EU RISK MANAGEMENT PLAN FOR LUNSUMIO®/MOSUNETUZUMAB

RMP version to be assessed as part of this application: 4.0

RMP Version number: 4.0

Data lock point for this RMP: 9 January 2026

Date of final sign off: See electronic signature on the last page of this document

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Rationale for Submitting an Updated RMP

This mosunetuzumab European Union Risk Management Plan (EU RMP) Version 4.0 was prepared to update the study milestones for Study GO42909, with the projected interim analysis Clinical Study Report (CSR) due in [redacted], the projected primary analysis CSR due in [redacted], and the projected final CSR after survival follow up period due in [redacted].

Summary of Significant Changes in This RMP

Part III: Module III.2 (Table 38) and Module III.3 (Table 39)	• The study milestones for PASS Category 3 Study GO42909 have been updated.
Part IV	• The study milestones for PAES Study GO42909 have been updated.
Annex 2	• The study milestones for the ongoing PASS Study GO42909 have been updated.
Annex 3	• Protocol for PASS Category 3 Study GO42909 has been updated to Version 8 in Part C.
Annex 5	• Protocol for PAES Study GO42909 has been updated to Version 8.
Annex 8	• Updated to reflect the changes made to this EU RMP.

EU = European Union; PAES = post-authorization efficacy study; PASS = post-authorization safety study; RMP = Risk Management Plan.

Additional minor changes have been made to improve clarity and consistency.

Other RMP Versions under Evaluation

RMP Version Number: Not applicable

Submitted on: Not applicable

Procedure Number: Not applicable

Details of Currently Approved RMP

RMP Version Number: Version 3.1

Approved with Procedure Number: EMEA/H/C/005680/X/0015

Date of approval (opinion date): 18 September 2025

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[redacted] (Deputy EU QPPV) | Date

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[redacted] | Date

PART I: PRODUCT(S) OVERVIEW

Table 1 Product(s) Overview

Active Substance(s) (INN or common name)	Mosunetuzumab
Pharmacotherapeutic group(s) (ATC Code)	L01FX25
Marketing Authorisation Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	Lunsumio®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Mosunetuzumab is a full-length, humanized anti-CD20/CD3 T-cell engaging bispecific antibody.
	Summary of mode of action: Mosunetuzumab is an anti-CD20/CD3 T-cell engaging 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 T-cell activation through the immunologic synapsis induce B-cell lysis leading to cell death.
	Important information about its composition: Mosunetuzumab is a full-length, humanized anti-CD20/CD3 immunoglobulin (Ig)G1 isotype that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.
Hyperlink to the Product Information	EU PI
Indication(s) in the EEA	Current: Lunsumio® 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.
	Proposed: the proposed indication for mosunetuzumab SC is the same as the current approved indication for mosunetuzumab IV

Table 1 Product(s) Overview (cont.)

<table>
<tr><td>Dosage in the EEA</td><td>Current:
Lunsumio® IV
The recommended dose of Lunsumio® for each 21-day cycle is:
<table>
<tr><th colspan="2">Day of Treatment</th><th>Dose of Lunsumio®</th><th>Rate of infusion</th></tr>
<tr><td rowspan="3">Cycle 1</td><td>Day 1</td><td>1 mg</td><td rowspan="3">Infusions of Lunsumio in Cycle 1 should be administered over a minimum of 4 hours.</td></tr>
<tr><td>Day 8</td><td>2 mg</td></tr>
<tr><td>Day 15</td><td>60 mg</td></tr>
<tr><td>Cycle 2</td><td>Day 1</td><td>60 mg</td><td rowspan="2">If the infusions were well-tolerated in Cycle 1, subsequent infusions of Lunsumio may be administered over 2 hours.</td></tr>
<tr><td>Cycles 3 and beyond</td><td>Day 1</td><td>30 mg</td></tr>
</table>
Proposed (if applicable):
Lunsumio® SC
The recommended dose of Lunsumio for each 21-day cycle is:
<table>
<tr><th colspan="2">Day of Treatment</th><th>Dose of Lunsumio</th></tr>
<tr><td rowspan="3">Cycle 1</td><td>Day 1</td><td>5 mg</td></tr>
<tr><td>Day 8</td><td>45 mg</td></tr>
<tr><td>Day 15</td><td>45 mg</td></tr>
<tr><td>Cycle 2 and beyond</td><td>Day 1</td><td>45 mg</td></tr>
</table></td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current:
<u>Lunsumio® IV</u>
Lunsumio® is provided as a clear, colorless liquid, pH 5.8 and osmolality of 240-356 mOsm/kg and concentrate for solution for infusion. Each vial contains:
• 1 mg of mosunetuzumab in 1 mL, at a concentration of 1 mg/mL.
• 30 mg of mosunetuzumab in 30 mL, at a concentration of 1 mg/mL.

Proposed (if applicable)
<u>Lunsumio® SC</u>
Lunsumio® is provided as a clear, colorless to slightly brownish-yellow, preservative free liquid, pH 5.8, solution for injection. Osmolality of the 5 mg mosunetuzumab is 260-360 mOsm/kg and osmolality of the 45 mg mosunetuzumab is 275-375 mOsm/kg. Each vial contains:
• 5 mg of mosunetuzumab in 0.5 mL, at a concentration of 10 mg/mL.
• 45 mg of mosunetuzumab in 1 mL, at a concentration of 45 mg/mL</td></tr>
<tr><td>Is or will the product be subject to additional monitoring in the European Union?</td><td>Yes</td></tr>
</table>

Table 1 Product(s) Overview (cont.)

CHO=Chinese hamster ovary; FL=follicular lymphoma; IgG1=immunoglobulin G1; IV=intravenous; EEA = European Economic Area; INN= international non-proprietary name; SC = subcutaneous.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
ADR	adverse drug reaction
AE	Adverse event
AEGT	Adverse Event Group Term
AESI	Adverse event of special interest
ALT	Adverse event of special interest
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
BTK	Bruton’s tyrosine kinase
CAR	Chimeric antigen receptor
CDS	Core data sheet
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CNS	Central nervous system
CLL	Chronic lymphocytic leukemia
CR	Complete response
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSR	Clinical Study Report
DILI	Drug-induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLP	Data lock point
DoT	Duration of treatment
DSR	Drug Safety Report
EBV	Epstein-Barr Virus
ECIS	European Cancer Information System
EMA	European Medicines Agency
EU	European Union
FL	Follicular lymphoma
HTLV	Human T-cell lymphotropic virus
IARC	International Agency for Research on Cancer
IBD	International Birth Date
IEC-HS	Immune Effector Cell-associated HLH-Like Syndrome
ICANS	Immune effector cell-associated neurotoxicity syndrome

Abbreviation	Definition
ITT	Intent-to-treat
IUFD	intrauterine fetal death
IV	intravenous
MAA	Marketing Authorization Application
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MZL	Marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin lymphoma
PASS	post-authorization safety study
PBRER	Periodic Benefit Risk Evaluation Report
PBMC	Peripheral blood mononuclear cells
PFS	Progression-free survival
PIL	Patient Information Leaflet
PMBCL	Primary mediastinal B-cell lymphoma
PR	Partial response
PSUR	Periodic Safety Update Reports
PT	Prothrombin time
RMP	Risk Management Plan
SEER	Surveillance, Epidemiology, and End Results
SIC	Similar-in-class
SLL	Small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
TB	Total bilirubin
TF	Tumor flare
TFR	Tumor flare reaction
TLS	Tumor lysis syndrome
ULN	Upper limit of normal
USPI	United States Prescribing Information
WBC	White blood cells
EEA	European Economic Area
RoW	Rest of World

PART II: SAFETY SPECIFICATION

PART II: MODULE SI— EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA ≥2 PRIOR THERAPIES

Incidence

According to The International Agency for Research on Cancer (IARC), non-Hodgkin lymphoma (NHL) is the 11th most common cancer worldwide with more than 500,000 incident cases (all ages) estimated in 2020, accounting for an age-standardized incidence of 5.8 per 100,000 population worldwide. In Europe also, NHL is the 11th most common cancer among all cancer types, accounting for an age-standardized incidence of 8.4 per 100,000 population in 2020. In the United States, NHL is the seventh most common cancer with an age-standardized incidence of 12.1 per 100,000 population in 2020 (GLOBOCAN 2020). Table 2 describes the incidence of NHL worldwide, in the United States, Europe, Asia and Africa (available from Global Cancer Observatory [GLOBOCAN] 2020 database, World Health Organization [WHO]).

Follicular lymphoma (FL) is the most common indolent lymphoma and the second most common type of NHL, accounting for 10-20% of all NHL cases (Mounier et al. 2015, SEER 2020, Smith et al. 2015). According to the Surveillance, Epidemiology, and End Results (SEER) cancer statistics, the 5-year (2013-2017) age-adjusted incidence of FL in the US was 2.7 per 100,000 for both sexes. The age-adjusted rates for new FL cases have been falling on average 1.9% each year over 2008–2017 (SEER Cancer Statistics 2020). A study aimed to assess FL epidemiology in Poland based on 2000-2014 data from the Polish National Cancer Registry found that the total number of registered FL cases was 3928 with age-standardized incidence of 0.87 per 100,000 (Szumera-Ciećkiewicz et al. 2020). A similar population-based study (using Hematological Malignancy Research Network, the UK) between 2004 and 2012 reported that the annual age-standardized incidence of FL was 2.73 per 100,000 population (Smith et al. 2015). Another population-based study from Canada diagnosed 22,625 patients with FL between 1992 and 2010 with annual age-standardized incidence of 3.8 per 100,000 population (Le et al. 2019). A study among six Asian ethnic groups in the US between 1996 and 2004 observed that the age-standardized incidence rates (per 100,000 PY) of FL were 2.0 (for Asian Indian), 1.3 (Chinese), 1.0 (Filipino), 2.3 (Japanese), 1.0 (Koreans) and 1.9 (Vietnamese) (Carreon et al. 2008).

Prevalence

IARC estimates that over 1.5 million people are living with NHL (all ages) globally with a 5-year prevalence proportion of 19.8 per 100,000 population in 2020. In Europe, the 5–year prevalence of NHL was 52.0 per 100,000 population in 2020, while the prevalence of NHL was 72.6 per 100,000 population in the US (GLOBOCAN 2020).

Table 2 describes the prevalence of NHL worldwide, in the US, Europe, Asia, and Africa (available from GLOBOCAN 2020 database and fact sheets, WHO).

A population-based study (Hematological Malignancy Research Network, the UK) between 2004 and 2012 reported that the 3-year, 5-year and 10-year prevalence proportion of FL was 9.7, 14.8 and 25.2 per 100,000 respectively (Smith et al. 2015). Another population-based study in Sweden reported that the 2-year, 5-year and 10-year prevalence of FL in 2016 was 7.1, 16.9 and 28.4 per 100,000 population respectively. The prevalence increased by 27% between 2004 and 2016 with annual increase of 2.6% (Ekberg et al. 2020).

Table 2 Estimates of Non-Hodgkin Lymphoma- Incidence, Mortality, and 5-Year Prevalence in 2020 (all ages) in different geographic locations

Country	Incidence per 100,000 population (World age-standardized rate)	Mortality per 100,000 population (World age-standardized rate)	5-year Prevalence proportion (per 100,000 population)
Worldwide	5.8	2.6	19.8
Europe	8.4	2.6	52.0
United States	12.1	2.7	72.6
Asia	4.4	2.4	13.8
Africa	5.2	3.5	8.3

Source: GLOBOCAN 2020

Demographics

Age: The incidence of NHL has been reported to increase with age. Evidence available from the SEER Explorer database (2013-2017) demonstrates that in the US, patients aged ≥65 years show highest incidence (90.3 per 100,000) of NHL compared to those aged between 50 and 64 years (30.7 per 100,000) and <50 years (4.9 per 100,000) (SEER Explorer Database 2020). The European Cancer Information System (ECIS) reported that in 2020, the age-standardized incidence rate of NHL was 21.4 per 100,000 in patients aged between 50 and 64 years and 51.2 per 100,000 in patients aged ≥65 years (ECIS 2020). According to the data from Cancer Research UK, NHL incidence is strongly related to age, with the highest incidence rates being in the 80 to 84 age group. In the UK (2015-2017), age-specific incidence rates rise steadily from around age 45-49 and more steeply from around age 55-59. Highest rates are in the 80 to 84 age group for females and the 85 to 89 age group for males. Also, on average each year more than a third of new cases (36%) were in people aged ≥75 years (Cancer Research UK).

According to the Polish National Cancer Registry data, FL was primarily diagnosed in adults between 2000 and 2014, with a median age of 61 years (60 years for men and 61 years for women). About 10% of cases are observed before the age of 40 years. The highest number of cases in men occurred between 75 and 99 years of age, and between 65 and 74 years in women (Szumera-Ciećkiewicz et al. 2020). In the US, the SEER cancer statistics estimated that FL is most frequently diagnosed among people aged 55-64 years (27.4%) followed by people aged 65-74 years (27%) (SEER Cancer Statistics 2020).

Gender: Based on the data from the SEER Explorer database (2013-2017), the 5-year age-adjusted incidence of NHL was reported to be higher in men (23.8 per 100,000) compared to women (16.2 per 100,000) in the US (SEER Explorer Database 2020). In Europe, a similar trend was observed from the ECIS database that reported the age and sex-standardized incidence of 20.9 and 13.2 per 100,000 in men and women respectively in 2020 (ECIS 2020). A retrospective population-based study in the UK reported a higher annual age-standardized incidence of NHL in men (16.63 per 100,000) compared to women (11.92 per 100,000) in 2014 (Smith et al. 2015).

In other studies, the incidence of FL has been reported to be almost similar in men and women. A study in France reported an age-standardized incidence of 2.5 and 2.1 per 100,000 for men and women respectively in 2012 (Le Guyader-Peyrou et al. 2016). Similarly, a study in Poland reported exact same age-standardized incidence of 0.87 per 100,000 of FL for men and women between 2000 and 2014 (Szumera-Ciećkiewicz et al. 2020). From SEER cancer statistics data on FL, the age-standardized incidence (per 100,000) of FL was 2.9 (for men) and 2.5 (for women) in the US between 2013 and 2017 (SEER Cancer Statistics 2020).

Race: The incidence of NHL varied across different races in the US**.** The highest 5-year (2013-2017) age-adjusted incidence (per 100,000) was recorded for non-Hispanics Whites (20.6), followed by Hispanics (18.1) and Blacks (14.1), and was lowest for Asians (13.5) and American Indians (10.9) (SEER Explorer Database 2020).

A similar trend was observed for FL from a study using the SEER database from 1992 to 2010. The age-adjusted incidence (per 100,000) was observed to be highest for non-Hispanics Whites (4.07), followed by Hispanics (2.69) and lowest for Blacks (1.62) and Asians and Pacific Islander (1.62) (Lee et al. 2015).

Geographical distribution: Based on the data from the GLOBOCAN 2020 database, the incidence of NHL (per 100,000 population) was highest in the US (12.1), followed by Europe (8.4) and Africa (5.2) and lowest in Asia (4.4) (GLOBOCAN 2020).

The Main Existing Treatment Options

According to the European Society for Medical Oncology (ESMO) 2020 guidelines (Dreyling et al. 2020) and National Comprehensive Cancer Network (NCCN) guidelines

on B-cell lymphomas (NCCN 2024), in patients with limited low tumor burden (Stages I–II), radiotherapy (RT)-based treatment (ISRT, 24–30 Gy) is the preferred approach with a curative intent. A combination of localized irradiation with single agent rituximab may potentially provide the best balance between efficacy and side effects. In selected cases, watch-and-wait or rituximab monotherapy may be considered. In Stage I–II patients with a high tumor burden, adverse clinical prognostic features or in cases where ISRT is not feasible, systemic therapy as indicated for advanced stages should be applied.

Per ESMO 2020 guidelines, in the majority of patients with advanced stage III and IV disease, no curative therapy has been established yet. In asymptomatic advanced cases, watch-and-wait is the standard approach. Therapy should be initiated only upon the development of symptoms, including B symptoms, hematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion or rapid lymphoma progression. Obinutuzumab or rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or bendamustine should be used if complete remission and long progression-free survival (PFS) are the therapeutic goals. If there is evidence of a more aggressive clinical course, obinutuzumab/rituximab-CHOP should be applied. Extended anti-infectious prophylaxis should be considered after bendamustine-containing induction therapy. Antibody monotherapy (rituximab, radioimmunotherapy) or chlorambucil plus rituximab remain alternatives for patients with a low-risk profile or when conventional chemotherapy is contraindicated. Rituximab maintenance every 2 months for 2 years is recommended after immunochemotherapy. Alternatively, radioimmunotherapy consolidation may be considered after chemotherapy.

In early systemic relapses (< 12–24 months), a non-cross-resistant regimen is preferred. Rituximab should be added if the previous antibody-containing scheme achieved >6-12-month duration of remission. In rituximab-refractory cases or remissions lasting <6 months, obinutuzumab-bendamustine (or other chemotherapy regimen) plus obinutuzumab maintenance is recommended. Rituximab maintenance every 3 months for up to two years is recommended in relapsed cases. High-dose chemotherapy with autologous stem cell transplantation (ASCT) should be considered in patients who experience brief first remissions after rituximab-containing regimens. In relapsed FL, lenalidomide plus rituximab may be considered for patients with short remissions after chemotherapy. In symptomatic cases with low tumor burden, rituximab monotherapy may be applied. Radioimmunotherapy may be considered in elderly patients with comorbidities. In later relapses, a non-chemotherapy approach is recommended: lenalidomide plus rituximab; idelalisib in double-refractory cases only with anti-infectious prophylaxis (co-trimoxazole/acyclovir) and cytomegalovirus (CMV) monitoring. In selected younger patients with later relapses with a high-risk profile or relapse after ASCT, allogenic stem cell transplantation may be considered (Dreyling et al. 2020).

Phosphoinositide 3-kinase (PI3K) inhibitors (idelalisib, copanlisib, and duvelisib) had been granted accelerated approval for the treatment of relapsed/refractory (R/R) disease

after two prior therapies by the US Food and Drug Administration (FDA), though recently the Sponsors of idelalisib, copanlisib, and duvelisib have voluntarily withdrawn the accelerated approvals of these agents for FL in the United States. Umbralisib, a fourth PI3K inhibitor, had been granted accelerated approval by the FDA in R/R FL patients who have received at least three prior lines of systemic therapy but this accelerated approval was also voluntarily withdrawn by the Sponsor of umbralisib. The PI3K inhibitor withdrawals were due to class-wide safety findings and potential detriment in overall survival due to increased toxicity (NCCN 2024). In the European Union, both idelalisib and duvelisib have been granted full approvals for adult patients with FL that is refractory to two prior lines of treatment.

Zanubrutinib in combination with obinutuzumab is another option for patients with R/R FL who have received at least two prior systemic therapies, that was granted accelerated approval by the FDA and marketing authorization by the European Medicines Agency (EMA) for R/R FL after two or more lines of therapy.

Tazemetostat (Tazverik®), a histone methyltransferase inhibitor, has been approved by the FDA in R/R FL positive for enhancer zeste homolog 2 (EZH2) mutations as detected by the FDA approved companion diagnostic test and have received at least 2 prior systemic therapies for R/R FL patients who have no alternative treatment options.

Yescarta® (axicabtagene ciloleucel), a CD19-directed chimeric antigen receptor T-cell (CAR-T) therapy received accelerated approval by the FDA for R/R FL after two or more lines of systemic therapy. In the EU, Yescarta has received approval for the treatment of adult patients with R/R FL after three or more lines of systemic therapy.

The CD19-directed CAR-T therapy Kymriah (tisagenlecleucel) has received approval in the EU and accelerated approval from FDA for treatment of adult patients with R/R FL after two or more lines of systemic therapy.

Another CAR-T cell therapy Breyanzi® (lisocabtagene maraleucel) received accelerated approval in the US for R/R FL patients who have received two or more prior lines of systemic therapy.

Mosunetuzumab (Lunsumio®) received accelerated approval in the US and conditional marketing authorization in the EU for the treatment of patients with R/R FL after two or more lines of systemic therapy.

Another CD20/CD3 bispecific monoclonal antibody, epcoritamab (Epkinly™/Tepkinly) has received accelerated approval from FDA and conditional marketing authorization in the European Union for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. Odronextamab (Ordspono), a third CD20/CD3 bispecific monoclonal antibody, has received conditional marketing authorization in the European Union for the treatment of adult patients with

relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Risk Factors for the Disease

Older age is a strong risk factor for FL, with most cases occurring in people in their 60s or older. Western lifestyle including sedentary lifestyle, obesity, and diets high in meat and milk are associated with an increased risk of FL (Castellino et al. 2017). Medical history of Sjögren's syndrome, influenza vaccination, and heart disease may be associated with FL incidence (Ambinder et al. 2012). Influenza vaccination was associated with increased risk (OR = 1.98, 95% CI 1.23–3.18) of FL while polio vaccination was associated with decreased risk (OR = 0.54, 95% CI 0.31–0.92) (Ambinder et al. 2012). Associations between FL and exposure to pesticides, industrial solvents, hair dyes, and alcohol/tobacco were inconsistent. Genetic risk factors include variants at the 6p21.32 region of the MHC II locus, polymorphisms of the DNA repair gene XRCC3, and UV exposure in individuals with certain polymorphisms of the vitamin D receptor (Ambinder et al. 2012). Infection with certain viruses and bacteria may also increase risk (Ambinder et al. 2012). Viruses that have been implicated in the development of FL include the Epstein-Barr Virus (EBV), human T-cell lymphotropic virus (HTLV) type I and the herpesvirus associated with Kaposi's sarcoma (i.e., human herpesvirus HHV-8) (Ma et al. 2012).

Natural History of the Indicated Condition in the (Untreated) Population

NHL ranks as the 11th most common cause of death among all cancers worldwide. An estimated 259,793 deaths were attributed to NHL in 2020 worldwide with an age-standardized mortality rate of 2.6 per 100,000 population. It is the 12th most common cancer death in Europe with 49,684 deaths and eighth most common in the US with 20,858 deaths in 2020 (GLOBOCAN 2020). Table 2 describes the mortality due to NHL worldwide, in the US, Europe, Asia, and Africa (available from GLOBOCAN 2020 database and fact sheets, WHO). Based on the SEER Explorer database, from 2000 to 2015, the 5-year and 10-year survival rate of NHL was 69.8% and 62.4% respectively, since the time of diagnosis (SEER Explorer Database 2020).

A European population-based data (EUROCARE-5) revealed that for FL, the 5-year net survival in northern Europe was 64% (1999–2001) versus 75% (2002–2004). Similarly, for Scotland and Wales, it was 71% versus 68%, for central Europe, it was 64% versus 72%, for southern Europe, it was 67% versus 73%, and for Eastern Europe, it was 50% versus 61% (Mounier et al. 2015). Per SEER cancer statistics, the 5-year relative survival for patients with FL was 89.0% in the United States between 2010 and 2016. The 5-year relative survival was 88.8% for Whites, 88.3% for Blacks and 91.2% for other races (SEER Cancer Statistics 2020). In Canada, the age-standardized mortality rate for FL during 1992–2010 was 0.13 cases per 100,000 population per year (Le et al. 2019).

Pregnancy and lactation

Pregnancy rates:

Lymphoma is the third most common malignancy occurring during pregnancy, with a reported frequency of 1 case per 6000 pregnancies in Western countries (Onishi et al. 2022). Diagnosis of NHL in pregnancy is estimated to be approximately 5 per 100,000 births (Maggen et al. 2021). FL accounts for approximately 10-20% of all NHL with median age 65 years at diagnosis and is therefore considered a disease of adults and elderly, hence resulting in limited evidence among pregnant females (Mounier et al. 2015, SEER 2020, Smith et al. 2015).

Adverse pregnancy outcomes:

Limited evidence was available for adverse pregnancy outcomes in FL patients. Information was available for adverse pregnancy outcomes in NHL patients without segregation by histological types. A study in Belgium between 1986 and 2019 included 80 patients diagnosed with NHL (8% FL) during pregnancy treated with either chemotherapy or were treatment naïve. A total of 75 ongoing pregnancies (all NHL subtypes) culminated in a live birth. There were 28 (37%) spontaneous deliveries, 2 (3%) preterm emergency caesarean sections and 45 (60%) planned deliveries. Of 39 preterm deliveries, 14 (36%) patients delivered spontaneously, 7 (18%) delivered as emergencies for medical or obstetric reasons, and 18 (46%) had a planned delivery for therapy planning. One pregnancy ended in a stillbirth after extensive vaginal bleeding, suggestive of placental abruption, prior to initiation of cancer treatment (Maggen et al. 2021). A retrospective study of clinically gathered data on 22 pregnant women with NHL in Japan showed that the 5-year overall survival was 63%. Among the 28 patients (22 NHL and 6 Hodgkin Lymphoma; 7 were diagnosed with lymphoma post-partum), 26 gave birth, 1 experienced intrauterine fetal death (IUFD) at 30 weeks of gestation and 1 experienced spontaneous abortion early in the first trimester. The incidence of spontaneous abortion, IUFD, and preterm birth was reported to be 3.6%, 3.6%, and 53.6% respectively (Onishi et al. 2022). A targeted literature review of 37 cases of mothers with high-grade NHL treated with rituximab during pregnancy was conducted from November 1997 to September 2021. The pregnancy outcomes of 19 women were published as individual case reports, while the pregnancy outcomes of 18 women were evaluated in 2 case reviews. Fatal fetal outcomes occurred in 3 (8%) pregnancies, with 2 pregnancies resulting in miscarriage and 1 resulting in stillborn (On and Chang 2022).

Pregnancy is an exclusion criterion in all mosunetuzumab clinical trials.

