Professional Information

Cytokine Release Syndrome (CRS), including serious or fatal reactions, can occur in patients receiving glofitamab. 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 glofitamab 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 glofitamab 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, antineoplastic agent.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

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

DS BH

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.

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

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 and lymphoid tissue B cells and thereby reduce the risk of CRS.

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

DS BH

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.

63 **Table 1 Premedication Before Columvi Infusion to Reduce the Risk of Cytokine Release**

64 **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	20 mg intravenous dexamethasone[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	20 mg intravenous dexamethasone[a]	Completed at least 1 hour prior to Columvi infusion.

a If patient has an intolerance to dexamethasone or dexamethasone is unavailable, administer 100 mg prednisone/prednisolone or 80 mg methylprednisolone.

b For example, 1000 mg acetaminophen/paracetamol.

c For example, 50 mg diphenhydramine.

65 ***Cytomegalovirus prophylaxis***

66 Consider prophylaxis for cytomegalovirus (CMV) infection in patients at increased risk (see
67 section 4.8 *Description of selected adverse reactions*).

68

69 **Recommended Dosage**

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

72 ***Columvi Monotherapy Dose Step-up Schedule***

73 Columvi must be administered as an intravenous infusion according to the dose step-up schedule

leading to the recommended dosage of 30 mg (as shown in Table 2), after completion of pre-treatment with obinutuzumab on Cycle 1 Day 1. Each cycle is 21 days.

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

Treatment Cycle, Day[a]		Dose of Columvi	Duration of infusion
Cycle 1 (Pre-treatment and step-up dose)	Day 1	Pre-treatment with obinutuzumab 1000 mg[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 and section 4.4)

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.

Columvi Dose Step-up Schedule in Combination with Gemcitabine and Oxaliplatin

Columvi must be administered as an intravenous infusion according to the dose step-up schedule leading to the recommended dosage of 30 mg (as shown in Table 3Table 3), after completion of pre-treatment with obinutuzumab on Cycle 1 Day 1. Administer Columvi in combination with gemcitabine and oxaliplatin at Cycles 1-8 and as monotherapy at Cycles 9-12. Each cycle is 21 days.

Table 3 Columvi Dose Step-Up Schedule in Combination with Gemcitabine and Oxaliplatin for Patients with Relapsed or Refractory DLBCL

Treatment Cycle, Day[a]		Dose of Columvi (duration of infusion)	Dose of gemcitabine	Dose of oxaliplatin
Cycle 1 (pre-treatment and step-up dose)	Day 1	Pre-treatment with obinutuzumab 1000 mg[b]		
	Day 2	--	1000 mg/m^2 [c]	100 mg/m^2 [c]
	Day 8	2,5 mg (4 hours)[d]	--	--
	Day 15	10 mg (4 hours)[d]	--	--
Cycle 2	Day 1	30 mg (4 hours)[d,e]	1000 mg/m^2 [e]	100 mg/m^2 [e]
Cycle 3 to 8	Day 1	30 mg (2 hours)[e,f]	1000 mg/m^2 [e]	100 mg/m^2 [e]
Cycle 9 to 12	Day 1	30 mg (2 hours)[f]	N/A	N/A

N/A=not applicable.

a Each treatment cycle is 21 days.

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

c Cycle 1: gemcitabine and oxaliplatin can be administered in any order.

d For patients who experience CRS with their previous dose of Columvi, the duration of infusion may be extended up to 8 hours (see Table and section 4.4).

e Cycles 2-8: Columvi, gemcitabine, and oxaliplatin can be administered in any order. Gemcitabine and oxaliplatin may be given on Day 1 or 2.

f Infusion time may be shortened to 2 hours at the discretion of the treating physician, if the previous infusion was well tolerated. If the patient experienced CRS with the previous dose, the duration of infusion should be maintained at 4 hours.

Monitoring after infusion

When Columvi is given as monotherapy, 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).When Columvi is given in combination with gemcitabine and oxaliplatin, patients must be monitored for signs and symptoms of potential CRS during and after completion of infusion of the first Columvi dose (2,5 mg on Cycle 1 Day 8) for a combined total of 8 hours.

Patients who experienced Grade ≥ 2 CRS with their previous infusion should be monitored after completion of the infusion. See Table 4.

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All patients should be monitored for signs and symptoms of CRS and/or neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS) following Columvi administration. All patients must be counselled on the risk, signs, and symptoms of CRS and/or neurologic toxicity including ICANS and advised to contact the healthcare provider immediately should they experience signs and symptoms of CRS and/or neurologic toxicity including ICANS at any time.

Duration of Treatment

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

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

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 and Table 3).

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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 2 and Table 3) 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 4.

Table 4 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

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 • 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]	

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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).

148

149 **Management of Neurologic Toxicity Including Immune Effector Cell-Associated**
150 **Neurotoxicity Syndrome (ICANS)**

151 Neurologic toxicity including ICANS should be identified based on the clinical presentation (see
152 section 4.4). At the first sign of neurologic toxicity, including ICANS, based on the type and
153 severity of neurologic toxicity consider supportive therapy, neurology evaluation, and withholding
154 Columvi per Table 5. Rule out other causes of neurologic symptoms. If ICANS is suspected, it
155 should be managed according to the recommendations in Table 5.

156

157 **Table 5 Neurologic Toxicity[a] Including ICANS[b] Management Guidance**

Grade[a,b]	Actions
Grade 1	• Continue Columvi and monitor neurologic toxicity symptoms. • If Grade 1 ICANS,[b] consider a single dose of dexamethasone 10 mg, if not taking other corticosteroids.
Grade 2	• Withhold Columvi until neurologic toxicity symptoms improve to Grade 1 or baseline.[c,d] • Provide supportive therapy and consider neurologic consultation and evaluation. • If Grade 2 ICANS,[b] treat with dexamethasone 10 mg intravenously every 12 hours, if not taking other corticosteroids, until improvement to Grade 1, then taper.
Grade 3	• Withhold Columvi until neurologic toxicity symptoms improve to Grade 1 or baseline for at least 7 days.[d,e] • For Grade 3 neurologic events lasting more than 7 days, consider permanently discontinuing Columvi. • Provide supportive therapy, which may include intensive care, and consider neurologic consultation and evaluation. • If Grade 3 ICANS,[b] treat with dexamethasone 10 mg intravenously every 6 hours, if not taking other corticosteroids, until improvement to Grade 1, then taper. Consider non-sedating anti-seizure medication for seizure prophylaxis until resolution of ICANS. Use anti-seizure medication for seizure management as needed.
Grade 4	• Permanently discontinue Columvi. • Provide supportive therapy, which may include intensive care, and consider neurology consultation and evaluation.

DS BH

	• If Grade 4 ICANS,[b] treat with dexamethasone 10 mg intravenously every 6 hours, if not taking other corticosteroids, until improvement to Grade 1, then taper. Consider non-sedating anti-seizure medication for seizure prophylaxis until resolution of ICANS. Use anti-seizure medication for seizure management as needed.

[a] Neurologic toxicity grading per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
[b] American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria.
[c] Consider the type of neurologic toxicity before deciding to withhold Columvi.
[d] See *Delayed or Missed Doses* for guidance on restarting Columvi after dose delay.
[e] Evaluate benefit/risk before restarting Columvi

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 (CrCL 30 to < 90 mL/min). Columvi has not been studied in patients with severe renal impairment. (See section 5.2).

