Summary Report of Benefit-Risk Assessment

LUNSUMIO CONCENTRATE FOR SOLUTION FOR INFUSION 1MG/ML, 30MG/30ML

NEW DRUG APPLICATION

Active Ingredient(s)	Mosunetuzumab
Product Registrant	Roche Singapore Pte. Ltd.
Product Registration Number	SIN17001P, SIN17002P
Application Route	Abridged
Date of Approval	8 May 2024

Table of Contents

A INTRODUCTION

Lunsumio as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.

The active substance, mosunetuzumab, is an anti-CD20/CD3 bispecific antibody targeting CD20-expressing B-cells. Engagement of both arms of mosunetuzumab results in the formation of an immunologic synapse between a target B cell and a cytotoxic T cell leading to T-cell activation. Subsequent directed release of perforin and granzymes from activated T cell induce B-cell lysis leading to cell death.

Lunsumio is available as concentrate for solution for infusion containing 1mg/mL or 30mg/30mL of mosunetuzumab. Other ingredients in the vial are L-histidine, glacial acetic acid, L-methionine, sucrose, polysorbate 20 and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, mosunetuzumab, and the drug product Lunsumio are manufactured at Genentech Inc, South San Francisco, USA.

Drug substance:

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

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

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

The packaging is stainless steel or Hastelloy tanks. The stability data presented was adequate to support the storage of the drug substance at -20ºC with a shelf life of 48months.

Drug product:

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

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

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

The container closure system is a clear type I glass vial with fluororesin-laminated rubber stopper, aluminium seal with plastic flip-off cap. The stability data submitted was adequate to support the approved shelf life of 24 months when stored between 2ºC to 8ºC; and in-use stability testing was performed to support the in-use period after reconstitution is 24 hours at 2ºC to 8ºC and 24 hours at ambient temperature (9ºC to 30ºC).

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of mosunetuzumab was based on a single pivotal study GO29781. This was an open-label, multi-centre, multi-cohort Phase I/II trial evaluating mosunetuzumab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. There were 5 groups (Group A, B, D, E and F) enrolled in the study, with Group B comprised 11 dose escalation and expansion cohorts of mosunetuzumab administered by intravenous (IV) infusion. The data supporting the indication sought in this application was derived from patients with follicular lymphoma (FL) treated with mosunetuzumab IV at the recommended Phase II dose (RP2D) in cohort B11 (n = 90). In the study, patients with relapsed or refractory FL (grade 1-3A) were required to have received at least two prior systemic therapies, including an anti-CD20 monoclonal antibody and an alkylating agent. Patients received mosunetuzumab intravenously as follows (RP2D):

- Cycle 1 Day 1 – 1mg
- Cycle 1 Day 8 – 2 mg
- Cycle 1 Day 15 – 60 mg
- Cycle 2 Day 1 – 60 mg
- Cycle 3 and beyond Day 1 – 30 mg

The primary efficacy endpoint was Independent Review Facility (IRF)-assessed Complete Response (CR) rate according to standard NHL response criteria (Cheson et al. 2007). The secondary efficacy endpoints were (i) Investigator-assessed CR rate; (ii) Objective Response Rate (ORR); (iii) Duration of Complete Response (DOCR); (iv) Duration of Response (DOR); (v) Progression-free survival (PFS) and (vi) Overall Survival. Tumour assessments were based on physical examinations, computed tomography (CT) scans, fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scans and/or magnetic resonance imaging (MRI) scans, and bone marrow examinations.

The study was a single-arm study with historical control comparator. Comparisons of CR rates between the efficacy-evaluable population and the historical control CR rate for the R/R FL population was conducted using an exact binomial test with two-sided alpha level of 5% to evaluate whether mosunetuzumab treatment results in a statistically significant increase in CR rate. 14% was selected as the historical control CR rate based on the CR rate demonstrated for a phosphoinositide 3-kinase (PI3K) inhibitor, copanlisib, which was investigated in a similar patient population and setting. The primary endpoint of CR rate is acceptable as a surrogate endpoint that is considered reasonably likely to be predictive of clinical benefit in relapsed or refractory FL.

The primary efficacy population comprised 90 patients with relapsed or refractory FL who had received at least two prior systemic therapies (R/R FL ≥2) and were treated with mosunetuzumab IV monotherapy at the RP2D/intended registration dose (referred as B11 FL RP2D cohort). The patients in the cohort had a median age of 60 years (range: 29-90 years). The majority of patients were White (82.2%) and male (61.1%), with Eastern Cooperative Oncology Group (ECOG) performance status of 0 (58.9%) or 1 (41.1%). Most patients at study entry had advanced Stage III/IV disease (76.7%). The median number of prior lines of anti-lymphoma therapies received was 3.0 (range: 2-10). In addition to anti-CD20 agents and alkylators (all patients), prior cancer therapies included anthracyclines (82.2%), autologous stem cell transplant (21.1%), PI3K inhibitors (18.9%), immunomodulatory imide drugs (14.4%), Bruton's Tyrosine Kinase (BTK) inhibitors (6.7%), and chimeric antigen receptor-modified T-cell therapy (CAR-T) (3.3%). Most of the patients who entered the study had FL that was refractory to their last prior cancer therapy (68.9%), had been refractory at least one time to a prior anti-CD20 therapy (78.9%), and were double refractory to a prior anti-CD20 therapy and an alkylator agent (53.3%).

The primary efficacy endpoint of the study was met at the time of the primary analysis (data cut-off date of 15 March 2021), with an IRF-assessed CR rate of 57.8% (95% CI: 46.9, 68.1), which was statistically significantly greater than a historical control CR rate of 14% for patients with R/R FL ≥2 prior therapies ($p<0.0001$). As of the updated data cut-off date of 27 Aug 2021, the primary efficacy endpoint, CR (by IRF) was 60.0% (95% CI: 49.1, 70.2). The Investigator-assessed CR rate was 60.0% (95% CI: 49.1, 70.2) and was the same as the IRF-assessed CR rate.

The IRF-assessed ORR (Partial Response [PR] or CR) was 80.0% (95% CI: 70.3, 87.7) and was consistent with the Investigator-assessed ORR of 77.8% (95% CI: 67.8, 85.9). The median IRF-assessed DOCR was not estimable, however the K-M estimated event-free rate among patients with a CR at 18 months after the first CR was 63.7% (95% CI: 48.0, 79.4), while the estimated median IRF-assessed DOR was 22.8 months (95% CI: 9.7, NE). The IRF assessed PFS was not fully mature (46.7% events) and OS was immature (8.9% events). The estimated median PFS was 17.9 months (95% CI: 10.1, NE) and OS was not estimable.

