Professional Information

Cytokine Release Syndrome (CRS), including serious or fatal reactions, can occur in patients receiving Glofitimab. Premedicate before each dose, and initiate treatment with the Glofitamab step-up dosing schedule to reduce the risk of CRS. Withhold Glofitamab until CRS resolves or permanently discontinue based on severity (see section 4.2).

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

COLUMVI 2,5 mg/2,5 mL, Concentrate for solution for infusion

COLUMVI 10 mg/10 mL, Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COLUMVI contains glofitamab as the active substance

COLUMVI 2,5 mg/2,5 mL concentrate for solution for infusion

Each vial contains 2,5 mg glofitimab per 2,5 mL of liquid concentrate, corresponding to a concentration of 1 mg/mL before dilution.

COLUMVI 10 mg/10 mL concentrate for solution for infusion

Each vial contains 10 mg glofitimab per 10 mL of liquid concentrate, corresponding to a concentration of 1 mg/mL before dilution.

Contains sugar (sucrose) 205,4 mg for 2,5 mg/2,5 mL vial and 821,5 mg for 10 mg/10 mL vial

For a full list of excipients, see section 6.1

Glofitamab is a recombinant humanized immunoglobulin G1 monoclonal antibody, a antineoplastic agent.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

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

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) and primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of systemic therapy.

4.2 Posology and method of administration

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

COLUMVI therapy should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients and who has access to appropriate medical support to manage severe reactions associated with cytokine release syndrome (CRS). At least 1 dose of tocilizumab for use in the event of CRS must be available prior to COLUMVI infusion at Cycles 1 and 2. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose must be ensured. See Section 4.4 Special warnings and precautions for use.

Posology

Pre-treatment with Obinutuzumab

All patients must receive a single 1000 mg dose of obinutuzumab on Cycle 1 Day 1 (7 days prior to initiation of COLUMVI treatment); see Table 2 and Delayed or Missed Doses. This is to deplete circulating B cells and thereby reduce the frequency and severity of CRS.

Obinutuzumab should be administered as an intravenous infusion at 50 mg/h. The rate of infusion can be escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h.

Refer to the obinutuzumab prescribing information for complete information on premedication, preparation, administration, and management of adverse reactions of obinutuzumab.

Premedication and Prophylactic Medications

Cytokine release syndrome prophylaxis

COLUMVI should be administered to well-hydrated patients. Premedication to reduce the risk of CRS (see Section 4.4) is outlined in Table 1.

Table 1 Premedication Before COLUMVI Infusion to Reduce the Risk of Cytokine Release Syndrome

Treatment Cycle (Day)	**Patients requiring premedication**	**Premedication**	**Administration**
Cycle 1 (Day 8, Day 15); Cycle 2 (Day 1); Cycle 3 (Day 1)	All patients	Intravenous glucocorticoid[a]	Completed at least 1 hour prior to COLUMVI infusion.
		Oral analgesic / anti-pyretic[b]	At least 30 minutes before COLUMVI infusion.
		Anti-histamine[c]	
All subsequent infusions	All patients	Oral analgesic / anti-pyretic[b]	At least 30 minutes before COLUMVI infusion.
		Anti-histamine[c]	
	Patients who experienced CRS with previous dose	Intravenous glucocorticoid[a]	Completed at least 1 hour prior to COLUMVI infusion.
		Oral analgesic / anti-pyretic[b]	At least 30 minutes before COLUMVI infusion.
		Anti-histamine[c]	

a 20 mg dexamethasone or 100 mg prednisone/prednisolone or 80 mg methylprednisolone.

b For example, 1000 mg acetaminophen/paracetamol.

c For example, 50 mg diphenhydramine.

Recommended Dosage

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

COLUMVI Dose Step-up Schedule

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

Table 2 COLUMVI Monotherapy Dose Step-Up Schedule for Patients with Relapsed or Refractory DLBCL

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

a Refer to *Pre-treatment with obinutuzumab* described above.

b For patients who experience CRS with their previous dose of COLUMVI, the duration of infusion may be extended up to 8 hours (see Table 3 and Section 2.4.1 *Warnings and Precautions*).

c 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.