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (total bilirubin > upper limit of normal [ULN] to ≤ 1,5 × ULN or aspartate transaminase [AST] > ULN).

No specific studies in patients with moderate or severe 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.

DS BH

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.

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.

DS BH

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

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

When Columvi is given in combination with gemcitabine and oxaliplatin, patients must be monitored during all Columvi infusions and for a combined total of 8 hours during and 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 4 (see section 4.2).

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

Neurologic toxicity including ICANS has been reported in patients receiving Columvi, including serious and fatal reactions. Manifestations of ICANS included somnolence, cognitive disorder, confusional state, delirium, and disorientation. The majority of cases of ICANS occurred during Cycle 1 of Columvi treatment, however, some events occurred at later cycles (see Section 4.8*)*. Patients should be monitored for signs and symptoms of neurologic toxicity including ICANS following Columvi administration. The prescriber must counsel patients to seek immediate medical attention should signs or symptoms occur at any time.

At the first signs or symptoms of ICANS, manage according to the ICANS guidance provided in Table 5. Treatment with Columvi should be withheld or discontinued as recommended (see Section 4.2*)*.

DS BH

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 Flare

Tumour flare has been reported in patients receiving Columvi. Manifestations included localized pain and swelling (see section 4.8 *Description of selected adverse events*).

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.

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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.

The highest drug-drug interaction risk is during the period of one week following each of the first 2 doses of Columvi (i.e., Cycle 1 Day 8 and Day 15) in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index (e.g., warfarin, cyclosporine). On initiation of Columvi therapy, close monitoring of patients being treated with CYP450 substrates with a narrow therapeutic index should be considered.

DS BH

The pharmacokinetics of Columvi are not affected by co-administration with gemcitabine or oxaliplatin.

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 neurologic toxicity including ICANS and/or CRS (pyrexia, tachycardia, hypotension, chills, and hypoxia) should be advised not to drive or use machines until symptoms resolve.

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4.8 Undesirable effects

Clinical Trials

a. Summary of the Safety Profile

Columvi monotherapy

Approximately 1530 patients with relapsed or refractory non-Hodgkin's lymphoma (NHL) have received Columvi as monotherapy in the clinical development program of Columvi.

The adverse drug reactions described below were identified from clinical studies in patients with relapsed or refractory DLBCL, who were treated with Columvi at the recommended dose as monotherapy (N=145) or in combination with gemcitabine and oxaliplatin (N=172).

b. Tabulated list of adverse reactions

Adverse medicine reactions from clinical trials (Table 6, Table 7) 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 6 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	67,6	4,1
Blood and lymphatic system disorders			
Neutropenia[b]	Very common	40,0	29,0
Anaemia[c]	Very common	30,3	7,6

Thrombocytopenia[d]	Very common	24,1	6,9
Lymphopenia[e]	Common	4,8	4,8
Febrile neutropenia[f]	Common	3,4	3,4
General disorders and administration site conditions			
Pyrexia	Very common	15,9	0
Metabolism and nutrition disorders			
Hypophosphataemia	Very common	18,6	6,2
Hypomagnesaemia	Very common	15,2	0
Hypocalcaemia	Very common	12,4	0
Hypokalaemia	Very common	10,3	0,7
Hyponatraemia	Common	8,3	1,4
Tumour lysis syndrome	Common	1,4	1,4
Skin and subcutaneous tissue disorders			
Rash[g]	Very common	20,0	1,4
Gastrointestinal disorders			
Constipation	Very common	14,5	0
Diarrhoea	Very common	13,8	0
Nausea	Very common	10,3	0
Gastrointestinal haemorrhage[h]	Common	2,8	2,8
Vomiting	Common	4,1	0
Colitis	Uncommon	0,7	0,7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour flare	Very common	11,7	2,8
Nervous system disorders			
Headache	Very common	10,3	0
Immune effector cell-associated neurotoxicity syndrome[a,q]	Common	4,8	0,7*

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Somnolence	Common	1,4	0,7
Tremor	Common	1,4	0
Myelitis[i]	Uncommon	0,7	0,7
Infections and infestations			
Viral infections[j]	Very common	11,0	3,4*
Bacterial infections[k]	Common	6,2	1,4
Upper respiratory tract infections[l]	Common	5,5	0
Sepsis[m]	Common	4,1	2,8*
Lower respiratory tract infections[n]	Common	2,1	0
Pneumonia	Common	4,1	0,7
Urinary tract infection[o]	Common	2,8	0,7
Fungal infections[p]	Common	1,4	0
Investigations			
Alanine aminotransferase increased	Common	9,0	2,8
Aspartate aminotransferase increased	Common	8,3	2,8
Blood alkaline phosphatase increased	Common	9,0	1,4
Gamma-glutamyltransferase increased	Common	6,9	2,8
Blood bilirubin increased	Common	4,1	0,7
Hepatic enzyme increased	Common	1,4	1,4,
Psychiatric disorders			
Confusional state	Common	1,4	0

* Grade 5 reactions reported include COVID-19 (2,1 %), sepsis (1,4 %), COVID-19 pneumonia (1,4 %), 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, palmar erythema, pruritus, and rash erythematous,

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

i Myelitis occurred concurrently with CRS.

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

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

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

m Includes sepsis and septic shock.

n Includes lower respiratory tract infection and bronchitis.

o Includes urinary tract infection and Escherichia urinary tract infection,

p Includes oesophageal candidiasis and oral candidiasis.

q Includes somnolence, cognitive disorder, confusional state, delirium, and disorientation.

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Table 7 Adverse Drug Reactions Occurring in Patients with Relapsed or Refractory DLBCL Treated with Columvi in Combination with Gemcitabine and Oxaliplatin

System Organ Class Adverse Drug Reaction	Columvi+GemOx N=172		
	All Grades (frequency category)	Any Grade (%)	Grade 3-4 (%)
Immune system disorders			
Cytokine release syndrome[a]	Very common	44,2	2,3
Blood and lymphatic system disorders			
Thrombocytopenia[b]	Very common	50,0	26,7
Neutropenia[c]	Very common	44,2	35,5
Anaemia	Very common	41,3	16,9
Lymphopenia[d]	Very common	24,4	12,2
Febrile neutropenia	Common	2,9	2,9
Gastrointestinal Disorders			
Nausea	Very common	41,3	0,6
Diarrhoea	Very common	34,9	3,5
Vomiting	Very common	23,8	0,6
Abdominal pain[e]	Very common	18,6	2,3
Constipation	Very common	18,6	0
Colitis[f]	Common	2,3	1,2
Pancreatitis[g]	Common	1,7	1,2
Nervous system disorders			
Peripheral neuropathy[h]	Very common	37,2	1,2
Headache	Common	8,7	0
ICANS[i]	Common	2,3	0,6
Tremor	Uncommon	0,6	0
Investigations			
Aspartate aminotransferase increased	Very common	34,3	3,5