Overview of Efficacy Results

Patient population	**B11 FL RP2D cohort (n=90)**	
	INV-assessed	**IRF-assessed**
Best Overall Response		
Responders (CR or PR), n (%), (95% CI)	70 (77.8%) (67.8, 85.9)	72 (80.0%) (70.3, 87.7)
Complete Response, n (%), (95% CI)	54 (60.0%) (49.1, 70.2)	54 (60.0%) (49.1, 70.2)
Partial Response, n (%)	16 (17.8%)	18 (20.0%)
Stable Disease, n (%)	8 (8.9%)	7 (7.8%)
Progressive Disease, n (%)	10 (11.1%)	9 (10.0%)
Not Evaluable (NE), n (%)	1 (1.1%)	0
Missing or not done, n (%)	1 (1.1%)	2 (2.2%)
Duration of Complete Response		
Patients with event, n (%)	12/54 (22.2%)	16/54 (29.6%)
Median, months 95% CI)	NE (17.8, NE)	NE (14.6, NE)
K-M event-free proportion, % (95% CI)		
12-months	80.4% (68.8, 92.0)	71.4% (57.9, 84.9)
18-months	66.6% (45.5, 87.8)	63.7% (48.0, 79.4)

Duration of Responses Patients with event, n (%) Median, months (95% CI) K-M event-free proportion, % (95% CI) 12-months 18-months	 27/70 (38.6%) 22.8 (18.7, NE) 64.8% (53.1, 76.5) 62.5% (50.4, 74.7)	 29/72 (40.3%) 22.8 (9.7, NE) 61.8% (50.0, 73.7) 56.9% (44.1, 69.6)
Progression-Free Survival Patients with event, n (%) Median, months 95% CI) K-M 12-month event-free proportion, % (95% CI)	41 (45.6%) 21.1 (11.8, NE) 57.6 (46.8, 68.4)	42 (46.7%) 17.9 (10.1, NE) 57.7 (46.9, 68.4)
Overall Survival Patients with event, n (%) Median, months 95% CI) K-M 12-month event-free proportion, % (95% CI)	8 (8.9%) NE (NE, NE) 93.0% (87.6, 98.4)	

Data cut-off date 27 August 2021

There were limitations with the single-arm, open label design of the study GO29781. In particular, the absence of a randomised control group did not allow any meaningful interpretation of the time-to-event efficacy endpoints PFS and OS. Nonetheless, considering that the majority of patients who entered the study had FL that was refractory to their last prior cancer therapy (68.9%) and to a prior anti-CD20 therapy (78.9%), as well as double refractory to a prior anti-CD20 therapy and an alkylator agent (53.3%), the overall evidence on efficacy as demonstrated by CR rate (60.0% [95% CI: 49.1, 70.2]) and ORR (80.0% [95% CI: 70.3, 87.7]), was deemed reasonable in patients with R/R FL after ≥2 prior systemic therapies. The favourable results were consistently observed with the secondary endpoints (DOCR, DOR). In view of the limited efficacy data, results from the ongoing confirmatory Phase III study, GO42909, evaluating mosunetuzumab in combination with lenalidomide versus rituximab in combination with lenalidomide in patients with follicular lymphoma after at least one line of systemic therapy, would be required to confirm the clinical benefit of mosunetuzumab.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of mosunetuzumab was assessed in the primary safety population of the B11 RP2D cohort (n = 218 patients). The cohort consisted of 4 indication-specific sub-cohorts, and all patients received mosunetuzumab at doses of 1/2/60/30 mg (RP2D/intended registration dose). In addition to the FL patient cohort (B11 FL RP2D; n = 90 patients) which represents the patient population for the proposed indication, the B11 RP2D cohort included diffuse large B-cell lymphoma/ transformed follicular lymphoma patients (n = 88), mantle cell lymphoma patients (n = 25), and Richter's transformation patients (n = 14).

Overview of Safety Profile

	B11 RP2D Cohort (n=218)	**B11 FL RP2D Cohort (n=90)**
Total number of patients with at least one AE	214 (98.2%)	90 (100%)
Total number of patents with at least one: Fatal AE Fatal AE (excluding Grade 5 PD)	 32 (14.7%) 4 (1.8%)	 2 (2.2%) 1 (1.1%)

SAE	114 (52.3%)	42 (46.7%)
SAE (excluding Grade 5 PD)	100 (45.9%)	42 (46.7%)
Mosunetuzumab-related SAE	75 (34.4%)	30 (33.3%)
Mosunetuzumab-related AE	188 (86.2%)	83 (92.2%)
AE of Grade 3-4	145 (66.5%)	63 (70.0%)
AE leading to withdrawal from mosunetuzumab treatment	9 (4.1%)	4 (4.4%)

AE= adverse event; PD=progressive disease; SAE=serious adverse event

In the primary safety population, the majority of patients treated with mosunetuzumab experienced at least one adverse event (AE) of any grade. The most common AE reported was cytokine release syndrome (CRS)[1] (39.4%), which occurred primarily in Cycle 1. CRS events were predominantly Grade 1–2 and reversible with all events resolved. Other common AEs (≥ 20% incidence) were fatigue, neutropenia/neutrophil count decreased, pyrexia, hypophosphatemia, and headache.

Grade 3-4 AEs were reported in 66.5% of patients. The most frequently reported Grade 3-4 AEs (≥5%) were neutropenia/neutrophil count decreased (24.3%), hypophosphatemia (14.7%), anaemia/haemoglobin decreased (8.3%), thrombocytopenia/platelet count decreased (6.9%), and hyperglycaemia (5.5%). The majority of Grade 3-4 AEs were manageable with dose modification or interruption of mosunetuzumab.

Serious adverse events (SAE) including the Grade 5 AEs were reported in 114/218 (52.3%) of patients. The most frequent SAEs (≥2% of patients) were CRS (20.6%), malignant neoplasm progression (12.8%), pyrexia (4.6%), and pneumonia (3.2%). Adverse events led to the discontinuation of mosunetuzumab treatment in 9/218 of patients (4.1%).

Grade 5 AEs (fatal AEs) were reported during the initial treatment with mosunetuzumab for 32/218 patients (14.7%). The majority, 28/32 Grade 5 AEs, were disease progression occurring during the protocol-specified AE reporting period. The non-disease progression Grade 5 AEs were pneumonia, sepsis, cholangitis, and death (not otherwise specified).