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.

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).

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).

Management of Cytokine Release Syndrome

Cytokine release syndrome should be identified based on the clinical presentation (see Section *4.4*). 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 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 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, 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).

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.

Special Populations

Geriatric use

No dose adjustment of COLUMVI is required in patients ≥ 65 years of age. (*See Section 5.2)*

Renal Impairment

No dose adjustment of COLUMVI is required in patients with mild or moderate renal impairment. COLUMVI has not been studied in patients with severe renal impairment. (See *Section 5.2).*

Hepatic Impairment

No specific studies in patients with hepatic impairment have been conducted with COLUMVI. (See *Section 5.2)*

Paediatric use

The safety and efficacy of COLUMVI in paediatric patients have not been established.

Method of Administration of COLUMVI

Preparation

COLUMVI must be diluted by a healthcare professional using aseptic technique, prior to intravenous administration. See *Section 6.6*.

Administration

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

4.3 Contraindications

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

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

4.4 Special Warnings and Precautions for Use

General

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

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

Cytokine Release Syndrome

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

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

CRS of any grade (ASTCT criteria) occurred in 61,8 % of patients in study NP30179. Grade 3 or 4 CRS occurred in 3,9 % of patients. There were no fatal cases of CRS. Most CRS events occurred following the first dose of COLUMVI. See Section 4.8, under *Description of adverse reactions*.

To reduce the occurrence of CRS, patients must be pre-treated with obinutuzumab, 7 days prior to initiation of COLUMVI, and should be premedicated with an anti-pyretic, anti-histamine, and a glucocorticoid. See *Section 4.2*.

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

Patients must be monitored during all COLUMVI infusions and for at least 10 hours after completion of the first infusion. For complete information on monitoring, see *Section 4.2*. The prescriber must counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.

Patients should be evaluated for other causes of fever, hypoxia, and hypotension, such as infections or sepsis. CRS should be managed based on the patient's clinical presentation and according to the CRS management guidance provided in Table 3 (see *Section 4.2*).

Serious Infections

Serious infections (such as sepsis and pneumonia) 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. 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 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 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.

Drug Abuse and Dependence

COLUMVI does not have the potential for abuse and dependence.

4.5 Interaction with other medicines and other forms of interaction

No clinical drug-drug interaction studies have been performed.

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

Physiologically based pharmacokinetic modelling was performed to estimate the magnitude of potential drug interactions caused by the COLUMVI-induced transient increase in interleukin-6 (IL-6) levels which may impact CYP activity. The modelling demonstrates that the magnitude of the suppressive effect of transient IL-6 increase on CYP activities is < 50 %. In addition, the changes in exposures to substrates of CYP3A4, CYP1A2, and CYP2C9 are expected to 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.

4.6 Fertility, pregnancy and lactation

Contraception in females

Women of childbearing potential should use highly effective contraceptive methods during treatment and for at least 2 months following the last dose of COLUMVI.

Labour and Delivery

The safe use of COLUMVI during labour and delivery has not been established

Pregnancy

Women of childbearing 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 foetal B-cell depletion when administered to a pregnant woman. 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.

Lactation

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical Trials

a. Summary of the Safety Profile

COLUMVI monotherapy

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

The adverse drug reactions described below were identified from 152 patients with relapsed or refractory DLBCL, who had received at least two prior lines of systemic therapy, including DLBCL arising from follicular lymphoma, high-grade B-cell lymphoma (HGBCL), and PMBCL, treated with COLUMVI monotherapy in study NP30179, an open-label multicentre clinical trial.

b. Tabulated list of adverse reactions

Adverse medicine reactions from clinical trials (Table 4) are listed by MedDRA system organ class. The corresponding frequency category for each adverse medicine reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 4 Adverse Drug Reactions Occurring in Patients with Relapsed or Refractory DLBCL Treated with COLUMVI Monotherapy

