22 April 2022
EMA/CHMP/63179/2022
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Lunsumio

International non-proprietary name: mosunetuzumab

Procedure No. EMEA/H/C/005680/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of contents

List of abbreviations

ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ASTCT	American Society for Transplantation and Cellular Therapy
C1D1	Cycle 1 Day 1
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor modified T-cell therapy
CCOD	clinical cutoff date
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CL	Clearance
CLL	chronic lymphocytic leukemia
CO	clinical overview
COVID-19	Coronavirus Disease 2019
CR	complete response
CRR	complete response rate
CRS	cytokine release syndrome
CSR	Clinical Study Report
CT	computed tomography
CVP	cyclophosphamide, vincristine, and prednisone
DCO	data cut-off
DI-CCNAE	driving-impacting cognition or consciousness neurologic adverse event
DIL	Dear Investigator Letter
DLBCL	diffuse large B-cell lymphoma
DOCR	duration of complete response
DOR	duration of response
EBV	Epstein-Barr Virus
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-5L	Euro−Quality-of-Life-5D-5L
E-R	exposure-response
EZH2	enhancer of zeste homolog 2
Fab	fragment antigen-binding
FACT-Lym	Functional Assessment of Cancer Therapy- Lymphoma
Fc	fragment crystallizable
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practice

GELF	Groupe d'Etude des Lymphomes Folliculaires
HCP	healthcare provider
HLH	hemophagocytic lymphohistiocytosis
IgG1	immunoglobulin G1
ILD	interstitial lung disease
IMC	Internal Monitoring Committee
IND	Investigational New Drug
INV	Investigator
IRF	Independent Review Facility
IV	Intravenous
MAA	Marketing Authorization Application
MCL	mantle cell lymphoma
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma
NAE	neurologic adverse events
NALT	new anti-lymphoma treatment
NHL	non-Hodgkin’s lymphoma
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDCO	Pediatric Committee
PET	positron emission tomography
PFS	progression free survival
PI3K	phosphoinositide 3-kinase
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PMBCL	primary mediastinal B-cell lymphoma
POD	progression of disease
popPK	population PK
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	preferred term
q3w	every 3 weeks
R/R	relapsed/refractory
RMP	Risk Management Plan
RP2D	recommended Phase II dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SC	Subcutaneous
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology

SCS	Summary of Clinical Safety
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SLL	small lymphocytic lymphoma
SOC	System Organ Class
SPD	sum of product diameters
TCR	T-cell receptor
TLS	tumor lysis syndrome
trFL	transformed follicular lymphoma
Updated CSR/uCSR	CSR with updated safety data from 15 March 2021 to 27 August 2021 (+24 weeks)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration GmbH submitted on 10 September 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Lunsumio, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. Lunsumio was designated as an orphan medicinal product EU/3/21/2517 on 12.11.2021 in the following condition: follicular lymphoma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Lunsumio as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/en/medicines/human/EPAR/lunsumio.

The applicant applied for the following indication:

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0108/2020 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver applying to the paediatric population from birth to less than 6 months of age.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's requests for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.3. New active Substance status

The applicant requested the active substance mosunetuzumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
30 April 2020	EMEA/H/SA/4405/1/2020/III	Walter Janssens, Paolo Foggi and Olli Tenhunen
15 October 2020	EMEA/H/SA/4405/1/FU/1/2020/III	Adriana Andric and Alexandre Moreau
25 February 2021	EMA/SA/0000049498	Stephan Lehr and Elena Wolff-Holz

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- the data on manufacturing process to support exemption of commercial in-process control or commercial release specification.
- the completed nonclinical studies to support a MAA;
- the need for a nonclinical combination efficacy study to support the use of mosunetuzumab and lenalidomide;
- the proposed dose and dosing schedule as monotherapy and in combination with lenalidomide for investigation in the confirmatory Phase III trial; the clinical pharmacology plan;
- the proposed Phase Ib study CO41942 to confirm the dose and dosing schedule before the start of the phase III study;
- the design of the GO29781 Phase II Expansion cohort to support a CMA, in particular, the study population, the primary and secondary endpoints, the sample size and inclusion of supportive data with longer duration of follow up from a lower-dose interim expansion cohort, the timing of the efficacy analysis;
- the proposed total patient exposure to support registration in the target population;
- options of randomized phase 3 confirmatory trial designs, to confirm the clinical benefit after CMA.
- the Phase III study design, in particular: the choice of PFS in ITT-FL and ITT population (FL and MZL) as dual primary endpoint; the choice of secondary endpoints (investigator assessed PFS, CRR, DOCR, ORR, DOR, OS); the patient population; the regimen of rituximab plus lenalidomide in the control arm and mosunetuzumab plus lenalidomide in the experimental arm; the fixed treatment duration without maintenance therapy in both control and experimental arms;
- the proposed patient-reported endpoints to measure HRQoL (EORTC QLC-C30 and FACTLymS);
- the statistical considerations for the Phase III Study to support full approval, in particular: the sample size of 400 FL patients in the ITT-FL population randomized 1:1; the interim analysis for efficacy at 70% of PFS events; the stratification factors; the statistical analyses for the primary and secondary efficacy endpoints including the hierarchical testing order; the sample

size of 80 MZL patients randomized 1:1; the strategy for testing MZL patients as part of the ITT population, including FL and MZL patients, as one of the dual-primary endpoints, including the hierarchical testing sequence;

- the size of the safety database at the time of the Type II variation as well as the safety monitoring plan and risk mitigation strategy for the Phase III study.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: Karin Janssen van Doorn

The application was received by the EMA on	10 September 2021
Accelerated Assessment procedure was agreed-upon by CHMP on	16 September 2021
The procedure started on	28 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 December 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 January 2022
The CHMP Co-Rapporteur's critique on the CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 January 2022
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 January 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 February 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	11 March 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 March 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	30 March 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	7 April 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lunsumio on	22 April 2022

The CHMP adopted a report on similarity of Lunsumio with Gazyvaro on	22 April 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	22 April 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Indication sought:

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

2.1.2. Epidemiology

FL is the most common indolent non-Hodgkin's lymphoma and the second most common lymphoma diagnosed in the United States and Europe, accounting for approximately 10-20% of all NHL cases (Mounier et al. 2015; Smith et al. 2015; SEER Cancer Statistics 2020). Population-based studies reported the annual age-standardized incidence of FL (new cases per 100,000 population) as 2.1 in France (2012; Le Guyader-Peyrou et al. 2016), 2.8 in the UK (2004-2012; Smith et al. 2015), 2.7 in the US (2014-2018; Surveillance, Epidemiology, and End Results [SEER] Cancer Statistics), 3.8 in Canada (1992-2010; Le et al. 2019), and 3.1 in Australia (1997-2006; van Leeuwen et al. 2014). The estimated total prevalence of FL in the EU27 is likely to lie between 3.2-3.8 per 10,000 population (EMA/OD/0000058552), based on estimates extracted from several EU countries' population-based cancer registries.

2.1.3. Biologic features

As in the majority of other mature B-cell lymphomas, FL is characterized by the expression of a surface membrane antigen, CD20. CD20 is an attractive target for anti-lymphoma therapies, being B-cell-specific, highly and stably expressed, exhibiting a low rate of internalization, and not being present on hematopoietic stem cells. The concept of targeting CD20 as an effective anti-lymphoma strategy has been validated by clinical data for the anti-CD20 monoclonal antibody rituximab, which has revolutionized the treatment of FL. The utility of CD20 as a therapeutic target has led to the continued development of improved anti-CD20 monoclonal antibodies, such as obinutuzumab, which was designed to overcome several postulated mechanisms of resistance to rituximab by binding CD20-antigen in a different orientation and through enhanced fragment crystallizable (Fc)-dependent immune effector mechanisms (Freeman and Sehn 2018). The efficacy of obinutuzumab in patients who have relapsed or are refractory to rituximab-based regimens as demonstrated in the GADOLIN study (Sehn et al 2016, Cheson et al. 2018) is supportive of the continued development of more effective therapies targeting CD20.

The current WHO edition defines FL in accordance to the number of centroblastic cells as Grade 1, Grade 2, Grade 3A and Grade 3B. The distinction between Grade 3A and 3B is important due to their apparent differences in molecular genetics and prognosis; it is suggested that Grade 3A FL is on the

same spectrum as Grade 1-2 FL, and Grade 3B FL (no centrocytes, centroblasts only) behaves as de novo DLBCL (Katzenberger et al., Am J Pathol 2004; Karube et al., Blood 2007).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Follicular lymphoma remains an incurable disease with currently available therapies. Beyond the front-line setting, prognosis is influenced by several factors, including number of prior regimens, refractory status, and progressive decline of bone marrow reserve (Smith 2013). In patients who progress from front-line therapies, the disease-free intervals and DOR become progressively shorter with increased refractoriness with each subsequent progression/relapse (Link et al. 2019; Rivas-Delgado et al. 2019). Nevertheless, for patients receiving a second course of rituximab-containing chemotherapy at the time of first relapse, achieving a CR or receiving autologous hematopoietic stem cell transplantation in the second-line setting has been shown to be associated with improved PFS (time to second disease progression) (Liu et al. 2020).

Patients with R/R FL after ≥2 prior lines of therapy are a particularly poor prognostic group. These patients have usually received anti-CD20 and chemotherapeutic regimens, and PFS and OS shortens with each subsequent relapse and line of therapy, with most deaths due to progressive lymphoma or complications of treatment. For patients who received ≥2 prior therapies, median PFS ranges from 1-1.1 years for third-line patients decreasing to 0.5 years for sixth-line patients with a corresponding median OS of 4.8-8.8 years and 1.9 years, respectively (Alperovich et al. 2016; Rivas-Delgado et al. 2019; Batlevi et al. 2020). A real-world analysis of patients with R/R FL receiving systemic therapy after ≥2 prior therapies (including an anti-CD20 antibody and an alkylator, 94% of whom had exactly 2 prior therapies) across eight academic centers in the United States participating in the LEO Cohort Study (NCT02736357; https://leocohort.org/) showed a median PFS of approximately 1.4 years. Heterogeneity of third-line therapies observed in this real-world analysis reflects the absence of an outstanding standard of care for patients with R/R FL ≥2 prior therapies, with median PFS under 2 years for all third-line therapies, and response rate varying by type of third-line therapy (Casulo et al. 2022).

FL can also undergo histologic transformation to high-grade NHL that is clinically more aggressive and has a poor outcome, at a rate of approximately 2-3% of patients with FL per year (Link et al. 2013).

Taken together, there is an unmet need for patients with R/R FL who have received ≥2 prior therapies, particularly for patients who are R/R to different classes of agents and are left with limited treatment options that may have challenging safety profiles. New treatment options that will significantly extend duration of remission and that can overcome resistance to existing therapies, while providing acceptable safety and tolerability are needed.

2.1.5. Management

For patients with FL who relapse after or are refractory to initial therapy, treatment decisions take into consideration efficacy and DOR of prior therapy, stage of disease and tumor burden at relapse, the presence of symptoms, and the age and comorbidities of the patient. As with patients with newly diagnosed FL, observation (watch-and-wait) is an accepted approach (e.g., in asymptomatic patients with low tumor burden and confirmed follicular histology) and may be of benefit to patients with disease relapse or progression after first-line treatment.

For patients who require second-line therapy, there is no treatment considered standard of care, and options vary widely.

Figure 1 ESMO recommendations in FL

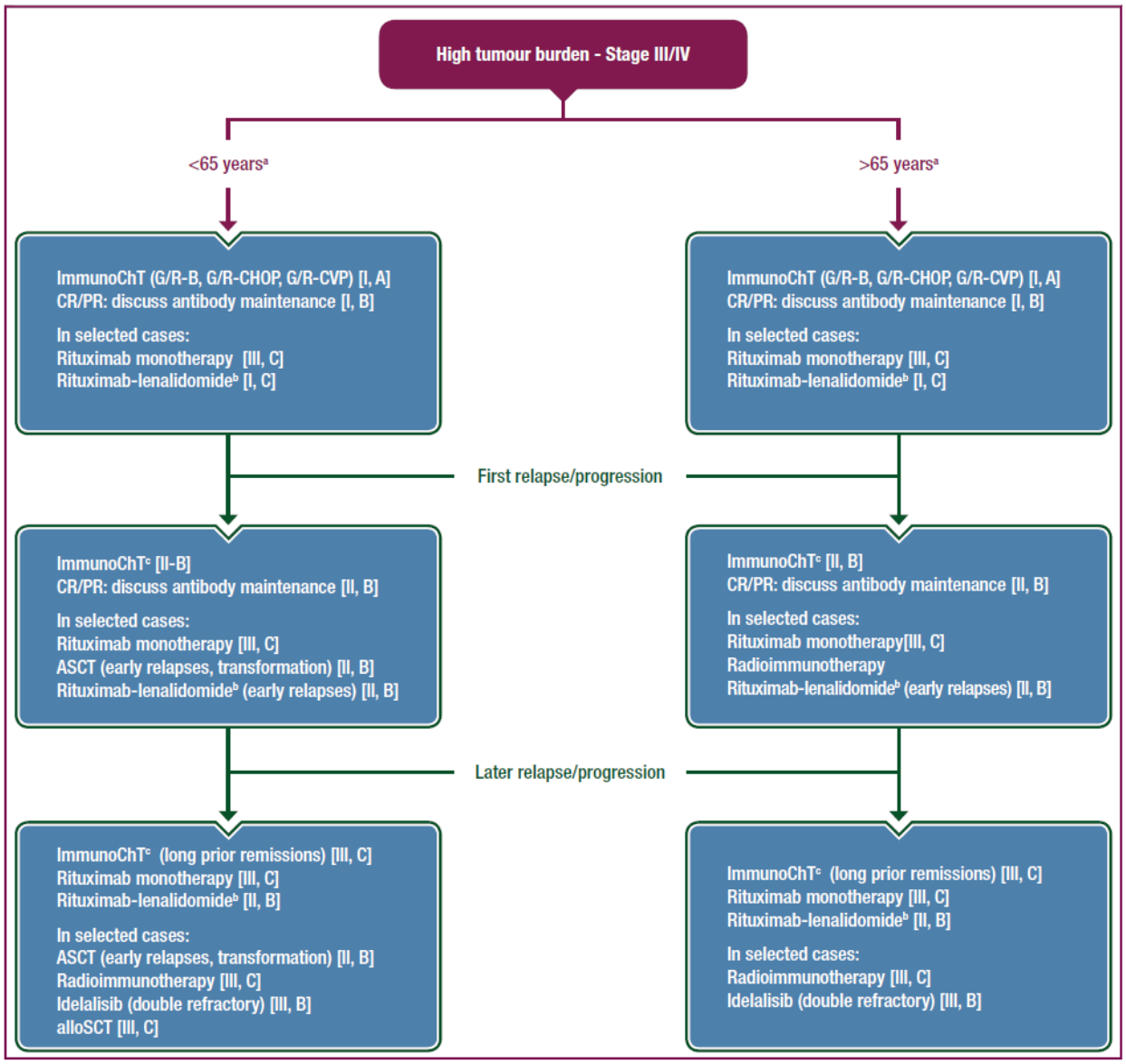


Figure 3. Consensus-driven recommendations—high tumour burden FL.
alloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; ChT, chemotherapy; CR, complete response; CVP, cyclophosphamide, vincristine, prednisolone; FL, follicular lymphoma; G, obinutuzumab; PR, partial response; R, rituximab.
[a] Biological age (years).
[b] Off-label.
[c] Preferred in rituximab-refractory cases.

Source: Dreyling et al., Ann. Oncol., 2021 (ESMO FL guideline)

Recently, therapies which utilize T-cells have been developed to treat B-cell malignancies. Two T-cell directed approaches that have led to approved treatments are CAR-T cells that target lineage-specific surface molecule CD19 (e.g., axicabtagene ciloleucel and tisagenlecleucel), and bispecific molecules that directly engage endogenous T-cells with tumor cells via binding to specific surface antigens on both cell types (e.g., blinatumomab).

2.2. About the product

Mosunetuzumab is a CHO-produced humanised full-length anti-CD20/CD3 T-cell-engaging bispecific antibody of isotype immunoglobulin G1 (IgG1)is intended for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL).

Mosunetuzumab is a conditional agonist, and the target B-cell lymphoma killing is expected to occur only when mosunetuzumab binds simultaneously to CD20 on B cells and CD3ε on T cells. Engagement of both arms of mosunetuzumab results in polyclonal T-cell activation through stimulation of T-cell receptor signaling, which results in formation of an immunologic synapse between a target B cell and a cytotoxic T cell. Subsequent T-cell activation and directed release of perforin and a cocktail of granzymes from T cells to B cells through the immunologic synapsis result in B-cell lysis. Mosunetuzumab contains the N297G amino acid substitution in the Fc region, which results in a non-glycosylated heavy chain. It is therefore expected that minimal binding to Fc receptors will occur and, consequently, significantly reduced Fc-mediated effector function.

The current MAA is based on study GO29781, an open-label, multicenter, Phase I/Ib (*Phase I/II per protocol v12*) trial evaluating the safety, efficacy, and PK of escalating doses of mosunetuzumab (BTCT4465A) as a single agent and combined with atezolizumab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia. The Interim CSR GO29781 reports all data in patients receiving IV monotherapy in both Group A and Group B (dose escalation and dose expansion stages) up to the clinical cut-off date (CCOD) of 15 March 2021.

2.3. Type of Application and aspects on development

Accelerated Assessment

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. The request for an accelerated assessment has been duly substantiated. Mosunetuzumab has the potential to address a high unmet need and will most likely impact medical practice. Also, mosunetuzumab provides a novel MoA, has a potential therapeutic advantage compared to available treatments, provides clinically meaningful ORR, CR and DOR, while having a clinically manageable safety profile. All this is highly welcomed in a patient population that needs new therapies with improved efficacy and safety.

Based on the assessment of the request provided by the applicant and the CHMP guideline on the procedure for accelerated assessment pursuant to Article 14 (9) of Regulation (EC) no 726/2004, the CHMP recommended to grant the accelerated assessment procedure pursuant to Article 14 (9) of Regulation (EC) No 726/2004 for Lunsumio.

Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data. Comprehensive data is expected from the recently commenced phase 3 study in FL patients after at least one prior treatment where mosunetuzumab in combination with lenalidomide is evaluated against rituximab + lenalidomide.
- Unmet medical needs will be addressed, as mosunetuzumab provides a novel MoA, has a potential therapeutic advantage compared to available treatments, provides clinically meaningful ORR, CR and DOR, while having a clinically manageable safety profile.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Mosunetuzumab has the potential to address a high unmet need and will most likely impact medical practice and is thus considered of major interest from the point of view of public health.

2.4. Quality aspects

2.4.1. Introduction

The active substance contained in Lunsumio is mosunetuzumab, a humanised full-length anti-CD20/CD3 T-cell-dependent bispecific IgG1 monoclonal antibody. One fragment antigen-binding (Fab) region of the antibody is directed against the extracellular domain of the CD3 subunit of the T-cell receptor (TCR) complex and the other Fab region is directed against the extracellular domain of CD20. The mechanism of action of mosunetuzumab involves recruitment of effector T-cells via CD3 to engage with target CD20-expressing B cells, leading to T-cell activation (independent of TCR epitope specificity) and T-cell mediated B cell cytolysis.

Lunsumio is presented as a concentrate for solution for infusion (pH 5.8) in single use vial where mosunetuzumab is formulated with the following commonly used excipients: L-histidine, L-methionine, acetic acid, sucrose, polysorbate 20 and water for injections. Two strengths are proposed: 1 mg (each vial contains 1 mg of mosunetuzumab in 1 mL) and 30 mg (each vial contains 30 mg of mosunetuzumab in 30 mL).

2.4.2. Active Substance

2.4.2.1. General Information

Mosunetuzumab (approximately 146 kDa) is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

2.4.2.2. Manufacture, process controls and characterisation

Mosunetuzumab active substance is manufactured at Genentech, Inc., 1 DNA Way South San Francisco (SSF), CA 94080, USA. Sufficient proof of GMP compliance has been provided for all sites involved in the manufacturing and controls.

Description of manufacturing process and process controls

Mosunetuzumab is produced using CHO cell lines. Cell culture process involves three stages: seed train, inoculum train, and production culture. The purification process consists of multiple steps, such as harvest, chromatography, filtration, and removal and inactivation of potential viral contaminants. The active substance is filtered into appropriate containers.

The in-process controls (IPCs) and associated limits are acceptable. The manufacturing process is sufficiently described.

The proposed reprocessing options are acceptable.

Control of materials

Cell banks

The protocol used for the generation of master cell bank (MCB) and working cell bank (WCB) have been adequately described in the dossier. WCB cells are used to initiate the production process.

The master and working cell banks were tested for microbial and viral purity, host cell identity and identity of the expressed protein. End-of-production cells (EPC) were tested for host cell line identity and viral purity.

Cells at limit of *in vitro* age (LIVCA) were tested for bacterial and viral contamination, and for genetic consistency. Overall, the generation and characterisation of the MCB, WCB, EPC and cells at LIVCA comply with the requirements set in the ICH Q5D guideline. In addition to genetic characterisation, phenotypic consistency was demonstrated during process validation.

Raw materials

The information provided on raw materials is overall sufficient.

Control of critical steps and intermediates

The mosunetuzumab active substance manufacturing process was developed with defined operational procedures, CPPs, and in-process limits to ensure control of critical steps. A process parameter is critical if varying the process parameter across its acceptable range impacts at least one critical quality attribute (CQA). The identification of CPPs is described in the dossier.

As part of the assurance of quality of mosunetuzumab active substance, IPCs have been established. IPC tests and limits applied to the cell culture and purification process as well as modification reactions are described. Depending on criticality, IPCs are tested against defined action limits or acceptance criteria. Data from IPC testing of the process verification and supportive batches are provided in the dossier.

Process validation

The mosunetuzumab active substance manufacturing process has been validated in accordance with relevant guidelines and the control strategy is acceptable.

Manufacturing process verification (also referred to as process performance qualification (PPQ))

Active substance PPQ was performed at the Applicant's commercial active substance manufacturing facility (Genentech, SSF) to show that the commercial v0.2 manufacturing process is capable of producing active substance of consistent quality at the manufacturing site and scale. The PPQ is considered adequate.

The PPQ data, supported by the data from the supportive batches, confirm that the process is in a validated state at the commercial manufacturing site and scale, and can deliver mosunetuzumab consistently with the expected product quality.

A sequence variant is present at low levels that were within clinical experience. Based on the risk evaluation conducted by the Applicant, it can be agreed that the sequence variant at the levels observed is unlikely to impact the clinical safety profile, bioactivity, immunogenicity, or PK of mosunetuzumab, and it can also be agreed that no routine testing is required. This position is in line with the CHMP/EMA Scientific Advice. In conclusion, the approach taken by the Applicant to control the level of the sequence variant is endorsed.

Process parameter ranges and CPPs

The process was developed using a Quality by Design (QbD) strategy driven by a science- and risk-based approach. This included prior knowledge gained from similar molecules and processes (the leveraging has been sufficiently justified) and mosunetuzumab-specific process validation studies, conducted both at scale and in sufficiently qualified scale-down models (SDMs).

An initial risk assessment was conducted to identify potentially critical process inputs and outputs. Selected process parameters were further investigated.

CPPs are acceptable and have been identified.

Clearance and worst-case linkage studies

Process linkage studies are designed to challenge individual steps, or the overall process, with higher levels of process-related impurities or product-variants than are typically present during routine manufacturing. Typically, the CQA level selected to challenge the process step was based on the highest observed value for the CQA from a process validation unit operation or in-process pool hold time study. The studies include spiking studies and unit-operation worst-case linkage studies. The high levels of process-related impurities and product variants were demonstrated to be cleared to acceptable levels by the purification steps for which high impurity clearance are claimed. Robust clearance has been demonstrated.

Process hold times

In addition to the IPCs for bioburden and endotoxin, the microbial quality of mosunetuzumab active substance is ensured through the manufacturing process designed for minimisation of risk of introduction and proliferation of microbial contaminants, and through implementation of validated in process hold times. The applicant has critically assessed the impact of each hold duration, as well as the cumulative hold time. The proposed active substance in-process hold times are considered justified.

Process impact assessment

A process impact (PI) assessment has been performed to assess the residual risk for the manufacturing process and its ability to produce active substance of consistent quality. PI assessments are based on the data from process validation studies to support process performance acceptable ranges and criticality, biochemical in-process pool hold studies (based on the acceptable pool hold times), and process linkage studies, as well as data from manufacturing-scale batches. The level of each CQA at different process steps was compared to an established limit; either an in-process pool limit (IPPL), active substance release acceptance criterion, or process validation assessment criterion.

The majority of the CQAs had low residual risk, meaning that they are well controlled during manufacturing and/or effectively removed during manufacturing. The data presented in the PI assessment support the conclusion that the manufacturing process produces active substance of consistent quality and as such the PI assessment is seen as support to the comparability study.

Media hold times, potential impact of input materials and the proposed possible refiltrations of active substance bulk have been sufficiently evaluated. As active substance and finished product are manufactured at the same site, shipping qualification is not applicable.

Sufficient information is provided on the potential residual levels of raw materials, potential leachable impurities from product-contacting materials, resin and membrane reuse and sanitisation and storage of resins.

Sufficient method descriptions for assays used in the process validation studies and/or in-process testing are provided.

Manufacturing process development

Developmental history

At the SSF active substance manufacturing site, three different versions of the active substance manufacturing process were developed; toxicology process, v0.1 process and v0.2 process. There are

no differences between the pivotal clinical process and commercial process (v0.2 manufacturing process).

Minor changes were made between the toxicology process and v0.1 process.

Further changes were implemented for the v0.2 active substance process.

Comparability

A comparability exercise considered the types of changes introduced in the mosunetuzumab manufacturing process with v0.2 and the potential impact of observed product quality differences on safety and efficacy. The comparability evaluation included active substance release analysis, extended characterisation comparison and in addition a pharmacokinetic study in cynomolgus monkeys, to compare the pharmacokinetic characteristics of mosunetuzumab from the v0.1 and v0.2 processes. Overall, the results of the comparability exercise showed that the manufacturing process changes did not have an adverse impact on the quality, safety, or efficacy of mosunetuzumab, and determined that v0.1 material and toxicology material were comparable to v0.2 material. In addition to comparability evaluation, process impact assessment was performed, see details in sections above. The data presented in the process impact assessment support the conclusion that the manufacturing process produces active substance of consistent quality. Comparability is considered sufficiently addressed.

Critical quality attribute assessment

A list of identified CQAs has been provided. Each CQA is controlled at the appropriate stage in the manufacturing process. QAs were first categorised to determine if a risk assessment was needed to classify an attribute as a CQA or non-CQA. The identified CQAs, as well as the approach used to classify attributes as CQAs, are found acceptable.

Characterisation

Overall, the structural, physiochemical and biological characterisation of mosunetuzumab active substance is considered comprehensive and sufficient.

The structural confirmation and characterisation of the physicochemical properties of mosunetuzumab has been performed using the secondary reference standard. The characterisation studies were performed using the proposed commercial release analytical methods and extended characterisation methods to assess the primary, secondary and higher order structure, as well as post-translational modifications.

Methods to assess mosunetuzumab biological properties include the proposed potency method used for commercial release as well as extended characterisation methods.

Data demonstrate that the *in vitro* biological activity measured by the potency assay is reflective of the key aspects of mosunetuzumab MOA.

Process-related impurities

Process-related impurities are impurities derived from the manufacturing process.

Process-related impurities have been sufficiently characterised and assessed.

2.4.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The commercial release and shelf life specifications for mosunetuzumab active substance were provided.

The specifications include general tests, test for identity, purity and impurity tests for product-related impurities, tests for excipients, test for protein content, test for potency, as well as tests for safety.

Sufficient justification for the tests which are not performed during shelf life has been provided.

The justification of the acceptance criteria for mosunetuzumab active substance is based on a combination of different information such as clinical experience, product-specific knowledge, Applicant's experience with related molecules, formulation development studies, storage and process effects, regulatory guidelines and manufacturing experience. For most attributes, acceptance criteria for the final specification (in most cases, finished product shelf life) are the anchor points for the sets of CQA acceptance criteria. Working backward from the final testing point, the potential storage- and process-related effects were considered for each preceding acceptance criteria, in order to ensure that the final acceptance criteria will be met. Overall, the approach used to set the active substance acceptance criteria is accepted.

The acceptance criteria set for the qualitative and quantitative attributes have been sufficiently justified and are accepted. In addition, the acceptance criteria have been tightened during development.

Overall, the parameters included in the active substance specification are found adequate to control the quality of mosunetuzumab active substance.

Analytical procedures

The analytical procedures used for batch release of mosunetuzumab active substance are a combination of compendial and non-compendial methods. Only methods specific to the active substance are described in this section. Descriptions of the analytical procedures used for both active substance and finished product are provided.

The panel of methods used to assure the quality of the active substance is in accordance with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008. The analytical procedures are in general described in sufficient details. Information on reference standard is included where relevant. The methods are considered suitable for their intended use.

The compendial analytical procedure Bioburden for testing of the active substance is performed in accordance with the method described in the relevant pharmacopoeia and was qualified for use with the active substance and in-process samples demonstrating recovery of challenge organisms in the presence of the different samples.

A summary of validation for the non-compendial methods has been provided. The non-compendial analytical methods have in general been sufficiently validated according to ICH Q2 to control active substance.

Reference standards

See finished product (the same reference standard is used for finished product and active substance testing).

Batch analysis

Batch analyses data have been provided for three full-scale clinical batches and three supportive batches produced by the process v0.1, as well as for three full-scale PPQ and three full-scale supportive batches produced with the process v0.2. All batch data comply with the specifications valid at the time of testing and demonstrate adequate batch-to-batch consistency.

Container closure

Mosunetuzumab active substance is filled and stored. The polymer primary packaging components of the tanks are compliant with USP Class VI Standards per USP <88> and the risk for potential leachables agreed to be sufficiently low.

2.4.2.4. Stability

The stability studies are designed in accordance with ICH Q5C Stability testing of biotechnological/ biological products. A shelf life of 48 months is proposed at a storage condition.

Long-term stability studies are on-going for three PPQ mosunetuzumab active substance batches; data are available for up to 48 months. Stability data at 48 months are also available for one supportive R&D batch. The four batches enrolled in stability were manufactured with the commercial process v0.2, except for the supportive batch. Trends were not observed at the intended storage temperature for any test.

In addition, the four batches were tested in accelerated and stress conditions for 6 months and 1 month, respectively. A set of active substance release methods was used to assess stability behaviour, some of the methods (i.e. purity and potency) being stability indicating. The provided stability data is sufficient to support the proposed shelf life and storage conditions for the active substance. The post-approval stability protocol and stability commitment are acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and Pharmaceutical Development

Description

The mosunetuzumab finished product is a sterile aqueous solution of mosunetuzumab, which is colourless, pH 5.8 and osmolality of 240-333 mOsm/kg.

The mosunetuzumab finished product is supplied as a 1 mg/mL solution in a single-use vial with L-histidine and acetic acid as buffering agents, L-methionine, sucrose as isotonicity/stabilising agent, polysorbate 20 as surfactant and water for injections.

All excipients are compendial.

Mosunetuzumab is presented in 2 sizes (pack of one vial each):

- 1 mg/vial with 1 mL solution in a 2 mL vial (1 mg strength);

- 30 mg/vial with 30 mL solution in a 50 mL vial (30 mg strength).

The container closure system consists of a Type 1 clear glass vial with a butyl rubber stopper and aluminium overseal with a plastic flip-off cap (dark grey for 1 mg strength and light blue for 30 mg strength). Vial and stopper are compliant with Ph. Eur 3.2.1 and 3.2.9, respectively.

Pharmaceutical Development

The finished product formulation is identical to the active substance formulation with the exception of the concentration of mosunetuzumab. Excipients include L-histidine and acetic acid as buffering/pH adjusting agents, sucrose as isotonicity/stabilising agent and polysorbate 20 as surfactant. No novel excipients or excipients of human or animal origin have been identified. Compatibility of active substance with the excipients is considered demonstrated.

Two different formulations have been used during the clinical studies. Formulation development included adjustment of the concentration of mosunetuzumab,. The fill volume has also been adjusted to fit clinical

needs. The mosunetuzumab finished product manufacturing process includes sterile filtration, filling into vials, capping & crimping and final visual inspection before secondary packaging.

Comparability assessments have been conducted between the Phase 1 clinical) and the pivotal Clinical and commercial) formulations as well as between the different presentations of the F02 formulation. Similar trends were seen between the formulations and presentations. Analytical profiles were similar and no new peaks were observed.

The selected formulation for commercial mosunetuzumab active substance and finished product is identical to the formulation F02 used in Phase 2 and Phase 3 clinical studies.

The mosunetuzumab finished product does not contain preservatives. The finished product is sterile filtered using an aseptic filling process. Satisfactory microbiological testing and container closure integrity testing (CCIT) is proposed as release and stability testing.

Container closure

The proposed container closure system is a Type I glass vial with a butyl stopper and aluminium overseal with a flip-off cap. The CCS is suitable for the finished product as documented by long-term and accelerated stability data incl. testing of container closure integrity and sterility. The secondary cardboard packaging protects the finished product from light as it is shown to be light sensitive. Comprehensive extractables and leachables (E/L) studies have been performed on the container closure system. All of the identified E/L are below the defined threshold permitted daily exposure (PDE) values.

Compatibility

The compatibility of the mosunetuzumab finished product with the infusion set and bag has been evaluated for both the 1 mg and the 30 mg strengths. The product is stable in a range of commercially available 0.45% and 0.9% saline infusion bags with a PVC infusion set without in-line filters during 24 hours at 5°C followed by 24 hours at 30°C with subsequent infusion over 480 minutes covering the proposed in-use period.

Overall, pharmaceutical development of mosunetuzumab finished product is considered acceptable.

2.4.3.2. Manufacture of the product and process controls

Manufacture

Batch certification for EU release is performed at Roche Pharma AG, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany.

The finished product manufacturing process was provided in a figure and includes sterile filtration, filling and capping, visual inspection and cold storage.

Process controls

The process parameters have been defined for all process steps and cover volumes, temperatures, mixing speeds and durations, filtration parameters and filling parameters. Process and hold times have likewise been defined for all steps. In-process controls are appropriate. The fill weight of the vial is checked during filling. Visual inspection is performed on 100% of the filled vials and on an acceptance quality limit (AQL) sample of the inspected vials. The proposed controls are considered adequate.

Process validation

The PPQ was performed on 1 mg/vial and 30 mg/vial commercial scale batches. In addition to controls defined by 3.2.P.3.3 and 3.2.P.3.4, homogeneity during filling was also performed.

The submitted data demonstrate that the process is generally well controlled with little variation in the reported results.

Comprehensive process design studies have been submitted.

Equipment, utilities and sterilising processes were adequately qualified prior to the PPQ including autoclaving of stoppers, decontamination of the filling isolator & aseptic processing media fill. A product specific filter validation including bacterial retention supporting the proposed processing limits is submitted.

A transport study covering the pallet transport to the site of secondary packaging is submitted.

In light of ongoing pandemic-related supply constraints, an alternate vessel was included to avoid potential supply issues at launch. The Applicant's proposed approach to qualify the alternate vessel for use in the commercial finished product manufacturing process is considered acceptable. However, the Applicant is recommended to submit the remaining verification data when available.

2.4.3.3. Product specification, analytical procedures, batch analysis

Specifications

The release and shelf life specifications for mosunetuzumab finished product were presented.

The proposed finished product release and shelf life specifications for mosunetuzumab have been provided for both dosage forms. The release specification includes general tests , test for identity, purity and impurity tests for product-related impurities, test for excipient, test for protein content, test for potency, as well as tests for safety. Overall, the parameters included in the finished product specification are found adequate to control the quality of mosunetuzumab finished product at release.

The shelf life specification has been provided. Sufficient justification has been provided. CCIT is included in the shelf life specification.

The justification of the acceptance criteria for mosunetuzumab is based on a combination of different information such as clinical experience, product-specific knowledge, Applicant's experience with related molecules, formulation development studies, storage and process effects and manufacturing experience. For most attributes, acceptance criteria for the final specification (in most cases, finished product shelf life) are the anchor points for the sets of CQA acceptance criteria. Working backward from the final testing point, the potential storage- and process-related effects were considered for each preceding acceptance criteria, in order to ensure that the final acceptance criteria will be met. In addition, acceptance criteria for Osmolality, Visible particles, Sub-visible particles, Sterility and Bacterial endotoxins are established to align with pharmacopoeia requirements. Overall, the approach used to set the acceptance criteria for the finished products is accepted.

The acceptance criteria set for the qualitative and quantitative attributes have been sufficiently justified and can be accepted.

The test for Visible particles on finished product is performed during shelf life. At release, the acceptance quality limit (AQL) testing results performed at the finished product manufacturing site (SSF) will be used for commercial release in the EU/EEA. The Applicant provided appropriate rationale and the proposed setup is from a scientific point of view acceptable.

The QC testing for Bacterial endotoxins is only performed at active substance release. For the finished product, the results from in-process testing performed at the finished product manufacturing site will be used for commercial release in the EU/EEA. The strategy is considered acceptable.

Analytical procedures

The panel of methods used to assure the quality of the finished product is in accordance with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008. The analytical procedures are in general described in sufficient details. Information on reference standard is included where relevant. The methods are considered suitable for their intended use.

The compendial analytical procedures are performed in accordance with the methods described in the relevant pharmacopoeia and were sufficiently verified for their suitability. Suitability verification has been performed for active substance and/or finished product, as well as for in-process samples.

Sterility testing is performed using either the compendial procedure or an alternative method. The compendial procedure was adequately verified for suitability with the finished product. Validation of the alternative method was designed in agreement with ICH guidelines, Ph. Eur. 5.1.6., USP <1223>, PDA Technical Report No. 33, and EDQM guidelines (Examples of Validation Protocols of the Alternative Microbiological Methods According to Chapter 5.1.6 "Alternative methods for control of microbiological quality," Edition 2018). Method validation using mosunetuzumab finished product was performed. The compendial sterility test method will be maintained until the alternative method is approved for ongoing clinical trials across the Applicant's manufacturing network. After this transition, the alternative method will be used as the commercial release test method, while the compendial sterility test method will be maintained as backup option (e.g. in case of equipment failure). With the Applicant's confirmation that the two methods cannot be used interchangeably for batch release testing, the approach is found acceptable.

In general, the non-compendial analytical procedures are described in sufficient detail. Information on the reference standards are included where relevant. The methods were adequately validated for their suitability for intended use. Further, the stability-indicating methods were identified.

Some methods were transferred using a method transfer protocol.

The testing of container closure integrity is performed. Sufficient evidence has been provided to demonstrate equivalence to the microbial ingress test. Therefore, the use of both methods is acceptable.

Reference standards

A two-tiered reference material system has been established. Three different reference standards (RS) – initial, primary and secondary – have been used throughout the development of mosunetuzumab. The initial RS was produced with process v0.1 while the primary and secondary RS were produced using process v0.2. Information on the batches (number, source, date of manufacture) and the use are included. The finished product batches used in the pivotal clinical study GO29781 were manufactured from the same active substance run as primary reference standard, supporting the link between the primary and secondary RS and the pivotal clinical material and commercial material.

The primary and secondary RS were prepared at the same time from the same active substance batches. Qualification included active substance release methods as well as additional characterisation. The acceptance criteria used to qualify the current RS are based on active substance release specification, except for the acceptance criterion for potency, which is tighter than the active substance release specification. Potency assignment is based on multiple independent determinations, which is found adequate to prevent shift of potency.

The procedure for preparation and qualification of future reference standards is provided and deemed sufficient (release and extended characterisation will be performed, chromatographic and electrophoretic profiles will be compared, potency assignment is described and suitable to prevent drift, approach for stability testing is given).

Batch analysis

PPQ batches were manufactured at the proposed commercial scale and used for clinical studies. In addition, batch data are provided for batches used for clinical studies and manufactured at, as well as for supportive nonclinical batches. All results are compliant with the established limits and are consistent across the batches with an acceptable batch-to-batch variation. The batch release data demonstrate consistent quality of the mosunetuzumab finished product throughout development and for commercial purpose.

Characterisation of impurities

The mosunetuzumab finished product manufacturing process includes aseptic filling and capping. No new impurities are generated during the finished product manufacturing process and all impurities observed in the finished product were characterised for the active substance.

The Applicant has provided a risk assessment for elemental impurities in accordance with ICH Q3D guideline and showed that the potential major contributions to the elemental impurities are from the freeze/thaw tank and container closure system. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment regarding the potential presence of nitrosamines in Lunsumio was provided where it is concluded that the risk is negligible. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

2.4.3.4. Stability of the product

A shelf-life of 24 months at 2°C-8°C is proposed. This is supported by the data presented.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C and 24 hours at 9°C-30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions

Primary stability studies were conducted on the commercial scale PPQ batches for up to 30 months in long term storage conditions and for up to 6 months in accelerated conditions are presented for all primary batches

Additional studies have been performed on 2 clinical batches, 1 representative technical and 2 supportive R&D stability batches at both long-term storage conditions (5°C) and accelerated conditions (25°C). 24 to 48 long term are presented as well as 6 months accelerated data.

Generally, no alarming trends are observed at 5°C. Slight increases of impurities and decrease of purity is observed and this is confirmed by the data at accelerated conditions. Trends are comparable across presentations. Stability stress studies have been conducted at 30°C/2 months and 40°C/1 months. These studies confirm the degradation pathways observed at lower temperatures.

In general, the proposed protocols are in accordance with current guidelines.

The Applicant committed to place one batch in long-term stability per year with yearly time points and testing according to the stability specification.

An ICH Q1B photostability study has been conducted concluding that the mosunetuzumab finished product is photosensitive. A temperature cycling (incl. freeze/thaw) study have been conducted on one PPQ batch of each presentation. Data show that the product is not susceptible to temperature cycling.

Lunsumio vial should be kept in the outer carton in order to protect from light.

2.4.3.5. Product Lifecycle Management (PLCM)

The Applicant initially provided a Product Lifecycle Management (PLCM) plan including Established Conditions. As requested, and due to the fact that such documents cannot currently be recognised in the EU, the Applicant removed the PLCM from the dossier.

2.4.3.6. Adventitious agents

Raw materials

Animal-derived raw materials are compliant with the guidance for minimizing the risk of transfer of TSE (EMA/410/01, Rev. 3). Based on the information provided, the risk of transmitting adventitious viral or non-viral agents is evaluated to be negligible.

Cell banks

Cell banks, including the master, working, and end of production cell banks, and cells at LIVCA have been characterised according to ICH Q5A and ICH Q5D,. No non-viral nor viral adventitious agents were detected. No endogenous retroviruses were detected except for retroviral like particles (RVLP), type A and C, which are known to be present in cells of CHO origin. Based on the results obtained, the cell banks are considered safe for use in manufacture of mosunetuzumab with regards to the risk of viral and non-viral adventitious agents and endogenous retroviruses.

Testing at appropriate stages of production

The mosunetuzumab active substance is tested for absence of bacteria and fungi (bioburden), and level of endotoxin during manufacture (IPC) and at release. In addition, the preharvest cell culture fluid is subjected to testing of absence of mycoplasma and general *in vitro* test for absence of viral adventitious agents . The finished product is tested for bioburden and level of endotoxin during manufacture and sterility and level of endotoxin at release. No contamination has been detected. The number of RVLPs have been determined in three batches by TEM. The highest number of the three batches was used to calculate the retrovirus safety factor (see below under "virus clearance validation". The testing conducted during manufacture and at release is considered sufficient and in line with current requirements.

Viral clearance studies.

The viral clearance capacity of the mosunetuzumab active substance purification process was evaluated by conducting viral clearance studies, using qualified scale down models in accordance with ICH Q5A. The scale down procedure is considered acceptable and the scale down models are representative of the commercial scale. Studies were conducted under worst-case conditions, when applicable. Virus detection assays included detector cell based tests and PCR. The assays used have been properly validated, including sample type (matrix) validation.

Efficient clearance (> 4 log reduction values) was observed for each of the three model viruses by at least two of the process steps validated. The studies show an acceptable viral clearance potential of the manufacturing process. The quantitative virus risk assessment demonstrates an acceptable safety margin for the studied viruses in the manufacturing process including the retroviral clearance.

Conclusion

Overall, the risk of contamination with adventitious agents, including TSE, mycoplasma, bacteria, fungi, and viruses, is considered well contained based on selection of safe raw materials, demonstration of absence of adventitious (and endogenous) agents in cell banks, testing at relevant stages of the process, and finally the substantial virus clearance capacity, demonstrated for the mosunetuzumab purification process.

Based on this, mosunetuzumab is considered safe for commercial purposes with regards to the risk of contamination with adventitious non-viral or viral agents or with endogenous viruses.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Overall, the quality of Lunsumio is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing ICH/CHMP guidelines.

The manufacturing processes of the active substance and finished product are adequately described, controlled and validated. Active substance and finished product batch release data indicate robust reproducible manufacturing processes within and between manufacturing sites. All pre-defined acceptance criteria were met. The active substance and finished product manufacturing history is described in sufficient detail and the outcome of the comparability evaluations of different processes used is satisfactory.

The active substance has been extensively characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. Process- and product-related impurities have been evaluated and are sufficiently cleared during the process and/or controlled at release.

The quality of the active substance and finished product is controlled by adequate test methods and specifications.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

No major objection was identified during the procedure.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Lunsumio is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the data provided, the marketing authorisation application for Lunsumio is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

In relation to the use of an alternate vessel in the commercial finished product manufacturing process, the Applicant is recommended to submit the remaining verification data when available.

2.5. Non-clinical aspects

2.5.1. Introduction

Several in vitro and in vivo studies have been conducted to investigate the pharmacological activity and mode of action of mosunetuzumab. During development and nonclinical testing, two earlier versions of mosunetuzumab were also investigated (referred to as 2H7v16/40G5c and the proof-of-concept (POC) molecule, referred to as 2H7v16/UCHT1v9). All three anti-CD20/CD3 T-cell-dependent bispecific (TDB) antibodies are based on the same modification technology; Cynomolgus monkey was selected as the appropriate animal species for assessing the nonclinical safety, pharmacokinetic (PK), and pharmacodynamic (PD) properties of mosunetuzumab and 2H7v16/40G5c.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

To evaluate the cross-species in vitro binding and potency of 2H7v16/40G5c, the binding affinity of the anti-CD3 antibody arm to human and cynomolgus monkey CD3εγ antigens was investigated. It was demonstrated that the binding affinities to human and cynomolgus monkey CD3εγ antigens were comparable, and furthermore, comparable in vitro potency for B-cell killing was demonstrated in human and cynomolgus monkey peripheral blood mononuclear cells (PBMCs). Due to technical limitations it was not possible to develop a robust, reproducible and accurate IHC assay to assess specific tissue binding and determine the potential cross-reactivity of mosunetuzumab in human and cynomolgus monkey tissue, as mosunetuzumab exhibits poor analytical sensitivity and specificity as an IHC reagent. No cross-reactivity studies were conducted in other species, e.g. rodents, dogs or rabbits. Mosunetuzumab showed marginal binding to human Fc gamma receptors FcγRs (including FcγRIA, IIA-H131, IIA-R131, IIB, IIIA-F158, and IIIA-V158) and human C1q.

During development, two different drug substance manufacturing processes were developed yielding mosunetuzumab v0.1 and v0.2. Mosunetuzumab v0.1 has been used for the investigational new drug (IND), enabling pharmacology, pharmacokinetic, and toxicology studies, as well as for the ongoing Phase I study, where mosunetuzumab v0.2 was since developed. Binding studies to both CD20 and CD3∑ on B cells and T cells showed comparable activity in human and cynomolgus monkey between the two versions, and the change in manufacturing process is not considered to have an impact on the nonclinical profile of mosunetuzumab.

It was confirmed in vitro that 2H7v16/UCHT1v9 is inactive with cynomolgus monkey PBMCs while only 2H7v16/40G5c was able to activate $CD8^+$ T cells and kill cynomolgus monkey B cells in a comparability study. In human PBMCs, both antibodies had comparable in vitro potency in B-cell killing and induced a similar extent of B-cell killing. Though not statistically significant, 2H7v16/40G5c appeared to have lower potency in $CD8^+$ T-cell activation and resulted in a lower extent of $CD8^+$ T-cell activation and cytokine production (IL-2, IL-6, IFN-γ, and TNF-α). Mosunetuzumab and 2H7v16/40G5c demonstrated comparable target antigen binding affinity as well as no apparent difference in their potency in B-cell killing, $CD8^+$ T-cell activation, and cytokine production

The binding and activity of 2H7v16/UCHT1v9 was investigated in vitro in human donor PBMCs against the B-cell line BJAB. It was demonstrated that B-cell killing does not appear to be dependent on Fc expression or Fc receptor–mediated effector functions. Furthermore, it was shown that the activity of 2H7v16/UCHT1v9 is dependent on both the presence of CD3 expressing T cells and CD20+ expressing B cells, confirming the bimodular action of 2H7v16/UCHT1v9, as no activity is detected in the absence of either cell type. Both $CD4^+$ and $CD8^+$ T cells can be activated by 2H7v16/UCHT1v9 in the presence of B cells. However, it appears that $CD8^+$ T cells are more potent in BJAB cell killing compared to $CD4^+$ T

cells, as $CD8^+$ T cells mediated a greater extent of cell killing as well as producing higher levels of granzyme B and perforin when activated. 2H7v16/UCHT1v9 was also potent in killing CD20 low-expressing B-lymphoma cells. Further, there was no particular correlation between EC50s and CD20 expression in cells where CD20 expression levels were available. EC50s from healthy donor B cells were of a wide range and wider range than for EC50s for lymphoma cell lines and primary CLL.

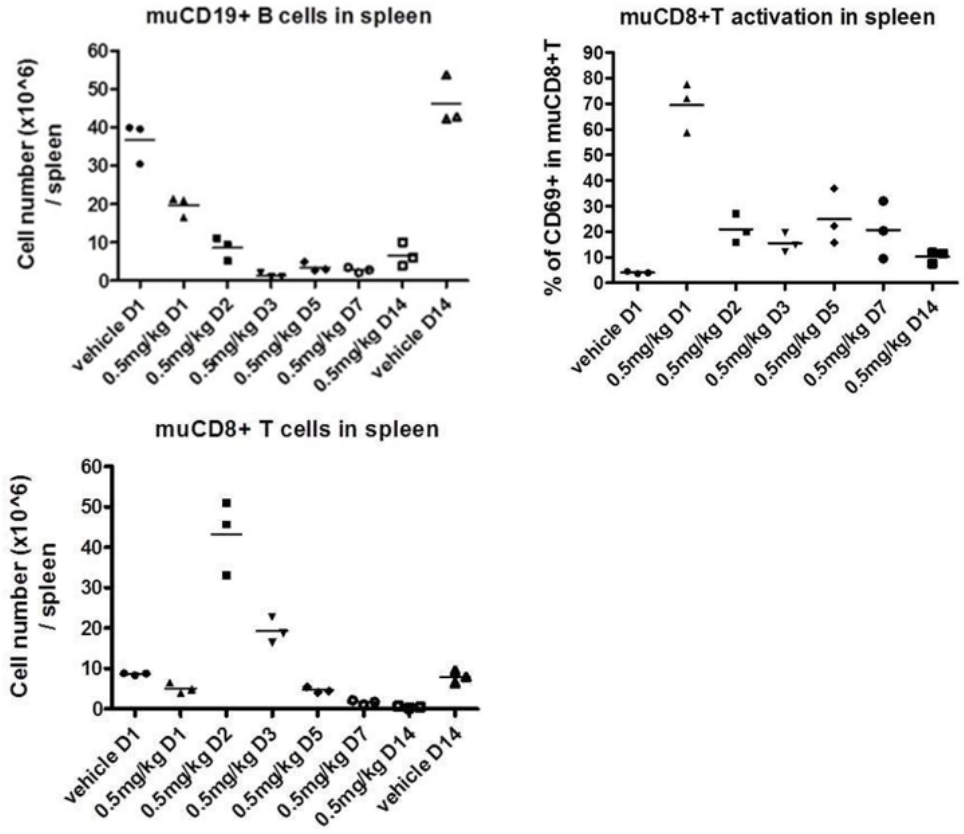
The activity of 2H7v16/UCHT1v9 was confirmed in vivo after single-dosing in a human CD20/CD3 double-transgenic mouse model in spleen samples. 2H7v16/UCHT1v9 bound to both mouse B and T cells and showed high activity as well as a significant clearance of splenic B cells. T-cell dependency as part of the mechanism of action for CD20 TDB antibodies was confirmed in vivo in a human CD20 single-transgenic mouse model, as 2H7v16/UCHT1v9 only bound to mouse B cells in this model and elicited no activity. The efficacious dose of 2H7v16/UCHT1v9 for complete B-cell depletion in blood and lymphoid tissues in double-transgenic mice was established at 0.5 mg/kg as single dosing, as this was the minimal dose to sustain depletion for 15 days. In a similar double-transgenic mouse model, 2H7v16/40G5c potently depleted tissue B cells starting at Day 1 post-dose which was complete at Day 3 post-dose, with some recovery observed at 14 days post-dose. Corresponding activation of both $CD8^+$ T cells and $CD4^+$ T cells (measured as CD69 expression) was detected in the spleen at Day 1 post-dose, with up to 5-fold increases in $CD8^+$ T-cell counts at Day 2 post-dose. Activation of T-cells gradually decreased to or below baseline levels between Days 2 and 14 post-dose, whereas the increase in T-cell numbers normalised between Days 5 and 14 post-dose, corresponding to depletion of B-cells and thus a lack of continued T-cell activation due to the missing TBD CD20 target. In the double-transgenic mouse model, it was also shown that 2H7v16/40G5c and mosunetuzumab have comparable profiles in potently depleting peripheral and tissue B cells as well as activation of T cells. Following repeat-dosing of 0.5 mg/kg administered once weekly for three weeks in humanized NSG mice, both 2H7v16/UCHT1v9 and 2H7v16/40G5c potently depleted peripheral B cells to a similar extent with almost complete depletion of B cells in blood until the end of the study (day 21 post-dose).

The PD effect of mosunetuzumab was investigated in cynomolgus monkey after single and repeat dose administration by evaluating effects on B-cell depletion, T-cell kinetics and activation as well as the cytokine release profile. In the pivotal GLP single-dose toxicity study (Study 14-1246) following 1-hour IV infusion of mosunetuzumab, dose levels above 0.1 mg/kg induced rapid dose-dependent B-cell depletion from peripheral blood, with complete or near complete depletion at dose levels above 0.1 mg/kg. As in mice, B-cell depletion was also sustained in cynomolgus monkeys through day 22 after dosing with recovery observed at day 57. Administration of mosunetuzumab was associated with transient and dose-dependent T-cell activation in both $CD4^+$ and $CD8^+$ T cells, with a tendency for greater activation among CD8+ cytotoxic T cells, as also observed in vitro. Transient decreases in circulating T cell, cytotoxic T cell, natural killer cell, and monocyte counts were detected as early as 2 hours after mosunetuzumab administration, which recovered to baseline by 3 days after dosing, most likely attributable to activation-induced T-cell margination followed by redistribution and/or expansion. Corresponding dose-dependent increases in cytokine and chemokine levels were detected rapidly after dosing (~2h) and declined to baseline levels within 24 hours following mosunetuzumab administration. Dose-dependent increases in serum levels of B-cell activating factor (BAFF) were detected with maximum fold increases in BAFF occurring on Day 9 (0.01 and 0.1 mg/kg) and Day 23 (1 mg/kg). SC dosing at 1 mg/kg resulted in similar findings for B-cell depletion and T-cell activation compared to IV administration of 1 mg/kg.

PD effects of 2H7v16/40G5c and mosunetuzumab were also investigated in several studies in cynomolgus monkeys after repeated dosing and generally confirmed the findings from the single dose studies. In a dose range finding (DRF) toxicity study (Study 12-3160), 2H7v16/40G5c was administered at doses of 0.01, 0.1 and 1 mg/kg weekly for 4 weeks including a 7-week recovery period. Within hours of dosing, a rapid depletion of circulating B cells was observed, which was

sustained in the majority of animals given 1 mg/kg as well as in recovery animals 6-8 weeks after the final dose.

Figure 2 B-Cell Depletion and T-Cell Count and Activation following a Single Dose of 2H7v16/40G5c in Human CD20/CD3 Double-Transgenic Mice (Study 12-0404M)



D = day; mu = murine.