The AEs of special interests (AESIs) reported with mosunetuzumab were CRS, neurological AEs, tumour flare and serious infections. Based on the mechanism of action of mosunetuzumab, T-cell activation against CD20-expressing cells may lead to an excess of systemic cytokine release, which may result in serious events. CRS is an important identified risk for mosunetuzumab. Overall, mosunetuzumab demonstrated a manageable CRS profile, including a low number of Grade ≥3 CRS events and no fatal CRS events in the clinical study. The majority of CRS events occurred in the first cycle of mosunetuzumab administration, mostly associated either with Day 1 or Day 15 dose administrations. The median duration of CRS events was 3 days (range 1-29 days) and all CRS events resolved. Information and guidance for premedication, monitoring and management of CRS risks have been provided in the package insert. Additional risk minimization measures including provision of patient educational materials would be required to ensure the necessary risk mitigation.

Serious neurological AEs were reported in 6.4% of patients and those reported in more than one patient were confusional state, subdural hematoma and neurotoxicity. A total of 9/218 patients (4.1%) experienced tumour flare events following initial treatment with mosunetuzumab. Serious infections were reported in 37/218 patients (17.0%), with pneumonia being the most frequent. Serious infections are not unexpected with mosunetuzumab

[1] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for CRS

administration due to its mode of action resulting in B-cell depletion. These AESIs have been adequately described in the warnings and precautions section of the package insert.

Overall, the AEs profile in the FL sub-cohort was consistent with that of the primary safety population. While treatment with mosunetuzumab was associated with considerable toxicities, the proportion of patients who discontinued treatment due to AEs remained low (4.1%), suggesting that the treatment was generally tolerable. Most AEs requiring intervention could be managed and were resolved following dose interruptions, dose modification, and/or supportive care. Considering the advanced nature of disease and the heavily pretreated patient population, the safety profile of mosunetuzumab in relapsed or refractory FL was assessed to be acceptable.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The clinical course of FL is characterized by a series of remissions and relapses, with generally increasing refractoriness and decreasing duration of response to therapy. The duration of remissions tends to become progressively shorter with each subsequent treatment and the disease typically becomes increasingly refractory to anti-CD20 and chemotherapy, limiting the utility and effectiveness of these therapies. Taken together, there is an unmet need for patients with R/R FL who have received ≥2 prior therapies, particularly for patients who are R/R to different classes of agents and are left with limited treatment options.

In the open-label, multi-cohort Phase I/II Study GO29781, mosunetuzumab IV monotherapy at the RP2D/intended registration dose demonstrated an IRR-assessed CR rate of 60.0% (95% CI: 49.1, 70.2) and ORR rate of 80.0% (95% CI: 70.3, 87.7). The responses achieved by mosunetuzumab were durable, while the median DOCR has not been reached, an estimated 63.7% (95% CI: 48.0, 79.4) of patients continued to benefit from remission at 18 months after first CR. The results supported the efficacy of the treatment considering the high CR rate in a patient population who have received at least 2 prior therapies and are associated with poor prognosis.

The AE with highest frequency was CRS events (39.4%) which were predominantly Grade 1-2, limited primarily to Cycle 1 and were manageable and reversible as all events were resolved. Other common AEs were fatigue, neutropenia/neutrophil count decreased, pyrexia, hypophosphatemia, and headache. CRS is a significant safety concern associated with T-cell engaging bispecific antibodies. Other adverse events of significant interest included neurological AEs, tumour flare and serious infections. These adverse events have been adequately described in the package insert, and guidance on management are presented in the package insert to support prescribers to mitigate the risks. As part of risk management plan, a patient card will be provided to the physician for distribution to patients to inform and explain the risks of CRS.

Overall, while mosunetuzumab was associated with significant toxicities, given the magnitude of the observed CR and ORR rates, and the durability of the response, the benefits of mosunetuzumab outweigh the risks in the treatment of patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies.

The results of the ongoing Phase III study GO42909 would be required to confirm the clinical benefit of mosunetuzumab.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of mosunetuzumab for the treatment of patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies was deemed favourable and approval of the product registration was granted on 9 May 2024. The approval of this application is subject to the submission of Study GO42909 to confirm the clinical benefit and favourable overall risk-benefit profile.

APPROVED PACKAGE INSERT AT REGISTRATION

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

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Lunsumio®

Mosunetuzumab

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Antineoplastic agents
ATC code: L01FX25

1.2 TYPE OF DOSAGE FORM

Concentrate for solution for Infusion

1.3 ROUTE OF ADMINISTRATION

Intravenous (IV) Infusion

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile Product

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient(s): mosunetuzumab

Mosunetuzumab is a full-length, humanized anti-CD20/CD3 T-cell dependent bispecific antibody of an immunoglobulin (Ig)G1 isotype that is produced in Chinese hamster ovary (CHO) cells.

Lunsumio is provided as a sterile, colorless, preservative-free concentrate for solution for intravenous infusion formulated at 1 mg/mL mosunetuzumab in colorless type I borosilicate single-use glass vials with fluororesin-laminated latex-free rubber stopper and aluminium seal with plastic flip-off cap.

- 1 mg in a 2 mL vial
- 30 mg in a 50 mL vial

Excipients: Glacial acetic acid, L-histidine, L-methionine, polysorbate 20, sucrose and water for injection.

The pH of lunsumio is between 5.5 to 6.1 and the osmolality is between 240 to 333 mOsm/kg.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

Lunsumio as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.

2.2 DOSAGE AND ADMINISTRATION

General

Lunsumio must only be administered as an intravenous infusion under the supervision of a qualified healthcare professional with appropriate medical support to manage severe reactions such as cytokine release syndrome and neurologic toxicity. *(see Section 2.4 Warnings and Precautions).*

Do not administer as an IV push or bolus.

Prophylaxis and premedication

Lunsumio should be administered to well-hydrated patients. Table 1 provides details on recommended premedication for cytokine release syndrome and infusion related reactions.

Table 1 Premedication to be administered to patients prior to Lunsumio Infusion

Patients requiring premedication	Premedication	Dosage	Administration
Cycles 1 and 2: all patients Cycles 3+: patients who experienced any grade CRS with previous dose	Corticosteroid	Dexamethasone 20 mg IV or methylprednisolone 80 mg IV	Complete at least 1 hour prior to infusion
	Anti-histamine	Diphenhydramine hydrochloride 50 100 mg or equivalent oral or IV antihistamine	At least 30 minutes prior to infusion
	Anti-pyretic	Oral acetaminophen or paracetamol (500-1000 mg)	At least 30 minutes prior to infusion

The recommended dose of Lunsumio for each 21-day cycle is detailed in Table 2.