Important Co-Morbidities

Limited information was available for co-morbidities in FL patients. A retrospective study using SEER data from 1999 through 2013 identified 6109 patients with FL in the US. The most prevalent comorbid conditions present were hypertension (78.8%), diabetes (18.9%), congestive heart failure (7.6%), cardiovascular disease (7.1%)

(Kenzik et al. 2018). Other comorbid conditions included chronic renal failure, peripheral vascular disease, chronic obstructive pulmonary disease, liver disease, rheumatoid arthritis, gastric ulcers, paralysis, and acquired immune deficiency syndrome (Kenzik et al.2018). The comorbid conditions are however consistent among the elderly population.

PART II: MODULE SII— NONCLINICAL PART OF THE SAFETY SPECIFICATION

Mosunetuzumab has similar target binding affinity and in vitro potency in cynomolgus monkey (*Macaca fascicularis*) and human peripheral blood mononuclear cells (PBMCs). It does not bind to rodent CD3 or CD20 with measurable affinity. Therefore, the cynomolgus monkey was selected as the appropriate animal species for assessing the safety of mosunetuzumab.

The nonclinical toxicology program was designed to evaluate the safety profile of mosunetuzumab when administered intravenously (IV) or subcutaneously (SC) to support clinical development and registration of mosunetuzumab as an anti-cancer therapeutic. The toxicology program to date consists of IV and SC single- and repeat-dose toxicity studies with durations up to 26-weeks in cynomolgus monkeys, in vitro tissue cross-reactivity study in human and cynomolgus monkey tissues, and in vitro cytokine release assay in PBMCs. Safety pharmacology assessment including cardiovascular, respiratory, and neurobehavioral functional endpoints were incorporated into the single- and repeat-dose studies. Male and female reproductive assessments were conducted as a part of the 26-week chronic toxicity study in sexually mature cynomolgus monkeys.

Administration of mosunetuzumab in cynomolgus monkeys induces pharmacologic effects of transient T-cell activation and cytokine release, which are primarily limited to the first dose, and B-cell depletion in circulation and lymphoid tissues that was reversible following drug washout. The key mosunetuzumab-related toxicities are related to cytokine release, are generally limited to the first dose, and include cytokine release syndrome (CRS)-like clinical signs, hypotension, tachycardia, fever, indicators of inflammation consistent with cytokine release and acute phase reactions, transient changes in circulating leukocytes attributable to cytokine-related cell margination and redistribution, minimal hepatocellular degeneration and single-cell hepatocyte necrosis with associated minimal increases in ALT/AST possibly due to cytokine-mediated hepatocyte damage, and microscopic findings of vascular/perivascular inflammatory cell infiltrates. In the 26-week study, evidence of opportunistic infections secondary to mosunetuzumab-related B-cell depletion was present. With the exception of cytokine-related hypotension, no additional findings were noted in the safety pharmacology (cardiovascular, respiratory or neurological) assessment.

SC administration of mosunetuzumab in cynomolgus monkeys was as effective as IV dosing at the same dose level in inducing B-cell depletion, and effectively reduced cytokine release, eliminated acute toxicities, and reduced the incidence of vascular/perivascular findings in a repeat-dose study, suggesting that SC administration may be a viable approach to mitigate mosunetuzumab-related toxicities without compromising efficacy.

Key safety findings from nonclinical studies and relevance to human usage:

- **Cytokine Release Syndrome (CRS)-like clinical signs**

Post-dose clinical signs were observed following the first dose of mosunetuzumab ≥ 0.2 mg/kg IV and included emesis, mucoid feces, hypoactivity/hunched posture, red/swollen face, and salivation. The clinical signs generally resolved spontaneously within the day but required fluid support in individual animals. The affected animals had transient hypotension, elevated body temperature, tachycardia, and elevated levels of inflammatory markers such as C-reactive proteins (CRP) and fibrinogen, and prolonged prothrombin time and activated partial thromboplastin time (aPTT). These findings were primarily limited to the first dose and attributed to cytokine release and associated acute phase protein response with minimal activation of the coagulation system. Clinical signs following subsequent doses either using weekly dosing regimen of up to 1 mg/kg or step-dose regimen (i.e., 0.2 mg/kg on Day 1, 0.8 mg/kg on Day 2) followed by weekly dosing were rare and with reduced severity when present.

Relevance to human usage: Yes

Discussion: The mechanism of action of mosunetuzumab is driven by B-cell-dependent T-cell activation and subsequent T-cell-mediated B-cell killing. As observed with other CD3 engagers such as blinatumomab and CAR T-cell therapy, T-cell activation may lead to an excess of systemic cytokine release which may lead to serious and even fatal events (Blinatumomab USPI; Hopfinger 2019). Signs or symptoms of CRS observed in mosunetuzumab-treated patients include pyrexia, chills, headache, tachycardia, and hypoxia. CRS is an important identified risk for mosunetuzumab. Serious and life-threatening CRS events occurred in patients treated with mosunetuzumab; however, none were fatal (Section SVII.3). The majority of CRS events occurred in the first cycle of mosunetuzumab administration, when administered IV or SC.

- **Hematologic effects**

Administration of mosunetuzumab in cynomolgus monkeys induces pharmacologic effects of transient T-cell activation and cytokine release within hours of dosing, which were primarily limited to the first dose, and rapid and sustained B-cell depletion in circulation and lymphoid tissues, which was reversible following drug washout.

Concurrent with T-cell activation and cytokine release, transient decreases in circulating white blood cells (WBCs), lymphocyte, monocyte, neutrophils, eosinophil, basophil, and

platelets were present following the first dose and showed recovery between Days 4 and 8. Minimal or no changes were present following the subsequent doses. Decreased WBC counts were primarily driven by the drop in lymphocytes, which reached near nadir within two hours after the first dose. The decreases in neutrophil and platelet counts were less consistent across studies. When present, they were generally within the normal range. These findings were consistent with direct pharmacologic effects of mosunetuzumab on lymphocytes, e.g., B-cell depletion and T-cell activation–induced transient margination followed by expansion/redistribution, and secondary effects on the other blood cell types including activation and redistribution in response to cytokine/chemokine release.

Relevance to human usage: Yes

Discussion: Neutropenia is a known class effect with other CD20-targeted therapies. In nonclinical testing of mosunetuzumab in cynomolgus monkeys, hematology findings included transiently decreased neutrophil count following the first dose, followed by recovery between Days 4 and 8. These findings are considered to be due to cytokine/chemokine-induced cell activation and redistribution. Neutropenia has been identified as a common treatment emergent adverse reaction of mosunetuzumab in patients. This may be partly attributed to CRS-related neutropenia or other mechanism of action which has not yet been entirely understood in a clinical setting. Neutropenia is clinically manageable and reversible with G-CSF use. Neutropenia is an identified risk for mosunetuzumab (Section SVII.1.1).

- **Hepatotoxicity**

Transient and mild elevation of ALT and AST was observed in individual animals on Day 2 and/or Day 3 following the first IV administration of mosunetuzumab at 1 mg/kg, correlating with microscopic findings of minimal to mild hepatocellular degeneration, single-cell necrosis, and immune cell infiltration in the portal area. These findings were attributed to cytokine-induced hepatocellular damage and/or related immune cell infiltration. No microscopic evidence of liver injury or inflammation was present following subsequent doses in the 4-week or 26-week studies.

Relevance to human usage: Yes

Discussion: Elevations of transaminases and/or bilirubin have occurred in patients following the initial treatment of mosunetuzumab, were reversible and did not cause liver injury. In some cases, these events occurred concurrently with CRS. Risk of hepatic injury is a potential risk for mosunetuzumab (Section SVII.1.1).

- **Secondary infection:**

In the 26-week chronic toxicity study, one male and one female animal were euthanized prematurely (one male at the 0.1 mg/kg weekly dose level on Study Day 96, one female at the 0.5 mg/kg weekly dose level on Study Day 158) due to morbidity following diarrhea and/or significant weight loss. Key findings in these two animals included inflammation in the kidney, urinary bladder, and/or intestines, which were consistent with opportunistic ascending urinary and/or enteric infections. The remaining animals underwent scheduled necropsy following 26 weeks of dosing, and microscopic evaluation revealed evidence of increased incidence of ascending urinary infection in males in both 0.1 and 0.5 mg/kg groups. These infections were deemed secondary to immunosuppression due to mosunetuzumab-induced prolonged B-cell depletion.

Relevance to human usage: Yes

Discussion: Serious, life-threatening and fatal infections occurred in patients receiving mosunetuzumab and contributory factors may include the patient's immunocompromised status due to the underlying disease, mosunetuzumab-induced B-cell depletion and prior immunosuppressive treatment that may predispose to infections. Serious infections are an important identified risk for mosunetuzumab (Section SVII.3.1).

- **CNS and systemic vascular/perivascular inflammatory infiltration**:

Microscopic findings of minimal to mild vascular/perivascular inflammatory cell infiltrates were present in mosunetuzumab-treated monkeys. These changes were primarily observed within the brain white matter, with less incidence within spinal cord and sciatic nerve in the single-dose and 4-week studies, and in other organs including heart, liver, kidney, gastrointestinal tract, and gall bladder in the 26-week study. Microscopically they were generally characterized as minimal to mild, focal or multifocal mixed inflammatory cell infiltrates accompanied by the presence of reactive endothelial cells. In the brain, the changes were accompanied with local microglial reaction; however, no neuronal degeneration or vascular damage was observed. Additionally, these findings did not show any evidence of progression following chronic mosunetuzumab dosing, and were deemed reversible based on the absence of similar findings in animals assessed following recovery. These vascular/perivascular infiltrates may be secondary to cytokine/chemokine-induced up-regulation of chemokine receptors and adhesion molecules in the vessels of the brain and other tissues. Means to blunt and delay cytokine/chemokine peak including lower infusion rate and SC administration reduced the incidence and severity of the CNS vascular/perivascular infiltrates. In-life neurologic abnormalities were limited to one incidence of convulsion in one animal on Day 11 following mosunetuzumab IV infusion of 0.2/0.8/1.0 mg/kg on Day 1/Day 2/Day 8. The animal was euthanized for humane reasons. The CNS microscopic lesions in this animal were more extensive than those identified in the CNS of the remaining study animals at similar or higher dose and were considered causal for the clinical signs of convulsion. The C_{max} and AUC values (time-averaged over 7 days) in this animal were approximately 3.3-fold and 1.8-fold higher, respectively, than those in patients receiving mosunetuzumab treatment (1/2/60/30 mg) in Study GO29781; for patients, the steady-state Cycle 4 C_{max} and AUC (time averaged over 42 days) values were used as the reference and were derived from population pharmacokinetic modeling. No other neurologic abnormalities were observed in any toxicity studies even after chronic administration.

Relevance to human usage: Yes

Discussion: Described or characterized by data from CD19-directed CAR-T therapies, symptoms of Immune effector cell-associated neurotoxicity syndrome (ICANS) include tremor, dysgraphia, expressive aphasia, impaired attention and apraxia (Lee et al. 2019). The etiology of toxicity in these settings is not well known and may not be responsive to cytokine directed therapy such as tocilizumab, but has generally improved with treatment discontinuations and corticosteroids (Viardot et al. 2010; Kochenderfer et al. 2015). ICANS is considered an important identified risk for mosunetuzumab (see SVII.2 for additional information and DSR 1131379).

- **Cardiovascular effects**

Mosunetuzumab was associated with dose-dependent and transient hypotension (IV only at ≥ 0.2 mg/kg) and tachycardia (≥ 0.1 mg/kg IV or SC at 1 mg/kg). The effects were generally associated with the first dose and diminished or were absent following subsequent weekly administrations. These findings are consistent with cytokine release and associated acute phase protein reactions observed in the studies. With the exception of decreased RR, PR, and QT intervals due to increased heart rate, no quantitative or qualitative changes in electrocardiography were present.

Relevance to human usage: Yes

Discussion: Hypotension and tachycardia have been reported as symptoms of CRS in patients treated with mosunetuzumab. Because mosunetuzumab is a high molecular weight monoclonal antibody, which in theory has a low likelihood of direct interaction with cardiac ion channels, the risk of cardiac arrhythmia is low.

- **Reproductive and Developmental Toxicity**

Male and female reproductive assessments were conducted as a part of the 26-week chronic toxicity study in sexually mature cynomolgus monkeys. Evaluation included organ weights, and macroscopic and microscopic evaluation of male and female reproductive organs (including qualitative spermatogenesis progression for males and general phases of menstrual cycles for females). There were no mosunetuzumab-related effects on male or female reproductive assessment.

A weight of evidence-based risk assessment for potential developmental effects was conducted. Based on low placental transfer of antibodies during the first trimester, the mechanism of action and available data of mosunetuzumab, and the data from other Sponsor-owned anti-CD20 antibodies (e.g., rituximab [Rituxan® USPI], obinutuzumab [Gazyva® USPI], ocrelizumab [Ocrevus® USPI]), the risk for teratogenicity is low. Studies with mosunetuzumab in non-pregnant animals have demonstrated that prolonged B-cell depletion in the dam can lead to increased risk of opportunistic infection, which may result in fetal loss, as shown with ocrelizumab [Ocrevus® USPI]). Transient CRS associated with mosunetuzumab administration may also be harmful to pregnancy.

Relevance to human usage: Yes

Discussion: No clinical studies have been performed in pregnant women. Women of childbearing potential are advised to use highly effective contraception to avoid pregnancy while undergoing mosunetuzumab treatment and for at least three months after the last dose. Contraception use in male patients receiving mosunetuzumab is not required. No pregnancies have been reported in patients treated with mosunetuzumab.

- **Genotoxicity**

In accordance with the current ICH, genotoxicity studies have not been conducted with mosunetuzumab because the potential of biotechnology products, in particular high molecular weight monoclonal antibodies, to elicit DNA damage in somatic or germ cells via electrophilic reactions is unlikely.

- **Carcinogenicity**

No carcinogenicity studies have been conducted with mosunetuzumab.

These findings support treatment of the proposed patient population with mosunetuzumab when administered IV or SC.

PART II: MODULE SIII— CLINICAL TRIAL EXPOSURE

The mosunetuzumab exposure and safety data included in this RMP are derived from Study GO29781. A brief description of this study is presented below:

Study GO29781 is a first-in-human, multicenter, open-label, Phase I/II dose-escalation and expansion study evaluating the efficacy, safety and tolerability, and pharmacokinetics (PK) of mosunetuzumab as a single agent and in combination with Tecentriq® (atezolizumab) in patients with R/R B-cell NHL and chronic lymphocytic leukemia (CLL).

In dose-escalation cohorts, patients with NHL that are expected to express the CD20 antigen who have relapsed after or failed to respond to at least one prior systemic treatment regimen were enrolled. This included patients with Grades 1-3b FL; marginal zone lymphoma (MZL; including splenic, nodal, and extra-nodal), transformed indolent NHL, Richter's transformation, diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), small lymphocytic lymphoma (SLL), or mantle cell lymphoma (MCL), etc.

In the expansion cohorts, patients with the following NHL histologies were enrolled:

- FL patients (Grade 1-3a) who have relapsed after or failed to respond to at least two prior lines of systemic therapy and must have received prior treatment with an anti-CD20-directed therapy and an alkylating agent.
- DLBCL/transformed FL patients who have relapsed after or failed to respond to at least two prior systemic treatment regimens (including at least one prior regimen containing anthracycline, and at least one containing an anti–CD20-directed therapy).
- MCL patients who have relapsed after or failed to respond to at least one prior treatment regimen containing an approved Bruton's tyrosine kinase (BTK) inhibitor.

- R/R Richter's transformation patients who have relapsed after or failed to respond to at least one prior systemic treatment regimen (must have received anthracycline and an anti–CD20-directed therapy).

Safety data from Study GO29781 presented in this submission support the use of mosunetuzumab IV or SC for the treatment of adult patients with R/R FL who have received ≥2 prior therapies.

To provide a comprehensive understanding of the safety profile of mosunetuzumab IV, the safety data (based on the safety-evaluable population, defined as patients who had received at least one dose of mosunetuzumab) is based on the following three cohorts:

- **Group B:** patients in Cycle 1 step-up dosing in dose-escalation and dose-expansion stages, irrespective of histology, who received mosunetuzumab IV at doses and regimen as specified in Table 3 (n=414). These patients support the primary safety population in B11 RP2D (recommended Phase II dose) cohort to provide a comprehensive overview of the safety profile of mosunetuzumab monotherapy with the IV Cycle 1 step-up dosing schedule. Patients in Group B received mosunetuzumab IV every 21 days up to a maximum of 8 or 17 cycles until confirmed objective disease progression or unacceptable toxicity, whichever occurs first.
- **B11 RP2D cohort:** primary safety population of patients in Cohort B11 as part of Group B, irrespective of histology, who received mosunetuzumab IV at 1/2/60/30 mg (RP2D/approved dose). The B11 RP2D cohort consisted of four indication-specific cohorts, FL (n=90 patients), DLBCL/ trFL (n=88 patients), MCL (n=25 patients), and Richter's transformation (n=14 patients)[1], for a total of N=218.
- **B11 FL RP2D cohort:** patients in the FL indication-specific cohort in the B11 RP2D cohort (n=90), which represents the patient population for the approved indication of R/R FL patients with ≥2 prior therapies who received mosunetuzumab IV monotherapy at the approved dose of 1/2/60/30 mg.

To provide a comprehensive understanding of the safety profile of mosunetuzumab SC, the safety data (based on the safety-evaluable population, defined as patients who had received at least one dose of mosunetuzumab) is based on the following three cohorts:

- **Group F:** patients in Cycle 1 step-up dosing in dose-escalation and dose-expansion cohorts irrespective of histology, who received mosunetuzumab SC at doses and regimen as specified in Table 3 (N=181). These patients provide additional safety data to support the F2 RP2D cohort, which is the primary safety population for mosunetuzumab SC. Patients in Group F received mosunetuzumab SC every 21 days up to a maximum of 8 or 17 cycles until confirmed objective disease progression or unacceptable toxicity, whichever occurs first.

[1]One patient with melanoma instead of NHL was enrolled in error in the DLBCL/trFL indication-specific cohort of B11 RP2D cohort and received one dose of study treatment. The patient was included in the safety-evaluable population for Group B and B11 RP2D cohort.

- **F2 RP2D cohort:** primary safety population of patients in F2 cohorts, irrespective of histology, who received mosunetuzumab SC at 5/45/45 mg (RP2D/proposed dose). The F2 RP2D cohort consisted of the F2 dose escalation cohort (n = 4) and two indication-specific dose expansion cohorts, FL (n = 94) and DLBCL/trFL (n = 41), for a total of N = 139.
- **F2 FL RP2D cohort:** patients with FL in the F2 RP2D cohort (N = 94), who received mosunetuzumab SC at the proposed dose of 5/45/45 mg. This cohort represents the patient population for the proposed mosunetuzumab SC indication (adult patients with R/R FL who have received ≥2 prior systemic therapies [see Table 1]).

Table 3 details mosunetuzumab Group B and Group F populations, which studied mosunetuzumab monotherapy using Cycle 1 step-up dosing schedule via IV infusion or SC injection, respectively, in NHL patients.

Table 3 Description of Mosunetuzumab Group B and Group F Populations

	Group B (mosunetuzumab IV monotherapy on a Cycle 1 step-up dose schedule)			Group F (mosunetuzumab SC monotherapy on a Cycle 1 step-up dose schedule)		
Population:	**R/R NHL Group B**	**R/R NHL B11 RP2D cohort**	**R/R FL B11 RP2D cohort**	**R/R NHL Group F**	**R/R NHL F2 RP2D cohort**	**R/R FL F2 RP2D cohort**
No. of patients	N=414[a]	N=218[a]	N=90	N = 181	N = 139	N = 94
Analysis in scope for population	Safety	Safety	Efficacy/Safety[b]	Safety	Safety	Efficacy/Safety[b]
Description of patients included	All R/R NHL patients in Group B dose-escalation/expansion administered mosunetuzumab IV as a single-agent.	Histology-specific RP2D expansion cohorts within Group B (pooled and analyzed separately by histology).	Pivotal R/R FL RP2D expansion cohort.	All R/R NHL patients in Group F dose-escalation/ expansion administered mosunetuzumab SC as a single-agent.	Dose escalation and pooled histology-specific dose expansion RP2D cohorts within Group F.	Pivotal R/R FL RP2D expansion cohort.
Prior lines of therapy	≥1	≥2[c]	≥2	≥1	≥2	≥2
Dose administered	0.4/1/2.8 to 1/2/60[d] and 1/2/60/30[e]	1/2/60/30[e]	1/2/60/30[e]	5/15/45 or 5/45/45[f] or 5/45/90/45[g]	5/45/45[h]	5/45/45[h]
Histologies included	FL, DLBCL/trFL, MCL, Richter's, others	FL, DLBCL/trFL, MCL, Richter's	FL	FL, DLBCL/trFL, MCL, others	FL, DLBCL/trFL	FL

Table 3 Description of Mosunetuzumab Group B and Group F Populations (cont.)

DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; IV = intravenous; MCL=mantle cell lymphoma; NHL = non-Hodgkin lymphoma; Q3W = every 3 weeks; PK = pharmacokinetic; PPP = Per Protocol PK (analysis population); R/R = relapsed/refractory; RP2D = recommended Phase II dose; SC = subcutaneous; trFL=transformed follicular lymphoma

[a] One patient with melanoma was enrolled in error into the B11 R/R DLBCL/trFL RP2D cohort and received one dose of mosunetuzumab treatment and discontinued treatment on Day 3 due to “other” reason.

[b] For PK analyses, the PPP analysis population included 90 patients from the B11 FL RP2D cohort and 68 patients from the F2 FL RP2D cohort.

[c] For patients with MCL and Richter’s transformation histologies, ≥ 1 prior lines of therapy were allowed.

[d] IV dose in mgs administered on C1D1/C1D8/C1D15, C2D1 and subsequent Q3W cycles.

[e] RP2D/approved IV dose administered as 1 mg on C1D1, 2 mg on C1D8, 60 mg on C1D15 and C2D1, 30 mg for C3D1 and subsequent Q3W cycles.

[f] SC dose in mg administered on C1D1/C1D8/C1D15, C2D1, and subsequent Q3W cycles.

[g] SC dose in mg administered as 5 mg on C1D1, 45 mg on C1D8, 90 mg on C1D15 and C2D1, and 45 mg on subsequent Q3W cycles.

[h] RP2D/proposed SC dose administered as 5 mg on C1D1, 45 mg on C1D8, 45 mg on C1D15, and 45 mg on C2D1 and subsequent Q3W cycles

Table 4 summarizes key design features, safety populations, and data cutoff dates for the Study GO29781.

Table 4 Summary of Studies Included in this Risk Management Plan

Study	Study Design	Patient Population	Dose, Route, Regimen, and Formulation	Analysis/Data cutoff	Patients Evaluable for Safety (n)
GO29781	First-In-Human, open-label, multicenter, Phase I/II, dose-escalation	Adult patients with relapsed/refractory B–cell NHL	Group B: IV infusion, step-up dose schedule with the following starting dose: Cycle 1 Day 1: 0.4-1 mg Cycle 1 Day 8: 1-2 mg Cycle 1 Day 15: 2.8-60 mg Group F: SC injection, step-up dose schedule with the following starting dose: Cycle 1 Day 1: 5 mg Cycle 1 Day 8: 15 mg or 45 mg Cycle 1 Day 15: 45 mg or 90 mg	Group B: 27 August 2021 Group F: 1 February 2024	Group B: 414[a] Group F: 181

IV = intravenous, NHL = non-Hodgkin lymphoma ; RP2D = recommended Phase II dose; R/R DLBCL = relapsed/refractory diffuse large B-cell lymphoma; SC = subcutaneous; trFL = transformed follicular lymphoma.

[a] One patient with melanoma was enrolled in error into the B11 R/R DLBCL/trFL RP2D cohort and received one dose of mosunetuzumab treatment and discontinued treatment on Day 3 due to “other” reason.

Clinical trial exposure data for Group B and Group F populations in Study GO29781 are presented below.

Duration of Exposure

Mosunetuzumab IV or SC is administered for 8-17 cycles, where each cycle lasts 21 days.

Group B

- In the overall safety population for mosunetuzumab IV from Study GO29781, Group B, a total of 414[2] patients (135.35 patient-years of exposure) with R/R B-cell NHL received mosunetuzumab IV.
- The majority of patients received mosunetuzumab IV from 0 to ≤3 months and >3 to ≤6 months (184 [44.4%] and 165 [39.9%], respectively).
- Six patients (1.4%) received mosunetuzumab IV for>12 months as a result of dose delay (Table 5).

Group B11 RP2D

- A total of 218[2] patients with R/R NHL in Study GO29781 received mosunetuzumab IV at the RP2D dose and schedule.
- Majority of patients received mosunetuzumab IV from 0 to ≤ 3 months (90 [41.3%]) and>3 to≤6 months (90 [41.3%]).
- Five patients (2.3%) received mosunetuzumab IV for>12 months as a result of dose delay.

Group B11 FL RP2D

- A total of 90 patients with R/R FL in Study GO29781 received mosunetuzumab IV at the RP2D dose and schedule.
- Majority of patients (55 [61.1%]) received mosunetuzumab IV from >3 to≤6 months.
- Two patients (2.2%) received mosunetuzumab IV for >12 months as a result of dose delay.

Group F

- In the overall safety population for mosunetuzumab SC from Study GO29781, Group F, a total of 181 patients (67.07 patient-years of exposure) with R/R B-cell NHL received mosunetuzumab SC.
- The majority of patients received mosunetuzumab SC from 0 to ≤3 months and >3 to ≤6 months (66 [36.5%] and 84 [46.4%], respectively).