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Alanine aminotransferase increased	Very common	32,6	2,9
Blood alkaline phosphatase increased	Very common	18,0	0,6
Gamma-glutamyltransferase increased[j]	Very common	15,1	2,3
Blood lactate dehydrogenase increased	Very common	11,6	0
Blood bilirubin increased[k]	Common	3,5	0
Hepatic enzyme increased	Uncommon	0,6	0
Skin and subcutaneous disorders			
Rash[l]	Very common	26,7	0,6
General disorders and administration site conditions			
Pyrexia	Very common	24,4	0,6
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[m]	Very common	18,6	2,3
Metabolism and nutrition disorders			
Hypokalaemia	Very common	18,6	2,9
Hyponatraemia	Very common	11,0	0,6
Hypomagnesaemia	Common	7,6	0
Hypocalcaemia	Common	6,4	0,6
Hypophosphataemia	Common	5,8	1,7
Tumour lysis syndrome	Common	1,7	1,7
Infections and infestations			
COVID-19*[,n]	Very common	17,4	3,5
Respiratory tract infections*[,o]	Very common	13,4	1,7
Pneumonia*[,p]	Very common	12,8	5,2
Cytomegalovirus infections[q]	Common	5,8	0,6
Herpes viral infections[r]	Common	5,8	0,6
Urinary tract infection[s]	Common	3,5	1,7
Sepsis*[,t]	Common	2,9	2,3

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Candida infections[u]	Common	1,7	0
Pneumocystis jirovecii pneumonia	Uncommon	0,6	0,6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour flare[v]	Common	2,3	0
Respiratory, thoracic, and mediastinal disorders			
Pneumonitis*	Common	1,2	0

* Grade 5 reactions reported include COVID-19 (1,7 %), pneumonitis (1,2 %), septic shock (0,6 %), pneumonia (0,6 %), and respiratory tract infection (0,6 %).

a Based on ASTCT consensus grading

b Includes thrombocytopenia and platelet count decreased.

c Includes neutropenia and neutrophil count decreased.

d Includes lymphopenia and lymphocyte count decreased.

e Includes abdominal pain, abdominal discomfort, abdominal pain upper, abdominal pain lower, and gastrointestinal pain.

f Includes colitis, colitis ischaemic, and enterocolitis.

g Includes pancreatitis and pancreatitis acute.

h Includes neuropathy peripheral, peripheral sensory neuropathy, dysaesthesia, paraesthesia, hypoaesthesia, peripheral motor neuropathy, and polyneuropathy.

i Includes confusional state, delirium, and ICANS.

j Includes gamma-glutamyltransferase increased and gamma-glutamyltransferase abnormal.

k Includes blood bilirubin increased and hyperbilirubinaemia.

l Includes rash, rash pruritic, rash maculo-papular, erythema, pruritus, rash erythematous, urticaria, and erythema multiforme.

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

n Includes COVID-19, COVID-19 pneumonia, and SARS-CoV-2 test positive.

o Includes upper respiratory tract infection, lower respiratory tract infection, respiratory tract infection, and respiratory tract infection bacterial.

p Includes pneumonia, pneumonia bacterial, and pneumonia pneumococcal.

q New onset or reactivation. Includes cytomegalovirus infection, cytomegalovirus test positive, cytomegalovirus infection reactivation, and cytomegalovirus viraemia.

r New onset or reactivation. Includes herpes zoster and herpes virus infection.

s Includes urinary tract infection and urosepsis.

t Includes sepsis, streptococcal sepsis, septic shock, and enterococcal sepsis.

u Includes oral candidiasis and candida infection.

v Includes tumour flare and tumour pain.

337

338 ***c. Description of selected adverse reactions***

339 The descriptions below reflect information for significant adverse reactions for Columvi monotherapy

340 and/or combination therapy. Details for the significant adverse reactions for Columvi when given in

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combination are presented separately if clinically relevant differences were noted in comparison to Columvi monotherapy.

Cytokine Release Syndrome

Columvi monotherapy

Any grade CRS (by ASTCT criteria) occurred in 67,6 % of patients who received Columvi monotherapy, with Grade 1 CRS being reported in 50,3 % of patients, Grade 2 CRS in 13,1 % of patients, Grade 3 CRS in 2,8 % of patients, and Grade 4 CRS in 1,4 % of patients. There were no fatal cases of CRS. CRS resolved in all patients except one. One patient discontinued Columvi due to CRS.

In patients with CRS, the most common manifestations of CRS included pyrexia (99,0 %), tachycardia (25,5 %), hypotension (23,5 %), chills (14,3 %), and hypoxia (12,2 %). Grade 3 or higher events associated with CRS included hypotension (3,1 %), hypoxia (3,1 %), pyrexia (2,0 %), and tachycardia (2,0 %).

CRS of any grade occurred in 54,5 % of patients following the 2,5 mg dose of Columvi at Cycle 1 Day 8 with median time to onset of 12,6 hours (range: 5,2 to 50,8 hours); in 33,3 % of patients following the 10 mg dose at Cycle 1 Day 15 with median time to onset of 26,8 hours (range: 6,7 to 125,0 hours); and in 26,8 % of patients following the 30 mg dose at Cycle 2 Day 1 with median time to onset of 28,2 hours (range: 15,0 to 44,2 hours). CRS was reported in 0,9 % of patients at Cycle 3 and in 2 % of patients beyond Cycle 3.

Grade ≥ 2 CRS occurred in 12,4 % of patients following the first Columvi dose (2,5 mg), with median time to onset of 9,7 hours (range: 5,2 to 19,1 hours) and median duration of 50,4 hours (range: 6,5 to 316,7 hours). Following Columvi 10 mg dose at Cycle 1 Day 15, the incidence of Grade ≥ 2 CRS decreased to 5,2 % of patients, with median time to onset of 26,2 hours (range: 6,7 to 144,2 hours) and median duration of 30,9 hours (range: 3,7 to 227,2 hours). Grade ≥ 2 CRS following Columvi 30 mg dose at Cycle 2 Day 1 occurred in one patient (0,8 %) with time to onset of 15,0 hours and duration of 44,8 hours. No Grade ≥ 2 CRS was reported beyond Cycle 2.

Among the 25 patients who experienced Grade 2 or higher CRS after Columvi, 22 (88 %) received

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tocilizumab, 15 (60 %) received corticosteroids, and 14 (56 %) received both tocilizumab and corticosteroids. Ten patients (40 %) received oxygen. All 6 patients (24,0 %) with Grade 3–4 CRS received a single vasopressor.

In patients who received dexamethasone premedication (N = 39) versus another glucocorticoid premedication (N = 106), CRS of any grade occurred in 48.7% vs. 56,6 % of patients; Grade 1 CRS in 38,5 % vs. 43,4 % of patients; Grade 2 CRS in 7,7 % vs. 9,4 % of patients; Grade 3 CRS in 2,6 % vs. 1,9 % of patients; and Grade 4 CRS in 0% vs. 1,9% of patients after the 2,5 mg dose of Columvi at Cycle 1 Day 8. After the 10 mg dose at Cycle 1 Day 15 (N = 36 for dexamethasone premedication, N = 99 for another glucocorticoid premedication), any grade CRS occurred in 22,2 % vs 37,4 % of patients; Grade 1 CRS in 22,2 % vs 30,3 % of patients; Grade 2 CRS in 0 % vs 6,1 % of patients; and Grade 3 CRS in 0 % vs 1 % of patients. After the 30 mg dose at Cycle 2 Day 1 (N = 32 for dexamethasone premedication, N = 95 for another glucocorticoid premedication) any grade CRS occurred in 6,3 % vs 33,7 % of patients; Grade 1 CRS in 6,3 % vs 32,6 % of patients; and Grade 2 CRS in 0 % vs 1,1 % of patients.