Table 2 Dose of Lunsumio for patients with Follicular Lymphoma

Day of Treatment		Dose of Lunsumio	Rate of infusion
Cycle 1	Day 1	1 mg	Infusions of Lunsumio in Cycle 1 should be administered over a minimum of 4 hours.
	Day 8	2 mg	
	Day 15	60 mg	
Cycle 2	Day 1	60 mg	If the infusions were well-tolerated in Cycle 1, subsequent infusions of Lunsumio may be administered over 2 hours.
Cycle 3+	Day 1	30 mg	

Duration of Treatment

Lunsumio should be administered for 8 cycles unless a patient experiences unacceptable toxicity or disease progression.

For patients who achieve a complete response, no further treatment beyond 8 cycles is required. For patients who achieve a partial response or have stable disease in response to treatment with Lunsumio after 8 cycles, an additional 9 cycles of treatment (17 cycles total) should be administered, unless a patient experiences unacceptable toxicity or disease progression.

Delayed or Missed Doses

If any dose in cycle 1 is delayed for >7 days, the previous tolerated dose should be repeated prior to resuming the planned treatment schedule.

If a dose interruption occurs between cycles 1 and 2 that results in a treatment-free interval of ≥6 weeks, administer Lunsumio at 1 mg on Day 1, 2 mg on Day 8, then resume the planned cycle 2 treatment of 60 mg on Day 15.

If a dose interruption occurs that results in a treatment-free interval of ≥6 weeks between any cycles in cycle 3 onwards, administer Lunsumio at 1 mg on Day 1, 2 mg on Day 8, then resume the planned treatment schedule of 30 mg on Day 15.

Dose Modifications

Identify cytokine release syndrome (CRS) based on clinical presentation (see section 2.4 *Warnings and Precautions*). Evaluate for and treat other causes of fever, hypoxia, and hypotension, such as infections/sepsis. Infusion related reactions (IRR) may be clinically indistinguishable from manifestations of CRS. If CRS or IRR is suspected, manage according to the recommendations in Table 3.

Table 3 CRS[1] Grading and Management

CRS Grade	CRS Management[2]	Next Scheduled Infusion of Lunsumio
Grade 1 Fever ≥38ºC	If CRS occurs during infusion: • Interrupt infusion and treat symptoms • Re-start infusion at the same rate when symptoms resolve • If symptoms recur with re-administration, discontinue current infusion If CRS occurs post-infusion: • Treat symptoms If CRS lasts >48 hours after symptomatic management: • Consider dexamethasone[3] and/or tocilizumab[4]	Ensure symptoms are resolved for at least 72 hours prior to next infusion Monitor patient more frequently
Grade 2 Fever ≥38ºC and/or hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen[5] by nasal cannula or blow-by	If CRS occurs during infusion: • Interrupt infusion and treat symptoms • Re-start infusion at 50% rate when symptoms resolve • If symptoms recur with re-administration, discontinue current dose If CRS occurs post-infusion: • Treat symptoms If no improvement occurs after symptomatic management: • Consider dexamethasone[3] and/or tocilizumab[4]	Ensure symptoms are resolved for at least 72 hours prior to next infusion Maximize premedication as appropriate[6] Consider infusing the next dose at 50% rate, with more frequent monitoring[7]
Grade 3 Fever ≥38ºC and/or hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high flow oxygen[7] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	If CRS occurs during infusion: • Discontinue current infusion • Treat symptoms • Administer dexamethasone[3] and tocilizumab[4] If CRS occurs post-infusion: • Treat symptoms • Administer dexamethasone[3] and tocilizumab[4] If CRS is refractory to dexamethasone and tocilizumab[5]: • Consider alternative immunosuppressants[8] and methylprednisolone 1000 mg/day IV until clinical improvement	Ensure symptoms are resolved for at least 72 hours prior to next infusion. Hospitalize for the next infusion. Maximize premedication as appropriate.[6] Administer the next infusion at 50% rate.
Grade 4 Fever ≥38ºC 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 or post-infusion: • Permanently discontinue treatment with Lunsumio • Treat symptoms • Administer dexamethasone[3] and tocilizumab[4] If CRS is refractory to dexamethasone and tocilizumab: • Consider alternative immunosuppressants[8] and methylprednisolone 1000 mg/day IV	

[1] ASTCT = American Society for Transplant and Cellular Therapy. Premedication may mask fever, therefore if clinical presentation is consistent with CRS, please follow these management guidelines
[2] If CRS is refractory to management, consider other causes including hemophagocytic lymphohistiocytosis
[3] Dexamethasone should be administered at 10 mg IV every 6 hours (or equivalent) until clinical improvement
[4] Tocilizumab should be administered at a dose of 8 mg/kg IV (8 mg/kg for participants at a weight of ≥30 kg only; 12mg/kg for participants at a weight of <30 kg; doses exceeding 800 mg per infusion are not recommended); repeat every 8 hours as necessary (up to a maximum of 4 doses)
[5] Low-flow oxygen is defined as oxygen delivered at <6 L/minute
[6] Refer to Table 1 for additional information
[7] High-flow oxygen is defined as oxygen delivered at ≥6 L/minute
[8] Riegler L et al. (2019)

Management recommendations for neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), is summarized in Table 4. At the first sign of neurologic toxicity, including ICANS, withhold Lunsumio and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care.

Table 4 Recommendations for Management of Neurologic Toxicity (including ICANS)

Adverse Reaction	Severity[1,2]	Actions
Neurologic Toxicity[1] (Including ICANS[2])	Grade 2	• Withold Lunsumio until neurologic toxicity symptoms improve to Grade 1 or baseline for at least 72 hours.[3] • Provide supportive therapy. If ICANS, manage per current practice guidelines.
	Grade 3	• Withold Lunsumio until neurologic toxicity symptoms improve to Grade 1 or baseline for at least 72 hours.[3] • Provide supportive therapy, which may include intensive care, and consider neurology evaluation. If ICANS, manage per current practice guidelines. • If recurrence, permanently discontinue Lunsumio.
	Grade 4	• Permanently discontinue Lunsumio. • Provide supportive therapy, which may include intensive care, and consider neurology evaluation. If ICANS, manage per current practice guidelines.

[1]Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.
[2]Based on American Society for Transplantation and cellular therapy (ASTCT) 2019 grading for ICANS.
[3]For recommendations on restarting Lunsumio after dose delays, see Section 2.2 Dosage and Administration.

Dose modifications for other clinically significant adverse reactions

Patients who experience grade 3 or 4 reactions should have treatment temporarily withheld until symptoms are resolved.

2.2.1 Special Dosage Instructions

Pediatric use

The safety and efficacy of Lunsumio in children below 18 years of age have not been established.