[2] One patient with melanoma was enrolled in error into the B11 R/R DLBCL/trFL RP2D cohort and received one dose of mosunetuzumab treatment and discontinued treatment on Day 3 due to “other” reason

- Six patients (3.3%) received mosunetuzumab SC for >12 months as a result of dose delay (Table 6).

Group F2 RP2D

- A total of 139 patients with R/R NHL in Study GO29781 received mosunetuzumab SC at the RP2D dose and schedule.
- Majority of patients received mosunetuzumab SC from 0 to ≤3 months (46 [33.1%]) and >3 to ≤6 months (65 [46.8%]).
- Five patients (3.6%) received mosunetuzumab SC for >12 months as a result of dose delay (Table 6).

Group F2 FL RP2D

- A total of 94 patients with R/R FL in Study GO29781 received mosunetuzumab SC at the RP2D dose and schedule.
- Majority of patients (58 [61.7%]) received mosunetuzumab SC from >3 to ≤6 months.
- Five patients (5.3%) received mosunetuzumab SC for >12 months as a result of dose delay (Table 6).

Exposure by Age Group and Gender

Group B

In the overall safety population for mosunetuzumab IV from Study GO29781, Group B, 269 (65.0%) male and 145 (35.0%) female patients received mosunetuzumab IV, and the majority (227 [54.8%]) were >18 to ≤64 years of age. Male patients had 85.32 patient-years of exposure versus 50.02 patient-years in female patients (Table 7).

Group B11 RP2D

In Group B11 RP2D cohort, 145 (66.5%) male and 73 (33.5%) female patients received mosunetuzumab IV, and the majority (116 [53.2%]) were >18 to ≤64 years of age. Male patients had 48.39 patient-years of exposure versus 27.82 patient-years in female patients (Table 7).

Group B11 FL RP2D

In Group B11 FL RP2D cohort, 55 (61.1%) male and 35 (38.9%) female patients received mosunetuzumab IV, and the majority (60 [66.7%]) were >18 to ≤64 years of age. Male patients had 24.65 patient-years of exposure versus 16.05 patient-years in female patients (Table 7).

Group F

In the overall safety population for mosunetuzumab SC from Study GO29781, Group F, 106 (58.6%) male and 75 (41.4%) female patients received mosunetuzumab SC, and the majority were ≥ 18 to ≤64 or >64 to ≤74 years of age (84 [46.4%] and 69 [38.1%], respectively). Male patients had 38.07 patient-years of exposure versus 28.99 patient-years in female patients (Table 8).

Group F2 RP2D

In Group F2 RP2D cohort, 83 (59.7%) male and 56 (40.3%) female patients received mosunetuzumab SC, and the majority were ≥18 to ≤64 or >64 to ≤74 years of age (69 [49.6%] and 52 [37.4%], respectively). Male patients had 31.89 patient-years of exposure versus 23.17 patient-years in female patients (Table 8).

Group F2 FL RP2D

In Group F2 FL RP2D cohort, 53 (56.4%) male and 41 (43.6%) female patients received mosunetuzumab SC, and the majority were ≥18 to ≤64 or >64 to ≤74 years of age (46 [48.9%] and 36 [38.3%], respectively). Male patients had 23.52 patient-years of exposure versus 17.48 patient-years in female patients (Table 8).

Exposure by Dose

Exposure was calculated according to a patient's actual initial treatment received, and includes only the highest dose received by a patient.

Group B

In the overall safety population for mosunetuzumab IV from Study GO29781, Group B, the majority of patients received the highest dose of 60 mg (202 [48.8%], 14.14 patient-years of exposure) or 13.5 mg (72 [17.4%], 20.5 patient-years of exposure) of mosunetuzumab IV (Table 9).

Group B11 RP2D

Overall, the majority of patients (199 [91.3%]) in Group B11 RP2D cohort received all doses in accordance to the planned dose and cycles. Nineteen patients (8.7%) received at least one dose outside of the planned cycle due to dose interruption or dose modification. Majority of patients (199 [91.3%], 14.04 patient-years of exposure) received the highest dose of 60 mg of mosunetuzumab IV (Table 10).

Group B11 FL RP2D

Overall, the majority of patients (80 [88.9%]) in Group B11 FL RP2D cohort received all doses in accordance to the planned dose and cycles. Ten patients (11.1%) received at least one dose outside of the planned cycle due to dose interruption or dose modification. Majority of patients (87 [96.7%], 6.63 patient-years of exposure) received the highest dose of 60 mg of mosunetuzumab IV (Table 10).

Group F

In the overall safety population for mosunetuzumab SC from Study GO29781, Group F, the majority of patients (173 [95.6%]) received the highest dose in the RP2D/proposed dosing regimen for mosunetuzumab SC of 45 mg, for a cumulative 60.95 patient-years of exposure (Table 11).

Group F2 RP2D

Overall, the majority of patients (124 [89.2%]) in Group F2 RP2D cohort received all doses in accordance to the planned cycles. Fifteen patients (10.8%) received at least one dose outside of the planned cycle due to dose interruption or dose modification. Majority of patients (137 [98.6%], 51.42 patient-years of exposure) received the highest dose in the RP2D/proposed dosing regimen for mosunetuzumab SC of 45 mg (Table 12).

Group F2 FL RP2D

Overall, the majority of patients (83 [88.3%]) in Group F2 FL RP2D cohort received all doses in accordance to the planned cycles. Eleven patients (11.7%) received at least one dose outside of the planned cycle due to dose interruption or dose modification. All patients (94 [100%], 38.54 patient-years of exposure) received the highest dose in the RP2D/proposed dosing regimen for mosunetuzumab SC of 45 mg (Table 12).

Exposure by Race

Group B

In the overall safety population for mosunetuzumab IV from Study GO29781, Group B, the majority of patients who received mosunetuzumab IV were White (320 [77.3%], 104.05 patient-years of exposure), followed by Asian (67 [16.2%], 22.27 patient-years of exposure). This was consistent across Group B11 FL RP2D and NHL RP2D cohorts (Table 13).

Group B11 RP2D

In Group B11 RP2D cohort, majority of the patients were White (179 [82.1%], 63.80 patient-years of exposure), followed by Asian (23 [10.6%], 7.51 patient-years of exposure), Unknown (9 [4.1%] 2.77 patient-years of exposure) and Black or African American (6 [2.8%], 1.70 patient-years of exposure) (Table 13).

Group B11 FL RP2D

In Group B11 FL RP2D cohort, the majority of the patients were White (74 [82.2%], 34.42 patient-years of exposure), followed by Asian (8 [8.9%], 3.07 patient-years of exposure), and Black or African American (4 [4.4%], 1.16 patient-years of exposure) (Table 13).

Group F

In the overall safety population for mosunetuzumab SC from Study GO29781, Group F, the majority of patients who received mosunetuzumab SC were White (147 [81.2%], 54.90 patient-years of exposure), followed by Asian (26 [14.4%], 9.62 patient-years of exposure). This was consistent across Group F2 RP2D and F2 FL RP2D cohorts (Table 14).

Group F2 RP2D

In Group F2 RP2D cohort, the majority of patients were White (111 [79.9%], 45.41 patient-years of exposure), followed by Asian (20 [14.4%], 7.09 patient years of exposure), and Black or African American and Unknown (3 [2.2%] each, 1.05 and 0.59 patient-years of exposure, respectively; Table 14).

Group F2 FL RP2D

In Group F2 FL RP2D cohort, the majority of patients were White (80 [85.1%], 34.87 patient-years of exposure), followed by Asian (10 [10.6%], 4.73 patient-years of exposure), and Black or African American (2 [2.1%], 0.88 patient-years of exposure; Table 14).

Table 5 Duration of Exposure: Mosunetuzumab Monotherapy, Intravenous (Group B Cohorts)

Summary of Duration of Exposure, Initial Treatment with Mosunetuzumab, Safety-Evaluable Patients
Protocol: GO29781

	B11 Exp FL (N=90)		B11 Exp (N=218)		Group B (N=414)	
Duration of exposure	Patients (N=90)	Person time*	Patients (N=218)	Person time*	Patients (N=414)	Person time*
0 <= 3 months	16 (17.8%)	2.08	90 (41.3%)	9.50	184 (44.4%)	18.24
> 3 <= 6 months	55 (61.1%)	22.55	90 (41.3%)	36.26	165 (39.9%)	65.47
> 6 <= 9 months	5 (5.6%)	2.90	15 (6.9%)	8.54	27 (6.5%)	15.78
> 9 <= 12 months	12 (13.3%)	11.07	18 (8.3%)	16.59	32 (7.7%)	29.54
>12 months	2 (2.2%)	2.10	5 (2.3%)	5.31	6 (1.4%)	6.32

* Person-time is defined as the sum of the exposure time (from first to last administration of mosunetuzumab) for every patient in unit: Years.
NE means that there were no subjects in this exposure duration category.
Data Cutoff Date - 27AUG2021

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary2_BLA_Aug2021/prod/program/t_ex_dur_rmp.sas
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t_ex_dur_rmp_INIT_SE_27AUG2021_29781.out
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Table 6 Duration of Exposure: Mosunetuzumab Monotherapy, Subcutaneous (Group F Cohorts)

Summary of Duration of Exposure, Initial Treatment with Mosunetuzumab, Safety-Evaluable Patients
Protocol: GO29781

	Group F (N=181)		F2 RP2D (N=139)		F2 RP2D FL Exp (N=94)	
Duration of exposure	Patients (N=181)	Person time*	Patients (N=139)	Person time*	Patients (N=94)	Person time*
0 <= 3 months	66 (36.5%)	7.92	46 (33.1%)	5.58	19 (20.2%)	2.63
> 3 <= 6 months	84 (46.4%)	34.85	65 (46.8%)	27.34	58 (61.7%)	24.42
> 6 <= 9 months	16 (8.8%)	9.51	14 (10.1%)	8.38	8 (8.5%)	4.69
> 9 <= 12 months	9 (5.0%)	8.13	9 (6.5%)	8.13	4 (4.3%)	3.62
>12 months	6 (3.3%)	6.66	5 (3.6%)	5.64	5 (5.3%)	5.64

* Person-time is defined as the sum of the exposure time (from first to last administration of Mosunetuzumab) for every patient in unit: Years.
NE means that there were no patients in this exposure duration category.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ex_dur_rmp.sas
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Table 7 Exposure by Age Group and Gender: Mosunetuzumab Monotherapy, Intravenous (Group B Cohorts)

Summary of Exposure by Age Group and Gender, Initial Treatment with Mosunetuzumab, Safety-Evaluable Patients
Protocol: GO29781

Age group (years)	Patients						Person time*					
	B11 Exp FL (N=90)		B11 Exp (N=218)		Group B (N=414)		B11 Exp FL (N=90)		B11 Exp (N=218)		Group B (N=414)	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
> 18 <=64	41 (74.5%)	19 (54.3%)	82 (56.6%)	34 (46.6%)	151 (56.1%)	76 (52.4%)	17.58	8.04	26.58	12.08	47.69	24.17
> 64 <=74	11 (20.0%)	12 (34.3%)	38 (26.2%)	25 (34.2%)	77 (28.6%)	45 (31.0%)	4.77	6.36	13.68	10.26	25.11	16.84
> 74 <=84	2 (3.6%)	3 (8.6%)	20 (13.8%)	11 (15.1%)	35 (13.0%)	20 (13.8%)	1.88	1.24	6.61	3.97	10.61	7.04
> 84	1 (1.8%)	1 (2.9%)	5 (3.4%)	3 (4.1%)	6 (2.2%)	4 (2.8%)	0.42	0.41	1.52	1.51	1.91	1.97

* Person-time is defined as the sum of the exposure time (from first to last administration of mosunetuzumab) for every patient in unit: Years.
NE means that there were no subjects in this exposure duration category.
Data Cutoff Date - 27AUG2021

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary2_BLA_Aug2021/prod/program/t_ex_aggnr_rmp.sas
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Table 8 Exposure by Age Group and Gender: Mosunetuzumab Monotherapy, Subcutaneous (Group F Cohorts)

Summary of Exposure by Age Group and Gender, Initial Treatment with Mosunetuzumab, Safety-Evaluable Patients
Protocol: GO29781

	Patients						Person time*					
	Group F (N=181)		F2 RP2D (N=139)		F2 RP2D FL Exp (N=94)		Group F (N=181)		F2 RP2D (N=139)		F2 RP2D FL Exp (N=94)	
Age group (years)	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
>=18 <=64	54 (50.9%)	30 (40.0%)	44 (53.0%)	25 (44.6%)	29 (54.7%)	17 (41.5%)	20.40	12.42	17.50	10.55	13.42	7.10
> 64 <=74	36 (34.0%)	33 (44.0%)	25 (30.1%)	27 (48.2%)	14 (26.4%)	22 (53.7%)	11.55	12.96	8.66	11.53	5.53	10.03
> 74 <=84	16 (15.1%)	10 (13.3%)	14 (16.9%)	4 (7.1%)	10 (18.9%)	2 (4.9%)	6.12	2.78	5.73	1.09	4.57	0.35
> 84	0	2 (2.7%)	0	0	0	0	NE	0.83	NE	NE	NE	NE

* Person-time is defined as the sum of the exposure time (from first to last administration of Mosunetuzumab) for every patient in unit: Years.
NE means that there were no patients in this exposure duration category.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ex_aggnr_rmp.sas
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Table 9 Exposure by Dose (Maximum Dose Received): Mosunetuzumab Monotherapy, Intravenous (Group B Cohorts)

Summary of Exposure, Initial Treatment with Mosunetuzumab, Safety-Evaluable Patients
Protocol: GO29781

	B11 Exp FL (N=90)		B11 Exp (N=218)		Group B (N=414)	
Maximum Dose	Patients (N=90)	Person time*	Patients (N=218)	Person time*	Patients (N=414)	Person time*
Total patients numbers/person time	90 (100%)	6.75	218 (100%)	14.25	414 (100%)	64.60
0.8 mg	0	NE	0	NE	2 (0.5%)	0.01
1.0 mg	1 (1.1%)	0.00	11 (5.0%)	0.03	13 (3.1%)	0.04
2.0 mg	1 (1.1%)	0.00	6 (2.8%)	0.02	13 (3.1%)	0.04
2.8 mg	0	NE	0	NE	6 (1.4%)	1.88
3.0 mg	0	NE	0	NE	1 (0.2%)	0.02
4.2 mg	0	NE	0	NE	15 (3.6%)	4.51
6.0 mg	0	NE	0	NE	33 (8.0%)	10.08
9.0 mg	0	NE	0	NE	5 (1.2%)	1.56
11.4 mg	1 (1.1%)	0.12	1 (0.5%)	0.12	1 (0.2%)	0.12
13.5 mg	0	NE	0	NE	72 (17.4%)	20.50
20.0 mg	0	NE	0	NE	10 (2.4%)	2.53
27.0 mg	0	NE	0	NE	24 (5.8%)	4.77
30.0 mg	0	NE	1 (0.5%)	0.04	2 (0.5%)	0.39
40.5 mg	0	NE	0	NE	15 (3.6%)	4.02
60.0 mg	87 (96.7%)	6.63	199 (91.3%)	14.04	202 (48.8%)	14.14

* Person-time is defined as the sum of the exposure time (from first dose of mosunetuzumab at the reported Maximum dose level to the day prior to the next different dose level, except if the last dose at the Maximum level) for every patient in unit: Years.
Data Cutoff Date - 27AUG2021

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary2_BLA_Aug2021/prod/program/t_ex_dose1_rmp.sas
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t_ex_dose1_rmp_INIT_SE_27AUG2021_29781.out
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Table 10 Exposure by Dose by Cycle: Mosunetuzumab Monotherapy, Intravenous (Group B Cohorts)

Summary of Exposure Within Each Dose Level, Initial Treatment with Mosunetuzumab, Safety-Evaluable Patients
Protocol: GO29781

	B11 Exp FL (N=90)		B11 Exp (N=218)	
Dose level	Patients (N=90)	Person time*	Patients (N=218)	Person time*
1 mg (C1D1)	86 (95.6%)	1.74	214 (98.2%)	4.26
2 mg (C1D8)	89 (98.9%)	1.72	206 (94.5%)	4.04
60 mg(C1D15,C2D1)	87 (96.7%)	6.63	199 (91.3%)	14.04
30 mg(C3+D1)	82 (91.1%)	29.70	166 (76.1%)	52.40
Other	10 (11.1%)	0.92	19 (8.7%)	1.46

* Person-time is defined as the sum of the exposure time (from first dose of mosunetuzumab at the reported dose level to the day prior to the next different dose level, except if the last dose is at the reported level) for every patient in unit: Years.
Patients are only counted as having received a particular dose if it was received at the planned cycle. Doses received outside of the planned cycles have been considered as Other.
Data Cutoff Date - 27AUG2021

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Table 11 Exposure by Dose (Maximum Dose Received): Mosunetuzumab Monotherapy, Subcutaneous (Group F Cohorts)

Summary of Exposure, Initial Treatment with Mosunetuzumab, Safety-Evaluable Patients
Protocol: GO29781

	Group F (N=181)		F2 RP2D (N=139)		F2 RP2D FL Exp (N=94)	
Maximum Dose	Patients (N=181)	Person time*	Patients (N=139)	Person time*	Patients (N=94)	Person time*
Total patients numbers/person time	181 (100%)	61.19	139 (100%)	51.43	94 (100%)	38.84
5.0 mg	3 (1.7%)	0.01	2 (1.4%)	0.01	0	NE
15.0 mg	2 (1.1%)	0.01	0	NE	0	NE
45.0 mg	173 (95.6%)	60.95	137 (98.6%)	51.42	94 (100%)	38.84
90.0 mg	3 (1.7%)	0.23	0	NE	0	NE

* Person-time is defined as the sum of the exposure time (from first to last administration of Mosunetuzumab) for every patient in unit: Years.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ex_dose1_rmp.sas
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Table 12 Exposure within Each Dose Level: Mosunetuzumab Monotherapy, Subcutaneous (Group F Cohorts)

Summary of Exposure Within Each Dose Level, Initial Treatment with Mosunetuzumab, Cohort F2 Escalation and Expansion, Safety-Evaluable Patients
Protocol: GO29781

	F2 Esc (N=4)		F2 Exp (N=135)		F2 Exp FL (N=94)	
Dose level	Patients (N=4)	Person time*	Patients (N=135)	Person time*	Patients (N=94)	Person time*
5 mg	4 (100%)	0.06	134 (99.3%)	2.66	93 (98.9%)	1.87
45 mg	3 (75.0%)	0.39	134 (99.3%)	50.65	94 (100%)	38.54
Other	1 (25.0%)	0.58	14 (10.4%)	0.72	11 (11.7%)	0.59

* Person-time is defined as the sum of the exposure time (from first dose of mosunetuzumab at the reported dose level to the day prior to the next different dose level, except if the last dose is at the reported level) for every patient in unit: Years.
Patients are only counted as having received a particular dose if it was received at the planned cycle. Doses received outside of the planned cycles have been considered as Other.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ex_dose3_rmp.sas
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Note: The F2 Esc (N=4) and F2 Exp (N=135) cohorts in this table constitute the F2 RP2D cohort (N=139).

Table 13 Exposure by Race Mosunetuzumab Monotherapy, Intravenous (Group B Cohorts)

Summary of Exposure by Racial Origin, Initial Treatment with Mosunetuzumab, Safety-Evaluable Patients
Protocol: GO29781

	B11 Exp FL (N=90)		B11 Exp (N=218)		Group B (N=414)	
Race	Patients (N=90)	Person time*	Patients (N=218)	Person time*	Patients (N=414)	Person time*
American Indian or Alaska Native	1 (1.1%)	0.43	1 (0.5%)	0.43	2 (0.5%)	0.49
Asian	8 (8.9%)	3.07	23 (10.6%)	7.51	67 (16.2%)	22.27
Black or African American	4 (4.4%)	1.16	6 (2.8%)	1.70	11 (2.7%)	3.52
White	74 (82.2%)	34.42	179 (82.1%)	63.80	320 (77.3%)	104.05
Multiple	0	NE	0	NE	1 (0.2%)	0.19
Unknown	3 (3.3%)	1.62	9 (4.1%)	2.77	13 (3.1%)	4.82

* Person-time is defined as the sum of the exposure time (from first to last administration of study drug) for every patient in unit: Years.
NE means that there were no subjects in this exposure duration category.
Data Cutoff Date - 27AUG2021

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary2_BLA_Aug2021/prod/program/t_ex_race_rmp.sas
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Table 14 Exposure by Race: Mosunetuzumab Monotherapy, Subcutaneous (Group F Cohorts)

Summary of Exposure by Racial Origin, Initial Treatment with Mosunetuzumab, Safety-Evaluable Patients
Protocol: GO29781

	Group F (N=181)		F2 RP2D (N=139)		F2 RP2D FL Exp (N=94)	
Race	Patients (N=181)	Person time*	Patients (N=139)	Person time*	Patients (N=94)	Person time*
Asian	26 (14.4%)	9.62	20 (14.4%)	7.09	10 (10.6%)	4.73
Black or African American	3 (1.7%)	1.05	3 (2.2%)	1.05	2 (2.1%)	0.88
Native Hawaiian or other Pacific Islander	1 (0.6%)	0.41	1 (0.7%)	0.41	1 (1.1%)	0.41
White	147 (81.2%)	54.90	111 (79.9%)	45.41	80 (85.1%)	34.87
Multiple	1 (0.6%)	0.51	1 (0.7%)	0.51	0	NE
Unknown	3 (1.7%)	0.59	3 (2.2%)	0.59	1 (1.1%)	0.12

* Person-time is defined as the sum of the exposure time (from first to last administration of Mosunetuzumab) for every patient in unit: Years.
NE means that there were no patients in this exposure duration category.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ex_race_rmp.sas
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PART II: MODULE SIV— POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Specific exclusion criteria discussed in this section are from the pivotal Study GO29781.