Columvi in combination with gemcitabine and oxaliplatin

Any grade CRS (by ASTCT criteria) occurred in 44,2 % of patients who received Columvi with gemcitabine and oxaliplatin, with Grade 1 CRS reported in 31,4 % of patients, Grade 2 CRS in 10,5 % of patients, and Grade 3 CRS in 2,3 % of patients. There were no Grade 4 or 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 (98,7 %), hypotension (22,4 %), chills (17,1 %) and hypoxia (14,5 %). Grade 3 or higher events associated with CRS included hypotension (6,6 %), hypoxia (5,3 %), pyrexia (3,9 %), chills (1,3 %), and diarrhoea (1,3 %).

CRS of any grade occurred in 34,9 % of patients following the 2,5 mg dose of Columvi at Cycle 1 Day 8 with median time to onset (from the start of infusion) of 12,6 hours (range: 4,4 to 54,7 hours); in 14,4 % of patients following the 10 mg dose at Cycle 1 Day 15 with median time to onset of 22,8 hours (range: 7,4 to 81,2 hours); and in 9,3 % of patients following the 30 mg dose at Cycle 2

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Day 1 with median time to onset of 23,5 hours (range: 14,7 to 33,4 hours). CRS was reported in 6,7 % of patients at Cycle 3 and in 11,0 % of patients beyond Cycle 3.

Grade ≥ 2 CRS occurred in 10,5 % of patients following the first Columvi dose (2,5 mg), with median time to onset of 12,0 hours (range: 4,4 to 30,5 hours) and median duration of 42,3 hours (range: 3,5 to 143,7 hours). The majority (14/18) of patients who experienced Grade ≥ 2 CRS had onset of CRS within 8 hours of the start of the first Columvi dose (2,5 mg). Following Columvi 10 mg dose at Cycle 1 Day 15, the incidence of Grade ≥ 2 CRS decreased to 1,8 % of patients, with median time to onset of 22,3 hours (range: 7,4 to 22,8 hours) and median duration of 37,0 hours (range: 34,8 to 248,5 hours). There were no Grade ≥ 2 CRS events following Columvi 30 mg dose at Cycle 2 Day 1. Three patients (2 %) had Grade ≥ 2 CRS beyond Cycle 2 (all Grade 2 events).

Among the 22 patients who experienced Grade 2 or higher CRS after Columvi, 16 (72,7 %) received tocilizumab, 15 (68,2 %) received corticosteroids, and 12 (54,5 %) received both tocilizumab and corticosteroids. Eleven patients (50,0 %) received oxygen. All 4 patients (18,2 %) with Grade 3 CRS received a single vasopressor.

Neurologic Toxicity, Including Immune Effector Cell-Associated Neurotoxicity Syndrome

Columvi monotherapy

Neurologic toxicity was reported in 40,0 % of patients who received Columvi monotherapy. The most frequent neurologic toxicities of any grade were headache (10,3 %), dizziness (5,5 %), anxiety (4,1 %), and paraesthesia (2,8 %). Grade 3 or higher neurologic adverse reactions occurred in 2,1 % of patients and included somnolence, delirium, and myelitis.

Seven patients (4,8 %) experienced ICANS: 5 patients (3,4 %) experienced Grade 1 events (2 patients with confusional state, and 1 patient each with somnolence, cognitive disorder, and disorientation), and 1 patient (0,7 %) experienced Grade 3 somnolence. One patient (0,7 %) experienced a fatal (Grade 5) event of delirium.

The median time to onset of the first ICANS event was 8 days (range: 1 to 106 days) from the first Columvi dose. The median time to resolution of ICANS was 1.5 days (range: 1 to 8 days). Of the 7 patients with ICANS, the onset of ICANS was concurrent with CRS in 5 patients and was non-

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concurrent with CRS in 2 patients.

Columvi in combination with gemcitabine and oxaliplatin

Neurologic toxicity was reported in 59,3 % of patients who received Columvi with gemcitabine and oxaliplatin. The most frequent neurologic toxicities of any grade were peripheral neuropathy (37,2 %), insomnia (11,6 %), headache (8,7 %), dizziness (7,0 %), and dysgeusia (5,2 %). Grade 3 or higher neurologic adverse reactions occurred in 5,8 % of patients and included peripheral sensory neuropathy, syncope, extrapyramidal disorder, confusional state, delirium, herpes zoster, meningitis aseptic, subdural hematoma, and cerebral haemorrhage.

Four patients (2,3 %) experienced ICANS: 1 patient (0,6 %) experienced a Grade 1 event (confusional state), 2 patients (1,2 %) experienced a Grade 2 event (1 patient with confusional state, and 1 patient with ICANS), and 1 patient (0,6 %) experienced Grade 3 delirium.

The onset of the 4 events of ICANS was concurrent with CRS. The median time to resolution of ICANS was 1,5 days (range: 1 to 4 days).

Serious Infections

Serious infections were reported in 15,9% of patients who received Columvi monotherapy. The most frequent serious infections reported in ≥ 2 % patients were sepsis (4,1 %), COVID-19 pneumonia (2,8 %), and COVID-19 (3,4 %). Infection-related deaths were reported in 4,8 % of patients (due to sepsis, COVID-19 pneumonia, and COVID-19). Four patients (2,8 %) experienced serious infections concurrently with Grade 3–4 neutropenia.

Serious infections were reported in 22,7 % of patients who received Columvi with gemcitabine and oxaliplatin. The most frequent serious infections reported in ≥ 2 % patients were pneumonia (5,8 %), COVID-19 (4,7 %), and lower respiratory tract infection (2,9 %). Infection-related deaths were reported in 3,5 % of patients (due to COVID-19, pneumonia, respiratory tract infection, and septic shock). One patient (0,6 %) experienced a serious infection (pneumonia) concurrently with Grade 3 neutropenia.

Pneumonitis

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Pneumonitis events (excluding pneumonia of infectious aetiology) were reported in 2 patients (1,2 %) who received Columvi with gemcitabine and oxaliplatin, both of which were fatal events. The median time to onset of pneumonitis from the first Columvi dose was 168 days (range: 102 to 255 days).

Colitis

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

Colitis events (excluding infectious aetiology) were reported in 4 patients (2,3 %) who received Columvi with gemcitabine and oxaliplatin. Two patients (1,2 %) had Grade 3 events. The median time to onset of colitis from the first Columvi dose was 154 days (range: 115 to 187 days).

Opportunistic Infections

CMV events were reported in 6/467 patients (1,3 %) who received Columvi monotherapy in study NP30179, with 1 patient (0,2 %) experiencing Grade 3 CMV chorioretinitis.

CMV events were reported in 10 patients (5,8 %) who received Columvi with gemcitabine and oxaliplatin, with 1 patient (0,6 %) experiencing Grade 3 CMV viremia. Oral candidiasis was reported in 3 patients (1,7 %), all of which were Grade 1-2 events. Pneumocystis jirovecii pneumonia (Grade 3) was reported in 1 patient (0,6 %), the same patient with Grade 3 CMV viremia. Borellia meningitis (Grade 2) was reported in 1 patient (0,6 %).

Neutropenia

Neutropenia (including neutrophil count decreased) was reported in 40,0 % of patients and severe neutropenia (Grade 3–4) was reported in 29,0 % of patients who received Columvi monotherapy. The median time to onset of the first neutropenia event was 29 days (range: 1 to 203 days). Prolonged neutropenia (lasting longer than 30 days) occurred in 11,7 % of patients. The majority of patients with neutropenia (79,3 %) were treated with G-CSF. Febrile neutropenia was reported in 3,4 % of patients.