System Organ Class **Adverse Reaction**	**COLUMVI** **N=152**		
	All Grades **(frequency category)**	**All Grades** **(%)**	**Grade 3–4** **(%)**
Immune system disorders			
Cytokine release syndrome[a]	Very common	61,8	3,9
Blood and lymphatic system disorders			
Neutropenia[b]	Very common	34,2	23,7
Anaemia[c]	Very common	28,3	6,6
Thrombocytopenia[d]	Very common	23,7	5,9
Lymphopenia[e]	Common	3,9	3,9
Febrile neutropenia[f]	Common	3,3	2,6
General disorders and administration site conditions			

Pyrexia	Very common	18,4	0
Metabolism and nutrition disorders			
Hypophosphataemia	Very common	17,8	5,9
Hypomagnesaemia	Very common	13,2	0
Hypocalcaemia	Very common	12,5	0
Hypokalaemia	Very common	10,5	0,7
Hyponatraemia	Common	7,9	0,7
Tumour lysis syndrome	Common	1,3	1,3
Skin and subcutaneous tissue disorders			
Rash[g]	Very common	13,8	1,3
Gastrointestinal disorders			
Constipation	Very common	11,8	0
Diarrhoea	Common	9,9	0
Nausea	Common	9,2	0
Gastrointestinal haemorrhage[h]	Common	2,6	2,6
Vomiting	Common	2,6	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour flare	Very common	11,2	2,6
Nervous system disorders			
Headache	Common	9,2	0
Somnolence	Common	1,3	0,7
Tremor	Common	1,3	0
Myelitis[i]	Uncommon	0,7	0,7
Infections and infestations			
Viral infections[j]	Common	8,6	2,6*
Bacterial infections[k]	Common	6,6	2,0
Upper respiratory tract infections[l]	Common	5,3	0

Sepsis	Common	3,9	2,6*
Lower respiratory tract infections[m]	Common	2,0	0
Pneumonia	Common	2,6	1,3
Urinary tract infection	Common	1,3	0
Fungal infections[n]	Uncommon	0,7	0
Investigations			
Alanine aminotransferase increased	Common	7,9	2,6
Aspartate aminotransferase increased	Common	7,2	2,6
Blood alkaline phosphatase increased	Common	7,2	1,3
Gamma-glutamyltransferase increased	Common	5,9	2,6
Blood bilirubin increased	Common	3,3	0,7
Hepatic enzyme increased	Common	1,3	1,3
Psychiatric disorders			
Confusional state	Common	2,0	0

* Grade 5 reactions reported include sepsis (1,3 %), COVID-19 pneumonia (2,0 %), and COVID-19 (0,7 %).

a Based on ASTCT consensus grading.

b Includes neutropenia and neutrophil count decreased.

c Includes anaemia and haemoglobin decreased.

d Includes thrombocytopenia and platelet count decreased.

e Includes lymphopenia and lymphocyte count decreased.

f Includes febrile neutropenia and neutropenic infection.

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

h Includes gastrointestinal haemorrhage, large intestinal haemorrhage, and gastric haemorrhage.

i Myelitis occurred concurrently with CRS.

j Includes COVID-19, COVID-19 pneumonia, herpes zoster, and ophthalmic herpes zoster.

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

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

m Includes lower respiratory tract infection and bronchitis.

n Includes oesophageal candidiasis.

c. Description of selected adverse reactions

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.

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.

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.

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 was reported involving lymph nodes in the head and neck presenting with pain and involving lymph nodes in the thorax with symptoms of breathlessness due to development of pleural effusion. Most tumour flare events (16/17) occurred during Cycle 1, and no tumour flare events were reported beyond Cycle 2. The median time to onset of tumour flare of any grade was 2 days (range: 1 to 16 days), and the median duration was 3,5 days (range: 1 to 35 days). No patients discontinued COLUMVI due to tumour flare.