Geriatric use

No dose adjustment of Lunsumio is required in patients ≥ 65 years of age (see section 2.5.5 *Use in Special Populations, Geriatric Use*).

Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. A recommended dose has not been determined for patients with CrCl <30 mL/min (see sections 2.5.6 *Renal Impairment* and 3.2.5 *Pharmacokinetics in Special Populations*).

Hepatic Impairment

No dose adjustment of Lunsumio is required for patients with mild hepatic impairment [total bilirubin greater than upper limit of normal (ULN) and ≤ 1.5x ULN or aspartate transaminase greater than ULN]. (*see 2.5.7 Hepatic Impairment* and *3.2.5 Pharmacokinetics in special populations*). A recommended dose has not been determined for Lunsumio in patients with moderate or severe hepatic impairment.

2.3 CONTRAINDICATIONS

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

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

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)

CRS, including life-threatening reactions, have occurred in patients receiving Lunsumio. Signs and symptoms included pyrexia, chills, hypotension, tachycardia, hypoxia, and headache. Infusion related reactions may be clinically indistinguishable from manifestations of CRS. CRS events occurred predominantly in cycle 1 and were mainly associated with Day 1 and Day 15 dose administrations.

Premedicate patients with corticosteroids, antipyretics and antihistamines at least through cycle 2. Ensure adequate hydration prior to the administration of Lunsumio. Monitor patients for signs or symptoms of CRS. Counsel patient to seek immediate medical attention should signs or symptoms of CRS occur at any time. Institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated (see section *2.3 Dosage and Administration*).

Immunisation

Live and/or live-attenuated vaccines should not be given concurrently with Lunsumio. Studies have not been conducted in patients who recently received live vaccines.

Neurologic Toxicity

Lunsumio can cause serious neurologic toxicity, including ICANS.

The most frequent neurologic toxicities were headache, peripheral neuropathy, dizziness, and mental status changes (including confusional state, disturbance in attention, cognitive disorder, delirium, encephalopathy, and somnolence).

Coadministration of Lunsumio with other products that cause dizziness or mental status changes may increase the risk of neurologic toxicity.

Monitor patients for signs and symptoms of neurologic toxicity during treatment. At the first sign of neurologic toxicity, including ICANS, immediately evaluate the patient, consider neurology evaluation as appropriate, and provide supportive therapy based on severity; withhold or permanently discontinue Lunsumio based on severity and follow management recommendations.

Patients who experience neurologic toxicity such as tremors, dizziness, insomnia, severe neurotoxicity, or any other adverse reactions that impair consciousness should be evaluated, including potential neurology evaluation, and patients at increased risk should be advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

Serious infections

Serious infections such as pneumonia, bacteremia, and sepsis or septic shock have occurred in patients receiving Lunsumio, some of which were life-threatening or fatal events. Febrile neutropenia was observed in patients after receiving Lunsumio infusion.

Lunsumio should not be administered in the presence of active infections. Caution should be exercised when considering the use of Lunsumio in patients with a history of recurring or chronic infections (e.g. chronic, active Epstein-Barr Virus), with underlying conditions that may predispose to infections or who have had significant prior immunosuppressive treatment. Administer prophylactic antibacterial, antiviral and/or antifungal medications, as appropriate. Monitor patients for signs and symptoms of infection before and after Lunsumio administration and treat appropriately. In the event of febrile neutropenia, evaluate for infection and manage with antibiotics, fluids and other supportive care.

Tumor flare

Tumor flare has been reported in patients treated with Lunsumio. Manifestations included new or worsening pleural effusions, localized pain and swelling at the sites of lymphoma lesions and tumor inflammation. Consistent with the mechanism of action of Lunsumio, tumor flare is likely due to the influx of T-cells into tumor sites following Lunsumio administration.

There are no specific risk factors for tumor flare that have been identified, however, there is a heightened risk of compromise and morbidity due to mass effect secondary to tumor flare in patients with bulky tumors located in close proximity to airways and/or a vital organ. Monitoring and evaluation for tumor flare at critical anatomical sites is recommended in patients treated with Lunsumio.

Tumor lysis syndrome (TLS)

TLS has been reported in patients receiving Lunsumio. Ensure adequate hydration prior to the administration of Lunsumio. Administer prophylactic anti-hyperuricemic therapy (e.g. allopurinol, rasburicase), as appropriate. Monitor patients for signs or symptoms of TLS, especially patients with high tumor burden or rapidly proliferative tumors, and patients with reduced renal function. Monitor blood chemistries and manage abnormalities promptly.

2.4.2 Drug Abuse and Dependence

Lunsumio does not have the potential for abuse and dependence.

2.4.3 Ability to Drive and Use Machines

Lunsumio may have a minor influence on the ability to drive and use machines.

Patients who experience events that impair consciousness should be evaluated and advised not to drive and refrain from operating heavy or potentially dangerous machinery until events are resolved.

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential

No text (see section *3.3.3 Impairment of Fertility*).

Contraception

Women of childbearing potential should use contraception while receiving Lunsumio and for at least 3 months after the last infusion of Lunsumio (see section *3.2.4 Pharmacokinetic Properties, Elimination*).

2.5.2 Pregnancy

Lunsumio should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. There are no adequate and well-controlled data from studies in pregnant women; however, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-

CD20 antibodies during pregnancy. (see section *3.3.4 Nonclinical Safety, Reproductive Toxicity*)

Labor and Delivery
The safe use of Lunsumio during labor and delivery has not been studied.

2.5.3 Lactation
It is unknown whether Lunsumio is excreted in human breast milk or has any effect on the breastfed child and on milk production. Because human IgG is excreted in human milk, and the potential for mosunetuzumab absorption leading to B-cell depletion is unknown, women should be advised to discontinue breastfeeding during Lunsumio therapy.

2.5.4 Pediatric Use
The safety and efficacy of Lunsumio in children and adolescents (<18 years of age) has not been studied.

2.5.5 Geriatric Use
Among the 218 patients treated with Lunsumio, 94 (43%) were 65 years of age or older. No clinically important differences in safety or effectiveness of Lunsumio were observed between these patients and younger patients.

2.5.6 Renal Impairment
The safety and efficacy of Lunsumio in patients with renal impairment has not been formally studied. Patients with mild and moderate renal impairment were included in clinical trials. Lunsumio is a monoclonal antibody and cleared via catabolism (rather than renal excretion), and a change in dose is not expected to be required for patients with renal impairment *(see section 3.2.5 Pharmacokinetics in Special Populations, Renal Impairment)*.