Tumour Flare

Tumour flare was reported in 11,7 % of patients who received Columvi monotherapy, including Grade 2 tumour flare in 4,8 % of patients and Grade 3 tumour flare in 2,8% of patients. Tumour flare

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

Tumour Lysis Syndrome

TLS was reported in 2 patients (1,4 %) who received Columvi monotherapy and was 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). Editorial for clarity

Laboratory Abnormalities

Table 8 summarises treatment-emergent shifts from baseline in laboratory abnormalities with Columvi monotherapy. Table 9 summarises treatment-emergent shifts from baseline in laboratory abnormalities with Columvi in combination with gemcitabine and oxaliplatin.

Table 8 Laboratory Abnormalities Worsening from Baseline, with Grade 3 to 4 Occurring in ≥ 10 % of Patients with Relapsed or Refractory DLBCL Treated with Columvi Monotherapy

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Laboratory Abnormality[a]	Columvi NCI CTCAE Grade	
	All Grades (%)[b]	Grade 3 or 4 (%)[b,c]
Haematology		
Decreased lymphocytes	90,2	83,2
Decreased neutrophils	55,6	25,7
Decreased leukocytes	71,0	13,8
Chemistry		
Hypophosphatemia	68,8	27,8
Hyperglycaemia	14,2	14,2
Hyperuricemia	22,6	22,6

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=137 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

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498 **Table 9 Laboratory Abnormalities Worsening from Baseline, with Grade 3 to 4**
499 **Occurring in ≥ 5% of Patients with Relapsed or Refractory DLBCL Treated with Columvi in**
500 **Combination with Gemcitabine and Oxaliplatin**

Laboratory Abnormality[a]	Columvi+GemOx NCI CTCAE Grade	
	All Grades (%)[b]	Grade 3 or 4 (%)[b,c]
Haematology		
Decreased platelets	82,6	29,7
Decreased lymphocytes	81,1	50,3
Decreased haemoglobin	73,8	19,8
Decreased neutrophils	65,3	39,5
Decreased leukocytes	58,1	26,2
Chemistry		
Hyperuricemia	21,9	21,9

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Hypokalaemia	23,3	5,8

a Percentages based on patients with a baseline and at least one post-baseline assessment for the specific laboratory parameter.
b N=172 for decreased platelets; N=143 for decreased lymphocytes; N=172 for decreased haemoglobin; N=147 for decreased neutrophils; N=172 for decreased leukocytes; N=160 for hyperuricemia; N=172 for hypokalaemia.
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 (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, Columvi mediates the formation of an immunological synapse with subsequent potent T-cell activation and proliferation, secretion of cytokines, and release of cytolytic proteins that results in the

lysis of CD20-expressing B cells.

Pharmacodynamics

In study NP30179, peripheral B-cell counts were < 70 cells/μL in almost all patients (98,6 %) with relapsed and refractory LBCL prior to Columvi treatment initiation and remained low during Columvi treatment.

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

In study GO41944 (STARGLO), peripheral B-cell counts were <70 cells/μL in the majority of patients (79,4 %) with relapsed and refractory DLBCL prior to Columvi treatment initiation and remained low during Columvi treatment.

Clinical efficacy and safety

Relapsed or Refractory DLBCL

Columvi monotherapy

The efficacy of Columvi monotherapy was evaluated in study NP30179, a single-arm, open-label, multicentre, multi-cohort trial, in 155 patients with relapsed or refractory DLBCL after at least two prior lines of systemic therapy. The study excluded patients with prior allogeneic hematopoietic stem cell transplant, previous or active central nervous system lymphoma, ECOG performance status ≥ 2, creatinine clearance (CrCL) < 50 mL/min, or hepatic transaminases > 3 × ULN.

Following pre-treatment with obinutuzumab at Cycle 1 Day 1, patients received 2,5 mg of Columvi at Cycle 1 Day 8, 10 mg of Columvi at Cycle 1 Day 15, and 30 mg of Columvi at Cycle 2 Day 1 as per the step-up dosing schedule. Patients continued to receive 30 mg of Columvi on Day 1 of Cycles 3 to 12. Patients received premedication including an anti-pyretic, an anti-histamine and a glucocorticoid (see section 4.2). The duration of each cycle was 21 days.

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

The baseline demographic and disease characteristics were: median age 66 years (range: 21 to

90 years); 65,2 % males; 76,8 % white, 4,5 % Asian, and 1,9 % Black or African American; 5,8 % Hispanic or Latino; and ECOG performance status of 0 (44,5 %) or 1 (54,2 %). Most patients (71,0 %) had DLBCL not otherwise specified, 18,7 % had DLBCL transformed from follicular lymphoma, 6,5 % had HGBCL, and 3,9 % had PMBCL. The median number of prior lines of therapy was 3 (range: 2 to 7), with 39,4 % of patients having received 2 prior lines and 60,6 % having received 3 or more prior lines of therapy. All patients had received prior chemotherapy and anti-CD20 monoclonal antibody therapy; 33,5 % of patients had received prior CAR T-cell therapy, and 18,1 % of patients had received autologous stem cell transplant. Most patients (89,7 %) had refractory disease, 58,7 % patients had primary refractory disease, and 84,5 % of patients were refractory to their last prior therapy, and 88,5% of patients who received prior CAR T-cell therapy were refractory to CAR T-cell therapy.

The overall median duration of follow-up was 13,4 months (range: 0 to 28 months). Median duration of follow-up from the date of first response per Independent Review Committee (IRC) assessment was 12,0 months (range: 0 to 27 months).

The primary efficacy outcome measure was complete response (CR) rate as assessed by IRC using 2014 Lugano criteria. The secondary efficacy outcome measures included Investigator (INV)-assessed CR, and overall response rate (ORR), duration of response (DOR), duration of complete response (DOCR), time to first response (TFOR), time to first complete response (TFCR), overall survival (OS), and progression-free survival (PFS), as assessed by IRC and by INV. Efficacy results are summarized in Table 10.

572 **Table 10 Efficacy in Patients with Relapsed or Refractory DLBCL Treated with**

573 **Columvi Monotherapy**

Efficacy Endpoints	**Columvi N=155**	
Primary Endpoint		
IRC-Assessed Complete Response		
Patients with CR, n (%)	62 (40,0)	
95 % CI	[32,22, 48,17]	
Secondary Endpoints		
INV-Assessed Complete Response		
Patients with CR, n (%)	59 (38,1)	
95 % CI	[30,39, 46,20]	
Overall Response Rate	*IRC-Assessed*	*INV-Assessed*
Patients with CR or PR, n (%)	80 (51,6)	91 (58,7)
95 % CI	[43,46, 59,70]	[50,53, 66,55]
Partial Response (PR), n (%)	18 (11,6)	32 (20,6)
95 % CI	[7,03, 17,73]	[14,57, 27,88]
Duration of Complete Response	*IRC-Assessed*	*INV-Assessed*
Median DOCR, months [95 % CI]	NE [16,8, NE]	NE [19,8, NE]
Range, months	0[b]–27[b]	0[b]–27[b]
9-month DOCR, % [95 % CI][c]	76,0 [63,26, 88,71]	72,5 [59,25, 85,68]
12-month DOCR, % [95 % CI][c]	73,1 [59,57, 86,53]	72,5 [59,25, 85,68]
Duration of Response	*IRC-Assessed*	*INV-Assessed*
Median DOR, months [95 % CI]	NE [16,8, NE]	NE [19,8, NE]
Range, months	0[b]–27[b]	0[b]–27[b]
9-month DOR, % [95 % CI][c]	76,0 [63,26, 88,71]	72,5 [59,25, 85,68]
12-month DOCR, % [95 % CI][c]	73,1 [59,57, 86,53]	72,5 [59,25, 85,68]
Time to First Response	*IRC-Assessed*	*INV-Assessed*
Median TFOR, days [95 % CI]	42 [41, 42]	42 [40, 42]