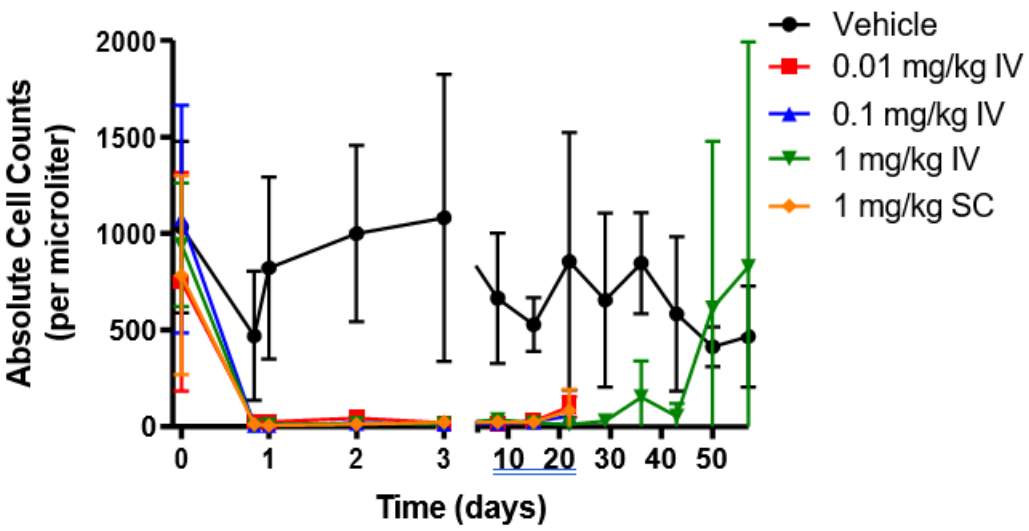
Single-Dose Studies in Cynomolgus Monkeys (Studies 14-1246, 13-2298, 13-1514, and 13-2135)

The PD effects of mosunetuzumab were evaluated in the GLP single-dose toxicity study (Study 14-1246) following 1-hour IV infusion at 0.01, 0.1, and 1 mg/kg or SC injection at 1 mg/kg, and in a single-dose pharmacokinetic and PD study (Study 13-2298) following IV bolus injection (approximately 30 seconds to 1 minute) of 0.001–1 mg/kg. In addition, the PD effects of 2H7v16/40G5c were assessed in two single-dose studies following IV slow bolus injection of 2H7v16/40G5c at 1 mg/kg. The first study (Study 13-1514) was conducted in a cohort of 3 animals followed for 7 days. The second study (Study 13-2135) expanded to 3 cohorts with necropsy after 3, 14, or 28 days. Results were similar between mosunetuzumab and 2H7v16/40G5c and across studies; data from Study 14-1246 are presented below.

B-Cell Depletion

Mosunetuzumab induced rapid B-cell depletion from peripheral blood within 2 hours at dose levels above 0.01 mg/kg. Dose-dependent B-cell depletion in the spleen and lymph nodes was observed in all dose groups with complete or near complete depletion achieved at dose levels ≥0.1 mg/kg by Day 8 post-dose. B-cell depletion was sustained in the periphery and lymphoid tissues through Day 22 after dose administration for animals given 1 mg/kg and recovered by Day 57. B-cell depletion in the blood and tissues were comparable for IV and SC dosing at 1 mg/kg.

Figure 3 Pharmacodynamic Effects following a Single Intravenous Administration of Mosunetuzumab (Study 14-1246) – Circulating B Cells (CD40⁺)



In the 0.01 and 0.1 mg/kg dose groups, a recovery in B cells was observed at the beginning of week two due to formation of ADA and subsequent loss of drug exposure, presumably due to an incomplete depletion of B cells at the lower dose levels, which are then available for production of ADA. 4 of 4 animals in the 0.01 mg/kg group developed high titers ADA while only one animal given 0.1 mg/kg did not develop ADA. In this animal, complete B-cell depletion in blood and lymphoid tissues was observed, confirming the PD effect at this dose level. 5 of 8 animals dosed with 1 mg/kg developed ADA. Increases in BAFF levels inversely correlated with B-cell depletion. A step-up mosunetuzumab dosing regimen was used in the 4-week DRF study and the pivotal GLP 26-week repeat-dose toxicity studies (Study 16-2088 and 16-1815) by splitting the first 1 mg/kg dose to Day 1 (0.2 mg/kg) and Day 2 (0.8 mg/kg), followed by weekly doses of 0.3, 1, or 3 mg/kg or 0.1 or 0.5 mg/kg, respectively. Using this approach, a split of the first dose resulted in a reduction in the observed cytokine-related acute toxicities while ADA formation was mitigated to some extent due to the high initial dose of 1 mg/kg IV administered within the first two days.

During both the 4-week and 26-week repeat-dose studies, a rapid and sustained depletion of B-cells and corresponding increase in BAFF was observed in animals that did not develop ADA, in line with previous results. In these animals, exposure was furthermore demonstrated as the mean serum concentration was approximately maintained over time as well as a maintained or slightly increasing Cmax and AUC over time (dose-normalized), confirming that ADA did not affect the results of the study. As also observed in the single dose studies, a transient reduction in T cells from peripheral blood at day 2 post-dose was observed primarily after the first dosing cycle with 2H7v16/40G5c, which returned to baseline at day 8 post-dose. T-cell activation was confirmed after repeated dosing of both 2H7v16/40G5c and mosunetuzumab, primarily $CD8^+$ T cells and to a lesser extent $CD4^+$ T cells. The response was most significant after cycle 1 compared to cycle 2-4 where only modest activation was observed. Corresponding increases in chemokines and cytokines was observed 2-6 hours post-dose, which returned to pre-dose levels by 24 hours post-dose following the first dose only. These findings support the mechanism of initial (complete) depletion of the entire pool of B cells with reduction in T cell count and release of cytokines/chemokines during cycle 1 and subsequent maintenance of the B-cell depletion with only moderate/slight changes in T cell count and cytokine production after the subsequent doses.

2.5.2.2. Secondary pharmacodynamic studies

In an in vitro binding assay for human Fcγ receptors, it was shown that while the positive control trastuzumab binds robustly to the Fcγ receptors, mosunetuzumab showed minimal detectable binding to the Fcγ receptor tested. This is expected due to the mutation introduced in the N297 residue in the Fc binding region which results in aglycosylation and minimal capability of binding to effector cells via this region. Thus, mosunetuzumab appears to have a low potential for Fcγ receptor cross-linking on immune cells leading to induction of nontargeted immune cell activation (e.g. ADCC and ADCP). The binding affinity to C1q was investigated in vitro. It was shown that mosunetuzumab exhibits minimal binding activities to C1q, thus, mosunetuzumab is not expected to induce complement-dependent cytotoxicity.

2.5.2.3. Safety pharmacology programme

Cardiovascular effects were investigated as part of the single dose GLP study in monkeys (Study 14-1246). Monkeys were instrumented with surgically-implanted telemetry devices and evaluated from pre-dose to 3 weeks post-dose. Increases in heart rate and body temperature were noted at 0.1 mg/kg (IV) and 1 mg/kg (IV or SC) on Day 1, resulting in attenuated diurnal patterns. Hypotension was furthermore observed at 1 mg/kg IV. Decreases in PR and QT intervals in animals given 1 mg/kg (IV or SC) correlated with increases in heart rates (RR interval decreases). When corrected for heart-rate, no significant differences were noted in the QT intervals (QTc) compared with pre-dose levels. It appears that effects on QT were heart-rate dependent and not indicative of an effect of mosunetuzumab on ventricular repolarization kinetics, which is accepted. All cardiovascular related findings generally occurred following the first dose and diminished or were absent following subsequent weekly administrations. The cardiovascular effects are considered to be secondary to mosunetuzumab-induced cytokine release and associated acute phase protein reactions. In clinical trials, 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 for QT prolongation is considered to be low. The NOAEL for the cardiovascular system following single IV administration is 0.1 mg/kg. Similar findings were observed in the 4-week repeat dose toxicity study in monkeys, which was also considered attributed to mosunetuzumab-induced cytokine release.

Microscopic findings of minimal to mild vascular/perivascular inflammatory cell infiltrates has been observed in single and repeat-dose studies in mosunetuzumab-treated monkeys, primarily in the brain white matter and with less incidence within spinal cord and sciatic nerve. In the brain, the changes were associated with local microglial phagocytosis reaction, though no neuronal degeneration or vascular damage was observed. The effects were not observed to progress and were considered reversible in recovery groups. Further, the Applicant considers that the 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. A case of in-life neurologic abnormalities was observed in one animal (IV infusion of 0.2/0.8/1.0 mg/kg on Day 1/Day 2/Day 8 (Study 16-2088)), as convulsions were observed on Day 11 after dosing. The animal showed extensive microscopic findings compared to the other test animals at similar or higher dose levels. Exposure margins based on AUC and C_{max} was calculated as 1.80 and 3.26, respectively, indicating that the effect was observed in the range of clinically relevant dose levels. No other neurologic abnormalities were observed in any non-clinical toxicity studies after chronic administration. Neurologic adverse events have been observed in the clinical trials and are considered potential clinical risks for mosunetuzumab treatment, which will be followed up by routine pharmacovigilance.

No mosunetuzumab- or 2H7v16/40G5c-related respiratory effects were observed in the GLP single-dose or 4-week repeated dose studies in monkeys. The NOEL for the respiratory system following a

single IV infusion or SC injections of mosunetuzumab and for 2H7v16/40G5c via IV dosing for 4 weeks was 1 mg/kg.

2.5.2.4. Pharmacodynamic drug interactions

Rituximab is widely used for the treatment of B-cell malignancies. To investigate potential interaction between the compounds, the efficacious activity of 2H7v16/40G5c to induce B-cell killing in the presence of rituximab-DANA (an effector-less variant of rituximab) was assessed in vitro (Study 15-0396). At a concentration well above what was required for saturating binding of CD20 antigen, rituximab-DANA only increased the EC50 values, but did not reduce the extent of B-cell killing mediated by 2H7v16/40G5c. The interaction with the steroid dexamethasone was investigated by pre-treating human PBMCs with concentrations of dexamethasone which could potentially impact T-cell immune response and reduce in vitro cytokine production (Study 15-0396). 2H7v16/40G5c was still active in B-cell killing in the presence of dexamethasone in vitro, however, dexamethasone could greatly reduce T-cell activation and cytokine production mediated by 2H7v16/40G5c. In a 4-week study in monkeys, the effect of pre-treatment with either dexamethasone or rituximab on the B-cell killing activity of 2H7v16/40G5c was investigated. The in vivo study confirmed the findings from the in vitro study, as the onset and the magnitude of B-cell depletion were similar in all animals that maintained 2H7v16/40G5c exposures, indicating that pre-treatment with dexamethasone or rituximab had no negative impact on 2H7v16/40G5c-induced B-cell depletion.

2.5.3. Pharmacokinetics

A series of non-clinical single-dose and repeat-dose PK/TK studies in humanized transgenic mice or cynomolgus monkeys were performed to characterize the IV and SC pharmacokinetics of 2H7v16/40G5c and/or mosunetuzumab. Of these, two pivotal GLP-compliant toxicity studies (Study 14-1246 and 16-1815) and additional PK and pilot toxicity studies were conducted with mosunetuzumab, while early explorative studies were conducted using 2H7v16/40G5c. Both mosunetuzumab and 2H7v16/40G5c cross-react in cynomolgus monkeys, but not in rodents, and have similar in vitro potency in both cynomolgus monkey and human peripheral blood mononuclear cells (PBMCs). Therefore, cynomolgus monkey was selected as the appropriate animal species for assessing the PK/TK of mosunetuzumab and 2H7v16/40G5c, which is accepted.

The methods developed to measure mosunetuzumab and anti-mosunetuzumab antibody in cynomolgus monkey serum in support of the GLP pivotal toxicology studies (14-1246, 16-1815) have been suitably validated. The ELISA method for detection of mosunetuzumab in cynomolgus monkey serum was validated across a calibration range of 0.125 to 16.0 ng/mL. The accuracy and precision of the within-run and between-run values is acceptable and in line with relevant guidance documents (*EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2)*. Furthermore, dilution integrity and minimum required dilution (MRD) as well as long-term stability and stability during freeze-thaw cycles was sufficiently addressed. Mosunetuzumab at QC levels (12.0, 30.0 and 140.0 ng/mL) is stable after up to 6 freeze/thaw cycles and 24 hours at room temperature. Frozen blocked plates containing mosunetuzumab at QC levels are stable up to two weeks when stored at -80°C±10°C. Further, the stability of mosunetuzumab at QC levels in frozen matrix (-80°C±10°C) was demonstrated for up to 1003 days. Incurred sample reanalysis (ISR) was investigated in the GLP-compliant study (14-1246) and results were acceptable in line with relevant guidance (*EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2)* for ligand-binding assays. The validated anti-mosunetuzumab bridging ELISA assay had a cut point factor of 1.05 and a relative sensitivity of 214 ng/mL (assessed using a surrogate positive control affinity-purified sheep anti-human IgG). This assay can detect 1000 ng/mL of the surrogate positive control in the presence of up to 3.13 µg/mL of mosunetuzumab. For both GLP-studies (14-1246 and 16-1815) serum concentrations of mosunetuzumab at the time of ADA determination were below this drug tolerance threshold, except for

those in the high-dose group in repeat-dose GLP-study 16-1815. However, the exposure levels did not seem affected in neither ADA-positive nor ADA-negative animals in this high-dose group.

Overall, there were no significant sex-related differences observed in exposure parameters across single-dose or repeat-dose studies using both male and female cynomolgus monkeys (14-1246, 12-3160, 16-1815, 16-2088) after dosing with mosunetuzumab or 2H7v16/40G5c, and therefore only combined exposure parameters are discussed below.

The bioavailability of mosunetuzumab or 2H7v16/40G5c after an SC dose of 1 mg/kg in cynomolgus monkeys was 75% and 60% after single- and repeat-dosing, respectively (study 14-1246 and 13-1689). Serum exposure parameters after SC dosing were reduced (72-80% for C_{max}, 25-40% for AUC-values) compared to IV dosing. As expected, T_{max} was delayed and occurred approximately 24 hours post SC-dosing compared to IV-dosing.

Single-dose IV/SC

Following IV single-dose administration to cynomolgus monkeys both 2H7v16/40G5c and mosunetuzumab displayed dose-dependent kinetics, however increases in exposure was not consistently dose-proportional, especially at doses below 0.01 mg/kg which could be attributed to differences in impact of target-mediated clearance or ADA-formation observed at different dose levels (i.e. higher ADA-formation and non-saturated target-mediated clearance at low doses, when B-cell depletion is incomplete). Accordingly, clearance appeared to increase inversely with dose across single- and repeat-dose studies with mosunetuzumab or 2H7v16/40G5c, with clearance estimates ranging from 6.24-18.9 ml/kg/day for animals dosed at 1 mg/kg IV, and ranging from 31.0-51.9 ml/kg/day in animals dosed from 0.001-0.1 mg/kg IV. Further, $t_{1/2}$ of 2H7v16/40G5c was estimated to be 8.91 days after a single IV dose of 1 mg/kg (13-2135), and for mosunetuzumab $t_{1/2}$ ranged from 4.21-5.95 days when dosed at 0.01-0.1 mg/kg (13-2298, 17-3165). Volume of distribution (V_{ss}) was determined from three IV single-dose studies with either mosunetuzumab (13-2298, 17-3165) or 2H7v16/40G5c (13-2135) and one repeat-dose study with 2H7v16/40G5c (13-2134) and ranged from 76.5-94.5 ml/kg in animals dosed at 1 mg/kg and from 120-225 ml/kg in animals dosed from 0.001-0.1 mg/kg. V_{ss}-values were greater than estimated serum volume of cynomolgus monkeys, most likely due to specific binding of mosunetuzumab to its target cells.

Repeat-dose IV/SC studies

A series of three initial repeat-dose studies was conducted with 2H7v16/40G5c (12-3160, 13-1689, 13-2134). In an initial four-week dose-range-finding toxicity study with 2H7v16/40G5c (12-3160) in cynomolgus monkeys, the frequency of ADA-formation was high in low-dose groups (≤0.1 mg/kg), and markedly impacted serum exposure beyond the second dose. Consequently only 1/8 animals dosed ≤0.1 mg/kg were able to maintain exposure throughout the dosing phase compared to 7/8 animals dosed 1 mg/kg. Further, exposure was confirmed throughout the recovery phase (7 weeks) in all animals dosed 1 mg/kg, although they progressively declined in 3 ADA-positive animals past Day 63. Serum exposure parameters increased with dose, and was greater than dose-proportional in the range of 0.1-1 mg/kg when comparing AUC_{0-7} where exposure profiles were least affected by ADA. Based on the high frequency of ADAs observed ≤0.1 mg/kg in study 12-3160, the following two repeat-dose studies with 2H7v16/40G5c (13-1689, 13-2134) incorporated only the high dose (1 mg/kg). In these two studies, ADA-formation was still observed, but exposure was maintained for the duration of the studies (four weeks) in the majority of animals, when dosed either IV or SC at 1 mg/kg. Across all repeat-dose studies conducted with 2H7v16/40G5c, moderate accumulation was observed after multiple dosing with accumulation ratios ranging from 1.96-3.57 in animals dosed at 1 mg/kg, probably indicating a lesser impact of target-mediated clearance over time (correlating with B-cell depletion).

Following the initial repeat-dose studies with 2H7v16/40G5c, a 25-day pilot repeat-dose toxicity study (16-2088) and a pivotal GLP 26-week toxicity study were conducted with mosunetuzumab. In the 25-day pilot toxicity study, it was evaluated whether IV step-up dosing could minimize first dose-associated cytokine release and adverse events, while avoiding ADA-formation to enable long-term dosing in the subsequent pivotal GLP 26-week repeat-dose study (16-1815). After splitting of the 1 mg/kg dose into a 0.2 and 0.8 mg/kg administered at Day 1 and 2, respectively, animals were dosed once-weekly at 0.3, 1 or 3 mg/kg from day 8-22. In all animals, exposure was maintained until end of study, and although ADA-formation was detected in some animals, it appeared to have little impact on exposure, even in the low target-dose group (0.3 mg/kg). Further, the split-dose approach (16-2088 and 16-1815) did not appear to influence exposure parameters notably within the first week of dosing when comparing to single IV infusion of 1 mg/kg (14-1246). Due to convulsions in one animal dosed at 0.2/0.8/1 mg/kg on Days 1, 2 and once-weekly from Day 8, respectively, the maximum tolerated once-weekly target-dose from this study was set at 0.3 mg/kg. Consequently, similar step-up doses and regimen with reduced once-weekly target-doses (0.1 and 0.5 mg/kg) were subsequently carried forward to the GLP 26-week toxicity study.

In the pivotal 26-week GLP toxicity study (16-1815), exposure was maintained in 7/7 animals in the 0.5 mg/kg target-dose group, and in 4/7 surviving animals past TK Day 84 in the 0.1 mg/kg group. ADA was detected in 5 of 8 animals in Group 2 (0.1 mg/kg) and in 4 of 8 animals in Group 3 (0.5 mg/kg) dosed with mosunetuzumab. Exposure appeared to be lower in ADA-positive animals in Group 2 (0.1 mg/kg), while exposure was not consistently impacted in ADA-positive animals in Group 3 (0.5 mg/kg). Exposure (C_{max} and AUC) increased with an increase in dose from 0.1-0.5 mg/kg, and the increase was greater than dose-proportional when evaluated at steady state conditions (TK Day 175-182). When comparing dose-normalized C_{max} and AUC-values from TK day 0-3 (1 mg/kg) and TK day 182-185 (0.1 or 0.5 mg/kg), exposure was shown to increase over time and was, as such, maintained throughout the 26 weeks of the study.

ADA-formation and impact on non-clinical exposure parameters

Generally, across early PK/TK studies in cynomolgus monkeys, there were high frequencies and titres of ADA following single- and repeat-dosing of mosunetuzumab or 2H7v16/40G5c which in some animals affected exposure, especially at doses below 1 mg/kg where incomplete B-cell depletion was observed. As such, it appeared that a dose of 1 mg/kg was needed to achieve rapid and complete B-cell depletion in order to prevent ADA development and thereby maintain drug exposure in long-term studies. Further, to mitigate cytokine release syndrome (CRS)-like acute toxicities associated with a single dose of 1 mg/kg, a step-up dosing approach was used in a repeat-dose pilot study (16-2088) and in the subsequent GLP-compliant pivotal repeat-dose study with mosunetuzumab in cynomolgus monkeys (16-1815). The step-up dosing approach appeared to mitigate CRS-like acute toxicities and ADA-related effects on exposure, and overall, it is considered acceptably established that exposure was adequately maintained in pivotal toxicity studies to evaluate toxicology and PD effects of mosunetuzumab, despite the occurrence of ADA. The drug tolerance threshold for the validated anti-mosunetuzumab assay was 3.13 µg/mL mosunetuzumab (able to detect 1000 ng/mL ADA). Trough concentrations in the high-target once-weekly dose (0.5 mg/kg) in repeat-dose GLP study 16-1815 were above this threshold, however exposure did not seem significantly affected in neither ADA-positive nor ADA-negative animals of this group, and as such this is not expected to have influenced overall results.

Interspecies comparisons of human exposure levels to established Cmax and AUCs from repeat-dose toxicity studies at the Lowest-Observed-Adverse-Effect-Level (LOAEL) are addressed in the toxicology section.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Single-dose toxicity of 2H7v16/40G5c or mosunetuzumab was assessed in three studies in cynomolgus monkeys, at doses of 0.01, 0.1, 1 mg/kg IV or 1 mg/kg SC and observation periods of 7 days, 28 days or 7 weeks (GLP-study, 14-1246). No test-article-related deaths were observed in any of the studies, and toxic findings were overall similar between studies.

Observed toxicities in GLP-study 14-1246 were largely attributed to a dose-dependent release of cytokines which occurred 2-6 hours post-dosing and returned to baseline values at 24 hours post-dose. Clinical signs were limited to the 1 mg/kg dose (IV) and included emesis, reduced appetite, hypoactivity, watery/mucoid feces and in a few cases hypothermia. There were transient and reversible changes in clinical pathology, cardiovascular parameters and body temperature which were considered consistent with, and secondary to mosunetuzumab-induced cytokine release and acute phase protein reactions. Microscopic findings were present in lymphoid tissues (consistent with expected PD effects), the liver and CNS. CNS-related findings included slight to minimal perivascular infiltrates of eosinophils with associated microgliosis in 2 females administered 1 mg/kg IV and 1 male and 1 female administered 1 mg/kg SC one week after dosing. These changes were not considered adverse as they were present at a frequency and severity that would not be expected to result in any clinical signs, and there was no associated astrocytosis or neuronal changes. Standard neurological examination revealed no drug-related findings. No findings were present in the CNS on Days 22 or 57 in the GLP-study.

SC-dosing appeared to be better tolerated than IV-infusion at 1 mg/kg, with no clinical signs or decreases in blood pressure observed in animals dosed SC. These findings seem consistent with the observed decreased exposure, and delayed t_{max} after SC dosing, and the associated reduction and delay of cytokine release in this group.

2.5.4.2. Repeat dose toxicity

Mosunetuzumab and 2H7v16/40G5c were investigated after repeated dosing up to 26 weeks in cynomolgus monkeys following IV administration (slow bolus injection (½-1 min) or infusion (1h)) or SC injection. The main findings were acute toxicities related to cytokine-release syndrome (CRS) primarily attributed to the first dose, vascular/perivascular inflammatory cell infiltrates mainly observed in the CNS and increased susceptibility to infection following chronic dosing. All observed toxicities could be related to the pharmacological mode of action, namely cytokine release following T-cell activation and B-cell depletion.

Microscopic findings of vascular/perivascular inflammatory cell infiltrates were present primarily within the brain but also infrequently in other organs and were observed in all the repeat dose studies at target dose levels from 0.1 mg/kg and above. A tendency for dose-dependency was observed with increase in incidence and severity and the findings in the brain were accompanied with local microglial reaction. However, no neuronal degeneration was observed and the findings were considered reversible in recovery animals. Convulsions were observed in one animal on day 11 following dosing of 0.2/0.8/1 mg/kg on day 1/2/8, respectively, in Study 16-2088. CNS microscopic findings were more severe in this animal than observed in other animals. The Applicant noted the uncertainty regarding the etiology of the CNS vascular/perivascular inflammatory cell infiltration. However, it was hypothesized that the effects could be secondary to cytokine/chemokine-induced up-regulation of chemokine receptors and adhesion molecules in the vessels of the brain and immune cell activation, margination, and transmigration. In the single dose study, minimal hepatocellular degeneration and single-cell hepatocyte necrosis was observed which was associated with minimal increases in ALT/AST at 1 mg/kg while transient increases in ALT/AST was observed following repeated dosing. The Applicant notes that the hepatotoxic findings

may be due to cytokine-mediated hepatocyte damage. Minimal activation of the coagulation system with increases in APTT and PT was also observed after repeated dosing at ≥0.2 mg/kg, which is furthermore indicated as a CRS-related acute toxicity. Changes in lymphoid tissue and bone marrow as well as increased susceptibility to infections, as observed in the 26-week study where 2 animals had to be euthanized due to moribund condition, is considered to occur secondary to the pharmacological effect of B-cell depletion.

To elucidate the CRS-related findings and observations that may occur secondary to CRS, a step-up dosing approach using a split of the first dose over the first two days (i.e. 0.2 and 0.8 mg/kg on day 1 and 2, respectively) was investigated with the aim to mitigate the CRS-related effects. It was found that step-up dosing alleviated some of the effects of CRS (i.e. hypotension) as cytokine release was reduced, while formation of ADA was partially mitigated, ensuring exposure in test animals. The maintenance of exposure in animals has been extensively discussed in the pharmacokinetic section, and it is considered that exposure has been sufficiently demonstrated in the repeat dose studies in spite of the ADA formation in cynomolgus monkeys.

As an alternative to step-up dosing, SC administration was investigated in relation to mitigating CRS effects and ADA formation. It was shown that exposure (Cmax) was significantly reduced by 72-80% with a corresponding reduction in cytokine levels and T-cell activation while still maintaining depletion of B cells. Further, findings of CRS-related clinical signs were minimal while hypotension was not observed and the incidence of CNS vascular/perivascular findings were reduced. Though it appears that SC administration may lead to a lesser incidence of CRS-related acute effects, note should be taken of the low number of animals tested, inter-animal variation and the mild degree of findings across dose groups.

As CRS related effects were observed at all dose levels, a LOAEL was derived for all studies at the lowest dose levels resulting in an overall LOAEL of 0.01 mg/kg/day in cynomolgus monkeys.

2.5.4.3. Genotoxicity

Genotoxicity studies have not been conducted (see discussion on Non-clinical aspects).

2.5.4.4. Carcinogenicity

Carcinogenicity studies have not been conducted (see discussion on Non-clinical aspects).

2.5.4.5. Reproductive and developmental toxicity

Male and female fertility was investigated as part of the 26-week GLP study in cynomolgus monkeys. No mosunetuzumab-related findings were observed in male and female reproductive endpoints up to the highest dose tested (0.5 mg/kg) at exposures (AUC) similar to exposure (AUC) in patients receiving the recommended dose.

In line with the ICH S9 guideline, no studies investigating the effect of mosunetuzumab on fertility and early embryonic development (FEED) or pre- and postnatal toxicology (PPND) were performed (see discussion on non-clinical aspects).

2.5.4.6. Toxicokinetic data

In order to perform an interspecies comparison, a normalization of the exposure data in cynomolgus monkeys and humans were carried out. To achieve a 0-24 h corrected AUC-value, AUC_{last} was divided by the duration of the study for each repeat-dose study as well as the $AUC_{0\text{-}42d}$-value reported for humans (Study GO29781 Interim CSR report 1106874, Table 35).

When applying the corrections of AUC, estimations of exposure multiples resulted in values of 0.008 to 1.84, implying that CRS related effects and immunosuppression leading to infections occur at clinically relevant dose levels. The same results are approximately achieved when comparing Cmax in cynomolgus monkeys with humans (i.e. exposure multiples of 0.01 to 1.66). A more comprehensive discussion of the approach for deriving LOAELs and establishing exposure multiples has been included in the Discussion section in the Overview document.

An occurrence of convulsion as well as extensive clinical findings was reported in one animal at 1 mg/kg in Study 16-2088, corresponding to C_{max} and $AUC_{0\text{-}7d}$ values of 22.9 µg/ml and 37.6 day*µg/ml. The Applicant was asked to provide amended calculations of exposure multiples based on time-normalized AUC and Cmax values in animals using the clinical exposure data for $C_{maxCYCLE4}$ (7.02 µg/mL) and for $AUC_{0\text{-}42}$ (125.7 µg/mL) at the recommended therapeutic dosage regimen of mosunetuzumab of 1/2/60/30 mg. For the calculated exposure margin based on AUC, the AUC values were normalized by their respective collection periods, yielding an average concentration of 5.37 µg/mL (37.6 µg/mL*day/7 days) in the convulsive animal and 2.99 µg/mL (125.7 µg/mL*day/42 days) in the typical patient at the recommended dose. The calculated exposure margin based on AUC and Cmax is 1.80 and 3.26 (22.9 µg/mL/7.02 µg/mL), respectively.

2.5.4.7. Local Tolerance

Local tolerance was evaluated as part of the single or repeat dose GLP studies following IV or SC administration in cynomolgus monkeys. No changes were observed that indicated local intolerance concerns.

2.5.4.8. Other toxicity studies

The formation of anti-drug antibodies (ADA) has been investigated as part of the pharmacology and toxicological studies and has been thoroughly discussed in the sections above. Overall, the interpretation of the data from the PD and toxicology studies are not considered to be compromised by potential ADA formation. No ADA formation has been observed in patients in the clinical studies.

Mosunetuzumab exerts its pharmacological action via B-cell killing, thus inducing immunosuppression. This has been observed in the general toxicity studies in cynomolgus monkeys, as microscopic evidence of ascending urinary tract infection has been observed as well as clinical changes related to inflammation. The Applicant conducted an in vitro binding assay for human Fcγ receptors, where mosunetuzumab showed minimal detectable binding to the Fcγ receptors tested. This is expected due to the mutation introduced in the N297 residue in the Fc binding region which results in aglycosylation and minimal capability of binding to effector cells via this region. Thus, mosunetuzumab appears to have a low potential for Fcγ receptor cross-linking on immune cells leading to induction of nontargeted immune cell activation (e.g. ADCC and ADCP). Further, binding to C1q was shown to be minimal and thus mosunetuzumab is not expected to induce complement-dependent cytotoxicity.

Monoclonal antibodies have limited penetration across the blood-brain barrier due to the size of the molecule. Further, no evidence of off-target binding related to CNS effects have been observed for mosunetuzumab and no evidence to suggest affected behaviour or activity patterns have been observed in general toxicity studies in cynomolgus monkeys. Though histopathological finding of perivascular/vascular inflammatory cell infiltration in the CNS has been observed, this is considered related to pharmacologically mediated cytokine release, and the weight of evidence indicates that mosunetuzumab has a low likelihood for abuse potential.

The active substance and drug product are generally well controlled at production level and potential process derived impurities are cleared to low levels. Thus, no impurities have been identified that are of toxicological concern

2.5.5. Ecotoxicity/environmental risk assessment

Mosunetuzumab is exempted from ERA studies (see discussion on non-clinical aspects).

2.5.6. Discussion on non-clinical aspects

The pharmacology of mosunetuzumab was thoroughly described in the provided non-clinical package. Mosunetuzumab showed minimal detectable binding to the Fcγ receptor tested, expectedly due to the mutation introduced in the N297 residue in the Fc binding region, resulting in aglycosylation and minimal capability of binding to effector cells via this region. As such, it appears there is a low potential for mosunetuzumab to induce nontargeted immune cell activation (e.g., ADCC and ADCP), via Fcγ receptor cross-linking on immune cells. Further, limited binding affinity of mosunetuzumab to C1q was shown and therefore, mosunetuzumab is considered of low potential to elicit activation of the complement system and trigger complement-dependent cytotoxicity (CDC).

Mosunetuzumab is produced from Chinese hamster ovary (CHO) cells; the functionally equivalent antibody, referred to as 2H7v16/40G5c and the proof-of-concept (POC) molecule, referred to as 2H7v16/UCHT1v9, were produced from E. coli. 2H7v16/40G5c displays the same properties as mosunetuzumab, as it cross-reacts with CD20 and CD3 in both humans and cynomolgus monkeys, but not in rodents. 2H7v16/40G5c lacks the N297G substitution in the Fc region, however, as it is produced from E. coli it is aglycosylated. The proof -of -concept molecule, 2H7v16/UCHT1v9, is also aglycosylated. However, where its CD20 arm (2H7v16) is the same as for the two other molecules and therefore binds human and monkey CD20, its CD3 arm (UCHT1v9) is different from the two other molecules and only binds human CD3.

Overall, the pharmacokinetics of mosunetuzumab or 2H7v16/40G5c were well-described, while extensive ADA formation was observed in cynomolgus monkeys.

The design of the TK studies with varying points of measurement as well as the step-up dosing approach for studies 16-2088 and 16-1815, somewhat complicated the possibility to compare data and assess exposure multiples in the nonclinical studies for comparison with human exposure values. It was decided to derive LOAELs on basis of the findings in the nonclinical toxicology studies at the lowest tested dose levels, as the effects occurred at all dose levels and were considered to be relevant toxic observations, though they were observed as secondary to pharmacological effects (i.e. B-cell depletion and CRS). These effects are also observed in the clinic and CRS has been included in the RMP as an important identified clinical risk. To obtain normalised exposure values relevant for interspecies comparison of exposures (at the LOAELs derived by the assessor), $AUC_{0\text{-}24h}$ was derived based on normalization of the AUC_{last} value (AUC_{last} value divided by the duration of the study in days), as it was assessed that this normalization would relay the most appropriate exposure values in order to facilitate a meaningful interpretation of exposure multiples. On the basis of the chosen approach, exposure multiples below or around approximately 1 were obtained for all studies indicating that the findings were observed at human relevant dose levels. These findings are all well-known effects in the clinic and are adequately described in the SmPC and have been discussed regarding human relevance in the RMP.

An occurrence of convulsion as well as extensive clinical findings was reported in one animal at 1 mg/kg in Study 16-2088, corresponding to exposure margins based on AUC and Cmax of 1.80 and 3.26, respectively. Thus, the nonclinical observation of convulsion in the animal from study 16-2088 occurs in the range of clinically relevant dose levels. Neurological adverse events are considered a potential risk

for patients being treated with mosunetuzumab and the finding has been included correspondingly in the SmPC section 5.3 and the RMP Part II module SII.

No data on genotoxicity or carcinogenic potential has been submitted, which is accepted as mosunetuzumab is a biotechnology-derived product (guideline ICH S6).

In line with the ICH S9 guideline, no studies investigating the effect of mosunetuzumab on fertility and early embryonic development (FEED) or pre- and postnatal toxicology (PPND) were performed. The Applicant submitted a waiver for not performing the embryofetal (EFD)/ enhanced (e)PPND study with mosunetuzumab, providing an extensive discussion of known class effects on pregnancy of anti-CD20 monoclonal antibodies (i.e. rituximab, obinutuzumab and ocrelizumab), which have been investigated in (e)PPND or EFD studies as well as the observed effects of mosunetuzumab in nonclinical and clinical studies. Common for the anti-CD20 monoclonal antibodies is the pharmacologic effect of B-cell depletion in dams and the offspring observed consistently across programs in animal studies, which was reversible upon drug washout.

While it has been shown that mosunetuzumab also depletes B cells as part of the pharmacological action, increasing the incidence of opportunistic infection secondary to B-cell depletion following long-term dosing, mosunetuzumab also exerts its pharmacological action via transient T-cell activation and cytokine release primarily following the first dose. As already discussed above, the cytokine release results in acute adverse reactions such as vomiting, diarrhea, hypoactivity/hunched posture, hypotension, tachycardia, fever, acute phase protein reactions, leukocyte margination, and minimal liver injury in cynomolgus monkeys, which may have a negative impact during pregnancy. Further, it appears that cytokines may be involved in establishing and maintaining pregnancy, thus potentially resulting in foetal loss when the cytokine levels are affected during the early period of pregnancy. Taken together, the toxicities associated with T cell activation and cytokine release as well as B-cell depletion may pose a risk to the maintenance of early pregnancy.

Based on the justification provided by the Applicant, and in accordance with ICH S6 (R1) it is agreed that no further testing is required in order to elucidate the reproductive toxicity of mosunetuzumab in cynomolgus monkeys, as it is not likely it will add further information to the current nonclinical and clinical knowledge to support the mitigation of this risk in humans. It is considered that mosunetuzumab should not be used during pregnancy in humans due to the identified risks, which has been adequately reflected in the SmPC section 4.6 and 5.3.

Mosunetuzumab is not expected to pose a risk to the environment, as the proteolytic breakdown of monoclonal antibodies will not alter the concentration or distribution of the substance in the environment.

Overall, the nonclinical safety and efficacy profile seems well documented in the submitted nonclinical dossier, which supports the findings in the clinic. The identified nonclinical risks have been discussed regarding human relevance and follow-up measures in patients have been proposed as relevant.

Assessment of paediatric data on non-clinical aspects

Not applicable

2.5.7. Conclusion on the non-clinical aspects

An adequate program of *in vitro* and *in vivo* pharmacology was conducted for mosunetuzumab, including in disease models, supporting the intended clinical use of mosunetuzumab. Pharmacokinetics of mosunetuzumab and 2H7v16/40G5c were well described. Toxicology was investigated sufficiently. Relevant information has been reflected in the SmPC.

The active substance being a monoclonal antibody is a natural substance, the use of which will not

alter the concentration or distribution of the substance in the environment. Therefore, mosunetuzumab is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The study GO29781, which was the single study included in this submission, was performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1: Tabular overview of clinical studies

Study No. (Phase)	Study Design, Control Type	Population	No. of Patients	Dose, Route, and Regimen[b]
Study GO29781 (Phase I/Ib [(Phase I/II per protocol v12])	Multicenter, open-label, dose escalation and expansion study; single arm: mosunetuzumab as a single agent and mosunetuzumab in combination with atezolizumab[a]	Patients with R/R B-cell NHL or CLL[a]	443 enrolled into mosunetuzumab IV monotherapy cohorts (Group A and Group B escalation + expansion); 214 were treated at RP2D/intended registration dose, of which 90 were patients with FL. Study is ongoing with continuing recruitment into cohorts in Group F, as well as the Richter's transformation expansion cohort in Group B. Patients contributing to the efficacy evaluation of mosunetuzumab monotherapy IV in R/R FL: 90 R/R FL treated at RP2D/intended registration dose of 1/2/60/30 mg (B11); 46 R/R FL patients treated at the next (lower) dose level of 1/2/13.5 mg (including 44 patients in the B7 interim expansion cohort, and 2 patients in the B7 dose escalation cohort)	Group A: Cycle 1 non-fractionated single-agent mosunetuzumab escalation in patients with mixed NHL histologies, IV infusion q3w, fixed dose range from 0.05 to 2.8 mg; Group B: Cycle 1 step-up single-agent mosunetuzumab escalation, IV infusion in patients with mixed NHL histologies, dose range from C1D1 0.4 mg/ C1D8 1 mg/ C1D15 2.8 mg to C1D1 1 mg/ C1D8 2 mg/ C1D15 60 mg; Expansion cohorts in R/R FL who received ≥2 Prior Therapies patients, Cycle 1 step-up single-agent mosunetuzumab escalation, IV infusion: • B11 cohort (RP2D/intended registration dose): C1D1 1 mg/ C1D8 2 mg/ C1D15 and C2D1 60 mg/ C3D1+ 30 mg; • B7 interim cohort: dose C1D1 1 mg/ C1D8 2 mg/ C1D15 13.5 mg; Expansion cohorts in R/R DLBCL/trFL, R/R MCL and R/R Richter's Transformation; Cycle 1 step-up single-agent mosunetuzumab escalation, IV infusion, B11 cohort (RP2D dose): C1D1 1 mg/ C1D8 2 mg/ C1D15 and C2D1 60 mg/ C3D1+ 30 mg.

CLL=chronic lymphocytic leukemia; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; MCL=mantle cell lymphoma; NHL=non-Hodgkin's lymphoma; q3w=every 3 weeks; RP2D=recommended Phase II dose; R/R=relapsed/refractory; trFL=transformed follicular lymphoma.

[a] No patients with CLL have been enrolled to date.

[b] Patients receiving subcutaneous (SC) treatment and combination treatment with atezolizumab (Groups D, E and F) are not included in this submission. Group D: Cycle 1 non-fractionated single-agent mosunetuzumab escalation, SC injection; Group E: Cycle 1 step-up single-agent mosunetuzumab escalation with concurrent administration of atezolizumab starting in Cycle 2, IV infusion; Group F: Cycle 1 step-up single-agent mosunetuzumab escalation, SC injection. Dose-Expansion Stage: Single-Agent Mosunetuzumab Dose-Expansion in NHL.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Table 2 Schedule of PK assessments in study GO29781

	PK Sample Timepoints [a]
Group A	Cycle 1: Day 1 (predose, end of infusion, 2 h post-infusion), 24 h, 48 h, 72 h, Day 8, Day 15. Cycles 2, 3, 4, 6, and 8: Day 1 (predose, end of infusion, 2 h post-infusion), Day 8. Cycles 12 and 16: Day 1 (predose). And the follow-up visit.
Group B Dose-Escalation and Expansion (dense)	Cycle 1: Day 1 (predose, end of infusion, 2 h post-infusion), Day 2, and Day 4; Day 8 (predose, end of infusion, 2 h post-infusion), Day 9, Day 11, Day 15 (predose, end of infusion, 2 h post-infusion), Day 16, and Day 18. Cycles 2, 3, 4, 6, and 8: Day 1 (predose, end of infusion, 2 h post-infusion) and Day 8. Cycles 12 and 16: Day 1 (predose). And the follow-up visit.
Group B Dose-Escalation and Expansion (sparse)	Cycle 1: Day 1 (predose, end of infusion, 2 h post-infusion), Day 8 (predose, end of infusion) and Day 15 (predose, end of infusion). Cycles 2, 3, 4, 6, and 8: Day 1(predose, end of infusion, 2 h post-infusion) and Day 8. Cycles 12 and 16: Day 1 (predose). And the follow-up visit.

h=hours; post-infusion= post the end of infusion; infusion duration is 4 hours for the first dose and 2 hours for the remaining doses.

[a] Day 1 is considered the first day of drug administration.

The serum pharmacokinetics of mosunetuzumab was characterized based on clinical PK data from 439 PK-evaluable patients from Study GO29781 who received mosunetuzumab by IV administration; specifically, 32 patients from Group A cohorts who received doses ranging from 0.05 to 2.8 mg q3w, and 407 patients from Group B step-up dosing cohorts who received doses ranging from 0.4/1.0/2.8 mg to 1.0/2.0/60 mg including 1.0/2.0/60/30 mg.

The PK-evaluable population included all enrolled patients (in Groups A and B) who received at least one dose of the study drug (mosunetuzumab IV monotherapy) and who had at least one measurable PK sample collected until the PK cut-off date of 4 December 2020.

Methods

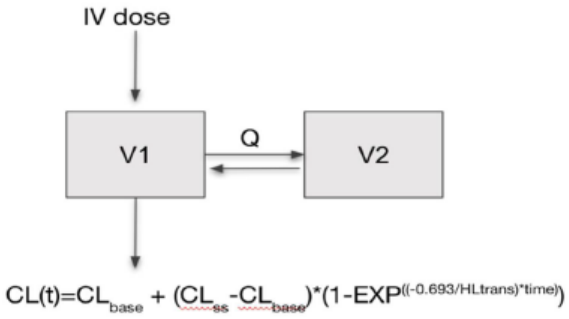
Quantification of mosunetuzumab serum levels in clinical studies was performed using a validated ELISA method. Anti-drug antibodies (ADAs) to mosunetuzumab in human serum were determined using a validated bridging ELISA assay and a 3-tiered screening, confirmation and titer determination approach.

Non-compartmental methods were used to estimate mosunetuzumab PK parameters using Phoenix WinNonlin. The population analyses and simulations were performed in the nonlinear mixed-effects modeling software NONMEM using the first-order condition estimation method with interaction. The Simcyp population-based ADME simulator was used for development of an IL-6 PBPK model.

Population PK analyses

Population PK analysis was conducted using 7259 mosunetuzumab concentrations from 439 PK-evaluable patients with R/R NHL in Study GO29781 who had received at least two prior systemic therapies. Mosunetuzumab was IV administered using either a fixed q3w dose (Group A) or step-up dosing cohorts receiving doses ranging from 0.4/1.0/2.8 mg to 1.0/2.0/60/30 mg (Group B). The number of excluded samples including BLQ samples were <10% of total.

Figure 4 Population PK model schematic



CL= clearance; CL_{SS} = steady state clearance; CL_{base} = initial baseline clearance; HL_{trans}=half-life for transition time from CL_{base} to CL_{SS}; IV= intravenous; Q= intercompartmental clearance; t=time; V1= central volume of distribution; V2= peripheral volume of distribution.

The final Pop PK model was two-compartmental with time-varying CL and additive residual error. IIV was included on all parameters except for Q. Covariates included were: sex on CLss (12.8% lower in female subjects) and V1 (12.6% lower in female subjects), albumin on both CLbase and V1, aCD20 drug concentration on CLbase and tumor burden on CLss. Body weight was included using allometric scaling with estimated effect on CLss, V1, and V2. Covariance was observed for CLbase-V1 and CLss-HLtrans. None of the significant covariates are considered to have clinically relevant effect on mosunetuzumab exposure (AUC0-42).

Table 3 Parameter estimates for the final PK model

Parameter	Estimate	% RSE	95% CI	Shrinkage (%)
CL_{base} (L/day)	1.08	5.6	[0.962;- 1.20]	–
V_1 (L)	5.49	2.5	[5.221 ; 5.76]	–
CL_{ss} (L/day)	0.584	2.0	[0.561 ; 0.607]	–
HL_{trans} (day)	16.3	7.1	[14.026 ; 18.6]	–
V_2 (L)	6.17	3.6	[5.729 ; 6.61]	–
Q (L/day)	1.46	3.7	[1.354 ; 1.57]	–
Body weight on CL_{ss}	0.549	10.5	[0.436 ; 0.662]	–
Body weight on V_1	0.433	13.4	[0.319 ; 0.547]	–
Body weight on V_2	0.737	15.9	[0.508 ; 0.966]	–
Albumin on CL_{base}	-1.51	19.1	[-2.074 ; -0.946]	–
aCD20 drug on CL_{base}	-0.573	20.2	[-0.8 ; -0.346]	–
Sex (female) on CL_{ss}	-0.128	18.8	[-0.175 ; -0.081]	–
Albumin on V_1	-0.481	23.3	[-0.701 ; -0.261]	–
Sex on V_1	-0.126	18.9	[-0.173 ; -0.079]	–
Tumor burden on CL_{ss}	0.0935	26.6	[0.045 ; 0.142]	–
IIV on CL_{base} (ω^2_{CLbase}, variance)	0.426	8.4	[0.356 ; 0.496]	4.8
CL_{base}-V_1 covariance ($\omega_{CLbase,CLss}$)	0.180¥	7.3	[0.169 ; 0.191]	–
IIV on V_1 (ω^2_{V1}, variance)	0.0981	5.8	[0.0722 ; 0.124]	4.6
IIV on CL_{ss} (ω^2_{CLss}, variance)	0.0343	11.5	[0.0266 ; 0.0420]	33.8
CL_{ss}-HL_{trans} covariance ($\omega_{CLSS,HL_{trans}}$)	-0.0892γ	24.8	[-0.133 ; -0.0459]	–
IIV on HL_{trans} ($\omega^2_{HL_{trans}}$, variance)	0.739	15.8	[0.510 ; 0.968]	40.9
IIV on V_2 (ω^2_{V2}, variance)	0.0621	16.7	[0.0417 ; 0.0825]	49.9
Residual variability (additive on log scale)**	0.259	0.257	[0.258 ; 0.260]	–
Objective function value	-9853.132			

CL_{base} = clearance at baseline; CL_{ss} =clearance at steady state; HL_{trans} = transition half-life for CL_{base} to CL_{ss}; IIV = interindividual variability; Q= intercompartmental clearance; V1= central volume of distribution; V2=peripheral volume of distribution.

*Calculated asymptotically from NONMEM-provided standard errors.

**Corresponds to proportional on normal scale.

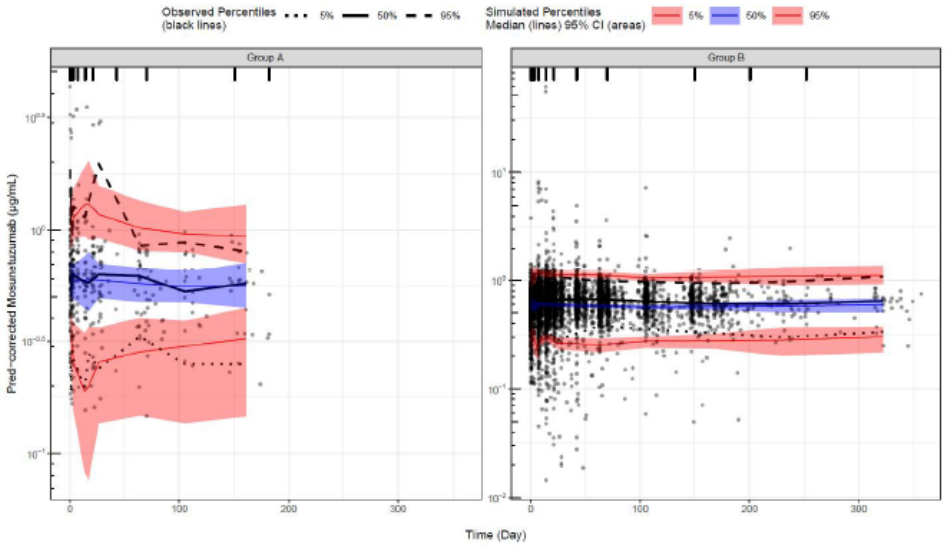
¥ correlation is 0.882.

γ correlation is -0.560.

Terminal beta half-lives for the PK system were derived using the individual PK parameters of CLbase, Q, V1, and V2 for HLbase, and CLss, Q, V1, and V2 for HLss. Geometric mean half-lives were estimated to 9.64 and 16.1 days for HLbase and HLss, respectively. Thus steady-state would be achieved by Cycle 4. Relative high inter-individual variability was observed for CLbase (CV=63%) and HLtrans (CV=86%) compared with CLss (CV=18%), V1 (CV=31%) and V2 (CV=25%). High shrinkage was observed for CLss and HLtrans (34% and 41%) with minimal impact since the E-R analyses were in close agreement to observed data.

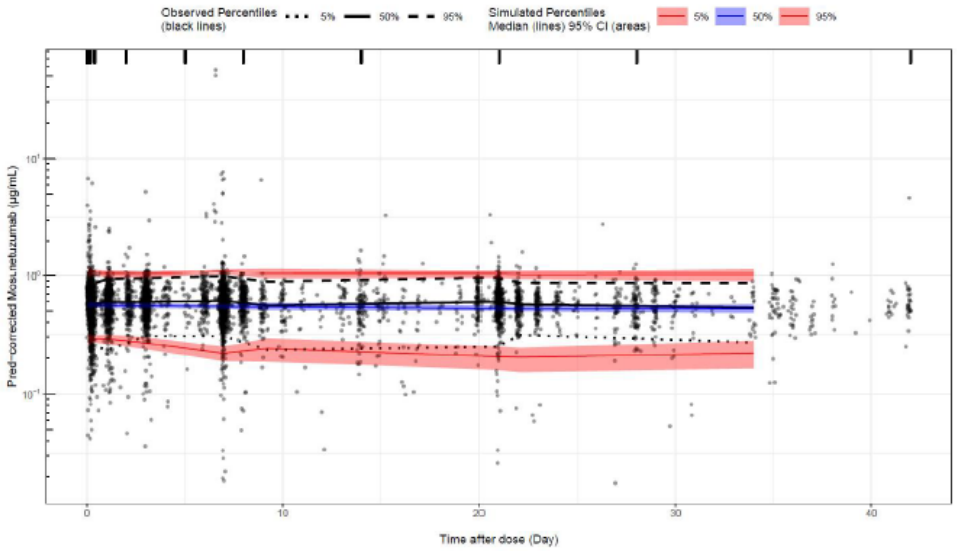
Simulation-type diagnostics, such as visual predictive checks (VPCs), were performed to assess the model predictive performance. The model demonstrated good predictive performance with observed data included within the predicted 95% CIs of predictions, throughout the study.

Figure 5 VPCs for the final PK model (prediction -corrected, full-time course, by cohort)



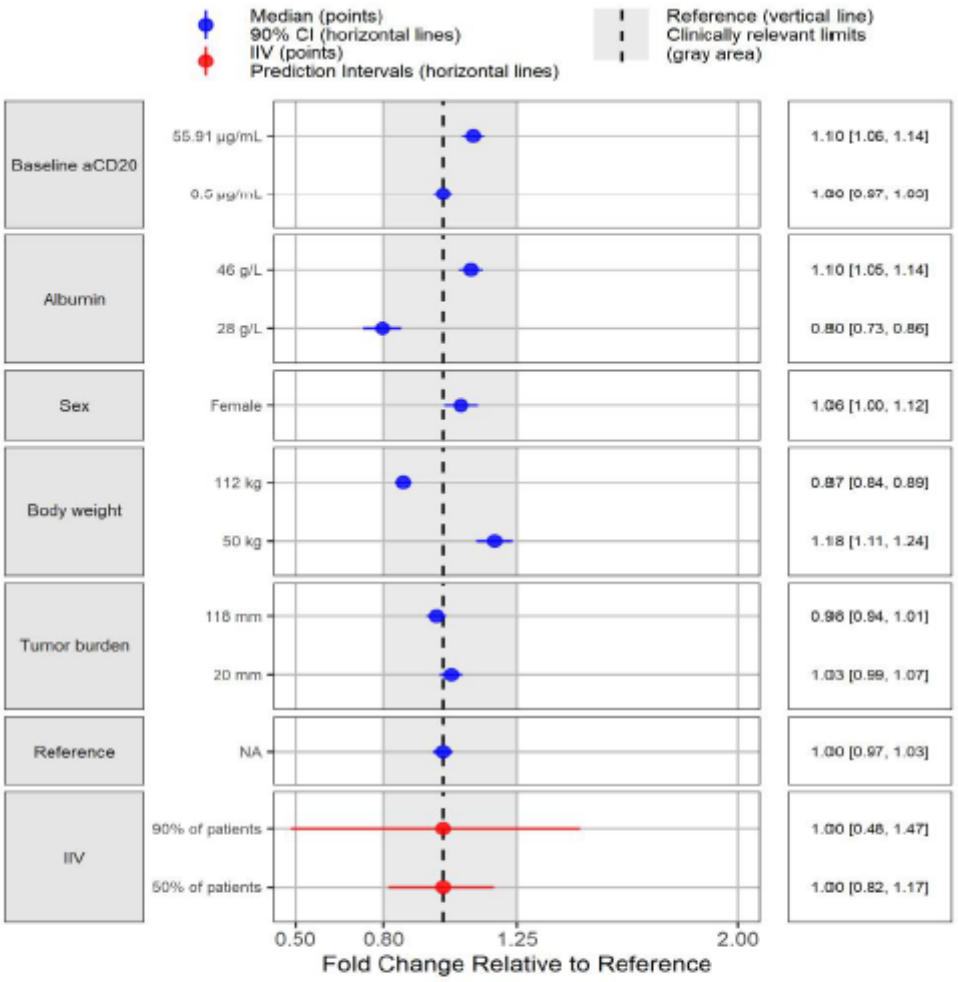
Points are observations. Solid red lines are medians of observations (by bin). Dashed and dotted red lines are upper and lower limits of the 95% intervals for the observations (by bin). Shaded red area in the 95% CI for the simulated median (by bin). Shaded red areas are 95% CIs for the upper and lower limits of the 95% prediction interval for the simulations (by bin).

Figure 6 VPCs for the final PK model (prediction -corrected, time after dose)



Points are observations. Solid black lines are medians of observations (by bin). Dashed and dotted black lines are upper and lower limits of the 95% intervals for the observations (by bin). Solid blue lines are medians of simulations (by bin). Solid red lines are upper and lower limits of the 95% intervals for the simulations (by bin). Shaded blue area in the 95% CI for the simulated median (by bin). Shaded red areas are 95% CIs for the upper and lower limits of the 95% prediction interval for the simulations (by bin).

Figure 7 Forest plot of covariate effects on mosunetuzumab PK exposure (i.e. AUC0-42)



aCD20= anti-CD20 drug, specifically Rituximab (R) and Obinutuzumab (G); AUC_{0-42}= cumulative area under the curve from Day 0 to Day 42; CI= confidence interval; IIV= interindividual variability.
Final model estimate, as represented by the black vertical line and value, refers to the predicted steady-state exposure of mosunetuzumab at 1/2/60/30 mg in a typical patient with covariates equal to medians. The typical patient is a male, weighing 78 kg, with an albumin level of 39 g/L, aCD20 drug concentration 0.5 µg/mL and a tumor burden of 54.5 mm (note the unit for tumor burden was redefined as the square root of the tumor sum of product diameter (SPD) for covariate modeling). Grey areas represent a change from the reference. Each horizontal bar represents the influence of a single covariate on the AUC_{0-42}. The label at left end of the bar represents the covariate being evaluated with values on the right end of the 5th and 95th percentiles of the covariate distribution. The length of each bar describes the potential impact of that particular covariate on mosunetuzumab exposure, with the percent change of exposure from the base.

Exposure-response methods

The following exposure endpoints were output by the popPK model for subsequent use in the ER modeling of mosunetuzumab:

- Mosunetuzumab Area Under the Curve
- Mosunetuzumab Receptor Occupancy
- Prior aCD20 Therapy
- Cycle 4 AUC, cycle 8 AUC,
- Cmax at Day 63, Day 84. Day 147, Day 168.

Prior treatment with aCD20 drugs e.g. rituximab or obinutuzumab have confounding effects on mosunetuzumab exposure/RO due to a high affinity for the CD20 binding site. Exposure metrics intended

for evaluation of E-R relations were generated using EBEs from the final Pop PK model with aCD20 drug concentration included as a significant covariate of mosunetuzumab clearance.

