read this carefully before you start taking **COLUMVI**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **COLUMVI**.

Serious Warnings and Precautions

- Cytokine Release Syndrome (CRS) has occurred in patients receiving COLUMVI. Call your healthcare provider or get emergency medical help right away if you experience CRS. Symptoms include fever (38 °C or higher), fast or irregular heartbeat, low blood pressure, feeling dizzy or lightheaded, chills, shortness of breath.

What is COLUMVI used for?

For the following indication(s) COLUMVI has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

COLUMVI is used to treat adults with a cancer called "diffuse large B-cell lymphoma" (DLBCL) who cannot take CAR-T cell treatment or who have already used CAR-T cell treatment. It is used when:
- the cancer has come back (relapsed) or
- the cancer did not respond to previous treatments (refractory).

Diffuse large B-cell lymphoma is a cancer of a part of your immune system (the body's defenses). It affects a type of white blood cell called 'B cells'. In DLBCL, B cells multiply in an uncontrolled manner and build up in your tissues.

What is a Notice of Compliance with Conditions (NOC/c)?
A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does COLUMVI work?
COLUMVI is a cancer medicine that contains the active substance glofitamab. COLUMVI binds to the surface of these cancerous B cells and also to the surface of T cells (another type of white blood cell). This binding on two targets activates T cells which causes them to multiply, and causes the rapid breakdown of the cancerous B cells.

What are the ingredients in COLUMVI?

Medicinal ingredients: glofitamab

Non-medicinal ingredients: L-histidine; L-histidine hydrochloride, monohydrate; L-methionine; polysorbate 20; D-sucrose; water for injection

COLUMVI comes in the following dosage forms:
Concentrate for solution for infusion. Each vial contains either 2.5 mg (in 2.5 mL) or 10 mg (in 10 mL) of glofitamab. Each mL contains 1 mg of glofitamab.

Do not use COLUMVI if:
- you are allergic to glofitamab or any of the other ingredients of COLUMVI

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take COLUMVI. Talk about any health conditions or problems you may have, including if you:
- you have an infection
- you have had a long-lasting infection (chronic) or an infection which keeps coming back (recurring)
- you have or had any kidney, liver, or heart problems
- have or had any type of neurological disease

Pregnancy and contraception
- Tell your doctor if you are pregnant, think you might be pregnant, or are planning to become pregnant.
- You should not be given COLUMVI if you are pregnant. This is because it is possible that COLUMVI could harm your unborn baby.
- If you could become pregnant, you must use effective contraception while you are being treated with COLUMVI and for 2 months after the last dose.
- If you become pregnant while you are being treated with COLUMVI tell your doctor immediately.

Breast-feeding
Do not breast-feed while receiving COLUMVI and for at least 2 months after the last dose. This is because it is not known if this medicine can pass into breast milk and harm your baby.

Other warnings you should know about:
- **Children and adolescents (< 18 years):** COLUMVI should not be used in children or adolescents under 18 years of age. This is because COLUMVI has not been studied in this age group.
- **Ability to drive and use machines:** COLUMVI mayaffect your ability to drive, cycle, or use any tools or machines. If you experience any symptoms that might make it difficult to drive

(e.g.,symptoms of cytokine release syndrome such as fever, fast heartbeat, feeling dizzy or lightheaded, chills or shortness of breath) – do not drive, cycle, or use any tools or machines until you feel better.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take COLUMVI:

You will be given COLUMVI under the supervision of a doctor experienced in cancer treatment, in a hospital or clinic.

Medicines given before COLUMVI treatment

- **Seven days before starting COLUMVI treatment**, you will be given another medicine, obinutuzumab, to deplete the B cells in your blood in order to prevent cytokine release syndrome.
- **During the 30 to 60 minutes before you are given COLUMVI**, you may be given other medicines (pre-medication) to help reduce reactions associated with cytokine release syndrome. These medicines may include:
  - A corticosteroid such as dexamethasone
  - A fever-reducing medicine such as paracetamol
  - An antihistamine such as diphenhydramine

Usual dose:
You will be given 12 treatment cycles of COLUMVI.