Table 15 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Pregnant or lactating, or intending to become pregnant during the study or within 3 months after the last dose of mosunetuzumab.	No clinical studies have been performed in pregnant women. There is no safety data to inform risk for pregnant or lactating women. It is not known whether mosunetuzumab is excreted in human milk.	No	Section 4.6 (Fertility, pregnancy and lactation) of the SmPC advises women of childbearing potential to avoid pregnancy and for breastfeeding women to discontinue while receiving mosunetuzumab.
Prior anti-lymphoma treatment with monoclonal antibodies, radioimmunoconjugates or antibody-drug conjugates within 4 weeks before first mosunetuzumab administration.	Such patients were excluded because recent anti-lymphoma therapies could affect interpretation of efficacy and safety results.	No	Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment.
Prior treatment with systemic immunotherapeutic agents for which the mechanism of action involves T-cells, including but not limited to cytokine therapy and anti-CTLA-4, anti–PD-1 and anti–PD-L1 therapeutic antibodies, within 12 weeks or five half-lives of the drug, whichever is shorter, before first mosunetuzumab administration.	Such patients were excluded because recent anti-lymphoma therapies could affect interpretation of efficacy and safety results. Additionally, patients who received recent immunotherapies could have elevated T-cell activation, which may result in overlapping toxicities with mosunetuzumab based on the mechanism of action.	No	Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Treatment emergent immune-related adverse events associated with prior immunotherapeutic agents (e.g., immune checkpoint inhibitor therapies) as follows: – Grade ≥3 adverse events with the exception of Grade 3 endocrinopathy managed with replacement therapy. – Grade 1-2 adverse events that did not resolve to baseline after treatment discontinuation. – For certain prior treatments, such as CAR-T cell therapies, patients with prior immune-related Grade ≥3 adverse events (e.g., CRS) may be allowed to enroll after discussion with and confirmation by the Medical Monitor.	To minimize the risk of exacerbating ongoing immune-related AEs associated with prior therapies.	No	Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment.
Treatment with any chemotherapeutic or anti-cancer agent with 4 weeks or 5 half-lives of the drug. Treatment with radiotherapy within 2 weeks prior to start of treatment.	Such patients were excluded because recent anti-lymphoma therapies could affect interpretation of efficacy and safety results.	No	Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Autologous SCT within 100 days prior to first mosunetuzumab administration, prior treatment with CAR-T therapy within 30 days before start of treatment.	To minimize the effect of the prior transplant /CAR-T therapy that could affect interpretation of efficacy and safety results.	Yes	Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment.
Prior allogeneic SCT, or prior solid organ transplant.	These patients were excluded to minimize effects of possible early and late complications from prior transplant or long-term treatment with immunosuppressives that could confound study results	No	Section 5.1 of the SmPC describes patients excluded from clinical trials, including those who have received prior allogeneic stem cell transplant prior to study entry. Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. It is considered part of routine oncology practice to assess a patient's fitness for treatment.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
History of autoimmune disease, including but not limited to myocarditis, pneumonitis, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis – Patients with a remote history of, or well-controlled autoimmune disease, may be eligible to enroll after discussion with and confirmation by the Medical Monitor.	To prevent exacerbation of patient's condition and to minimize the risk of a therapy that was potentially immune activating. Could also interfere with the determination of safety of study treatment.	No	Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. Section 5.1 of the SmPC describes patients excluded from clinical trials, including those with active autoimmune disease requiring immunosuppressive therapy. It is considered part of routine oncology practice to assess a patient's fitness for treatment.
History of macrophage activation syndrome/hemophagocytic lymphohistiocytosis (HLH).	To prevent exacerbation of patient's condition and to minimize the risk of a therapy that was potentially immune activating. Could also interfere with the determination of safety of study treatment.	No	Section 5.1 of the SmPC describes patients excluded from clinical trials, including those with a history of macrophage activation syndrome and HLH. It is considered part of routine oncology practice to assess a patient's fitness for treatment. See SVII.1.1 for more details on HLH.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
History of progressive multifocal leukoencephalopathy.	To prevent exacerbation of patient's condition and to minimize the risk of a therapy that is known to cause neutropenia and B-cell depletion. Could also interfere with the determination of safety or efficacy of study treatment.	No	Section 5.1 of the SmPC describes patients excluded from clinical trials, including those with progressive multifocal leukoencephalopathy. Section 4.4 of the SmPC warns regarding serious infections. It is considered part of routine oncology practice to assess a patient's fitness for treatment. See SVII.3.1 for more details on Serious Infection.
Current or past history of CNS lymphoma/disease.	CNS penetration/activity of mosunetuzumab is unknown. Other CNS diseases, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease could confound safety data.	No	Section 5.1 of the SmPC describes patients excluded from clinical trials, including those with current or a history of CNS lymphoma or CNS disease. Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. It is considered part of routine oncology practice to assess a patient's fitness for treatment.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
History of other malignancy that could affect compliance with the protocol or interpretation of results.	Patients with a history of malignancies that had a high risk of relapsing early could confound efficacy data.	No	Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment.
Significant cardiovascular disease such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina.	To prevent exacerbation of patient's condition and the comorbidities could affect the compliance with study treatment or affect the safety or efficacy of study treatment.	No	Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. Section 5.1 of the SmPC describes patients excluded from clinical trials, including those with significant cardiovascular disease. It is considered part of routine oncology practice to assess a patient's fitness for treatment.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Significant active pulmonary disease (e.g., bronchospasm and/or obstructive pulmonary disease).	The comorbidities could affect the compliance with study treatment or interpretation of results especially with safety.	No	Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. Section 5.1 of the SmPC describes patients excluded from clinical trials, including those with significant active pulmonary disease. It is considered part of routine oncology practice to assess a patient's fitness for treatment.
History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins).	Such patients cannot be treated with study treatment.	No	Mosunetuzumab contains a humanized IgG1 monoclonal antibody, therefore such patients should not be treated with mosunetuzumab. Hypersensitivity to mosunetuzumab or any of the excipients is listed as a contraindication in SmPC Section 4.3.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to first mosunetuzumab administration.	To minimize possible risks of mosunetuzumab that is known to cause neutropenia and B-cell depletion. Additionally, infections may exacerbate immune-related safety risks associated with mosunetuzumab.	No	Section 5.1 of the SmPC describes patients excluded from clinical trials, including patients with known active infections. Section 4.4 of the SmPC warns regarding serious infections. See SVII.3.1 for more details on Serious Infection.
Recent major surgery within 4 weeks prior to first mosunetuzumab administration.	To minimize risks the therapy may have to surgical healing and to the risk of infection in an acutely post-surgical patient. In addition, post-surgical complications that may confound interpretation of results.	No	Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Known or suspected chronic active Epstein-Barr Virus infection.	Such patients were excluded to minimize the risk of a therapy that is known to cause neutropenia and B-cell depletion	No	Section 5.1 of the SmPC describes patients excluded from clinical trials, including patients with active infections. Section 4.4 of the SmPC provides caution when considering the use of mosunetuzumab in patients with a history of recurring or chronic infections, including chronic, active Epstein-Barr Virus). It is considered part of routine oncology practice to assess a patient's fitness for treatment. See SVII.3.1 for more details on Serious Infection.
Acute or chronic HBV or HCV infection.	Such patients were excluded to minimize the risk of a therapy that is known to cause neutropenia and B-cell depletion	No	Section 5.1 of the SmPC describes patients excluded from clinical trials, including those with acute or chronic HBV or HCV infection. Section 4.4 of the SmPC warns regarding serious infections. Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. It is considered part of routine oncology practice to assess a patient's fitness for treatment. See SVII.3.1 for more details on Serious Infection.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Positive serologic test results for HIV infection.	Such patients were excluded to minimize the risk of a therapy that is known to cause neutropenia and B-cell depletion	No	Section 5.1 of the SmPC describes patients excluded from clinical trials, including those with positive serologic test results for HIV infection. Section 4.4 of the SmPC warns regarding serious infections. Given the life-threatening nature of the approved/proposed indication, treatment with mosunetuzumab should be an option for such patients. It is considered part of routine oncology practice to assess a patient's fitness for treatment. See SVII.3.1 for more details on Serious Infection.
Vaccination with a live, attenuated vaccine within 4 weeks prior to treatment or anticipation that such a live attenuated vaccine will be required during the study.	To minimize the risk of possible infection with live vaccines in immunocompromised patients while on treatment with mosunetuzumab which could cause further immunosuppression.	No	Section 4.4 of SmPC warns regarding immunization.

AE = adverse event; CAR-T = chimeric antigen receptor T-cells; CNS = central nervous system; CRS = cytokine release syndrome; HBV = hepatitis B virus; HCV = hepatitis C virus; HLH = hemophagocytic lymphohistiocytosis; HIV = human immunodeficiency virus; IgG1 = immunoglobulin G1; IV = intravenous; SCT = stem cell transplant; SmPC = summary of product characteristics.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

The clinical trial development program for mosunetuzumab was unable to detect adverse drug reactions that are:

- Rare adverse reactions
- Adverse reactions caused by prolonged exposure
- Adverse reactions caused by cumulative exposure
- Adverse reactions that have a long latency

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Use in Pregnancy and Lactation

The median age at diagnosis for NHL is 65 years; NHL including FL is therefore considered a disease of adults and elderly, hence resulting in limited evidence among pregnant females (SI.1). No clinical studies have been performed with mosunetuzumab in pregnant women.

Reproductive assessments and evidence-based risk assessment for potential developmental effects with mosunetuzumab are described in SII.

Because mosunetuzumab may cause fetal harm when administered to pregnant women based on its mechanism of action, it is recommended that mosunetuzumab not be administered to pregnant women unless the potential benefit to the mother outweighs the potential risk to the fetus. The EU Summary of Product Characteristics (SmPC) advises women of childbearing potential to use contraception while receiving mosunetuzumab and at least 3 months after the last dose of mosunetuzumab. It is unknown whether mosunetuzumab is excreted in human breastmilk. Because a risk to nursing infants cannot be excluded, the EU SmPC advises nursing mothers to discontinue breastfeeding during mosunetuzumab therapy.

Period and cumulative data of the pregnancy outcomes (Overall Exposure, Exposure by Parents, and Exposure by Source) are presented in Annex 7D. Overall, no safety concerns related to the use of mosunetuzumab during pregnancy or lactation were identified.

Exposure data of special populations presented in Table 16 are from the pivotal study GO29781.

Table 16 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
Patients with hepatic impairment*	Mild hepatic impairment: n=88; Moderate hepatic impairment: n=3; Severe hepatic impairment: n=1
Patients with renal impairment**	Mild renal impairment: n=270; Moderate renal impairment: n=94; Severe renal impairment: n=2
Patients with cardiovascular impairment***	Not included in the clinical development program
Immunocompromised patients****	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	2 patients***** with a history of lymphoma involvement in the CNS
Population with relevant different ethnic origin	Refer to Table 13 and Table 14
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	Not applicable

Table 16 Exposure of Special Populations Included or Not in Clinical Trial Development Program (cont.)

* Excluded patients with AST or ALT > 3 × ULN, or total bilirubin > 1.5 × ULN. Patients with a documented history of Gilbert syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible.

Hepatic impairment category is based on baseline AST, ALT and total bilirubin (TB) values in patients from Study GO29781 per NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction (HD):

Normal: TB & AST ≤upper limit of normal (ULN)]

Mild hepatic impairment (TB > ULN to 1.5 × ULN or AST > ULN)

Moderate hepatic impairment (TB > 1.5–3 × ULN, any AST)

Severe hepatic impairment (TB > 3–10 × ULN, any AST)

** Excluded patients with creatinine > ULN and a measured creatinine clearance < 60 mL/min.

Renal impairment category is based on estimated creatinine clearance per FDA guidance

Normal: ≥ 90 mL/min

Mild: 60-89 mL/min

Moderate: 30-59 mL/min

Severe: 15-29 mL/min

*** Patients with significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) were excluded.

**** Patients with positive serologic test results for HIV infection were excluded.

***** 1 patient is from Study GO29781 Group B2 / IV and 1 patient is from Study GO29781 Group D5 / SC.

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 METHOD USED TO CALCULATE EXPOSURE

The cumulative post authorization exposure provided below is for the IV formulation only. The data presented are derived from the mosunetuzumab Periodic Benefit Risk Evaluation Report (PBRER; RDR No. 1131059) with data lock point (DLP) of 2 June 2024. The International Birth Date (IBD) of mosunetuzumab is 3 June 2022.

Methodology: European Economic Area (EEA) and RoW (Rest of World)

The volume sold by Roche is sourced from Roche supply chain and financial systems (Controlling Profitability Analysis). The sales data are provided on a monthly basis; therefore, the exposure is available from the IBD to the nearest point of DLP (i.e., 2 June 2024).

Mosunetuzumab (Lunsumio®) is currently available to the market in the form of 1 mg and 30 mg vials for IV injection. In order to convert vials volume into commercial patient exposure data, factors such as epidemiology, treatment duration, dosing and patient compliance from the best available sources are used. Indication split is used as 100%,

Compliance factor considered is 85% and Persistence factor is 90% for FL. Since two kinds of responses are observed (complete response [CR] and partial response [PR]), there are two different patterns of duration of treatment (DoT) followed for each cohort.

For the EEA and RoW patient exposure estimation, the dosage per patient was calculated from dosage administration suggested in the EMA label. As per the Lunsumio® SmPC, the dosage of Lunsumio® IV is for 8 cycles for CR and 17 cycles for PR with each cycle being 3 weeks long. The first cycle has 1 mg in the first week, 2 mg in the second week, and 60 mg in the third week. The second cycle has 60 mg, and the subsequent cycles have 30 mg each. From the above, it is safe to assume that, for a patient with FL to start treatment with Lunsumio®, the patient has to consume three 1 mg vials. Based on this analogy, the consumption of three 1 mg vials is considered to be a patient start.

To estimate the exposure in each individual country, monthly volume sales of 1 mg vials are split among CR and PR patient consumption. Based on clinical trials data, patients split, and volume splits were calculated for CR and PR patients. The output is further divided by 3 mg (three 1 mg vials) to obtain the number of new patient starts on mosunetuzumab. DoT (6 months for CR and 12 months for PR) based patient drop offs are taken into account to ensure the logical accuracy of maintenance and existing patients on mosunetuzumab.

The Interval Active Patient Exposure is equal to the sum of Existing Patients in the First Month of the Interval and the sum of New Patients in the remaining Months of the Interval. The Cumulative Patient Exposure is equal to the sum of all new patients until DLP. Hence, current cumulative will not equal the sum patient exposures of previous cumulative and current interval.

Methodology: United States

Lunsumio® has been commercially available in the United States since 9 January 2023. As per the dosing pattern of mosunetuzumab IV, a patient needs to consume three 1 mg vials to start the treatment. This indicates that the 1 mg vial sales are consumed as loading doses by patients.

Interval patient exposure is calculated as the total 1 mg vial volume consumption in the interval divided by the loading dosage per patient (i.e., 3 mg).

Methodology: Japan

Mosunetuzumab was not marketed in Japan during the reporting period for this PBRER. Zero patient exposure for Lunsumio® was reported by Chugai for Japan.

SV.1.2 EXPOSURE

Since the IBD (3 June 2022) until the DLP (2 June 2024), an estimated cumulative total of 1278 patients have been exposed to Lunsumio® from marketing experience (see Annex 7C).

PART II: MODULE SVI— ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Drugs that have a potential for misuse for illegal purposes are expected to share general characteristics such as psychoactive, stimulant, or sedative effects, or less commonly, anabolic effects or enhancement of hemoglobin levels.

For mosunetuzumab, there is neither nonclinical nor current clinical evidence supporting psychostimulatory effects or dependency, which would induce misuse for illegal purposes.

A review of safety information obtained in patients exposed to mosunetuzumab concluded that there was no indication of abuse or dependence-related AEs.

Therefore, the potential for mosunetuzumab to be misused for illegal purposes is low.

PART II: MODULE SVII— IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 RISKS NOT CONSIDERED IMPORTANT FOR INCLUSION IN THE LIST OF SAFETY CONCERNS IN THE RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Risk of bleeding or hemorrhage

Thrombocytopenia occurred in 24 of 214 patients (11.2%) treated at RP2D in Group B11 RP2D cohort (primary safety population), of which incidence of Grade 3-4 severity was low (6.1%) and there were no serious events. Dose modifications occurred infrequently (4 [1.9%] patients) and no patients discontinued mosunetuzumab. No clinically significant consequences such as risk of bleeding or hemorrhage were observed (Annex 7A.1, Annex 7A.2, Annex 7A.3).

- Risk of hepatic injury

Hepatic AEs occurred in 28 of 214 patients (13.1%) treated at RP2D in Group B11 RP2D cohort (primary safety population), of which incidence of Grade 3-4 severity was low (5.6%), and serious events were infrequent (1.4%). Dose modifications occurred in 5 patients (2.3%) and no patients discontinued mosunetuzumab. These events were

transient and reversible and in some cases occurring concurrently with CRS. Drug-induced liver injury (DILI) events were not reported (Annex 7A.1, Annex 7A.4).

- Immunogenicity

A key immunogenicity risk factor for mosunetuzumab includes its novel bispecific antibody structure. Since the expected mechanism of action for mosunetuzumab is to deplete B-cell production, it should limit the development of anti-drug antibodies (ADAs). Therefore, the overall immunogenicity risk for mosunetuzumab is considered as low. Nonetheless, all patients in the clinical studies are monitored as required at regular intervals for the development of ADAs. No patient tested positive for ADAs against mosunetuzumab in Group B11 RP2D cohort (primary safety population) (Annex 7A.5).

Adverse reactions with clinical consequences, even serious but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Tumor Lysis Syndrome (TLS)

TLS occurred with a low frequency in patients treated with mosunetuzumab; 2 of 214 patients (0.9%) treated at RP2D in Group B11 RP2D cohort (primary safety population) experienced TLS, including one Grade 3 and one Grade 4 (which occurred concurrently with CRS Grade 4) (Annex 7A.6, Annex 7A.7). TLS is an oncological emergency when it occurs, however it is well understood by healthcare professionals (HCPs) in the hematology treatment landscape. TLS is described in SmPC Section 4.4 Special Warnings and Precautions for Use with guidance to consider prophylaxis when appropriate, and further presented in Section 4.8 Undesirable Effects.

Known risks that are followed up via routine pharmacovigilance—namely, through signal detection and adverse reaction reporting—and for which the risk-minimization messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized):

- Neutropenia

Neutropenia occurred in 59 of 214 patients (27.6%) treated at RP2D in Group B11 RP2D cohort (primary safety population), including Grade 3-4 events in 52 patients (24.3%), and 2 serious events (0.9%). Dose modifications occurred in 24 patients (11.2%) and no patients discontinued mosunetuzumab (Annex 7A.1, Annex 7A.2). Neutropenia is included in the SmPC Section 4.8 in Undesirable Effects.

- Hemophagocytic lymphohistiocytosis (HLH)

HLH is a hyperinflammatory syndrome characterized by dysregulated activation of T-cells and macrophages, and results in hypercytokinemia leading to cytolysis, tissue infiltration and organ injury (Teachey et al. 2013; Hines et al. 2023; Lee and Logan 2023). The signs and symptoms of HLH largely overlap with CRS. Patients with

persistent or refractory CRS should be evaluated for HLH and treated per current practice guidelines. HLH occurred in 1 of 214 patients (0.5%) treated at RP2D in Group B11 RP2D cohort and 1 of 181 patients (0.6%) in the Group F SC cohort. These were a Grade 4 event in a patient diagnosed with Stage IV DLBCL, assessed as not related to mosunetuzumab and driven by the patient's progressive disease (Annex 7A.1, Annex 7A.7), and Grade 5 HLH assessed as related to mosunetuzumab SC which occurred with concurrent EBV and CMV infection as well as recent disease transformation. Based on the mechanism of action of mosunetuzumab, and data available from Group B11 RP2D and Group F cohort, HLH is considered an identified risk that will be followed up by routine pharmacovigilance.

Potential risks that are followed up via routine pharmacovigilance

- Neurologic Adverse Events

Neurotoxicity has been observed in cynomolgus monkeys administered with mosunetuzumab (refer to SII).

Neurotoxicity has also been reported frequently with other CD3 engagers such as blinatumomab and CAR T-cell therapy (Blinatumomab USPI; Maude et al. 2014; Kochenderfer et al. 2015). The etiology of toxicity in these settings is not well known and may not be responsive to cytokine directed therapy such as tocilizumab, but has generally improved with treatment discontinuations and corticosteroids (Blinatumomab USPI; Maude et al. 2014; Kochenderfer et al. 2015).

For mosunetuzumab, neurologic adverse events (NAEs) were broadly defined as all AEs reported as primary or secondary Preferred terms (PTs) in either the System Organ Class (SOC) of Nervous System Disorders or SOC of Psychiatric Disorders. NAEs therefore encompass a broad group of heterogeneous terms, for which causal association of each adverse event/term with mosunetuzumab has not been established. Since there is insufficient scientific evidence of a causal relationship between NAEs and mosunetuzumab, NAEs are considered a potential risk rather than an identified risk that will be followed up via routine pharmacovigilance activities.

A total of 119 of 214 patients (55.6%) in the B11 RP2D cohort (primary safety population) experienced 239 NAEs following initial treatment with mosunetuzumab. The most frequently reported NAEs (≥5% of patients) in the B11 RP2D cohort were headache (44/214 patients [20.6%]), insomnia (22/214 patients [10.3%]), and dizziness (20/214 patients [9.3%]) (Annex 7A.9).

In the group of patients who experienced NAEs (119/214 patients; 55.6%), the majority of patients had NAEs of Grade 1-2 maximum severity (108/214 patients; 50.5%) and 11 patients (11/214 patients; 5.1%) had Grade 3 NAEs. The Grade 3 NAEs included subdural hematoma (2 patients) and the following PTs that were reported in 1 patient each: headache, presyncope, syncope, encephalopathy, cerebrovascular accident, toxic

neuropathy, confusional state, muscular weakness, spinal stenosis. No patients experienced Grade 4 or 5 NAEs (Annex 7A.9).

Serious NAEs were reported in 14 of 214 patients (6.5%). Serious NAEs reported in more than one patient were confusional state (3 patients), subdural hematoma (2 patients), and neurotoxicity (2 patients). The following serious NAEs were reported in 1 patient each: encephalopathy, syncope, balance disorder, cerebrovascular accident, toxic neuropathy, fear, herpes zoster, vision blurred (Annex 7A.10).

One patient (0.5%) had mosunetuzumab treatment withdrawn due to a NAE; a Grade 3 serious subdural hematoma considered by the investigator to be unrelated mosunetuzumab (Annex 7A.11). NAEs led to mosunetuzumab dose interruption or modification in 9 patients (4.2%) (Annex 7A.3).

The median time to onset of first NAEs was 15.0 days (range: 1.0–331.0 days), with median duration of 5.0 days (range: 1.0–344.0 days). At the time of CCOD, the majority of the NAEs (184 of 239 events [77.0%]) had resolved (Annex 7A.12).

Given that the majority of NAEs were of low-grade maximum severity (Grade 1-2 maximum severity) and had resolved, NAEs are not considered to have an impact on the benefit-risk balance of mosunetuzumab nor have any implications for public health. Reflective of the observed NAEs, in the SmPC Section 4.7 Effects on Ability to Drive and Use Machines, information is provided that mosunetuzumab has a minor influence on the ability to drive and use machines. Further guidance is included that patients who experience events that impair consciousness should be evaluated and advised not to drive and refrain from operating heavy or potentially dangerous machines until events are resolved.

SVII.1.2 RISKS CONSIDERED IMPORTANT FOR INCLUSION IN THE LIST OF SAFETY CONCERNS IN THE RMP

Important Identified Risk of Cytokine Release Syndrome

Risk-benefit impact:

The mechanism of action of mosunetuzumab is driven by T-cell activation against CD20-expressing cells. T-cell activation may lead to an excess of systemic cytokine release from cells targeted by antibodies, immune effector cells recruited to the tumor area and the subject's immune cells activated during this process.

Based on the American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading criteria (Lee et al. 2019), 84 of 214 patients (39.3%) in Group B11 RP2D cohort (primary safety population) experienced a total of 122 CRS events following the initial treatment of mosunetuzumab. The majority of patients experienced Grade 1-2 CRS events (Grade 1 in 47 patients [22.0%] and Grade 2 in 31 patients [14.5%]). Grade 3 CRS event was reported in 5 patients (2.3%), and Grade 4 CRS event in 1 patient (0.5%). No Grade 5 CRS events were reported. All CRS events had resolved [Note that

one Grade 1 CRS event in a patient in this cohort, although resolved one day following the onset of the event, was listed as having an unknown outcome due to a discrepancy in the data entry]. Two patients (0.9%) had mosunetuzumab treatment withdrawn due to a CRS event. CRS events leading to mosunetuzumab dose interruption were reported in 18 patients (8.4%) and dose modification in 2 patients (0.9%) (Table 18, Table 20). The frequency, severity and outcomes of CRS events that occurred in the overall safety population from Study GO29781 (Group B) and in Group B11 FL RP2D cohort are presented in SVII.3.

The majority of CRS events were of Grade 1-2 intensity and all resolved with appropriate management. Although the frequency of severe and life-threatening CRS events of Grade 3-4 intensity was low, the impact on the benefit-risk balance of mosunetuzumab may differ depending on the grade and severity of CRS. Appropriate comprehensive labeling, and the patient educational material as a risk-minimization activity, increases the likelihood of an early diagnosis followed by appropriate treatment, further reducing the impact of CRS on the benefit-risk balance of the product.

Important Identified Risk of Tumor Flare

Risk-benefit impact:

Tumor flare is likely due to the influx of T-cells into tumor sites following mosunetuzumab administration. Manifestations include localized pain at sites of lymphoma lesions, and possible volumetric increase of lymphoma lesions leading to local compression and accompanying organ dysfunction.

In the Group B11 RP2D cohort (primary safety population), a total of 9 of 214 patients (4.2%) experienced 9 events that met the definition of tumor flare events (see SVII.3 for definition of tumor flare events). Of the 9 events, 6 were assessed as related to mosunetuzumab by the investigator. All events were Grades 2-3 in severity; Grade 2 in 4 patients [1.9%]) and Grade 3 in 5 patients [2.3%]). The majority of tumor flare events (n=8) resolved and 1 event was unresolved at the time of reporting. None of the tumor flare event led to mosunetuzumab treatment withdrawn or dose modification or dose interruption (Table 26, Table 28). The frequency, severity and outcomes of tumor flare events that occurred in the overall safety population from Study GO29781 (Group B) and in Group B11 FL RP2D cohort are presented in SVII.3.

Considering the low incidence of tumor flare events, and that the majority of events resolved without mosunetuzumab treatment modification, the impact on benefit-risk balance is considered to be minimal. However, there is a potential for clinically significant impact based on anatomical site of lesions secondary to mass effect, with patients with bulky tumors located in close proximity to airways and/or a vital organ being at heightened risk, of which prescribers should be warned. Therefore, tumor flare represents an important identified risk for mosunetuzumab. Appropriate comprehensive labeling as a risk-minimization activity increases the likelihood of early recognition and

allows planning for mitigations in patients with tumors at critical anatomic locations, further reducing the impact of tumor flare on the benefit-risk balance of the product.

Important Identified Risk of Serious Infections

Risk-benefit impact:

Serious infections are anticipated with mosunetuzumab administration due to its mode of action resulting in B-cell depletion. Increased risk of serious infections is also inherent to the target patient population due to prior lines of treatment and underlying disease, which results in various degrees of immune compromise.

In the Group B11 RP2D cohort (primary safety population), 43 serious infections events were reported in 35 patients (16.4%), with pneumonia (7 patients [3.3%]) being the most frequent. Other serious infections reported in more than one patient were sepsis and urinary tract infection (4 patients [1.9%] each), Pneumocystis jirovecii pneumonia (3 patients [1.4%]), and upper respiratory tract infection, COVID-19, Epstein-Barr viremia, and septic shock (2 patients [0.9%] each). One serious infection event (sepsis) led to treatment withdrawal in one patient (0.5%). Serious infections led to mosunetuzumab dose interruption in 5 patients (2.3%). Serious infections resolved in the majority of patients (32 patients) (Table 35). The frequency, severity and outcomes of serious infections that occurred in the primary safety population from Study GO29781 (Group B11 RP2D) and in Group B11 FL RP2D cohort are presented in SVII.3.

Serious infections represent an important identified risk for mosunetuzumab. The risk of infections is well-recognized by healthcare professionals for the patient population in view of underlying conditions or prior immunosuppressive treatment that may predispose to infections. The management of serious infections in the patient population does not differ from routine oncology practice and standard of care. However, given the patient impact of serious infections coupled with the need to characterize the risk in larger patient population, serious infections is classified as an important identified risk. Appropriate comprehensive guidance is included in the product information of mosunetuzumab to allow for early recognition of serious infections and allow planning for mitigations in patients, further reducing the impact of serious infections on the benefit-risk balance of the product.

Important Potential Risk

Not applicable

Missing Information of Long-term Safety

Risk-benefit impact:

In Group B11 RP2D cohort (primary safety population), patients received a median of 8 cycles (range: 1-17). The median duration of treatment of mosunetuzumab was 4.9 months (range 0.03-13.8), which corresponds approximately to the median of 8 x q3w cycles received. At the time of the clinical cut-off date (15 March 2021), the median

observation time in the B11 RP2D cohort was 11.5 months (range: 0.1-23 months). Thus, long-term safety of mosunetuzumab is considered missing information and needs to be further characterized. Long-term safety data is being collected and monitored from the ongoing GO42909 study. Refer to Part III.2 for further details.