Table 4 Updated Summary statistics of exposure endpoints at 1/2/60/30 mg

Endpoint	AUC_{0-42} (µg/mL•day)	AUC_{CYCLE4} (µg/mL•day)	$Cmax_{CYCLE4}$ (µg/mL)	$Cmin_{CYCLE4}$ (µg/mL)
Geometric mean	125.7	52.9	~~5.47~~ **7.02**	1.25
Geometric CV%	44.4	40.7	~~33.7~~ **37.9**	70.3

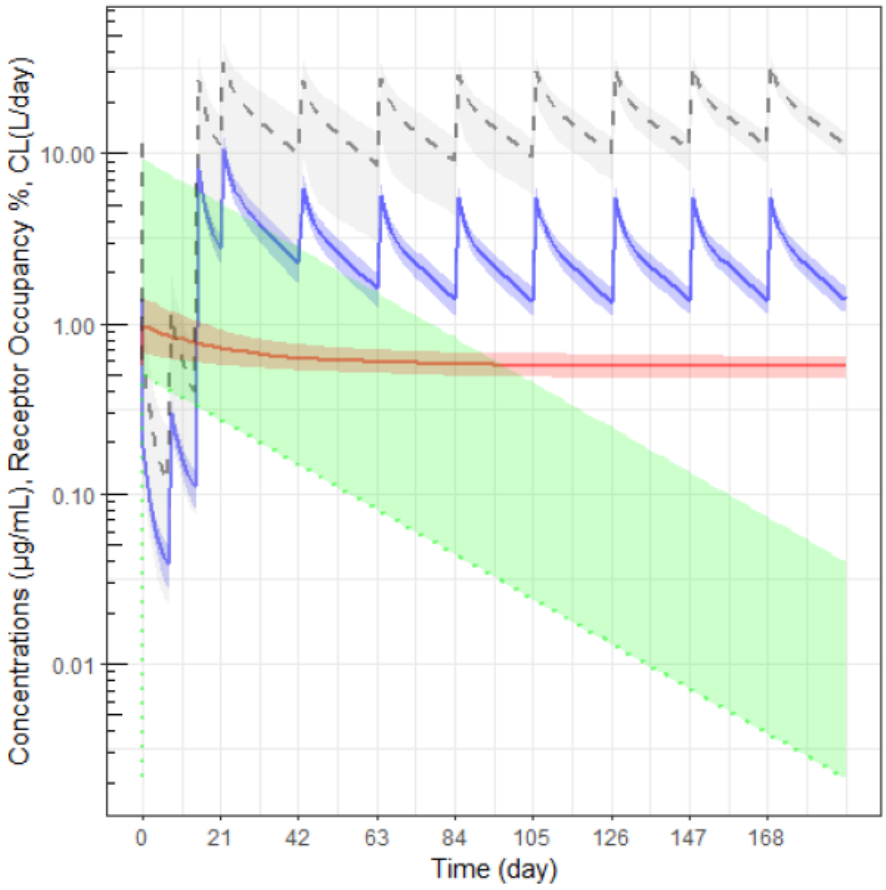
Endpoint	AUC_{CYCLE8} (µg/mL•day)	$Cmax_{CYCLE8}$ (µg/mL)	$Cmin_{CYCLE8}$ (µg/mL)	AUC_{ss}[1] (µg/mL•day)
Geometric mean	52.9	~~5.38~~ **6.89**	1.31	55.3
Geometric CV%	27.7	~~27.2~~ **33.4**	38.8	21.5

~~Strike-through~~: previous value in error; Numbers in bold: corrected values.

AUC_{0-42}= cumulative area under the curve from Day 0 to Day 42; CV= coefficient of variation; C_{max}= maximum drug concentration in plasma; C_{min} = minimum mosunetuzumab concentration; AUC_{SS} = steady state AUC.

[1]AUC_{ss} is derived by $CL_{ss}(i)/30$ mg, where $CL_{ss}(i)$ is the individual patient EBE for CL_{ss}, and 30 mg is the steady state q3w dose for the 1/2/60/30 mg regimen.

Figure 8 model-predicted mosunetuzumab concentration (blue) RO (grey) CL (red) and rituximab (green) concentration time – profiles for 1/2/60/30 mg dose regimen based on all patient EBEs (N= 439)



CL= clearance at steady state.

Shaded regions for each curve represent the 25th and 75th percentiles. Solid or stippled lines represent the median value. For the rituximab time–course (green), the lower bound is set by the BLQ concentration of 0.5 µg/mL, which is the median for the FL patient population.

AUC0-42 was the main exposure metric used for investigation of E-R for efficacy measures, CR and OR using logistic regression modelling with an Emax function. A linear logistic model was used to describe cytokine release syndrome E-R analysis with ROmax as the exposure endpoint. Kaplan-Meier time-to-event plots with AUC0-42 exposure tertiles were used to describe other safety time-to-events.

Table 5 model parameter estimates for the ER models between AUC0-42 and CR/OR

Clinical Objective Response	E_{max}[a] (%RSE)	E50[a] (%RSE)	β0[a] (%RSE)	Maximal Response[b] (90% CI)	AIC	BIC	OFV
CR	3.57 (79.7)	5.84 (154)	-3.01 (98.6)	63.7% (56.5–80.5%)	216.873	226.080	210.873
OR	6.23 (92.3)	3.12 (156)	-4.76 (124)	81.4% (75.6–91.5%)	181.758	190.965	175.758

AIC = Akaike information criterion; BIC = Bayesian information criterion; CI = confidence interval; CR=complete response; E50 = AUC_{0-42} at 50% E_{max}; E_{max} = model estimated maximal effect; OFV=objective function value, or minus twice the log-likelihood of the model given the data; OR=overall response; SE = standard error.

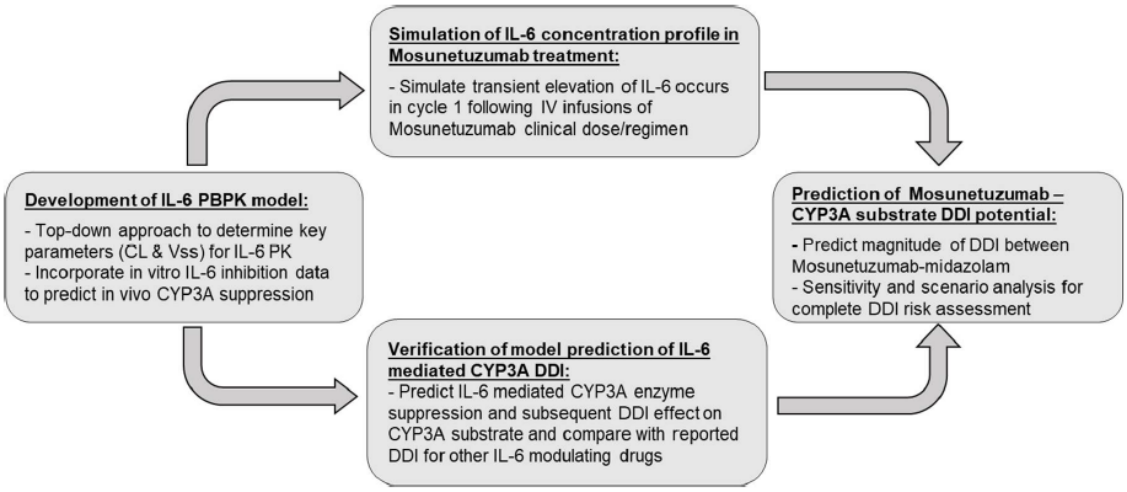
[a] E_{max}, E50, and β0 parameter estimates on logit scale.

[b] Maximal Response (i.e., therapeutic potential) was derived as follows: Maximal Response=$\exp(\beta0+E_{max})/[1+\exp(\beta0+E_{max})]$; 90% CI from bootstrap analysis.

PBPK modelling

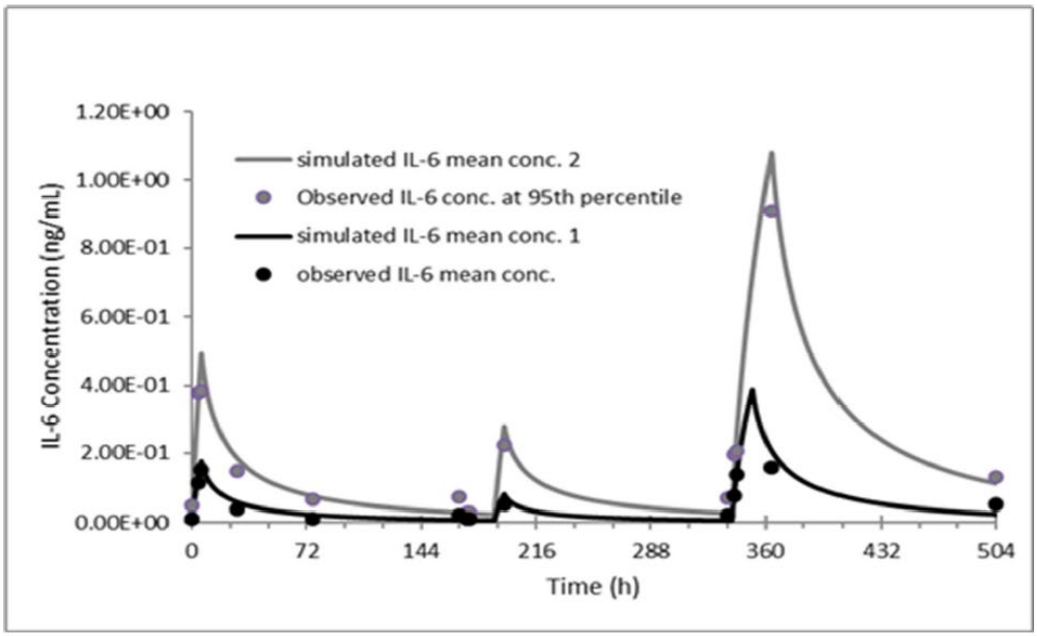
An IL-6 PBPK model was built using observed IL-6 data following mosunetuzumab administration from study GO29781 to assess the magnitude of potential CYP3A4 suppression caused by cytokines.

Figure 9 scheme of IL-6 PBPK model development, verification and application



CL=clearance; CYP3A=cytochrome P4503A; DDI=drug-drug interaction; IL-6=interleukin-6; IV=intravenous; PBPK= physiologically based pharmacokinetics; V_{ss}= volume of distribution at steady state.

Figure 10 Simulated and observed mean IL-6 plasma concentration at the observed mean level and 95th percentile level for sensitivity analysis



conc.=concentration; IL-6=interleukin-6; h=hours.

The magnitude of DDI was simulated using two substrates, midazolam and simvastatin, and evaluated at C1D15 where the CYP3A4 suppression was largest following the proposed dose regimen. Assuming the inhibitory impact on CYP3A4 activity was similar in the gut and liver, in contrast to liver only, did not have a major impact on the substrate exposure. A sensitivity test was conducted assuming a 5-fold higher mean IL-6 level than observed in Study GO29781 close to the observed 95th percentile level. The result of the sensitivity testing indicated that mosunetuzumab induced CRS may have a mild inhibitory effect on CYP3A4 at 5-times the mean observed IL-6 level (<two-fold increase in AUC). The conclusions are further discussed under drug-drug interactions.

ADME properties

Absorption

The drug product is administered intravenously.

Non-compartmental analyses indicate that mosunetuzumab serum concentration reaches the maximal level (Cmax) at the end of the IV infusion.

In group A a moderate to high PK parameter variability was observed (% coefficient of variation [%CV] for the first-cycle AUC and Cmax ranged from approximately 20% to 120%). In Group B (step-up escalation) the total Cycle 1 mosunetuzumab exposure AUC0-21 increased as the total amount of the three mosunetuzumab dose in Cycle 1 in each dose group increased, ranging from 2.8 day·∫g/mL to 50.2 day·∫g/mL.

Two formulations have been used during clinical development: F01 and F02. The F01 formulation was used for initial clinical studies. The F02 formulation was used for subsequent clinical studies, including the B11 RP2D cohort and is the intended commercial formulation. No formal bioequivalence studies have been performed.

No dedicated food-interaction studies have been performed as mosunetuzumab is administered intravenously, and therefore no food effect would be expected with parenteral administration.

Study GO29781

A total of 33 patients enrolled in Group A received mosunetuzumab IV q3w treatment with the dosing range 0.05-2.8 mg. Of these, 32 patients were included in the PK analysis. All data for the only patient at the 0.05 mg dose group were below the assay lower limit of quantification (LLOQ) of 10 ng/mL. The summary of PK parameters is provided in the table below:

Table 6: Summary of Serum Mosunetuzumab Pharmacokinetic Parameters following Administration as IV Monotherapy in Non-Fractionated Dose Escalation Cohorts in Group A, PK-Evaluable Patients

Patient Cohort and Dose		Half-life (day)	T_{max} (day)	C_{max} (μg/mL)	AUC_{0-21} (day•μg/mL)	AUC_{inf} (day•μg/mL)	CL (L/day)	V_{ss} (L)
A2: 0.2 mg	N	1	1	1	1	1	1	1
	Mean	2.66	0.319	0.0323	0.0604	0.108	1.85	7.02
	CV%	NA	NA	NA	NA	NA	NA	NA
A3: 0.4 mg	N	3	3	3	3	3	3	3
	Mean	6.94	0.191	0.109	0.447	0.591	0.694	6.69
	CV%	9.8	5.1	40.5	21.6	19.6	18.5	26.1
A4: 0.8 mg	N	4	4	4	4	4	4	4
	Mean	6.82	0.176	0.171	0.818	0.995	0.875	7.54
	CV%	18.6	3.0	23.2	40.2	36.9	29.9	25.0
A5: 1.6 mg	N	6	6	6	6	6	6	6
	Mean	7.46	0.191	0.258	1.04	1.23	1.75	15.5
	CV%	32.8	15.1	44.0	56.4	55.6	60.3	55.4
A6: 1.2 mg	N	7	7	7	7	7	7	7
	Mean	7.77	0.174	0.385	1.85	2.32	1.01	8.13
	CV%	44.2	1.8	89.0	118	116.5	69.6	49.8
A7: 2.0 mg	N	3	3	3	3	3	3	3
	Mean	9.17	0.789	0.282	1.56	2.04	1.04	12.7
	CV%	18.1	67.7	50.0	38.6	32.0	27.0	35.6
A8: 2.8 mg	N	8	8	8	8	8	8	8
	Mean	9.69	0.258	0.402	1.99	2.53	1.16	14.4
	CV%	27.3	40.4	52.4	45.9	45.7	28.0	39.7

AUC_{inf} = area under serum concentration curve from time zero extrapolated to infinity; AUC_{0-21} = area under Cycle 1 (21 days) serum concentration curve; CV = coefficient of variation; C_{max} = maximum serum concentration from 0 to 21 days; CL = total body clearance; PK=pharmacokinetic; T_{max} = time from dosing to maximum concentration; V_{ss} = volume of distribution at steady state; NA=not applicable.
Note: All data at the 0.05 mg dose group (Cohort A1, N=1) were below the assay lower limit of quantification (LLOQ) of 10 ng/mL.
Source: Study GO29781 Interim CSR Report 1106874, Table 33.

Patient Cohort and Dose		Half-life (day)	T_{max} (day)	C_{max} (µg/mL)	AUC_{0-21} (day•µg/mL)
B1 (0.4/1.0/2.8 mg)	N	6	6	6	6
	Mean	4.37	14.2	0.565	2.80
	CV%	16.1	0.3	23.9	29.0
B2 (0.8/2.0/4.2 mg)	N	14	15	15	14
	Mean	7.23	14.8	0.871	5.27
	CV%	137.7	21.7	47.0	39.8
B3 (1.0/1.0/3.0 mg)	N	1	1	1	1
	Mean	4.74	14.1	0.622	3.74
	CV%	0.00	0.00	0.00	0.00
B4 (1.0/2.0/6.0 mg)	N	5	6	6	5
	Mean	4.99	16.6	1.43	8.57
	CV%	7.6	22.9	53.4	28.1
B5 (0.8/2.0/6.0 mg)	N	25	27	27	25
	Mean	4.81	14.3	1.43	8.04
	CV%	28.8	14.0	64.6	76.0
B6 (1.0/2.0/9.0 mg)	N	5	5	5	5
	Mean	3.56	14.5	2.03	8.11
	CV%	27.5	2.0	18.1	24.2
B7 DE and expansion (1.0/2.0/13.5 mg)	N	66	73	73	68
	Mean	3.78	15.1	2.54	12.4
	CV%	32.4	17.3	36.1	42.5
B8 (1.0/2.0/20.0 mg)	N	9	10	10	9
	Mean	4.09	14.2	4.09	17.6
	CV%	28.2	5.5	29.4	27.3
B9 (1.0/2.0/27.0 mg)	N	23	24	24	23
	Mean	3.98	14.7	5.35	24.4
	CV%	46.1	11.6	25.5	43.1
B10 (1.0/2.0/40.5 mg)	N	15	15	15	15
	Mean	3.73	14.2	9.32	32.0
	CV%	20.2	2.7	29.5	24.8
B11 DE (1.0/2.0/60 mg)	N	2	3	3	2
	Mean	5.12	14.2	14.1	50.2
	CV%	3.3	0.5	20.7	9.3

CV = coefficient of variation; C_{max}= maximum serum concentration from 0 to 21 days; DE = dose escalation; T_{max} = time from dosing to maximum concentration; AUC = area under Cycle 1 (21 days) serum concentration curve.
Source: Study GO29781 Interim CSR Report 1106874, Table 34.

Distribution

The serum concentration-time data was best described by a two-compartment popPK model. The central volume of distribution of 5.49 L is larger than plasma volume, suggesting the potential impact of binding to immediately accessible targets following IV administration of mosunetuzumab. Following Administration as IV Monotherapy in Non-Fractionated Dose Escalation Cohorts in Group A, the Vss (L) is in the range of 6.69 to 15.5L (+-11.7 L).

As mosunetuzumab is an antibody, protein binding studies were not conducted.

Elimination

Mosunetuzumab is a full-length IgG1 bispecific monoclonal antibody metabolized to peptides and amino acids by circulating phagocytic cells or by their target antigen-containing cells. Neither hepatic metabolism nor renal excretion are considered as major elimination routes. Accordingly, no active metabolites are expected.

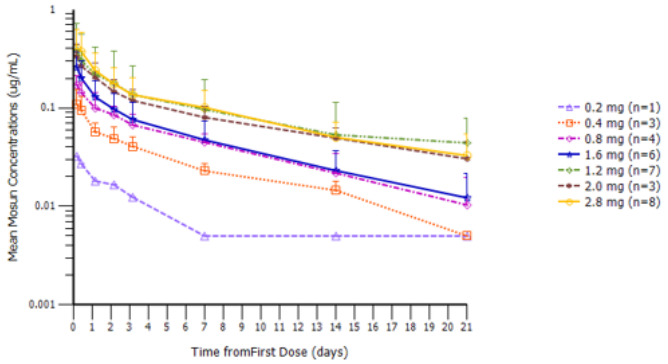
The serum concentration-time data was well-described by a popPK model with two-compartment and time-dependent clearance (CL), which was parameterized as an initial baseline clearance (CLbase ~ 1.08

L/day) which transitions over time to a steady state clearance (CLSS ~ 0.584 L/day). The apparent half-life (t1/2) is approximately 3 to 10 days. The terminal half-life estimate was 16.1 days at steady state based on population PK (popPK) model simulations.

Dose proportionality and time dependencies

Mosunetuzumab exhibits linear and dose-proportional PK in the dose range studied (0.2–60 mg) and in the clinically active dose range (≥1.2 mg).
In Group A, a moderate to high PK parameter variability was observed in that the % coefficient of variation for the first-cycle Cmax, which ranged from approximately 20% to 120%;

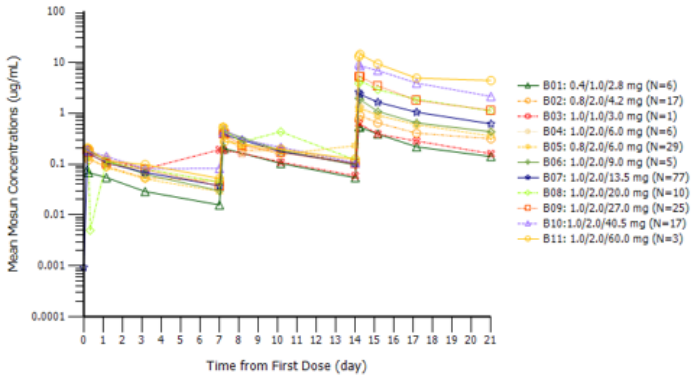
Figure 11 Cycle 1 Mean (+SD) Mosunetuzumab Concentration-Time Profiles Following Administration of a Fixed (Non-Fractionated) Doss by IV Infusion in Group A, PK-Evaluable Patients



Note: All data at the 0.05 mg dose group were below the assay lower limit of quantification (LLOQ) of 10 ng/mL. For all data below the LLOQ, half LLOQ (5ng/mL) were used for plotting.
Source: Study GO29781 Interim CSR Report 1106874, Figure 9.

The results indicate that mosunetuzumab serum concentration reaches the maximal level (C_{max}) at the end of the IV infusion and declines in a bi-exponential fashion, with an estimated apparent half-life $t_{1/2}$ of about 3–10 days. Mosunetuzumab concentrations increased in a dose-proportional manner over the dose ranges tested (0.2–2.8 mg following q3w fixed dosing schedule in Group A). Moderate to high PK parameter variability was observed (% coefficient of variation [%CV] for the first-cycle AUC and C_{max} ranged from approximately 20% to 120%).

Figure 12 Cycle 1 Mean Mosunetuzumab Concentration-Time Profiles Following Administration of Step-up Dose by IV Infusion in Group B Dose Escalation Cohorts, PK-Evaluable Patients

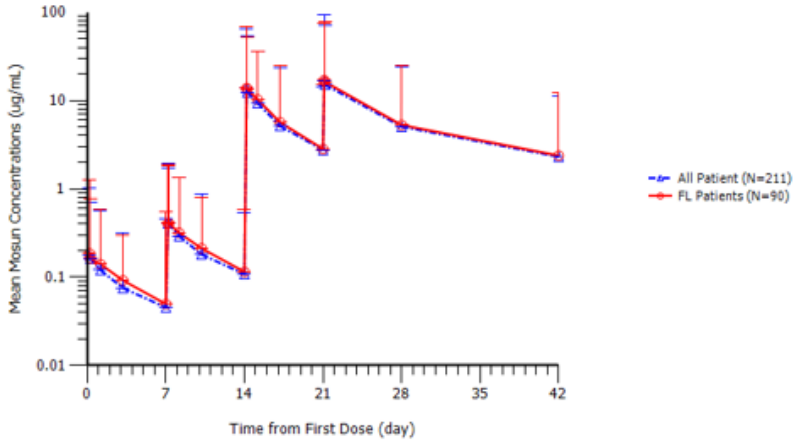


Note: Assay LLOQ is 10 ng/mL. For all data below the LLOQ, half LLOQ (ng/mL) were used for plotting.
Source: Study GO29781 Interim CSR Report 1106874, Figure 10.

The results indicate that following three step-up doses in Cycle 1, the mosunetuzumab serum concentration reaches C_{max} at the end of the third mosunetuzumab IV infusion (Cycle 1 Day 15) with an average maximal concentration ranging from 0.565 µg/mL to 14.1 µg/mL. The total Cycle 1 mosunetuzumab exposure $AUC_{0\text{-}21}$ increased as the total amount of the three mosunetuzumab dose in Cycle 1 in each dose group increased, ranging from 2.8 day•µg/mL to 50.2 day•µg/mL.

Among 214 patients enrolled in the B11 RP2D cohort, 211 patients were PK evaluable, which includes the 90 patients in the B11 FL RP2D cohort.

Figure 13 Cycle 1 and Cycle 2 Mean (+SD) Mosunetuzumab Concentration-Time Profiles Following Administration of Two Cycles of a Step-up Dose of 1/2/60/30 mg by IV Infusion in the RP2D Expansion Cohort in Group B, PK-Evaluable Patients



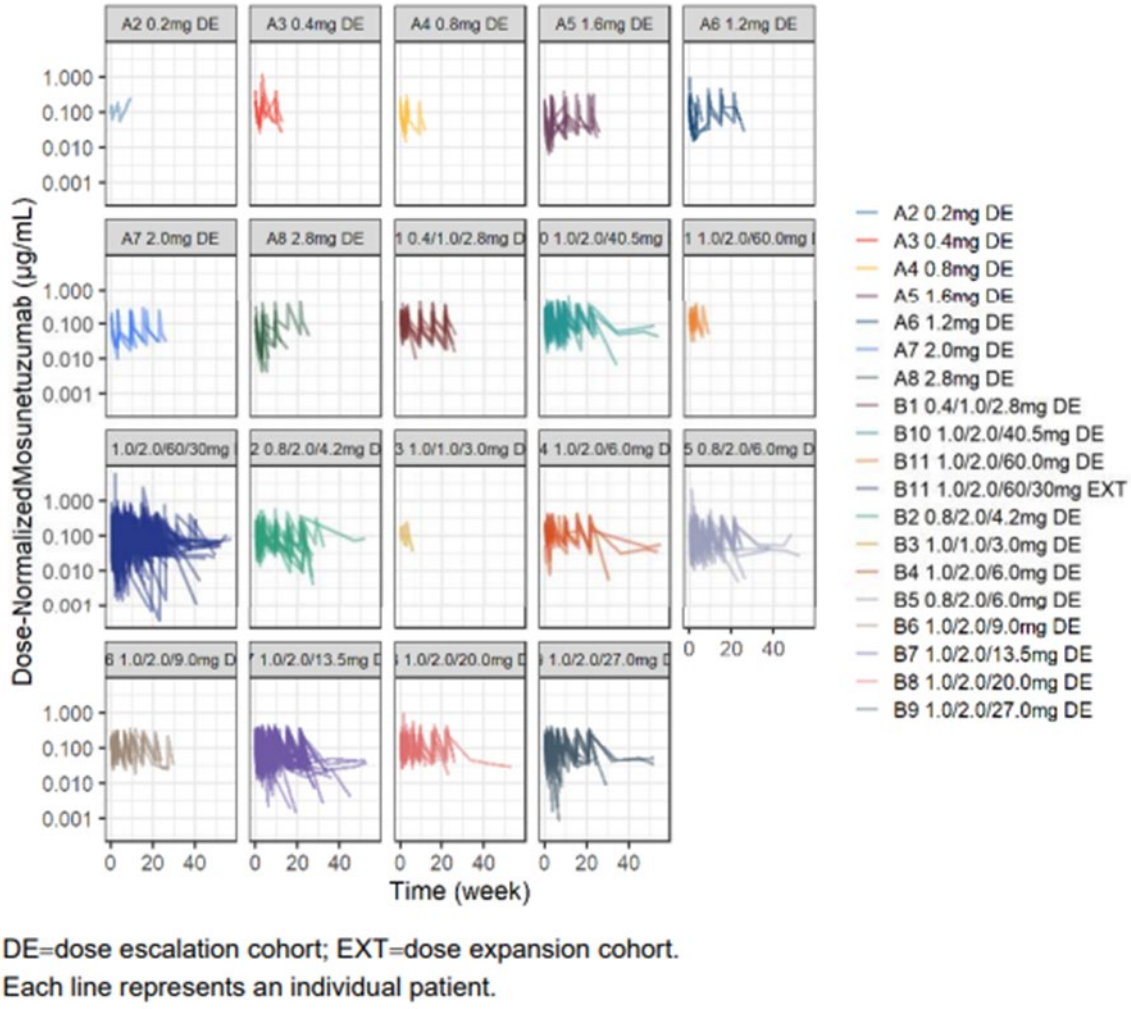
Note: Assay LLOQ is 10 ng/mL. For all data below the LLOQ, half LLOQ (ng/mL) were used for plotting.

Following two cycles (i.e., 42 days) of the RP2D dose of 1/2/60/30 mg, the mosunetuzumab serum concentration reaches the C_{max} at the end of Cycle 2 Day 1 of the mosunetuzumab IV infusion with an average maximal concentration of 17.9 ⌠g/mL and %CV of 49.6%. The average total two Cycles (42 days) mosunetuzumab exposure AUC was 246 day·⌠g/mL with %CV of 46.9%.

Concentration- and/or time-dependency in pharmacokinetics were evaluated and compared using POP PK analysis, as plots of dose-normalized (using nominal dose level) concentration against time after dose, stratified by treatment cohort. There was no evidence of dose nonlinearity in low doses.

Overall, the time dependency of mosunetuzumab pharmacokinetics (PK) and accumulation patterns were well characterized by the popPK model. Mosunetuzumab behaves like a typical IgG1 monoclonal antibody, and steady state exposure is achieved by ~Cycle 4.

Mosunetuzumab exhibits linear and dose-proportional pharmacokinetics in the dose range studied (0.2 to 60 mg) and in the clinically active dose range (≥1.2 mg). Target-mediated drug disposition (TMDD) was tested in the popPK model, but the results did not indicate improvement in descriptions of the data over simpler linear models, either with or without time-dependent clearance approaches.



DE=dose escalation cohort; EXT=dose expansion cohort.
Each line represents an individual patient.

Figure 14: Mosunetuzumab Concentration Over Time, by Treatment Cohort with Dose-Normalization

Intra-individual variability

No information provided.

Inter-individual variability

Moderate to high inter-individual variability (IIV) was observed for mosunetuzumab key PK parameters (range from 18% to 86%).

In the population PK analysis, relative high inter-individual variability was observed for CLbase (CV=63%) and HLtrans (CV=86%) compared with CLss (CV=18%), V1 (CV=31%) and V2 (CV=25%).

No information is provided on intra-individual variability. Overall, the inter-individual variability of mosunetuzumab PK parameters is moderate to high, which is consistent with other mAbs.

Target population

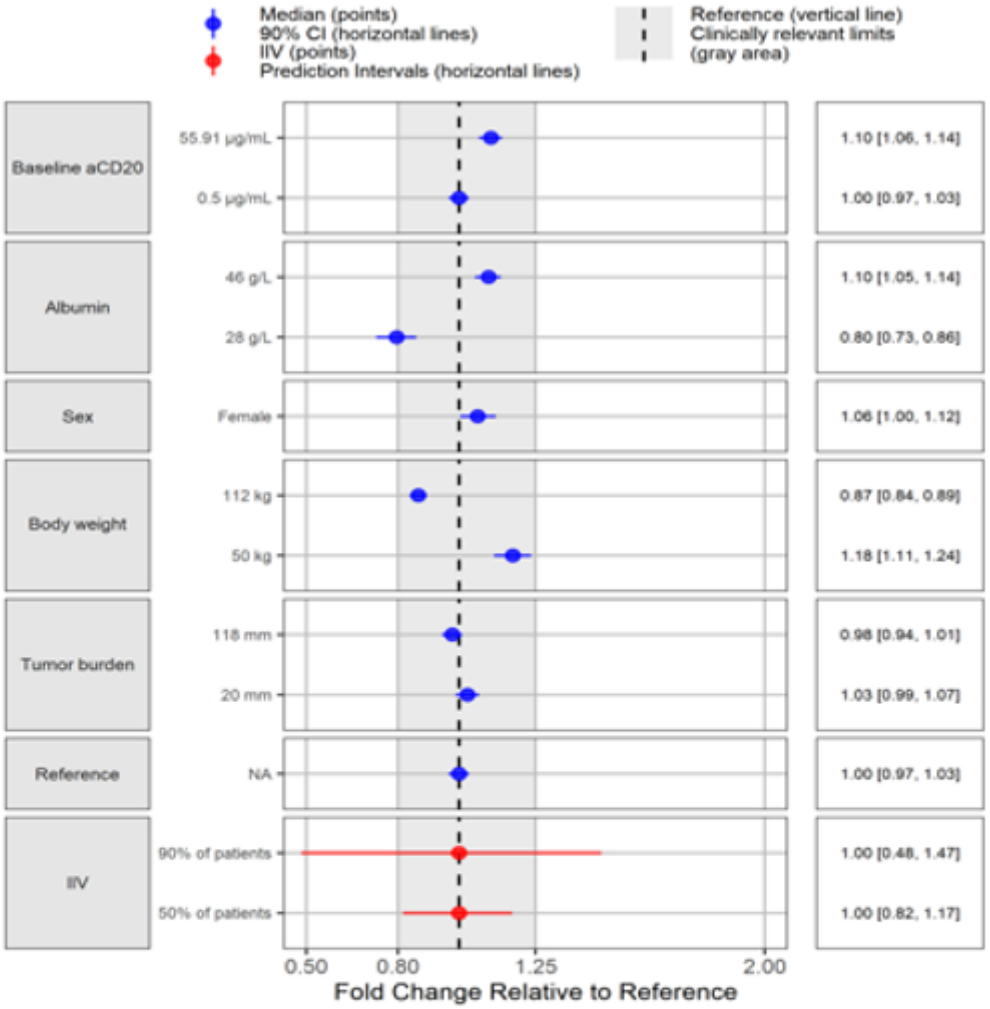
The pharmacokinetics of mosunetuzumab was not evaluated in healthy volunteers as mosunetuzumab was developed primarily for oncology indications.

There was no dedicated clinical study for mosunetuzumab patient PK and tolerability. Evaluation of mosunetuzumab patient PK and initial tolerability was included in study GO29781 which is a phase I/Ib dose-escalation and dose-expansion study in patients with R/R hematologic malignancies expected to express CD20, including B-cell NHL and CLL.

The following studies are ongoing: GO40515, GO40516, GO40554, CO41942, GO41943, JO40295 and BO43243 in different populations including R/R NHL, CLL, 1L DLBCL, FL and MCL.

Special populations

Figure 15: Forest Plot of Covariate Effects on Mosunetuzumab PK exposure (i.e., AUC0-42)

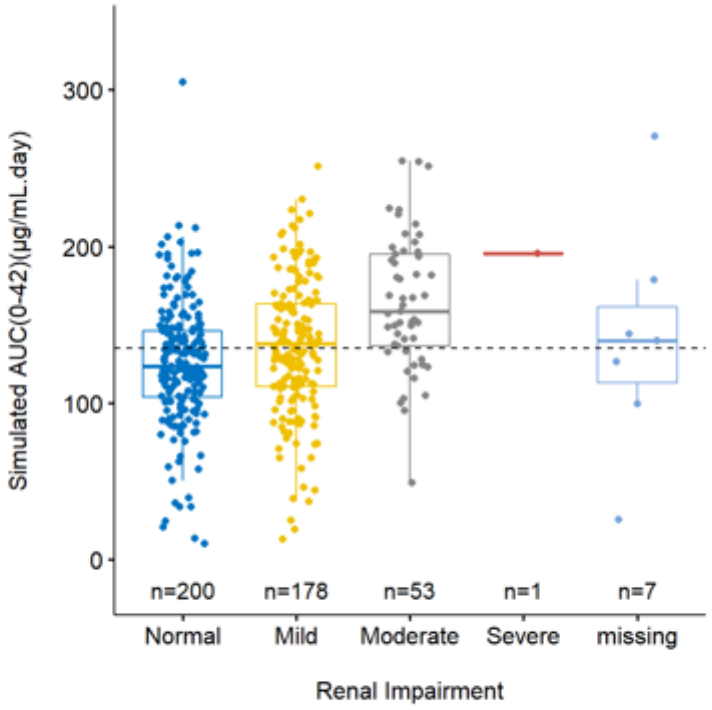


aCD20– anti-CD20 drug, specifically Rituximab (R) and Obinutuzumab (G); AUC_{0-42}– cumulative area under the curve from Day 0 to Day 42; CI– confidence interval; IIV– interindividual variability.
Final model estimate, as represented by the black vertical line and value, refers to the predicted steady-state exposure of mosunetuzumab at 1/2/60/30 mg in a typical patient with covariates equal to medians. The typical patient is a male, weighing 78 kg, with an albumin level of 39 g/L, aCD20 drug concentration 0.5 µg/mL and a tumor burden of 54.5 mm (note the unit for tumor burden was redefined as the square root of the tumor sum of product diameter (SPD) for covariate modeling). Grey areas represent a change from the reference. Each horizontal bar represents the influence of a single covariate on the AUC_{0-42}. The label at left end of the bar represents the covariate being evaluated with values on the right end of the 5^{th} and 95^{th} percentiles of the covariate distribution. The length of each bar describes the potential impact of that particular covariate on mosunetuzumab exposure, with the percent change of exposure from the base.

Renal impairment

Mosunetuzumab is a full-length IgG1 bispecific monoclonal antibody, and the Applicant states that the PK is not expected to be impacted by renal impairment. A tendency towards increased AUC in patients with moderate and severe renal impairment is observed (see figure below).

Figure 16 Comparison of mosunetuzumab PK exposure at 1, 2, 60, 30 mg dose with different renal function



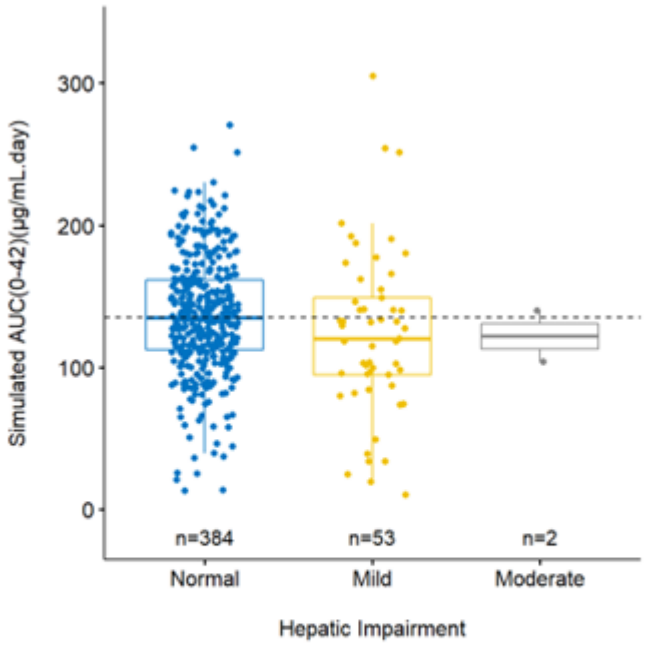
AUC_{0-42}= AUC from time 0 to 42 days; n=number of patients.
Dotted line: mean of simulated AUC_{0-42} across all the patients.
Boxplots represent medians (central horizontal lines), 50% ranges (box hinges), and whiskers extend from the hinge to the largest or smallest values no further than 1.5 * the interquartile range from the hinges.

Hepatic impairment

Mosunetuzumab is a full-length IgG1 bispecific monoclonal antibody. The PK is not expected to be impacted by hepatic impairment, as confirmed by the popPK modeling assessment.

Mosunetuzumab has not been investigated in subjects with severe hepatic impairment and the data from subjects with moderate hepatic impairment are very sparse (n=2).

Figure 17: Comparison of Mosunetusumab PK exposure (i.e., AUC0-42) at the clinical dose of 1/2/60/30 mg with different hepatic function (study GO29781)



AUC_{0-42}= AUC from time 0 to 42 days; n=number of patients.
Dotted line: mean of simulated AUC_{0-42} across all the patients.
Boxplots represent medians (central horizontal lines), 50% ranges (box hinges), and whiskers extend from the hinge to the largest or smallest values no further than 1.5 * the interquartile range from the hinges.
Source: PopPK Report No. 1110345, Figure 26.

Gender

The Applicant states that PopPK modeling based on Study GO29781 in 284 men (64.7%) and 155 women (35.3%) indicate no clinical meaningful effect of gender on mosunetuzumab PK. However, significant baseline covariate effects include sex on CL_{ss} and V1 i.e. AUC_{0-42} for a typical female patient (weighing 78 kg) is approximately 6% higher than a typical male patient.

Race

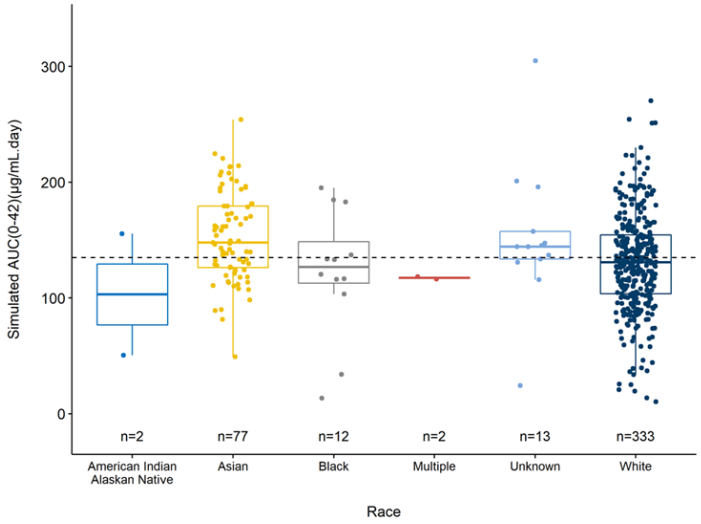
PopPK modeling based on Study GO29781 indicate no statistically significant effect of race (Asian vs. Non-Asian) on mosunetuzumab PK.

The Applicant has provided figures on Eta distribution on Cl(base), V1 and Cl(ss) from the Pop PK analysis. The demographic information for capturing study participant race on GO29781 included the following options: "American Indian or Alaska Native"; "Asian"; "Black or African American"; "Native Hawaiian or Other Pacific Islander"; "White"; "Unknown." The following options were used by sites for recording study participant ethnicity: "Hispanic or Latino"; "Not Hispanic or Latino"; "Not reported"; "Unknown." Based on the visual inspection of plots for individual values of random effects (i.e., ETA) stratified by these categories, there were no apparent ethnic differences with respect to key mosunetuzumab PK parameters, including the baseline clearance (CL_{base}), central volume of distribution (V_1), and steady-state clearance (CL_{ss}). Note, that the low sample sizes for "American Indian/Alaskan Native" (N=2) and "Black" (N=12) categories precluded these groups from robust assessments, either visually by stratified ETA plots, or formally in the covariate analysis.

The formal popPK covariate analyses tested "Asian" (N=77) versus "Non-Asian" (N=362) as a potential factor impacting PK; results indicated no significant differences in mosunetuzumab PK by these

categories. However, it is noted that the overall body weight distribution is lower in Asian patients compared to the Non-Asian patients – median [95% percentile] body weight for Asian patients of 65.7 [42.4-86.5] kg and 80.4 [49.8-121] kg for Non-Asian patients. Hence, the slightly higher exposure (AUC_{0-42}) difference comparing Asian versus non-Asian participants is considered to be attributable to differences in body weight between the two groups and not ethnic-related differences in mosunetuzumab PK disposition. Body weight was identified as a statistically significant covariate and included in the final popPK model.

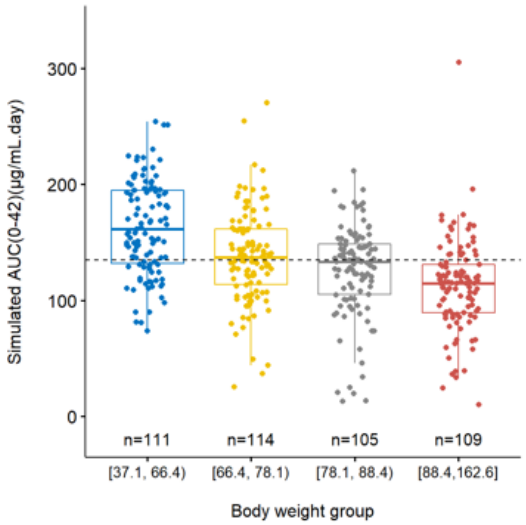
Figure 18 Comparison of AUC_{0-42} across race in PK-evaluable study participants



Body weight

Significant baseline covariate effects include bodyweight on CL_{ss}, V1 and V2. The model covariates are judged not to have a meaningful effect if the impact of extreme, or categorical, values fall within 0.80-1.25 -fold change from the reference.

Figure 19 Comparison of PK exposure (AUC_{0-42}) at 1 /2/60/30 mg dose across body-weight quartiles



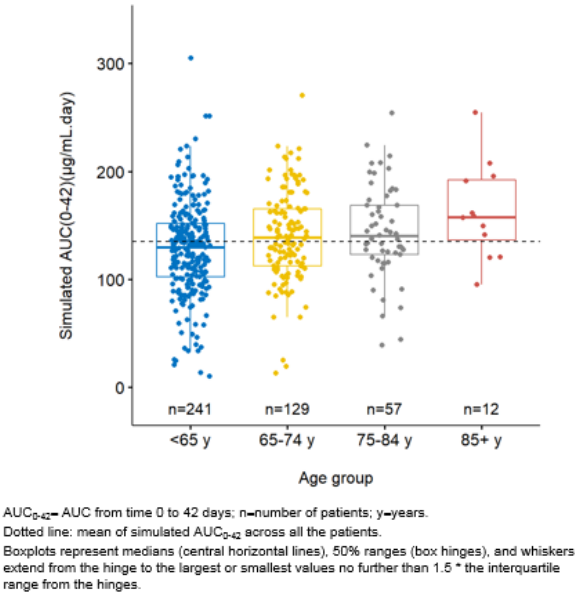
AUC_{0-42}= AUC from time 0 to 42 days; n=number of patients.
Dotted line: mean of simulated AUC_{0-42} across all the patients.
Boxplots represent medians (central horizontal lines), 50% ranges (box hinges), and whiskers extend from the hinge to the largest or smallest values no further than 1.5 * the interquartile range from the hinges.

Significant baseline covariates also included albumin (CL and V1), tumor burden (CLss) and anti- CD20 (CLbase).

Elderly

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials GO29781	129 (29.4%)	57 (12.9%)	12 (2.7%)

Figure 20 Comparison of PK exposure (AUC_{0-42}) at 1 /2/60/30 mg dose in patients stratified by age



AUC_{0-42}= AUC from time 0 to 42 days; n=number of patients; y=years.
Dotted line: mean of simulated AUC_{0-42} across all the patients.
Boxplots represent medians (central horizontal lines), 50% ranges (box hinges), and whiskers extend from the hinge to the largest or smallest values no further than 1.5 * the interquartile range from the hinges.

In the above figure, a tendency towards an increased exposure in subjects above 85 years of age is observed.

Children

No studies in the paediatric population have been presented.

Histology

The effect of NHL histology on mosunetuzumab pharmacokinetics was investigated as a categorical covariate (DLBCL, FL, and others) in the popPK model based on patients in Study GO29781. The Applicant states that NHL histology had no statistically significant impact on the mosunetuzumab pharmacokinetics parameters.

Pharmacokinetic interaction studies

In vitro

No specific non-clinical DDI studies were conducted.

In vivo

No clinical DDI studies have been conducted with mosunetuzumab.

Classical drug-drug interactions that occur through effects on enzyme systems such as the cytochrome P450 (CYP) system are not expected for monoclonal antibodies (Keizer et al. 2010). In several specifically designed clinical trials, no relevant influence of monoclonal antibodies on metabolism of co-medication has been shown, confirming the general principle that pharmacokinetic interactions are generally not to be expected with monoclonal antibody co-treatment (Keizer et al. 2010; Ettlinger et al. 2006; Gaudreault et al. 2005; Xu et al. 2008; Zinner et al. 2004). Since the vast majority of immunoglobulin is eliminated by catabolism (Wang et al. 2008), monoclonal antibodies are presumably not substrates for CYP enzymes or drug transporters such as P-glycoprotein. In many cases, IgG elimination is driven primarily by affinity for the neonatal Fc receptor (FcRn) receptor, and the nature of and affinity for the specific target of the antibody. Accordingly, inhibitors or inducers of CYP, or of transporters such as P-glycoprotein, are not expected to affect the pharmacokinetics of mosunetuzumab, as a victim of DDIs. Therefore, no direct victim or perpetrator based DDIs are anticipated for mosunetuzumab from monoclonal antibodies' absorption, distribution, metabolism, excretion perspective.

Study GO29781 has shown that treatment with mosunetuzumab results in transient elevations of cytokines including IL-6, the key cytokine associated with CYP enzyme suppression in humans (Xu et al. 2015; Haas et al. 2003; Lee et al. 2010; Nakai et al. 2008). The systemic elevation associated with mosunetuzumab treatment appears to be primarily a first cycle effect, and IL-6 concentration peaks following the Cycle 1 Day 1 and Day 15 doses with no changes from baseline in later cycles (Figure 24). Importantly, the cytokine elevation was mitigated by the use of the Cycle 1 step up dosing regimen, as implemented in Group B and for the proposed dose intended for registration of 1/2/60/30 mg. The mean observed IL-6 peak concentrations at C1D1, C1D8, and C1D15 are 152, 52.7 and 160 pg/mL, respectively, based on n=212 patients in B11 who received 1, 2, and 60 mg on Cycle 1 Days 1, 8, and 15.

PBPK model

A PBPK model was developed to assess the potential DDI risk for mosunetuzumab due to the transient IL-6 elevation. Other than IL-6, mosunetuzumab does not meaningfully elevate the systemic level of other proinflammatory cytokines, such as IFN-γ, IL-2, TNF-〈, which have been reported to alter CYP enzyme expression or activity (Huang et al. 2010).

Physiologically based pharmacokinetics (PBPK) modelling and simulations based on IL-6 and CYP3A4 interaction indicated low risk of cytokine-mediated drug-drug interaction potential for mosunetuzumab.

Table 6 Predicted DDI between Mosunetuzumab and Sensitive CYP3A Substrate Midazolam Caused by Transient IL-6 Elevation during Mosunetuzumab Treatment

Mosunetuzumab Administration	C1D1	C1D8	C1D15
MDZ AUC ratio	1.18 (1.15-1.22)	1.19 (1.15-1.22)	1.37 (1.31-1.44)
MDZ C_{max} ratio	1.09 (1.07-1.11)	1.09 (1.07-1.11)	1.17 (1.14-1.19)

AUC=area under the plasma drug concentration-time curve; C1D1=Cycle 1 Day 1; D8=Day 8; D15=Day 15; MDZ= Midazolam.

C_{max} ratio and AUC ratio =C_{max} or AUC in the presence of IL-6 /C_{max} or AUC in the absence of IL-6; expressed as GM mean ratio and 90% confidence interval.

Source: PBPK Report No.1110241, Table 3.

The PBPK model is considered of high impact since it is used to replace a dedicated DDI study. The most important issue foreseen with the proposed PBPK modelling are related to (1) the modelling of time course of IL-6 concentrations and (2) the verification the appropriateness of in-vitro in vivo extrapolation of the suppressive effects of IL-6 on CYP3A activity based on in vitro parameters from the literature.

The IL-6 levels were modelled using a PK top-down approach calibrated with in house clinical data from study GO29781. In addition, a hypothetical dose was used to force the model to fit the observed concentrations.

The graphical figures of simulated vs observed interleukin-6 (IL-6) concentrations, midazolam and simvastatin for Schmitt et al. (2011) and Zhuang et al. (2015) study data have been presented by the applicant. For IL-6 - midazolam (MDZ) drug-drug interaction (DDI) prediction by the physiologically-based pharmacokinetic (PBPK) model described in the report, a single 5 mg oral dose of MDZ was used while 0.03 mg/kg was stated in the reference. To provide simulated vs. observed MDZ pharmacokinetic (PK) profile as in the reference, additional DDI simulations using 0.03 mg/kg MDZ with IL-6 at 50 pg/mL and 100 pg/mL were conducted. The predicted DDI, expressed as MDZ exposure (maximum serum concentration [Cmax] and area under concentration time curve [AUC]) ratio, was similar at 0.03 mg/kg MDZ dose versus the 5 mg MDZ dose.

The figures demonstrate that both observed simvastatin and MDZ PK in the presence and absence of IL-6 are described reasonably well by the PBPK simulations.

Figure 21 Simulated and Observed Simvastatin (40 mg on Day 19) Pharmacokinetics in Presence and Absence of IL-6 (TOP Row: Steady State Concentration of 50 pg/mL, Bottom Row: Steady State concentration of 100 pg/mL)

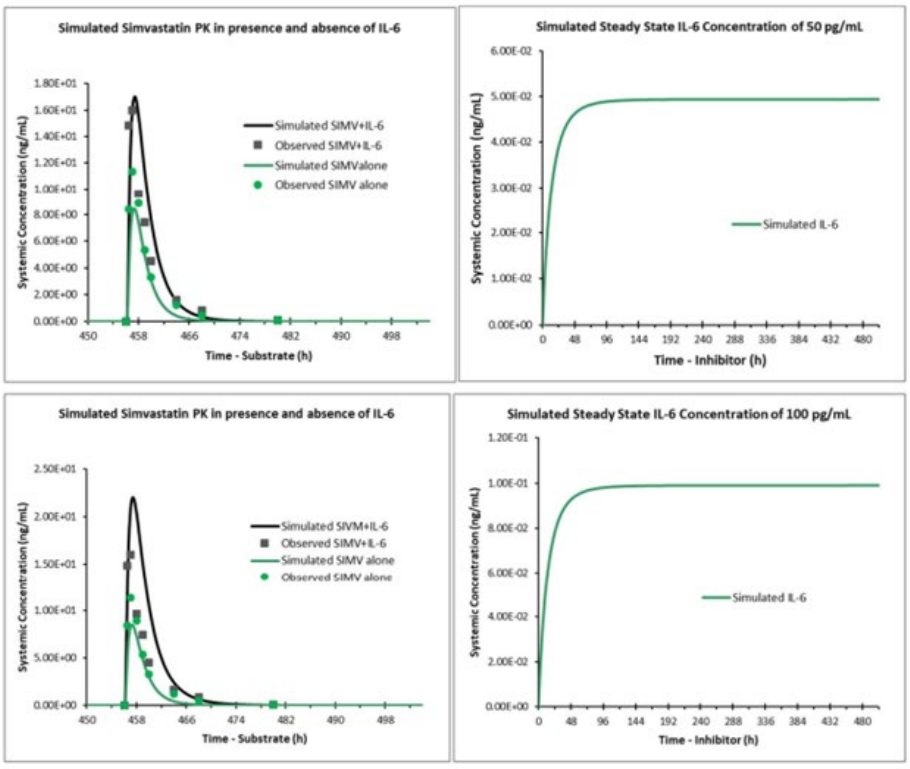
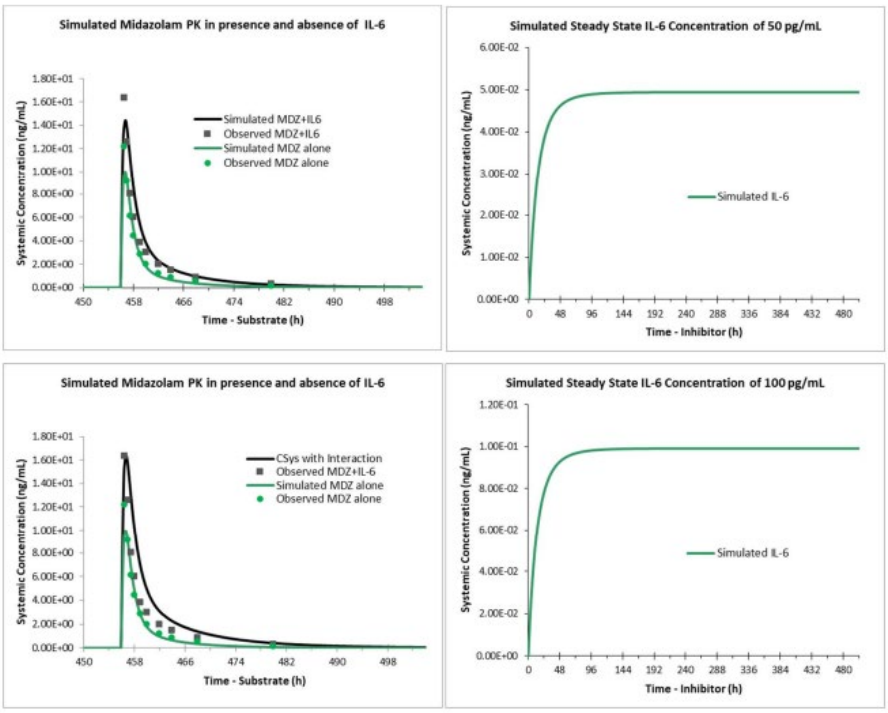


Figure 22 Simulated and Observed Simvastatin (0.03 mg/kg on Day 19) Pharmacokinetics in Presence and Absence of IL-6 (TOP Row: Steady State Concentration of 50 pg/mL, Bottom Row: Steady State concentration of 100 pg/mL)



2.6.2.2. Pharmacodynamics

Mechanism of action

The mechanism of action of mosunetuzumab involves recruitment of effector T-cells via CD3 to engage with target CD20-expressing B cells, leading to T-cell activation (independent of TCR epitope specificity) and T-cell mediated B cell cytolysis.

Primary and Secondary pharmacology

Exposure-response relationships for safety were assessed based on 439 patients receiving IV administration of mosunetuzumab from Study GO29781; specifically, 32 patients from Group A cohorts receiving doses ranging from 0.05 to 2.8 mg q3w, and 407 patients from Group B step-up dosing cohorts receiving doses ranging from 0.4/1.0/2.8 mg to 1.0/2.0/60/30 mg.