2.5.7 Hepatic Impairment
The safety and efficacy of Lunsumio in patients with hepatic impairment has not been formally studied. Patients with mild hepatic impairment were included in clinical trials. Lunsumio is a monoclonal antibody and cleared via catabolism (rather than hepatic metabolism), and a change in dose is not expected to be required for patients with hepatic impairment *(see section 3.2.5 Pharmacokinetics in Special Populations, Hepatic Impairment)*.

2.6 UNDESIRABLE EFFECTS
2.6.1 Clinical Trials
The adverse drug reactions (ADRs) described in this section were identified from the clinical studies in patients treated at the recommended dose (n=218). The median number of cycles was 8, 37% received 8 cycles, and 15% received more than 8 cycles up to 17 cycles.

Table 5 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Lunsumio.

Table 5 Summary of Adverse Drug Reactions Occurring in Patients Treated with Lunsumio

MedDRA PT	All grades (%)	Grade 3 – 4 (%)	Frequency Category
Blood and lymphatic system disorders			
Neutropenia[1]	27.5	24.3	Very common
Anemia	15.1	8.3	Very common
Thrombocytopenia[2]	11.5	6.9	Very common
Febrile neutropenia	2.3	2.3	Common
Gastrointestinal disorders			
Diarrhea	17.4	0	Very common
General disorders and administration site conditions			
Pyrexia	24.3	1.8	Very common
Chills	10.6	0.5	Very common
Immune system disorders			
Cytokine release syndrome[3]	39.4	2.8	Very common
Infections and infestations			
Upper respiratory tract infection	9.6	1.4	Common
Urinary tract infection	6.9	1.4	Common
Pneumonia	5.5	2.3	Common
Investigations			
Alanine aminotransferase, increased	10.6	4.6	Very common
Aspartate aminotransferase, increased	6.9	3.2	Common
Metabolism and nutrition disorders			
Hyperglycaemia	7.8	5.5	Very common
Hypophosphatemia	22.5	14.7	Very common
Hypokalemia	15.6	1.8	Very common
Hypomagnesemia	13.3	0	Very common
Tumor lysis syndrome	0.9	0.9	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Tumor flare	1.8	1.4	Common
Nervous system disorders			
Headache	20.2	0.5	Very common
Skin and subcutaneous tissue disorders			
Rash	19.3	0.9	Very common
Pruritus	14.2	0	Very common
Dry skin	12.4	0	Very common

[1] Neutropenia includes neutropenia and neutrophil count decreased
[2] Thrombocytopenia includes thrombocytopenia and platelet count decreased
[3] American Society for Transplant and Cellular Therapy

Additional information for selected adverse drug reactions
The data below reflect information for significant adverse reactions for Lunsumio.

Cytokine release syndrome
Cytokine release syndrome (ASTCT grading system) of any grade occurred in 39% (86/218) of patients, with grade 2 occurring in 14%, grade 3 occurring in 2.3%, and grade 4 occurring in 0.5% of patients treated with Lunsumio. The one patient with the grade 4 event was a patient with FL in the leukemic phase and also experienced concurrent TLS. No patients had a fatal CRS event.

CRS of any grade occurred in 15% of patients after the Cycle 1, Day 1 dose; 5% after the Cycle 1, Day 8 dose; 33% after the Cycle 1, Day 15 dose, 5% occurring in patients after the Cycle 2 and 1% in Cycles 3 and beyond. The median time to CRS onset from the start of administration in Cycle 1 Day 1 was 5 hours (range: 1-73 hours), Cycle 1 Day 8 was 28 hours (range: 5-81 hours), Cycle 1 Day 15 was 25 hours (range: 0.1-391 hours), and Cycle 2 Day 1 was 46 hours (range: 12-82 hours). CRS resolved in all patients, and the median duration of CRS events was 3 days (range 1-29 days).

Of the 86 patients that experienced CRS, the most common signs and symptoms of CRS included pyrexia (98%), chills (36%), hypotension (35%), tachycardia (24%), hypoxia (22%) and headache (16%).

Sixteen percent (34/218) of patients received tocilizumab and/or a corticosteroid, 10% (21/218) received tocilizumab, 10% (22/218) received corticosteroids, including 4% (9/218) who received both tocilizumab and corticosteroids.

In patients experiencing grade 2 CRS, 48% (16/33) of patients were treated with symptomatic management without corticosteroids or tocilizumab, 33% (11/33) received corticosteroids, 30% (10/33) received tocilizumab, and 12% (4/33) received both corticosteroids and tocilizumab. Patients with grade 3 (n=5) or grade 4 (n=1) CRS received tocilizumab, corticosteroids, vasopressors and/or oxygen supplementation.

Hospitalizations due to CRS occurred in 20% (44/218) of patients and the median duration of hospitalization was 5 days (range 0-30 days).

Neutropenia
Neutropenia of any grade occurred in 28% (60/218), including 24% grade 3-4 events. The median time to onset of first neutropenia/neutrophil count decreased events was 48 days (range: 1-280 days), with median duration of 8 days (range: 1-314 days). Of the 60 patients who had neutropenia/neutrophil count decreased events, 68% (41/60) received G-CSF treatment to treat the events.

Serious Infections
Serious infections of any grade occurred in 17% (37/218) of patients. Four (1.8%) patients experienced serious infections concurrently with grade 3-4 neutropenia. The median time to onset of first serious infection was 50 days (range: 1-561 days), with median duration of 12 days (range: 2-174 days). grade 5 events occurred in 0.9% (2/218) patients, which included pneumonia and sepsis.

Tumor Flare
Tumor flare (including pleural effusion and tumor inflammation) occurred in 4% (9/218) of patients, which included 1.8% grade 2 and 2.3% grade 3 events. The median time to onset was 13 days (range: 5-84 days), and median duration was 10 days (range: 1-77 days).

Tumor Lysis Syndrome (TLS)
TLS occurred in 0.9% (2/218) of patients, concurrent with CRS. One patient with follicular lymphoma was in the leukemic phase who experienced grade 4 TLS. TLS onset was on days 2 and 24, and resolved within 3 and 6 days, respectively.

2.6.2 Post marketing Experience
Not applicable

2.7 OVERDOSE
Not applicable

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
No dedicated pharmacokinetic drug-drug interaction studies have been conducted with mosunetuzumab. Physiologically based pharmacokinetics modeling and simulations based on IL-6 and cytochrome P450 (CYP) 3A interaction indicated a low risk of cytokine-mediated drug-drug interaction potential for mosunetuzumab. No dose adjustment for Lunsumio is recommended with coadministration of Lunsumio with small molecule drugs, which are CYP3A substrates.