Tumour Lysis Syndrome

TLS was reported in 2 patients (1,3 %) and was Grade 3 in severity in both cases. The median time to TLS onset was 2 days, and the median duration was 4 days (range: 3 to 5 days).

Laboratory Abnormalities

Table 5 summarises treatment-emergent shifts from baseline in laboratory abnormalities in study NP30179.

Table 5 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]
Haematology		
Decreased lymphocytes	88,1	80,4
Decreased neutrophils	50,0	23,6
Decreased leukocytes	66,2	11,7
Chemistry		
Hypophosphatemia	68,1	26,4
Hyperglycaemia	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 hyperglycaemia; 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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, monoclonal antibody (recombinant humanized immunoglobulin G1)

ATC code: L01FX28

Mechanism of action:

COLUMVI 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, COLUMVI mediates the formation of a 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.

Clinical efficacy and safety

Relapsed or Refractory DLBCL

The efficacy of COLUMVI monotherapy was evaluated in study NP30179, an open-label multicentre trial, in 108 patients with relapsed or refractory DLBCL who had received at least two prior lines of systemic therapy. The study excluded patients with prior allogeneic hematopoietic stem cell transplant, previous or active central nervous system lymphoma, ECOG performance status ≥ 2, creatinine clearance (CrCL) < 50 mL/min, or hepatic transaminases $> 3 \times$ ULN.

Following pre-treatment with obinutuzumab at Cycle 1 Day 1, patients received 2.5 mg of COLUMVI at Cycle 1 Day 8, 10 mg of COLUMVI at Cycle 1 Day 15, and 30 mg of COLUMVI at Cycle 2 Day 1 as per the step-up dosing schedule. Patients continued to receive 30 mg of COLUMVI on Day 1 of Cycles 3 to 12. 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 % 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 (47,2 %) or 1 (50,0 %). Most patients (73,1 %) had DLBCL not otherwise specified, 15.7% had DLBCL transformed from follicular lymphoma, 5,6 % had 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 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 IRC using 2014 Lugano criteria. The secondary efficacy outcome measures included Investigator (INV)-assessed CR, and overall response rate (ORR), duration of response (DOR), duration of complete response (DOCR), time to first response (TFOR), time to first complete response (TFCR), overall survival (OS), and progression-free survival (PFS), as assessed by IRC and by INV. Efficacy results are summarized in **Table 6**.

Table 6 Efficacy in Patients with Relapsed or Refractory DLBCL Treated with COLUMVI Monotherapy

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		
INV-Assessed Complete Response		
Patients with CR, n (%)	36 (33,3)	
95 % CI	[24,55, 43,05]	
Overall Response Rate	*IRC-Assessed*	*INV-Assessed*
Patients with CR or PR, n (%)	54 (50,0)	58 (53,7)
95 % CI	[40,22, 59,78]	[43,85, 63,35]
Partial Response (PR), n (%)	16 (14,8)	22 (20,4)
95 % CI	[8,71, 22,94]	[13,23, 29,20]
Duration of Complete Response	*IRC-Assessed*	*INV-Assessed*
Median DOCR, months [95 % CI]	14,4 [NE] [a]	NE [NE]
Range, months	0[b]–14	0[b]–14[b]
9-month DOCR, % [95 % CI][c]	83,8 [68,92, 98,65]	73,8 [56,22, 91,45]
Duration of Response	*IRC-Assessed*	*INV-Assessed*
Median DOR, months [95 % CI]	14,4 [7,3, NE] [a]	7,9 [3,8, NE]
Range, months	0[b]–14	0[b]–14[b]
9-month DOR, % [95 % CI][c]	60,9 [46,49, 75,38]	49,9 [35,19, 64,59]
Time to First Response	*IRC-Assessed*	*INV-Assessed*
Median TFOR, days [95 % CI]	42 [41, 42]	41 [40, 42]