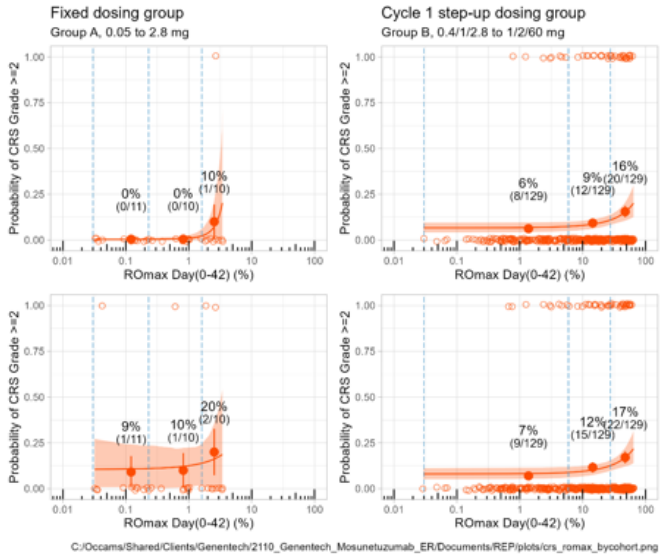
Exposure-Response Analyses for Cytokine Release Syndrome (CRS)

Grade ≥2 CRS was identified as an exposure- and regimen- dependent AE where the administration of mosunetuzumab following the step-up dosing regimen was associated with a low frequency but RO_{max}-dependent increase of Grade ≥2 CRS transiently during Cycle 1 following the 60 mg dose administration on Day 15.

Dosing of mosunetuzumab following the step-up dosing regimen was associated with a relatively low frequency of Grade ≥2 CRS transiently during Cycle 1 following the 60 mg dose administration on Day 15. Higher receptor occupancy values increase the rate of Grade ≥2 CRS. Cycle 1 step-up dosing schedule mitigated the acute CRS risks, and the frequency of Grade ≥3 CRS was less than 3% at the RP2D/intended registration dose and schedule of 1/2/60/30 mg.

The safety cohort on which the E-R analyses were based was large, however it should be noticed that for 20 subjects, RO was not evaluable, and that also for E-R analyses for the other grade ≥3 AEs, analyses were based on a lower number of subjects, only including subjects from Group B step-up dosing cohorts, as subjects from Group A, which received a much lower dose exposure, were not included in order to better assess safety under the proposed step-up dose regimen.

Figure 23 Exposure – response for the occurrence of grade ≥ CRS by dosing regimens and grading

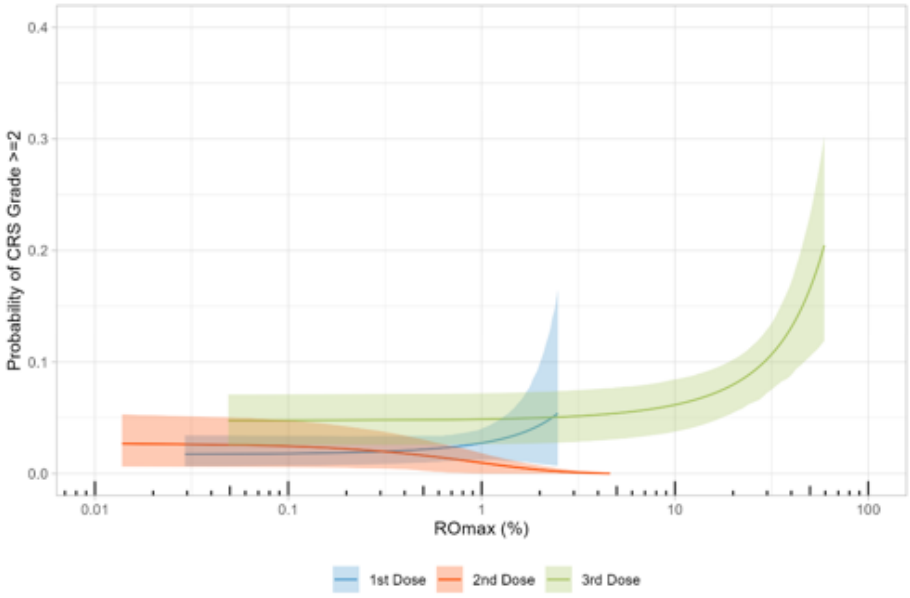


ER by both CRS grading criteria were assessed for completeness. Top row: ASTCT grading criteria; bottom row: Lee grading criteria.

For historical context, the protocol initially used Lee 2014 CRS Grading during the conduct of Group A and the initial cohorts of Group B, and included assessment by ASTCT grading in recent years given the evolution of CRS grading in the scientific field.

RO_{max} Day(0-42) (%)= model–predicted maximum CD20 receptor occupancy (RO%) over 0–42 days post-dose; Grade ≥2 CRS event (0= no event; 1= event) are represented by red circles; stippled blue vertical lines represent tertiles of RO_{max} Day(0-42); solid red line represents the model fit; shaded regions represent the 90% prediction intervals; red filled circles at each tertile indicate the observed median RO_{max} Day(0-42) and observed probability of an event; red vertical lines represent the standard error.

Figure 24 Cycle 1 exposure response curves between dosing windows for the occurrence of grade ≥ 2 CRS following cycle 1 step up dosing regimen

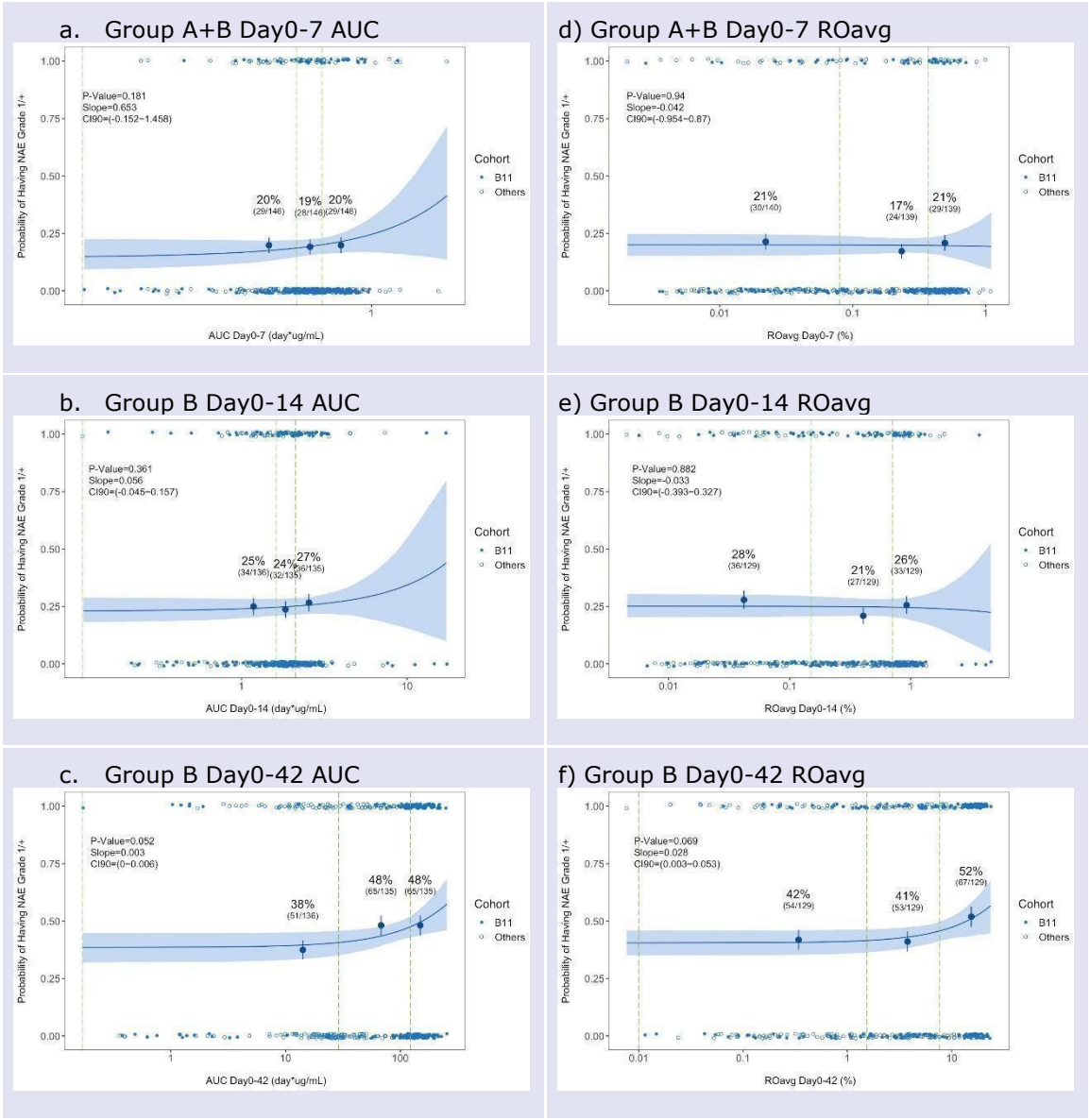


ASTCT= American Society for Transplantation and Cellular Therapy; RO_{max}(%)=model-predicted maximum CD20 receptor occupancy (RO%) for each dose interval. Solid lines represent the model fit; shaded regions represent the 90% prediction intervals. Note that the x-range of each curve represents the available data range as a result of the dose ranging tested (i.e., Day 1 dose from 0.4 to 1 mg; Day 8 dose from 1 to 2 mg; Day 15 dose from 2.8 to 60 mg).

Exposure-Response Analyses for Neurologic Adverse Events (NAEs)

The logistic regression ER analyses indicate a slightly positive ER slope for increased NAE (broadly defined as all AEs reported as primary or secondary PTs in either the SOC of Nervous System Disorders or SOC of Psychiatric Disorders) frequency that occurs with AUC_{0-42} and $ROmax_{0-42}$ metrics ($p>0.05$). This directional trend is consistent with directional trends in Kaplan-Meier analyses, conducted by tertiles of exposure, demonstrating a visual separation occurring near the timing of the higher 60 mg loading dose; however, overall log-rank tests for time-to-event analyses show non-significant p-values in range of ~0.3. The overall effect size of the trend appears small with ~10% difference in NAE incidence observed between the lowest and highest tertile of exposure. Note, 61% (130/213) B11 patients' AUC belongs to 3rd tertile, 28% (60/213) B11 patients' AUC belongs to 2nd tertile, and 11% (28/213) B11 patients' AUC belongs to 1st tertile. A flat ER relationship for NAE was observed following the Cycle 1 Day 1 (C1D1) doses of 0.05 to 2.8 mg when mosunetuzumab was administered as fixed q3w doses (i.e., Group A).

Figure 25 E-R Analyses for Occurrence of Any-grade NAE Based on Specified Time Intervals of AUC or ROavg Following Mosunetuzumab IV Treatment in R/R NHL Patients (aNHL + iNHL)



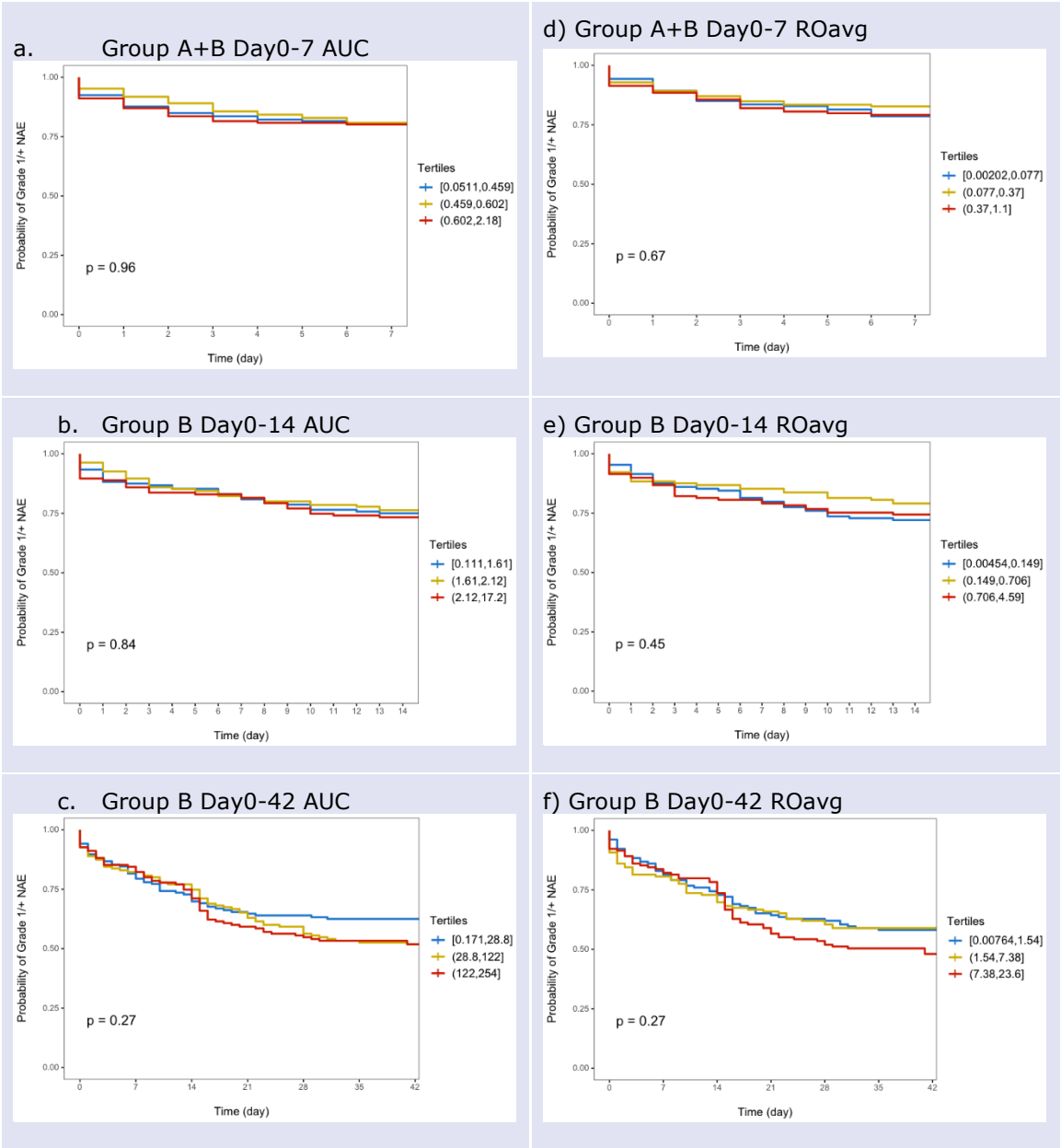
(Subplots a, b and c describe AUC-based E-R analyses; and subplots d, e and f describe ROavg-based E-R analyses) AUC = model–predicted area under the curve; ROavg (%)= model–predicted averaged CD20 receptor occupancy (RO%); Clinical objective responses (0=non-responder; 1=responder) are represented by blue circles; stippled green vertical lines represent tertiles of AUC or ROavg; solid blue line represents the model fit; shaded regions represent the 90% prediction intervals; blue filled circles at each quartile indicate the observed median AUC or ROavg and observed median probability of response; blue vertical lines represent the standard error.

Table 7 Logistic Regression Modeling Results: E-R Assessments of Occurrence of Any-Grade NAE in R/R NHL Patients

PK Exposure Metrics	Dosing Group	Slope	p-value	N	90%CI
AUC (0-7)	Group A+B	0.653	0.181	438	(-0.152,1.458)
ROavg (0-7)	Group A+B	-0.042	0.94	418	(-0.954, 0.87)
AUC (0-14)	Group B	0.056	0.361	406	(-0.045,0.157)
ROavg (0-14)	Group B	-0.033	0.882	387	(-0.393,0.327)
AUC (0-42)	Group B	0.003	0.052	406	(0, 0.006)
ROavg (0-42)	Group B	0.028	0.069	387	(0.003, 0.053)

AUC= area under the curve; CI= confidence interval; N= number; ROavg = average receptor occupancy.

Figure 26 TTE Analyses for any-Grade NAE Onset, Grouped by AUC or ROavg Tertiles Over Specified Time Intervals



AUC0-7, AUC0-14, AUC0-42 tertiles in ug/ml*day, respectively:

- [0.0511, 0.459], (0.459, 0.602], (0.602, 2.18]
- [0.111, 1.61], (1.61, 2.12], (2.12, 17.2]
- [0.171, 28.8], (28.8, 122], (122, 254]

ROavg0-7, ROavg 0-14, ROavg 0-42 tertiles in %, respectively:

- [0.00202, 0.077], (0.077, 0.37], (0.37, 1.1]
- [0.00454, 0.149], (0.149, 0.706], (0.706, 4.59]
- [0.00764, 1.54], (1.54, 7.38], (7.38, 23.6].

Table 8 Log-Rank Test Results: TTE Analyses of any-Grade NAE Onset

PK Exposure Metrics	Dosing Group	p-value
AUC (0-7)	Group A+B	0.96
ROavg (0-7)	Group A+B	0.67
AUC (0-14)	Group B	0.84
ROavg (0-14)	Group B	0.45
AUC (0-42)	Group B	0.27
ROavg (0-42)	Group B	0.27

AUC= area under the curve; ROavg = average receptor occupancy.

Exposure-Response Analyses for Selected Grade ≥3 Adverse Events

Dosing of mosunetuzumab following the step-up dosing regimen did not lead to exposure-dependent increases for Grade ≥3 neutropenia, Grade ≥3 infections or infestations, or all Grade ≥3 adverse events (AEs). Higher mosunetuzumab exposure did not appear to lead to an earlier onset of Grade ≥3 neutropenia, Grade ≥3 infections or infestations, or all Grade ≥3 AEs (see below).

Table 9 AEs by model predicted Mosunetuzumab Exposure

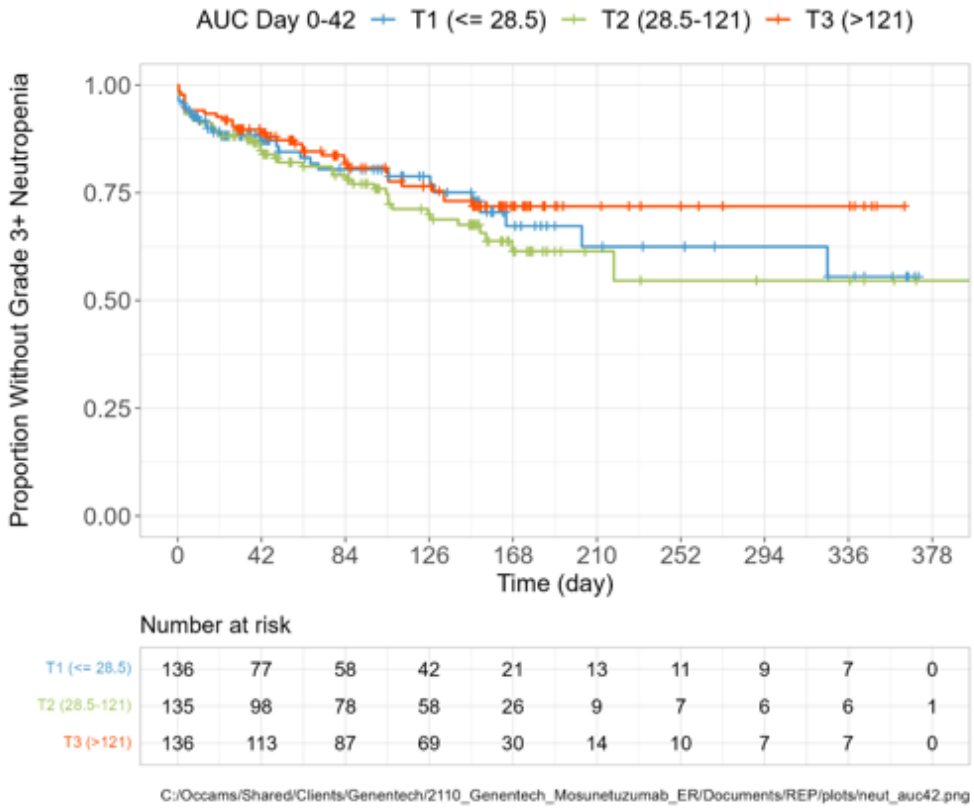
Mosunetuzumab Exposure AUC_{0-42} Tertiles in R/R NHL Patients following IV Mosunetuzumab Administrations Using the Step-Up Dosing Regimen (Group B)

Mosunetuzumab Exposure AUC_{0-42} (day*µg/mL)	Grade 3+ Neutropenia/Neutrophil Count Decreased	Grade 3+ Infections and Infestations (SOC)	All Grade 3+ AEs
Tertile 1 [0.177,28.5]	21.3% (N=29/136)	20.6% (N=28/136)	75.7% (N=103/136)
Tertile 2 (28.5,121]	29.6% (N=40/135)	16.3% (N=22/135)	74.1% (N=100/135)
Tertile 3 (121,254]	23.5% (N=32/136)	8.82% (N=12/136)	60.3% (N=82/136)

AE=adverse event; AUC_{0-42}= AUC from time 0 to 42 days; N=number of patients; SOC=System Organ Class.

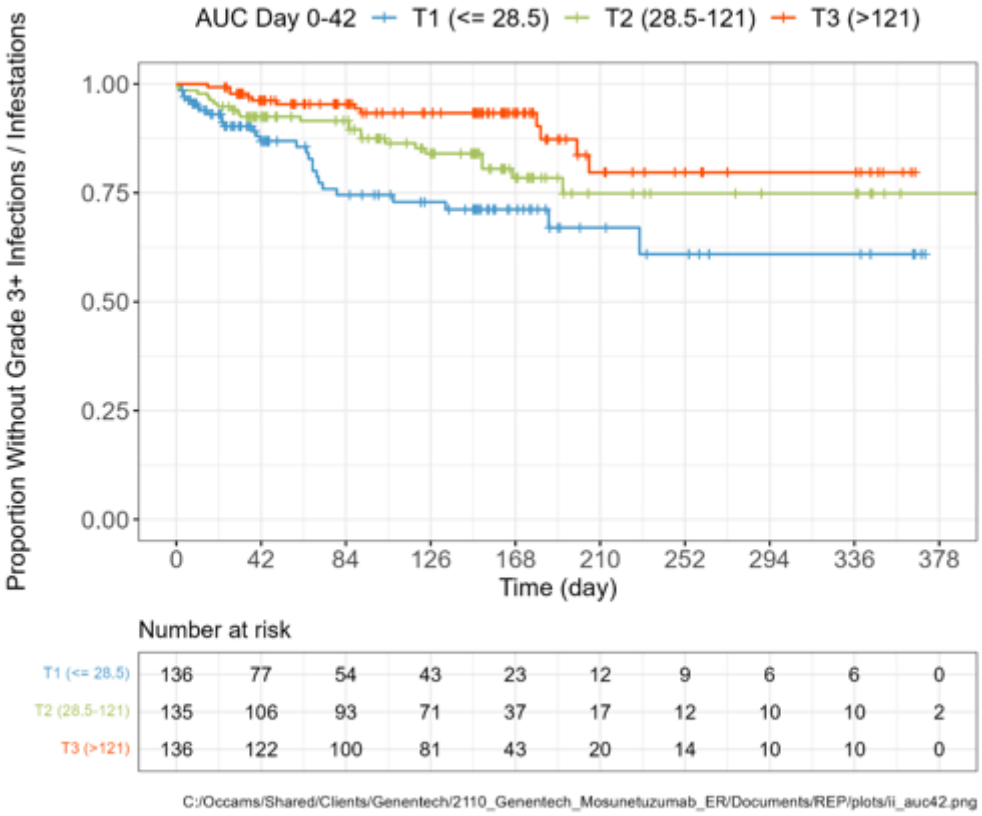
Figure 27 time to event analyses for selected Grade > 3 AEs by AUC0-42 tertiles in R/R NHL patients following mosunetuzumab iv using the step-up dosing regimen(Group B)

a) Grade ≥3 Neutropenia/Neutrophil Count Decreased



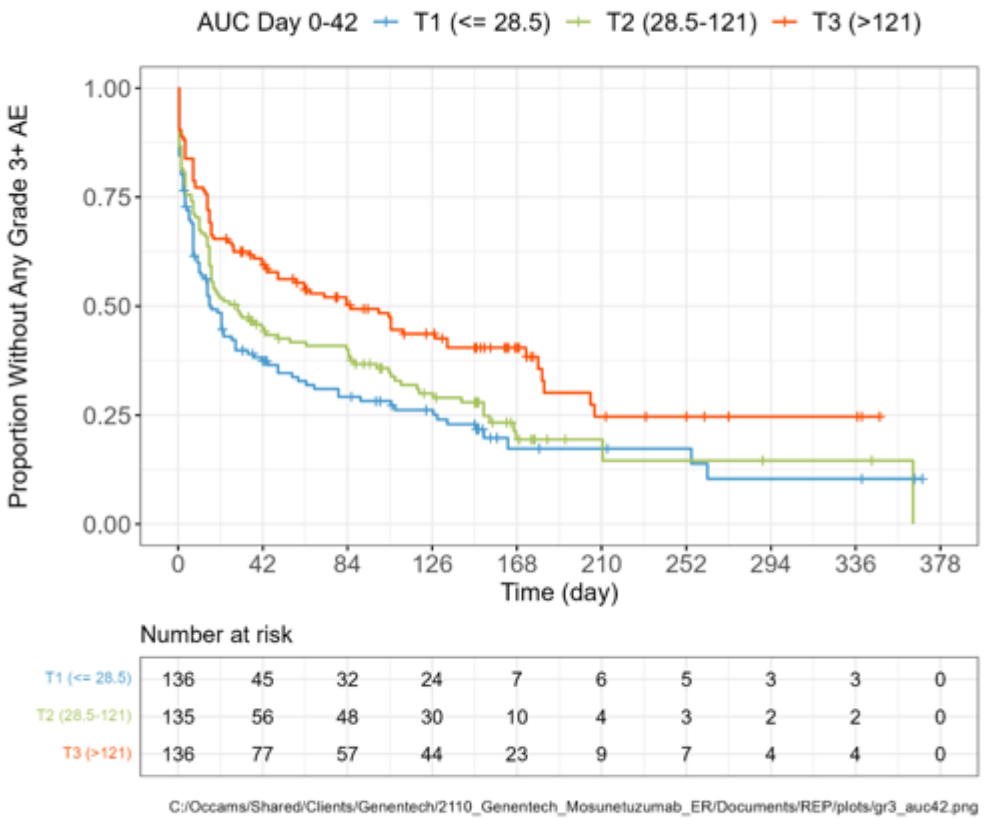
T1 = tertile 1 of mosunetuzumab AUC_{0-42} exposure (≤28.5 day µg/mL).
T2 = tertile 2 of mosunetuzumab AUC_{0-42} exposure > 28.5 day µg/mL and ≤121 day µg/mL).
T3 = tertile 3 of mosunetuzumab AUC_{0-42} exposure (> 121 day·µg/mL).

b) Grade ≥3 Infections and Infestations (SOC)



SOC = System Organ Class.
T1 = tertile 1 of mosunetuzumab AUC_{0-42} exposure (≤ 28.5 day μg/mL).
T2 = tertile 2 of mosunetuzumab AUC_{0-42} exposure > 28.5 day μg/mL and ≤121 day·μg/mL).
T3 = tertile 3 of mosunetuzumab AUC_{0-42} exposure (> 121 day μg/mL).

c) All Grade ≥3 Adverse Event



T1 = tertile 1 of mosunetuzumab AUC_{D-42} exposure (≤ 28.5 day μg/mL).
T2 = tertile 2 of mosunetuzumab AUC_{D-42} exposure > 28.5 day μg/mL and ≤ 121 day·μg/mL).
T3 = tertile 3 of mosunetuzumab AUC_{D-42} exposure (> 121 day μg/mL).

Immunogenicity

As of the anti-drug antibodies (ADA) data cutoff date of 4 December 2020, there was no ADA detected in 418 ADA evaluable patients who received mosunetuzumab single-agent IV treatments in Study GO29781.

QT/QTc Prolongation Potential

No formal QT/QTc studies were performed. The Applicant states that there is a low risk for mosunetuzumab to cause QT/QTc prolongation as mosunetuzumab is not expected to interact directly with the hERG channel.

Drug-Drug Interaction through Effect on Pharmacodynamics

For patients with R/R FL, clinical data to date from Study GO29781 suggest low risk for clinically meaningful DDI through competition of CD20 target engagement with obinutuzumab (G) or rituximab (R). The residual concentrations of baseline G or R were low (median value is below quantitation limit where BQL = 0.5 ⌈g/mL and 0.00405 ⌈g/mL for R and G PK assays, respectively).

Relationship between plasma concentration and effect

The E-R relationships for efficacy were characterized based on INV-assessed clinical objective response data from 159 patients with R/R FL who received ≥2 prior therapies and treated with IV administration of mosunetuzumab in Study GO29781.

The results presented on E-R modelling of CR and OR show that most model parameters are poorly estimated with very high values of RSE. The modelling and simulation results should therefore be interpreted with caution.

The E-R analyses indicate that clinical responses (CR rate and ORR) increase with increasing mosunetuzumab exposure (AUC_{0-42}) and approach a plateau estimated by the model as the maximal clinical responses of 63.7% and 81.4% for CR rate and ORR, respectively.

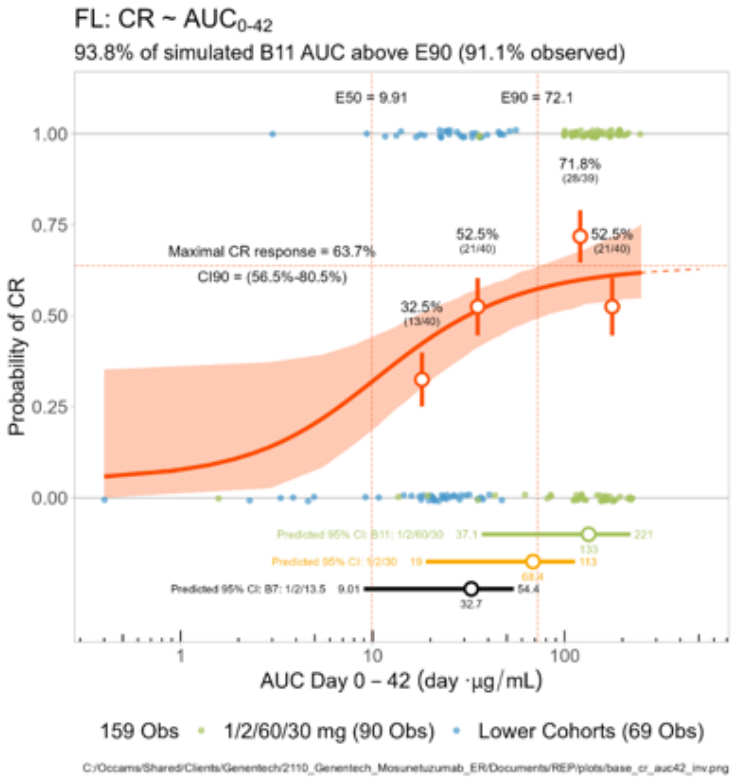
The results indicated that ER curves shift to the right (with an increasing E_{90}) as baseline tumor size in patients increases. Furthermore, the clinical response was lower in the subset of patients who had residual aCD20 concentrations at baseline. The clinical dose of 1/2/60/30 mg achieved average PK exposure (AUC_{0-42}) at or near the plateau of the ER curves, except for the 5% of patients at the highest 95th percentile of baseline tumor SPD (10816 mm^2 or square root of baseline tumor SPD equal to 104 mm).

Based on the 15 March CCOD, the finding of the covariate analysis for efficacy E-R (CRR) with regard to lower clinical response in the subset of patients who had residual aCD20 concentrations at baseline seems to be confirmed by efficacy subgroup analyses in the B11 FL RP2D Expansion Cohort, which suggest that subjects with 3 months or less time since last anti-CD20 therapy (n = 23) had particular less favourable CRR and ORR (35% [95% CI: 16%, 57%]) and 65% [95% CI: 43%, 84%], respectively) compared to subjects with more than 3 months since last anti-CD20 therapy (n = 67; CRR = 66% [95% CI: 53%; 77%]).

Clinical response increases in an exposure-dependent manner and plateaus at the AUC_{0-42} values of approximately 72.1 and 38.4 day*μg/mL corresponding to the estimated E_{90} for CRR and ORR, respectively.

Figure 28 Exposure (AUC0-42) Analyses for Inv assessed clinical response following mosunetuzumab iv using the step-up dosing regimen(Group B)

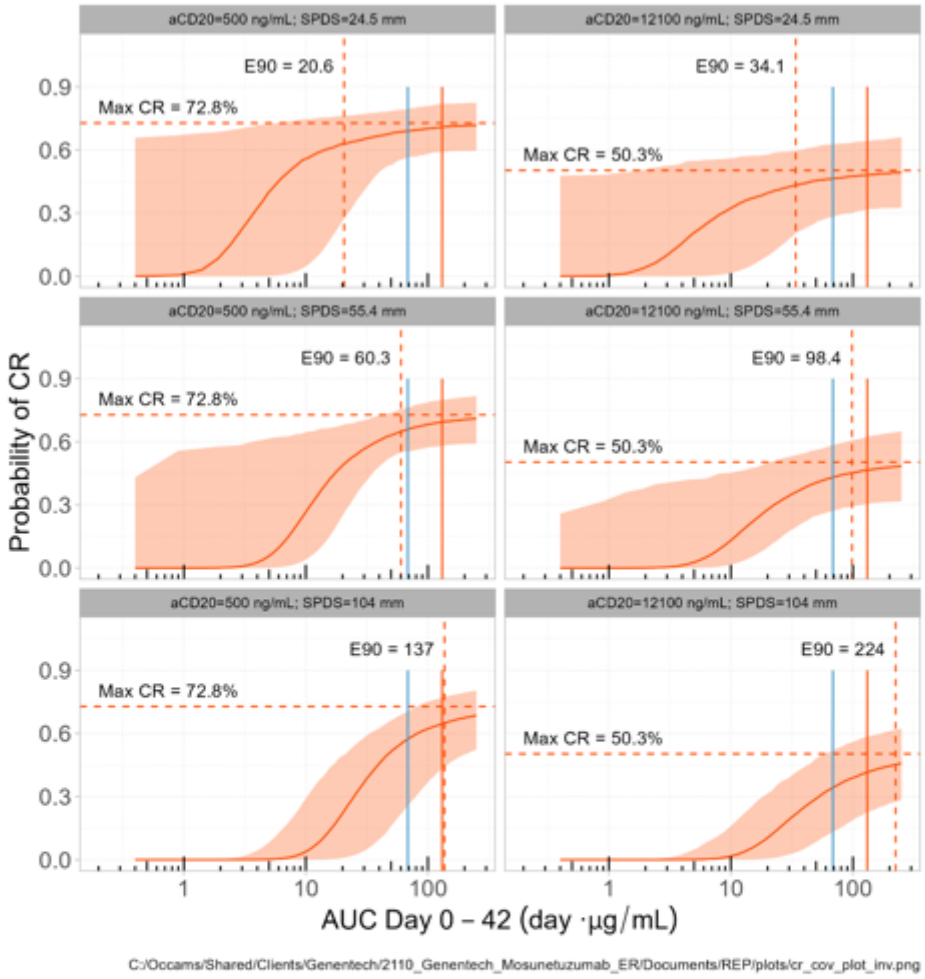
a) Complete Response Rate (CRR)



AUC= area under the curve; CI= confidence interval; CI90 = 90% confidence interval; CR=complete response; E_{50} = AUC_{0-42} at 50% of maximal response; E_{90} =AUC_{0-42} at 90% of maximal response; FL=follicular lymphoma.

Filled circles represent the individual patient AUC_{0-42} (green = 1/2/60/30 mg; blue = lower dose cohorts) and response assessment (0=no event, 1=event); orange solid line represents the ER curve based on the final parameter estimates; orange shaded area represents the ER model-estimated 90% CI. Percentages indicate the observed response rate (%; (x/y = x responders out of y patients) within each exposure quartile. Open circles are the observed median probability of patients having a clinical response; error bars are the SE [sqrt(P*(1-P)/N)] at each exposure quartiles of exposure. Horizontal lines at the bottom represent simulated AUC distributions (median with 95% CI) at selected dose levels (green = 1/2/60/30 mg; yellow =1/2/30 mg; black=1/2/13.5 mg); simulations are based on the popPK model EBEs.

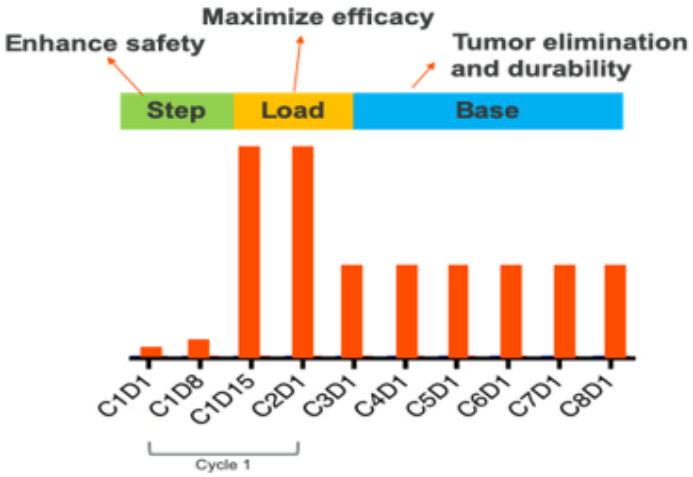
Figure 29 Effects of Baseline Tumor Size (SPDS) and aCD20 Baseline Concentration On the Exposure (AUX_{0-42}) – Response Analyses for Investigator-Assessed Clinical Response Following IV Administrations of Mosunetuzumab Monotherapy (Study GO29781)



CR = complete response; E_{90} = AUC_{0-42} at 90% of maximal response; SPDS= square root of tumor sum of product diameter
Figure 8 (left panel) represents the majority (~65%) of R/R FL patients, who do not measurable R or G concentrations at baseline (assay limit of quantification = 0.5 µg/mL for R and 0.004 µg/mL for G PK assays, respectively). Figure 8 (right panel) represents the ER in the subset (~35%) of patients who have a median level of ~12.1 µg/ml of R or G at baseline (or at the 82nd percentile of the overall R/R FL patient population); Panels from top to bottom represents the 5th, 50th, and 95th percentile splits used for square root of SPD (mm); shaded region reflects ER model uncertainty; Vertical solid lines represent the mean $AUC_{Day0-42}$ at simulated dose levels of 1/2/30 mg (blue) and 1/2/60/30 mg (red); Vertical dashed lines represent E_{90}.
Source: ER Report No. 1110347, Figure 8.

The proposed registration dose and schedule of mosunetuzumab is administered using the Cycle 1 step-up regimen (i.e., 1 mg and 2 mg on Cycle 1 Day 1 and 8, respectively, as the "step doses", followed by two "loading doses" of 60 mg on Cycle 1 Day 15 and Cycle 2 Day 1, and then maintained at the "base dose" of 30 mg for the remaining Cycles 3–8; treatment continues for 17 cycles - approximately 1 year - if CR is not achieved by Cycle 8), referred to as 1/2/60/30 mg.

Figure 30 Conceptual Illustration of the Intended Registration Dose and Schedule for Mosunetuzumab in R/R FL*



*With the option to dose up to 17 cycles if Complete Response is not achieved by Cycle 8.

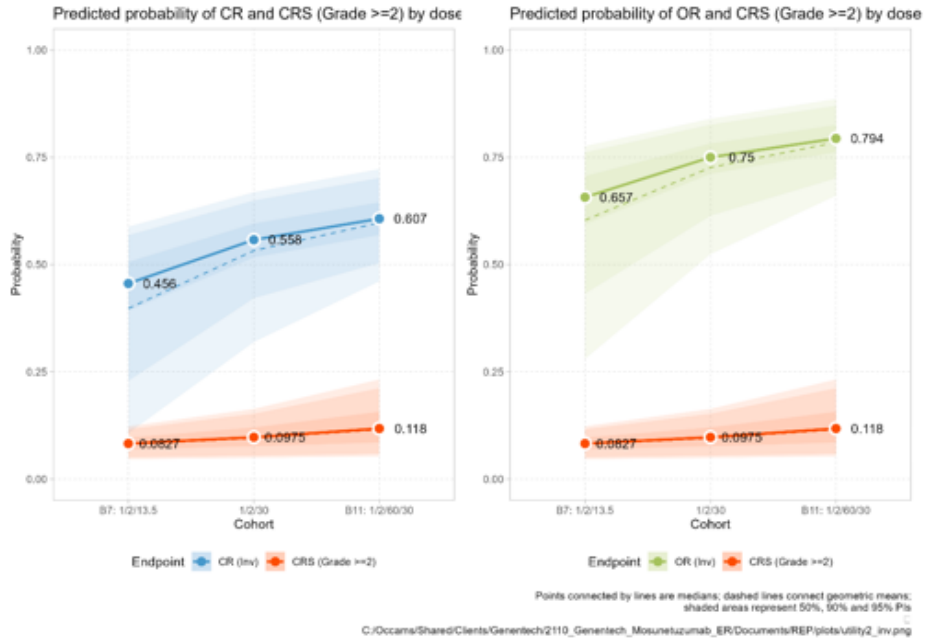
Exposure-efficacy

Based on 15 March 2021 CCOD, at the proposed registration dose and schedule of 1/2/60/30 mg, mosunetuzumab IV monotherapy showed IRF-assessed CR rate of 57.8% (95% CI: 46.9, 68.1) and ORR of 78.9% (95% CI: 69.0, 86.8) with associated durability. The proposed registration dose and schedule of 1/2/60/30 mg was predicted to achieve PK exposures at the plateau of the ER curves for CRR and ORR.

Exposure-safety

Grade ≥2 CRS was identified as an exposure- and regimen- dependent AE where the administration of mosunetuzumab following the step-up dosing regimen was associated with a relatively low frequency but RO_{max}-dependent increase of Grade ≥2 CRS transiently during Cycle 1 following the 60 mg dose administration on Day 15. The occurrence of Grade ≥3 CRS frequency was <3%.

Figure 31 Integrated Understanding of Mosunetuzumab Clinical Dose-Response Relationships Predicted by Modeling for CR, OR and Grade ≥2 CRS



CR= complete response; CRS= cytokine release syndrome; Inv= investigator; OR=objective response.

Filled circles represent the model-predicted probability of response (blue for CR, green for OR, red for of Grade ≥2 CRS) at selective dose levels; Points connected by solid lines are medians; dashed lines connect geometric means; shaded areas represent 50%, 90%, and 95% confidence intervals.

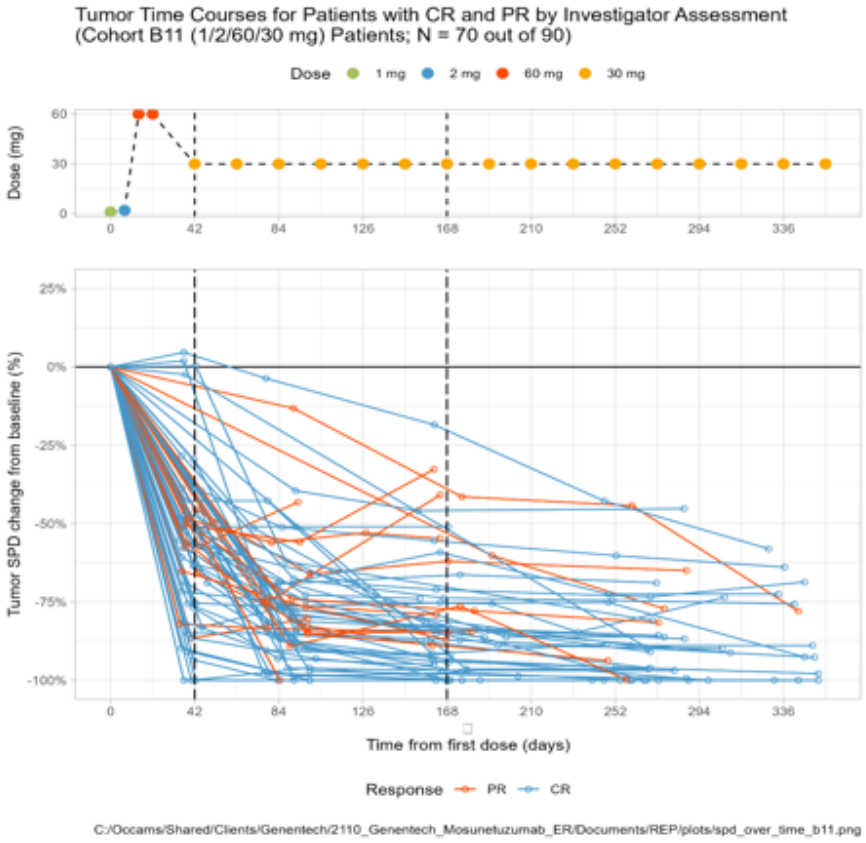
For the 1/2/60/30 mg dose regimen, the modeling predicts 1) a median CRR of 60.7% (95% prediction interval = 46.1–70.2%), 2) a median ORR of 79.4% (66.1–88.6%), and 3) a median Grade ≥2 CRS rate of 11.8% (5.27–23.2%).

For the 1/2/30 mg dose regimen, the modeling predicts 1) a median CRR of 55.8% (95% prediction interval = 32.0–66.9%), 2) a median ORR of 75.0% (52.5–84.0%), and 3) a median Grade ≥2 CRS rate of 9.75% (4.90–16.3%).

For the 1/2/13.5 mg dose regimen, the modeling predicts 1) a median CRR of 45.6% (95% prediction interval = 10.7–58.8%), 2) a median ORR of 65.7% (28.0–77.6%), and 3) a median Grade ≥2 CRS rate of 8.27% (4.60–12.3%).

Source: ER Report No. 1110347, Figure 18 and Table 12.

Figure 32 Individual Change from Baseline (%) in Tumor Size (i.e.; SPD=SUM of the Product of Diameters) vs. Time in Responding Patients with R/R FL ≥2 Prior Therapies Who Received IV Administrations of Mosunetuzumab at 1/2/60/30 mg (GO29781; n=70)



CR= complete response; Inv= investigator; PR=partial response.
This figure illustrates the nominal mosunetuzumab dose regimen of 1/2/60/30 mg (top panel) overlaid with the observed tumor responses for the 70 out of 90 patients who had an objective response (i.e., CR or PR) in this dose group. The stippled line at Day 42 illustrates the time point (Day 42) that was used for the primary efficacy ER endpoint of AUC_{0-42}. The stippled line at Day 168 is the end of Cycle 8 time point, illustrating that the tumor response from the 1/2/60/30 mg mosunetuzumab treatment appears durable over this interval.
Source: ER Report No. 1110347, Appendix 13.

- Post-baseline B-cell depletion:

Per Applicant's analysis, B-cell depletion was defined as a CD19 measurement of <70 counts/µL that occurred after at least one dose of study drug administration. Time to depletion was defined as the number of cycles between the first intake of study drug at baseline and the date of the first depletion. B-cell recovery was defined as a CD19 measurement of ≥70/µL, for which the patient's previous CD19 measurement revealed B-cell depletion. B-cell recovery was considered possible only after the patient had completed study treatment.

Of the 152 evaluable patients in the B11 RP2D cohort who had a baseline sample and at least one follow-up sample to assess B-cell counts, a majority of patients (110/152; 72.4%) enrolled with B-cell counts below 70 cells/µL. This is likely reflective of prior anti-CD20 therapy in R/R NHL patients. By Cycle 2 Day 1 treatment with mosunetuzumab IV monotherapy, 135/139 (97.1%) patients had CD19+ B-cell counts <70 cells/µL and by Cycle 8, Day 1, 102 out of 102 patients (100%) had B-cell counts <70 cells/µL.

At the time of the updated CCOD (27 August 2021), only 18 patients had follow-on samples available for analysis and B-cell counts. B-cell counts remained depleted in all 18 patients at 3 months post-treatment and had recovered in only one patient with prior B-cell depletion at 6 months post-treatment. Limited data of an additional 32 patients with B-cell recovery data at time points later than 6 months after treatment completion, including 2 patients with data for more than one follow-up visit, suggest an increase in B-cell recovery at later timepoints, consistent with the time to recovery for other anti-CD20 therapies.

- Post-baseline IgG level:

At the time of the updated CCOD (27 August 2021), of the 105 evaluable patients in the B11 RP2D cohort who had a baseline IgG measurement and at least one post-baseline IgG measurement, a total of 38 patients enrolled with IgG levels <5 g/L, while the remaining 67 patients had baseline IgG levels ≥5 g/L.

Among patients with baseline IgG levels <5 g/L, a majority (30/38 patients; 78.9%) maintained their post-baseline IgG levels <5 g/L. Among patients with baseline IgG levels ≥5 g/L, a greater proportion of patients maintained their post-baseline IgG levels ≥5 g/L, while the remaining patients (27/67; 40.3%) had depletions in their IgG values post treatment with mosunetuzumab IV monotherapy to values <5 g/L.

- Hypogammaglobulinemia:

As of CCOD 27 August 2021, hypogammaglobinemia was reported in 9 of 414 patients (2.2%) in Group B and 7 of 218 patients (3.2%) in B11 recommended Phase II dose (RP2D) cohort. All the events were Grade 1-2. All the events were non-serious. Immunoglobulin decreased was reported in 1 patient (0.2%) in B11 RP2D cohort. The event was Grade 1 and non-serious. The onset date of hypogammaglobinemia or immunoglobulin decreased events ranged from 17-563 days. Seven patients with hypogammaglobinemia or immunoglobulin decreased from Group B received treatment with immunoglobulin and 5 patients recovered. The duration of the resolved events ranged from 0-55 days. Infections with concurrent hypogammaglobinemia or Immunoglobulin decreased (infections events occurred within 30 days of hypogammaglobinemia/Immunoglobulin decreased) occurred in 3 patients. Except for 1 Grade 3 serious lower respiratory tract infection, all other events were Grade 1-2, non-serious. Infections were also observed in patients without hypogammaglobinemia or immunoglobulin decreased. The frequency of infections concurrent with hypogammaglobinemia/Immunoglobulin decreased was lower than the frequency of infections observed in the whole population of Group B (11.1% in Group B as of CCOD 27 August 2021). Therefore, the clinical safety data did not suggest that hypogammaglobinemia/immunoglobulin decreased contributed to increased risk of infections or serious infections.

No hypogammaglobinemia or immunoglobulin decreased events were reported in Group A.

After mosunetuzumab initiation, 25 patients (6.0%) in Group B received immune globulin as a concomitant medication. In 15 patients (3.6%), this was for the treatment of hypogammaglobinemia, low hypogammaglobinemia or low IgG, including 2 patients concurrent with infections. In 6 patients, immune globulin were indicated for the treatment of infections or infections prophylaxis. Other indications for immune globulin included disease related immune deficiency, pre-medication of leukapheresis, infusion related reaction, and supplement, reported in one patient, respectively.

- Intratumoral CD20:

Correlation analyses between CD20 expression level and PK and efficacy outcomes did not show a clear relationship, nor in terms of response rates (similar range of CD20+ staining for both responders and non-responders), nor in terms of duration of response (3/4 patients with ≤50% CD20+ staining had

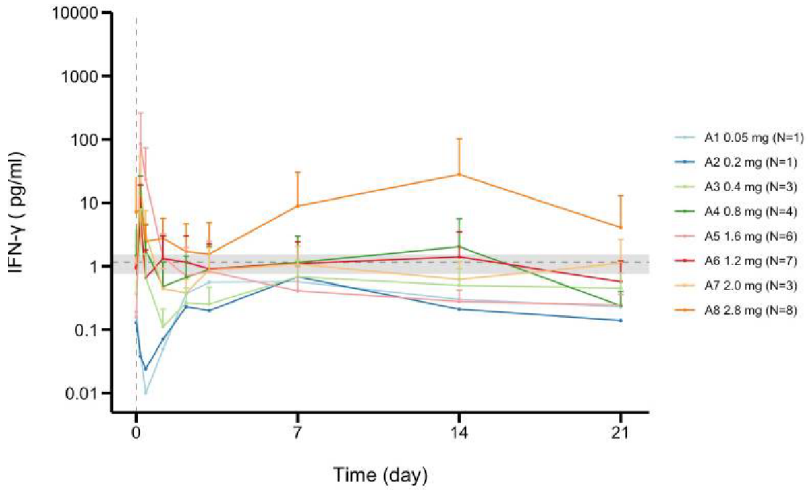
durable responses), nor in terms of exposure (similar ranges of exposure in patients with lower CD20 expression levels).

- Cytokine levels:

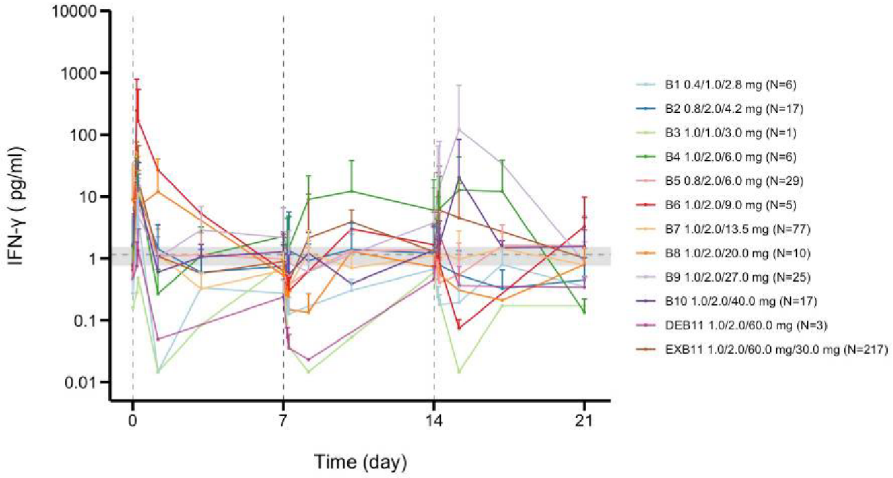
Only IL-6 and INFγ were cytokines that were measured in all cohorts, including the Group B step-up dosing cohorts. The PD profiles of IL-6 and INFγ were similar and were for the step-up dosing Cohort Group B characterized by an acute and transient elevation, predominantly limited to the first cycle of treatment, despite the continued accumulation in the serum of mosunetuzumab. In general, no changes from baseline were observed in later cycles. It is likely that this initial acute transient elevation in cytokine levels reflects the initial target engagement and is associated with an acute clinical safety profile (e.g., CRS).

Figure 33 Arithmetic Mean (+SD) of Plasma IFN-γ Concentration vs. Nominal Time Following IV Administrations of Mosunetuzumab in R/R NHL Patients (Top: Group A, Fixed Dosing from 0.05 mg to 2.8 mg; Bottom: Group B, Step-Up Dosing from 0.4/1.0/2.8 mg to 1.0/2.0/60.0/30.0 mg)

Group A



Group B



2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

ELISA based methods were used for the bioanalysis and for ADA determination.

To ensure detection of 100 ng/mL positive control ADA, drug concentrations should be ≤1 µg/mL. Most samples taken for ADA evaluation had a drug concentration >1 µg/mL.

Two mouse anti-idiotypic antibodies against the anti-CD3 (PC1) and anti CD20 (PC2) portion of mosunetuzumab were used as positive controls in the ADA assay. 100 ng/mL PC1 remained positive at 5.00 µg/mL of mosunetuzumab while 100 ng/mL PC2 was positive at 1.00 µg/mL and negative at 5.00 µg/mL of mosunetuzumab. 99% of samples had mosunetuzumab levels <5.00 µg/mL. The drug tolerance of ADAs raised against the anti-CD3 part of mosunetuzumab is adequate as tested by the mouse surrogate marker PC1. The drug tolerance of ADAs raised against the anti-CD20 part of mosunetuzumab is less good. However, ~50% samples had mosunetuzumab levels <1.00 µg/mL (reported DT of PC2) and 78% samples had mosunetuzumab <2.12 µg/mL. Therefore, the impact of potential false negatives against the anti-CD20 is considered low and a new assay will not be requested.

Interference of previous monoclonal antibody (mAb) treatments (including rituximab, obinutuzumab and polatuzumab vedotin) in screening and confirmatory mosunetuzumab anti-drug antibodies (ADA) assays were evaluated and no interference was observed.

No neutralising antibody assay was developed because minimal immunogenicity responses are expected.

Population PK analysis

Population PK analysis was conducted on data from 439 PK evaluable patients in Study GO29781. The final model was 2-compartmental with time-varying CL and allometric scaled weight effect. The model demonstrated good predictive performance and is adequate for the intended purpose. The conclusion related to the lack of clinical relevance of the covariate tested are endorsed.

ADME

There have been no dedicated clinical biopharmaceutic studies for mosunetuzumab to support the MA, because mosunetuzumab is administered intravenously and no food effect would be expected with parenteral administration.

The serum concentration-time data was best described by a two-compartmental popPK model and a time-dependent clearance. The central volume of distribution of 5.49 L is larger than plasma volume, suggesting the potential impact of binding to immediately accessible targets following IV administration of mosunetuzumab. The apparent half-life (t1/2) was approximately 3 to 10 days. The terminal half-life estimate was 16.1 days at steady state based on population PK (popPK) model simulations.

Monoclonal antibodies are metabolized to peptides and amino acids in several tissues. The liver is not considered the major clearance organ for IgG, as well as renal excretion is not considered as a major elimination pathway.