Missing Information of Safety in Patients with Prior CAR-T Therapy

Risk-benefit impact:

In Group B11 RP2D cohort (primary safety population), there were 29 patients who received prior CAR-T therapy (prior CAR-T group; including 3 patients with R/R FL) and 185 patients who did not receive prior CAR-T therapy (no prior CAR-T group). Patients in the prior CAR-T group appeared to have more aggressive NHL histology, heavier disease burden, worse Eastern Cooperative Oncology Group (ECOG) performance status (PS) at baseline, and more prior therapies received. The frequency of fatal adverse events (AEs), serious AEs, AE of Grade 3-4, AE leading to withdrawal from treatment was numerically higher in the prior CAR-T group compared to the no prior CAR-T group. Further characterization of the safety profile in this patient population will be monitored through routine pharmacovigilance activities.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No new safety concerns were identified based on results from patients treated with mosunetuzumab SC in Group F in Study GO29781. Information from Group F (N = 181), F2 RP2D cohort (N = 139), and F2 FL RP2D cohort (N = 94) is included in SVII.3 for each important identified risk and missing information safety concern.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Information on Important Identified Risks

Cytokine Release Syndrome

MedDRA terms: Cytokine release syndrome (PT)

Potential mechanisms:

The mechanism of action of mosunetuzumab is driven by T-cell activation against CD20-expressing cells. T-cell activation may lead to an excess of systemic cytokine release from cells targeted by antibodies, immune effector cells recruited to the tumor area and the subject's immune cells activated during this process. CRS may lead to serious and even fatal events. Signs or symptoms of CRS observed in mosunetuzumab-treated patients include pyrexia, chills, hypotension, tachycardia, hypoxia, and headache.

Exposure-response relationships for safety were assessed based on patients receiving IV administrations of mosunetuzumab from Study GO29781. Dosing of mosunetuzumab

IV following the step-up dosing regimen is associated with a low frequency (<15%) of Grade ≥2 CRS transiently during Cycle 1, typically following the 1 mg dose administration on Day 1 or the 60 mg dose administration on Day 15. Higher receptor occupancy values modestly increase the rate of Grade ≥2 CRS.

Overall, there was a lower frequency and severity of CRS for mosunetuzumab SC as compared to IV (F2 RP2D cohort versus B11 RP2D cohort). Exposure-response relationships for safety were also assessed based on patients receiving SC administration of mosunetuzumab from Study GO29781. Dosing of mosunetuzumab SC following the step-up dosing regimen is associated with a low frequency (<10%) of Grade ≥2 CRS transiently during Cycle 1 Day 1 following the 5 mg dose, and Cycle 1 Day 8 following the 45 mg dose. Similar to mosunetuzumab IV, higher receptor occupancy values modestly increase the rate of Grade ≥2 CRS.

Evidence source(s) and strength of evidence:

Nonclinical studies showing transient T-cell activation and cytokine release and in clinical studies, the majority of CRS events occurred in the first cycle of mosunetuzumab administration, mostly associated either with Day 1 or Day 15 doses for mosunetuzumab IV and Day 1 or Day 8 doses for mosunetuzumab SC, and evidence is also based on Study GO29781 (See SII and SIII).

Characterization of the risk:

Overview of CRS by ASTCT 2019 grading criteria (Lee et al. 2019)

Group B

In the overall safety population for mosunetuzumab IV from Study GO29781, Group B, 133 of 414 patients (32.1%) experienced a total of 189 CRS events following the initial treatment with mosunetuzumab IV based on the ASTCT 2019 grading criteria (Table 17, Table 20).

The majority of patients experienced Grade 1–2 CRS events (Grade 1 in 89 patients [21.5%] and Grade 2 in 37 patients [8.9%]). Grade 3 CRS events were reported in 6 patients (1.4%), and 1 patient (0.2%) experienced a Grade 4 CRS event. No Grade 5 CRS events were reported (Table 17, Table 20). All CRS events had resolved (Table 18, Table 20). Two patients (0.5%) had mosunetuzumab treatment withdrawn due to a CRS event. CRS events leading to dose interruption were reported in 23 patients (5.6%) and dose modification in 2 patients (0.5%) (Table 17, Table 20).

Group B11 RP2D

In the Group B11 RP2D cohort (the primary safety population for mosunetuzumab IV), 86 of 218 patients (39.4%) experienced a total of 123 CRS events following the initial treatment with mosunetuzumab IV. (Table 18, Table 20).

The majority of patients experienced Grade 1-2 CRS events (Grade 1 in 49 patients [22.5%] and Grade 2 in 31 patients [14.2%]). Grade 3 CRS event were reported in 5 patients (2.3%), and 1 patient (0.5%) experienced Grade 4 CRS event. No Grade 5 CRS events were reported. All CRS events resolved. Two patients (0.9%) had mosunetuzumab treatment withdrawn due to a CRS event. CRS events leading to mosunetuzumab IV dose interruption were reported in 17 patients (7.8%) and dose modification in 2 patients (0.9%) (Table 18, Table 20).

Group B11 FL RP2D

In the Group B11 FL RP2D cohort, 40 of 90 patients (44.4%) experienced a total of 71 CRS events following the initial treatment with mosunetuzumab IV. Seventy CRS events were assessed as related to mosunetuzumab by the investigator Table 19 , Table 20).

The majority of patients experienced Grade 1-2 CRS events (Grade 1 in 23 patients [25.6%] and Grade 2 in 15 patients [16.7%]). Grade 3 CRS event was reported in 1 patient (1.1%), and Grade 4 CRS event in 1 patient (1.1%). No Grade 5 CRS events were reported. All CRS events had resolved. Two patients (2.2%) had mosunetuzumab treatment withdrawn due to a CRS event. CRS events leading to mosunetuzumab IV dose interruption were reported in 7 patients (7.8%) and dose modification in 1 patient (1.1%) (Table 19 , Table 20).

CRS Events by Dose Cycle in Group B, Group B11 RP2D, and Group B11 FL RP2D

In all three groups, CRS events occurred predominantly in Cycle 1 and were mainly associated with Day 1 and Day 15 dose administrations, with a higher frequency of CRS of any grade observed following Day 15 dose compared with Day 1 dose, most pronounced in Group B11 FL RP2D (36.4%) (Table 19).

In Group B, within the first cycle of treatment, 5 patients (1.3%) had Grade 3 CRS events and 1 patient (0.3%) had Grade 4 CRS event following Day 15 dose administrations (Table 17). The proportion of patients experiencing CRS and the number of CRS events of any grade decreased in the subsequent treatment cycles. Grade 1-3 CRS events were reported in Cycle 2, the majority reported as Grade 1. Only Grade 1 CRS events were reported in Cycle 3 and beyond (Table 17).

Group F

In the overall safety population for mosunetuzumab SC from Study GO29781, Group F, 52 of 181 patients (28.7%) experienced a total of 62 CRS events following the initial treatment with mosunetuzumab SC based on the ASTCT 2019 grading criteria (Table 24).

The majority of patients experienced Grade 1–2 CRS events (Grade 1 in 34 patients [18.8%] and Grade 2 in 16 patients [8.8%]). Grade 3 CRS events were reported in 2 patients (1.1%), who were also part of the F2 FL RP2D cohort. No Grade 4 or 5 CRS events were reported. All CRS events had resolved. CRS events leading to mosunetuzumab SC dose interruption were reported in 3 patients (1.7%). No patient had a CRS event leading to mosunetuzumab treatment withdrawal or dose modification (Table 24).

Group F2 RP2D

In the Group F2 RP2D cohort (primary safety population for mosunetuzumab SC), 36 of 139 patients (25.9%) experienced a total of 42 CRS events following the initial treatment with mosunetuzumab SC (Table 24).

The majority of patients experienced Grade 1–2 CRS events (Grade 1 in 24 patients [17.3%] and Grade 2 in 10 patients [7.2%]). Grade 3 CRS events were reported in 2 patients (1.4%), who were also part of the F2 FL RP2D cohort. No Grade 4 or 5 CRS events were reported. All CRS events had resolved. CRS events leading to mosunetuzumab SC dose interruption were reported in 3 patients (2.2%). No patient had a CRS event leading to mosunetuzumab treatment withdrawal or dose modification (Table 24).

Group F2 FL RP2D

In the Group F2 FL RP2D cohort, 28 of 94 patients (29.8%) experienced a total of 32 CRS events following the initial treatment with mosunetuzumab SC. All 32 CRS events were assessed as related to mosunetuzumab by the investigator (Table 24).

The majority of patients experienced Grade 1–2 CRS events (Grade 1 in 19 patients [20.2%] and Grade 2 in 7 patients [7.4%]). Grade 3 CRS events were reported in 2 patients (2.1%) following Cycle 1 Day 15 dose administration of 45 mg mosunetuzumab SC. No Grade 4 or 5 CRS events were reported. All CRS events had resolved. CRS events leading to mosunetuzumab SC dose interruption were reported in 2 patients (2.1%). No patient had a CRS event leading to mosunetuzumab treatment withdrawal or dose modification (Table 24).

CRS events by dose cycle in Group F, Group F2 RP2D, and Group F2 FL RP2D

In all three groups, CRS events occurred predominantly in Cycle 1 and were mainly associated with Day 1 and Day 8 dose administrations, with the highest frequency of CRS of any grade observed following Day 1 dosing (Table 21, Table 22, Table 23).

In Group F, 2 patients (1.1%) had Grade 3 CRS events within the first cycle of treatment, following Day 15 dose administrations of 45 mg mosunetuzumab SC. The proportion of patients experiencing CRS and the number of CRS events of any grade decreased in

the subsequent treatment cycles. Beyond Cycle 1, 1 patient had Grade 1 CRS in Cycle 2 and 1 patient had Grade 1 CRS in Cycle 3 in Group F (Table 21).

Risk factors and risk groups:

Patient-specific factors which may account for the greater likelihood to have excessive cytokine release are yet to be clearly defined but may include tumor burden, peripheral/circulating target cells, higher levels of macrophages or monocytes or the presence of hyperactive T-cells primed to react.

Preventability:

Patients receiving mosunetuzumab should be carefully monitored for clinical signs and symptoms of CRS and treated as clinically appropriate. Based on the severity of the CRS event, treatment with mosunetuzumab should be withheld until symptoms resolve.

Premedication consisting of corticosteroids, antipyretics and antihistamines should be administered at least through Cycle 2 for patients receiving mosunetuzumab IV and at least through Cycle 1 for patients receiving mosunetuzumab SC.

Grade 1 events have been manageable and reversible with supportive measures. The impact on benefit/risk balance is considered low. If CRS event lasts > 48 hours after symptomatic management, dexamethasone and/or tocilizumab administration can be considered.

Grade 2 events may require hospitalization and medical intervention in some cases, such as administration of fluids for blood pressure support and low-flow oxygen supplementation for hypoxia. If no clinical improvement is observed after symptomatic management, dexamethasone and/or tocilizumab administration can be considered.

Grade 3+ CRS events require hospitalization for more aggressive treatment, such as vasopressors for circulatory support and high flow oxygen or positive pressure airway support, and patients may need ICU admission. Dexamethasone and tocilizumab can be administered and if CRS continues to progress rapidly, alternative anti-cytokine therapy and methylprednisolone can be considered.

To minimize the risk and sequelae of CRS, mosunetuzumab IV will be administered over a minimum of 4 hours in a clinical setting during the first cycle, and over a minimum of 2 hours if the first cycle is tolerated. Following each mosunetuzumab IV dose administration, patients were observed for at least 90 minutes.

Following mosunetuzumab SC administration, patients were observed for 30 minutes for the Cycle 1 Day 1 dose, and if tolerated, reduced to 15 minutes at subsequent injections, for fever, chills, rigors, hypotension, nausea, or other signs and symptoms of CRS.

Sections 4.2 and 4.4 of the SmPC provide monitoring, dose modification recommendations and management guidelines for this event.

Impact on the benefit-risk balance of the product:

The majority of CRS events were of Grade 1-2 intensity and resolved with appropriate management. Although the frequency of severe and life-threatening CRS events of Grade 3-4 intensity was low, the impact on the benefit-risk balance of mosunetuzumab may differ depending on the grade and severity of CRS. Guidance regarding premedication, careful monitoring and management provided in the product label reduces the risk of CRS.

In addition to comprehensive product labeling, additional risk-minimization measure includes an educational material for patients in the form of a Patient Card. The comprehensive product labeling and current pharmacovigilance plan including routine risk-minimization measures and additional risk-minimization measure are considered adequate to manage the risk of CRS.

Public health impact:

Severe CRS may impact the patient's quality of life although this is short lived, occurred predominantly in Cycle 1, and is likely to be confined to the duration of CRS events. In the IV B11 RP2D and the SC F2 RP2D cohorts, all CRS events resolved, and no fatal cases were observed.

No public health impact is envisaged since the events can be effectively treated and risk mitigation measures associated with CRS are included in the product label. Use outside of controlled environments by non-healthcare professionals is not anticipated.

Table 17 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B Cohort, by Cycle

Seriousness, Outcomes, Severity - Group B Cohort, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=414)	C1D8-14 (N=398)	C1D15+ (N=386)	C2 (N=373)	C3+ (N=300)
Number of patients with at least one AE	55 (13.3%)	20 (5.0%)	94 (24.4%)	11 (2.9%)	3 (1.0%)
95% CI for % of patients with at least one AE	(10.17%, 16.94%)	(3.10%, 7.65%)	(20.15%, 28.95%)	(1.48%, 5.22%)	(0.21%, 2.89%)
Total number of AEs	55	20	96	11	7
Total number of AEs related to mosun	54	20	96	11	7
Number of patients with at least one AE by worst grade					
Grade 1	44 (10.6%)	16 (4.0%)	61 (15.8%)	9 (2.4%)	3 (1.0%)
Grade 2	11 (2.7%)	4 (1.0%)	27 (7.0%)	1 (0.3%)	0
Grade 3	0	0	5 (1.3%)	1 (0.3%)	0
Grade 4	0	0	1 (0.3%)	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one serious AE	15 (3.6%)	6 (1.5%)	42 (10.9%)	8 (2.1%)	1 (0.3%)
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	0	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	55 (100%)	20 (100%)	94 (100%)	11 (100%)	3 (100%)
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
Investigator text for AEs encoded using MedDRA version 24.0.
Data Cutoff Date - 27AUG2021

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Table 17 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B Cohort, by Cycle (cont.)

Seriousness, Outcomes, Severity - Group B Cohort, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=414)	C1D8-14 (N=398)	C1D15+ (N=386)	C2 (N=373)	C3+ (N=300)
Mosun related AE leading to withdrawal from treatment	0	0	1 (0.3%)	1 (0.3%)	0
Mosun related AE leading to dose interruption	11 (2.7%)	1 (0.3%)	12 (3.1%)	0	0
Mosun related AE leading to dose modification	0	0	2 (0.5%)	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
Investigator text for AEs encoded using MedDRA version 24.0.
Data Cutoff Date - 27AUG2021

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Table 18 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B11 RP2D Cohort, by Cycle

Seriousness, Outcomes, Severity - B11 Exp Cohort, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=218)	C1D8-14 (N=206)	C1D15+ (N=201)	C2 (N=198)	C3+ (N=167)
Number of patients with at least one AE	33 (15.1%)	10 (4.9%)	67 (33.3%)	9 (4.5%)	2 (1.2%)
95% CI for % of patients with at least one AE	(10.65%, 20.60%)	(2.35%, 8.75%)	(26.86%, 40.31%)	(2.10%, 8.45%)	(0.15%, 4.26%)
Total number of AEs	33	10	69	9	2
Total number of AEs related to mosun	32	10	69	9	2
Number of patients with at least one AE by worst grade					
Grade 1	24 (11.0%)	7 (3.4%)	38 (18.9%)	8 (4.0%)	2 (1.2%)
Grade 2	9 (4.1%)	3 (1.5%)	24 (11.9%)	0	0
Grade 3	0	0	4 (2.0%)	1 (0.5%)	0
Grade 4	0	0	1 (0.5%)	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one serious AE	11 (5.0%)	4 (1.9%)	33 (16.4%)	7 (3.5%)	1 (0.6%)
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	0	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	33 (100%)	10 (100%)	67 (100%)	9 (100%)	2 (100%)
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
Investigator text for AEs encoded using MedDRA version 24.0.
Data Cutoff Date - 27AUG2021

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Table 18 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B11 RP2D Cohort, by Cycle (cont.)

Seriousness, Outcomes, Severity - B11 Exp Cohort, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=218)	C1D8-14 (N=206)	C1D15+ (N=201)	C2 (N=198)	C3+ (N=167)
Mosun related AE leading to withdrawal from treatment	0	0	1 (0.5%)	1 (0.5%)	0
Mosun related AE leading to dose interruption	8 (3.7%)	0	10 (5.0%)	0	0
Mosun related AE leading to dose modification	0	0	2 (1.0%)	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
Investigator text for AEs encoded using MedDRA version 24.0.
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Table 19 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B11 FL RP2D Cohort, by Cycle

Seriousness, Outcomes, Severity - B11 Exp FL Cohort, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=90)	C1D8-14 (N=89)	C1D15+ (N=88)	C2 (N=87)	C3+ (N=83)
Number of patients with at least one AE	21 (23.3%)	5 (5.6%)	32 (36.4%)	9 (10.3%)	2 (2.4%)
95% CI for % of patients with at least one AE	(15.06%, 33.43%)	(1.85%, 12.63%)	(26.37%, 47.31%)	(4.84%, 18.73%)	(0.29%, 8.43%)
Total number of AEs	21	5	34	9	2
Total number of AEs related to mosun	20	5	34	9	2
Number of patients with at least one AE by worst grade					
Grade 1	17 (18.9%)	4 (4.5%)	18 (20.5%)	8 (9.2%)	2 (2.4%)
Grade 2	4 (4.4%)	1 (1.1%)	13 (14.8%)	0	0
Grade 3	0	0	0	1 (1.1%)	0
Grade 4	0	0	1 (1.1%)	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one serious AE	8 (8.9%)	2 (2.2%)	13 (14.8%)	7 (8.0%)	1 (1.2%)
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	0	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	21 (100%)	5 (100%)	32 (100%)	9 (100%)	2 (100%)
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
Investigator text for AEs encoded using MedDRA version 24.0.
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Table 19 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B11 FL RP2D Cohort, by Cycle (cont.)

Seriousness, Outcomes, Severity - B11 Exp FL Cohort, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=90)	C1D8-14 (N=89)	C1D15+ (N=88)	C2 (N=87)	C3+ (N=83)
Mosun related AE leading to withdrawal from treatment	0	0	1 (1.1%)	1 (1.1%)	0
Mosun related AE leading to dose interruption	4 (4.4%)	0	4 (4.5%)	0	0
Mosun related AE leading to dose modification	0	0	1 (1.1%)	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
Investigator text for AEs encoded using MedDRA version 24.0.
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Table 20 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B, B11 RP2D and B11 FL RP2D Cohort Overview

Seriousness, Outcomes, Severity - B11 Exp FL Cohort, B11 Exp, Group B, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	B11 Exp FL Cohort (N=90)	B11 Exp (N=218)	Group B (N=414)
Number of patients with at least one AE	40 (44.4%)	86 (39.4%)	133 (32.1%)
95% CI for % of patients with at least one AE	(33.96%, 55.30%)	(32.92%, 46.27%)	(27.65%, 36.86%)
Total number of AEs	71	123	189
Total number of AEs related to mosun	70	122	188
Number of patients with at least one AE by worst grade			
Grade 1	23 (25.6%)	49 (22.5%)	89 (21.5%)
Grade 2	15 (16.7%)	31 (14.2%)	37 (8.9%)
Grade 3	1 (1.1%)	5 (2.3%)	6 (1.4%)
Grade 4	1 (1.1%)	1 (0.5%)	1 (0.2%)
Grade 5	0	0	0
Number of patients with at least one serious AE	21 (23.3%)	45 (20.6%)	59 (14.3%)
Number of patients with at least one AE by outcome			
Fatal outcome	0	0	0
Unresolved	0	0	0
Recovering/Resolving	0	0	0
Recovered/Resolved	40 (100%)	86 (100%)	133 (100%)
Resolved with sequelae	0	0	0
Unknown outcome	0	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included.
Investigator text for AEs encoded using MedDRA version 24.0.
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Table 20 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B, B11 RP2D and B11 FL RP2D Cohort Overview (cont.)

Seriousness, Outcomes, Severity - B11 Exp FL Cohort, B11 Exp, Group B, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	B11 Exp FL Cohort (N=90)	B11 Exp (N=218)	Group B (N=414)
Mosun related AE leading to withdrawal from treatment	2 (2.2%)	2 (0.9%)	2 (0.5%)
Mosun related AE leading to dose interruption	7 (7.8%)	17 (7.8%)	23 (5.6%)
Mosun related AE leading to dose modification	1 (1.1%)	2 (0.9%)	2 (0.5%)

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included.
Investigator text for AEs encoded using MedDRA version 24.0.
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Table 21 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F Cohort, by Cycle

Seriousness, Outcomes, Severity - Group F, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=181)	C1D8-14 (N=178)	C1D15+ (N=176)	C2 (N=170)	C3+ (N=146)
Number of patients with at least one AE	31 (17.1%)	20 (11.2%)	8 (4.5%)	1 (0.6%)	1 (0.7%)
95% CI for % of patients with at least one AE	(11.94%, 23.42%)	(7.00%, 16.82%)	(1.98%, 8.76%)	(0.01%, 3.23%)	(0.02%, 3.76%)
Total number of AEs	31	20	8	1	2
Total number of AEs related to mosun	31	20	8	1	2
Number of patients with at least one AE by worst grade					
Grade 1	25 (13.8%)	12 (6.7%)	4 (2.3%)	1 (0.6%)	1 (0.7%)
Grade 2	6 (3.3%)	8 (4.5%)	2 (1.1%)	0	0
Grade 3	0	0	2 (1.1%)	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one serious AE	13 (7.2%)	9 (5.1%)	4 (2.3%)	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	0	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	31 (100%)	20 (100%)	8 (100%)	1 (100%)	1 (100%)
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
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Table 21 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F Cohort, by Cycle (cont.)

Seriousness, Outcomes, Severity - Group F, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=181)	C1D8-14 (N=178)	C1D15+ (N=176)	C2 (N=170)	C3+ (N=146)
Mosun related AE leading to withdrawal from treatment	0	0	0	0	0
Mosun related AE leading to dose interruption	1 (0.6%)	2 (1.1%)	0	0	0
Mosun related AE leading to dose modification	0	0	0	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

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Table 22 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F2 RP2D Cohort, by Cycle

Seriousness, Outcomes, Severity - Group F2 RP2D, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=139)	C1D8-14 (N=137)	C1D15+ (N=137)	C2 (N=132)	C3+ (N=116)
Number of patients with at least one AE	22 (15.8%)	16 (11.7%)	3 (2.2%)	1 (0.8%)	0
95% CI for % of patients with at least one AE	(10.19%, 22.98%)	(6.82%, 18.27%)	(0.45%, 6.27%)	(0.02%, 4.15%)	(0.00%, 3.13%)
Total number of AEs	22	16	3	1	0
Total number of AEs related to mosun	22	16	3	1	0
Number of patients with at least one AE by worst grade					
Grade 1	18 (12.9%)	10 (7.3%)	1 (0.7%)	1 (0.8%)	0
Grade 2	4 (2.9%)	6 (4.4%)	0	0	0
Grade 3	0	0	2 (1.5%)	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one serious AE	9 (6.5%)	7 (5.1%)	1 (0.7%)	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	0	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	22 (100%)	16 (100%)	3 (100%)	1 (100%)	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

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Table 22 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F2 RP2D Cohort, by Cycle (cont.)

Seriousness, Outcomes, Severity - Group F2 RP2D, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=139)	C1D8-14 (N=137)	C1D15+ (N=137)	C2 (N=132)	C3+ (N=116)
Mosun related AE leading to withdrawal from treatment	0	0	0	0	0
Mosun related AE leading to dose interruption	1 (0.7%)	2 (1.5%)	0	0	0
Mosun related AE leading to dose modification	0	0	0	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

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Table 23 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F2 FL RP2D Cohort, by Cycle

Seriousness, Outcomes, Severity - Group F2 RP2D FL Exp, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=94)	C1D8-14 (N=94)	C1D15+ (N=94)	C2 (N=91)	C3+ (N=88)
Number of patients with at least one AE	18 (19.1%)	12 (12.8%)	2 (2.1%)	0	0
95% CI for % of patients with at least one AE	(11.76%, 28.56%)	(6.77%, 21.24%)	(0.26%, 7.48%)	(0.00%, 3.97%)	(0.00%, 4.11%)
Total number of AEs	18	12	2	0	0
Total number of AEs related to mosun	18	12	2	0	0
Number of patients with at least one AE by worst grade					
Grade 1	15 (16.0%)	8 (8.5%)	0	0	0
Grade 2	3 (3.2%)	4 (4.3%)	0	0	0
Grade 3	0	0	2 (2.1%)	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one serious AE	8 (8.5%)	6 (6.4%)	1 (1.1%)	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	0	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	18 (100%)	12 (100%)	2 (100%)	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ae_out_rmp3.sas
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Table 23 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F2 FL RP2D Cohort, by Cycle (cont.)