Time to First Complete Response	*IRC-Assessed*	*INV-Assessed*
Median TFCR, days [95 % CI]	42 [41, 48]	42 [42, 48]
Progression-Free Survival	*IRC-Assessed*	*INV-Assessed*
Patients with event, n (%)	65 (60,2)	69 (63,9)
Median PFS, months [95 % CI]	3,7 [3,3, 5,7]	3,4 [2,8, 4,9]
6-month PFS, % [95 % CI][c]	39,7 [29,98, 49,39]	34,7 [25,21, 44,10]
9-month PFS, % [95 % CI][c]	34,4 [24,74, 44,14]	31,9 [22,51, 41,36]
12-month PFS, % [95 % CI][c]	34,4 [24,74, 44,14]	27,1 [16,95, 37,25]
Overall Survival	*IRC-Assessed*	*INV-Assessed*
Patients with event, n (%)	N/A	53 (49,1)
Median OS, months [95 % CI]	N/A	8,9 [6,9, NE]
6-month OS, % [95 % CI][c]	N/A	67,1 [57,81, 76,31]
9-month OS, % [95 % CI][c]	N/A	49,2 [39,06, 59,32]
12-month OS, % [95 % CI][c]	N/A	47,8 [37,58, 57,99]

CI=confidence interval; INV=Investigator; IRC=Independent Review Committee; N/A=not applicable; NE=not estimable.

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.

Patient Reported Outcomes

Study NP30179 evaluated patient-reported outcomes of COLUMVI treatment. Patients reported moderate to moderate-high levels at baseline of Physical Functioning, Role Functioning, and Global Health Status/QoL and low levels of fatigue (weakness, tiredness) as measured by the EORTC QLQ-C30 at baseline which were maintained during treatment. Most patients indicated that symptoms commonly associated with COLUMVI treatment (constipation, diarrhoea, and nausea) were not present or were of low severity if present, and maintained during treatment. Patients reported low

levels of lymphoma symptoms at baseline as measured by the FACT-Lym Lymphoma scale which were maintained during treatment.

Immunogenicity

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

No patients developed treatment-emergent antidrug 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.

5.2 Pharmacokinetic Properties

Non-compartmental analyses indicate that COLUMVI serum concentration reaches the maximal level (C_{max}) at the end of infusion and declines in a bi-exponential fashion. COLUMVI exhibits linear and dose-proportional pharmacokinetics over the dose range studied (0,005 to 30 mg) and is independent of time.

Absorption

COLUMVI is administered as an IV infusion. Peak concentration of COLUMVI (Cmax) was reached at the end of the infusion.

Distribution

Following IV administration, the central volume of distribution was 3,33 L, which is close to total serum volume. The peripheral volume of distribution was 2,18 L.

Metabolism

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

Elimination

The COLUMVI 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 0,602 L/day and the initial time-varying clearance pathway as 0,396 L/day, with an exponential decay over time (Kdes ~ 0,445/day). The estimated decay half-life from the initial total clearance value to the time-independent clearance only was estimated as 1,56 days.
The effective half-life in the linear phase (i.e., after the contribution of time-varying clearance has collapsed to a negligible amount) can be approximated to a typical linear effective half-life of 6,54 days (95% CI: 3,74 - 9,41) based on the population pharmacokinetic analysis.

Pharmacokinetics in Special Populations

Paediatric Population

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

Geriatric Population

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

Renal impairment

Population pharmacokinetic analyses showed that creatinine clearance does not affect the pharmacokinetics of COLUMVI. The pharmacokinetics of COLUMVI in patients with mild or moderate renal impairment were similar to those in patients with normal renal function. No dose adjustment is required for patients with mild or moderate renal impairment. COLUMVI has not been studied in patients with severe renal impairment.

Hepatic impairment

No formal pharmacokinetic study has been conducted in patients with hepatic impairment. Population pharmacokinetic analysis showed that the pharmacokinetics of COLUMVI are not affected in patients with mild hepatic impairment.