Overall, the time dependency of mosunetuzumab pharmacokinetics (PK) and accumulation patterns were well characterized by the popPK model. Mosunetuzumab behaves like a typical IgG1 monoclonal antibody, and steady state exposure is achieved by ~Cycle 4. The overall pharmacokinetic (PK) disposition and accumulation patterns of mosunetuzumab are still consistent with that of other monoclonal antibody therapeutics. Mosunetuzumab exhibits linear and dose-proportional pharmacokinetics in the dose range studied (0.2 to 60 mg) and in the clinically active dose range (≥1.2

mg). Target-mediated drug disposition (TMDD) was tested in the popPK model, but the results did not indicate improvement in descriptions of the data over simpler linear models, either with or without time-dependent clearance approaches. A moderate to high inter-individual variability (IIV) was observed for mosunetuzumab key PK parameters (range from 18% to 86%).

Special populations

No clinically meaningful baseline covariates were found for mosunetuzumab PK requiring dose modifications

Based on exposure-response analysis and clinical exposure margins, no dose adjustment is required due to patient bodyweight.

No dose adjustment of Lunsumio is required in patients ≥ 65 years of age (see section 5.2).

Lunsumio has not been studied in patients with severe renal impairment. Dose adjustments are not considered necessary in patients with mild to moderate renal impairment based on pharmacokinetics (see section 5.2).

Lunsumio has not been studied in patients with hepatic impairment. Dose adjustments are not considered necessary based on pharmacokinetics (see section 5.2).

Drug-drug interactions

No clinical DDI studies have been conducted with mosunetuzumab.

A PBPK model for IL-6 was built using a top-down approach based on a modified literature model and used to assess the magnitude of potential CYP3A4 suppression caused by cytokines. Clinical IL-6 data from study GO29781 were used to optimise/build the PBPK model and also to verify the simulations of IL-6 profiles following mosunetuzumab 1/2/60 mg dosing.

Graphical figures of simulated vs observed interleukin-6 (IL-6) concentrations, midazolam and simvastatin for Schmitt et al. (2011) and Zhuang et al. (2015) study data were presented. For IL-6 - midazolam (MDZ) drug-drug interaction (DDI) prediction by the physiologically-based pharmacokinetic (PBPK) model described in the report, a single 5 mg oral dose of MDZ was used while 0.03 mg/kg was stated in the reference. To provide simulated vs. observed MDZ pharmacokinetic (PK) profile as in the reference, additional DDI simulations using 0.03 mg/kg MDZ with IL-6 at 50 pg/mL and 100 pg/mL were conducted. The predicted DDI, expressed as MDZ exposure (maximum serum concentration [Cmax] and area under concentration time curve [AUC]) ratio, was similar at 0.03 mg/kg MDZ dose versus the 5 mg MDZ dose. Both observed simvastatin and MDZ PK in the presence and absence of IL-6 are described reasonably well by the PBPK simulations. However, the modelling platform is not considered adequately qualified for prediction of CYP3A4 interactions according to the PBPK guideline.

No dose adjustment for mosunetuzumab is recommended when co-dosing mosunetuzumab with small molecule drugs which are CYP3A substrates. However, a clinically relevant effect on CYP450 substrates with a narrow therapeutic index, in which the dose is individually adjusted (e.g. warfarin) cannot be excluded, since initiation of mosunetuzumab treatment causes a transient increase in cytokine levels which may cause inhibition of CYP450 enzymes. On initiation of therapy in patients being treated with CYP450 substrates with a narrow therapeutic index, therapeutic monitoring should be considered. The dose of the concomitant medicinal product should be adjusted as needed. This information has been provided adequately in the SmPC section 4.5.

Pharmacodynamics

Primary pharmacodynamics

B-cell aplasia is an expected on-target toxicity of both mosunetuzumab treatment and prior anti-CD20 therapy. By Cycle 8 Day 1, all patients with available baseline and follow-up B-cell count measurements experienced B-cell aplasia (defined as CD19 measurement of <70 counts/µL), however more than 70% of subjects already had B-cell aplasia at baseline. Limited data of B-cell counts post treatment suggest that B-cell aplasia may persist at longer term (at 6 months post treatment only 1 out of 18 patients with available follow-on samples for analysis and B-cell counts shows B-cell recovery). B-cell aplasia might indicate the durability of the mosunetuzumab effect. Further characterisation of B-cell aplasia and the time to B-cell recovery is expected from further data collected with longer follow-up in ongoing study GO29781.

Also, IgG decrease is an on-target toxicity expected to result from B-cell aplasia. For a proportion of patients (40.0%) with baseline IgG levels ≥ 5 g/L depletions in their IgG values were observed post treatment to values <5 g/L. For the majority of patients (78.9%) with baseline IgG level < 5 g/L, this low level was maintained post-baseline.

With regard to hypogammaglobulinemia, this was reported in 9 of 414 patients (2.2%) in Group B, with all events being Grade 1-2 and non-serious. Seven of them were treated with immunoglobulin therapy and 5 recovered within a range of 0 to 55 days. Overall, 25 patients (6.0%) in Group B received immune globulin as a concomitant medication, for the treatment of hypogammaglobinemia, low hypogammaglobinemia or low IgG, including 2 patients concurrent with infections.

No clear relationship has been observed between CD20 expression level and PK and efficacy outcomes.

IL-6 and INFγ time profiles were similar and were for the step-up dosing Cohort Group B characterized by an acute and transient elevation, predominantly limited to the first cycle of treatment, despite the continued accumulation in the serum of mosunetuzumab. In general, no changes from baseline were observed in later cycles.

The Applicant is planning to further characterize and publish the primary pharmacology data for the remaining exploratory PD endpoints (changes CD19+ cells, T-cell subsets and NK-cells, T-cell activation by flow cytometry, and evaluation of intratumoral changes).

Exposure-efficacy

The proposed registration dose and schedule of mosunetuzumab is administered using the Cycle 1 step-up regimen (i.e., 1 mg and 2 mg on Cycle 1 Day 1 and 8, respectively, as the "step doses", followed by two "loading doses" of 60 mg on Cycle 1 Day 15 and Cycle 2 Day 1, and then maintained at the "base dose" of 30 mg for the remaining Cycles 3−8; treatment continues for 17 cycles [approximately 1 year] if CR is not achieved by Cycle 8), referred to as 1/2/60/30 mg.

Based on 15 March 2021 CCOD, at the proposed registration dose and schedule of 1/2/60/30 mg, mosunetuzumab IV monotherapy showed IRF-assessed CR rate of 57.8% (95% CI: 46.9, 68.1) and ORR of 78.9% (95% CI: 69.0, 86.8) with associated durability. The proposed registration dose and schedule of 1/2/60/30 mg was predicted to achieve PK exposures at the plateau of the ER curves for CRR and ORR.

"Step Doses" of 1 mg and 2 mg on Cycle 1 Day 1 and 8 are clinically active and well tolerated doses shown to mitigate the ROmax-dependency of the acute CRS. The two loading doses of 60 mg induced rapid and durable tumor reduction in responding patients who received the 1/2/60/30 mg clinical regimen. This rapid response over the first 2 cycles further supports the rationale of the Applicant to incorporate loading doses in early cycles in order to maximize clinical benefits, particularly, for patients with larger baseline tumor burden; the 30 mg base dose following such rapid initial tumor debulking was shown to induce durable clinical response. The lowering of the dose from 60 mg loading to 30 mg base

dose (from cycle 3 onwards) minimizes unnecessary over-exposure in patients during the treatment duration to minimize any potential for acute or chronic/cumulative toxicity.

The rationale for the 60 mg loading doses for the first 2 cycles (on Cycle 1 Day 15 and Cycle 2 Day 1) is illustrated by comparing to a simulated dose regimen of 1/2/30 mg (replacing the 60 mg loading doses with 30 mg). The model predicts further increase in clinical CRR and ORR with minimal increase in Grade ≥2 CRS. Furthermore, the 60 mg loading doses better ensure the majority of patients achieve PK exposure corresponding to the efficacy plateau of the ER curves (as assessed by E90 and 90% CI) thereby maximizing the therapeutic potential of mosunetuzumab in patients with R/R FL ≥2 Prior Therapies.

The dose and schedule of mosunetuzumab is recommended as a Cycle 1 step-up regimen (i.e., 1 mg and 2 mg on Cycle 1 Day 1 and 8, respectively, as the "step doses", followed by two "loading doses" of 60 mg on Cycle 1 Day 15 and Cycle 2 Day 1, and then maintained at the "base dose" of 30 mg for the remaining Cycles 3−8; treatment continues for 17 cycles [approximately 1 year] if CR is not achieved by Cycle 8), referred to as 1/2/60/30 mg.

Raised PK concerns regarding supplied data in the present Application have been adequately addressed by the MAH. As of the anti-drug antibodies (ADA) data cutoff date of 4 December 2020, there was no ADA detected in 418 ADA evaluable patients who received mosunetuzumab single agent IV treatments in Study GO29781.

Exposure-safety

Grade ≥2 CRS was identified as an exposure- and regimen- dependent AE where the administration of mosunetuzumab following the step-up dosing regimen was associated with a relatively low frequency but RO_{max}-dependent increase of Grade ≥2 CRS transiently during Cycle 1 following the 60 mg dose administration on Day 15. The occurrence of Grade ≥3 CRS frequency was <3%.

The overall clinical experience and ER data support that neurological events are mostly lower grade and have a modest exposure-dependency across the dose range tested (i.e., 0.4/1/2.8 mg to 1/2/60/30 mg) using the step-up dosing regimen.

No exposure-related increases were seen using the step-up dosing regimen with regard to the rates of other Grade ≥3 AEs including neutropenia and infections/infestations. A slightly positive ER slope for increased NAE frequency with AUC_{0-42} and $ROmax_{0-42}$ metrics has been observed, however this trend is not significant ($p>0.05$), indicating only a small effect size. In addition, clinical data with the target step-up dosing regimen, indicating NAEs are overall manageable (Mostly grade 1-2, only 4.4% grade 3 and no grade 4-5), further support that NAEs are not considered to be an important risk for r/r FL patients receiving mosunetuzumab monotherapy.

Two mouse anti-idiotypic antibodies against the anti-CD3 (PC1) and anti CD20 (PC2) portion of mosunetuzumab were used as positive controls in the ADA assay. 100 ng/mL PC1 remained positive at 5.00 µg/mL of mosunetuzumab while 100 ng/mL PC2 was positive at 1.00 µg/mL and negative at 5.00 µg/mL of mosunetuzumab. 99% of samples had mosunetuzumab levels <5.00 µg/mL. The drug tolerance of ADAs raised against the anti-CD3 part of mosunetuzumab is adequate as tested by the mouse surrogate marker PC1. The drug tolerance of ADAs raised against the anti-CD20 part of mosunetuzumab is less good, however, the impact of potential false negatives against the anti-CD20 is considered low as ~50% samples had mosunetuzumab levels <1.00 µg/mL (reported DT of PC2) and 78% samples had mosunetuzumab <2.12 µg/mL and a new assay will not be requested. The Applicant is recommended to improve the assay drug tolerance for PC2 for future applications, if possible.

As of the anti-drug antibodies (ADA) data cutoff date of 4 December 2020, there was no ADA detected in 418 ADA evaluable patients who received mosunetuzumab single-agent IV treatments in Study GO29781.

No formal QT/QTc studies were presented as mosunetuzumab is not expected to constitute a cardiac risk.

Numerical differences in response rates were observed in patients depending on time since last anti-CD20 therapy, although, it should be noted that time since last anti-CD20 therapy could be confounded by other clinical characteristics, for example, refractory status to prior anti-CD20-containing regimens. No dose adjustment for mosunetuzumab is recommended based on prior anti-CD20 therapies.

2.6.4. Conclusions on clinical pharmacology

The Clinical pharmacology programme for Lunsumio is considered adequate. All relevant information has been included in the SmPC.

The Applicant is planning to further characterize and publish the primary pharmacology data for the remaining exploratory PD endpoints (changes in CD19+ cells, T-cell subsets and NK-cells, T-cell activation by flow cytometry, and evaluation of intratumoral changes). This data is expected to be available and published by the end of 2022.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

Study GO29781 is both the dose-finding study and the pivotal efficacy and safety study. For an assessment of dose-response see the pharmacology section.

2.6.5.2. Main study

Title of Study

Study GO29781: An open-label, multicenter, Phase I/Ib (Phase I/II per protocol v12) trial evaluating the safety, efficacy, and PK of escalating doses of mosunetuzumab (BTCT4465A) as a single agent and combined with atezolizumab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Interim Analysis (CCOD 15 March 2021).

Methods

Study Participants

The number of patients enrolled in Group A and Group B per country, followed by the number of centers (in parentheses), is summarized below in descending order:

- Group A (n=33): United States 25 (5), Republic of Korea 7 (2), Canada 1 (1).
- Group B (n=410): United States 185 (13), Australia 76 (9), Canada 59 (3), Republic of Korea 50 (3), Spain 29 (4), Germany 7 (4), United Kingdom 4 (2).

Key inclusion criteria

Patients had to meet the following criteria for study entry:

- Signed Informed Consent Form(s)

- Age ≥18 years
- ECOG Performance Status of 0 or 1
- History of one of the following histologically-documented hematologic malignancies that were expected to express the CD20 antigen, who had relapsed after or failed to respond to at least one prior systemic treatment regimen and for whom there was no available therapy expected to improve survival (e.g., standard chemotherapy, autologous SCT, CAR-T):

  – Dose-Escalation:

    Grades 1-3b FL; MZL (including splenic, nodal, and extra-nodal), transformed indolent NHL, Richter's transformation, DLBCL, PMBCL, SLL, or MCL

      Patients with Richter's transformation who had an absolute lymphocyte count ≥5000/μL were not eligible for enrollment in the NHL dose-escalation cohorts.

      Burkitt lymphoma and lymphoplasmacytic lymphoma were not eligible diagnoses for enrollment into this study.

  – Dose-Expansion:

    Follicular lymphoma cohort: Grades 1-3a FL; patients had relapsed after or failed to respond to at least two prior lines of systemic therapy and had received prior treatment with an anti-CD20-directed therapy and an alkylating agent.

    DLBCL/transformed FL cohort: patients had 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).

      Transformed FL was an eligible diagnosis for enrolment in the DLBCL cohort but had to be relapsed or refractory to standard therapies for transformed FL.

    MCL cohort: patients had relapsed after or failed to respond to at least one prior treatment regimen containing a Bruton's tyrosine kinase (BTK) inhibitor. If BTK inhibitor had been received during participation in a clinical trial, patients had received treatment at a therapeutic dose level.

    Richter's transformation cohort: Patients had relapsed after or failed to respond to at least one prior systemic treatment regimen. Patients had received anthracycline and an anti-CD20-directed therapy in prior treatment regimen(s).

- NHL patients only: had at least one bi-dimensionally measurable lesion (>1.5 cm in its largest dimension for nodal lesions, or >1.0 cm in its largest dimension for extranodal lesions by computerized tomography [CT] scan or MRI)
- Laboratory values as follows:

  – Hepatic Function

    AST and ALT ≤3x the upper limit of normal (ULN) Total bilirubin ≤1.5x ULN; patients with a documented history of Gilbert syndrome and in whom total bilirubin elevations were accompanied by elevated indirect bilirubin were eligible

  – Hematologic Function

    Platelet count ≥75,000/mm3 without transfusion within 14 days prior to first dose of mosunetuzumab

absolute neutrophil count ≥1000/mm3

Total hemoglobin ≥10 g/dL without transfusion within 21 days prior to first dose of mosunetuzumab

Patients who did not meet criteria for hematologic function because of extensive marrow involvement of NHL/CLL and/or disease-related cytopenias (e.g., immune thrombocytopenia) could be enrolled into the study after discussion with and confirmation by the Medical Monitor.

– Serum creatinine ≤ULN or estimated creatinine CL ≥60 mL/min by Cockcroft-Gault method or other institutional standard methods (e.g., based on nuclear medicine renal scan)

- *For women of childbearing potential*: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that resulted in a failure rate of <1% per year, and agreement to refrain from donating eggs, during the treatment period and for at least 3 months after the last dose of mosunetuzumab, 5 months after the last dose of atezolizumab (if applicable), and 3 months after the last dose of tocilizumab (if applicable), whichever was longer. *For men*: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm.

Key Exclusion Criteria

Patients who met any of the following criteria were to be excluded from study entry:

- Pregnant or lactating, or intending to become pregnant during the study or within 3 months after the last dose of mosunetuzumab, 5 months after the last dose of atezolizumab (if applicable), and 3 months after the last dose of tocilizumab (if applicable)
- Prior use of any monoclonal antibody, radioimmunoconjugate or antibody-drug conjugate within 4 weeks before first mosunetuzumab administration
- 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 was shorter, before first mosunetuzumab administration
- Treatment with any chemotherapeutic agent, or treatment with any other anti-cancer agent (investigational or otherwise) within 4 weeks or five half-lives of the drug, whichever was shorter, prior to first mosunetuzumab administration
- Treatment with radiotherapy within 2 weeks prior to the first mosunetuzumab administration. If patients had received radiotherapy within 4 weeks prior to the first mosunetuzumab administration, patients must have had at least one measurable lesion outside of the radiation field. Patients who had only one measurable lesion that was previously irradiated but subsequently progressed were eligible.
- Autologous SCT within 100 days prior to first mosunetuzumab administration
- Prior treatment with CAR-T therapy within 30 days before first mosunetuzumab administration
- Current eligibility for autologous SCT in patients with R/R DLBCL or R/R transformed FL
- Prior allogeneic SCT
- Prior solid organ transplantation

- 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 history of macrophage activation syndrome / hemophagocytic lymphohistiocytosis (HLH)
- Patients with history of confirmed progressive multifocal leukoencephalopathy
- History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins)
- History of other malignancy that could have affected compliance with the protocol or interpretation of results
- Current or past history of CNS lymphoma
- Current or past history of CNS disease, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease

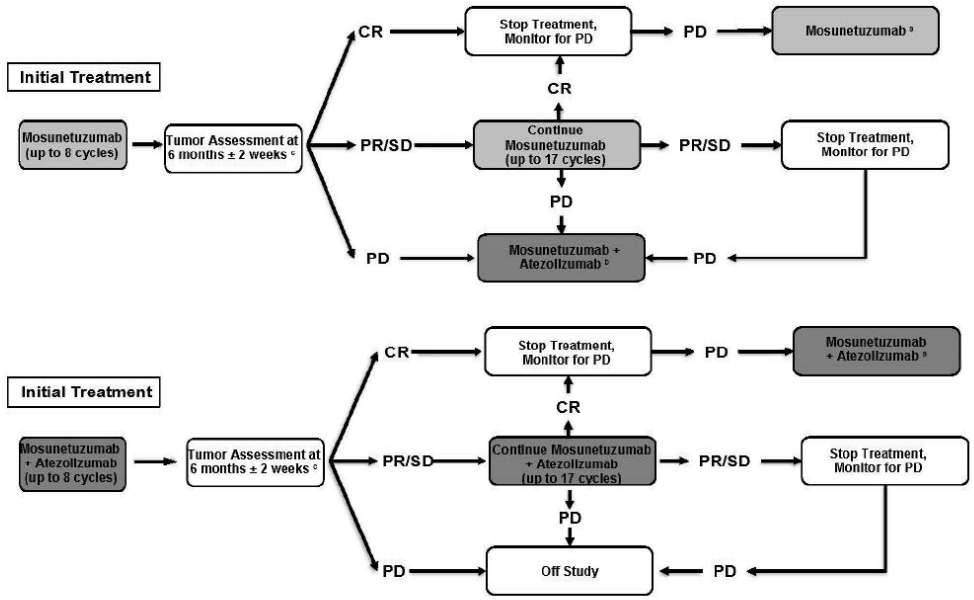
  - Patients with a history of stroke who had not experienced a stroke or transient ischemic attack in the past 2 years and had no residual neurologic deficits as judged by the investigator were allowed.

  - Patients with a history of epilepsy who had no seizures in the past 2 years while not receiving any anti-epileptic medications were allowed in the expansion cohorts only.
- 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
- Significant active pulmonary disease (e.g., bronchospasm and/or obstructive pulmonary disease)
- 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
- Known or suspected chronic active Epstein Barr Virus infection
- Recent major surgery within 4 weeks prior to first mosunetuzumab administration **–** Protocol-mandated procedures (e.g., tumour biopsies and bone marrow biopsies) were permitted.
- Positive serologic or polymerase chain reaction (PCR) test results for acute or chronic hepatitis B virus (HBV) infection
- Acute or chronic hepatitis C virus (HCV) infection **–** Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.
- Positive serologic test results for human immunodeficiency virus (HIV) infection

Enrolment of patients with R/R NHL in Study GO29781 as well as grading of FL was based on local assessment of diagnosis only. Dose-expansion FL cohorts in Study GO29781 did not include patients with diagnosis of Grade 3B FL or transformed FL patients.

Treatments

Figure 34 Mosunetuzumab Treatment/Re-treatment Schema



CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

[a] Additional rounds of re-treatment permitted, follow treatment flow for initial treatment.

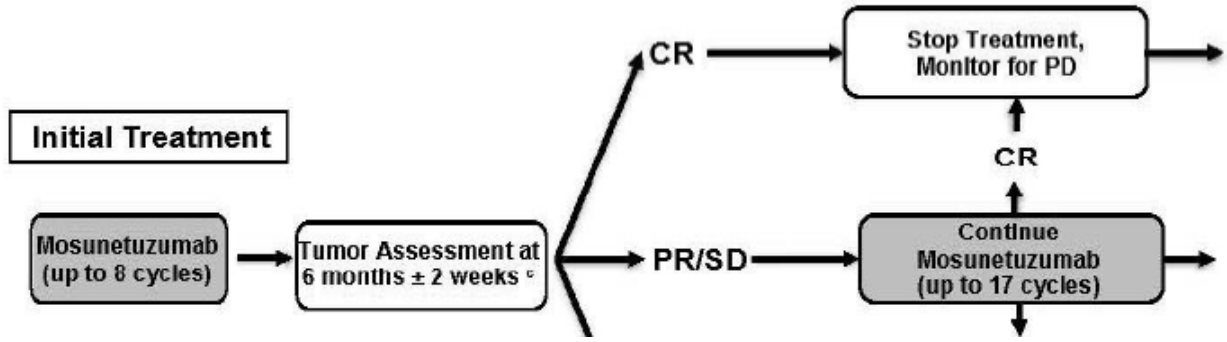
[b] Follow treatment flow for mosunetuzumab+atezolizumab initial treatment.

[c] Scan should be scheduled to avoid/minimize any dose delay between Cycles 8 and 9 as much as possible.

Note: Patients exhibiting acceptable safety and evidence of clinical benefit as described in Section 3.1.1.4 may continue to receive mosunetuzumab every 21 days for a maximum of 8 or 17 cycles.

Mosunetuzumab (BTCT4465A) and Atezolizumab—Genentech, Inc.
102/Protocol GO29781, Version 12

Data in the CSR focuses on the initial treatment. Patients exhibiting acceptable safety and evidence of clinical benefit were eligible to continue receiving mosunetuzumab q3w up to a maximum of 8 or 17 cycles based on tumor response:



Dose of mosunetuzumab for patients with relapsed or refractory follicular lymphoma:

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

Premedication to be administered to patients prior to infusion:

Patients requiring premedication	Premedication	Administration
Cycles 1 and 2: all patients Cycles 3+: patients who experienced any grade CRS with previous dose	Intravenous corticosteroid[1]	Complete at least 1 hour prior to mosunetuzumab infusion
	Anti-histamine[2]	At least 30 minutes prior to mosunetuzumab infusion
	Anti-pyretic[3]	

[1] 20 mg dexamethasone IV or 80 mg methylprednisolone IV
[2] 50-100 mg diphenhydramine hydrochloride or equivalent oral or IV anti-histamine
[3] 500-1000 mg acetaminophen/paracetamol

Tocilizumab (anti-IL6R MAb) will be used to manage safety risks in patients with severe cytokine-release syndrome (CRS).

Objectives

Table 10 Summary of objectives and endpoints for the entire study GO29781:

Objectives	Endpoints/Outcome Measures
Primary • To evaluate the safety, tolerability, and PK of mosunetuzumab in patients with R/R NHL[a] and CLL[c] as described below: – Administered intravenously (IV) as a single agent on a Cycle 1 non fractionated dose schedule (Group A);[a] – Administered IV as a single agent on a Cycle 1 step-up dose schedule (Group B);[a] – Administered subcutaneously (SC) as a single agent on a Cycle 1 non-fractionated dose schedule (Group D);[b] – Administered IV as a single agent on a Cycle 1 step-up dose schedule with concurrent administration of atezolizumab starting in Cycle 2 (Group E)[b] – Administered SC as a single agent on a Cycle 1 step-up dose schedule (Group F)[b]. • To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of mosunetuzumab in patients with R/R NHL[a] and CLL[c] as described below: – Administered IV on a Cycle 1 non-fractionated dose schedule (Group A);[a] – Administered IV on a Cycle 1 step-up dose schedule (Group B);[a] – Administered SC on a Cycle 1 non-fractionated dose schedule (Group D);[b] – Administered IV as a single agent on a Cycle 1 step-up dose schedule with concurrent administration of atezolizumab starting in Cycle 2 (Group E);[b] – Administered SC as a single agent on a Cycle 1 step-up dose schedule (Group F).[b] • To identify, on the basis of safety, PK, and pharmacodynamic data, the recommended Phase II dose(s) and schedule(s) of mosunetuzumab as a single agent[a] and in combination with atezolizumab[a] in patients with R/R NHL[a] and for CLL[c] • To evaluate the efficacy of mosunetuzumab using a Cycle 1 step-up dosing schedule as a single agent (Group B)[a] and in combination with atezolizumab (Group E)[b] in patients with R/R DLBCL and transformed FL and patients with R/R FL, as measured by Independent Review Facility (IRF)-assessed complete response (CR) rate according to standard NHL response criteria.	**Primary safety and tolerability outcome measures:** • The safety and tolerability of mosunetuzumab was assessed using the following primary safety outcome measures: – Incidence and nature of DLTs when mosunetuzumab was given as a single agent IV or SC. – Incidence and nature of DLTs when mosunetuzumab was given in combination with atezolizumab. • Safety and tolerability were additionally assessed using the following secondary safety outcome measures: – Incidence, nature, and severity of AEs – Incidence of CRS (per Lee 2014 grading criteria), as well as interventions for CRS. – Incidence of AEs leading to mosunetuzumab dose modifications – Changes in vital signs and clinical laboratory values – Incidence of ECG abnormality **Primary pharmacokinetic outcome measures:** • The following PK parameters were derived from the serum concentration–time profiles of mosunetuzumab following administration, when appropriate as data allowed: – Total exposure (area under the concentration-time curve [AUC]) – Maximum serum concentration (C_{max}) – Minimum serum concentration (C_{min}) – Clearance (CL) – Volume of distribution at steady state (V_{ss}) Serum trough and maximum concentrations for atezolizumab and tocilizumab, where applicable, were to be summarized, as appropriate and as data allowed. Compartmental, non-compartmental, and/or population methods may be considered. Other parameters, such as accumulation ratio, $t_{1/2}$, and dose proportionality, may also be calculated. **Primary Efficacy Endpoint (for the R/R FL Expansion Cohort and R/R DLBCL and trFL Expansion Cohort, at Group B RP2D)** The primary efficacy endpoint was IRF-assessed CR rate, defined as the proportion of patients whose best overall response was a CR based upon IRF assessment using standard criteria for NHL (Cheson et al. 2007).

Objectives	Endpoints/Outcome Measures
Secondary • To assess the incidence of anti-drug antibodies (ADAs) to mosunetuzumab and atezolizumab (when given in combination with mosunetuzumab), and their relationship to relevant clinical outcomes • Where evaluation of efficacy of mosunetuzumab as single agent and in combination with atezolizumab was not a primary objective as described above, to make a preliminary assessment of the anti-tumor activity of mosunetuzumab, as a single agent[a] and in combination with atezolizumab[b], in patients with R/R NHL[a] and CLL[c] • To assess impact of treatment- and disease-related symptoms on health-related quality of life (HRQoL) and health status according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) subscale, and the EuroQol 5 Dimension-5 Level (EQ-5D-5L) questionnaire in the NHL expansion cohorts[a].	**Secondary Safety Outcome Measure:** • Safety and tolerability were additionally assessed using the following secondary safety outcome measures: – Incidence of ADAs against mosunetuzumab and their relationship to clinical outcomes **Secondary Efficacy Endpoints (for the R/R FL and R/R DLBCL and trFL Expansion Cohorts at Group B RP2D):** • Investigator-assessed CR rate, defined as the proportion of patients whose best overall response was a CR based upon investigator assessment using standard criteria for NHL (Cheson et al. 2007). • ORR, defined as the proportion of patients whose best overall response was a PR or CR using standard criteria for NHL (Cheson et al. 2007). ORR was assessed by the IRF and by the investigator. • Duration of complete response, defined as the time from the initial occurrence of a documented CR until documented disease progression or death due to any cause, whichever occurred first. Duration of complete response was assessed by the IRF and by the investigator, using standard criteria for NHL. • Duration of response, defined as the time from the initial occurrence of a documented PR or CR until documented disease progression or death due to any cause, whichever occurred first. Duration of response was assessed by the IRF and by the investigator, using standard criteria for NHL. • PFS, defined as the time from the first study treatment to the first occurrence of disease progression or death from any cause, whichever occurred first. PFS was assessed by the IRF and by the investigator, using standard criteria for NHL. • OS, defined as the time from the first study treatment to the date of death from any cause. **Secondary Patient-Reported Outcome Measures:** • The HRQoL and health status measures that were used in NHL expansion cohorts to evaluate PROs are as follows: – Summary statistics and change from baseline in HRQoL based on EORTC QLQ-C30 – Summary statistics and change from baseline in disease-related symptoms based on the FACT-Lym subscale – Descriptive results of the EQ-5D-5L data during patients' participation in the study.

ADA = anti-drug antibody; AE = adverse event; AUC = area under the concentration-time curve; CL = clearance; CLL = chronic lymphocytic leukemia; Cmax = maximum serum concentration; Cmin = minimum serum concentration; CR = complete response; CRS = cytokine release syndrome; CSR = clinical study report; DLT = dose-limiting toxicity; ECG = electrocardiogram; IRF = independent review facility; IV = intravenous; MTD = maximum tolerated dose; NHL = non-Hodgkin's Lymphoma; ORR = objective response rate; OS = overall survival; PK = pharmacokinetic(s); PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; RP2D = recommended Phase II dose; SC = subcutaneous.

[a] Results reported in this interim CSR for mosunetuzumab IV monotherapy.

[b] Will be reported subsequently.

For Group B11 RP2D:

To evaluate the efficacy of mosunetuzumab using a Cycle 1 step-up dosing schedule as a single agent (Group B) in patients with R/R DLBCL and transformed FL and patients with R/R FL, as measured by Independent Review Facility (IRF)-assessed CR rate according to standard NHL response criteria (Cheson et al. 2007).

Outcomes/endpoints

The **primary efficacy outcome measure** for this study is IRF-assessed CR rate according to standard NHL response criteria (Cheson et al. 2007). CR rate is defined as the proportion of patients whose best overall response is a CR based upon IRF assessment.

The **secondary efficacy outcome measures** are described in the SAP for study GO29781, and are as follows:

- **Investigator-assessed CR rate**, using standard criteria for NHL (Cheson et al. 2007).
- **ORR**, using standard criteria for NHL (Cheson et al. 2007). ORR was assessed by the IRF and by the INV.
- **DOCR**, assessed by the IRF and by the INV, using standard criteria for NHL (Cheson et al. 2007).
- **DOR**, assessed by the IRF and by the INV, using standard criteria for NHL (Cheson et al. 2007).
- **PFS**, assessed by the IRF and by the INV, using standard criteria for NHL (Cheson et al. 2007).
- **OS**.

Patient-Reported Outcomes

The results for the following PRO analyses are described for patients with R/R FL in the B11 and B7 cohorts who have received ≥2 prior systemic therapies:

- Change from baseline scores in physical functioning and fatigue symptom domains of the EORTC QLQ-C30, disease-related symptoms or concerns of the FACT-Lym subscale, and health status according to the index utility score and the VAS of the EQ-5D-5L.
- Responder analyses of proportion of patients with a clinically meaningful improvement from baseline at any time in physical functioning (≥10-point increase) and fatigue symptom (≥10-point decrease) domains of the EORTC QLQ-C30, and the FACT-Lym subscale (≥3-point increase).
- Time to deterioration from baseline to first documentation of a ≥10-point decrease from baseline in physical functioning, or ≥10-point increase from baseline in fatigue scales of the EORTC QLQ-C30, or a ≥3-point decrease from baseline in FACT-Lym subscale.

Radiographic Assessments

In protocol version 7 (16 August 2018), FDG PET/CT imaging for baseline tumor burden assessment in FDG-avid lymphomas was changed to a requirement, while it was clarified that conventional CT scans were the preferred modality for subsequent imaging timepoints for lymphomas that are shown to not be FDG-avid or have variable FDG uptake at screening.

From protocol version 9 (30 January 2019) onwards, it was clarified that FDG PET and diagnostic-quality CT scans were required at screening and for response assessments during study treatment for lymphoma patients (the specific distinction between FDG-avid/ not FDG-avid was removed). It was also added that during post-treatment follow-up, CT scans with or without PET scans could be utilized for these patients.

Of note, the first patient with R/R FL ≥2 prior therapies in the B7 cohort was treated on 23 February 2018 and in the B11 cohort on 14 May 2019.

All FL patients in the B11 cohort had positive PET-scans at baseline. Of the three patients that also had PET-negative enlarged lymph nodes at baseline, two developed CR (confirmed by CT measurement) and the third had SD.

Sample size

The sample size was selected to be able to show a CR rate superior to 14%. This cut-off value was selected based on the CR rate of idelalisib and copanlisib: 8% and 14%, respectively (the clinical studies included different FL patient populations). The expansion cohorts for FL have been designed to rule out a 14% CR rate and are powered to detect a 14% increase in CR rate from 14% to 28%.

For the R/R FL expansion cohorts of Group B: with observed CR rates of 24% and 28%, a sample size of 80 patients will result in 95% CIs of (15%, 35%) and (18%, 39%), respectively, i.e., a true CR rate below 14% is ruled out. Additionally, 80 patients will provide an 83% power to detect a 14% increase in CR rate from 14% to 28%, at the 5% two-sided significance level.

The Sponsor may enroll more than 80 patients in the R/R FL expansion cohorts of Group B to obtain data from at least 60 patients with R/R FL who are refractory to both anti-CD20 therapy and an alkylating agent to perform statistical analyses.

Randomisation and blinding (masking)

Study GO29781 is an open-label study - a blinded outcome evaluation by IRF is implemented.

Statistical methods

Analysis sets: The primary efficacy analyses will cover Group B efficacy evaluable patients with R/R FL or R/R DLBCL/trFL who have enrolled in the RP2D (1/2/60/30 mg of mosunetuzumab) cohort.

Primary endpoint IRF-CR: Comparisons of CR rate between each efficacy-evaluable population and historical controls will be conducted using an exact binomial test with two-sided alpha level of 5%. The control CR rate is assumed to be 14% for R/R FL population. Patients with missing or no response assessments will be classified as non-complete responders. The exact 95% CIs using the Clopper-Pearson method for CR rate will be provided.

Estimand Framework for Primary Endpoint

Variable: Number of patients who achieve an IRF-assessed CR

Population: The primary endpoint will be conducted separately in R/R DLBCL/trFL and R/R FL efficacy evaluable populations

Treatment: Patients will receive mosunetuzumab monotherapy. Tocilizumab will be used to manage safety risks in patients with severe CRS

Intercurrent events and strategy:

- Discontinuation from study (including COVID-related reasons) prior to achieving CR. Composite Strategy: Patients will be included as non-complete responders.
- Start of new anti-lymphoma therapy (NALT) prior to achieving CR. Composite Strategy: Patients will be included as non-complete responders.

- Discontinuation of study drug (including COVID-related reasons) prior to achieving CR. Treatment policy: Available assessments after the discontinuation of study drug will be used to determine CR status
- Missed any scheduled response assessments (including COVID-related reasons) prior to achieving CR. Treatment policy: Available assessments will be used to determine CR status

Population Level Summary: The proportion of patients in each of the R/R DLBCL/trFL and R/R FL efficacy evaluable populations whose best overall response is a CR based on IRF assessment. Comparisons of CR between the efficacy-evaluable population and historical controls will be conducted using an exact binomial test with two-sided alpha level of 5%.

The primary efficacy analysis population is based on all enrolled patients. The Applicant aims to estimate the complete response rate regardless of missing assessments or treatment discontinuations prior to achieving a CR. . Starting a new anti-lymphoma therapy or study discontinuation prior to achieving a CR is considered as a non-complete response.

Secondary Response Endpoints; Inv-CR rate and IRF- and Inv-ORR rate: The exact 95% confidence intervals using the Clopper-Pearson method for CR rate /PR+CR rate will be provided.

Secondary Time to Event Endpoints: DOCR, DOR, PFS, and OS: The time to event secondary endpoints will be assessed by the IRF and by the investigator. The Kaplan-Meier method will be used. For DOCR and DOR only efficacy evaluable patients who achieve a CR (DOCR, DOR) or at least PR (DOR) will be included. The censoring rules are listed in the clinical assessment report. According to the implemented censoring rules, patients who start a new anti-lymphoma therapy or discontinue the study before PD are considered to have the same risk of events as patients who remained in the study treated with study drug. Sensitivity analyses were planned in case more than 5 % of the patients discontinued study due to starting a new anti-lymphoma therapy.

Table 11: Reasons for censoring for the time to event endpoints (CCOD 15.03.2021)

Group/cohort No. of patients	B11 FL RP2D N=90		
Endpoint	**Reason for censoring**	**IRF n (%)**	**INV n (%)**
Duration of response	Total n censored	51	51
	Due to reached clinical cut-off	46 (90.2%)	47 (92.2%)
	Due to NALT	3 (5.9%)	3 (5.9%)
	Due to study discontinuation[1]	1 (2.0%)	1 (2.0%)
	Due to re-treatment[2]	1 (2.0%)	0
Duration of response in patients who achieved CR	Total n censored	44	47
	Due to reached clinical cut-off	41 (90.2%)	44 (93.6%)
	Due to NALT	1 (2.3%)	2 (4.3%)
	Due to study discontinuation[1]	1 (2.3%)	1 (2.1%)
	Due to re-treatment[2]	1 (2.3%)	0
Progression-free survival	Total n censored	57	57
	Due to reached clinical cut-off	48 (84.2%)	49 (86.0%)
	Due to NALT	5 (8.8%)	5 (8.8%)
	Due to study discontinuation[1]	3 (5.3%)	3 (5.3%)
	Due to re-treatment[2]	1 (1.8%)	0
Overall survival	Total n censored	84	
	Due to reached clinical cut-off	81 (96.4%)	
	Due to study discontinuation[1]	3 (3.6%)	

[1] Reasons for study discontinuations were all withdrawal by subject.

[2] One patient was assessed PD by investigator after a best response of CR, and was enrolled in re-treatment per protocol. The same patient was assessed to have maintained CR by IRF and was therefore censored at the last available assessment prior to re-treatment.

Table 12 Reasons for discontinuation in patients who did not achieve a CR (CCOD 15.03.2021)

	B7 FL (N=46)	B11 FL RP2D (N=90)	Total (N=136)
Patients who discontinued from initial treatment prior to CR (INV)	21	31	52
Reasons:			
Progressive disease	16 (76.2%)	23 (74.2%)	39 (75.0%)
Adverse event	4 (19.0%)	3 (9.7%)	7 (13.5%)
Physician's decision	0	3 (9.7%)	3 (5.8%)
Use of another anti-cancer therapy	0	1 (3.2%)	1 (1.9%)
Death	1 (4.8%)	0	1 (1.9%)
Withdrawal by subject	0	1 (3.2%)[a]	1 (1.9%)

CR=complete response; FL=follicular lymphoma; INV=investigator; RP2D=recommended Phase II dose.

Percentages calculated based on denominator of patients who discontinued from initial treatment prior to CR.

[a] Patient completed one post-baseline tumor assessment (non-evaluable) on Day 177

Multiplicity and interim analyses

The study has one primary endpoint and several secondary endpoints. Hypothesis testing will be conducted on the primary endpoint of IRF assessed CR rate. The R/R DLBCL/trFL and R/R FL cohorts at RP2D will be each tested at the 5% alpha level.

"The primary efficacy analysis in the Group B R/R FL and R/R DLBCL/tr FL expansion cohorts occurred when all the following conditions were met:

- At least approximately 6 months after last patient in (LPI) in Group B R/R FL and R/R DLBCL/tr FL expansion cohorts, whichever is later;
- Efficacy-evaluable population includes approximately 80 patients in this cohort for each histology"

The performed interim analyses do not inflate the type I error. The protocol also includes several other cohorts to increase operational efficiency and patients belong to only one cohort. The type I error is thus not affected.

Changes in the SAP

There were two versions of the SAP. The current version was dated 21 May 2021. The Applicant has described the changes made to the SAP v1.

No significant changes were made in the planned analyses of the main endpoints in the CSR.

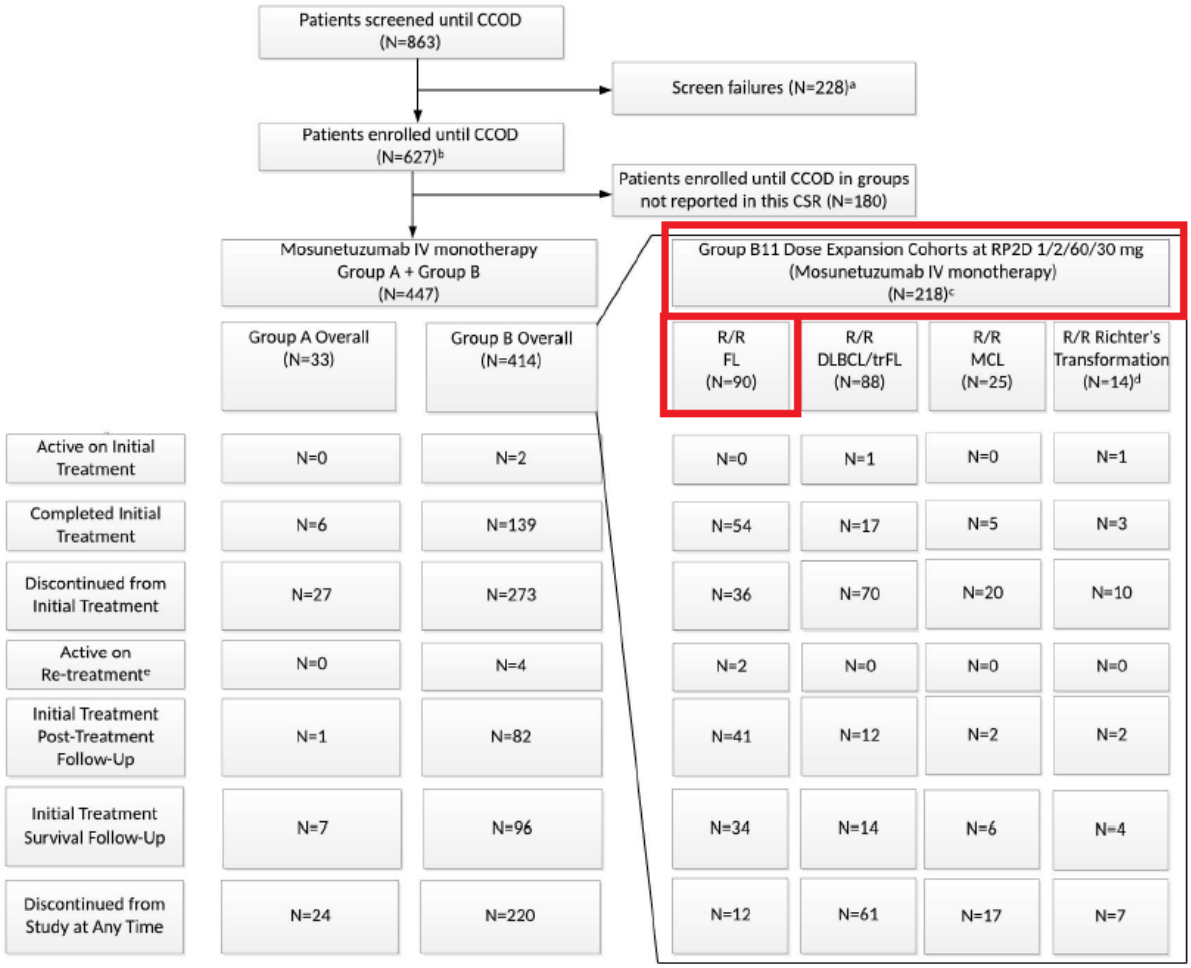
Results

Participant flow

A total of 785 patients were screened for enrollment into this study across all planned treatment groups until the CCOD (see Figure 2/CSR).

An overview of the reasons why patients were excluded from the study after screening but before treatment is only available for the entire study and not for Group B specifically.

Figure 35 Disposition of patients in study GO29781 (Group A and Group B dose escalation and group B dose expansion) as of CCOD: 27.08.2021



[a]A further 4 patients who were screened pror to the CCOD of 27 August 2021, had screen failure dates after this date.

[b]Out of 631 screened patients eligible for study entry up to the CCOD of 27 August 2021, a total of 627 patients were enrolled into the study to receive any study treatment on or prior to the CCOD. The remaining 4 patients were enrolled after the CCOD (3 patients) or awaiting enrolment (1 patient) and hence are not shown in this figure.

[c]One patient with a non-hematological malignancy (melanoma) was enrolled in error in the R/R DLBCL/trFL patient cohort that would receive the RP2D dose of mosunetuzumab IV monotherapy. This patient is considered within the 218 patients in the Group B safety evaluation population that received the RP2D dose, but is excluded from the Group B efficacy evaluable population as well as in the 88 patients in the Group B R/R DLBCL/trFL efficacy evaluable population (see Section 4.4).

[d]At the CCOD of 27 August 2021, enrolment into the R/R Richter's transformation cohort was still ongoing.

[e]Four patients with R/R FL in Group B were receiving first or second re-treatment with mosunetuzumab IV monotherapy at the CCOD.

Special notes:

(1) Group A dose escalation was stopped beyond 2.8 mg Cycle 1 fixed dose of mosunetuzumab IV monotherapy to prioritize assessment of Cycle 1 step-up dosing schedule and other routes of mosunetuzumab administration (including subcutaneous [not in the scope of this CSR]).

(2) Within the dose escalation cohorts, R/R FL patients were not dosed higher than Group B7 (1/2/13.5 mg).

(3) The B11 dose escalation cohort contains 3 patients who received 1/2/60 mg mosunetuzumab IV monotherapy. These patients are excluded from analyses of the 218 patients in the Group B11 dose expansion cohorts at RP2D.

(4) Discontinued study at any time is different from discontinued study during initial treatment and includes study discontinuations that occurred during the follow-up periods also.

(5) Active in Initial Treatment Post-Treatment Follow-up: Includes patients who completed or discontinued initial treatment, but remained on the study without disease progression.

(6) Active in Initial Treatment Survival Follow-up: Includes patients who discontinued initial treatment or post-treatment follow-up, but remain in the study for survival follow-up.

B11 R/R FL RP2D Cohort

Of the 152 patients in the Group B FL cohort, 90 patients in Group B11 had received the RP2D of 1/2/60/30 mg mosunetuzumab IV monotherapy as initial treatment during the dose expansion stage in this study.

At the most recent data cut-off (27 Aug 2021), 0 patients of the 90 R/R FL patients were active on initial treatment, 54 patients (60%) had completed initial treatment, and 36 patients (40%) had discontinued initial treatment. The main reason for discontinuation was PD (25/36). Four were due to AEs, four were due to physician's decision, two were due to use of another anti-cancer therapy, and one is listed as withdrawal by subject. Given the potentially serious and very uncomfortable AE of CRS one could envision that some of the reasons for withdrawal were due to this AE. The Applicant was requested to supply narratives (with direct links) for the 11 FL patients in group B11 and the seven FL patients in the B7 group that discontinued due to reasons other than PD.

For the B7 cohort it is considered that 6 and not 4 patients experienced adverse events leading to discontinuation.

The efficacy assessment will focus on the 90 patients with R/R FL who received the intended registration dose and schedule of 1/2/60/30 mg (B11 FL RP2D: primary efficacy population). Supportive efficacy data for 46 patients with R/R FL enrolled and treated at the lower dose level of 1/2/13.5 mg (B7; including 44 patients in the Group B interim expansion cohort, and 2 patients in the dose escalation cohort) will also be described here as the results are presented side-by-side in the tables.

Table 13 Summary of Studies Contributing to Efficacy Evaluation

Table 1 Summary of Studies Contributing to Efficacy Evaluation

Study No. (Phase)	Study Design, Control Type	Population	No. of Patients	Dose, Route, and Regimen[b]
Study GO29781 (Phase I/Ib [(Phase I/II per protocol v12])	Multicenter, open-label, dose escalation and expansion study; single arm: mosunetuzumab as a single agent and mosunetuzumab in combination with atezolizumab[a]	Patients with R/R B-cell NHL or CLL[a]	443 enrolled into mosunetuzumab IV monotherapy cohorts (Group A and Group B escalation + expansion); 214 were treated at RP2D/intended registration dose, of which 90 were patients with FL. Study is ongoing with continuing recruitment into cohorts in Group F, as well as the Richter's transformation expansion cohort in Group B. Patients contributing to the efficacy evaluation of mosunetuzumab monotherapy IV in R/R FL: 90 R/R FL treated at RP2D/intended registration dose of 1/2/60/30 mg (B11); 46 R/R FL patients treated at the next (lower) dose level of 1/2/13.5 mg (including 44 patients in the B7 interim expansion cohort, and 2 patients in the B7 dose escalation cohort)	Group A: Cycle 1 non-fractionated single-agent mosunetuzumab escalation in patients with mixed NHL histologies, IV infusion q3w, fixed dose range from 0.05 to 2.8 mg; Group B: Cycle 1 step-up single-agent mosunetuzumab escalation, IV infusion in patients with mixed NHL histologies, dose range from C1D1 0.4 mg/ C1D8 1 mg/ C1D15 2.8 mg to C1D1 1 mg/ C1D8 2 mg/ C1D15 60 mg; Expansion cohorts in R/R FL who received ≥2 Prior Therapies patients, Cycle 1 step-up single-agent mosunetuzumab escalation, IV infusion: • B11 cohort (RP2D/intended registration dose): C1D1 1 mg/ C1D8 2 mg/ C1D15 and C2D1 60 mg/ C3D1+ 30 mg; • B7 interim cohort: dose C1D1 1 mg/ C1D8 2 mg/ C1D15 13.5 mg; Expansion cohorts in R/R DLBCL/trFL, R/R MCL and R/R Richter's Transformation; Cycle 1 step-up single-agent mosunetuzumab escalation, IV infusion, B11 cohort (RP2D dose): C1D1 1 mg/ C1D8 2 mg/ C1D15 and C2D1 60 mg/ C3D1+ 30 mg.

CLL=chronic lymphocytic leukemia; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; MCL=mantle cell lymphoma; NHL=non-Hodgkin's lymphoma; q3w=every 3 weeks; RP2D=recommended Phase II dose; R/R=relapsed/refractory; trFL=transformed follicular lymphoma.

[a] No patients with CLL have been enrolled to date.

[b] Patients receiving subcutaneous (SC) treatment and combination treatment with atezolizumab (Groups D, E and F) are not included in this submission. Group D: Cycle 1 non-fractionated single-agent mosunetuzumab escalation, SC injection; Group E: Cycle 1 step-up single-agent mosunetuzumab escalation with concurrent administration of atezolizumab starting in Cycle 2, IV infusion; Group F: Cycle 1 step-up single-agent mosunetuzumab escalation, SC injection. Dose-Expansion Stage: Single-Agent Mosunetuzumab Dose-Expansion in NHL.

The efficacy, safety, and pharmacokinetic (PK) data supporting the proposed indication are based on the analysis populations presented below:

Table 14 Key analysis populations supporting the evaluation of Efficacy, Safety, PK of mosunetuzumab iv in patients with FL in study GO29781 (based on the 15 March 2021 CCOD)

Population:	Group A	B7 FL interim dose	B11 FL RP2D	B11 RP2D	Group B
No. of patients	N=33[a]	N=46[b]	N=90	N=214[c]	N=410[c,d]
Analysis Population for:	Supportive Safety, PK	Supportive Efficacy	Efficacy, Safety	Safety	Safety, PK
Description of patients included	R/R NHL patients with fixed dosing in dose escalation	R/R FL cohort expanded to evaluate dose initially identified as putative R2PD	Pivotal R/R FL RP2D expansion cohort	Histology-specific RP2D expansion cohorts within Group B (pooled and analyzed separately by histology)	All R/R NHL patients in Group B dose escalation/expansion administered mosunetuzumab IV as a single agent on a Cycle 1 step-up dose schedule.
Minimum prior line of therapy	≥1	≥2	≥2	≥1	≥1
Dose administered	0.05 to 2.8 mg q3w	1/2/13.5[e]	1/2/60/30[f]	1/2/60/30[f]	0.4/1/2.8 to 1/2/60[e] and 1/2/60/30[f]
Histologies included	B-cell NHL[g]	FL	FL	FL, DLBCL/trFL, MCL, RS	B-cell NHL[g]

DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; MCL=mantel cell lymphoma; NHL=non-Hodgkin's lymphoma; PK=pharmacokinetics; R/R=relapsed or refractory; RS=Richter's transformation; trFL=transformed follicular lymphoma.

[a] note that only 32 of 33 patients in Group A were available for PK and exposure-response analyses for safety, as one patient did not have at least one post-dose mosunetuzumab concentration measurement. Exposure-response analyses for efficacy included 7 patients with R/R FL ≥2 prior therapies from Group A, who received doses ranging from 0.2–2.8 mg q3w.

[b] includes 44 patients in the B7 dose expansion and 2 patients in the B7 dose escalation.

[c] includes one patient with melanoma who was enrolled in error in the R/R DLBCL/trFL RP2D expansion cohort and included in safety analyses because they received one dose of mosunetuzumab treatment.

[d] note that only 407 of 410 patients in Group B were available for PK and exposure-response analyses for safety, as three patients did not have at least one post-dose mosunetuzumab concentration measurement. Exposure-response analyses for efficacy included 152 patients with R/R FL ≥2 prior therapies from Group B, who received doses ranging from 0.4/1/2.8 mg to 1/2/60/30 mg.

[e] dose in mgs administered on C1D1/C1D8/C1D15, C2D1 and subsequent q3w cycles.

[f] RP2D/intended registration 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.

[g] eligible histologies included Grades 1-3 FL, MCL, DLBCL, transformed indolent NHL, RS, primary mediastinal B-cell lymphoma, small lymphocytic lymphoma, or MCL.