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Range, days	31–178	31–178
Time to First Complete Response	*IRC-Assessed*	*INV-Assessed*
Median TFCR, days [95 % CI]	42 [42, 44]	43 [42, 48]
Range, days	31–308	31–274
Progression-Free Survival	*IRC-Assessed*	*INV-Assessed*
Patients with event, n (%)	95 (61,3)	98 (63,2)
Median PFS, months [95 % CI]	4,9 [3,4, 8,1]	3,8 [3,3, 5,4]
6-month PFS, % [95 % CI][c]	46,7 [38,40, 54,92]	39,1 [30,98, 47,14]
9-month PFS, % [95 % CI][c]	39,6 [31,34, 47,76]	35,1 [27,08, 43,03]
12-month PFS, % [95 % CI][c]	95 (61,3)	98 (63,2)
Overall Survival		*INV-Assessed*
Patients with event, n (%)		81 (52,3)
Median OS, months [95 % CI]		12 [8,0, 16,1]
6-month OS, % [95 % CI][c]		71,6 [64,34, 78,89]
9-month OS, % [95 % CI][c]		54,8 [46,65, 62,87]
12-month OS, % [95 % CI][c]		50,4 [42,06, 58,71]

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

a From date of first complete response until disease progression or death due to any cause,

b Censored observations

c Event-free rates based on Kaplan-Meier estimates

d From date of first response (PR or CR) until disease progression or death due to any cause,

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575 The efficacy population included a cohort of patients (N=40) where dexamethasone was mandated
576 as the glucocorticoid premedication. In this cohort, the IRC-assessed ORR was 52,5% (95 % CI:
577 36,1, 68,5) and the CR was 47,5% (95% CI: 31,5, 63,9).

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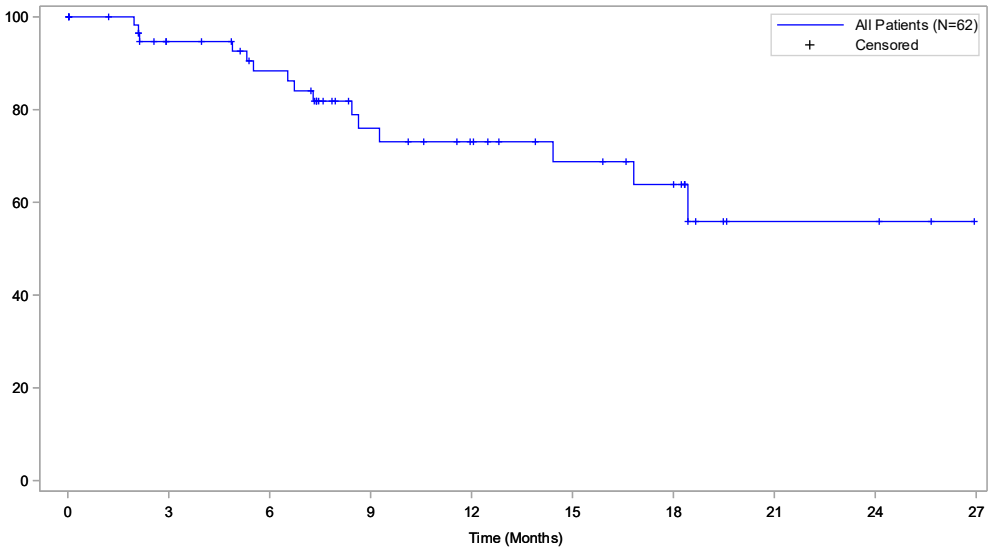
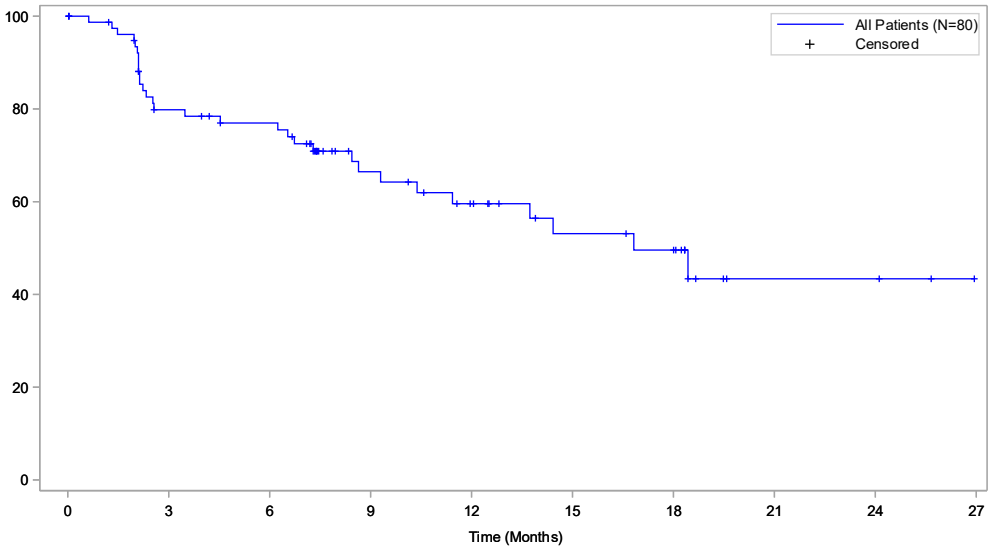
Figure 1: Duration of IRC-Assessed Complete Response in Patients with Relapsed or Refractory DLBCL Treated with Columvi Monotherapy



All Patients (N=62)	62	48	41	26	21	16	13	3	3	NE

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



All Patients (N=80)	80	57	52	30	23	16	14	3	3	NE

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 scale which were maintained during treatment.

Columvi in combination with gemcitabine and oxaliplatin

The efficacy of Columvi in combination with gemcitabine and oxaliplatin (Columvi+GemOx) was evaluated in study GO41944 (STARGLO), an open-label multicentre, randomized clinical trial that included 274 patients with relapsed or refractory DLBCL not otherwise specified (DLBCL NOS). The study excluded patients who received only one prior line of therapy who were candidates for stem cell transplant, patients with HGBCL, PMBCL, history of transformation of indolent disease to DLBCL, prior allogeneic hematopoietic stem cell transplant, previous or active CNS lymphoma, ECOG performance status > 2, CrCL < 30 mL/min, or hepatic transaminases > 2,5 × ULN. Patients were randomized 2:1 to receive Columvi+GemOx (N = 183) or rituximab in combination with gemcitabine and oxaliplatin (R-GemOx; N = 91) for 8 cycles, followed by 4 additional cycles of Columvi monotherapy for patients in the Columvi+GemOx arm. Randomization was stratified by number of previous lines of systemic therapy for DLBCL (1 vs. ≥ 2) and outcome of last systemic therapy (relapsed vs. refractory).