- Each cycle lasts 21 days.

Your doctor will begin COLUMVI treatment with a low-dose and will gradually increase it to the full dose.

A typical schedule is shown below.

Cycle 1: This will include a pre-treatment and 2 low doses of COLUMVI during the 21 days:

- Day 1 – Pre-treatment with obinutuzumab
- Day 8 – starting low COLUMVI dose of 2.5 mg
- Day 15 – the second low COLUMVI dose of 10 mg

Cycle 2 to Cycle 12: During these cycles, you will only be given one dose every 21 days:

- Day 1 – full COLUMVI dose of 30 mg

COLUMVI is given as a drip into a vein (an intravenous infusion). Your doctor will adjust the time required for infusion depending on how you respond to treatment.

- Your first infusion will be given over 4 hours. Your doctor will monitor you carefully during the first infusion and for 10 hours after completion of infusion. This is to watch for any signs or symptoms of cytokine release syndrome.
- For following infusions, your doctor may require to monitor you after completion of infusion. This will be necessary if you have had moderate or severe CRS with your previous dose.
- If you do not have any cytokine release syndrome after 3 doses, your doctor may give the following infusions over 2 hours.

Overdose:

If you think you have taken too much COLUMVI, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss any appointments, call you healthcare provider as soon as possible to reschedule your appointment.

What are possible side effects from using COLUMVI?
These are not all the possible side effects you may have when taking COLUMVI. If you experience any side effects not listed here, tell your healthcare professional.

Very common (may affect more than 1 in 10 people):
- reduced levels in blood tests of:
  - neutrophils (a type of white blood cell), which may cause fever or any symptoms of an infection (symptoms include: chills, sore throat, shortness of breath, nasal congestion, diarrhea)
  - red blood cells (anemia), which may cause tiredness, feeling unwell, and pale skin
  - platelets (a type of blood cell), which may cause unusual bruising or bleeding
- fever
- low levels in blood tests of:
  - phosphate, magnesium, calcium, or potassium
- rash
- constipation

Common (may affect up to 1 in 10 people):
- diarrhea
- feeling sick (nausea)
- headache
- low sodium levels in blood tests, which may cause tiredness, muscle twitching, or cramps
- increased levels in blood tests of liver enzymes and bilirubin (yellow substance in blood) which may cause yellowing of skin or eyes and dark urine
- viral infections, such as lung infection and shingles
- bacterial infections, such as urinary tract infection and infection in or around the stomach
- respiratory tract infections, such as runny nose, sore throat, sinus infections, and chest colds
- lung infection (pneumonia) which may cause fever, cough, and difficulty breathing
- vomiting
- confusion
- trembling
- sleepiness

Uncommon (may affect less than 1 in 100 people):
- fungal infection

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Cytokine release syndrome: fever, fast heartbeat, feeling dizzy or lightheaded, chills, shortness of breath		✓	
Tumour Flare: tender swollen lymph nodes, chest pain, cough, inability to breathe easily, pain at the site of the tumour		✓	
COMMON			
Severe infections: fever, chills, difficulty breathing, burning pain when passing urine, confusion		✓	
Tumour Lysis Syndrome: kidney problems (weakness, shortness of breath, fatigue, feeling confused), heart problems (irregular heartbeat or fluttering of the heart or a faster or slower heartbeat), vomiting, diarrhea, tingling in the mouth, hands or feet, muscle cramps		✓	
Gastrointestinal hemorrhage (bleeding in the stomach or gut): black stools or blood in vomit		✓	
UNCOMMON			
Myelitis (swelling of the spinal cord): muscle weakness or numbness		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
COLUMVI will be stored by your healthcare professionals at the hospital or clinic. The storage details are as follows:

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C to 8 °C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help to protect the environment.

If you want more information about COLUMVI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drugproduct-database.html; the manufacturer's website (www.rochecanada.com), or by calling 1-888- 762-4388.

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