Seriousness, Outcomes, Severity - Group F2 RP2D FL Exp, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=94)	C1D8-14 (N=94)	C1D15+ (N=94)	C2 (N=91)	C3+ (N=88)
Mosun related AE leading to withdrawal from treatment	0	0	0	0	0
Mosun related AE leading to dose interruption	1 (1.1%)	1 (1.1%)	0	0	0
Mosun related AE leading to dose modification	0	0	0	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ae_out_rmp3.sas
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Table 24 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F, F2 RP2D, and F2 FL RP2D Cohort Overview

Seriousness, Outcomes, Severity - Group F, F2 RP2D, F2 RP2D FL Exp, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	Group F (N=181)	F2 RP2D (N=139)	F2 RP2D FL Exp (N=94)
Number of patients with at least one AE	52 (28.7%)	36 (25.9%)	28 (29.8%)
95% CI for % of patients with at least one AE	(22.26%, 35.91%)	(18.85%, 34.01%)	(20.79%, 40.10%)
Total number of AEs	62	42	32
Total number of AEs related to mosun	62	42	32
Number of patients with at least one AE by worst grade			
Grade 1	34 (18.8%)	24 (17.3%)	19 (20.2%)
Grade 2	16 (8.8%)	10 (7.2%)	7 (7.4%)
Grade 3	2 (1.1%)	2 (1.4%)	2 (2.1%)
Grade 4	0	0	0
Grade 5	0	0	0
Number of patients with at least one serious AE	23 (12.7%)	16 (11.5%)	14 (14.9%)
Number of patients with at least one AE by outcome			
Fatal outcome	0	0	0
Unresolved	0	0	0
Recovering/Resolving	0	0	0
Recovered/Resolved	52 (100%)	36 (100%)	28 (100%)
Resolved with sequelae	0	0	0
Unknown outcome	0	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

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Table 24 Important Identified Risk of Cytokine Release Syndrome: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F, F2 RP2D and F2 FL RP2D Cohort Overview (cont.)

Seriousness, Outcomes, Severity - Group F, F2 RP2D, F2 RP2D FL Exp, Initial Treatment with Mosunetuzumab, CRS events, By ASTCT Grade, Safety-Evaluable Patients
Protocol: GO29781

	Group F (N=181)	F2 RP2D (N=139)	F2 RP2D FL Exp (N=94)
Mosun related AE leading to withdrawal from treatment	0	0	0
Mosun related AE leading to dose interruption	3 (1.7%)	3 (2.2%)	2 (2.1%)
Mosun related AE leading to dose modification	0	0	0

Only treatment emergent AEs are displayed.
Only CRS signs and symptoms associated with CRS event with a valid ASTCT grade are included. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

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Tumor Flare

MedDRA terms: Tumor flare (PT)

Potential mechanisms:

Adverse events associated with tumor flare have been reported with T-cell engaging or checkpoint inhibitor therapies (Taleb 2019; Carlo-Stella et al. 2024) and are consistent with the mechanism of action, leading to influx of T-cells into tumor sites. Tumor flare is likely due to the influx of T-cells into tumor sites following mosunetuzumab administration and may be associated with pseudoprogression. Manifestations include localized pain at sites of lymphoma lesions, and possible volumetric increase of lymphoma lesions leading to local compression and accompanying organ dysfunction. Patients with tumors at critical anatomic locations should be closely monitored for tumor flare, and considerations dependent on the anatomic locations of lymphoma lesions need to be applied and specific mitigations planned with collaboration of multidisciplinary teams.

Evidence source(s) and strength of evidence:

Evidence is based on Study GO29781 (See SIII).

Characterization of the risk:

Tumor flare events were identified by PT of 'tumor flare' or 'suspected tumor flare' (event identified by eCRF check box) or protocol-specific Adverse event of special interest Grade ≥2 'tumor flare/tumor inflammation specific for mosunetuzumab' (event identified by eCRF check box).

Group B

In the overall safety population for mosunetuzumab IV Study GO29781, Group B, a total of 18 of 414 patients (4.3%) experienced 19 events that met the definition of tumor flare events. The reported tumor flare events included tumor flare in 10 patients (2.4%), pleural effusion in 7 patients (1.7%), and tumor inflammation in 1 patient (0.2%) (Annex 7A.13).

The reported events were of Grade 1 (2 patients [0.5%]), Grade 2 (9 patients [2.2%]) and Grade 3 (7 patients [1.7%]) in severity. Out of these 19 events, 16 events were assessed as related to mosunetuzumab IV by the investigator. No patient had mosunetuzumab treatment withdrawn due to any tumor flare event. Tumor flare events leading to mosunetuzumab IV dose interruption were reported in 1 patient (0.2%) and dose modification in 1 patient (0.2%) (Table 25, Table 28).

Group B11 RP2D

A total of 9 of 218 patients (4.1%) experienced 9 events that met the definition of tumor flare events. Out of these 9 events, 6 events were assessed as related to mosunetuzumab IV by the investigator. The events were of Grade 2 (4 patients [1.8%]) and Grade 3 (5 patients [2.3%]) in severity. The majority of tumor flare events (n=8) resolved and 1 event was unresolved at the time of reporting. None of the tumor flare events led to mosunetuzumab IV treatment withdrawal or dose modification or dose interruption (Table 26, Table 28).

Group B11 FL RP2D

A total of 3 of 90 patients (3.3%) experienced 3 events that met the definition of tumor flare events. These 3 events were assessed as related to mosunetuzumab IV by the investigator and were of Grade 2 (1 patient [1.1%]) and Grade 3 (2 patients [2.2%]) in severity. All tumor flare events resolved and none of the tumor flare events led to mosunetuzumab IV treatment withdrawal or dose modification or dose interruption (Table 27, Table 28).

Group F

In the overall safety population for mosunetuzumab SC from Study GO29781, Group F, a total of 5 of 181 patients (2.8%) experienced 5 events that met the definition of tumor flare events. The reported tumor flare events included tumor flare in 2 patients (1.1%), and tumor pain, peripheral swelling, and flank pain in 1 patient (0.6%) each (Annex 7A.14).

The reported events were of Grade 1 (1 patient [0.6%]), Grade 2 (2 patients [1.1%]), or Grade 3 (2 patients [1.1%]) in severity. Out of these 5 events, 3 events were assessed as related to mosunetuzumab SC by the investigator. The two Grade 3 events were ‘tumour flare’ and ‘tumour pain’ (PT). Both Grade 3 events were considered serious by the investigator and the Grade 3 tumor pain was assessed as related to mosunetuzumab. One event (Grade 2 tumor flare) led to mosunetuzumab SC dose interruption (1 patient [0.6%]). No patient had a tumor flare event leading to mosunetuzumab treatment withdrawal or dose modification (Table 29, Table 32).

Group F2 RP2D

A total of 2 of 139 patients (1.4%) experienced 2 events that met the definition of tumor flare events. These events were Grade 1 flank pain and Grade 2 tumor flare. The Grade 2 tumor flare event led to mosunetuzumab SC dose interruption and was assessed as related to mosunetuzumab by the investigator. Grade 2 tumor flare resolved; Grade 1 flank pain was unresolved at the time of reporting. None of the tumor

flare events led to mosunetuzumab SC treatment withdrawal or dose modification (Table 30, Table 32; Annex 7A.14).

Group F2 FL RP2D

In Group F2 FL RP2D, 1 of 94 patients (1.1%) experienced 1 event (flank pain) that met the definition of tumor flare events. This event was assessed as not related to mosunetuzumab SC by the investigator, was of Grade 1 in severity, and was unresolved at the time of reporting. The event did not lead to mosunetuzumab SC treatment withdrawal, or dose modification, or dose interruption (Table 31, Table 32; Annex 7A.14).

Risk factors and risk groups:

Tumor flare events tend to occur within the first few weeks following mosunetuzumab administration. In addition, depending on tumor size and anatomic location, tumor flare may potentially result in mass effects on vital structures including airways, major blood vessels, gastrointestinal tract (risk of perforation and hemorrhage), and/or major organs.

Preventability:

Depending on the nature of the tumor inflammation, further medical and/or surgical management may be necessary (e.g. anti-inflammatory agents, airway management, decompression, prolonged hospitalization, etc.). Important differential diagnosis needs to be made with disease progression.

Sections 4.4 and 4.8 of the SmPC provide monitoring and management advice to reduce the potential for negative outcomes in patients experiencing the event.

Impact on the benefit-risk balance of the product:

Based on safety data collected, tumor flare associated with mosunetuzumab administration have manifested as new or worsening pleural effusions, and localized pain and swelling at sites of lymphoma lesions. Considering the low incidence of tumor flare events, and that all events resolved without mosunetuzumab treatment withdrawal, the impact on benefit/risk balance is considered to be minimal.

To enhance the early recognition and management of tumor flare, the SmPC provides comprehensive guidance for patient management of tumor flare.

Public health impact:

Given the low frequency of serious events, coupled with the responsiveness to tumor flare management, the impact of tumor flare on public health is considered to be low.

Table 25 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B Cohort, by Cycle

Seriousness, Outcomes, Severity - Group B Cohort, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=414)	C1D8-14 (N=398)	C1D15+ (N=386)	C2 (N=373)	C3+ (N=300)
Number of patients with at least one AE	5 (1.2%)	6 (1.5%)	6 (1.6%)	1 (0.3%)	1 (0.3%)
95% CI for % of patients with at least one AE	(0.39%, 2.80%)	(0.56%, 3.25%)	(0.57%, 3.35%)	(0.01%, 1.48%)	(0.01%, 1.84%)
Total number of AEs	5	6	6	1	1
Total number of AEs related to mosun	4	5	6	1	0
Number of patients with at least one AE by worst grade					
Grade 1	2 (0.5%)	0	1 (0.3%)	0	0
Grade 2	1 (0.2%)	3 (0.8%)	3 (0.8%)	1 (0.3%)	1 (0.3%)
Grade 3	2 (0.5%)	3 (0.8%)	2 (0.5%)	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one serious AE	2 (0.5%)	2 (0.5%)	1 (0.3%)	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	2 (33.3%)	2 (33.3%)	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	5 (100%)	4 (66.7%)	4 (66.7%)	1 (100%)	1 (100%)
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0
Mosun related AE leading to withdrawal from treatment	0	0	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 24.0.
Data Cutoff Date - 27AUG2021

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Table 25 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B Cohort, by Cycle (cont.)

Seriousness, Outcomes, Severity - Group B Cohort, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=414)	C1D8-14 (N=398)	C1D15+ (N=386)	C2 (N=373)	C3+ (N=300)
Mosun related AE leading to dose interruption	1 (0.2%)	0	0	0	0
Mosun related AE leading to dose modification	1 (0.2%)	0	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 24.0.
Data Cutoff Date - 27AUG2021

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary2_BLA_Aug2021/prod/program/t_ae_out_rmp3.sas
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Table 26 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B11 RP2D Cohort, by Cycle

Seriousness, Outcomes, Severity - B11 Exp Cohort, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=218)	C1D8-14 (N=206)	C1D15+ (N=201)	C2 (N=198)	C3+ (N=167)
Number of patients with at least one AE	1 (0.5%)	5 (2.4%)	1 (0.5%)	1 (0.5%)	1 (0.6%)
95% CI for % of patients with at least one AE	(0.01%, 2.53%)	(0.79%, 5.57%)	(0.01%, 2.74%)	(0.01%, 2.78%)	(0.02%, 3.29%)
Total number of AEs	1	5	1	1	1
Total number of AEs related to mosun	0	4	1	1	0
Number of patients with at least one AE by worst grade					
Grade 1	0	0	0	0	0
Grade 2	0	2 (1.0%)	0	1 (0.5%)	1 (0.6%)
Grade 3	1 (0.5%)	3 (1.5%)	1 (0.5%)	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one serious AE	1 (0.5%)	2 (1.0%)	1 (0.5%)	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	1 (20.0%)	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	1 (100%)	4 (80.0%)	1 (100%)	1 (100%)	1 (100%)
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0
Mosun related AE leading to withdrawal from treatment	0	0	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 24.0.
Data Cutoff Date - 27AUG2021

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Table 26 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B11 RP2D Cohort, by Cycle (cont.)

Seriousness, Outcomes, Severity - B11 Exp Cohort, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=218)	C1D8-14 (N=206)	C1D15+ (N=201)	C2 (N=198)	C3+ (N=167)
Mosun related AE leading to dose interruption	0	0	0	0	0
Mosun related AE leading to dose modification	0	0	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 24.0.
Data Cutoff Date - 27AUG2021

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary2_BLA_Aug2021/prod/program/t_ae_out_rmp2.sas
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Table 27 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B11 FL RP2D Cohort, by Cycle

Seriousness, Outcomes, Severity - B11 Exp FL Cohort, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=90)	C1D8-14 (N=89)	C1D15+ (N=88)	C2 (N=87)	C3+ (N=83)
Number of patients with at least one AE	0	1 (1.1%)	1 (1.1%)	1 (1.1%)	0
95% CI for % of patients with at least one AE	(0.00%, 4.02%)	(0.03%, 6.10%)	(0.03%, 6.17%)	(0.03%, 6.24%)	(0.00%, 4.35%)
Total number of AEs	0	1	1	1	0
Total number of AEs related to mosun	0	1	1	1	0
Number of patients with at least one AE by worst grade					
Grade 1	0	0	0	0	0
Grade 2	0	0	0	1 (1.1%)	0
Grade 3	0	1 (1.1%)	1 (1.1%)	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one serious AE	0	1 (1.1%)	1 (1.1%)	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	0	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	0	1 (100%)	1 (100%)	1 (100%)	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0
Mosun related AE leading to withdrawal from treatment	0	0	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 24.0.
Data Cutoff Date - 27AUG2021

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary2_BLA_Aug2021/prod/program/t_ae_out_rmp1.sas
Output: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary2_BLA_Aug2021/prod/output/t_ae_out_rmp1_INIT_TFE_SE_27AUG2021_29781.out
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Table 27 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B11 FL RP2D Cohort, by Cycle (cont.)

Seriousness, Outcomes, Severity - B11 Exp FL Cohort, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=90)	C1D8-14 (N=89)	C1D15+ (N=88)	C2 (N=87)	C3+ (N=83)
Mosun related AE leading to dose interruption	0	0	0	0	0
Mosun related AE leading to dose modification	0	0	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 24.0.
Data Cutoff Date - 27AUG2021

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary2_BLA_Aug2021/prod/program/t_ae_out_rmp1.sas
Output: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary2_BLA_Aug2021/prod/output/t_ae_out_rmp1_INIT_TFE_SE_27AUG2021_29781.out

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Table 28 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B, B11 RP2D and B11 FL RP2D Cohort Overview

Seriousness, Outcomes, Severity - B11 Exp FL Cohort, B11 Exp, Group B, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	B11 Exp FL Cohort (N=90)	B11 Exp (N=218)	Group B (N=414)
Number of patients with at least one AE	3 (3.3%)	9 (4.1%)	18 (4.3%)
95% CI for % of patients with at least one AE	(0.69%, 9.43%)	(1.90%, 7.69%)	(2.60%, 6.78%)
Total number of AEs	3	9	19
Total number of AEs related to mosun	3	6	16
Number of patients with at least one AE by worst grade			
Grade 1	0	0	2 (0.5%)
Grade 2	1 (1.1%)	4 (1.8%)	9 (2.2%)
Grade 3	2 (2.2%)	5 (2.3%)	7 (1.7%)
Grade 4	0	0	0
Grade 5	0	0	0
Number of patients with at least one serious AE	2 (2.2%)	4 (1.8%)	5 (1.2%)
Number of patients with at least one AE by outcome			
Fatal outcome	0	0	0
Unresolved	0	1 (11.1%)	4 (22.2%)
Recovering/Resolving	0	0	0
Recovered/Resolved	3 (100%)	8 (88.9%)	14 (77.8%)
Resolved with sequelae	0	0	0
Unknown outcome	0	0	0

Only treatment emergent AEs are displayed.
Tumor Flare includes events with preferred term of Tumor Flare, AESI criteria selected for Tumor Flare, or reported as suspected tumor flare.
Investigator text for AEs encoded using MedDRA version 24.0.
Data Cutoff Date - 27AUG2021

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary2_BLA_Aug2021/prod/program/t_ae_out_rmp4.sas
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Table 28 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B, B11 RP2D and B11 FL RP2D Cohort Overview (cont.)

Seriousness, Outcomes, Severity - B11 Exp FL Cohort, B11 Exp, Group B, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	B11 Exp FL Cohort (N=90)	B11 Exp (N=218)	Group B (N=414)
Mosun related AE leading to withdrawal from treatment	0	0	0
Mosun related AE leading to dose interruption	0	0	1 (0.2%)
Mosun related AE leading to dose modification	0	0	1 (0.2%)

Only treatment emergent AEs are displayed.
Tumor Flare includes events with preferred term of Tumor Flare, AESI criteria selected for Tumor Flare, or reported as suspected tumor flare.
Investigator text for AEs encoded using MedDRA version 24.0.
Data Cutoff Date - 27AUG2021

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary2_BLA_Aug2021/prod/program/t_ae_out_rmp4.sas
Output: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary2_BLA_Aug2021/prod/output/t_ae_out_rmp4_INIT_TFE_SE_27AUG2021_29781.out
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Table 29 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F Cohort, by Cycle

Seriousness, Outcomes, Severity - Group F, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=181)	C1D8-14 (N=178)	C1D15+ (N=176)	C2 (N=170)	C3+ (N=146)
Number of patients with at least one AE	1 (0.6%)	1 (0.6%)	1 (0.6%)	1 (0.6%)	1 (0.7%)
95% CI for % of patients with at least one AE	(0.01%, 3.04%)	(0.01%, 3.09%)	(0.01%, 3.12%)	(0.01%, 3.23%)	(0.02%, 3.76%)
Total number of AEs	1	1	1	1	1
Total number of AEs related to mosun	1	1	1	0	0
Number of patients with at least one AE by worst grade					
Grade 1	0	0	0	0	1 (0.7%)
Grade 2	1 (0.6%)	1 (0.6%)	0	0	0
Grade 3	0	0	1 (0.6%)	1 (0.6%)	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one serious AE	1 (0.6%)	0	1 (0.6%)	1 (0.6%)	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	0	0	0	1 (100%)
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	1 (100%)	1 (100%)	1 (100%)	1 (100%)	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0
Mosun related AE leading to withdrawal from treatment	0	0	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ae_out_rmp1.sas
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t_ae_out_rmp1_INIT_TFE_SE_01FEB2024_29781.out
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Table 29 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F Cohort, by Cycle (cont.)

Seriousness, Outcomes, Severity - Group F, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=181)	C1D8-14 (N=178)	C1D15+ (N=176)	C2 (N=170)	C3+ (N=146)
Mosun related AE leading to dose interruption	1 (0.6%)	0	0	0	0
Mosun related AE leading to dose modification	0	0	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ae_out_rmp1.sas
Output: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/output/
t_ae_out_rmp1_INIT_TFE_SE_01FEB2024_29781.out
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Table 30 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F2 RP2D Cohort, by Cycle

Seriousness, Outcomes, Severity - Group F2 RP2D, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=139)	C1D8-14 (N=137)	C1D15+ (N=137)	C2 (N=132)	C3+ (N=116)
Number of patients with at least one AE	1 (0.7%)	0	0	0	1 (0.9%)
95% CI for % of patients with at least one AE	(0.02%, 3.94%)	(0.00%, 2.66%)	(0.00%, 2.66%)	(0.00%, 2.76%)	(0.02%, 4.71%)
Total number of AEs	1	0	0	0	1
Total number of AEs related to mosun	1	0	0	0	0
Number of patients with at least one AE by worst grade					
Grade 1	0	0	0	0	1 (0.9%)
Grade 2	1 (0.7%)	0	0	0	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one serious AE	1 (0.7%)	0	0	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	0	0	0	1 (100%)
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	1 (100%)	0	0	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0
Mosun related AE leading to withdrawal from treatment	0	0	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ae_out_rmp2.sas
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t_ae_out_rmp2_INIT_TFE_SE_01FEB2024_29781.out
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Table 30 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F2 RP2D Cohort, by Cycle (cont.)

Seriousness, Outcomes, Severity - Group F2 RP2D, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=139)	C1D8-14 (N=137)	C1D15+ (N=137)	C2 (N=132)	C3+ (N=116)
Mosun related AE leading to dose interruption	1 (0.7%)	0	0	0	0
Mosun related AE leading to dose modification	0	0	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ae_out_rmp2.sas
Output: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/output/
t_ae_out_rmp2_INIT_TFE_SE_01FEB2024_29781.out
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Table 31 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F2 FL RP2D Cohort, by Cycle

Seriousness, Outcomes, Severity - Group F2 RP2D FL Exp, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=94)	C1D8-14 (N=94)	C1D15+ (N=94)	C2 (N=91)	C3+ (N=88)
Number of patients with at least one AE	0	0	0	0	1 (1.1%)
95% CI for % of patients with at least one AE	(0.00%, 3.85%)	(0.00%, 3.85%)	(0.00%, 3.85%)	(0.00%, 3.97%)	(0.03%, 6.17%)
Total number of AEs	0	0	0	0	1
Total number of AEs related to mosun	0	0	0	0	0
Number of patients with at least one AE by worst grade					
Grade 1	0	0	0	0	1 (1.1%)
Grade 2	0	0	0	0	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one serious AE	0	0	0	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	0	0	0	1 (100%)
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	0	0	0	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0
Mosun related AE leading to withdrawal from treatment	0	0	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ae_out_rmp3.sas
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Table 31 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F2 FL RP2D Cohort, by Cycle (cont.)

Seriousness, Outcomes, Severity - Group F2 RP2D FL Exp, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	C1D1-7 (N=94)	C1D8-14 (N=94)	C1D15+ (N=94)	C2 (N=91)	C3+ (N=88)
Mosun related AE leading to dose interruption	0	0	0	0	0
Mosun related AE leading to dose modification	0	0	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ae_out_rmp3.sas
Output: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/output/t_ae_out_rmp3_INIT_TFE_SE_01FEB2024_29781.out
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Table 32 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F, F2 RP2D, and F2 FL RP2D Cohort Overview

Seriousness, Outcomes, Severity - Group F, F2 RP2D, F2 RP2D FL Exp, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	Group F (N=181)	F2 RP2D (N=139)	F2 RP2D FL Exp (N=94)
Number of patients with at least one AE	5 (2.8%)	2 (1.4%)	1 (1.1%)
95% CI for % of patients with at least one AE	(0.90%, 6.33%)	(0.17%, 5.10%)	(0.03%, 5.79%)
Total number of AEs	5	2	1
Total number of AEs related to mosun	3	1	0
Number of patients with at least one AE by worst grade			
Grade 1	1 (0.6%)	1 (0.7%)	1 (1.1%)
Grade 2	2 (1.1%)	1 (0.7%)	0
Grade 3	2 (1.1%)	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Number of patients with at least one serious AE	3 (1.7%)	1 (0.7%)	0
Number of patients with at least one AE by outcome			
Fatal outcome	0	0	0
Unresolved	1 (20.0%)	1 (50.0%)	1 (100%)
Recovering/Resolving	0	0	0
Recovered/Resolved	4 (80.0%)	1 (50.0%)	0
Resolved with sequelae	0	0	0
Unknown outcome	0	0	0
Mosun related AE leading to withdrawal from treatment	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ae_out_rmp4.sas
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Table 32 Important Identified Risk of Tumor Flare: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F, F2 RP2D, and F2 FL RP2D Cohort Overview (cont.)

Seriousness, Outcomes, Severity - Group F, F2 RP2D, F2 RP2D FL Exp, Initial Treatment with Mosunetuzumab, Tumor Flare Events, Safety-Evaluable Patients
Protocol: GO29781

	Group F (N=181)	F2 RP2D (N=139)	F2 RP2D FL Exp (N=94)
Mosun related AE leading to dose interruption	1 (0.6%)	1 (0.7%)	0
Mosun related AE leading to dose modification	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/program/t_ae_out_rmp4.sas
Output: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/output/t_ae_out_rmp4_INIT_TFE_SE_01FEB2024_29781.out
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ICANS

MedDRA terms: MedDRA Adverse Event Group Term (AEGT) CD3 Bispecifics ICANS + adjudication using the ICANS Medical Review Adjudication Framework v.1.7

Potential mechanisms:

ICANS pathophysiology is unclear and currently includes cytokine-mediated endothelial activation and compromise of the blood-brain barrier leading to extravasation of inflammatory cytokines into cerebrospinal fluid and brain parenchyma. Thus, ICANS is biologically plausible with mosunetuzumab considering its mechanism of action involving T-cell activation and cytokine release and the cytokine-mediated pathophysiology of ICANS.

Evidence source(s) and strength of evidence:

- The biological plausibility of ICANS with mosunetuzumab is supported by its mechanism of action, which involves T-cell activation and cytokine release, and aligns with the cytokine-mediated pathophysiology of ICANS.
- Preclinical findings: Secondary to cytokine release CNS vascular/perivascular inflammatory infiltration and convulsion with more extensive CNS infiltration under mosunetuzumab dosing that suggest a potential for neurotoxicity.
- Clinical trials: Suspected ICANS cases (including cases with PT ICANS), particularly in the presence of short first dose latency, concurrence with CRS, with response to systemic steroids and absence of alternative explanations.
- Class effect: ICANS is labelled (in the EU SmPC and the USPI) for all SIC CD3 bispecific antibodies (epcoritamab, teclistamab, talquetamab, and elrantamab, blinatumomab, including now glofitamab [COLUMVI]), and classified as an Important Identified risk in their RMPs, as well as for CAR-T therapies.

Characterization of the risk:

Suspected ICANS were identified cumulatively in the clinical database and global safety database using MedDRA AEGT CD3 bispecifics ICANS followed by adjudication using the ICANS Medical Review Adjudication Framework v1.7.