Upon initiation of Lunsumio in patients who are receiving concomitant drugs that are sensitive CYP3A substrates with a narrow therapeutic index, monitor for effect or drug concentration or dose adjust the CYP3A substrate accordingly, if warranted.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS
3.1 PHARMACODYNAMIC PROPERTIES
3.1.1 Mechanism of Action
Mosunetuzumab is an anti-CD20/CD3 bispecific antibody targeting CD20-expressing B-cells. It is a conditional agonist; targeted B-cell killing is observed only upon simultaneous binding to CD20 on B-cells and CD3 on T-cells. Engagement of both arms of mosunetuzumab results in the formation of an immunologic synapse between a target B cell and a cytotoxic T cell leading to T-cell activation. Subsequent directed release of perforin and granzymes from activated T cell induce B-cell lysis leading to cell death.

3.1.2 Pharmacodynamic Effects
Lunsumio caused B-cell depletion (defined as CD19 B-cell counts < 0.07 x 10^9/L) and hypogammaglobulinemia (defined as IgG levels < 500 mg/dL).

3.1.3 Clinical / Efficacy Studies
An open-label, multicenter, multi-cohort study (GO29781) was conducted to evaluate Lunsumio in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. In the follicular lymphoma (FL) cohort (n=90), patients with relapsed or refractory FL (grade 1-3A) were required to have received at least two prior systemic therapies, including an anti-CD20 monoclonal antibody and an alkylating agent.

The study excluded patients with active autoimmune disease, active infections (i.e. chronic active EBV, acute or chronic hepatitis C, hepatitis B, HIV), progressive multifocal leukoencephalopathy, a history of CNS lymphoma, a history of macrophage activation syndrome/hemophagocytic lymphohistiocytosis, prior allogeneic stem cell transplant, or prior organ transplantation.

Patients received Lunsumio intravenously as follows:
- Cycle 1 Day 1 – 1mg
- Cycle 1 Day 8 – 2 mg
- Cycle 1 Day 15 – 60 mg
- Cycle 2 Day 1 – 60 mg
- Cycle 3+ Day 1 – 30 mg

The median number of cycles was 8, 59% received 8 cycles, and 18% received more than 8 cycles up to 17 cycles.

The median age was 60 years (range: 29-90 years) with 31% being > age 65, 61% were male, 82% were White, 9% were Asian, 4% were Black, 100% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and 34% of patients had bulky disease (at least one lesion > 6 cm). The median number of prior therapies was 3 (range: 2-10), with 38% receiving 2 prior therapies, 31% receiving 3 prior therapies and 31% receiving more than 3 prior therapies.

All patients received prior anti-CD20 and alkylator therapies, 21% received autologous stem cell transplant, 19% received PI3K inhibitors, 9% received prior rituximab plus lenalidomide therapy, and 3% received CAR-T therapies. Seventy-nine percent of patients were refractory to prior anti-CD20 monoclonal antibody therapy and 53% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy. Sixty-nine percent of patients were refractory to the last prior therapy and 52% had progression of disease within 24 months of first systemic therapy.

The primary efficacy endpoint was complete response as assessed by an independent review facility [according to standard criteria for NHL (Cheson 2007)]. The efficacy results are summarized in Table 6.

Table 6 Summary of efficacy in patients with FL

Efficacy parameter	Lunsumio N=90
	Median observation time 18.3 months
Complete Response (CR), n (%) (95% CI)	54 (60.0) (49.1, 70.2)
Objective Response Rate (ORR), n (%) Partial Response (PR), n (%) (95% CI)	72 (80.0) (70.3, 87.7) 18 (20.0) (12.3, 29.8)
Duration of Response (DOR)[1] Patients with event, n (%) Median, months (95% CI) K-M event-free proportion 12 months (95% CI) 18 months (95% CI)	 29 (40.3) 22.8 (9.7, NR) 61.8 (50.0, 73.7) 56.9 (44.1, 69.6)
Duration of Response in Patients who achieved CR (DORC)[2] Patients with event, n (%) Median, months (95% CI) K-M event-free proportion 12 months (95% CI) 18 months (95% CI)	 16 (29.6) 22.8 (18.7, NR) 76.4 (64.6, 88.1) 70.2 (56.7, 83.8)

CI = confidence interval; K-M = Kaplan-Meier; NR = not reached
[1] DOR is defined as the time from the initial occurrence of a documented PR or CR until documented disease progression or death due to any cause, whichever occurs first
[2] DORC is defined as the time from the initial occurrence of a documented PR or CR until documented disease progression or death due to any cause, whichever occurs first, in patients with a best overall response of CR

Baseline levels in EORTC QLQ-C30 Physical Functioning, EORTC QLQ-C30 Fatigue and FACT-Lym Subscale were maintained during treatment (up to cycle 8).

3.1.4 Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of anti-Lunsumio antibodies in the study described below with the incidence of antibodies to other products may be misleading.

The immunogenicity of Lunsumio was evaluated using an enzyme-linked immunosorbent assay (ELISA). No patients tested positive for anti-Lunsumio antibodies in 418 ADA-evaluable patients who received Lunsumio single-agent IV treatments in Study GO27981. Based on the available information, the clinical relevance of anti-Lunsumio antibodies could not be assessed.

3.2 PHARMACOKINETIC PROPERTIES
Lunsumio PK exposure increased in an approximately dose-proportional manner over the dose range studied. The population PK following intravenous administrations of Lunsumio was described by a 2-compartment PK model with time-dependent clearance, which was parameterized as descending to a steady-state plateau (CL_{ss}) from a baseline value (CL_{base}) at the start of treatment according to transitional half-life of 16.3 days. Moderate to high pharmacokinetic variability for Lunsumio was observed and characterized by inter-individual variability ranging from 18% to 86% coefficient of variation (CV) for mosunetuzumab PK parameters.

After the first two cycles (i.e. 42 days) of the dosing with mosunetuzumab, the serum concentration reaches the C_{max} at the end of dose of cycle 2 Day 1 of the mosunetuzumab IV infusion with an average maximal concentration of 17.9 µg/mL and %CV of 49.6%. The average total two cycles (42 days) mosunetuzumab exposure AUC was 126 day·mg/mL with %CV of 44.4%.

3.2.1 Absorption
Lunsumio is administered intravenously.

3.2.2 Distribution
The population estimate of central volume of distribution for Lunsumio was 5.49 L with intravenous infusion of Lunsumio.

3.2.3 Metabolism
The metabolic pathway of Lunsumio has not been directly studied. Like other protein therapeutics, Lunsumio is expected to be degraded into small peptides and amino acids via catabolic pathways.