Summary of Patient Disposition, Initial Treatment with Mosunetuzumab, Group B (including by NHL histology for B11 expansion and selected subtotals plus A+B), Safety-Evaluable Patients
Protocol: GO29781

	Group B Mosunetuzumab Cycle 1 Step-Up Dosing (N=414)				
	B10 1.0/2.0/40.5 mg (N=17)	B11 DE 1.0/2.0/60.0 mg (N=3)	B11 Exp 1.0/2.0/60.0 mg w/30.0 mg on C3+ (N=218)	SUBTOTAL (N=414)	B11 Exp 3L FL (N=90)
Active on Initial Treatment	0	0	2 (0.9%)	2 (0.5%)	0
Completed Initial Treatment	4 (23.5%)	0	79 (36.2%)	139 (33.6%)	54 (60.0%)
Received Retreatment	0	0	3 (1.4%)	30 (7.2%)	3 (3.3%)
Disposition at Clinical Cut Off					
ACTIVE ON RE-TREATMENT 1	0	0	2 (0.9%)	3 (0.7%)	2 (2.2%)
ACTIVE ON INITIAL TREATMENT	0	0	2 (0.9%)	2 (0.5%)	0
INITIAL TREATMENT POST-TREATMENT FOLLOW-UP	3 (17.6%)	0	57 (26.1%)	82 (19.8%)	41 (45.6%)
INITIAL TREATMENT SURVIVAL FOLLOW-UP	0	0	58 (26.6%)	96 (23.2%)	34 (37.8%)
RETREATMENT 1 POST-TREATMENT FOLLOW-UP	0	0	0	3 (0.7%)	0
RETREATMENT 1 SURVIVAL FOLLOW-UP	0	0	1 (0.5%)	6 (1.4%)	1 (1.1%)
ACTIVE ON RE-TREATMENT 2	0	0	0	1 (0.2%)	0
STUDY DISCONTINUATION/COMPLETION	14 (82.4%)	3 (100%)	98 (45.0%)	221 (53.4%)	12 (13.3%)
Discontinued from Initial Treatment	13 (76.5%)	3 (100%)	137 (62.8%)	273 (65.9%)	36 (40.0%)
ADVERSE EVENT	0	0	7 (3.2%)	15 (3.6%)	4 (4.4%)
DEATH	1 (5.9%)	0	2 (0.9%)	4 (1.0%)	0
OTHER	0	0	1 (0.5%)	2 (0.5%)	0
PHYSICIAN DECISION	0	0	11 (5.0%)	15 (3.6%)	4 (4.4%)
PROGRESSIVE DISEASE	12 (70.6%)	3 (100%)	109 (50.0%)	224 (54.1%)	25 (27.8%)
USE OF ANOTHER ANTI-CANCER THERAPY	0	0	2 (0.9%)	5 (1.2%)	2 (2.2%)
WITHDRAWAL BY SUBJECT	0	0	5 (2.3%)	8 (1.9%)	1 (1.1%)
Discontinued from Post-Treatment Follow-Up (Initial Treatment)	1 (5.9%)	0	17 (7.8%)	47 (11.4%)	11 (12.2%)
DEATH	0	0	2 (0.9%)	3 (0.7%)	1 (1.1%)
NON-COMPLIANCE	0	0	0	0	0
PHYSICIAN DECISION	0	0	0	3 (0.7%)	0
PROGRESSIVE DISEASE	0	0	14 (6.4%)	38 (9.2%)	9 (10.0%)
USE OF ANOTHER ANTI-CANCER THERAPY	0	0	0	1 (0.2%)	0
WITHDRAWAL BY SUBJECT	1 (5.9%)	0	1 (0.5%)	2 (0.5%)	1 (1.1%)
Discontinued from Re-treatment	0	0	1 (0.5%)	22 (5.3%)	1 (1.1%)
ADVERSE EVENT	0	0	0	1 (0.2%)	0
PHYSICIAN DECISION	0	0	0	1 (0.2%)	0
PROGRESSIVE DISEASE	0	0	1 (0.5%)	19 (4.6%)	1 (1.1%)
USE OF ANOTHER ANTI-CANCER THERAPY	0	0	0	1 (0.2%)	0
Discontinued from Study during Initial Treatment	14 (82.4%)	3 (100%)	98 (45.0%)	203 (49.0%)	12 (13.3%)
DEATH	4 (23.5%)	1 (33.3%)	10 (4.6%)	20 (4.8%)	1 (1.1%)
DEATH DUE TO ADVERSE EVENT	1 (5.9%)	0	4 (1.8%)	6 (1.4%)	1 (1.1%)
DEATH DUE TO PROGRESSION OF DISEASE	7 (41.2%)	1 (33.3%)	68 (31.2%)	138 (33.3%)	6 (6.7%)
LOST TO FOLLOW-UP	0	0	0	1 (0.2%)	0
OTHER	0	0	1 (0.5%)	2 (0.5%)	0
PHYSICIAN DECISION	0	0	3 (1.4%)	5 (1.2%)	0
WITHDRAWAL BY SUBJECT	2 (11.8%)	1 (33.3%)	12 (5.5%)	31 (7.5%)	4 (4.4%)
Discontinued from Study at Any Time	14 (82.4%)	3 (100%)	98 (45.0%)	220 (53.1%)	12 (13.3%)
DEATH	4 (23.5%)	1 (33.3%)	10 (4.6%)	20 (4.8%)	1 (1.1%)
DEATH DUE TO ADVERSE EVENT	1 (5.9%)	0	4 (1.8%)	6 (1.4%)	1 (1.1%)
DEATH DUE TO PROGRESSION OF DISEASE	7 (41.2%)	1 (33.3%)	68 (31.2%)	148 (35.7%)	6 (6.7%)
LOST TO FOLLOW-UP	0	0	0	1 (0.2%)	0
OTHER	0	0	1 (0.5%)	2 (0.5%)	0
PHYSICIAN DECISION	0	0	3 (1.4%)	7 (1.7%)	0
WITHDRAWAL BY SUBJECT	2 (11.8%)	1 (33.3%)	12 (5.5%)	36 (8.7%)	4 (4.4%)

Percentages are based on N in the column headings.
Data Cutoff Date - 27AUG2021

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Recruitment

First Patient Enrolled: 15-Sep-2015

This interim CSR reports data in R/R NHL patients receiving mosunetuzumab intravenous (IV) monotherapy in both Group A and Group B (dose escalation and dose expansion stages) up to the clinical **cutoff date (CCOD) of 15 March 2021**. Since the study was ongoing at the time of the CCOD (and will remain ongoing at the time of the finalization of this interim CSR), a database lock was deemed not appropriate to be applied at the CCOD. Rather, a database snapshot, which is a stable extract of the

final data based on the CCOD, was taken on 21 May 2021. Updated efficacy and safety data has been provided during the procedure so that relevant data is presented for the CCOD of 27 Aug 2021.

Conduct of the study

Study GO29781, which is the single study included in this submission, was conducted in accordance with the principles of GCP, the principles of the Declaration of Helsinki, and applicable local, state, and federal laws, as well as other applicable national legal requirements. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved this study.

The Roche Clinical Quality Assurance group or designee conducted audits, and one critical finding of non-compliance was observed; Study Monitoring processes failed to ensure that subjects were verbally informed about the emerging safety risks contained in the Actemra (tocilizumab). Dear Investigator Letters (DILs) on the hepatotoxicity risks at their next study visit, as specified in the DIL communication plan, and the master informed consent form was not revised to include these risks for six months until the next protocol amendment was issued.

Corrective and preventative actions were established and implemented to ensure adequate study oversight, subject consent and communication of safety information were in place to protect the subjects' rights to be informed of emerging safety information and to prevent similar issues in the future. The impact of the critical finding on patient safety is minimal considering that tocilizumab in Study GO29781 is administered as an acute rescue medication to treat patients who experience CRS, a different patient population than outlined in the DIL; and it is anticipated that patients may need to only receive 1-2 doses of tocilizumab.

The Applicant has provided a tabulated overview of major protocol changes related to Group B (see below). A subset of patients in the B7 FL cohort were enrolled under protocol v6-8 under which the FDG PET imaging was not strictly required.

Table 15 Study GO29781 protocol versions active at enrolment and during conduct of group B cohorts

	Group B	B7 FL	B11 RP2D expansion	B11 FL RP2D expansion
Date of first patient enrolled	21 Oct 2016 (B1 dose escalation)	23 Feb 2018 (B7 dose escalation)	24 Apr 2019 (B11 DLBCL RP2D)	2 May 2019 (B11 FL RP2D)
Date last patient enrolled	ongoing at 15 Mar 2021 (Richter's only)	6 May 2019	ongoing at 15 Mar 2021 (Richter's only)	25 Sep 2020
Protocol versions active	v2 (13 Aug 2016) - v11 (13 May 2020)*	v6 (27 Nov 2017)- v9 (20 Jan 2019)	v9 (30 Jan 2019)- v11 (13 May 2020)*	v9 (30 Jan 2019)- v11 (13 May 2020)*

*Health authority approval of protocol v12 (dated 23 February 2021) occurred after CCOD of 15 March 2021.

Table 16 key changes to study protocol affecting patients enrolled in group B

Protocol Version Number (Approval Date) Summary of Key changes
2 (13 August 2016) (active at time of opening Group B dose escalation cohorts included in Group B safety population) • The Group B dose escalation group evaluating mosunetuzumab monotherapy administered IV by Cycle 1 step-up doing schedule was opened. • DLT criteria were modified to include exceptions for the following which was not considered a DLT: • AST or ALT >3×ULN and total bilirubin >2×ULN where no individual laboratory value exceeds Grade 3, that occurs in the context of Grade ≤2 CRS and lasts <3 days. • The initial tumor assessment was changed to 6 weeks following the initiation of mosunetuzumab therapy rather than 12 weeks, followed by subsequent tumor assessments every 3 months thereafter to ensure rapid responses to be observed.
3 (24 February 2017) • Known or suspected chronic active EBV infection and treatment emergent immune-related AEs with a prior immunotherapeutic agent were added as exclusion criteria. • Lee et al 2014 criteria were introduced for grading and treatment of CRS (as alternative to NCI CTCAE v4 grading scale). CRS reported prior to v3 were retrospectively regraded according to Lee et al. 2014. • A preliminary assessment of the efficacy of tocilizumab in ameliorating the symptoms of severe CRS following mosunetuzumab treatment was added as an exploratory objective of the study. The rationale and recommendations for the use of tocilizumab who develop severe CRS was added. • Guidelines for the management of neurologic toxicities and recommendations for the diagnosis and management of MAS/HLH were added. • AE reporting period after initiation of study drug was amended to require that all AEs be reported until 90 days after the last dose of study drug or the initiation of another anti-cancer agent, whichever was earlier. In addition, it was possible that expansion cohorts could be initiated prior to the identification of the recommended Phase II dose, at doses previously determined to be safe and demonstrating clinical activity.

Protocol Version Number (Approval Date) Summary of Key changes

4 (14 June 2017)
• Group B dose expansion cohorts were modified as follows:
  • For the DLBCL/trFL cohort, inclusion criteria specified that patients must have relapsed after or failed to respond to at least two prior treatment regimens (including at least one prior regimen containing anthracycline, and at least one containing an anti-CD20-directed therapy), and are not eligible for SCT. The number of patients in this cohort was increased to enroll up to approximately 80 patients.
  • The number of patients with R/R indolent (iNHL) including Grade 1-3a FL and MZL was increased to 40.
  • An histology-specific expansion cohort was added to include up to approximately 20 patients with R/R MCL who failed to respond to or relapsed after an ibrutinib-containing treatment regimen was opened.
• The number of mosunetuzumab treatment cycles was modified to allow patients who achieve a PR or maintain SD after receiving 8 cycles of treatment to continue mosunetuzumab treatment up to 17 cycle of study treatment and be eligible for re-treatment.
• An IRF was established for the independent review of the radiographic assessments in the study.
• The primary objectives of the study were modified to include the evaluation of efficacy of mosunetuzumab as a single agent using a Cycle 1 step-up doing schedule (Group B) in patients with R/R DLBCL/trFL as measured by IRF-assessed CR rates according to standard NHL response criteria (Cheson et al. 2007). Activity outcome measures were expanded to include ORR, DOR, and PFS by IRF assessment (in addition to INV), DOCR by IRF and investigator, and OS.

5 (5 October 2017)
• DLT criteria were modified to include exceptions for the following which were not considered DLTs:
  • Grade 4 neutropenia that is not accompanied by temperature elevation (as a single oral temperature of ≥ 38.3°C [101°F] or an oral temperature of ≥ 38.0°C [100.4°F] sustained for ≥ 1 h) and improves to Grade ≤ 2 (or to ≥ 80% of the baseline value, whichever is lower) within 1 week without the use of growth factor support
  • Grade 3 (NCI CTCAE, v4) individual signs and symptoms of CRS that occurs in the context of Grade ≤ 2 CRS and lasts <3 days.
• Dose escalation rules for Group B were modified to clarify how DLTs observed between C1D1 and C1D7 and between C1D8 and C1D14 affect dose escalation.

6 (27 November 2017) (active at time of opening B7 FL escalation/interim expansion cohort supporting efficacy) • The number of patients with R/R FL in dose expansion using a Cycle 1 step-up dosing schedule (Group B) was increased to up to 80 patients (from 40 patients in protocol v4). • The primary objectives of the study were modified to include the evaluation of efficacy of mosunetuzumab as a single agent using a Cycle 1 step-up doing schedule (Group B) in patients with R/R FL (as well as R/R DLBCL/trFL) as measured by IRF-assessed CR rates according to standard NHL response criteria (Cheson et al. 2007). • Statistical considerations were incorporated to robustly assess the clinical activity of mosunetuzumab in both R/R FL and R/R DLBCL/trFL expansion cohorts: • Hypothesis testing of the primary efficacy endpoint were included to determine whether the IRF-CR rates in the treated patient populations were different to historical control CR rates for the R/R FL and R/R DLBCL populations and represent a meaningful therapeutic benefit over existing treatments. • Patient-reported outcome (PRO) –based assessment of HRQoL in the NHL expansion cohorts were included as secondary objectives.

Protocol Version Number (Approval Date) Summary of Key changes

7 (16 August 2018)
• Timepoints for imaging-based tumor assessment during post-treatment follow-up were modified to every 3 months during the first 18 months on study, at 24 months, and then every 12 months thereafter (previously every 3 months during post-treatment follow-up).
• FDG PET/CT imaging to assess baseline tumor was changed to a requirement at screening (from a recommendation in protocol v6). FDG PET/CT imaging is the preferred radiologic modality for assessing FDG-avid lymphomas, while conventional CT scans were the preferred modality for subsequent imaging timepoints for lymphomas that are shown to not be FDG-avid or have variable FDG uptake at screening.
• Clarification was added that hospitalization was not mandatory after any dose day for patients who received mosunetuzumab at a dose that had been tested to be safe and tolerable, including patients enrolled in the Group B expansion cohorts and those patients who received study re-treatment using Group B schedule. Instead, the investigator should actively assess the need for hospitalization, and patients should be hospitalized after mosunetuzumab administration whenever clinically indicated.
• DLT criteria were modified to include exceptions for the following which were not considered DLTs:
  • Asymptomatic Grade 3 lab abnormalities deemed by the investigator not to be clinically significant
  • Any AST or ALT >3×ULN and total bilirubin >2×ULN where no individual lab value exceeds Grade 3 and lasts <3 days
  • Grade 3 AST or ALT elevation which last <3 days.
• Adverse events of special interest were updated to include Grade ≥2 CRS and Grade ≥2 tumor flare.
• Infusion-related reactions (IRRs) which are attributed to mosunetuzumab were to be reported, graded and treated singularly as CRS.
• Additional guidance for management of neurologic events was added: to consider treatment with corticosteroids to treat suspected neurologic toxicity.
• Additional guidance was added on the dose of tocilizumab to be used for severe or life-threatening CRS: doses exceeding 800 mg per infusion were not recommended; 12 mg/kg instead of 8 mg/kg for patients less than 30-kg weight.

Protocol Version Number (Approval Date) Summary of Key changes
8 (23 October 2018) • The driving restriction period that investigators were to counsel patients to refrain from driving or engaging in hazardous occupations or activities until at least 28 days after the final dose of mosunetuzumab period (originally implemented by the US FDA in protocol v1) was reduced to Cycles 1-3, with some exceptions if patients develop serious NAEs in this period.
9 (30 January 2019) (active at time of opening B11 RP2D [primary safety population at intended registration dose and schedule] and B11 FL RP2D [primary efficacy population]) • The imaging modality was clarified for patients with NHL enrolled in the study: FDG PET scans in conjunction with diagnostic-quality CT scans were required at screening and for response assessments during study treatment (the specific distinction between FDG-avid/not FDG-avid was removed). During post-treatment follow-up, CT scans with or without PET scans could be utilized for these patients. • Dose escalation increments up to 100% of the preceding dose level during the dose escalation phase for Group B could be recommended by the IMC based on exposure-safety analyses indicating that administration of higher doses of mosunetuzumab on the Group B Cycle 1 step-up schedule did not result in increased safety risks • The Mini-Mental State Examination (MMSE) was removed from the protocol.

10 (26 September 2019)
• A Richter's transformation histology-specific cohort was added as a dose expansion cohort in Group B (B11 Richter's RP2D)
• The driving restriction period that investigators were to counsel patients to refrain from driving or engaging in hazardous occupations or activities was revised as follows:
  • The scope of the baseline driving restriction was narrowed from all patients to patients with the combination of an aggressive NHL subtypes and abnormal (above institutional ULN) C-reactive protein (CRP) at screening
  • The duration of the baseline driving restriction was reduced from the first 3 cycles to the first 2 cycles
• The corticosteroid premedication requirement was changed to be optional for Cycle 3 and beyond for patients in Group B, per investigator's assessment.
• Neutropenia was changed from a potential risk to a recognized risk with mosunetuzumab.
• Adverse events of special interest for mosunetuzumab were updated to include Grade ≥ 2 pleural effusion as part of the description for tumor flare.

Protocol Version Number (Approval Date) Summary of Key changes
11 (13 May 2020) • The periodic interim analyses for futility was changed to be conducted at least once in each expansion cohort to reduce multiple analyses of the study data, which could potentially introduce bias. • DLT criteria were modified to include exceptions for Grade ≥3 neutropenia that resolves with or without the use of growth factor support within 1 week, which was not considered a DLT. • Exclusion criteria were updated to exclude patients with history of MAS/HLH who were considered to be at increased risk for excessive inflammatory reactions. • Management of CRS was updated to clarify that mosunetuzumab should be permanently discontinued for Grade 4 or recurrent Grade 3 CRS events CRS events. • PRO questionnaires were permitted to be conducted by phone in the event that patients were not able to come into the clinic due to COVID-19 restrictions.

AE = Adverse event; AESI = adverse event of special interest; CRP = C-reactive protein; CRS = cytokine release syndrome; CT = computed tomography; DLBCL/trFL = diffuse large B-cell lymphoma/transformed follicular lymphoma; DLT = dose-limiting toxicity; FDG = fluorodeoxyglucose; FL = follicular lymphoma; HLH= hemophagocytic lymphohistiocytosis; IRF = independent review facility; IRR = infusion-related reaction; MAS= macrophage activation syndrome; NAE = neurological adverse event; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography; PK = pharmacokinetics; PRO = patient-reported outcome; RP2D = recommended Phase II dose; R/R = relapsed/refractory.

At CCOD (15 March 2021), 44 major protocol deviations IPDs were reported in 30 subjects (33,3%) in the B11 RP2D FL cohort. Out of these 4 (4.4%) were related to the outbreak of the COVID-19 pandemic. The most common major protocol deviations in the B11 FL RP2D cohort was "Incomplete/missing/out-of-window tumor-related assessments" reported in 11% of patients (n = 10). According to the narratives provided, all of the 10 major protocol deviations were related to delayed confirmation of complete response by bone marrow assessment. In addition, an analysis of subject incidence of major and overall

protocol deviations by study site was provided, suggesting a slightly increased median number of major and overall protocol deviations per subject in 6 sites (3 located in Spain, 2 in Germany and 1 in Australia). The major protocol deviations observed in these sites were distributed across various subcategories. In addition, these sites had only few subjects enrolled (n ≤ 3).

Table 17 Key Major Protocol Deviations (Procedural) during Initial Treatment with Mosunetuzumab IV Monotherapy in Patients With at least 1 Major Protocol Deviation in Selected Group B Dose Escalation and Dose Expansion Patient Cohorts; CCOD: 15 March 2021, Safety-Evaluable Patients

Patient population: Group/cohort No. of patients	R/R FL B7 interim* escalation/ expansion N=46	R/R FL B11 RP2D** expansion N=90	R/R DLBCL/trFL B11 RP2D** expansion N=88	R/R NHL B11 RP2D** expansion N=214	R/R NHL Group B overall N=410
Patients with at least 1 major protocol deviation	14 (30.4%)	30 (33.3%)	20 (22.7%)	58 (27.1%)	109 (26.6%)
Number of Major protocol deviations	16	44	26	82	144
Failure to report AEs, SAEs, AESIs, DLTs, and pregnancy to IEC/sponsor/ regulatory authorities	5 (10.9%)	8 (8.9%)	5 (5.7%)	17 (7.9%)	44 (10.7%)
Incomplete/missing/ out-of-window tumor-related assessments	6 (13.0%)	10 (11.1%)	4 (4.5%)	17 (7.9%)	25 (6.1%)
Subsequent consent after ICF updates not obtained at next study visit	0	4 (4.4%)	4 (4.5%)	8 (3.7%)	9 (2.2%)
Use of consent forms not approved by IRB/IEC	2 (4.3%)	3 (3.3%)	3 (3.4%)	6 (2.8%)	9 (2.2%)
Failure to complete/comply with I/E criteria, incl. discrepancy with source doc./raw data	0	1 (1.1%)	3 (3.4%)	5 (2.3%)	9 (2.2%)
Consent process not executed by adequately qualified site staff member	0	2 (2.2%)	2 (2.3%)	4 (1.9%)	7 (1.7%)
Incorrect/incomplete/missing non-tumor related assessments	1 (2.2%)	3 (3.3%)	0	3 (1.4%)	7 (1.7%)
Incorrect study drug dose, frequency, or method of drug delivery	0	4 (4.4%)	0	4 (1.9%)	5 (1.2%)

AE = adverse events; AESI = adverse event of special interest; DLBCL/trFL = diffuse large B-cell lymphoma/transformed follicular lymphoma; DLT = dose-limiting toxicity; FL = follicular lymphoma; IEC = independent ethics committee; IRB = independent review board; NHL = non-Hodgkin's lymphoma; RP2D = recommended Phase II dose; R/R = relapsed/refractory; SAE = serious adverse event.

*Interim dose of mosunetuzumab by IV monotherapy = 1/2/13.5 mg

**RP2D of mosunetuzumab by IV monotherapy = 1/2/60/30 mg

Table 18 Reasons for Major Protocol Deviations Due to Covid-19 Pandemic in Group A and Group B (Mosunetuzumab IV Monotherapy) in Study GO29781, CCOD: 15 March 2021, Safety-Evaluable Patients

Summary of Reasons for Major Protocol Deviations, Deviation due to Epidemic/Pandemic, Initial Treatment with Mosunetuzumab, Group B (including by NHL histology for B11 expansion and selected subtotals plus A+B), Safety-Evaluable Patients
Protocol: GO29781

	Group B Mosunetuzumab Cycle 1 Step-Up Dosing (N=410)					Group A+B (N=443)
Primary Reason	B7 1.0/2.0/13.5 mg (N=77)	B11 Exp 1.0/2.0/60.0 mg w/30.0 mg on C3+ (N=214)	SUBTOTAL (N=410)	B11 Exp 3L FL (N=90)	B11 Exp MCL (N=25)	SUBTOTAL (N=443)
Total number of patients with at least one major protocol deviation related to epidemic/pandemic	5 (6.5%)	5 (2.3%)	10 (2.4%)	4 (4.4%)	1 (4.0%)	10 (2.3%)
Total number of major protocol deviations related to epidemic/pandemic	6	6	12	5	1	12
Site action due to epidemic/pandemic						
Incomplete/missing/out-of-window tumor-related assessments (e.g., scans, bone marrow)	4 (5.2%)	1 (0.5%)	5 (1.2%)	0	1 (4.0%)	5 (1.1%)
Incorrect study drug dose, frequency, or method of drug delivery	0	2 (0.9%)	2 (0.5%)	2 (2.2%)	0	2 (0.5%)
Incorrect/incomplete/missing non-tumor related assessments (e.g., physical examination, labs, PROs)	1 (1.3%)	1 (0.5%)	2 (0.5%)	1 (1.1%)	0	2 (0.5%)
Use of Consent Forms not approved by the IRB/IEC	0	1 (0.5%)	1 (0.2%)	1 (1.1%)	0	1 (0.2%)

Data Cutoff Date - 15MAR2021

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Page 1 of 1

Baseline data

Table 19 Key demographic data, baseline disease characteristics and prognostic factors – Group B

Escalation and Expansion Cohorts for Patients with R/R FL who have Received ≥2 Prior Systemic Therapies

	Group/cohort No. of patients		FL B7 Interim Dose Escalation and Expansion N=46	FL B11 Expansion N=90
	Dose (mg)		C1 step-up dosing, mosunetuzumab IV 1/2/13.5 mg[a] (interim dose)	C1 step-up dosing, mosunetuzumab IV 1/2/60/30 mg[b] (RP2D/intended registration dose and schedule)
	Patient population		R/R FL with ≥2 prior therapies	R/R FL with ≥2 prior therapies
	Source of patients		Group B: B7 interim expansion cohort and B7 dose escalation	Group B: B11 expansion (R/R FL cohort)
Demographics and Baseline Characteristics	Age	median (range), years	61.0 (27-85)	60.0 (29–90)
	n (%)	18-65 years	31 (67.4)	62 (68.9)
		>65 years	15 (32.6)	28 (31.1)
	Sex, n (%)	male	30 (65.2)	55 (61.1)
		female	16 (34.8)	35 (38.9)
	Race, n (%)	White	36 (78.3)	74 (82.2)
		Asian	7 (15.2)	8 (8.9)
		Black/African American	3 (6.5)	4 (4.4)
		American Indian/Alaska Native	0	1 (1.1)
		Multiple	0	0
		Unknown	0	3 (3.3)
	ECOG PS, n (%)	0	28 (60.9)	53 (58.9)
		1	18 (39.1)	37 (41.1)
		2	0	0
Cancer History at Study Entry	Time from initial diagnosis to study entry	median (range), months	62.8 (11–380)	82.2 (11–292)
	Diagnosis, n (%)	FL	46 (100)	90 (100)
	Ann Arbor Stage, n (%)	I	1 (2.2)	5 (5.6)
		II	8 (17.4)	16 (17.8)
		III	13 (28.3)	25 (27.8)
		IV	24 (52.2)	44 (48.9)

Table 3 Key Demographic Data, Baseline Disease Characteristics and Prognostic Factors for Group B (Cycle 1 Step-up Dose) Dose Escalation and Expansion Cohorts for Patients with R/R FL who have Received ≥2 Prior Systemic Therapies (cont.)

	Patient population: Group/cohort No. of patients		R/R FL B7 interim expansion N=46	R/R FL B11 (RP2D) expansion N=90
	Bulky Disease (>6 cm)		20 (43.5)	31 (34.4)
	SPD by INV (mm^2), median (range)		3922 (320-22167)	3014 (234–15799)
Prognostic Factors	FLIPI Risk Group, n (%)	low (0,1)	12 (26.1)	26 (28.9)
		intermediate (2)	12 (26.1)	24 (26.7)
		high (3-5)	21 (45.6)	40 (44.4)
		Unknown	1 (2.2)	0
Prior Cancer Treatment	No. of prior lines of anti-lymphoma therapies n (%)	Median (range)	3.0 (2–9)	3.0 (2–10)
		1	0	0
		2	17 (37.0)	34 (37.8)
		3	13 (28.3)	28 (31.1)
		>3	16 (34.8)	28 (31.1)
	Prior cancer therapy, n (%)	anti-CD20	46 (100)	90 (100)
		alkylator	46 (100)	90 (100)
		auto-SCT	8 (17.4)	19 (21.1)
		CAR-T	2 (4.3)	3 (3.3)
		PI3K	6 (13.0)	17 (18.9)
	refractory to:	last prior therapy	36 (78.3)	62 (68.9)
		any prior anti-CD20	40 (87.0)	71 (78.9)
		double refractory to prior anti-CD20 and alkylator	27 (58.7)	48 (53.3)
	<24 months from start of first systemic therapy to PD		21 (45.7)	47 (52.2)

auto-SCT= autologous stem cell transplantation; ECOG= Eastern Cooperative Oncology Group; FL=follicular lymphoma; FLIPI=follicular lymphoma International Prognostic Index; INV=investigator; IV=intravenous; PD=progressive disease; PS=performance status; RP2D=recommended Phase II dose; R/R= relapsed or refractory; SPD=sum of product diameters;

[a]1 mg on C1D1, 2 mg on C1D8, 13.5 mg on C1D15, and 13.5 mg on C2D1 and subsequent q3w cycles.

[b]1 mg on C1D1, 2 mg on C1D8, 60 mg on C1D15 and C2D1, 30 mg for C3D1 and subsequent q3w cycles.

Source: t_dm_canhis_INIT_3LFL_GRPBC_SE_15MAR2021_29781;
t_dm_canhis_INIT_GRPBH_SE_15MAR2021_29781;
t_cm_prior_cantrt_INIT_GRPBH_SE_15MAR2021_29781;
t_cm_prior_cantrt_INIT_3LFL_GRPBC_SE_15MAR2021_29781

Table 19 summary table of the FL grade at study entry in the B11 FL recommended RP2D expansion cohort (n= 90 cut-off 15.03.2021)

Table 1 Follicular Grade at Study Entry by Local Laboratory Assessment in the B11 FL RP2D Expansion Cohort (n=90; Cutoff Date: 15 March 2021)

FL grade at study entry by local laboratory assessment n, (%)	B11 FL RP2D Expansion Cohort (n=90)
FL Grade 1	6 (6.7%)
FL Grade 2	7 (7.8%)
FL Grade 3A	27 (30.0%)
FL Grade 1-2	29 (32.2%)
FL Grade 1-3A	18 (20.0%)
FL Grade 2-3A	3 (3.3%)

FL=follicular lymphoma; RP2D=recommended Phase II dose.
Source: t_dm_canhis_FLTP_INIT_B11EXP_FL_SE_15MAR2021_29781

Numbers analysed

The primary efficacy population are the 90 patients with R/R FL (≥2 prior lines of systemic therapy) receiving the RP2D/intended registration dose and schedule of 1/2/60/30 mg in cohort B11.

The 46 patients with R/R FL enrolled and treated at the lower dose level of 1/2/13.5 mg in cohort B7 (≥2 prior lines of systemic therapy) are considered a supportive efficacy population.

Outcomes and estimation (CCOD: 27 August 2021)

Primary efficacy endpoint

In the main efficacy cohort B11 FL RP2D the CR (by IRF) was 60% (95% CI: 49.1, 70.2) and for the supportive cohort B7 (FL), which received a lower dose, the CR rate 45.7% (95% CI: 30.9, 61.0).

Table 14 Overview of Efficacy of Mosunetuzumab IV Monotherapy in Patients with R/R FL ≥2 Prior Therapies (CCOD: 27 August 2021), Efficacy-Evaluable Patients

	Group B mosunetuzumab IV Cycle 1 step-up dosing			
Group/cohort No. of patients	**B7 FL interim dose N=46**		**B11 FL RP2D N=90**	
Dose	**1.0/2.0/13.5[a]**		**1/2/60/30[b]**	
Tumor assessed by:	**INV**	**IRF**	**INV**	**IRF**
Best Overall Response (±PET)				
Responders (CR or PR), n (%), (95% CI)[c]	29 (63.0%) (47.6, 76.8)	31 (67.4%) (52.0, 80.5)	70 (77.8%) (67.8, 85.9)	72 (80.0%) (70.3, 87.7)
Complete Response, n (%), (95% CI)[c]	22 (47.8%) (32.9, 63.1)	21 (45.7%) (30.9, 61.0)	54 (60.0%) (49.1, 70.2)	54 (60.0%) (49.1, 70.2)
Partial Response, n (%)	7 (15.2%)	10 (21.7%)	16 (17.8%)	18 (20.0%)
Stable Disease, n (%)	5 (10.9%)	6 (13.0%)	8 (8.9%)	7 (7.8%)
Progressive Disease[d], n (%)	11 (23.9%)	6 (13.0%)	10 (11.1%)	9 (10.0%)
Not Evaluable (NE), n (%)	0	0	1 (1.1%)	0
Missing or not done, n (%)	1 (2.2%)	3 (6.5%)	1 (1.1%)	2 (2.2%)
Duration of Complete Response (±PET)				
Patients with event, n (%)	9/22 (40.9%)	5/21 (23.8%)	12/54 (22.2%)	16/54 (29.6%)
Median, months (95% CI)[e]	NE (13.8, NE)	NE (NE, NE)	NE (17.8, NE)	NE (14.6, NE)
K-M event-free proportion, % (95% CI) at: 12 months	72.4% (53.6, 91.3)	73.7% (53.9, 93.5)	80.4% (68.8, 92.0)	71.4% (57.9, 84.9)
K-M event-free proportion, % (95% CI) at: 18 months	67.6% (47.8, 87.4)	73.7% (53.9, 93.5)	66.6% (45.5, 87.8)	63.7% (48.0, 79.4)
Duration of Response (±PET)				
Patients with event, n (%)	14/29 (48.3%)	13/31 (41.9%)	27/70 (38.6%)	29/72 (40.3%)
Median, months (95% CI)[e]	28.6 (11.5, NE)	NE (9.7, NE)	22.8 (18.7, NE)	22.8 (9.7, NE)
K-M event-free proportion, % (95% CI) at: 12 months	65.5% (48.2, 82.8)	57.6% (39.3, 75.8)	64.8% (53.1, 76.5)	61.8% (50.0, 73.7)
K-M event-free proportion, % (95% CI) at: 18 months	62.1% (44.4, 79.7)	54.0% (35.5, 72.4)	62.5% (50.4, 74.7)	56.9% (44.1, 69.6)

	Group B mosunetuzumab IV Cycle 1 step-up dosing			
Group/cohort No. of patients	**B7 FL interim dose N=46**		**B11 FL RP2D N=90**	
Dose	**1.0/2.0/13.5[a]**		**1/2/60/30[b]**	
Tumor assessed by:	**INV**	**IRF**	**INV**	**IRF**
Duration of Response in Patients who achieved CR (±PET)				
Patients with event, n (%)	9/22 (40.9%)	5/21 (23.8%)	12/54 (22.2%)	16/54 (29.6%)
Median, months (95% CI)[e]	NE (13.8, NE)	NE (NE, NE)	22.8 (19.9, NE)	22.8 (18.7, NE)
K-M event-free proportion, % (95% CI) at: 12 months	72.7% (54.1, 91.3)	73.7% (53.9, 93.5)	84.3% (74.3, 94.3)	76.4% (64.6, 88.1)
K-M event-free proportion, % (95% CI) at: 18 months	68.2% (48.7, 87.6)	73.7% (53.9, 93.5)	81.3% (70.0, 92.5)	70.2% (56.7, 83.8)
Progression-Free Survival (±PET)				
Patients with event, n (%)	29 (63.0%)	23 (50.0%)	41 (45.6%)	42 (46.7%)
Median, months (95% CI)[e]	11.8 (8.4, 31.1)	11.2 (5.9, NE)	21.1 (11.8, NE)	17.9 (10.1, NE)
K-M 12-month event-free proportion, % (95% CI)	48.7 (34.0, 63.4)	49.8 (34.0, 65.5)	57.6 (46.8. 68.4)	57.7 (46.9, 68.4)
Overall Survival				
Patients with event, n (%)	8 (17.4%)		8 (8.9%)	
Median, months (95% CI)[e]	NE (NE, NE)		NE (NE, NE)	
K-M 12-month event-free proportion, % (95% CI)	85.6% (74.9, 96.3)		93.0% (87.6, 98.4)	

CI=confidence interval; CR=complete response; FL=follicular lymphoma; INV=investigator; IRF=Independent review facility; K-M=Kaplan-Meier; NE=not estimable; PET=^{18}F-fluorodeoxyglucose positron emission tomography; PR=partial response; RP2D=recommended Phase II dose.

[a] 1 mg on C1D1, 2 mg on C1D8, 13.5 mg on C1D15, and 13.5 mg on C2D1 and subsequent q3w cycles.

[b] 1 mg on C1D1, 2 mg on C1D8, 60 mg on C1D15 and C2D1, 30 mg for C3D1 and subsequent 3w cycles.

[c] 95% CIs calculated using the Clopper-Pearson method.

[d] PD includes missing, not evaluable (NE) and not done (ND) assessments where the patient has otherwise had a PD recorded in the IRF data.

[e] Summaries of time-to-event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Secondary endpoints

Updated analyses were provided by the Applicant with an increase in median follow-up for DOR from 10.3 to 14.9 months for the B11 FL RP2D Cohort and from 21.0 to 24.2 months for the B7 FL Interim Cohort.

Table 20 Extent of follow up for Duration of response in R/R FL patients≥ 2 prior therapies 27.08.21

	Group B mosunetuzumab IV Cycle 1 step-up dosing			
Group/cohort No. of patients	B7 FL interim N=46		B11 FL RP2D N=90	
Tumor assessed by:	INV	IRF	INV	IRF
Number of responders	29	31	70	72
DOR follow-up[a] (months), median (95% CI)	27.9 (22.8, 31.6)	24.2 (21.4, 28.3)	15.8 (13.5, 17.1)	14.9 (13.4, 16.6)

CI=confidence interval; DOR=duration of response; FL=follicular lymphoma; INV=investigator; IRF=Independent review facility; RP2D=recommended Phase II dose

[a] estimated by reverse Kaplan-Meier methodology in responders.

Agreement between IRF- and investigator-assessed response on whether a patient achieved a CR was high: 93.3% (83/89). IRF-assessed ORR was 80.0% (95% CI: 70.3%, 87.7%).

The results of the secondary endpoints in the B7 FL interim dose cohort receiving the lower dose of 1/2/13.5 mg were slightly lower than in the B11 FL cohort and are generally thought to support efficacy.

Of the 54 patients in the B11 FL RP2D cohort who achieved a CR as assessed by the IRF, 16 patients (29.6%) subsequently had disease progression by the time of the CCOD (27 Aug 2021). The median DOCR was not estimable. The K-M estimated event-free rates among complete responders at 12 and 18 months after the first complete response were 71.4% and 63.7%, respectively. The Kaplan-Meier plot of DOCR as assessed by IRF is provided. The median DOR has been reached and is 22.8 months (95% CI: 9.7, NE). Among responders, the event-free rates at 12 and 18 months after the first response were 61.8% and 56.9%, respectively. Median PFS is 17.9 months with a 12-month and 18-months PFS event-free rate of 57.7% and 47.0%, respectively. Median OS is not reached, with a K-M-estimated 12-month survival rate of 93.0%.

Figure 36 Kaplan Meier plot of duration of complete response by IRF

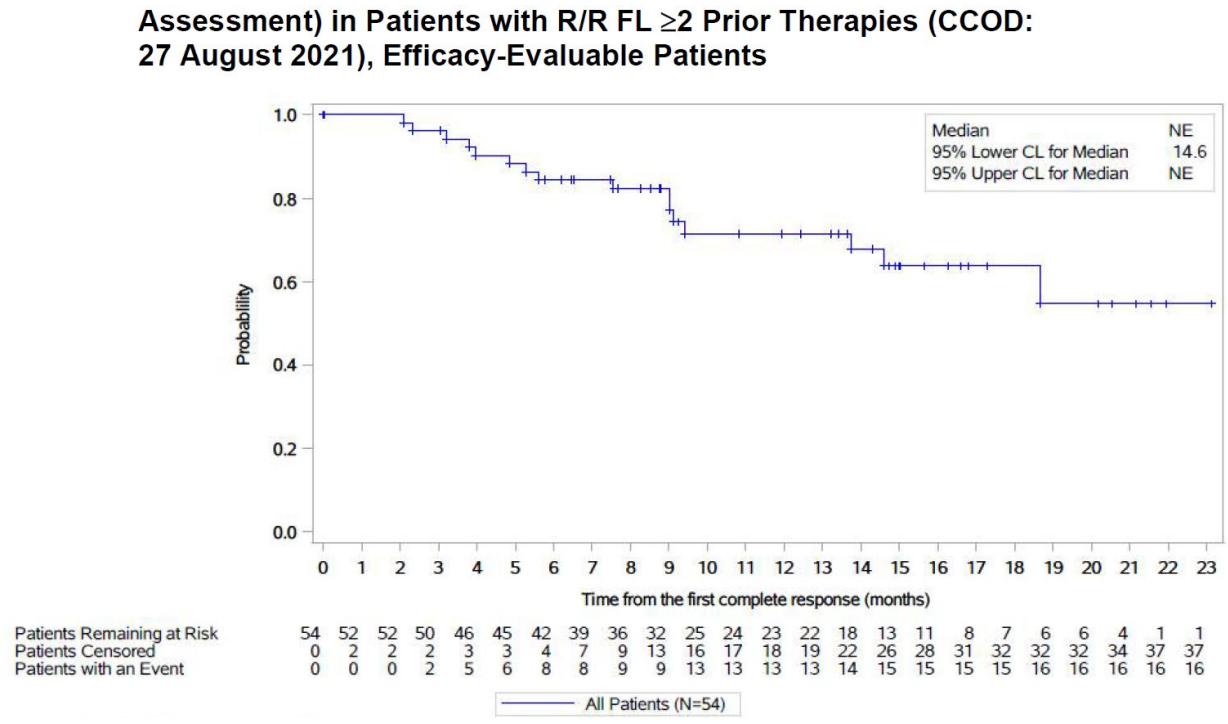
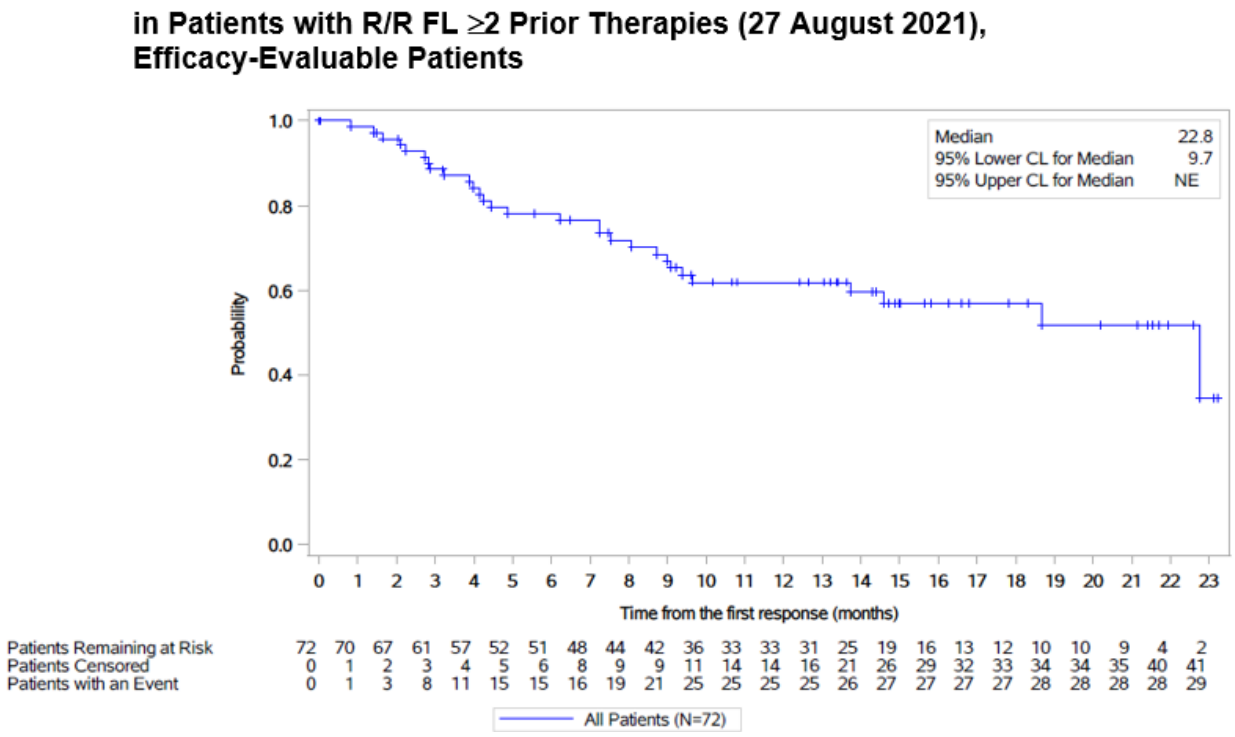


Figure 30 Kaplan Meier plot of duration of response by IRF Assessment



Although not included as a secondary endpoint in the study protocol, it is of importance to note that for the majority of patients a response and/or complete response was achieved relatively short after start of treatment, with a median time to first response in the 72 patients who achieved an objective response (CR or PR) of 1.4 months (range: 1.1 – 8.9 months) and with median time to first complete response in the 54 patients who achieved a CR of 3.0 months (range: 1.1 – 18.9 months).

From 11 patients who received >8 cycles of mosunetuzumab treatment and had tumor assessments beyond Cycle 8, 4 patients (36.4%) who had a best response of SD or PR by the end of Cycle 8 had a late initial response or deepening of response, with 3 patients deepening their response from PR to CR and 1 patient with a PR after having SD by the end of Cycle 8. In addition, 5 patients maintained their PR or SD. One patient progressed, and 1 patient already had CR by the end of cycle 8 (major protocol deviation). While the safety profile reported after 8 cycles of mosunetuzumab treatment was more tolerable compared to that within the first 8 cycles and no new safety signals were detected beyond 8 cycles, these results justify the appropriateness of continuing treatment beyond Cycle 8 for patients with SD or PR at the end of Cycle 8 and for the proposed treatment duration.

In response to a request for additional information, the Applicant also provided a summary of data of primary and key secondary endpoints using a modified Lugano response criteria (based on Cheson 2014 criteria with conservative modifications including the requirement of bone marrow confirmation for CR assessment, and at least 50% SPD reduction for PR assessment) used for exploratory purposes (CCOD 15 March 2021). Compared to the efficacy results reports with the Cheson 2007 response criteria (IRF assessment, CCOD of 15 March 2021), consistent efficacy outcomes in terms of CRR and ORR have been reported using the modified Lugano response criteria (CRR of 57.8% and 58.9% respectively; ORR of 78.9% and 77.8%, respectively); in terms of DOR and PFS, even slightly higher 12-month DOR and PFS rates were reported using the modified Lugano response criteria (12-month DOR of 65.4% and 77.1%, respectively; 12-month PFS rate of 59.7% and 69.6%, respectively).

Table 21 Comparison of Efficacy of Mosunetuzumab IV Monotherapy in Patients with R/R FL ≥2 Prior Therapies based on IRF-Assessed Tumor Response Applying Modified Lugano Criteria (CCOD: 15 March 2021; B11 FL RP2D Cohort)

Group/cohort **No. of patients**		**B11 FL RP2D** **N=90**
Tumor response criteria		**Modified Lugano** Cheson et al. 2014
Best Overall Response (±PET)		
Responders (CR or PR), n (%), (95% CI)[a]		70 (77.8%) (67.8, 85.9)
Complete Response, n (%), (95% CI)[a]		53 (58.9%) (48.0, 69.2)
Partial Response, n (%)		17 (18.9%)
Stable Disease, n (%)		9 (10.0%)
Progressive Disease[b], n (%)		9 (10.0%)
Not Evaluable (NE), n (%)		0
Missing or not done, n (%)		2 (2.2%)
Duration of Complete Response (±PET)		
Patients with event, n (%)		5/53 (9.4%)
Median, months (95% CI)[c]		NE (NE, NE)
K-M event-free proportion, % (95% CI) at:	9 months	93.3 (84.4, 100)
	12 months	81.8% (67.2, 96.3)
Duration of Response (±PET)		
Patients with event, n (%)		11/70 (15.7%)
Median, months (95% CI)[c]		NE (NE, NE)
K-M event-free proportion, % (95% CI) at:	9 months	85.9% (76.6, 95.2)
	12 months	77.1 (64.4, 89.8)
Duration of Response in Patients who achieved CR (±PET)		
Patients with event, n (%)		5/53 (9.4%)
Median, months (95% CI)[c]		NE (NE, NE)
K-M event-free proportion, % (95% CI) at:	9 months	94.6 (87.3, 100)
	12 months	84.5% (71.7, 97.2)
Progression-Free Survival (±PET)		
Patients with event, n (%)		25 (27.8%)
Median, months (95% CI)[c]		NE (17.9, NE)
K-M event-free proportion, % (95% CI) at:	9 months	74.1 (64.4, 83.8)
	12 months	69.6% (58.7, 80.6)

In addition, the Applicant provided sensitivity analyses using EMA censoring rules, considering other new anticancer therapies or retreatment in the absence of prior documented progression as an event (CCOD: 15 March 2021). Overall, although 12-month event free rate for DOR, PFS and DOCR (for both IRF and INV assessed data) are slightly lower using the EMA censoring rules compared to the original analysis (12-month DOR rate: 60.3% vs 65.4%; 12-months DOCR rate: 72.6% vs 76.9%; 12-months PFS rate:

54.0% vs 59.7%; per IRF assessment), 95% confidence intervals are overlapping and medians were highly consistent.

Table 22 Sensitivity Analyses of PFS Treating Patients Who Were Censored due to NALT/retreatment as Events (CCOD: 15 March 2021)

Group/cohort No. of patients	B11 FL RP2D N=90			
	IRF		INV	
	Original analysis	Sensitivity analysis	Original analysis	Sensitivity analysis
Events, n (%)	33 (36.7%)	39 (43.3%)	33 (36.7%)	38 (42.2%)
Median (95% CI)	17.9 (9.5, NE)	17.9 (9.5, NE)	17.9 (12.0, NE)	17.9(11.1, NE)
12-month event free rate (%) (95% CI)	59.7 (48.2, 71.2)	54.0 (42.6, 65.3)	58.6 (46.8, 70.3)	54.6 (43.1, 66.1)

CCOD=clinical cutoff date; FL=follicular lymphoma; IRF= Independent Review Facility; INV=investigator; NE=not evaluable; RP2D= recommended Phase II dose.

Table 23 Sensitivity Analyses of DOR Treating Patients Who Were Censored due to NALT/retreatment as Events (CCOD: 15 March 2021)

Group/cohort No. of patients	B11 FL RP2D N=90			
	IRF (n=71)		INV (n=70)	
	Original analysis	Sensitivity analysis	Original analysis	Sensitivity analysis
Events, n (%)	20 (28.2%)	24 (33.8%)	19 (27.1%)	22 (31.4%)
Median (95% CI)	NE (NE, NE)	NE (9.4, NE)	NE (NE, NE)	NE (11.9, NE)
12-month event free rate (%) (95% CI)	65.4 (52.6, 78.1)	60.3 (47.6, 73.1)	64.9 (51.1, 78.6)	61.3 (47.8, 74.9)

CCOD=clinical cutoff date; FL=follicular lymphoma; IRF= Independent Review Facility; INV=investigator; NE=not evaluable; RP2D= recommended Phase II dose.

Table 24 Sensitivity Analyses of DOCR Treating Patients Who Were Censored due to NALT/retreatment as Events (CCOD: 15 March 2021)

Group/cohort No. of patients	B11 FL RP2D N=90			
	IRF (n=52)		INV (n=51)	
	Original analysis	Sensitivity analysis	Original analysis	Sensitivity analysis
Events, n (%)	8 (15.4%)	10 (19.2%)	4 (7.8%)	6 (11.8%)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
12-month event free rate (%) (95% CI)	76.9 (62.2, 91.7)	72.6 (57.4, 87.8)	87.7 (76.1, 99.3)	83.0 (70.3, 95.8)

CCOD=clinical cutoff date; FL=follicular lymphoma; IRF= Independent Review Facility; INV=investigator; NE=not evaluable; RP2D= recommended Phase II dose.

Patient Reported Outcomes

In terms of patient-reported outcomes, high compliance rates of >70% (in some cases, >80%) were consistently observed for all questionnaires across the scheduled assessments for these cohorts.

Post-baseline assessments for the B11 FL RP2D cohort and the B7 FL interim dose cohort indicated that physical functioning and fatigue scores were generally maintained per the EORTC QLQ-C30 questionnaire and that lymphoma symptom-related burden at baseline was also maintained according to the FACT-Lym subscale.

It is considered that the uncontrolled/unblinded nature of the HR-QoL data and the lack of any strategy to control for multiplicity do not allow for specific HR-QoL claims and preclude the inclusion of HRQoL data in the SmPC.

Ancillary analyses

Subgroup analyses - CCOD (27 August 2021)

Subgroup analyses of the treatment effect across relevant subpopulations defined by demographic, prior treatment (number and refractory status; PD <24 months after initial treatment), and prognostic factors (FLIPI) were provided.

Patients refractory to alkylator- and anti-CD20-therapy were observed to have a lower CR rate (CR=50%; CI 35%, 65%) compared to non-refractory patients (CR=71%, CI 55%, 84%). The expansion cohorts for FL have been designed to rule out a 14% CR rate and are powered to detect a 14% increase in CR rate from 14% to 28%. As CR in refractory patients is well above the 28%, it is agreed, that the indication in FL after 2 prior systemic therapies should include both refractory and relapsed FL patients.

Forest plots for 12-month event-free rate for DOR and DOCR for relevant subgroups in the B11 FL RP2D Cohort (CCOD: 27 August 2021), were provided.