In the Columvi+GemOx arm, following pre-treatment with obinutuzumab at Cycle 1 Day 1, patients received 2,5 mg of Columvi at Cycle 1 Day 8, 10 mg of Columvi at Cycle 1 Day 15, and 30 mg of Columvi at Cycle 2 Day 1 as per the step-up dosing schedule. Patients continued to receive 30 mg of Columvi on Day 1 of Cycles 3 to 12. Patients received premedication including an anti-pyretic, an antihistamine, and dexamethasone. For patients who were unable to receive dexamethasone, an alternate corticosteroid was used (see section 4.2). Gemcitabine (1000 mg/m^2) and oxaliplatin (100 mg/m^2) were administered intravenously on Day 2 of Cycle 1 and then on Day 1 of subsequent cycles, up to Cycle 8. The duration of each cycle was 21 days.

Patients received a median of 11 cycles of Columvi treatment (range: 1 to 13 cycles).

The baseline demographic and disease characteristics were: median age 68 years (range: 20 to 88 years); 57,7 % males; 42,0 % white, 50,0 % Asian, and 1,1% Black or African American; 5,8 % Hispanic or Latino; and ECOG performance status of 0 (43,3 %), 1 (46,6 %), or 2 (10,1 %). The majority of patients (62,8 %) had received 1 prior line of systemic therapy; 37,2 % of patients

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received 2 or more prior lines. All patients had received prior chemotherapy and most (98,5 %) had received anti-CD20 monoclonal antibody therapy; 7,7 % of patients had received CAR T-cell therapy, and 4,0 % had received autologous stem cell transplant. The majority of patients (66,8 %) had refractory disease; 55,8 % had primary refractory disease, and 60,6 % of patients were refractory to their last prior therapy.

The primary efficacy outcome measure was overall survival (OS). At the time of the prespecified primary analysis, a statistically significant improvement in OS was observed for patients randomized to the Columvi+GemOx arm compared to patients randomized to R-GemOx. Statistically significant improvements in PFS and CR rate, as assessed by an IRC, were also observed with Columvi+GemOx over R-GemOx.

Overall survival, PFS, and CR results from an updated analysis conducted after an additional 10,5 months of follow-up continue to demonstrate benefit of Columvi+GemOx over R-GemOx. Median OS was 25,5 months in the Columvi+GemOx arm compared with 12,9 months in the R-GemOx arm in the updated analysis. The 24-month OS rate was 52,8 % (95 % CI: 44,8, 60,7) in the Columvi+GemOx arm and 33,5 % (95 % CI: 22,2, 44,9) in the R-GemOx arm.

Efficacy results are summarized in Table 11.

Table 11 Efficacy in Patients with Relapsed or Refractory DLBCL Treated with Columvi in Combination with Gemcitabine and Oxaliplatin (ITT)

	Primary Analysis Median observation time = 11,3 months		**Updated Analysis Median observation time = 20,7 months**	
	Columvi+GemOx (N=183)	**R-GemOx (N=91)**	**Columvi+GemOx (N=183)**	**R-GemOx (N=91)**
Primary Endpoint				
Overall Survival				

Number (%) of deaths	61 (33,3)	40 (44,0)	80 (43.7)	52 (57.1)
Median [95 % CI], months	NE [13,8, NE]	9,0 [7,3, 14,4]	25.5 [18.3, NE]	12.9 [7.9, 18.5]
HR [95 % CI]	0,59 [0,40, 0,89]		0,62 [0,43, 0,88]	
p-value	0,011		N/A	
Secondary Endpoints - IRC-assessed				
Progression-Free Survival				
Number (%) of patients with events	68 (37,2)	44 (48,4)	90 (49.2)	54 (59.3)
Median [95 % CI], months	12,1 [6,8, 18,3]	3,3 [2,5, 5,6]	13.8 [8.7, 20.5]	3.6 [2.5, 7.1]
HR [95 % CI]	0,37 [0,25, 0,55]		0,40 [0,28, 0,57]	
p-value	< 0,001		N/A	
Complete Response Rate				
Responders (%)	92 (50,3)	20 (22,0)	107 (58,5)	23 (25,3)
Difference in response rate (%) [95 % CI]	28,3 [16,3, 40,3]		33,2 [20,9, 45,5]	
p-value	<0,001		N/A	
Objective Response Rate				
Responders (%) (CR, PR)	110 (60,1)	29 (31,9)	125 (68.3)	37 (40.7)
Difference in response rate (%) [95 % CI]	28,2 [15,5, 50,0]		27,7 [14,7, 40,6]	

CI=confidence interval; HR=hazard ratio; N/A=not applicable; NE=not estimable.

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Figure 1 Kaplan-Meier Plot of Overall Survival in Study GO41944 (STARGLO, Updated Analysis; ITT)

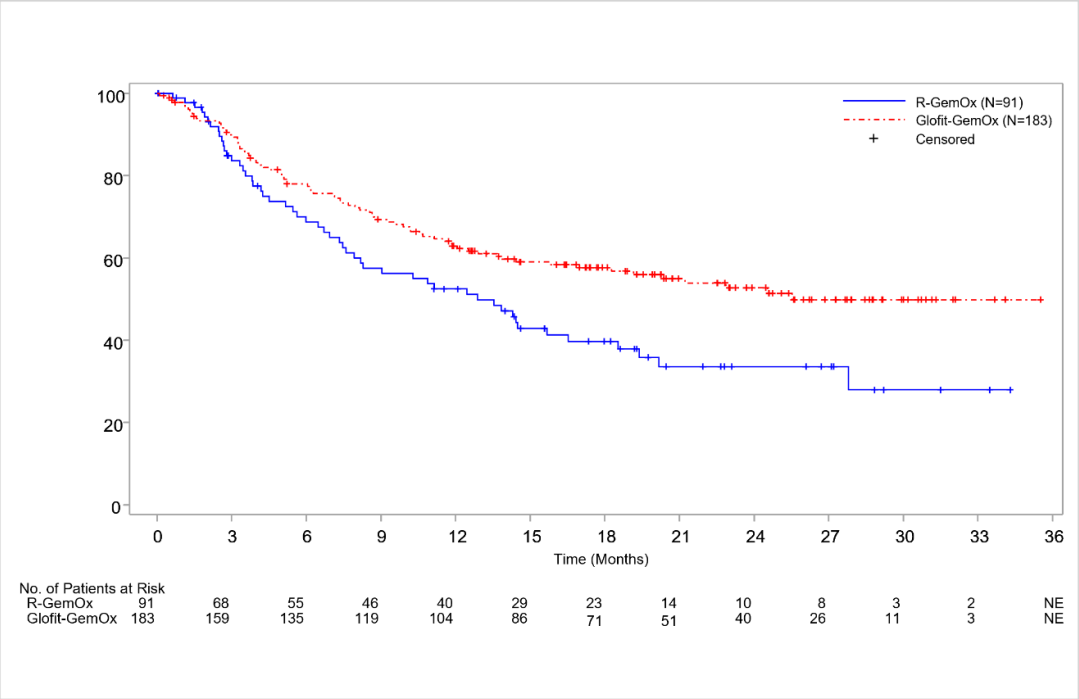
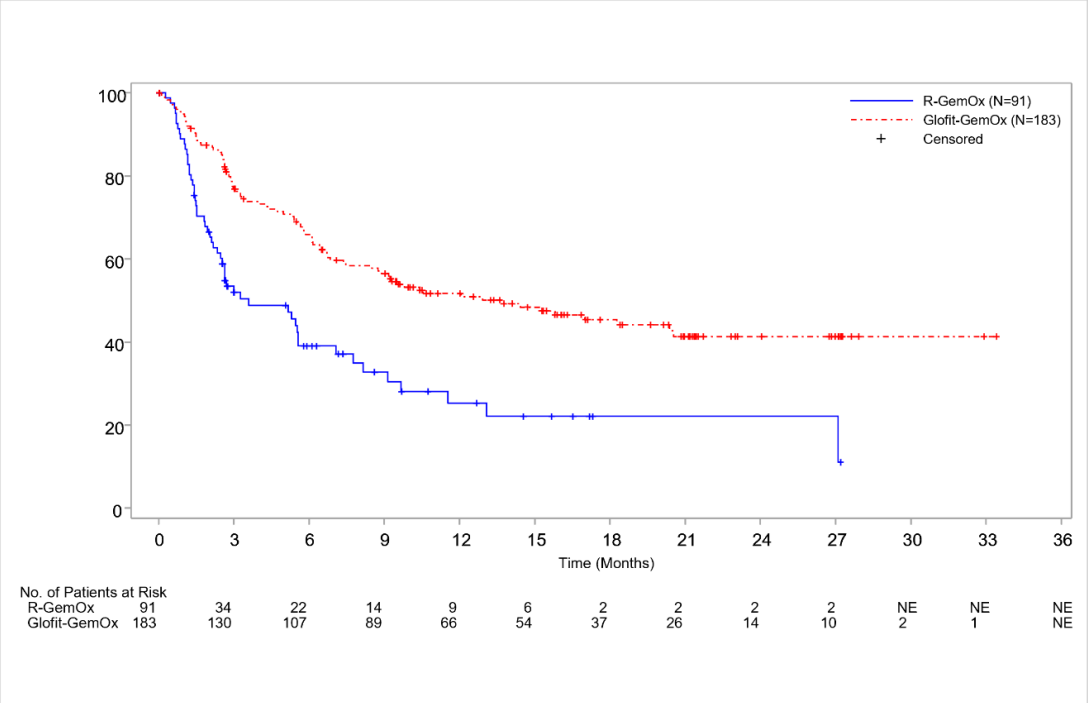