3.2.4 Elimination
Based on a population pharmacokinetic analysis, the estimated mean steady-state clearance (CL_{ss}) and baseline clearance ($CL_{baseline}$) were 1.08 L/day and 0.584 L/day, respectively. The terminal half-life estimate was 16.1 days at steady state based on population PK model estimates.

Pharmacokinetics in Special Populations
No clinically meaningful baseline covariates were found for mosunetuzumab PK requiring dose adjustments.

Pediatric Population
No studies have been conducted to investigate the pharmacokinetics of Lunsumio in pediatric patients (<18 years old).

Geriatric Population
Age did not have an effect on the pharmacokinetics of Lunsumio based on a population PK analysis with patients aged 19-96 years (n= 439). No clinically important difference was observed in the pharmacokinetics of Lunsumio for patients in this age group.

Renal impairment
The population pharmacokinetic analysis of Lunsumio showed that creatinine clearance (CrCl) does not affect pharmacokinetics of Lunsumio. Pharmacokinetics of Lunsumio in patients with mild (CrCl 60 to 89 mL/min, n=178) or moderate (CrCl 30 to 59 mL/min, n= 53) renal impairment were similar to those in patients with normal renal function (CrCl ≥ 90 mL/min, n=200). Pharmacokinetic data in patients with severe renal impairment (CrCl 15 to 29 mL/min) is limited (n=1), therefore no dosage recommendations can be made. Lunsumio was not studied in patients with end-stage renal disease and/or who are on dialysis.

Hepatic impairment
The population pharmacokinetic analysis of Lunsumio showed that hepatic impairment does not affect pharmacokinetics of Lunsumio. Pharmacokinetics of Lunsumio in patients with mild hepatic impairment (total bilirubin >ULN to 1.5 x ULN or AST > ULN, n=53) were similar to those in patients with normal hepatic function (n=384). The number of patients with moderate hepatic impairment is limited (total bilirubin >1.5–3 × ULN, any AST, n=2) and no patients with severe hepatic impairment have been studied.

3.3 NONCLINICAL SAFETY
3.3.1 Carcinogenicity
No carcinogenicity studies have been conducted with Lunsumio.

3.3.2 Genotoxicity
No genotoxicity studies have been conducted with Lunsumio. As an antibody, Lunsumio is not expected to interact directly with DNA.

3.3.3 Impairment of Fertility
An assessment of the male and female reproductive organs was included in a 26-week chronic toxicity study in sexually mature cynomolgus monkeys administered by intravenous infusion. mosunetuzumab had no effect on either male or female reproductive organs at exposures (AUC) approximately 5 times the AUC in patients receiving the recommended dose.

3.3.4 Reproductive toxicity
No developmental toxicity studies in animals have been conducted with Lunsumio. Based on low placental transfer of antibodies during the first trimester, the mechanism of action and available data of mosunetuzumab and the data on the anti-CD20 antibody class, the risk for teratogenicity is low. Studies with mosunetuzumab in non-pregnant animals have demonstrated that prolonged B-cell depletion can lead to increased risk of opportunistic infection, which may cause fetal loss. Transient CRS associated with Lunsumio administration may also be harmful to pregnancy.

3.3.5 Other
Key nonclinical findings with Lunsumio identified in single- and repeat-dose toxicity studies up to 26-weeks in duration included transient post-dose CRS primarily limited to the first dose, vascular/perivascular inflammatory cell infiltrates that were primarily in the CNS and infrequently in other organs that were likely secondary to cytokine release and immune cell activation, and increased susceptibility to infection following chronic dosing due to sustained B-cell depletion.

All of the findings were considered pharmacologically-mediated effects and reversible. Across studies there was a single incidence of convulsion in one animal at C_{max} and AUC exposures over 50- and 20-times, respectively, higher than those in patients exposed to Lunsumio for the similar duration. No other neurological abnormalities were observed in any toxicity studies.

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

Shelf life
As registered locally
This medicine should not be used after the expiry date (EXP) shown on the pack.

Shelf-life of the solution for infusion containing the product
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C and 24 hours at 9°C-30°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user

and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Lunsumio does not contain antimicrobial preservatives. Therefore, care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Lunsumio must be diluted into an infusion bag containing 0.9% or 0.45% sodium chloride solution by a healthcare professional using aseptic technique prior to administration.

Use sterile needle and syringe to prepare Lunsumio. The product contains no preservative and is intended for single-dose use only. Discard any unused portion.

A dedicated infusion line should be used during intravenous administration.

Do not use an in-line filter to administer Lunsumio. Drip chamber filters can be used to administer Lunsumio.

Dilution

1. Withdraw a volume of 0.9% or 0.45% sodium chloride solution equal to the volume of the Lunsumio required for the patient's dose from the infusion bag according to the Table 7 below and discard.
2. Withdraw the required volume of Lunsumio from the vial using a sterile syringe and needle and dilute into the infusion bag. Discard any unused portion left in the vial.

Table 7 Dilution of Lunsumio

Day of Treatment		Dose of Lunsumio	Volume of Lunsumio in 0.9% or 0.45% sodium chloride solution	Size of infusion bag
Cycle 1	Day 1	1 mg	1 mL	50 mL or 100 mL
	Day 8	2 mg	2 mL	50 mL or 100 mL
	Day 15	60 mg	60 mL	250 mL
Cycle 2	Day 1	60 mg	60 mL	250 mL
Cycle 3+	Day 1	30 mg	30 mL	100 mL or 250 mL

3. Gently mix the infusion bag by slowly inverting the bag. *Do not shake.*
4. Inspect the infusion bag for particulates and discard if present.

Incompatibilities

- Do not mix Lunsumio with, or administer through the same infusion line, as other medicinal products.
- Do not use diluents other than 0.9% or 0.45% sodium chloride solution to dilute Lunsumio since its use has not been tested.
- No incompatibilities have been observed between Lunsumio and IV infusion bags with product contacting materials of polyvinyl chloride (PVC), or polyolefins (PO) such as polyethylene (PE) and polypropylene (PP). In addition, no incompatibilities have been observed with infusion sets or infusion aids with product contacting materials of PVC, PE, polyurethane (PUR), polybutadiene (PBD), silicone, acrylonitrile butadiene styrene (ABS), polycarbonate (PC), polyetherurethane (PEU), fluorinated ethylene propylene (FEP), or polytetrafluorethylene (PTFE), or with drip chamber filter membrane composed of polyamide (PA).

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.

4.3 PACKS

Vials 1mg/ml 1
Vials 30mg/30ml 1

Medicine: keep out of reach of children

Current at Apr 2024

Roche F. Hoffmann-La Roche Ltd, Basel, Switzerland