5.3 Preclinical safety data

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.

Impairment of Fertility

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

Reproductive Toxicity

No reproductive toxicity studies in animals have been performed to evaluate the effect of COLUMVI. Based on low placental transfer of antibodies during the first trimester, the mechanism of action of COLUMVI (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 foetal loss. Transient CRS associated with COLUMVI administration may also be harmful to the foetus.

Other

In a study in cynomolgus monkeys, 3 out of 7 animals with severe CRS after a single intravenous dose of COLUMVI (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. Inflammatory cell infiltrates were likely secondary to cytokine-induced immune cell activation.

Pre-treatment with obinutuzumab resulted in the attenuation of cytokine release allowing at least 10 times higher doses of COLUMVI (1 mg/kg) in animals resulting in a Cmax of up to 5 times the human Cmax at the recommended 30 mg dose.

All findings with COLUMVI were considered pharmacologically mediated effects and reversible. Studies longer than 4 weeks were not performed, as COLUMVI was highly immunogenic in cynomolgus monkeys and led to loss of exposure and loss of the pharmacologic effect.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine,

L-Histidine Hydrochloride monohydrate,

L-Methionine,

Polysorbate 20,

D-Sucrose,

Water for Injection

6.2 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.

6.3 Shelf life

30 months

COLUMVI should not be used after the expiry date (EXP) shown on the carton.

6.4 Special precautions for storage

Vials

Store at 2 °C to 8 °C.

Keep vial in the outer carton in order to protect from light.

Do not freeze. Do not shake.

Diluted solution for intravenous solution

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

6.5 Nature and contents of container

COLUMVI 2,5 mg/vial: Pack of 1 vial. Colourless 6 mL, Type I, borosilicate glass vial with a flouroresin laminated gray rubber stopper, sealed with an aluminium seal with pink plastic flip-off cap.
COLUMVI 10 mg/vial: Pack of 1 vial. Colourless 15 mL, Type I, borosilicate glass vial with a flouroresin laminated gray rubber stopper, sealed with an aluminium seal with avocado plastic flip-off cap.

6.6 Special Instructions for Use, Handling and Disposal

Instructions for dilutions

- COLUMVI contains no preservative and is intended for single use only.
- COLUMVI must be diluted by a healthcare professional using aseptic technique, prior to intravenous administration.
- Visually inspect the COLUMVI vial for particulate matter or discoloration prior to administration. COLUMVI is a colourless, clear solution. Discard the vial if the solution is cloudy, discoloured, or contains visible particles.
- Withdraw the required volume of 0,9 % or 0,45 % sodium chloride solution from the infusion bag (see Table 7) 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 7). Discard any unused portion left in the vial.
- The final drug concentration after dilution must be 0,1 mg/mL to 0,6 mg/mL.

- Gently invert the infusion bag to mix the solution in order to avoid excessive foaming. Do not shake.
- Inspect the infusion bag for particulates and discard if present.
- Prior to the start of the intravenous infusion, the content of the infusion bag should be at room temperature

Table 7 Dilution of COLUMVI for Infusion

Dose of COLUMVI to be administered	Volume of saline infusion bag	Volume of saline solution to be withdrawn and discarded	Volume of COLUMVI concentrate to be added
2,5 mg	50 mL	27,5 mL	2,5 mL
	100 mL	77,5 mL	2,5 mL
10 mg	50 mL	10 mL	10 mL
	100 mL	10 mL	10 mL
30 mg	50 mL	30 mL	30 mL
	100 mL	30 mL	30 mL

Disposal of unused/expired medicines

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

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

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

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road

Hertford Office Park

Building E, Vorna Valley

Midrand

Gauteng

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER

COLUMVI 2,5 mg/2,5 mL: 57/30.5/0287

COLUMVI 10 mg/10 mL: 57/30.5/0288

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 04 February 2025

10. DATE OF REVISION OF THE TEXT