Figure 2 Kaplan-Meier Plot of IRC-Assessed Progression-Free Survival in Study GO41944 (STARGLO, Updated Analysis; ITT)



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Patient-Reported Outcomes

At baseline, patients in both treatment arms (Columvi+GemOx and R-GemOx) reported moderate to moderate-high levels of Physical Functioning and low levels of fatigue as measured by the EORTC QLQ-C30 and low to low-moderate levels of lymphoma symptoms as measured by the FACT-Lym LymS. During treatment, patients in both arms maintained their baseline level of physical functioning and experienced a similar deterioration in fatigue and lymphoma-specific symptoms.

There were no clinically meaningful differences in median time to deterioration between arms in fatigue or physical functioning or lymphoma symptoms, demonstrating that Glofit-GemOx does not add additional burden. Both arms experienced clinically meaningful improvement in pain, and Columvi+GemOx patients saw larger improvements at earlier time points in pain as compared to R-GemOx patients.

Immunogenicity

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

Across studies, the majority of patients (574/608 patients; 94,4 %) who received Columvi were negative for ADAs at baseline and remained negative throughout treatment with Columvi. Four patients (0.7%) were negative for ADAs at baseline and became positive for ADAs during treatment. Four patients (0,7 %) were ADA-positive at baseline and at one or more post-dose timepoints. Due to the limited number of patients with antibodies against Columvi, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.

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

5.2 Pharmacokinetic Properties

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

Absorption

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

Distribution

Following IV administration, the central volume of distribution was 3,34 L, which is close to total serum volume. The peripheral volume of distribution was 2,35 L.

Metabolism

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

Elimination

The glofitamab serum concentration-time data are described by a population pharmacokinetic model with two compartments and both time-independent clearance and time-varying clearance. The time-independent clearance pathway was estimated as 0,633 L/day and the initial time-varying clearance pathway as 0,814 L/day, with an exponential decay over time (K_{des} ~ 1,5/day). The estimated decay half-life from the initial total clearance value to the time-independent clearance only was estimated as 0,471days.

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

Pharmacokinetics in Special Populations

Paediatric Population

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

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Geriatric Population

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

Renal impairment

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

Hepatic impairment

Population pharmacokinetic analyses showed hepatic impairment does not affect the pharmacokinetics of glofitamab. The pharmacokinetic of glofitamab in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1,5 × ULN or AST > ULN) were similar to those with normal hepatic functions. No dose adjustment is required for patients with mild hepatic impairment. Columvi has not been studied in patients with moderate and severe hepatic impairment.

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 glofitamab (B-cell depletion, target-dependent T-cell activation, and cytokine release), the available safety data with glofitamab, and the data on other anti-CD20 antibodies, the risk for teratogenicity

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is low. Prolonged B-cell depletion can lead to increased risk of opportunistic infection, which may cause foetal loss. Transient CRS associated with glofitamab administration may also be harmful to the foetus.

Other

In a study in cynomolgus monkeys, animals experiencing severe CRS after a single intravenous dose of glofitamab (0,1 mg/kg) without obinutuzumab pre-treatment had erosions in the gastrointestinal tract and inflammatory cell infiltrates in spleen and sinusoids of the liver and sporadically in some other organs. These inflammatory cell infiltrates were likely secondary to cytokine-induced immune cell activation.

Pre-treatment with obinutuzumab resulted in the attenuation of glofitamab-induced cytokine release and related adverse effects by depleting B cells in peripheral blood and lymphoid tissue. This allowed at least 10 times higher doses of glofitamab (1 mg/kg) in cynomolgus monkeys resulting in a C_{max} of up to 5 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.

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

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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.

Columvi when diluted with 0,9 % or 0,45 % sodium chloride solution is compatible with syringes composed of PP.

No incompatibilities have been observed with infusion sets with product-contacting surfaces of polyurethane (PUR), PVC, or PE, polybutadiene (PBD), polyetherurethane (PEU), polycarbonate (PC), silicone, polytetrafluoroethylene (PTFE), or acrylonitrile butadiene styrene (ABS), and in-line filter membranes composed of polyethersulfone (PES) or polysulfone. The use of in-line filter membranes is optional.

6.3 Shelf life

36 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.

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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 grey 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 grey 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 12) 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 12). 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

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- When administering Columvi using syringe infusion, withdraw the entire content of the infusion bag into a syringe. Alternatively, a two-syringe method using a connector can be used to prepare the dose for the syringe pump infusion.

Table 12 Dilution of Columvi for Infusion

Dose of Columvi to be administered	Size of 0,9% or 0,45% sodium chloride solution infusion bag	Volume of 0,9% or 0,45% sodium chloride solution to be withdrawn and discarded	Volume of Columvi concentrate to be added
2,5 mg	50 mL	27,5 mL	2,5 mL
	100 mL	77,5 mL	2,5 mL
10 mg	50 mL	10 mL	10 mL
	100 mL	10 mL	10 mL
30 mg	50 mL	30 mL	30 mL
	100 mL	30 mL	30 mL

Administration

Only administer as an intravenous infusion.

Do not administer as an intravenous push or bolus.

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

The Columvi infusion bag or syringe may empty before the recommended duration of infusion is reached. To ensure the entire dose of Columvi is administered, clear the infusion line by replacing the emptied Columvi infusion bag or syringe with an infusion bag or syringe containing 0,9 % or 0,45 % sodium chloride solution connected to the same infusion line. Continue the infusion at the same rate until the recommended infusion duration is reached according to Table 2.

Disposal of unused/expired medicines

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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

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10. DATE OF REVISION OF THE TEXT

860 10 May 2026