Figure 37 Summary of Response by Subgroups, Initial Treatment with Mosunetuzumab, Complete Responder, Response Assessed by Independent Oncologists, Cohort B11 Expansion, 3L + FL Patients, ITT Patient (1/2)

Subgroups	No Patients	CR (95% CI)
Overall	90 (100%)	60% (49%, 70%)
Sex	n=90	
Female	35 (39%)	71% (54%, 85%)
Male	55 (61%)	53% (39%, 66%)
Age Group	n=90	
< 65	60 (67%)	55% (42%, 68%)
>= 65	30 (33%)	70% (51%, 85%)
Ethnicity	n=90	
HISPANIC OR LATINO	7 (8%)	43% (10%, 82%)
NOT HISPANIC OR LATINO	77 (86%)	60% (48%, 71%)
Not Stated or Unknown	6 (7%)	83% (36%, 100%)
Race	n=90	
AMERICAN INDIAN OR ALASKA NATIVE	1 (1%)	0%
ASIAN	8 (9%)	75% (35%, 97%)
BLACK OR AFRICAN AMERICAN	4 (4%)	75% (19%, 99%)
WHITE	74 (82%)	58% (46%, 69%)
UNKNOWN	3 (3%)	67% (9%, 99%)
Baseline BMI (kg/m2)	n=82	
< Median	41 (50%)	63% (47%, 78%)
>= Median	41 (50%)	59% (42%, 74%)
Baseline ECOG	n=90	
0	53 (59%)	58% (44%, 72%)
>=1	37 (41%)	62% (45%, 78%)
No.of Prior Systemic Therapies	n=90	
2	34 (38%)	74% (56%, 87%)
3+	56 (62%)	52% (38%, 65%)
Baseline CD20	n=68	
Positive	68 (100%)	56% (43%, 68%)
Relapse or Refractory to Last Prior Therapy	n=90	
Refractory	62 (69%)	52% (39%, 65%)
Non-Refractory	28 (31%)	79% (59%, 92%)
Received prior CAR-T therapy	n=90	
Yes	3 (3%)	33% (1%, 91%)
No	87 (97%)	61% (50%, 71%)
Relapse or Refr. to Any Prior Anti-CD20 Therapy	n=90	
Refractory	71 (79%)	55% (43%, 67%)
Non-Refractory	19 (21%)	79% (54%, 94%)
Time Since Last CD20 (Days)	n=90	
3 months or less	23 (26%)	35% (16%, 57%)
More than 3 months	67 (74%)	69% (56%, 79%)

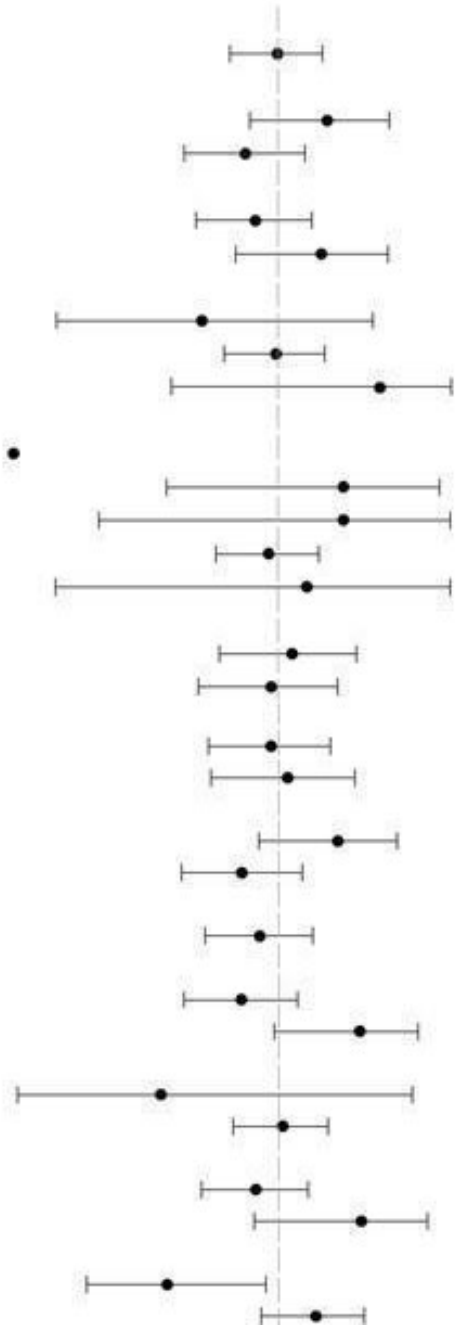


Figure 38 Cont. Summary of Response by Subgroups, Initial Treatment with Mosunetuzumab, Complete Responder, Response Assessed by Independent Oncologists, Cohort B11 Expansion, 3L + FL Patients, ITT Patient (2/2)

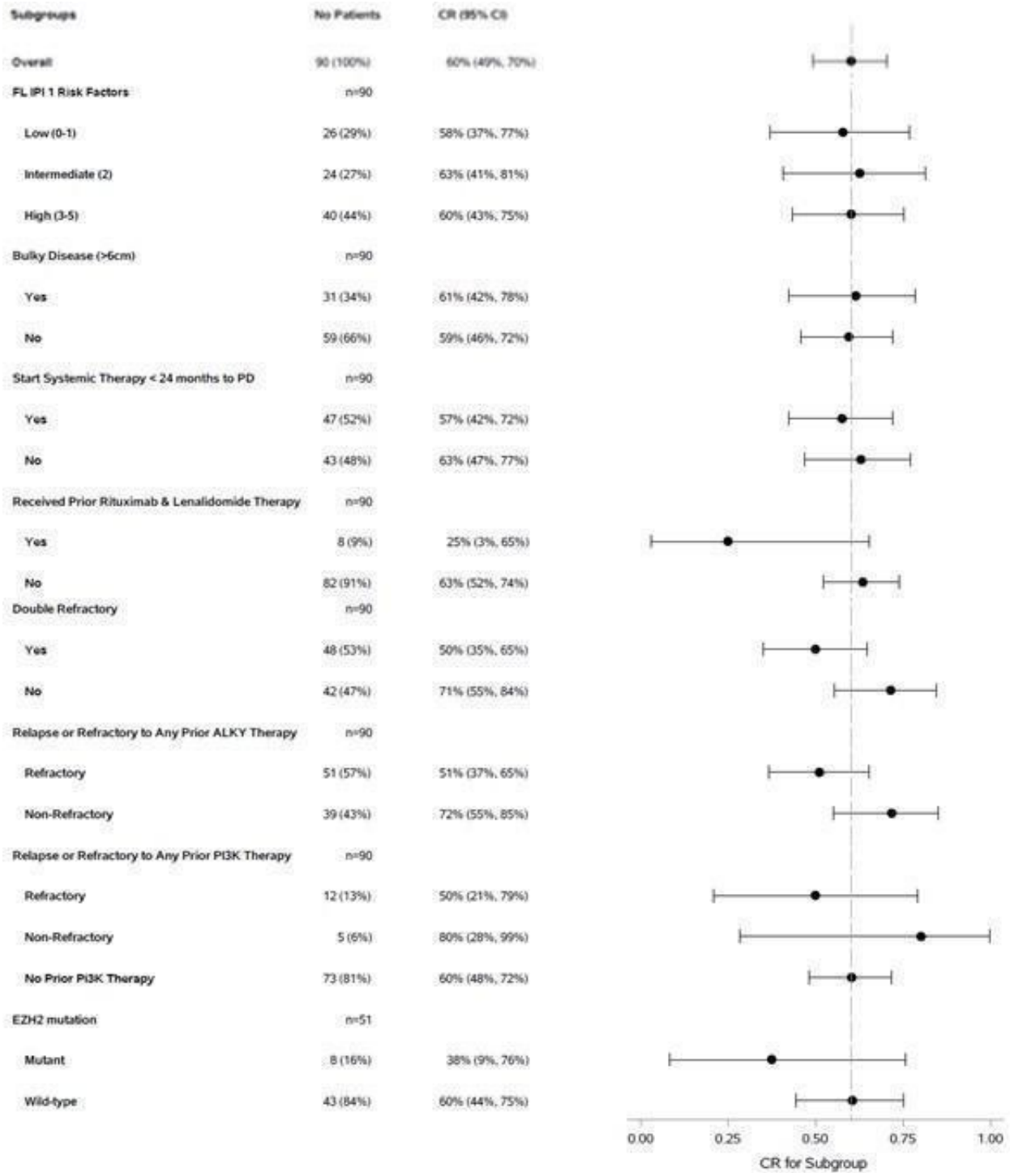


Figure 39: Summary of Response by Subgroups, Initial Treatment with Mosunetuzumab, Overall Responder, Response Assessed by Independent Oncologists, Cohort B11 Expansion, 3L + FL Patients, ITT Patient (1/2)

Subgroups	No Patients	ORR (95% CI)
Overall	90 (100%)	80% (70%, 88%)
Sex	n=90	
Female	35 (39%)	86% (70%, 95%)
Male	55 (61%)	76% (63%, 87%)
Age Group	n=90	
< 65	60 (67%)	77% (64%, 87%)
>= 65	30 (33%)	87% (69%, 96%)
Ethnicity	n=90	
HISPANIC OR LATINO	7 (8%)	71% (29%, 96%)
NOT HISPANIC OR LATINO	77 (86%)	81% (70%, 89%)
Not Stated or Unknown	6 (7%)	83% (36%, 100%)
Race	n=90	
AMERICAN INDIAN OR ALASKA NATIVE	1 (1%)	100%
ASIAN	8 (9%)	75% (35%, 97%)
BLACK OR AFRICAN AMERICAN	4 (4%)	100% (40%, 100%)
WHITE	74 (82%)	80% (69%, 88%)
UNKNOWN	3 (3%)	67% (9%, 99%)
Baseline BMI (kg/m2)	n=82	
< Median	41 (50%)	83% (68%, 93%)
>= Median	41 (50%)	78% (62%, 89%)
Baseline ECOG	n=90	
0	53 (59%)	79% (66%, 89%)
>=1	37 (41%)	81% (65%, 92%)
No.of Prior Systemic Therapies	n=90	
2	34 (38%)	85% (69%, 95%)
3+	56 (62%)	77% (64%, 87%)
Baseline CD20	n=68	
Positive	68 (100%)	78% (66%, 87%)
Relapse or Refractory to Last Prior Therapy	n=90	
Refractory	62 (69%)	77% (65%, 87%)
Non-Refractory	28 (31%)	86% (67%, 96%)
Received prior CAR-T therapy	n=90	
Yes	3 (3%)	100% (29%, 100%)
No	87 (97%)	79% (69%, 87%)
Relapse or Refr. to Any Prior Anti-CD20 Therapy	n=90	
Refractory	71 (79%)	77% (66%, 87%)
Non-Refractory	19 (21%)	89% (67%, 99%)
Time Since Last CD20 (Days)	n=90	
3 months or less	23 (26%)	70% (47%, 87%)
More than 3 months	67 (74%)	84% (73%, 92%)

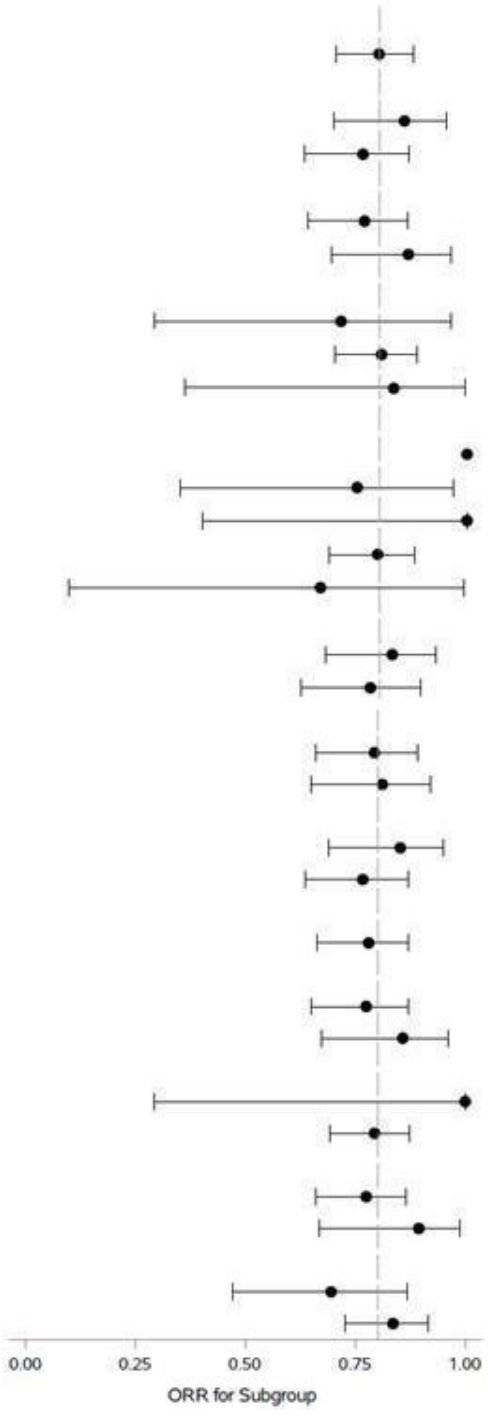


Figure 40 cont;: Summary of Response by Subgroups, Initial Treatment with Mosunetuzumab, Overall Responder, Response Assessed by Independent Oncologists, Cohort B11 Expansion, 3L + FL Patients, ITT Patient (2/2)

Subgroups	No Patients	ORR (95% CI)
Overall	90 (100%)	80% (70%, 88%)
FL IPI 1 Risk Factors	n=90	
Low (0-1)	26 (29%)	81% (61%, 93%)
Intermediate (2)	24 (27%)	75% (53%, 90%)
High (3-5)	40 (44%)	83% (67%, 93%)
Bulky Disease (>6cm)	n=90	
Yes	31 (34%)	74% (55%, 88%)
No	59 (66%)	83% (71%, 92%)
Start Systemic Therapy < 24 months to PD	n=90	
Yes	47 (52%)	85% (72%, 94%)
No	43 (48%)	74% (59%, 86%)
Received Prior Rituximab & Lenalidomide Therapy	n=90	
Yes	8 (9%)	75% (35%, 97%)
No	82 (91%)	80% (70%, 88%)
Double Refractory	n=90	
Yes	48 (53%)	71% (56%, 83%)
No	42 (47%)	90% (77%, 97%)
Relapse or Refractory to Any Prior ALKY Therapy	n=90	
Refractory	51 (57%)	71% (56%, 83%)
Non-Refractory	39 (43%)	92% (79%, 98%)
Relapse or Refractory to Any Prior PI3K Therapy	n=90	
Refractory	12 (13%)	75% (43%, 95%)
Non-Refractory	5 (6%)	100% (48%, 100%)
No Prior Pi3K Therapy	73 (81%)	79% (68%, 88%)
EZH2 mutation	n=51	
Mutant	8 (16%)	75% (35%, 97%)
Wild-type	43 (84%)	79% (64%, 90%)

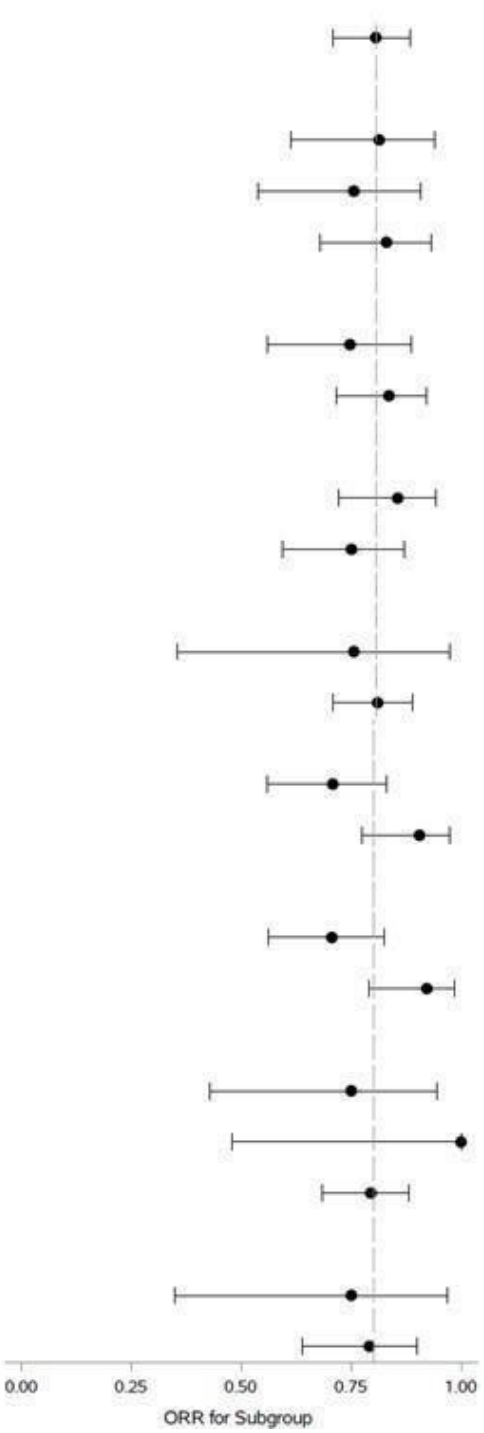


Figure 41: Summary of Response by Subgroups, Initial Treatment with Mosunetuzumab, Duration of response, Response Assessed by Independent Oncologists, Cohort B11 Expansion, 3L + FL Patients, ITT Patient (1/2)

Subgroups	No Patients	DOR 12 months event-free rate (95% CI)
Overall	72 (100%)	62% (50%,74%)
Sex	(n=72)	
Female	30 (42%)	67% (49%,85%)
Male	42 (58%)	58% (42%,74%)
Age Group	(n=72)	
< 65	46 (64%)	59% (43%,74%)
>=65	26 (36%)	67% (49%,86%)
Ethnicity	(n=72)	
NOT HISPANIC OR LATINO	62 (86%)	58% (45%,71%)
HISPANIC OR LATINO	5 (7%)	75% (33%,100%)
Not Stated or Unknown	5 (7%)	100% (100%,100%)
Race	(n=72)	
AMERICAN INDIAN OR ALASKA NATIVE	1 (1%)	0%
ASIAN	6 (8%)	80% (45%,100%)
BLACK OR AFRICAN AMERICAN	4 (6%)	75% (33%,100%)
WHITE	59 (82%)	59% (46%,72%)
UNKNOWN	2 (3%)	100% (100%,100%)
Baseline BMI (kg/m2)	(n=66)	
< Median	34 (52%)	66% (49%,82%)
>= Median	32 (48%)	54% (35%,72%)
Baseline ECOG	(n=72)	
0	42 (58%)	68% (53%,83%)
>=1	30 (42%)	53% (34%,72%)
No.of Prior Systemic Therapies	(n=72)	
2	29 (40%)	72% (55%,90%)
3+	43 (60%)	55% (39%,71%)
Baseline CD20	(n=53)	
Positive	53 (100%)	61% (47%,75%)
Relapse or Refractory to Last Prior Therapy	(n=72)	
Refractory	48 (67%)	49% (34%,64%)
Non-Refractory	24 (33%)	87% (73%,100%)
Received prior CAR-T therapy	(n=72)	
Yes	3 (4%)	33% (0%,87%)
No	69 (96%)	63% (51%,75%)
Relapse or Refr. to Any Prior Anti-CD20 Therapy	(n=72)	
Refractory	55 (76%)	53% (39%,68%)
Non-Refractory	17 (24%)	88% (71%,100%)
Time Since Last CD20 (Days)	(n=72)	
3 months or less	16 (22%)	38% (7%,69%)
More than 3 months	56 (78%)	67% (54%,79%)
Prior auto-Stem Cell Transplant	(n=72)	
Yes	14 (19%)	85% (65%,100%)
No	58 (81%)	56% (42%,70%)

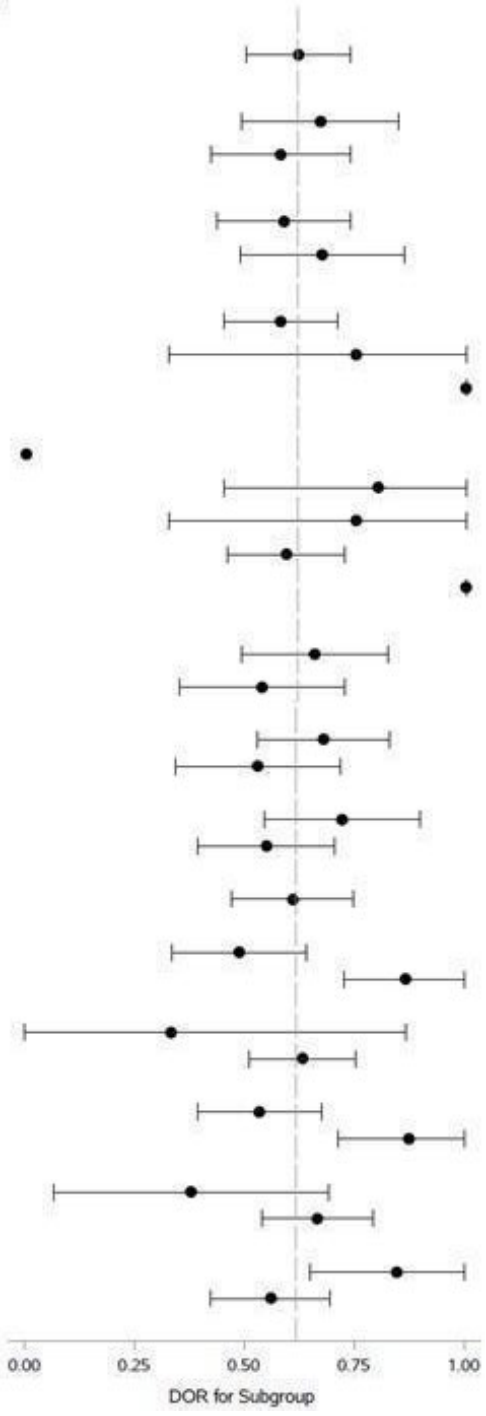


Figure 41 cont;: Summary of Response by Subgroups, Initial Treatment with Mosunetuzumab, Duration of response, Response Assessed by Independent Oncologists, Cohort B11 Expansion, 3L + FL Patients, ITT Patient (2/2)

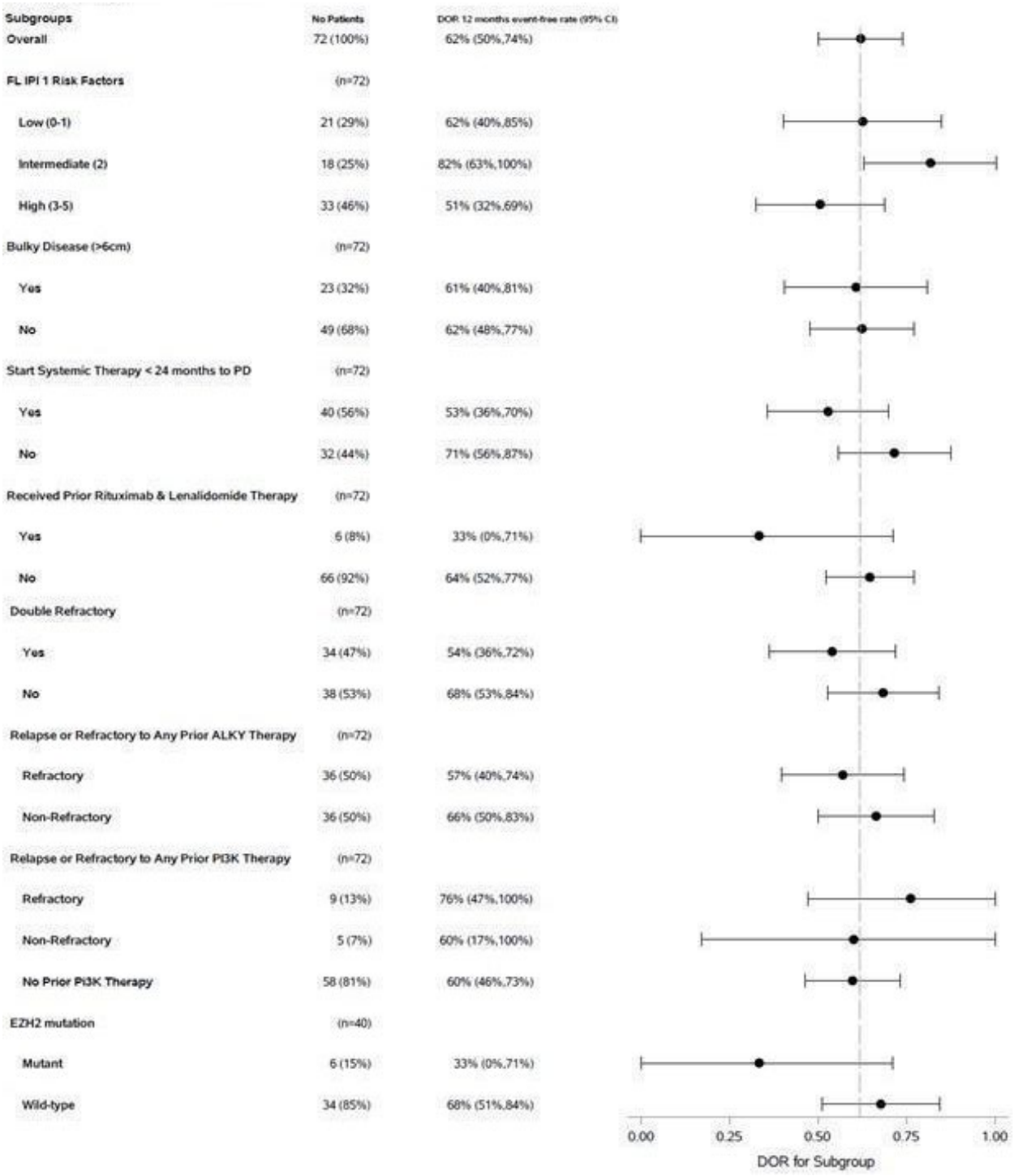


Figure 42: Summary of Response by Subgroups, Initial Treatment with Mosunetuzumab, Duration of Complete Response, Response Assessed by Independent Oncologists, Cohort B11 Expansion, 3L + FL Patients, ITT Patient (1/2)

Subgroups	No Patients	DOCR 12 months event-free rate (95% CI)
Overall	54 (100%)	71% (58%,85%)
Sex	(n=54)	
Female	25 (46%)	75% (56%,95%)
Male	29 (54%)	68% (49%,87%)
Age Group	(n=54)	
< 65	33 (61%)	67% (48%,85%)
>=65	21 (39%)	78% (59%,97%)
Ethnicity	(n=54)	
NOT HISPANIC OR LATINO	46 (85%)	69% (54%,84%)
HISPANIC OR LATINO	3 (6%)	67% (13%,100%)
Not Stated or Unknown	5 (9%)	100% (100%,100%)
Race	(n=54)	
AMERICAN INDIAN OR ALASKA NATIVE	0 (0%)	
ASIAN	6 (11%)	60% (17%,100%)
BLACK OR AFRICAN AMERICAN	3 (6%)	100% (100%,100%)
WHITE	43 (80%)	71% (57%,86%)
UNKNOWN	2 (4%)	
Baseline BMI (kg/m2)	(n=50)	
< Median	26 (52%)	74% (56%,92%)
>= Median	24 (48%)	68% (48%,87%)
Baseline ECOG	(n=54)	
0	31 (57%)	77% (61%,94%)
>=1	23 (43%)	63% (40%,86%)
No.of Prior Systemic Therapies	(n=54)	
2	25 (46%)	76% (57%,95%)
3+	29 (54%)	68% (50%,87%)
Baseline CD20	(n=38)	
Positive	38 (100%)	76% (62%,91%)
Relapse or Refractory to Last Prior Therapy	(n=54)	
Refractory	32 (59%)	57% (38%,77%)
Non-Refractory	22 (41%)	91% (78%,100%)
Received prior CAR-T therapy	(n=54)	
Yes	1 (2%)	100% (100%,100%)
No	53 (98%)	71% (57%,84%)
Relapse or Refr. to Any Prior Anti-CD20 Therapy	(n=54)	
Refractory	39 (72%)	62% (44%,80%)
Non-Refractory	15 (28%)	93% (79%,100%)
Time Since Last CD20 (Days)	(n=54)	
3 months or less	8 (15%)	54% (14%,93%)
More than 3 months	46 (85%)	74% (60%,88%)
Prior auto-Stem Cell Transplant	(n=54)	
Yes	12 (22%)	92% (76%,100%)
No	42 (78%)	64% (47%,81%)

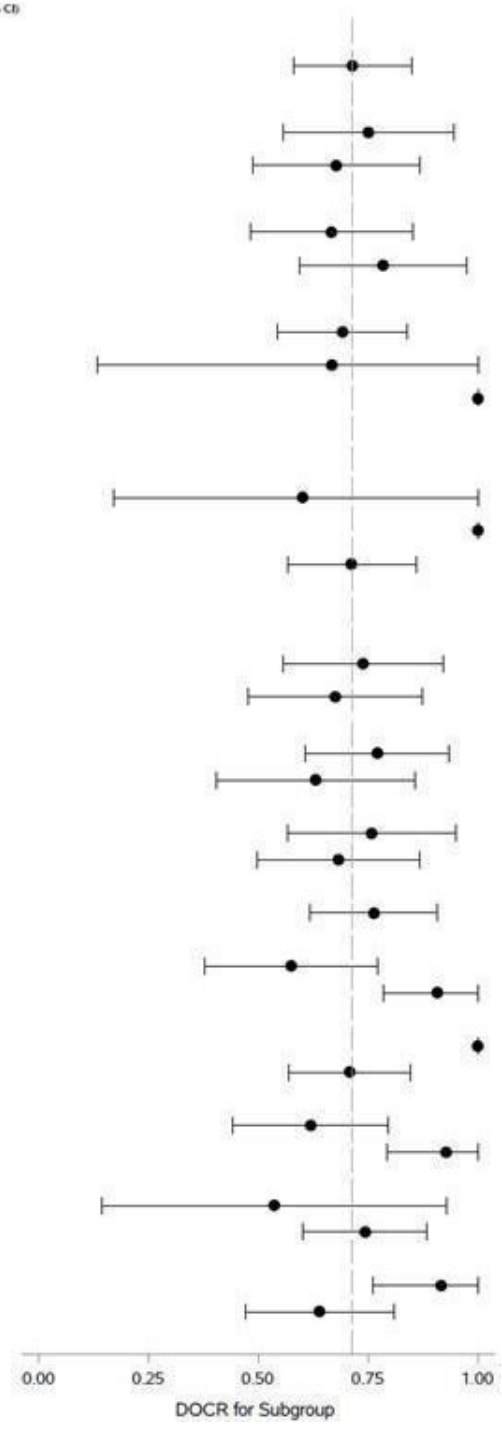
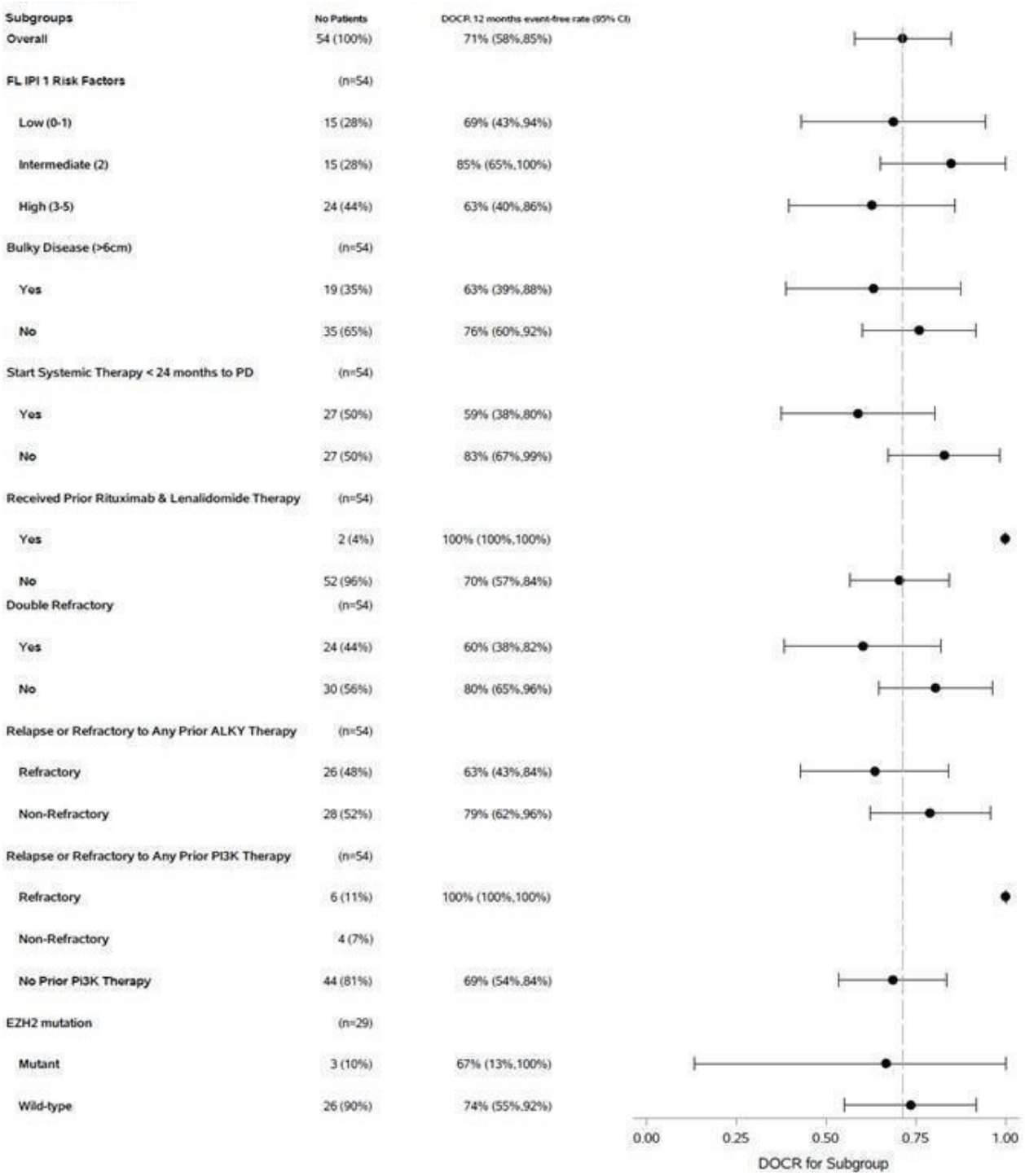


Figure 42 cont;: Summary of Response by Subgroups, Initial Treatment with Mosunetuzumab, Duration of Complete Response, Response Assessed by Independent Oncologists, Cohort B11 Expansion, 3L + FL Patients, ITT Patient (2/2)



In the subgroup analysis bulky disease is listed as > 6 cm and no clinically relevant difference between the two cohorts is seen.

Time to response

Swimmer's plots are presented with PR, CR and/or PD based on investigator assessment, as well as the duration of mosunetuzumab treatment is provided for all patients in the B11 FL RP2D expansion cohort

for the 16 patients who received >8 cycles of mosunetuzumab treatment and the remaining 74 patients who received ≤8 cycles of mosunetuzumab treatment.

Figure 43: Swimlane Plot, Initial Treatment with Mosunetuzumab, Cohort B11 Expansion, 3L + FL Patients who received ≤8 cycles of mosunetuzumab treatment, Safety- Evaluable Patients

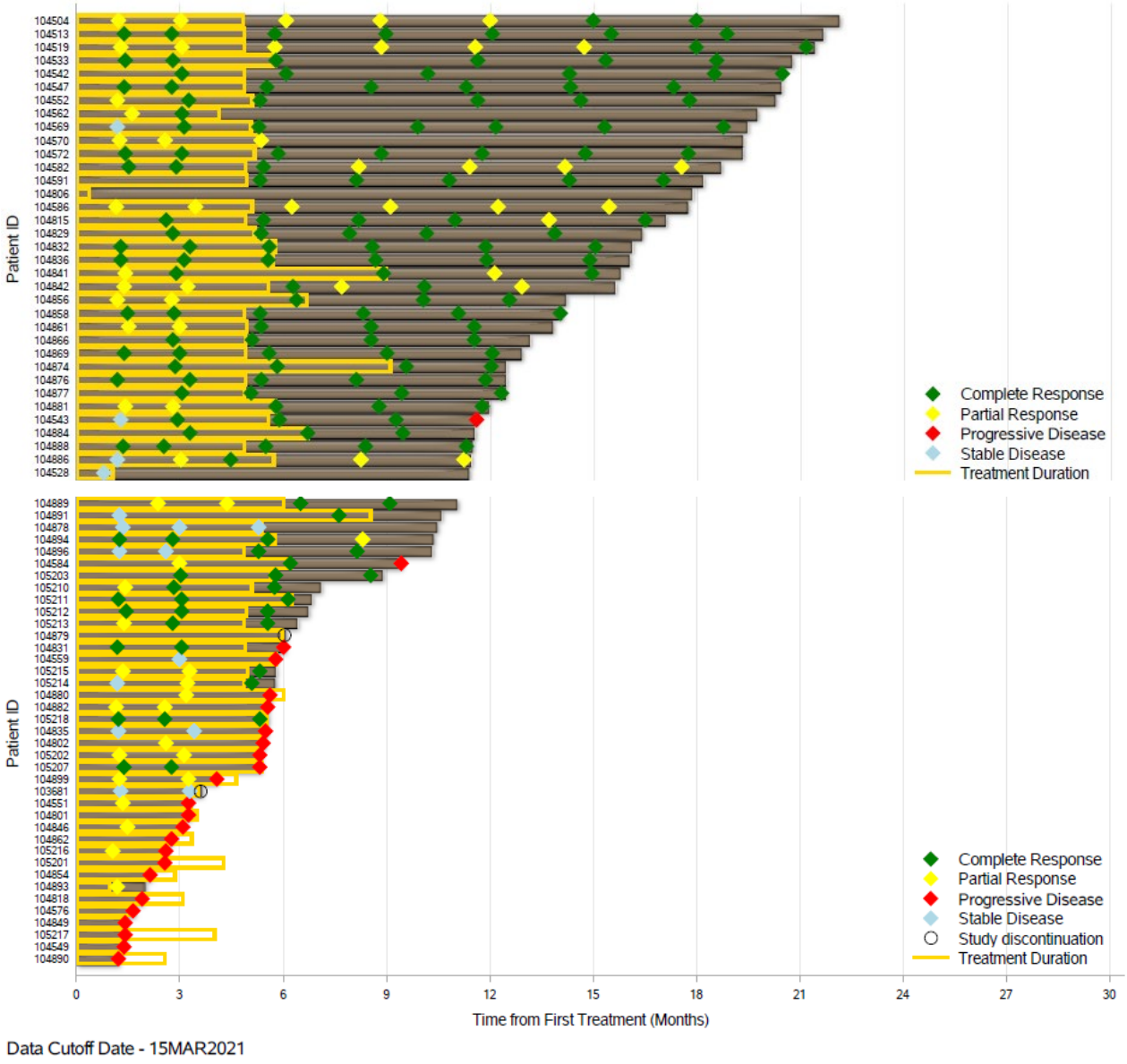
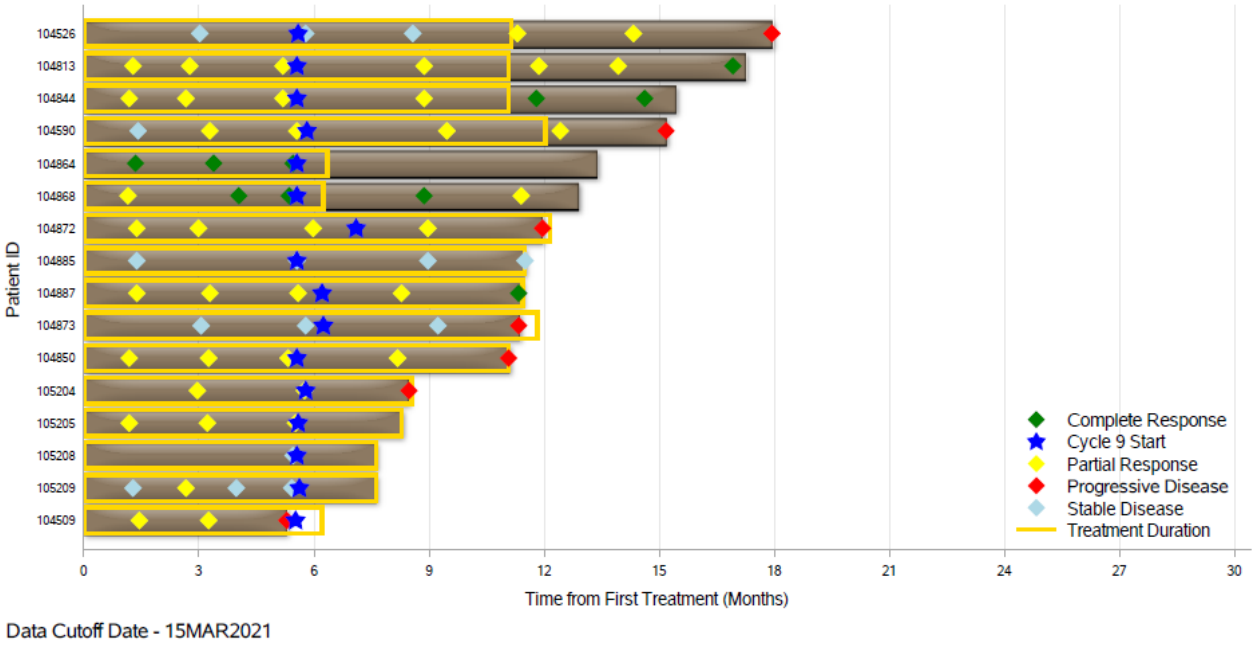


Figure 44: Figure 2: Swimlane Plot, Initial Treatment with Mosunetuzumab, Cohort B11 Expansion, 3L + FL Patients who received >8 cycles of mosunetuzumab, Safety- Evaluable **Patients**



2.6.5.2 Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25: Summary of efficacy for trial GO29781, part B11 FL

Title: Interim CSR Study GO29781, AN OPEN-LABEL, MULTICENTER, PHASE I/II TRIAL EVALUATING THE SAFETY, EFFICACY, AND PHARMACOKINETICS OF ESCALATING DOSES OF MOSUNETUZUMAB (BTCT4465A) AS A SINGLE AGENT AND COMBINED WITH ATEZOLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA OR CHRONIC LYMPHOCYTIC LEUKEMIA.		
Study identifier	Study GO29781	
Design	Study GO29781 is an ongoing Phase I/Ib (Phase I/II per protocol Version 12), multicenter, open-label, dose-escalation and dose-expansion study of mosunetuzumab administered as a single agent and in combination with atezolizumab in patients with R/R hematologic malignancies expected to express CD20, including B-cell NHL and CLL. The study is divided into a dose-escalation and dose-expansion stage. Group B is comprised of dose escalation and dose expansion cohorts (B1-B11), which included two major dose expansion cohorts in R/R follicular lymphoma (FL) ≥2 prior therapies, B7 (dose of 1/2/13.5 mg) and B11 (dose at RP2D/ intended registration dose of 1/2/60/30 mg).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	CR at 6 months (after 8 cycles): stop treatment PR or SD at 6 months: continue up to 17 cycles (app. 1 year) not applicable not applicable
Hypothesis	Superiority (over historical complete responses in follicular lymphoma patients)	

Title: Interim CSR Study GO29781, AN OPEN-LABEL, MULTICENTER, PHASE I/II TRIAL EVALUATING THE SAFETY, EFFICACY, AND PHARMACOKINETICS OF ESCALATING DOSES OF MOSUNETUZUMAB (BTCT4465A) AS A SINGLE AGENT AND COMBINED WITH ATEZOLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA OR CHRONIC LYMPHOCYTIC LEUKEMIA.			
Study identifier	Study GO29781		
Treatments group	B11 FL = B11 FL RP2D FL patients with ≥2 prior systemic therapies.		Mosunetuzumab 1/2/60/30 mg IV: 1 mg Cycle1Day1, 2 mg C1D8, 60 mg C1D15, 60 mg C2D1, 30 mg D1 of C3-C8 or C3-C17 depending on disease status after C8. Three-week cycles.
Endpoints and definitions	Primary endpoint	**CR rate by IRF**: (Complete Remission rate by Independent Review Committee)	Comparisons of CR rate (Cheson et al., 2007) between each efficacy-evaluable population and historical controls will be conducted using an exact binomial test with two-sided alpha level of 5%. The control CR rate is assumed to be 14% for R/R FL population. The exact 95% confidence intervals using the Clopper-Pearson method for CR rate is provided.
	Secondary endpoint	**CR rate by** Investigator **(INV)**	Complete Remission rate as by Cheson et al., 2007. The exact 95% confidence intervals using the Clopper-Pearson method for CR rate is provided.
	Secondary endpoint	**ORR**: Overall response rate	The exact 95% confidence intervals using the Clopper-Pearson method for ORR is provided. Assessed by the IRF and by the INV
	Secondary endpoint	**DOCR**: Duration of CR	This analysis only included efficacy evaluable patients who achieve a CR. The Kaplan-Meier (KM) estimate is provided. Assessed by the IRF and by the INV.
	Secondary endpoint	**DOR**: Duration of response	This analysis will only include efficacy evaluable patients who achieve a CR or at least PR. The KM estimate is provided. Assessed by the IRF and by the INV.
	Secondary endpoint	**PFS**: Progression-free survival	The KM estimate is provided. Assessed by the IRF and by the INV.
	Secondary endpoint	**OS**: Overall survival	
CCOD	27 August 2021		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Patients with follicular lymphoma (FL) after ≥2 prior systemic treatments receiving the RP2D of mosunetuzumab 1/2/60/30 mg IV enrolled in cohort B11 of study GO29781.	
Descriptive statistics and estimate variability	Treatment group	Cohort B11 FL
	Number of subjects	N=90
	Primary endpoint	

Title: Interim CSR Study GO29781, AN OPEN-LABEL, MULTICENTER, PHASE I/II TRIAL EVALUATING THE SAFETY, EFFICACY, AND PHARMACOKINETICS OF ESCALATING DOSES OF MOSUNETUZUMAB (BTCT4465A) AS A SINGLE AGENT AND COMBINED WITH ATEZOLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA OR CHRONIC LYMPHOCYTIC LEUKEMIA.		
Study identifier	Study GO29781	
	CR by IRF n (%) (95% CI)[1]	54 (60.0%) (49.1, 70.2)
	Secondary endpoints:	
	CR by INV n (%) (95% CI)[1]	54 (60.0%) (49.1, 70.2)
	ORR (by IRF) n (%) (95% CI)	72 (80.0%) (70.3, 87.7)
	DOCR (by IRF) Patients with event, n (%) Median (months) K-M event-free proportion, % (95% CI) 12 months 18 months	 16/54 (29.6%) NE (14.6, NE) 71.4% (57.9, 84.9) 63.7% (48.0, 79.4)
	DOR (by IRF) Patients with event, n (%) Median (months) K-M event-free proportion, % (95% CI) 12 months 18 months	 29/72 (40.3%) 22.8 (9.7, NE) 61.8% (50.0, 73.7) 56.9% (44.1, 69.6)
	PFS (by IRF) Patients with event, n (%) Median (months) (95% CI)[2] K-M 12-month event-free proportion, % (95% CI)	 42 (46.7%) 17.9 (10.1, NE) 57.7 (46.9, 68.4)
	OS Patients with event, n (%) Median (months) K-M 12-month event-free proportion, % (95% CI)	 8 (8.9%) NE 93.0% (87.6, 98.4)
Notes	[1]95% CIs calculated using the Clopper-Pearson method. [2]Summaries of time-to-event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.	

2.6.5.3 Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Non-Controlled trials	GO29781 Group B: 120/410 (29.3%) B11 RP2D cohort: 61/214 (28.5%) B11 FL cohort: 23/90 (25.6%)	GO29781 Group B: 55/410 (13.4%) B11 RP2D cohort: 31/214 (14.5%) B11 FL cohort: 5/90 (5.6%)	GO29781 Group B: 10/410 (2.4%) B11 RP2D cohort: 8/214 (3.7%) B11 FL cohort: 2/90 (2.2%)

2.6.5.4 In vitro biomarker test for patient selection for efficacy

Not applicable

2.6.5.5 Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.6.5.6 Supportive study

There is only one study with multiple subgroups. Subgroup B7 included 46 FL patients having received ≥ 2 prior therapies treated with mosunetuzumab 1/2/13.5 mg. The Applicant has presented the results side-by-side with the pivotal B11 cohort, so the results in this cohort are briefly commented upon in the main study section.

2.6.6 Discussion on clinical efficacy

Design and conduct of clinical studies

Study GO29781: An open-label, multicenter, Phase I/Ib (Phase I/II per protocol v12) trial evaluating the safety, efficacy, and PK of escalating doses of mosunetuzumab (BTCT4465A) as a single agent and combined with atezolizumab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia. The Interim CSR GO29781 reports all data in patients receiving IV monotherapy in both Group A and Group B (dose escalation and dose expansion stages) up to the clinical cut-off date (CCOD) of 15 March 2021.

Efficacy results are described for 90 patients with R/R FL (≥2 prior systemic therapies that included treatment with an anti-CD20-directed therapy and an alkylating agent) receiving the RP2D/intended registration dose and schedule of 1/2/60/30 mg (B11 FL). The 46 patients with R/R FL enrolled and treated at the lower dose level of 1/2/13.5 mg (B7) are considered supportive. Enrolment of patients with R/R FL in Study GO29781 as well as grading of FL was based on local assessment of diagnosis. Confirmation of FL by central assessment in all subjects was not planned as the study has been initially designed as a FIH study. Moreover, a reliable pathological diagnosis of FL depends largely on size and

quality of the tissue sample. Consequently, the implementation of the central confirmation after local histopathological diagnosis would result in potentially insufficient size and/or quality of tissue samples for a proportion of patients to confirm diagnosis.

Dose-expansion FL cohorts in Study GO29781 did not include patients with diagnosis of Grade 3B FL or transformed FL patients (see SmPC section 5.1). The distinction between Grade 3A and 3B in the current WHO edition is important due to their apparent differences in molecular genetics and prognosis; it is suggested that Grade 3A FL is on the same spectrum as Grade 1-2 FL, and Grade 3B (no centrocytes, centroblasts only) FL behaves as de novo DLBCL (Katzenberger et al., Am J Pathol 2004; Karube et al., Blood 2007)".

Based on the sought indication (*Mosunetuzumab as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies)* the population included in the trial is considered at high risk and representative for the intended population, although patients with various detrimental conditions (ECOG ≥2, cardiac, conditions, moderate-severe renal and hepatic impairment) were excluded, as they generally are in clinical trials.

The endpoints are considered relevant for a SAT and the primary endpoint of CR (by IRF) is a potential surrogate endpoint for PFS (Zhu et al. 2017; Mangal et al. 2018), which is considered the most relevant endpoint in indolent lymphomas (including FL), where new treatments are applied for PD on a regular basis.

At CCOD (15 March 2021), 44 major protocol deviations were reported in 30 subjects (33,3%) in the B11 RP2D FL cohort. Out of these 4 (4.4%) were related to the outbreak of the COVID-19 pandemic. The most common major protocol deviations in the B11 FL RP2D cohort was "Incomplete/missing/out-of-window tumor-related assessments" reported in 11% of patients (n = 10). According to the narratives provided, all of the 10 major protocol deviations were related to delayed confirmation of complete response by bone marrow assessment which may have contributed to an underestimate of the CR rate and DOCR. In addition, an analysis of subject incidence of major and overall protocol deviations by study site was provided, suggesting a slightly increased median number of major and overall protocol deviations per subject in 6 sites (3 located in Spain, 2 in Germany and 1 in Australia). However, the major protocol deviations observed in these sites were distributed across various subcategories, indicating there was no specific protocol deviation causing consistent errors in study conduct. In addition, these sites had only few subjects enrolled (n ≤ 3), which might also explain the slightly higher rates of major and minor protocol deviations. In overall, the deviations were not considered to affect the overall conclusions of the study.

Efficacy data and additional analyses

Exposure-efficacy: At the proposed registration dose and schedule of 1/2/60/30 mg, mosunetuzumab IV monotherapy showed IRF-assessed CR rate of 60% (95% CI: 49.1, 70.2) and ORR of 80% (95% CI: 70.3, 87.7) with associated durability (CCOD of 27 August 2021). The proposed registration dose and schedule of 1/2/60/30 mg was predicted to achieve PK exposures at the plateau of the ER curves for CRR and ORR.

For the supportive cohort B7, which received a lower dose, the CR rate was 45.7% (95% CI: 30.9, 61.0).

The secondary endpoints support the primary endpoint although at the CCOD of 15 March 2021 data were immature with a median follow-up for DOR of 10.3 months in an indolent disease like FL. Updated data with a CCOD of 27 Aug 2021, with an improved data maturity (median follow-up for DOR of 14.9 months), have been submitted and confirms the initial results. The results of the secondary endpoints in

the B7 FL interim dose cohort receiving the lower dose of 1/2/13.5 mg were slightly lower than in the B11 FL cohort and are generally thought to support efficacy.

The limited efficacy and safety results for patients who received more than 8 cycles of mosunetuzumab treatment (n = 11) support the appropriateness of continuing treatment beyond Cycle 8 for patients with SD or PR at the end of Cycle 8 and for the proposed treatment duration.

Subgroup analyses of the CR rate by IRF assessment in general demonstrated the consistency of the treatment effect across relevant subpopulations defined by demographic, prior treatment (number and refractory status; PD <24 months after initial treatment), and prognostic factors (FLIPI). Consistent response rates were also observed for subgroups with anticipated poor prognosis, such as for frailer patients aged ≥ 65 years, patients with PD within 24 months after start of first line treatment, patients with bulky disease and patients with intermediate/high risk FLIPI scores. Consistency of the treatment effect across relevant subpopulations has also been shown in terms of response durability (12-Months event-free rate for DOR and DOCR).

Given the limitations associated with the uncontrolled single-arm design of the pivotal study and that the primary endpoint, CR, is not an established surrogate endpoint in r/r FL, sufficiently mature DOR data are important. At the CCOD of 15 March 2021, data were immature in an indolent disease like FL, with a median follow-up for DOR of 10.3 months with the proposed dosing regimen (1/2/60/30 mg). Therefore, updated data with an improved data maturity were requested and have been provided, which confirm the initial results (CCOD 15 March 2021 to CCOD of 27 Aug 2021).

The efficacy results with mosunetuzumab monotherapy have been contextualized through a systematic literature review conducted by the Applicant including approved and unapproved therapies. These cross-trial indirect comparisons are however associated with well-known limitations, mainly related to differences in study populations. This is in particular the case for studies including patients with r/r FL, known to be a very heterogeneous patient population in terms of disease course, treatment history and prognosis. Contextualisation using an external real-world control based on a non-interventional study applying similar eligibility criteria as for study GO29781 would have partially overcome these issues and would have been preferred. However, such an external real-world control is lacking, which poses uncertainty on the value of the efficacy results obtained with this single-arm study in the context of available alternatives. Despite the uncertainties associated with cross-trial comparisons and given there is no standard of care in the target disease setting, the clinical data with mosunetuzumab monotherapy in general show a substantial effect size compared to most of the currently approved and unapproved alternative therapies (including PI3K inhibitors, rituximab + lenalidomide and bendamustine + obinutuzumab). Overall, these indirect comparisons support the contextualization of the mosunetuzumab efficacy and safety results and suggest that the benefits to public health of the immediate availability outweigh the risks in this patient population with high unmet need.

In addition, in response to a request for additional information, the Applicant provided results of several RWD studies involving patients with R/R FL having received ≥ 2 prior lines of systemic therapies, including 2 RWD analyses conducted by the Applicant. Despite methodological issues preventing any definite conclusion based on comparative analyses, RWD study data might give an idea on the validity of the pre-defined threshold for CR rate. In this respect, these RWD data support the issue with regard to the validity of the predefined threshold CR rate of 14% used for superiority testing, as CR rates provided for all RWD studies are higher than 14% (ranging from 17.7% to 47%). However, the compelling response rates observed with mosunetuzumab monotherapy, supported by contextualizing with RWD study data as well as with study data with alternative approved and unapproved therapies, do overcome this issue.

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical efficacy

Not applicable.

Additional efficacy data needed in the context of a conditional MA

From a regulatory point of view, an RCT would have been preferred based on the availability of alternative therapies for the included population. Instead, the results from the study are contextualised through a systematic literature review. This presents certain limitations, as discussed.

Mosunetuzumab is still in development, but based on the promising CR rate, particularly compared to other treatments for FL, it is considered appropriate for the Applicant to request approval in the context of a conditional MA as requirements for a CMA are fulfilled (see B/R section). A confirmatory phase III study evaluating PFS is considered necessary for a conversion of the CMA to full approval and has recently commenced: *Study GO42909: 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*.

2.6.7 Conclusions on the clinical efficacy

The efficacy of Lunsumio as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies - is considered promising based on the CR rate.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- The MAH will provide results from Study GO42909, a randomised, open-label, multicentre trial evaluating mosunetuzumab in combination with lenalidomide in comparison to rituximab in combination with lenalidomide in patients with follicular lymphoma after at least one line of systemic therapy.

2.6.8 Clinical safety

Key safety summary tables are presented side by side for the following safety-evaluable patients (defined as those who had received at least one dose of mosunetuzumab) who received mosunetuzumab IV monotherapy in Study GO29781 in the following order:

- All 33 patients with R/R NHL in **Group A** (Cycle 1 non-fractionated dosing [fixed dosing])
- All 414 patients with R/R NHL in **Group B** (Cycle 1 step-up dosing)
- The subgroup of 218 patients with R/R NHL in Group B expansion cohort treated at the RP2D/intended registration dose and schedule (1/2/60/30 mg; hereinafter referred to as **B11 RP2D cohort**)
- All 90 patients with R/R FL within the B11 RP2D cohort (hereinafter referred to as **B11 FL RP2D cohort** or **B11 FL**), which represent the patient population for the intended indication, R/R FL patients with ≥2 prior therapies, at the RP2D/intended registration dose and schedule

The primary safety population of 218 patients with lymphoid malignancies (DLBCL, FL, MCL; in cohort B11) having received the RP2D is the cohort to be mainly assessed. Supportive information from an additional 196 patients having received for most patients considerably lower doses in group B, which have been added to the primary population, will be taken into consideration as well as results in the B11 FL RP2D cohort.

Table 26 Overview of mosunetuzumab intravenous monotherapy cohorts (Group A and B) of pivotal Study GO29781 contributing to safety evaluation

Study Design	Study Objectives	Population	No. of Patients	Dose and Regimen
Dose-escalation stage Group A: Cycle 1 non-fractionated (fixed dosing schedule) mosunetuzumab monotherapy escalation; IV infusion Group B: Cycle 1 step-up mosunetuzumab monotherapy escalation; IV infusion **Dose-expansion stage** Group B (B11 RP2D cohort): Mosunetuzumab monotherapy dose expansion in patients with R/R NHL at RP2D, specifically in (1) FL, (2) DLBCL/trFL, (3) MCL, and (4) Richter's transformation	Primary objectives: • Evaluate safety, tolerability, and PK • Determine the MTD and DLTs • Identify the recommended RP2D(s) and schedule(s) • Evaluate efficacy using a Cycle 1 step-up dosing schedule as a single agent The secondary and exploratory objectives are described in the Update Interim CSR GO29781, Report 1111637, Section 2.	Patients with R/R B-cell NHL	A total of 447 patients with R/R B-cell NHL were enrolled in Group A and Group B. Group A (dose escalation; Cohorts A1–A8): 33 patients Group B (dose escalation and dose expansion): 414 patients [a] • Dose escalation and interim expansion (Cohorts B1–B11): 196 patients • Dose expansion at the RP2D (B11 RP2D cohort): 218 patients [a] (90 FL patients, 88 DLBCL/trFL patients, 25 MCL patients, and 14 Richter's patients)	Fixed duration of treatment: 8 or 17 cycles based on the tumor response Group A (dose escalation; Cohorts A1–A8): fixed dosing from 0.05 mg to 2.8 mg on Day 1 of q3w cycles Group B (dose escalation and dose expansion): Cycle 1 step-up dosing • Dose escalation and interim expansion (Cohorts B1–B11): 0.4/1/2.8 mg to 1/2/60 mg [b] • Dose expansion at the RP2D (B11 RP2D cohort): 1/2/60/30 mg [c]

CSR=Clinical Study Report; DLBCL=diffuse large B-cell lymphoma; DLT=dose-limiting toxicity; FL=follicular lymphoma; IV=intravenous; MCL=mantle cell lymphoma; MTD=maximum tolerated dose; NHL=non-Hodgkin's lymphoma; PK=pharmacokinetic; q3w=every 3 weeks; RP2D=recommended Phase II dose; R/R=relapsed or refractory; trFL=transformed follicular lymphoma.

[a] One patient with melanoma instead of NHL was enrolled in error in the B11 DLBCL/trFL RP2D cohort and received one dose of study treatment. The patient was included in the safety-evaluable population for Group B (N=414 patients) and the overall B11 RP2D cohort (N=218 patients) but was excluded from the safety-evaluable population in the B11 DLBCL/trFL RP2D cohort (N=88 patients) for the purpose of safety analyses by histology.

[b] Step-up dosing was administered on Cycle 1 Day 1, Day 8, and Day 15. Cycle 1 Day 15 dose was administered on Day 1 of subsequent q3w cycles (Cycle 2 onwards).

[c] This dose reflects the RP2D/intended registration dose and schedule. Step-up dosing was administered in Cycle 1 (1 mg on Day 1, 2 mg on Day 8, and 60 mg on Day 15), 60 mg on Cycle 2 Day 1, and 30 mg on Cycle 3 Day 1 and subsequent q3w cycles.

2.6.8.1 Patient exposure

Most patients in the B11 RP2D cohort received their planned doses of mosunetuzumab with a median dose intensity of 99.4% (range: 10–114) and 81.7% of patients achieved a dose intensity of >90%. 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.

For the 90 patients in the B11 FL cohort the exposure was similar to the B11 RP2D cohort of 218 patients. One difference was the number of cycles received, which was higher in the FL population than in the entire B11 RP2D cohort (which includes the 90 FL patients): Forty-eight percent received <8 cycles in the entire cohort compared to 23% in the FL cohort whereas the corresponding number for 8 cycles were 37% vs 59%. Correspondingly, the time on study was longer for the FL cohort compared to the entire B11 RP2D cohort; a median of 392 days compared to 348.5 days, respectively.

Given the higher median cumulative dose and longer time on treatment in the B11 FL cohort compared to the entire B11 RP2D population, adverse events in this cohort will also be considered separately.

Exposure for 6 months (corresponding to app. 8 cycles) and 1 year (approximately 17 cycles for patients who achieved a PR or maintained SD after 8 cycles) were seen for 79 and 13 patients in the primary

safety population, respectively. The median observation time in cohort B11 RP2D was 14.3 months. The initial CCOD is from 15th March 2021; an updated analysis has been provided with CCOD from 27th August 2021 (+24 weeks).