As of 7 May 2024, a cumulative total of 29 Suspected ICANS cases were identified (this includes 8 cases with PT ICANS), 28 of them originated from the clinical trials and 1 case from the Compassionate Use Program (DSR 1131379). In most cases from the clinical trial source, suspected ICANS were of Grade 1–2 (22 of 28 cases), high Grade suspected ICANS occurred in 6 patients (Grade 3 [4 cases] and Grade 4 [2 cases]; there were no Grade 5 events).

The most frequently reported manifestations (by PT) were Confusional state in 10 cases, ICANS in 8 cases, and Lethargy in 5 cases; PTs Encephalopathy, Depressed level of consciousness, and Memory impairment were reported in 2 cases each and PTs

Delirium, Cognitive disorder, Disturbance in attention, Amnesia, Agitation, Dysarthria, and Dysphonia were reported in one case each.

Suspected ICANS occurred with a median of 17 days (range: 1–147) after initiation of mosunetuzumab treatment and with a median of 4 days (range: 0–4) after the most recent mosunetuzumab dose. In 10 of the 28 cases, suspected ICANS was reported in concurrence with CRS; in 4 of these 10 cases, the event was of a high grade (Grade 3 and Grade 4). In most cases suspected ICANS resolved at the time of the last report (25 of 28 cases) and median event duration was 3 days (range: 1–48). In the majority of cases (24 of 28), the patients were able to resume mosunetuzumab treatment after suspected ICANS resolution. The 1 suspected ICANS case from the Compassionate Use Program had similar ICANS characteristics, as described above.

Group B

In the overall safety population for mosunetuzumab IV from Study GO29781 Group B, upon adjudication, 11 of 414 patients (2.7%) experienced a total of 14 events of suspected ICANS. Manifestations (by PT) were Confusional state in 7 patients, Disturbance in attention in 2 patients and Cognitive disorder, Delirium and ICANS in 1 patient each (see Annex 7A.15).

The reported events were of Grade 1 (9 patients [2.2%]) and Grade 2 (2 patients [0.5%]). Out of these 14 events, 13 events were assessed as related to mosunetuzumab IV by the investigator. All the events had resolved. None of the suspected ICANS events had led to mosunetuzumab IV treatment withdrawal or dose modification, or dose interruption (Table 33).

Group B11 RP2D

In the Group B11 RP2D cohort (primary safety population for mosunetuzumab IV), upon adjudication, 9 of 218 patients (4.1%) experienced a total of 11 events of suspected ICANS. Manifestations (by PT) were Confusional state in 6 patients and Disturbance in attention, Cognitive disorder, Delirium and ICANS in 1 patient each (see Annex 7A.15).

The reported events were of Grade 1 (7 patients [3.2%]) and Grade 2 (2 patients [0.9%]). Out of these 11 events, 10 events were assessed as related to mosunetuzumab IV by the investigator. All the events had resolved. None of the suspected ICANS events had led to mosunetuzumab IV treatment withdrawal or dose modification or dose interruption (Table 33).

Group B11 FL RP2D

In the Group B11 FL RP2D cohort, upon adjudication, 3 of 90 patients (3.3%) experienced a total of 4 events of suspected ICANS. Manifestations (by PT) were Confusional state in 3 patients and Cognitive disorder in 1 patient (see Annex 7A.15).

The reported events were of Grade 1 (2 patients [2.2%]) and Grade 2 (1 patient [1.1%]). All the 4 events were assessed as related to mosunetuzumab IV by the investigator. All the events had resolved. None of the suspected ICANS events had led to mosunetuzumab IV treatment withdrawal or dose modification or dose interruption (Table 33).

Group F

In the overall safety population for mosunetuzumab SC from Study GO29781, Group F, upon adjudication, 5 of 181 patients (2.8%) experienced a total of 5 events of suspected ICANS. Manifestations (by PT) were Lethargy in 2 patients, and Confusional state, Memory impairment, and ICANS in 1 patient each (see Annex 7A.16).

All of the suspected ICANS events were of Grade 1 in severity (5 patients [2.8%]). Out of these 5 events, 4 events were assessed as related to mosunetuzumab SC by the investigator. All the events had resolved. None of the suspected ICANS events that were assessed as related to mosunetuzumab SC by the investigator had led to mosunetuzumab SC treatment withdrawal, or dose modification, or dose interruption (Table 34).

Group F2 RP2D and Group F2 FL RP2D

In the Group F2 RP2D cohort (primary safety population for mosunetuzumab SC), upon adjudication, 3 of 139 patients (2.2%) experienced a total of 3 events of suspected ICANS. Manifestations (by PT) were Lethargy in 2 patients and Memory impairment in 1 patient (see Annex 7A.16).

All of the suspected ICANS events were of Grade 1 in severity (3 patients [2.2%]). Out of these 3 events, 2 events were assessed as related to mosunetuzumab SC by the investigator. All the events had resolved. None of the suspected ICANS events that were assessed as related to mosunetuzumab SC by the investigator had led to mosunetuzumab SC treatment withdrawal, or dose modification, or dose interruption (Table 34).

The 3 patients in Group F2 RP2D who experienced adjudicated suspected ICANS events were also part of the Group F2 FL RP2D cohort (Table 34).

Risk factors and risk groups:

No specific risk factors for ICANS induced by mosunetuzumab and bispecific antibodies in general are identified through literature and the mosunetuzumab clinical data review.

The reported risk factors for ICANS after CAR-T cell infusion include older age, high tumor burden, high CAR T-cell dose, high intensity lymphodepleting therapy, early/severe CRS, presence of cytopenias, high ferritin, cytokine and CRP levels and

pre-existing neurological/medical conditions (Sievers et al. 2020; Salvaris et al. 2021; Grant et al. 2022; Sterner and Sterner 2022); however, whether these risk factors are also applicable to bispecific antibodies is unknown. Additionally, Endothelial Activation and Stress Index score (EASIX > 2.1) was shown predictive of ICANS in patients with large B-cell lymphoma (Grant et al. 2022).

Preventability:

Patients should be monitored for signs and symptoms of ICANS. Patients should be counseled to seek immediate medical attention should signs or symptoms of ICANS occur at any time.

At the first sign of ICANS, based on the type and severity of neurologic toxicity, supportive therapy, corticosteroids and anti-seizure medication should be instituted as indicated; neurology evaluation, and mosunetuzumab withholding should be considered. Other causes of neurologic symptoms should be ruled out.

Sections 4.2 of the EU SmPC provide ICANS management recommendations. Section 4.4 of the EU SmPC provide special warnings and precautions for use regarding ICANS. Recommendation to exercise caution while driving and using machines is included in the EU SmPC Sections 4.2 and 4.7.

Patient Card is proposed as an additional risk-minimization measure (see V.2. [Table 42]).

Impact on the benefit-risk balance of the product:

Given severe and life-threatening suspected ICANS cases observed with mosunetuzumab, though with “very rare” frequency, as well as literature evidence on SIC CD3 bispecific antibodies suggesting ICANS can be severe, including fatal cases, there is an impact on the benefit-risk, however the overall benefit-risk remains positive.

Public health impact:

Given “very rare” frequency of severe and life-threatening suspected ICANS cases observed with mosunetuzumab from the clinical and global safety databases and appropriate ICANS management guidance included in the label coupled with evidence of ICANS responsiveness to dexamethasone/systemic corticosteroids, the impact of ICANS associated with mosunetuzumab on public health is considered to be low.

Table 33 Important Identified Risk of ICANS: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B, B11 RP2D and B11 FL RP2D Cohort Overview

Seriousness, Outcomes, Severity - B11 Exp FL Cohort, B11 Exp, Group B, Adjudicated ICANS, Initial Treatment with Mosunetuzumab, Safety-Evaluable Patients
Protocol: GO29781

	B11 Exp FL Cohort (N=90)	B11 Exp (N=218)	Group B (N=414)
Number of patients with at least one AE	3 (3.3%)	9 (4.1%)	11 (2.7%)
95% CI for % of patients with at least one AE	(0.69%, 9.43%)	(1.90%, 7.69%)	(1.33%, 4.70%)
Total number of AEs	4	11	14
Total number of AEs related to mosun	4	10	13
Number of patients with at least one AE by worst grade			
Grade 1	2 (2.2%)	7 (3.2%)	9 (2.2%)
Grade 2	1 (1.1%)	2 (0.9%)	2 (0.5%)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Number of patients with at least one serious AE	1 (1.1%)	2 (0.9%)	2 (0.5%)
Number of patients with at least one AE by outcome			
Fatal outcome	0	0	0
Unresolved	0	0	0
Recovering/Resolving	0	0	0
Recovered/Resolved	3 (100%)	9 (100%)	11 (100%)
Resolved with sequelae	0	0	0
Unknown outcome	0	0	0
Mosun related AE leading to withdrawal from treatment	0	0	0

Investigator text for AEs encoded using MedDRA version MedDRA v27.0.
Data Cutoff Date - 27AUG2021

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Table 33 Important Identified Risk of ICANS: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B, B11 RP2D and B11 FL RP2D Cohort Overview (cont.)

Seriousness, Outcomes, Severity - B11 Exp FL Cohort, B11 Exp, Group B, Adjudicated ICANS, Initial Treatment with Mosunetuzumab, Safety-Evaluable Patients
Protocol: GO29781

	B11 Exp FL Cohort (N=90)	B11 Exp (N=218)	Group B (N=414)
Mosun related AE leading to dose interruption	0	0	0
Mosun related AE leading to dose modification	0	0	0

Investigator text for AEs encoded using MedDRA version MedDRA v27.0.
Data Cutoff Date - 27AUG2021

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Table 34 Important Identified Risk of ICANS: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F, F2 RP2D, and F2 FL RP2D Cohort Overview

Seriousness, Outcomes, Severity - Group F, F2 RP2D, F2 RP2D FL Exp, Adjudicated ICANS, Initial Treatment with Mosunetuzumab, Safety-Evaluable Patients
Protocol: GO29781

	Group F (N=181)	F2 RP2D (N=139)	F2 RP2D FL Exp (N=94)
Number of patients with at least one AE	5 (2.8%)	3 (2.2%)	3 (3.2%)
95% CI for % of patients with at least one AE	(0.90%, 6.33%)	(0.45%, 6.18%)	(0.66%, 9.04%)
Total number of AEs	5	3	3
Total number of AEs related to mosun	4	2	2
Number of patients with at least one AE by worst grade			
Grade 1	5 (2.8%)	3 (2.2%)	3 (3.2%)
Grade 2	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Number of patients with at least one serious AE	0	0	0
Number of patients with at least one AE by outcome			
Fatal outcome	0	0	0
Unresolved	0	0	0
Recovering/Resolving	0	0	0
Recovered/Resolved	5 (100%)	3 (100%)	3 (100%)
Resolved with sequelae	0	0	0
Unknown outcome	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

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Table 34 Important Identified Risk of ICANS: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F, F2 RP2D, and F2 FL RP2D Cohort Overview (cont.)

Seriousness, Outcomes, Severity - Group F, F2 RP2D, F2 RP2D FL Exp, Adjudicated ICANS, Initial Treatment with Mosunetuzumab, Safety-Evaluable Patients
Protocol: GO29781

	Group F (N=181)	F2 RP2D (N=139)	F2 RP2D FL Exp (N=94)
Mosun related AE leading to withdrawal from treatment	0	0	0
Mosun related AE leading to dose interruption	0	0	0
Mosun related AE leading to dose modification	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

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Output: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimarySC_Feb2024_adhoc/prod/output/t_ae_out_adjicans_rmp4_INIT_SE_01FEB2024_29781.out
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Serious Infections

MedDRA terms: Infections and Infestations (SOC)

Potential mechanisms:

The mechanism of action of mosunetuzumab results in B-cell depletion which is associated with an increased risk of infections. Infections have been reported in patients receiving other CD20 directed therapies. Serious, life-threatening and fatal infections occurred in patients receiving mosunetuzumab and contributory factors may include mosunetuzumab-induced B-cell depletion as well as the patient's immunocompromised status due to the underlying disease, and prior immunosuppressive treatment that may predispose to infections.

Evidence source(s) and strength of evidence:

Nonclinical chronic toxicity study showed infections that were deemed secondary to immunosuppression due to mosunetuzumab-induced prolonged B-cell depletion (See SII) and evidence is also based on Study GO29781 (See SIII).

Characterization of the risk:

Group B

In the overall safety population for mosunetuzumab IV from Study GO29781, Group B, 81 serious infections were reported in 64 of 414 patients (15.5%), with pneumonia (11 patients [2.7%]) being the most frequent. Other serious infections reported in more than one patient were sepsis and urinary tract infection (6 patients [1.4%] each), Pneumocystis jirovecii pneumonia (5 patients [1.2%]), upper respiratory tract infection and bacteremia (4 patients [1.0%] each), lower respiratory tract infection (3 patients [0.7%]), and COVID-19, Epstein-Barr viremia, septic shock, Herpes zoster, Staphylococcal bacteremia, influenza, Metapneumovirus infection, and Parainfluenzae virus infection (2 patients [0.5%] each) (see Annex 7A.17). The majority of serious infections were Grade 3 maximum severity in 44 patients (10.6%). Grade 2 serious infections were reported in 9 patients (2.2%), Grade 4 serious infections in 7 patients (1.7%) and Grade 5 serious infections were reported in 4 patients (1%: Pneumonia and Sepsis in 0.5%, each). Serious infections led to mosunetuzumab IV treatment withdrawal in 3 patients (0.7%) and mosunetuzumab IV dose interruption in 9 patients (2.2%).

Serious infections resolved in the majority of patients (58 patients [90.6%]: recovered/resolved [53 patients; 82.8%] and resolved with sequelae [5 patients; 7.8%]) (Table 35, Annex 7A.8, Annex 7A.17).

Group B11 RP2D

In Group B11 RP2D cohort (primary safety population for mosunetuzumab IV), 46 serious infections events were reported in 37 of 218 patients (17.0%), with pneumonia (7 patients [3.2%]) being the most frequent. Other serious infections reported in more than one patient were sepsis and urinary tract infection (4 patients [1.8%] each), Pneumocystis jirovecii pneumonia (3 patients [1.4%]), and upper respiratory tract infection, lower respiratory tract infection, COVID-19, Epstein-Barr viremia, septic shock, and Staphylococcal bacteremia (2 patients [0.9%] each) (see Annex 7A.17). The majority of serious infections were Grade 3 maximum severity in 22 patients (10.1%). Grade 2 serious infections were reported in 8 patients (3.7%), Grade 4 serious infections in 5 patients (2.3%) and Grade 5 serious infections in 2 patients (0.9%) [pneumonia and sepsis in 1 patient each]. The Grade 5 sepsis event led to treatment withdrawal in 1 patient (0.5%). Serious infections led to mosunetuzumab IV dose interruption in 5 patients (2.3%).

Serious infections resolved in the majority of patients (33 patients [89.2%]: recovered/resolved [31 patients; 83.8%] and resolved with sequelae [2 patients; 5.4%]) (Table 35, Annex 7A.8, Annex 7A.17).

Group B11 FL RP2D

A total of 18 of 90 patients (20.0%) experienced 21 serious infection events. These events were of Grade 2 (5 patients [5.6%]), Grade 3 (10 patients [11.1%]) and Grade 4 (3 patients [3.3%]) in severity. There was no Grade 5 serious infection event in this patient cohort. None of the serious infection events led to mosunetuzumab IV treatment withdrawal and dose interruption was reported in 1 patient (1.1%).

Serious infections resolved in the majority of patients (16 patients [88.9%]: recovered/resolved [15 patients; 83.3%] and resolved with sequelae [1 patient; 5.6%]) (Table 35, Annex 7A.17).

Group F

In the overall safety population for mosunetuzumab SC from Study GO29781, Group F, 32 serious infections were reported in 28 of 181 patients (15.5%), with COVID-19 pneumonia (8 patients [4.4%]) and COVID-19 (6 patients [3.3%]) being the most frequent. Other serious infections reported in more than one patient were pneumonia (5 patients [2.8%] each), sepsis, cytomegalovirus infection reactivation, and device related infection (2 patients [1.1%] each) (see Annex 7A.18). The majority of serious infections were Grade 3 maximum severity in 13 patients (7.2%). Grade 2 serious infections were reported in 2 patients (1.1%), Grade 4 serious infections were reported in 4 patients (2.2%), and Grade 5 serious infections were reported in 9 patients (5.0%: COVID-19 pneumonia and COVID-19 in 4 patients [2.2%] each, and septic shock in 1 patient [0.6%]). Serious infections that were assessed as related to mosunetuzumab

SC by the investigator led to mosunetuzumab SC treatment withdrawal in 2 patients (1.1%) and mosunetuzumab SC dose interruption in 5 patients (2.8%).

Serious infections resolved in the majority of patients (18 patients [64.3%]) (Table 36, Annex 7A.18, Annex 7A.19).

Group F2 RP2D

In Group F2 RP2D cohort (primary safety population for mosunetuzumab SC), 26 serious infections events were reported in 23 of 139 patients (16.5%), with COVID-19 pneumonia (8 patients [5.8%]) being the most frequent. Other serious infections reported in more than one patient were COVID-19 (4 patients [2.9%]), pneumonia, sepsis, cytomegalovirus infection reactivation, and device related infection (2 patients [1.4%] each) (see Annex 7A.18). The majority of serious infections were Grade 3 maximum severity in 10 patients (7.2%). Grade 2 serious infections were reported in 2 patients (1.4%), Grade 4 serious infections were reported in 4 patients (2.9%), and Grade 5 serious infections were reported in 7 patients (5.0%: COVID-19 pneumonia in 4 patients [2.9%], COVID-19 in 2 patients [1.4%], and septic shock in 1 patients [0.7%]). Serious infections that were assessed as related to mosunetuzumab SC by the investigator led to mosunetuzumab SC treatment withdrawal in 2 patients (1.4%) and mosunetuzumab SC dose interruption in 4 patients (2.9%).

Serious infections resolved in the majority of patients (15 patients [65.2%]) (Table 36, Annex 7A.18, Annex 7A.19).

Group F2 FL RP2D

A total of 16 of 94 patients (17.0%) experienced 17 serious infection events. The majority of serious infections were Grade 3 maximum severity in 7 patients (7.4%). Grade 2 serious infections were reported in 2 patients (2.1%), Grade 4 serious infections were reported in 4 patients (4.3%), and Grade 5 serious infections were reported in 3 patients (3.2%: COVID-19 pneumonia in 2 patients [2.1%] and COVID-19 in 1 patient [1.1%]) (see Annex 7A.18). Serious infections that were assessed as related to mosunetuzumab SC by the investigator led to mosunetuzumab SC treatment withdrawal in 1 patient (1.1%) and mosunetuzumab SC dose interruption in 4 patients (4.3%).

Serious infections resolved in the majority of patients (12 patients [75.0%]) (Table 36, Annex 7A.18).

Risk factors and risk groups:

Serious infections is a recognized risk associated with B-cell depletion treatment effect and a major cause of morbidity and mortality in patients with hematological malignancies. Underlying medical conditions in the patient population including history

of recurring or chronic infections (e.g., chronic, active EBV) and prior immunosuppressive treatment are risk factors that may predispose to infections.

Preventability:

Guidance is provided in the SmPC that mosunetuzumab should not be administered in the presence of active infections. Caution should be exercised when considering the use of mosunetuzumab in patients with a history of recurring or chronic infections (e.g., chronic, active EBV), with underlying conditions that may predispose to infections or who have had significant prior immunosuppressive treatment. Anti-infective prophylaxis should be considered, as appropriate. Patients should be monitored for signs and symptoms of infection before and after mosunetuzumab administration and treated appropriately.

Descriptions of serious infections events observed in the clinical trial experience are also described in the Undesirable effects section of the SmPC.

Sections 4.4 and 4.8 of the SmPC provide comprehensive monitoring and management advice to improve outcomes of serious infections in patients.

Impact on the benefit-risk balance of the product:

Serious infections are anticipated with mosunetuzumab administration due to its mode of action resulting in B-cell depletion. However, the risk is well recognized by healthcare professionals for the patient population in view of underlying conditions and/or prior immunosuppressive treatment that may predispose to infections. The management of serious infections in the patient population does not differ from routine oncology practice and the standard of care.

No additional risk minimization measures are deemed necessary, the impact on the benefit-risk balance is considered low since the majority of serious infection events were of Grade ≤ 3 in intensity and resolved with appropriate management. The risk will continue to be monitored via routine pharmacovigilance activities.

Public health impact:

Given that the appropriate guidance associated with mosunetuzumab treatment are included in product label and the fact that the majority of serious infections responded well to treatment, the impact of serious infections on public health is considered to be low.

Table 35 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B, B11 RP2D, and B11 FL RP2D Cohort Overview

Seriousness, Outcomes, Severity - B11 Exp FL Cohort, B11 Exp, Group B, Initial Treatment with Mosunetuzumab, Serious Infection Events, Safety-Evaluable Patients
Protocol: GO29781

	B11 Exp FL Cohort (N=90)	B11 Exp (N=218)	Group B (N=414)
Number of patients with at least one AE	18 (20.0%)	37 (17.0%)	64 (15.5%)
95% CI for % of patients with at least one AE	(12.31%, 29.75%)	(12.24%, 22.63%)	(12.11%, 19.31%)
Total number of AEs	21	46	81
Total number of AEs related to mosun	6	14	22
Number of patients with at least one AE by worst grade			
Grade 1	0	0	0
Grade 2	5 (5.6%)	8 (3.7%)	9 (2.2%)
Grade 3	10 (11.1%)	22 (10.1%)	44 (10.6%)
Grade 4	3 (3.3%)	5 (2.3%)	7 (1.7%)
Grade 5	0	2 (0.9%)	4 (1.0%)
Number of patients with at least one serious AE	18 (20.0%)	37 (17.0%)	64 (15.5%)
Number of patients with at least one AE by outcome			
Fatal outcome	0	2 (5.4%)	4 (6.3%)
Unresolved	1 (5.6%)	2 (5.4%)	3 (4.7%)
Recovering/Resolving	1 (5.6%)	1 (2.7%)	1 (1.6%)
Recovered/Resolved	15 (83.3%)	31 (83.8%)	53 (82.8%)
Resolved with sequelae	1 (5.6%)	2 (5.4%)	5 (7.8%)
Unknown outcome	0	0	0
Mosun related AE leading to withdrawal from treatment	0	1 (0.5%)	3 (0.7%)

Only treatment emergent AEs are displayed.
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Table 35 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group B, B11 RP2D and B11 FL RP2D Cohort Overview (cont.)

Seriousness, Outcomes, Severity - B11 Exp FL Cohort, B11 Exp, Group B, Initial Treatment with Mosunetuzumab, Serious Infection Events, Safety-Evaluable Patients
Protocol: GO29781

	B11 Exp FL Cohort (N=90)	B11 Exp (N=218)	Group B (N=414)
Mosun related AE leading to dose interruption	1 (1.1%)	5 (2.3%)	9 (2.2%)
Mosun related AE leading to dose modification	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version "MedDRA v24.0".
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Table 36 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F, F2 RP2D, and F2 FL RP2D Cohort Overview

Seriousness, Outcomes, Severity - Group F, F2 RP2D, F2 RP2D FL Exp, Initial Treatment with Mosunetuzumab, Serious Infection Events, Safety-Evaluable Patients
Protocol: GO29781

	Group F (N=181)	F2 RP2D (N=139)	F2 RP2D FL Exp (N=94)
Number of patients with at least one AE	28 (15.5%)	23 (16.5%)	16 (17.0%)
95% CI for % of patients with at least one AE	(10.53%, 21.58%)	(10.79%, 23.79%)	(10.05%, 26.16%)
Total number of AEs	32	26	17
Total number of AEs related to mosun	10	7	6
Number of patients with at least one AE by worst grade			
Grade 1	0	0	0
Grade 2	2 (1.1%)	2 (1.4%)	2 (2.1%)
Grade 3	13 (7.2%)	10 (7.2%)	7 (7.4%)
Grade 4	4 (2.2%)	4 (2.9%)	4 (4.3%)
Grade 5	9 (5.0%)	7 (5.0%)	3 (3.2%)
Number of patients with at least one serious AE	28 (15.5%)	23 (16.5%)	16 (17.0%)
Number of patients with at least one AE by outcome			
Fatal outcome	9 (32.1%)	7 (30.4%)	3 (18.8%)
Unresolved	3 (10.7%)	3 (13.0%)	1 (6.3%)
Recovering/Resolving	0	0	0
Recovered/Resolved	18 (64.3%)	15 (65.2%)	12 (75.0%)
Resolved with sequelae	0	0	0
Unknown outcome	0	0	0
Mosun related AE leading to withdrawal from treatment	2 (1.1%)	2 (1.4%)	1 (1.1%)

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

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Table 36 Important Identified Risk of Serious Infections: Seriousness, Outcomes, Severity and Frequency with 95% CI, Group F, F2 RP2D, and F2 FL RP2D Cohort Overview (cont.)

Seriousness, Outcomes, Severity - Group F, F2 RP2D, F2 RP2D FL Exp, Initial Treatment with Mosunetuzumab, Serious Infection Events, Safety-Evaluable Patients
Protocol: GO29781

	Group F (N=181)	F2 RP2D (N=139)	F2 RP2D FL Exp (N=94)
Mosun related AE leading to dose interruption	5 (2.8%)	4 (2.9%)	4 (4.3%)
Mosun related AE leading to dose modification	0	0	0

Only treatment emergent AEs are displayed.
Investigator text for AEs encoded using MedDRA version 26.1.
Data Cutoff Date - 01FEB2024

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Information on Important Potential Risks

Not applicable

SVII.3.2. Presentation of the Missing Information

Information on Missing Information

Long-term safety

In Group B11 RP2D cohort (primary safety population for mosunetuzumab IV), patients received a median of 8 cycles (range: 1–17 cycles) of mosunetuzumab IV. The median DoT of mosunetuzumab IV was 4.9 months (range 0.03–13.8 months), which corresponds approximately to the median of 8 × Q3W cycles received. At the time of the clinical cut-off date (27 August 2021), the median observation time in the B11 RP2D cohort was 14.3 months (range: 0.1–27.9 months) (Annex 7A.20).

In Group F2 RP2D cohort (primary safety population for mosunetuzumab SC), patients received a median of 8 cycles (range: 1–17 cycles) of mosunetuzumab SC. The median DoT with mosunetuzumab SC was 4.9 months (range: 0.03–17.7 months), which corresponds approximately to the median of 8 × Q3W cycles received. At the time of the clinical cut-off date (1 February 2024), the median observation time in the F2 RP2D cohort was 19.3 months (range: 1–37 months) (Annex 7A.21).

Limited data are available in terms of long-term safety of patients treated with mosunetuzumab. No dedicated studies of long-term safety of mosunetuzumab have been conducted. The long-term safety of patients treated with mosunetuzumab is unknown and therefore is considered missing information.

Evidence Source:

Population in need of further characterization.

The assessment of long-term safety of mosunetuzumab is not fully understood and ongoing analysis of future safety information is needed. Thus, long-term safety data are being collected and monitored from the ongoing GO42909 study with survival follow-up planned for five years after last patient in (LPI). Refer to Part III.2 for further details.

Safety in Patients with Prior CAR-T Therapy

In Group B11 RP2D cohort (primary safety population), there were 30 patients who received prior CAR-T therapy (prior CAR-T group; including 3 patients with R/R FL) and 188 patients who did not receive prior CAR-T therapy (no prior CAR-T group). Patients in the prior CAR-T group appeared to have more aggressive NHL histology, heavier disease burden, worse ECOG PS at baseline, and more prior therapies received (Annex 7A.22 – Annex 7A.25). The frequency of fatal adverse events (AEs), serious AEs, AE of Grade 3-4, AE leading to withdrawal from treatment was numerically higher in the prior CAR-T group compared to the no prior CAR-T group (Annex 7A.25).

In Group F2 RP2D cohort (primary SC safety population), there were 25 patients who received prior CAR-T therapy (prior CAR-T group; including 4 patients with R/R FL) and 114 patients who did not receive prior CAR-T therapy (no prior CAR-T group). Patients in the prior CAR-T group appeared to have more aggressive NHL histology, higher ECOG PS at baseline, and more prior therapies received (Annex 7A.26 – Annex 7A.29). The frequency of fatal AEs, serious AEs, AE of Grade 3–4, and AE leading to withdrawal from treatment was numerically higher in the prior CAR-T group compared to the no prior CAR-T group (Annex 7A.29).

Although the small number of patients in the prior CAR-T group (n=30 in Group B11 RP2D and n = 25 in Group F2 RP2D) and differences in baseline characteristics may explain the observed frequency imbalances, characterization of the safety profile of patients with prior CAR-T therapy is limited and is therefore considered missing information.

Evidence Source:

Population in need of further characterization.

The safety profile in patients with prior CAR-T therapy is limited and ongoing analysis of future safety information in this patient population through routine pharmacovigilance activities is planned.

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 37 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Cytokine release syndrome • Tumor Flare • ICANS • Serious Infections
Important potential risks	None
Missing information	• Long-term safety • Safety in patients with prior CAR-T therapy

CAR-T = chimeric antigen receptor T-cell; ICANS = immune effector cell-associated neurotoxicity syndrome.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

ROUTINE PHARMACOVIGILANCE ACTIVITIES BEYOND ADVERSE REACTIONS REPORTING AND SIGNAL DETECTION

Specific adverse reaction follow-up questionnaires: None

Other forms of routine pharmacovigilance activities:

The Roche standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

Cumulative data will be presented in Periodic Safety Update Reports (PSURs)/PBRERs.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Long-term safety information in patients treated with mosunetuzumab will be collected from the ongoing clinical Study GO42909 (PASS Category 3; Table 38) that will support the characterization of this safety concern listed under missing information.

Table 38 Study GO42909

Study/activity short name and title: Study GO42909: Phase III randomized, open-label, multicenter study evaluating efficacy and safety of mosunetuzumab in combination with lenalidomide in comparison to rituximab in combination with lenalidomide with a non-randomized, single arm, US extension of mosunetuzumab in combination with lenalidomide in patients with follicular lymphoma after at least one line of systemic therapy.
Rationale and Study Objectives: The randomized phase of the study will evaluate the efficacy and safety of M+Len compared with R+Len in patients with R/R FL who were treated with at least one prior systemic therapy. The non-randomized extension arm will further evaluate efficacy and safety of M+Len in U.S. patient populations with FL. Safety objectives for the randomized phase and non-randomized extension arm will be assessed on the basis of the following endpoints: • Incidence and severity of adverse events, with severity determined according to the NCI CTCAE Version 5.0, including CRS, with severity determined according to the ASTCT CRS grading criteria • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results • Tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of adverse events The exploratory safety objective for the randomized phase and non-randomized extension arm will be assessed on the basis of the following endpoints: • Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities as assessed through use of the NCI PRO-CTCAE • Change from baseline in symptomatic treatment toxicities, as assessed through use of the PRO-CTCAE
Study design: An open-label, multicenter, randomized controlled trial in patients with R/R FL after receiving at least 1 line of systemic therapy. Patients with FL will be randomized in a 1:1 ratio to receive either M + Len or R + Len. Non-randomized Extension arm will enroll patients with R/R FL to receive M + Len. Long-Term Follow-Up visit will occur every 3 months (± 14 days) for 5 years from the time of randomization. Survival follow-up will continue for 5 years after LPI.
Study populations: The study enrollment in the randomized phase is completed with 404 patients with FL who were treated with at least one prior systemic therapy across all sites in a global enrollment phase of this study.
Milestones: Study status: Ongoing Launch of study: [redacted] Projected interim analysis CSR: [redacted] Projected primary analysis CSR (based on primary endpoint of PFS) [redacted] Projected final CSR after the survival follow-up period: [redacted]

Table 38 Study GO429099 (cont.)

ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; CSR =clinical study report; FL = follicular lymphoma; LPI =last patient in; M + Len = mosunetuzumab in combination with lenalidomide; NCI = National Cancer Institute; PASS = post-authorization safety study; PFS = progression-free survival; PRO-CTCAE = Patient–Reported Outcome Common Terminology Criteria for Adverse Events; R/R = relapsed/refractory; R + Len = rituximab in combination with lenalidomide, U.S.= United States.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 39 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk-minimization activities				
PASS GO42909: Phase III randomized, open-label, multicenter study evaluating efficacy and safety of mosunetuzumab in combination with lenalidomide in comparison to rituximab in combination with lenalidomide with a non-randomized, single arm, U.S. extension of mosunetuzumab in combination with lenalidomide in patients with follicular lymphoma after at least one line of systemic therapy. *Ongoing*	The randomized phase of the study will evaluate the efficacy and safety of M + Len compared with R + Len in patients with R/R FL who were treated with at least one prior systemic therapy. The non-randomized extension arm will further evaluate efficacy and safety of M + Len in U.S. patient populations with FL. Safety objectives for the randomized phase and non-randomized extension arm will be assessed on the basis of the following endpoints: • Incidence and severity of adverse events, with severity determined according to the NCI CTCAE Version 5.0, including CRS, with severity determined according to the ASTCT CRS grading criteria • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory tests • Tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of adverse events	• Long-term safety	Launch of study: Projected interim analysis CSR: Projected primary analysis CSR (based on primary endpoint of PFS): Projected final CSR after the survival follow-up period:	[redacted] [redacted] [redacted] [redacted]

Table 39 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
	The exploratory safety objective for the randomized phase and non-randomized extension arm will be assessed on the basis of the following endpoints: • Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities as assessed through use of the NCI PRO-CTCAE • Change from baseline in symptomatic treatment toxicities, as assessed through use of the PRO−CTCAE Long-Term Follow-Up visit will occur every 3 months (±14 days) for 5 years from the time of randomization. Survival follow-up will continue for 5 years after LPI.			

ASTCT = American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; CSR= clinical study report; FL = follicular lymphoma; LPI= last patient in; M + Len = mosunetuzumab in combination with lenalidomide; NCI = National Cancer Institute; PASS = post-authorization safety study; PFS= progression-free survival; PRO-CTCAE = Patient-Reported Outcome Common Terminology Criteria for Adverse Events; R/R = relapsed/refractory; R + Len = rituximab in combination with lenalidomide.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

To confirm clinical benefit as a condition of conditional marketing authorization, a randomized Phase III trial of mosunetuzumab plus lenalidomide (M+Len) versus rituximab plus lenalidomide (R+Len) in patients with R/R FL after at least one prior systemic therapy regimen is ongoing (Study GO42909). After completion of the global enrollment to randomized phase, approximately 50 additional subjects with R/R FL will be enrolled into a non-randomized single-arm extension cohort in the United States.

Study GO42909 is preceded by Study CO41942, a Phase Ib/II dose-escalation and expansion study designed to evaluate the safety and tolerability of mosunetuzumab plus lenalidomide in patients with R/R FL after at least one prior systemic therapy before conducting a larger scale trial.

The purpose of the randomized Phase III Study GO42909 is to evaluate the efficacy of M+Len compared with R+Len using PFS (assessed by the Independent Review Committee) as the primary endpoint. The randomized phase of the study completed enrollment with 404 patients with FL. The study population includes adult patients with FL Grade 1-3a, who have relapsed after or have disease refractory to at least one prior line of systemic therapy. The primary endpoint is PFS by IRF, and key secondary endpoints include CR, ORR, OS, safety, and time to deterioration in the physical functioning subscale/patient-reported outcomes. The Sponsor has requested scientific advice for planning and conducting this Phase III study (EMEA/H/SA/4405/1/FU/1/2020/III). The Committee for Medicinal Products for Human Use has been in broad agreement with the proposed study design and endpoints. The first patient of Study GO42909 was enrolled in October 2021, and the projected interim analysis and primary analysis CSRs based on primary endpoint of PFS are expected in [redacted] and [redacted], respectively. A final CSR is expected in [redacted] when the survival follow up period is completed.

Table 40 Planned and Ongoing Post-Authorization Imposed Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorization				
Study GO42909: Phase III randomized, open-label, multicenter study evaluating efficacy and safety of mosunetuzumab in combination with lenalidomide in comparison to rituximab in combination with lenalidomide with a non-randomized, single arm, US extension of mosunetuzumab in combination with lenalidomide in patients with follicular lymphoma after at least one line of systemic therapy. *Ongoing*	The randomized phase of the study will evaluate the efficacy and safety of M+Len compared with R+Len in patients with R/R FL who were treated with at least one prior systemic therapy. Primary efficacy objective: Progression-free survival, defined as the time from randomization to the first occurrence of disease progression as determined by the IRC with use of the 2014 Lugano Response Criteria or death from any cause in the intent-to-treat (ITT) population. Safety objectives: • Incidence and severity of adverse events, with severity determined according to the NCI CTCAE Version 5.0, including CRS, with severity determined according to the ASTCT CRS grading criteria • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results • Tolerability, as assessed by dose interruptions, dose reductions, and dose	• To confirm treatment benefit over standard of care in a randomized, controlled study, where PFS is the primary endpoint. • To study the efficacy and safety of mosunetuzumab in combination setting with lenalidomide.	Launch of Study Projected interim analysis CSR: Projected primary analysis CSR (based on primary endpoint of PFS): Projected final CSR after the survival follow up period:	[redacted] [redacted] [redacted] [redacted]

Table 40 Planned and Ongoing Post-Authorization Imposed Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
	intensity, and study treatment discontinuation because of adverse events			
Efficacy studies that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
N/A				

ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; FL = follicular lymphoma; IRC = independent review committee; M + Len = mosunetuzumab in combination with lenalidomide; NCI = National Cancer Institute; PFS = progression-free survival; R/R = relapsed/refractory; R + Len = rituximab in combination with lenalidomide.

PART V: RISK-MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK-MINIMIZATION ACTIVITIES)

RISK-MINIMIZATION PLAN
V.1 ROUTINE RISK-MINIMIZATION MEASURES

Table 41 Description of Routine Risk-Minimization Measures by Safety Concern

Safety Concern	Routine Risk-Minimization Activities
Cytokine Release Syndrome	**Routine risk communication:** **SmPC:** • Section 4.2 Posology and method of administration • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects **Package Leaflet:** • Section 2 What you need to know before you use Lunsumio® • Section 4 Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** Recommendation for monitoring for the development of CRS is included in SmPC section 4.2. **Other risk-minimization measures beyond the Product Information:** **Pack size:** None **Medicine's legal status:** Mosunetuzumab is a prescription only medicine.

Table 41 Description of Routine Risk-Minimization Measures by Safety Concern (cont.)

Safety Concern	Routine Risk-Minimization Activities
Tumor Flare	**Routine risk communication:** **SmPC:** • Section 4.2 Posology and method of administration • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects **Package Leaflet:** • Section 2 What you need to know before you use Lunsumio • Section 4 Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** Recommendation for monitoring for the development of TF is included in SmPC Section 4.4. **Other risk-minimization measures beyond the Product Information:** **Pack size:** None **Medicine's legal status:** Mosunetuzumab is a prescription only medicine.

Table 41 Description of Routine Risk-Minimization Measures by Safety Concern (cont.)

Safety Concern	Routine Risk-Minimization Activities
ICANS	**Routine risk communication:** **SmPC:** • Section 4.2 Posology and method of administration • Section 4.4 Special warnings and precautions for use • Section 4.7 Effects on ability to drive and use machines • Section 4.8 Undesirable effects **Package Leaflet:** • Section 2 What you need to know before you use Lunsumio® • Section 4 Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • ICANS grading and management recommendations are included in the SmPC Section 4.2. • Recommendation for monitoring for the development of ICANS is included in the SmPC Section 4.2. • Recommendation to exercise caution while driving and using machines is included in the SmPC Sections 4.2. and 4.7. **Other risk minimization measures beyond the Product Information:** **Pack size:** None **Medicine's legal status:** Mosunetuzumab is a prescription only medicine.
Serious Infections	**Routine risk communication:** **SmPC:** • Section 4.2 Posology and method of administration • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects **Package Leaflet:** • Section 2 What you need to know before you use Lunsumio® • Section 4 Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** Recommendation for monitoring for the development of Serious Infections is included in SmPC Section 4.4.

Safety Concern	Routine Risk-Minimization Activities
	Other risk-minimization measures beyond the Product Information: **Pack size:** None **Medicine's legal status:** Mosunetuzumab is a prescription only medicine.
Long-term safety	No risk-minimization measures required.
Safety in patients with prior CAR-T therapy	No risk-minimization measures required.

CAR-T = chimeric antigen receptor T-cells; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; SmPC = summary of product characteristics; TF = tumor flare.

V.2. ADDITIONAL RISK-MINIMIZATION MEASURES

Table 42 Additional Risk-Minimization Measures

Additional risk-minimization measure	**Patient Card**
Objective(s)	The Patient Card will promote awareness of the key signs and symptoms of CRS and ICANS, thereby enhancing early recognition of CRS and ICANS by patients and timely reporting to their physicians, encouraging prompt intervention.
Rationale for the additional risk-minimization activity	Based on the characterization of CRS and ICANS, the Patient Card will enable the patient to receive education on the presentation of CRS and ICANS and key recommendations to be followed during the treatment with mosunetuzumab, with the aim of minimizing the worsening of adverse reactions relevant to the risk of CRS and ICANS. The intent is that the Patient Card will encourage patients to seek immediate medical attention if signs and symptoms of CRS and ICANS present, with the aim of optimizing the time to intervention, appropriate management of the adverse reactions or further worsening of the adverse reactions, and maximizing recovery potential.
Target audience and planned distribution path	The Patient Card is targeted for adult patients with R/R FL who have received at least two prior systemic therapies. The Patient Card will be provided to the physician for distribution to the patient prior to their first dose of mosunetuzumab.
Plans for evaluating the effectiveness of the interventions and criteria for success	**How effectiveness will be measured:** • Metrics of distribution channels of Patient Card to physicians • Periodic medical review of clinical trial and post-marketing cases in terms of reporting rate and severity to determine whether the additional risk minimization measures have led to improved patient outcomes **Milestones for reporting:** • Distribution metrics of distribution channels of Patient Card to physicians, periodically in PBRERs • Monitoring of reporting rate and severity of CRS and ICANS, periodically in PBRERs

CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; PBRER = periodic benefit-risk evaluation report; R/R FL = relapsed/refractory follicular lymphoma.

REMOVAL OF ADDITIONAL RISK-MINIMIZATION ACTIVITIES

Not applicable.

V.3 SUMMARY OF RISK-MINIMIZATION MEASURES

Table 43 Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
Cytokine Release Syndrome	**Routine risk-minimization measures:** **SmPC:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Package Leaflet:** Section 2 What you need to know before you use Lunsumio® Section 4 Possible side effects **Additional risk-minimization measures:** Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting. **Additional pharmacovigilance activities:** None
Tumor Flare	**Routine risk-minimization measures:** **SmPC:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Package Leaflet:** Section 2 What you need to know before you use Lunsumio® Section 4 Possible side effects **Additional risk-minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting. **Additional pharmacovigilance activities:** None

Table 43 Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern (cont.)

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
ICANS	**Routine risk minimization measures:** **SmPC:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.7 Effects on ability to drive and use machines Section 4.8 Undesirable effects **Package Leaflet:** Section 2 What you need to know before you use Lunsumio® Section 4 Possible side effects **Additional risk minimization measures:** Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting. **Additional pharmacovigilance activities:** None
Serious Infections	**Routine risk-minimization measures:** **SmPC:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Package Leaflet:** Section 2 What you need to know before you use Lunsumio® Section 4 Possible side effects **Additional risk-minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting. **Additional pharmacovigilance activities:** None
Long-term safety	**Routine risk minimization measures:** • None **Additional risk-minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting.

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
		Additional pharmacovigilance activities: • PASS Category 3 Study GO42909
Safety in patients with prior CAR-T therapy	**Routine risk minimization measures:** • None **Additional risk-minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** None

CAR-T = chimeric antigen receptor T-cells; PBRER = periodic benefit-risk evaluation report; ICANS = immune effector cell-associated neurotoxicity syndrome; PASS = post-authorization safety study; PSUR = periodic safety update report; SmPC = summary of product characteristics.

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PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

Summary of Risk Management Plan for Lunsumio® (Mosunetuzumab)

This is a summary of the risk-management plan (RMP) for Lunsumio® (mosunetuzumab). The RMP details important risks of Lunsumio, how these risks can be minimized, and how more information will be obtained about Lunsumio's risks and uncertainties (missing information).

Lunsumio's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Lunsumio should be used.

This summary of the RMP for Lunsumio® should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Lunsumio's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Lunsumio as monotherapy is authorized for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies (see SmPC for the full indication). It contains mosunetuzumab as the active substance, and is administered as an intravenous infusion or subcutaneous injection.

Further information about the evaluation of Lunsumio's benefits can be found in Lunsumio's EPAR, including in its plain-language summary, available on the EMA Website, under the medicine's Web Page.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Lunsumio®, together with measures to minimize such risks and the proposed studies for learning more about Lunsumio's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size—The amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly.
- The medicine's legal status—The way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Lunsumio, these measures are supplemented with *additional risk-minimization* measures mentioned under relevant risks below:

- Patient Card

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Lunsumio is not yet available, it is listed under “missing information” below.

II.A List of Important Risks and Missing Information

Important risks of Lunsumio are risks that need special risk-management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lunsumio. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information about the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• Cytokine release syndrome • Tumor flare • ICANS • Serious infections
Important potential risks	• None
Missing information	• Long-term safety • Safety in patients with prior CAR-T therapy

II.B Summary of Important Risks

Important Identified Risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine	Non-clinical studies showing transient T-cell activation and cytokine release and in clinical studies, the majority of CRS events occurred in the first cycle of mosunetuzumab administration (IV or SC) and evidence is also based on Study GO29781.
Risk factors and risk groups	Patient-specific factors which may account for the greater likelihood to have excessive cytokine release are yet to be clearly defined but may include tumor burden, peripheral/circulating target cells, higher levels of macrophages or monocytes or the presence of hyperactive T-cells primed to react.
Risk-minimization measures	**Routine risk-minimization measures:** **SmPC:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Package Leaflet:** Section 2 What you need to know before you use Lunsumio Section 4 Possible side effects **Additional risk-minimization measures:** Patient Card

CRS = cytokine release syndrome; IV=intravenous; SmPC = Summary of product characteristics; SC=subcutaneous.

Important Identified Risk: Tumor flare	
Evidence for linking the risk to the medicine	Evidence is based on Study GO29781.
Risk factors and risk groups	Tumor flare events tend to occur within the first few weeks following mosunetuzumab administration. In addition, depending on tumor size and anatomic location, tumor flare may potentially result in mass effects on vital structures including airways, major blood vessels, gastrointestinal tract (risk of perforation and hemorrhage), and/or major organs.

Important Identified Risk: Tumor flare	
Risk-minimization measures	**Routine risk-minimization measures:** **SmPC:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Package Leaflet:** Section 2 What you need to know before you use Lunsumio Section 4 Possible side effects **Additional risk-minimization measures:** No additional risk-minimization measures

SmPC = Summary of Product Characteristics; TF = tumor flare.

Important Identified Risk: ICANS	
Evidence for linking the risk to the medicine	The biological plausibility, preclinical findings, suspected ICANS cases in clinical trials, and class effect.
Risk factors and risk groups	No specific risk factors for ICANS induced by mosunetuzumab and bispecific antibodies in general are identified through literature and the mosunetuzumab clinical data review.
Risk-minimization measures	**Routine risk-minimization measures:** **SmPC:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.7 Effects on ability to drive and use machines Section 4.8 Undesirable effects **Package Leaflet:** Section 2 What you need to know before you use Lunsumio Section 4 Possible side effects **Additional risk-minimization measures:** Patient Card

ICANS = immune effector cell-associated neurotoxicity syndrome; SmPC = Summary of Product Characteristics.

Important Identified Risk: Serious Infections	
Evidence for linking the risk to the medicine	Nonclinical chronic toxicity study showed infections that were deemed secondary to immunosuppression due to mosunetuzumab-induced prolonged B-cell depletion and evidence is also based on Study GO29781.
Risk factors and risk groups	Serious infections is a recognized risk associated with B–cell depletion treatment effect and a major cause of morbidity and mortality in patients with hematological malignancies. Underlying medical conditions in the patient population including history of recurring or chronic infections (e.g., chronic, active Epstein-Barr Virus) and prior immunosuppressive treatment are risk factors that may predispose to infections.
Risk-minimization measures	**Routine risk-minimization measures:** **SmPC:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Package Leaflet:** Section 2 What you need to know before you use Lunsumio Section 4 Possible side effects **Additional risk-minimization measures:** No additional risk-minimization measures

SmPC = Summary of Product Characteristics.

Missing information: Long-term safety	
Risk-minimization measures	**Routine risk minimization measures:** No routine risk-minimization measures **Additional risk minimization measures:** No additional risk-minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study GO42909 See Section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Safety in patients with prior CAR-T therapy	
Risk-minimization measures	**Routine risk minimization measures:** No routine risk-minimization measures **Additional risk minimization measures:** No additional risk-minimization measures

II.C Post-Authorization Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization.

Study short name: Study GO42909

Purpose of the study: The randomized phase of the study will evaluate the efficacy and safety of M+Len compared with R+Len in patients with R/R FL who were treated with at least one prior systemic therapy.

II.C.2 Other Studies in Post-Authorization Development Plan

There is one other study in the post-authorization development plan for Lunsumio:

Study short name: Study GO42909

Purpose of the study: Phase III randomized, open-label, multicenter study evaluating efficacy and safety of mosunetuzumab in combination with lenalidomide in comparison to rituximab in combination with lenalidomide with a non-randomized, single arm, US extension of mosunetuzumab in combination with lenalidomide in patients with follicular lymphoma after at least one line of systemic therapy. In this case, this study will be used to evaluate the long-term safety and tolerability of mosunetuzumab, which will address the missing information of long-term safety of mosunetuzumab.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Specific Adverse Reactions Follow-Up Forms/Questionnaires

Not applicable

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES

Draft Key Messages of the Additional Risk-Minimization Measures

Prior to the launch of mosunetuzumab in each Member State the Marketing Authorization Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The educational program is aimed at adequately informing patients on the risk of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) with mosunetuzumab, the key signs and symptoms of CRS and ICANS and when to seek urgent attention from their physician or seek emergency help with the objective to minimize the risk and any resultant complications by encouraging prompt intervention.

The MAH shall ensure that in each Member State where mosunetuzumab is marketed, all healthcare professionals who are expected to prescribe mosunetuzumab and patients who are expected to receive mosunetuzumab, respectively have access to/are provided with the following educational package:

- Patient Card

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1. PATIENTS

1.1 PATIENT CARD

Patients will be given a Patient card that they should carry with them at all times with information about the key signs and symptoms of CRS and ICANS, and instructions on when to contact their doctor or seek emergency help if they experience CRS and ICANS-related symptoms.

The Patient Card also includes a warning message for healthcare professionals treating the patient, that the patient is receiving mosunetuzumab.

The key elements of the Patient Card provide:

- A description of the key signs and symptoms of CRS and ICANS
- A description of when to seek urgent attention from the health care provider or seek emergency help, should signs and symptoms of CRS and ICANS present themselves
- The prescribing physician’s contact details

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Approval Task	[redacted] Deputy EU QPPV 20-May-2026 06:52:23 GMT+0000

Approval Task	[redacted] Company Signatory 20-May-2026 17:54:01 GMT+0000

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