Table 27 Summary of exposure in Group B, B11 RP2D Cohort CCOD 27.08.2021 Safety-Evaluable patients

Group/cohort No. of patients		Group B N=414	B11 RP2D Cohort N=218
No. cycles received	median (range)	6 (1-17)	8 (1-17)
	<8	220 (53.1%)	105 (48.2%)
	8	135 (32.6%)	80 (36.7%)
	>8 and <17	29 (7.0%)	16 (7.3%)
	17	30 (7.2%)	17 (7.8%)
No. of doses administered, median (range)		8 (1–21)	10 (1–21)
Total cumulative dose (mg), median (range)		123 (1–692)	298 (1-576)
Dose intensity (%)[a]	median (range)	99.3 (10–143)	99.4 (10–114)
	Patients with >90%, n (%)	346 (83.6%)	178 (81.7%)
Treatment duration (months), median (range)		3.9 (0.03-13.8)	4.9 (0.03-13.8)
Time on study (months), median (range)		14.3 (0.1-58.1)	14.3 (0.1-27.9)

RP2D=recommended Phase II dose

[a] Dose intensity is derived as (actual dose received/actual time on treatment based on date of last dose received)/(planned dose received/planned time on treatment based on actual cycles received).

Treatment duration is time from the date of first valid dose to end of the last valid dose.

Time on study (months) is from start of first dose to study discontinuation date, death date or CCOD, whichever is the earliest.

Demographics and baseline disease characteristics including cancer history:

Two-thirds of the patients in Group B and cohort B11 RP2D were male. FL patients were younger with 1/3 being > 65 years, and there were more patients with ECOG=0 compared to the primary safety population.

Table 28 Key Demographics and baseline disease characteristics of group B cohorts receiving mosunetuzumab iv monotherapy CCOD 27.08.2021 Safety- evaluable patients

	Patient population:	R/R FL	R/R FL	R/R DLBCL/trFL	R/R NHL	R/R NHL
	Group/cohort	B7 interim* escalation/ expansion	B11 RP2D** expansion	B11 RP2D** expansion	B11 RP2D** expansion	Group B overall
	No. of patients	N=46	N=90	N=88	N=218	N=414
Key Demographics and Baseline Characteristics	Age median (range), years	61.0 (27–85)	60.0 (29–90)	66.5 (24–96)	64.0 (24–96)	63.0 (19–96)
	n (%) 18–65 years	31 (67.4)	62 (68.9)	43 (48.9)	124 (56.9)	246 (59.4)
	> 65 years	15 (32.6)	28 (31.1)	45 (51.1)	94 (43.1)	168 (40.6)
	Sex, n (%) male	30 (65.2)	55 (61.1)	60 (68.2)	145 (66.5)	269 (65.0)
	female	16 (34.8)	35 (38.9)	28 (31.8)	73 (33.5)	145 (35.0)
	Race, n (%) White	36 (78.3)	74 (82.2)	68 (77.3)	179 (82.1)	320 (77.3)
	Asian	7 (15.2)	8 (8.9)	13 (14.8)	23 (10.6)	67 (16.2)
	Black/African American	3 (6.5)	4 (4.4)	2 (2.3)	6 (2.8)	11 (2.7)
	American Indian/Alaska Native	0	1 (1.1)	0	1 (0.5)	2 (0.5)
	Multiple	0	0	0	0	1 (0.2)
	Unknown	0	3 (3.3)	5 (5.7)	9 (4.1)	13 (3.1)
	ECOG PS, n (%) 0	28 (60.9)	53 (58.9)	31 (35.2)	100 (45.9)	178 (43.0)
	1	18 (39.1)	37 (41.1)	57 (64.8)	118 (54.1)	235 (56.8)
	2	0	0	0	0	1 (0.2)
	BMI (kg/m^2), median (range)	26.3 (20–41)	27.5 (17–45)	26.2 (15–40)	26.7 (15–52)	26.3 (15–52)

BMI = body mass index; DLBCL/trFL = diffuse large B-cell lymphoma/transformed follicular lymphoma; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; NHL = non-Hodgkin's lymphoma; RP2D = recommended Phase II dose; R/R = relapsed/refractory.

*Interim dose of mosunetuzumab by IV monotherapy = 1/2/13.5 mg.

**RP2D of mosunetuzumab by IV monotherapy = 1/2/60/30 mg.

The Applicant has added information regarding baseline hepatic and renal function; there were no patients with severe hepatic or renal impairment included in Group B and only 2/214 patients with moderate hepatic impairment and 28/214 with moderate renal impairment in the B11 RP2D cohort.

Receiving Mosunetuzumab IV Monotherapy; CCOD: 15 March 2021, Safety-Evaluable Patients (cont.)

Patient population: Group/cohort No. of patients		R/R FL B7 interim* escalation/ expansion N=46	R/R FL B11 RP2D** expansion N=90	R/R DLBCL/trFL B11 RP2D** expansion N=88	R/R NHL B11 RP2D** expansion N=214	R/R NHL Group B overall N=410
Baseline Hepatic Impairment, n (%)	No impairment	43 (93.5)	81 (90.0)	74 (84.1	183 (85.5)	359 (87.6)
	Mild impairment	3 (6.5)	8 (8.9)	13 (14.8)	29 (13.5)	49 (11.9)
	Moderate impairment	0 (0)	1 (1.1)	1 (1.1)	2 (0.9)	2 (0.5)
	Severe impairment	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Baseline Renal Function, n (%)	No impairment	22 (47.8)	44 (48.9)	42 (47.3)	97 (45.3)	186 (45.8)
	Mild impairment	14 (30.4)	37 (41.1)	31 (35.2)	88 (41.1)	165 (40.2)
	Moderate impairment	9 (19.6)	8 (8.9)	15 (17.1)	28 (13.1)	51 (12.4)
	Severe impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
	Missing values	1 (2.2)	1 (1.1)	0 (0.0)	1 (0.5)	7 (1.7)

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 and 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).

Renal impairment category is based on estimated creatinine clearance per FDA guidance per Cockcraft and Gault equation.

Normal: ≥90 mL/min.

Mild: 60-89 mL/min.

Moderate: 30-59 mL/min.

Severe: 15-29 mL/min.

Table 29 Key Cancer history data of group B cohorts receiving mosunetuzumab iv monotherapy CCOD 27.08.2021 Safety- evaluable patients

	Patient population:		R/R FL	R/R FL	R/R DLBCL/trFL	R/R NHL	R/R NHL
	Group/cohort		B7 interim* escalation & expansion	B11 RP2D** expansion	B11 RP2D** expansion	B11 RP2D** expansion	Group B
	No. of patients		N=46	N=90	N=88	N=218	N=414
Cancer History and Prognostic Factors at Study Entry	Time from initial diagnosis to first study treatment	median (range), months	62.8 (11–380)	82.2 (11–292)	27.2 (4–295)	53.3 (3–295)	44.9 (3–573)
	Diagnosis, n (%)	FL	46 (100)	90 (100)	0	90 (41.3)	154 (37.2)
		DLBCL/trFL	0	0	88 (100)[b]	88 (40.4)	196 (47.3)
		MCL	0	0	0	25 (11.5)	38 (9.2)
		Richter's	0	0	0	14 (6.4)	19 (4.6)
		Other	0	0	0	1 (0.5)	7 (1.7)
	Ann Arbor Stage, n (%)	I	1 (2.2)	5 (5.6)	4 (4.5)	9/217 (4.1)	14/413 (3.4)
		II	8 (17.4)	16 (17.8)	10 (11.4)	26/217 (12.0)	49/413 (11.9)
		III	13 (28.3)	25 (27.8)	19 (21.6)	50/217 (23.0)	102/413 (24.7)
		IV	24 (52.2)	44 (48.9)	55 (62.5)	132/217 (60.8)	248/413 (60.0)
	Bulky Disease (>6 cm)		20 (43.5)	31 (34.4)	29 (33.0)	75 (34.4)	148 (35.7)
	SPD by INV at initial treatment baseline	median (range)	3921 (320–22167)	3014 (234–15799)	2298.5 (96–30273)	2851.5 (96–33072)	3066.5 (96–70931)
	FLIPI Risk Group, n(%)	low (0,1)	12 (26.1)	26 (28.9)	ND[a]	ND[a]	ND[a]
		intermediate (2)	12 (26.1)	24 (26.7)	ND[a]	ND[a]	ND[a]
		high (3-5)	21 (45.6)	40 (44.4)	ND[a]	ND[a]	ND[a]
		Unknown	1 (2.2)	0	ND[a]	ND[a]	ND[a]

DLBCL/trFL = diffuse large B-cell lymphoma/transformed follicular lymphoma; FL = follicular lymphoma; FLIPI = Follicular lymphoma international prognostic index; INV = investigator; NHL = non-Hodgkin's lymphoma; RP2D = recommended Phase II dose; R/R = relapsed/refractory; SPD = sum of product diameters.

*Interim dose of mosunetuzumab by IV monotherapy = 1/2/13.5 mg.

**RP2D of mosunetuzumab by IV monotherapy = 1/2/60/30 mg.

[a] ND, not determined for the NHL population as FLIPI is specific to those patients with FL only.

[b] Cell of origin distribution for the DLBCL/trFL patient cohort, was as follows: GCB (n=49, 55.7%); non-GCB (n=29, 33.0%); and unknown (n=10, 11.4%).

Table 30 Key prior cancer treatment data of group B cohorts receiving mosunetuzumab iv monotherapy CCOD 27.08.2021 Safety- evaluable patients

	Patient population:		R/R FL	R/R FL	R/R DLBCL/trFL	R/R NHL	R/R NHL
	Group/cohort		B7 interim* escalation & expansion	B11 RP2D** expansion	B11 RP2D** expansion	B11 RP2D** expansion	Group B
	No. of patients		N=46	N=90	N=88	N=218	N=414
Prior Cancer Treatment	No. of prior lines of anti-lymphoma therapies n (%)	Median (range)	3.0 (2–9)	3.0 (2–10)	3.0 (2–13)	3.0 (1–13)	3.0 (1–14)
		1	0	0	0	5 (2.3)	13 (3.1)
		2	17 (37.0)	34 (37.8)	31 (35.2)	74 (33.9)	142 (34.3)
		3	13 (28.3)	28 (31.1)	28 (31.8)	65 (29.8))	111 (26.8)
		>3	16 (34.8)	28 (31.1)	29 (33.0)	74 (33.9)	148 (35.7)
	Prior cancer therapy, n (%)	anti-CD20	46 (100)	90 (100)	88 (100)	218 (100)	414 (100)
		alkylator	46 (100)	90 (100)	86 (97.7)	214 (98.2)	410 (99.0)
		auto-SCT	8 (17.4)	19 (21.1)	15 (17.0)	41 (18.8)	83 (20.0)
		CAR-T	2 (4.3)	3 (3.3)	26 (29.5)	30 (13.8)	49 (11.8)
		PI3K	6 (13.0)	17 (18.9)	3 (3.4)	22 (10.1)	42 (10.1)
	Refractory to:	last prior therapy	36 (78.3)	62 (68.9)	70 (79.5)	165 (75.7)	328 (79.2)
		any prior therapy	41 (89.1)	78 (86.7)	82 (93.2)	195 (89.4)	378 (91.3)
		any prior anti-CD20	40 (87.0)	71 (78.9)	77 (87.5)	175 (80.3)	339 (81.9)
		double refractory to prior anti-CD20 and alkylator	27 (58.7)	48 (53.3)	68 (77.3)	138 (63.3)	279 (67.4)
	<24 months from start of first systemic therapy to PD		21 (45.7)	47 (52.2)	70 (79.5)	144 (66.1)	272 (65.7)

DLBCL/trFL = diffuse large B-cell lymphoma/transformed follicular lymphoma; FL = follicular lymphoma; FLIPI = Follicular lymphoma international prognostic index; INV = investigator; NHL = non-Hodgkin's lymphoma; RP2D = recommended Phase II dose; R/R = relapsed/refractory; SPD = sum of product diameters.

*Interim dose of mosunetuzumab by IV monotherapy = 1/2/13.5 mg.

**RP2D of mosunetuzumab by IV monotherapy = 1/2/60/30 mg.

Populations not studied (based on the exclusion criteria):

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.

- a history of autoimmune disease.

- significant active pulmonary disease.

- a history of severe allergic or anaphylactic reactions to monoclonal antibody therapy.

- acute or chronic HBV or HCV infection.

- severe hepatic impairment (only two with moderate hepatic impairment were included).

- severe renal impairment.

2.6.8.2 Adverse events

Table 31 Safety Summary for Group B and B11 RP2D Cohort (CCOD: 27 August 2021), Safety-Evaluable Patients

	Group B (N=414)	B11 RP2D Cohort (N=218)
Total number of patients with at least one AE	408 (98.6%)	214 (98.2%)
Total number of events	4321	2467
Total number of deaths [a]	174 (42.0%)	82 (37.6%)
Total number of patients withdrawn from initial treatment due to AE or death	19 (4.6%)	9 (4.1%)
Total number of patients with at least one:		
Fatal AE	59 (14.3%)	32 (14.7%)
Fatal AE (not including PD)	6 (1.4%)	4 (1.8%)
SAE	197 (47.6%)	114 (52.3%)
SAE (excluding Grade 5 PD)	166 (40.1%)	100 (45.9%)
Mosunetuzumab-related SAE	110 (26.6%)	75 (34.4%)
Mosunetuzumab-related AE	335 (80.9%)	188 (86.2%)
AE of Grade 3-4 [b]	273 (65.9%)	145 (66.5%)
AE leading to withdrawal from mosunetuzumab treatment	19 (4.6%)	9 (4.1%)
Mosunetuzumab-related AE leading to withdrawal from mosunetuzumab treatment	10 (2.4%)	4 (1.8%)
AE leading to mosunetuzumab dose modification	11 (2.7%)	7 (3.2%)
AE leading to mosunetuzumab dose interruption	135 (32.6%)	72 (33.0%)

AE=adverse event; PD=progressive disease; RP2D=recommended Phase II dose; SAE=serious adverse event.

Investigator text for AEs encoded using MedDRA version 24.0.

Only treatment-emergent AEs are displayed.

Percentages are based on N in the column headings.

[a] All deaths from the start of treatment up to the clinical cutoff date are included.

[b] Includes all patients who experienced Grade 3-4 AEs during initial treatment. It should be noted that some of these patients could have also experienced a Grade 5 event as their worst grade event.

Source: t_ae_summary_INIT_GRPBH_SE_27AUG2021_29781.

The proportion of various adverse events (SAEs, Grade 3-4 AEs, AEs leading to discontinuation/dose-reduction/dose-modification) was comparable between the primary safety cohort (B11 RP2D) and the B11 FL.

Table 32 Summary of Common (≥10%) Adverse Events by Preferred Term in Group B and B11 RP2D Cohort (CCOD: 27 August 2021)

Group/cohort No. of patients	Group B N=414	B11 RP2D Cohort N=218
No. of patients with at least one AE, n (%)		
CRS (by Lee 2014 grade)	148 (35.7)	93 (42.7)
(by ASTCT 2019 grade)	133 (32.1)	86 (39.4)
Neutropenia/neutrophil count decreased	114 (27.5)	60 (27.5)
Fatigue	113 (27.3)	70 (32.1)
Hypophosphatemia	92 (22.2)	49 (22.5)
Pyrexia	83 (20.0)	53 (24.3)
Headache	78 (18.8)	44 (20.2)
Diarrhea	78 (18.8)	38 (17.4)
Constipation	69 (16.7)	36 (16.5)
Nausea	69 (16.7)	38 (17.4)
Anemia/hemoglobin decreased	68 (16.4)	33 (15.1)
Rash	64 (15.5)	42 (19.3)
Hypokalemia	62 (15.0)	34 (15.6)
Cough	61 (14.7)	33 (15.1)
Malignant neoplasm progression [a]	53 (12.8)	28 (12.8)
Edema peripheral	52 (12.6)	30 (13.8)
Hypomagnesemia	51 (12.3)	29 (13.3)
Upper respiratory tract infection	49 (11.8)	21 (9.6)
Back pain	49 (11.8)	17 (7.8)
Pruritus	46 (11.1)	31 (14.2)
Insomnia	44 (10.6)	23 (10.6)
Abdominal pain	42 (10.1)	25 (11.5)
Chills	41 (9.9)	23 (10.6)
ALT increased	36 (8.7)	23 (10.6)
Thrombocytopenia/platelet count decreased	34 (8.2)	25 (11.5)
Dry skin	32 (7.7)	27 (12.4)

AE=adverse event; ALT=alanine aminotransferase, ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; RP2D=recommended Phase II dose.

[a] Death attributed to progression of disease was a reportable AE per study protocol if the event occurred within 90 days of the last dose of study drug and before the initiation of another anti-cancer agent.

All AEs with incidence of ≥10% in Group B (N=414) and the B11 RP2D cohort (N=218) are shown.

Source: t_ae_INC10PER_INIT_GRPBH_SE_27AUG2021_29781; t_ae_INIT_GRPBH_SE_27AUG2021_29781; t_ae_ctc_heme_INIT_GRPBH_SE_27AUG2021_29781; t_aesi_bysmq_INIT_GRPBH_SE_27AUG2021_29781.

Common AEs (by preferred term) in the B11 FL cohort were comparable to the primary safety cohort with CRS as the most frequent.

A tabular overview of the most frequent AEs (all and grade 3-4) by SOC and preferred term has been provided for Group B, cohort B11 RP2D, and cohort B11 FL.

Table 33 Summary of Most Frequent (≥10% Incidence by Preferred Term or SOC) Adverse Events (CCOD: 27 August 2021)

System Organ Class (SOC)/PTs	Treatment Group					
	Group B N=414 n (%)		B11 RP2D N=218 n (%)		B11 FL RP2D N=90 n (%)	
	All grade	Grade 3-4	All grade	Grade 3-4	All grade	Grade 3-4
General disorders and administration site conditions	**235 (56.8)**	**13 (3.1)**	**134 (61.5)**	**7 (3.2)**	**58 (64.4)**	**1 (1.1)**
Fatigue	113 (27.3)	4 (1.0)	70 (32.1)	2 (0.9)	33 (36.7)	0
Pyrexia	83 (20.0)	5 (1.2)	53 (24.3)	4 (1.8)	26 (28.9)	1 (1.1)
Oedema peripheral	52 (12.6)	1 (0.2)	30 (13.8)	0	10 (11.1)	0
Chills	41 (9.9)	2 (0.5)	23 (10.6)	1 (0.5)	12 (13.3)	1 (1.1)
Gastrointestinal disorders	**221 (53.4)**	**20 (4.8)**	**120 (55.0)**	**8 (3.7)**	**53 (58.9)**	**2 (2.2)**
Diarrhea	78 (18.8)	2 (0.5)	38 (17.4)	0	15 (16.7)	0
Constipation	69 (16.7)	2 (0.5)	36 (16.5)	0	16 (17.8)	0
Nausea	69 (16.7)	1 (0.2)	38 (17.4)	1 (0.5)	15 (16.7)	0
Abdominal pain	42 (10.1)	3 (0.7)	25 (11.5)	2 (0.9)	9 (10.0)	1 (1.1)
Metabolism and nutrition disorders	**222 (53.6)**	**93 (22.5)**	**114 (52.3)**	**53 (24.3)**	**49 (54.4)**	**25 (27.8)**
Hypophosphatemia	92 (22.2)	60 (14.5)	49 (22.5)	32 (14.7)	24 (26.7)	15 (16.7)
Hypokalemia	62 (15.0)	6 (1.4)	34 (15.6)	4 (1.8)	17 (18.9)	2 (2.2)
Hypomagnesemia	51 (12.3)	1 (0.2)	29 (13.3)	0	11 (12.2)	0
Infections and infestations	**195 (47.1)**	**61 (14.7)**	**102 (46.8)**	**31 (14.2)**	**46 (51.1)**	**15 (16.7)**
Upper respiratory tract infection	49 (11.8)	5 (1.2)	21 (9.6)	3 (1.4)	8 (8.9)	2 (2.2)
Urinary tract infection	30 (7.2)	8 (1.9)	15 (6.9)	3 (1.4)	9 (10.0)	1(1.1)
Skin and subcutaneous tissue disorders	**186 (44.9)**	**7 (1.7)**	**123 (56.4)**	**5 (2.3)**	**58 (64.4)**	**4 (4.4)**
Rash	64 (15.5)	2 (0.5)	42 (19.3)	2 (0.9)	14 (15.6)	1 (1.1)
Pruritus	46 (11.1)	0	31 (14.2)	0	19 (21.1)	0
Dry skin	32 (7.7)	0	27 (12.4)	0	14 (15.6)	0
Skin exfoliation	16 (3.9)	0	13 (6.0)	0	9 (10.0)	0
Immune system disorders[c]	**156 (37.7)**	**9 (2.2)**	**99 (45.4)**	**5 (2.3)**	**41 (45.6)**	**3 (3.3)**
Cytokine release syndrome (by Lee 2014)	148 (35.7)	7 (1.7)	93 (42.7)	4 (1.8)	41 (45.6)	3 (3.3)
Cytokine release syndrome (by ASTCT 2019)	133 (32.1)	7 (1.7)	86 (39.4)	6 (2.8)	40 (44.4)	2 (2.2)
Nervous system disorders	**158 (38.2)**	**11 (2.7)**	**86 (39.4)**	**6 (2.8)**	**49 (54.4)**	**2 (2.2)**
Headache	78 (18.8)	1 (0.2)	44 (20.2)	1 (0.5)	28 (31.1)	1 (1.1)
Dizziness	41 (9.9)	0	21 (9.6)	0	9 (10.0)	0
Respiratory, thoracic and mediastinal disorders	**160 (38.6)**	**14 (3.4)**	**84 (38.5)**	**10 (4.6)**	**40 (44.4)**	**4 (4.4)**

System Organ Class (SOC)/PTs	Treatment Group					
	Group B N=414 n (%)		B11 RP2D N=218 n (%)		B11 FL RP2D N=90 n (%)	
	All grade	Grade 3-4	All grade	Grade 3-4	All grade	Grade 3-4
Cough	61 (14.7)	0	33 (15.1)	0	16 (17.8)	0
Blood and lymphatic system disorders	**145 (35.0)**	**114 (27.5)**	**70 (32.1)**	**55 (25.2)**	**27 (30.0)**	**25 (27.8)**
Neutropenia	84 (20.3)	75 (18.1)	40 (18.3)	35 (16.1)	18 (20.0)	17 (18.9)
Anemia	68 (16.4)	35 (8.5)	33 (15.1)	18 (8.3)	12 (13.3)	7 (7.8)
Musculoskeletal and connective tissue disorders	**139 (33.6)**	**11 (2.7)**	**70 (32.1)**	**5 (2.3)**	**37 (41.1)**	**2 (2.2)**
Back pain	49 (11.8)	4 (1.0)	17 (7.8)	1 (0.5)	9 (10.0)	1 (1.1)
Arthralgia	28 (6.8)	1 (0.2)	15 (6.9)	0	10 (11.1)	0
Investigations	**129 (31.2)**	**63 (15.2)**	**78 (35.8)**	**37 (17.0)**	**33 (36.7)**	**15 (16.7)**
Alanine aminotransferase increased	36 (8.7)	13 (3.1)	23 (10.6)	10 (4.6)	11 (12.2)	5 (5.6)
Neutrophil count decreased	33 (8.0)	29 (7.0)	22 (10.1)	19 (8.7)	8 (8.9)	7 (7.8)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**89 (21.5)**	**14 (3.4)**	**50 (22.9)**	**8 (3.7)**	**9 (10.0)**	**3 (3.3)**
Malignant neoplasm progression[a]	53 (12.8)	0	28 (12.8)	0	1 (1.1)	0
Psychiatric disorders	**82 (19.8)**	**4 (1.0)**	**42 (19.3)**	**1 (0.5)**	**21 (23.3)**	**0**
Insomnia	44 (10.6)	0	23 (10.6)	0	11 (12.2)	0
Vascular disorders[b]	**65 (15.7)**	**5 (1.2)**	**35 (16.1)**	**2 (0.9)**	**17 (18.9)**	**0**
Cardiac disorders[b]	**43 (10.4)**	**4 (1.0)**	**25 (11.5)**	**1 (0.5)**	**10 (11.1)**	**0**
Renal disorders[b]	**41 (9.9)**	**10 (2.4)**	**21 (9.6)**	**6 (2.8)**	**9 (10.0)**	**4 (4.4)**
Injury, poisoning and procedural complications[b]	**39 (9.4)**	**3 (0.7)**	**22 (10.1)**	**3 (1.4)**	**13 (14.4)**	**2 (2.2)**
Eye disorders[b]	**34 (8.2)**	**1 (0.2)**	**24 (11.0)**	**1 (0.5)**	**12 (13.3)**	**1 (1.1)**

Table only shows AEs with incidence rate of ≥10% by preferred term or System Organ Class in either Group B (N=414), the B11 RP2D (N=218) or B11 FL RP2D (N=90) cohorts.

Frequencies for System Organ Class categories are for all PTs under the SOC.

[a]All malignant neoplasm events were Grade 5.

[b]No preferred term within SOC was reported at a frequency of ≥10%.

[c]Percentages listed for this SOC include only CRS by Lee 2014

Source: adapted from t_ae_ctc_INIT_GRPBH_SE_27AUG2021_29781; t_ae_ctc_CRS_ASTCT_INIT_GRPBH_SE_27AUG2021_29781.

Source: Response to updated Q103

Adverse events considered related to mosunetuzumab forms the basis for the ADR table in the SmPC, section 4.8 (not in frequency but for the list of preferred terms to be included). A table listing these treatment-related AEs (by SOC and PT) for cohorts B11 RP2D and B11 FL has been provided:

Table 34 Summary of Most Frequent (≥10% Incidence by Preferred Term or SOC) Treatment-related Adverse Events

System Organ Class (SOC)/PTs	Treatment Group								
	Group B N=410 n (%)			B11 RP2D N=214 n (%)			B11 FL RP2D N=90 n (%)		
	All grade	Gr 3-4	Gr 5	All grade	Gr 3-4	Gr 5	All grade	Gr 3-4	Gr 5
Immune system disorders	**150 (36.6)**	**8 (2.0)**	**0**	**93 (43.5)**	**4 (1.9)**	**0**	**41 (45.6)**	**3 (3.3)**	**0**
Cytokine release syndrome (by Lee 2014)	147 (35.9)	7 (1.7)	0	92 (43.0)	4 (1.9)	0	41 (45.6)	3 (3.3)	0
Cytokine release syndrome (by ASTCT 2019)	131 (32.0)	7 (1.7)	0	84 (39.3)	6 (2.8)	0	40 (44.4)	2 (2.2)	0
Skin and subcutaneous tissue disorders	**117 (28.5)**	**5 (1.2)**	**0**	**83 (38.8)**	**5 (2.3)**	**0**	**44 (48.9)**	**4 (4.4)**	**0**
Rash	46 (11.2)	2 (0.5)	0	31 (14.5)	2 (0.9)	0	12 (13.3)	1 (1.1)	0
Pruritus	27 (6.6)	0	0	22 (10.3)	0	0	15 (16.7)	0	0
General disorders and administration site conditions	**112 (27.3)**	**5(1.2)**	**0**	**69 (32.2)**	**2 (0.9)**	**0**	**36 (40.0)**	**0**	**0**
Fatigue	52 (12.7)	3 (0.7)	0	33 (15.4)	1 (0.5)	0	16 (17.8)	0	0
Pyrexia	41 (10.0)	1 (0.2)	0	30 (14.0)	1 (0.5)	0	17 (18.9)	0	0
Metabolism and nutrition disorders	**98 (23.9)**	**51 (12.4)**	**0**	**48 (22.4)**	**30 (14.0)**	**0**	**19 (21.1)**	**11 (12.2)**	**0**
Hypophosphatemia	55 (13.4)	42 (10.2)	0	26 (12.1)	24 (11.2)	0	11 (12.2)	10 (11.1)	0
Blood and lymphatic system disorders	**90 (22.0)**	**76 (18.5)**	**0**	**44 (20.6)**	**37 (17.3)**	**0**	**19 (21.1)**	**18 (20.0)**	**0**
Neutropenia	64 (15.6)	58 (14.1)	0	31 (14.5)	26 (12.1)	0	14 (15.6)	13 (14.4)	0
Gastrointestinal disorders[a]	**79 (19.3)**	**4 (1.0)**	**0**	**47 (22.0)**	**1 (0.5)**	**0**	**20 (22.2)**	**0**	**0**
Investigations[a]	**72 (17.6)**	**41 (10.0)**	**0**	**45 (21.0)**	**25 (11.7)**	**0**	**18 (20.0)**	**10 (11.1)**	**0**
Nervous system disorders	**71 (17.3)**	**4 (1.0)**	**0**	**41 (19.2)**	**3 (1.4)**	**0**	**25 (27.8)**	**1 (1.1)**	**0**
Headache	31 (7.6)	**0**	**0**	18 (8.4)	**0**	**0**	10 (11.1)	**0**	**0**
Infections and infestations[a]	**46 (11.2)**	**16 (3.9)**	**2 (0.5)**	**28 (13.1)**	**10 (4.7)**	**1 (0.5)**	**10 (11.1)**	**6 (6.7)**	**0**
Musculoskeletal and connective tissue disorders[a]	**44 (10.7)**	**2 (0.5)**	**0**	**25 (11.7)**	**1 (0.5)**	**0**	**15 (16.7)**	**0**	**0**
Respiratory, thoracic and mediastinal disorders[a]	**36 (8.8)**	**6 (1.5)**	**0**	**22 (10.3)**	**6 (2.8)**	**0**	**11 (12.2)**	**1 (1.1)**	**0**

Table only shows treatment–related AEs with incidence rate of ≥10% or most common by preferred term under System Organ Class in either Group B (N=410), the B11 RP2D cohort (N=214) or B11 FL RP2D (N=90) cohorts.

Frequencies for System Organ Class categories are for all PTs under the SOC.

[a] No preferred term within SOC was reported at a frequency of ≥10%.

Source: adapted from: t_ae_ctc_RELMOS_INIT_GRPBH_SE_15MAR2021_29781; t_aesi_bysmq_INIT_SCS_SE_15MAR2021_29781.

2.6.8.3 Serious adverse event/deaths/other significant events

Serious adverse events

Table 40/CSR includes deaths as part of the SAEs (32 patients including 28 patients with PD). Grade 5 events occurred for all patients with progressive disease (53 in Group B and 28 in cohort B11 RP2D), and for 2 patients with pneumonia and 2 patients with sepsis in Group B of which one of each occurred in cohort B11 RP2D.

In the B11 RP2D cohort 75 patients (34.4%) had at least one SAE that was assessed as related to mosunetuzumab by the investigator, and seven patients (3.2%) had mosunetuzumab treatment withdrawn due to an SAE.

CRS stands out as the SAE (and AE) with the highest incidence (21.6% by Lee 2014 grading).

Table 35 Summary of Serious Adverse Events Occurring at Incidence of ≥1% in Group B and B11 RP2D Cohort (CCOD: 15 March 2021), Safety-Evaluable Patients

Group/cohort No. of patients	Group B N=410		B11 RP2D Cohort N=214	
No. of patients with at least one AE, n (%)	**All grade**	**Grade 3-5**	**All grade**	**Grade 3-5**
CRS (by Lee 2014 grade)	62 (15.1)	6 (1.5)	47 (22.0)	4 (1.9)
(by ASTCT 2019 grade)	58 (14.1)	7 (1.7)	44 (20.6)	6 (2.8)
Malignant neoplasm progression[a]	51 (12.4)	51 (12.4)	27 (12.6)	27 (12.6)
Pyrexia	12 (2.9)	2 (0.5)	9 (4.2)	2 (0.9)
Pneumonia	11 (2.7)	9 (2.2)	7 (3.3)	5 (2.3)
Febrile neutropenia	8 (2.0)	8 (2.0)	3 (1.4)	3 (1.4)
Acute kidney injury	7 (1.7)	3 (0.7)	4 (1.9)	2 (0.9)
Sepsis	6 (1.5)	6 (1.5)	4 (1.9)	4 (1.9)
Urinary tract infection	6 (1.5)	4 (1.0)	4 (1.9)	2 (0.9)
Neutropenia/neutrophil count decreased	6 (1.5)	6 (1.5)	2 (0.9)	2 (0.9)
Pneumocystis jirovecii pneumonia	5 (1.2)	4 (1.0)	3 (1.4)	2 (0.9)
Bacteremia	4 (1.0)	4 (1.0)	1 (0.5)	1 (0.5)
Pleural effusion	4 (1.0)	4 (1.0)	4 (1.9)	4 (1.9)
Dyspnea	4 (1.0)	3 (0.7)	2 (0.9)	2 (0.9)
Confusional state	4 (1.0)	1 (0.2)	3 (1.4)	1 (0.5)
ALT increased	3 (0.7)	3 (0.7)	3 (1.4)	3 (1.4)
AST increased	3 (0.7)	3 (0.7)	3 (1.4)	3 (1.4)

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; RP2D=recommended Phase II dose.

All serious AEs with incidence of ≥1% in Group B (N=410) and B11 RP2D cohort (N=214) are shown.

[a] Death attributed to progression of disease was a reportable AE per study protocol if the event occurred within 90 days of the last dose of study drug and before the initiation of another anti-cancer agent.

Source: t_ae_ctc_SER_INIT_GRPBH_SE_15MAR2021_29781,
t_ae_ctc_SER_CRS_ASTCT_INIT_GRPBH_SE_15MAR2021_29781;
t_ae_ctc_heme_SER_INIT_GRPBH_SE_15MAR2021_29781.

The incidences of SAEs (related and unrelated and leading to withdrawal) in the B11 FL cohort were comparable to the primary safety cohort.

Deaths

Table 36 Deaths and Causes of Death in Group B and B11 RP2D Cohort (CCOD: 27 August 2021), Safety-Evaluable Patients

Group/cohort No. of patients	Group B N=414	B11 RP2D Cohort N=218
Total no. of deaths [a], n (%)	174 (42.0) [b, c]	82 (37.6)
Cause of death, n (%)		
Death due to progression of disease [a]	93 (22.5) [b]	40 (18.3)
Fatal AE malignant neoplasm progression [d]	53 (12.8) [c]	28 (12.8)
Total deaths due to PD	148 (35.7)	68 (31.2)
Fatal AE (not PD)	6 (1.4)	4 (1.8)
Other [a]	20 (4.8)	10 (4.6)

AE=adverse event; PD=progressive disease; RP2D=recommended Phase II dose.

[a] Captured as primary cause of death on Study Completion/Early Discontinuation page of electronic Case Report Form if death was the reason for discontinuing the study.

[b] Includes two deaths following the re-treatment with mosunetuzumab intravenous monotherapy.

[c] Includes two deaths during the re-treatment period with mosunetuzumab in combination with atezolizumab.

[d] Per protocol, death attributed to progression of disease was a reportable AE if the event occurred within 90 days of the last dose of study drug or before the initiation of another anti-cancer treatment, whichever occurred first.

All deaths from the start of treatment up to the clinical cutoff date are included in this table.

Source: t_dd_GRPBH_SE_27AUG2021_29781; t_ae_FATAL_INIT_GRPBH_SE_27AUG2021_29781; l_dd_GRPAB_SE_27AUG2021_29781.

Table 37 Deaths Due to Adverse Events (Other Than Disease Progression) in Group B (CCOD: 27 August 2021), Safety-Evaluable Patients

Adverse Event	Related to Study Treatment	Study Day of Onset	Day of Last Mosunetuzumab Administration	Day of Death
B7 (1.0/2.0/13.5 mg)				
Pneumonia	yes [a]	73	65	81
B10 (1.0/2.0/40.5 mg)				
Sepsis	no [b]	92	85	106
B11 RP2D Cohort (1.0/2.0/60.0 mg with 30.0 mg on Cycle ≥3)				
Sepsis	yes	19	14	20
Cholangitis	no	399	375	428
Pneumonia	no	237	165	251
Death [c]	no	60	22	60

RP2D=recommended Phase II dose.

[a] Immunosuppressed status of the patient was considered as a contributing factor to the death.

[b] Considered by investigator to be related to concurrent illness.

[c] Patient was enrolled in the B11 FL RP2D cohort, received 2 cycles of mosunetuzumab treatment, and was found unresponsive in bed on study Day 60. Cause of death was unknown.

Source: Update Interim CSR GO29781, Report 1111637, Table 39.

Selected adverse events / Adverse events of special interest

Adverse events of special interest (AESIs) specific for mosunetuzumab (including but not limited to CRS) were defined based on evolving clinical experience with mosunetuzumab in clinical studies.

Cytokine release syndrome (CRS)

Per the protocol, investigators reported and graded CRS events according to the Lee 2014 grading criteria (Lee et al. 2014). CRS events according to the ASTCT 2019 grading criteria (Lee et al. 2019) were derived programmatically from the reported data based on the presence of fever and presence and management of hypotension or hypoxia as reported in the CRS signs/symptoms eCRF.

In the B11 RP2D cohort, the AE with highest frequency was CRS events (39.3% by ASTCT grading) which were predominantly Grade 1-2 (88/92), limited primarily to Cycle 1. CRS as SAEs were reported in 44/92 (20.6%) patients (by ASTCT grading). All events resolved. According to the Applicant ASTCT 2019 grades could not be derived from 19 CRS events (10 Grade 1 events, 8 Grade 2 events, and 1 Grade 3 event) by Lee 2014 due to the lack of reported fever. Details of the Grade 2 and Grade 3 CRS events by Lee 2014 that were not graded by ASTCT 2019 are presented below.

No patient among the 410 patients in Group B died due to a CRS event (within 30 days of onset). With the updated safety data 2 additional Grade 1 CRS events in the cohort B11 RP2D occurred (CCOD: 27 Aug 2021).

Table 38 Overview of Cytokine Release Syndrome in Group A and Group B (CCOD: 15 March 2021), Safety-Evaluable Patients

Group/Cohort No. of Patients	Group A N=33		Group B N=410		B11 RP2D Cohort N=214		B11 FL RP2D Cohort N=90	
CRS grading criteria	Lee 2014 CRS Grade	ASTCT 2019 CRS Grade	Lee 2014 CRS Grade	ASTCT 2019 CRS Grade	Lee 2014 CRS Grade	ASTCT 2019 CRS Grade	Lee 2014 CRS Grade	ASTCT 2019 CRS Grade
Total number of events	8	6	224	188	141	122	76	71
Total number of patients with at least one, n (%)								
Event	7 (21.2)	6 (18.2)	147 (35.9)	131 (32.0)	92 (43.0)	84 (39.3)	41 (45.6)	40 (44.4)
Event of Grade 1 max. severity	3 (9.1)	5 (15.2)	97 (23.7)	87 (21.2)	52 (24.3)	47 (22.0)	23 (25.6)	23 (25.6)
Event of Grade 2 max. severity	4 (12.1)	1 (3.0)	43 (10.5)	37 (9.0)	36 (16.8)	31 (14.5)	15 (16.7)	15 (16.7)
Event of Grade 3 max. severity	0	0	5 (1.2)	6 (1.5)	2 (0.9)	5 (2.3)	1 (1.1)	1 (1.1)
Event of Grade 4 max. severity	0	0	2 (0.5)	1 (0.2)	2 (0.9)	1 (0.5)	2 (2.2)	1 (1.1)
Serious event	1 (3.0)	1 (3.0)	62 (15.1)	58 (14.1)	47 (22.0)	44 (20.6)	21 (23.3)	21 (23.3)
Event related to mosunetuzumab	7 (21.2)	6 (18.2)	147 (35.9)	131 (32.0)	92 (43.0)	84 (39.3)	41 (45.6)	40 (44.4)
Event leading to withdrawal of mosunetuzumab	0	0	2 (0.5)	2 (0.5)	2 (0.9)	2 (0.9)	2 (2.2)	2 (2.2)
Event leading to dose modification/ interruption of mosunetuzumab	3 (9.1)	3 (9.1)	27 (6.6)	24 (5.9)	20 (9.3)	18 (8.4)	8 (8.9)	7 (7.8)
Unresolved or ongoing event	0	0	1 (0.2) [a]	1 (0.2) [a]	1 (0.5) [a]	1 (0.5) [a]	1 (1.1) [a]	1 (1.1) [a]
Total patients with all events resolved, n (%)	7 (21.2)	6 (18.2)	146 (35.6) [a]	130 (31.7) [a]	91 (42.5) [a]	83 (38.8) [a]	40 (44.4) [a]	39 (43.3) [a]
Total patients with treatment received for the event [b], n (%)	5 (15.2)	4 (12.1)	129 (31.5)	118 (28.8)	81 (37.9)	76 (35.5)	35 (38.9)	34 (37.8)
Duration of event (days), median (range)	2 (1–8)	3 (2–8)	3.0 (1.0–29.0)	3.0 (1.0–29.0)	3.0 (1.0–29.0)	3.0 (1.0–29.0)	3.0 (1.0–29.0)	3.0 (1.0–29.0)

AE=adverse event; ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; RP2D=recommended Phase II dose.

[a] All CRS events had resolved as of the CCOD. One Grade 1 CRS event by Lee 2014 and ASTCT 2019 in one patient in the B11 FL RP2D cohort had resolved but was listed as having an unknown outcome due to a discrepancy in the data entry. [b] Counted based on the investigator's answer to the AE Case Report Form question "Was medication given for AE?"

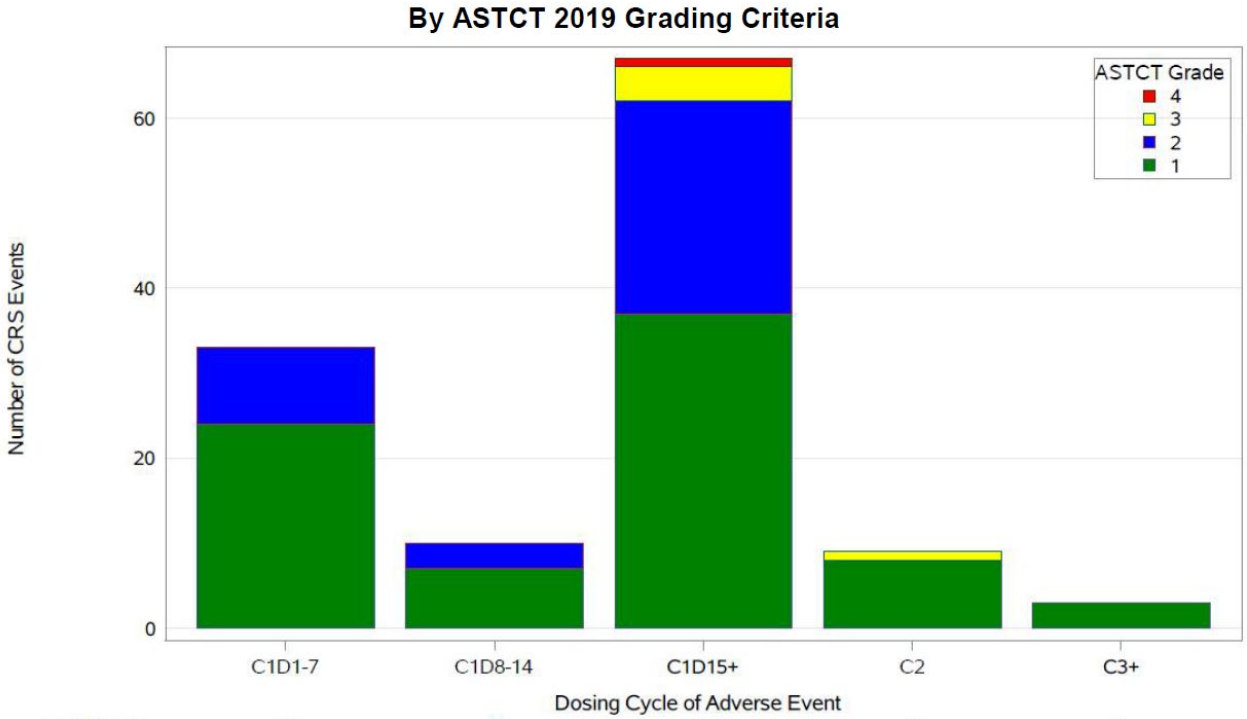
Source: Interim CSR GO29781, Report 1106874, Table 48; Interim CSR GO29781, Report 1106874, Table 52; t_aesi_bysmq_INIT_SCS_SE_15MAR2021_29781; t_ae_dur_INIT_GRPBH_SE_15MAR2021_29781.

Table 39 Patients with CRS Events with Differing Maximum Severity by Lee 2014 (Grade ≥2) and ASTCT 2019 in B11 RP2D Cohort (CCOD: 15 March 2021), Safety-Evaluable Patients

Lee 2014 Grade (Max. Grade)	Key Symptoms	ASTCT 2019 Grade (Max. Grade)	Dose Cycle
CRS Events with Differing Grades by Lee 2014 and ASTCT 2019			
Grade 2 [a]	**Fever**, tachypnea requiring oxygen	Grade 1	Cycle 1 Day 15–21
Grade 2	**Fever**, **hypoxia managed with (high flow) oxygen**	Grade 3	Cycle 1 Day 15–21
Grade 2	**Fever**, **hypotension managed with (single) vasopressor**, hypoxia managed with (low flow) oxygen	Grade 3	Cycle 1 Day 15–21
Grade 2	**Fever**, **hypotension managed with (single) vasopressor**, hypoxia managed with (low flow) oxygen	Grade 3	Cycle 1 Day 15–21
Grade 3	**Fever**, Grade 4 transaminitis	Grade 1	Cycle 2
Grade 4 [a]	**Fever**, **hypotension managed with (single) vasopressor**, Grade 4 acute kidney injury	Grade 3	Cycle 2
CRS Events by Lee 2014 without Derived ASTCT 2019 Grades Due to Lack of Reported Fever			
Grade 2	**No fever,** hypotension managed with fluids	NA	Cycle 2
Grade 2 [b]	**No fever**, hypoxia managed with (low flow) oxygen, hypotension not requiring management	NA	Cycle 3 [b]
Grade 2	**No fever**, hypoxia managed with (low flow) oxygen	NA	Cycle 1 Day 1–7
Grade 2	**No fever**, hypotension managed with fluids	NA	Cycle 1 Day 1–7
Grade 2	**No fever**, hypotension managed with fluids	NA	Cycle 1 Day 1–7
Grade 2 [c]	**No fever**, hypotension managed with fluids	NA	Cycle 1 Day 8–14
Grade 2 [c]	**No fever**, hypotension managed with fluids	NA	Cycle 1 Day 15–21
Grade 2 [c]	**No fever**, hypertension	NA	Cycle 2
Grade 3 [b]	**No fever**, hypoxia managed with (low flow) oxygen	NA	Cycle 2 [b]

ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; NA=not applicable; RP2D=recommended Phase II dose.
[a] These Grade 2 and Grade 4 events by Lee 2014 were reported in the same patient.
[b] These Grade 2 and Grade 3 events by Lee 2014 were reported in the same patient. Due to the CRS Grade 4 event following Cycle 1 Day 15 dose administration, the patient repeated the step-up dosing of 1.0/2.0/9.0 mg. The planned dose for Cycle 2 Day 15 and Cycle 3 was 9 mg.
[c] These three Grade 2 events by Lee 2014 were reported in the same patient.
Source: Interim CSR GO29781, Report 1106874, Table 53.

Figure 45: Number of CRS Events by Dose Cycle in B11 RP2D Cohort (CCOD: 15 March 2021), Safety-Evaluable Patients



	C1D1-7	C1D8-14	C1D15+	C2	C3+
Total Events	33	10	67	9	3
ASTCT Grade 1	24	7	37	8	3
ASTCT Grade 2	9	3	25	0	0
ASTCT Grade 3	0	0	4	1	0
ASTCT Grade 4	0	0	1	0	0

Cycles are based on the individual patient study drug dosing dates compared to event start date, where patient received a valid dose
Multiple occurrences of the same preferred term in one individual are each reported separately, even if the same cycle or grade.
Only treatment emergent AEs are displayed. Any with missing grades are excluded.
Note: Data Extraction Date - 15MAR2021
Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary_GrpAB_May2021/prod/program/g_ae_bar_bydosecyc.sas/g_ae_bar_bydosecyc.sas
Output: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary_GrpAB_May2021/prod/output/g_ae_bar_bydosecyc_CRS_ASTCT_INIT_B11EXP_SE_15MAR2021_29781.pdf
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Table 40 Time to Onset and Duration of CRS Events by Dose Cycle in Group B and B11 RP2D Cohort (CCOD: 15 March 2021), Safety-Evaluable Patients)

Group B No. of patients	Cycle 1 Days 1–7 N=410	Cycle 1 Days 8–14 N=394	Cycle 1 Days 15+ N=382	Cycle 2 N=369
Lee 2014 Grade				
Patients with any grade CRS	70/410	24/394	100/382	14/369
Time to onset				
Total number of CRS events [a]	58	15	72	14
Median, hours (range)	3.9 (0.5–127.9)	14.4 (0.8–80.6)	28.8 (0.1–390.9)	36.2 (3.0–82.2)
Duration				
Total number of CRS events [b]	71	24	102	14
Median, days (range)	1.0 (1.0–19.0)	2.5 (1.0–20.0)	3.0 (1.0–20.0)	4.0 (1.0–29.0)
ASTCT 2019 Grade				
Patients with any grade CRS	55/410	20/394	92/382	11/369
Time to onset				
Total number of CRS events [a]	45	12	68	11
Median, hours (range)	4.8 (0.5–127.9)	31.1 (4.8–80.6)	28.8 (0.1–390.9)	37.6 (12.0–82.2)
Duration				
Total number of CRS events [b]	55	20	94	11
Median, days (range)	2.0 (1.0–16.0)	3.0 (1.0–20.0)	3.0 (1.0–20.0)	5.0 (1.0–29.0)
B11 RP2D cohort **No. of patients**	**Cycle 1** **Days 1–7** **N=214**	**Cycle 1** **Days 8–14** **N=202**	**Cycle 1** **Days 15+** **N=197**	**Cycle 2** **N=194**
Lee 2014 Grade				
Patients with any grade CRS	40/214	12/202	70/197	12/194
Time to onset				
Total number of CRS events [a]	34	8	50	12
Median, hours (range)	5.0 (0.7–72.9)	19.6 (4.8–80.6)	26.0 (0.1–390.9)	41.7 (3.0–82.2)
Duration				
Total number of CRS events [b]	41	12	72	12
Median, days (range)	1.0 (1.0–8.0)	2.5 (1.0–9.0)	3.0 (1.0–20.0)	4.0 (1.0–29.0)
ASTCT 2019 Grade				
Patients with any grade CRS	33/214	10/202	65/197	9/194
Time to onset				
Total number of CRS events [a]	28	7	48	9
Median, hours (range)	5.0 (1.1–72.9)	28.1 (4.8–80.6)	26.0 (0.1–390.9)	45.8 (12.0–82.2)
Duration				
Total number of CRS events [b]	33	10	67	9
Median, days (range)	1.0 (1.0–5.0)	3.0 (1.0–9.0)	3.0 (1.0–20.0)	5.0 (1.0–29.0)

AE=adverse event; ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; RP2D=recommended Phase II dose.
[a] Only CRS events with complete date and time were included. Any events without a valid time were not included. The time to onset of AEs was calculated from the start of infusion of the last mosunetuzumab dose per patient and included any events during safety follow-up. For any patient who had more than one dose in Cycle 2, the time to onset of AE was taken from the time of the dose immediately preceding it.
[b] Only CRS events with complete date were included.

Concurrent NAEs:

Among the 86 patients who experienced CRS in the B11 RP2D cohort (by ASTCT 2019), 14 patients had NAEs occurring concurrently with CRS events.

Concurrent liver enzyme elevation events:

Concurrent (with CRS) liver enzyme elevation events were seen in 4/92 patients by Lee 2014 and 3/84 patients by ASTCT 2019 in the B11 RP2D cohort and were Grade 2-4 events. All CRS events with concurrent liver enzyme elevation events resolved.

Neurologic Adverse Events (NAEs)

NAEs were broadly defined as all AEs reported as primary or secondary PTs in either the SOC of Nervous System Disorders or SOC of Psychiatric Disorders.

DI-CCNAEs (Driving-Impacting Cognition or Consciousness Neurologic Adverse Events) include a subset of these neurologic AEs with the following PTs that the Sponsor adjudicated as potentially impacting cognition, consciousness, and ability to drive: Amnesia, aphasia, cerebrovascular accident, cognitive disorder, confusional state, delirium, depressed level of consciousness, disturbance in attention, encephalopathy, hallucination, hallucination visual, hepatic encephalopathy, immune effector cell-associated neurotoxicity syndrome, lethargy, memory impairment, neurotoxicity, psychotic disorder, seizure, somnolence, subdural haematoma, syncope, and vertigo.

In cohort B11 RP2D, serious NAEs were reported in 14 patients (6.4%), and those reported in more than one patient were confusional state (3 patients; one Grade 3), subdural hematoma (2 patients; all Grade 3), and neurotoxicity (2 patients; all Grade 2. The median time to onset of first NAEs was 15.0 days, with median duration of 5.0 days. The majority of the NAEs (188 of 244 events) had resolved at the cutoff date. Most of the unresolved NAEs were Grade 1-2 and three unresolved Grade 3 events could not safely be related to mosunetuzumab as there were several confounding factors.

Twenty-six patients (11.9%) in cohort B11 RP2D experienced DI-CCNAEs of which 10 patients (4.6%) experienced serious DI-CCNAEs. The median duration was 3 days, but the range was 1-259 days.

Table 41 Overview of NAEs and DI-CCNAEs in Group B and B11 CCOD 27.08.2021 Safety - Evaluable patients

Group/cohort No. of patients	Group B N=414		B11 RP2D Cohort N=218	
	NAEs	DI-CCNAEs	NAEs	DI-CCNAEs
Total number of events	429	61	244	29
Total number of patients with at least one, n (%)				
Event	218 (52.7)	49 (11.8)	122 (56.0)	26 (11.9)
Event of Grade 1 max. severity	144 (34.8)	28 (6.8)	79 (36.2)	15 (6.9)
Event of Grade 2 max. severity	56 (13.5)	10 (2.4)	32 (14.7)	5 (2.3)
Event of Grade 3 max. severity	18 (4.3)	11 (2.7)	11 (5.0)	6 (2.8)
Serious event	21 (5.1)	15 (3.6)	14 (6.4)	10 (4.6)
Event related to mosunetuzumab	91 (22.0)	24 (5.8)	55 (25.2)	18 (8.3)
Event leading to withdrawal of mosunetuzumab	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)
Event leading to dose modification/ interruption of mosunetuzumab	23 (5.6)	8 (1.9)	10 (4.6)	2 (0.9)
Unresolved or ongoing event	77 (18.6)	12 (2.9)	45 (20.6)	6 (2.8)
Total patients with all events resolved, n (%)	141 (34.1)	37 (8.9)	77 (35.3)	20 (9.2)
Total patients with treatment received for the event [a], n (%)	93 (22.5)	10 (2.4)	50 (22.9)	6 (2.8)
Time to onset of first event (days), median (range)	15.0 (1.0–518.0)	17.0 (1.0–266.0)	15.0 (1.0–518.0)	18.5 (1.0–207.0)
Duration of event (days), median (range)	5.0 (1.0–500.0)	3.0 (1.0–375.0)	5.0 (1.0–344.0)	3.0 (1.0–259.0)

AE=adverse event; DI-CCNAE=driving-impacting cognition or consciousness neurologic adverse event; NAE=neurologic adverse event; RP2D=recommended Phase II dose.

[a] Counted based on the investigator's answer to the AE Case Report Form question "Was medication given for AE?"

Table 42 Summary of common NAEs (≥ 2%) by PT in group B and B11 RP2D cohort CCOD 27.08.2021

	Group B N=414	B11 RP2D Cohort N=218
No. of patients with at least one NAE, n (%)		
Headache	78 (18.8)	44 (20.2)
Insomnia	44 (10.6)	23 (10.6)
Dizziness	41 (9.9)	21 (9.6)
Confusional state	18 (4.3)	8 (3.7)
Herpes zoster	14 (3.4)	7 (3.2)
Anxiety	11 (2.7)	7 (3.2)
Paresthesia	10 (2.4)	8 (3.7)
Peripheral sensory neuropathy	10 (2.4)	7 (3.2)
Neuropathy peripheral	9 (2.2)	7 (3.2)
Tremor	9 (2.2)	5 (2.3)
Vision blurred	8 (1.9)	7 (3.2)

AE=adverse event; NAE=neurologic adverse event; RP2D=recommended Phase II dose.
All AEs with incidence of ≥2% in Group B (N=414) and B11 RP2D cohort (N=218) are shown.

Haematologic Adverse Events

Neutropenia/neutrophil count decreased

Grade 3 or 4 neutropenia/neutrophil count decreased were reported in 53 patients in cohort B11 RP2D (24.3%) with a comparable incidence for the B11 RP2D FL cohort (26.6%). A total of six serious infection events (including one death) in five patients (2.3%) occurred concurrently with neutropenia/neutrophil count decreased events (including febrile neutropenia events) in the B11 RP2D cohort.

Table 43 Overview of Neutropenia/Neutrophil Count Decreased Events in Group B and B11 RP2D cohort (CCOD: 27 August 2021), Safety-Evaluable Patients

Group/cohort No. of patients	Group B N=414	B11 RP2D Cohort N=218
Total number of events	216	123
Total number of patients with at least one, n (%)		
Event	114 (27.5)	60 (27.5)
Event of Grade 1 max. severity	7 (1.7)	4 (1.8)
Event of Grade 2 max. severity	5 (1.2)	3 (1.4)
Event of Grade 3 max. severity	44 (10.6)	24 (11.0)
Event of Grade 4 max. severity	58 (14.0)	29 (13.3)
Serious event	6 (1.4)	2 (0.9)
Event related to mosunetuzumab	87 (21.0)	47 (21.6)
Event leading to withdrawal of mosunetuzumab	1 (0.2)	0
Event leading to dose modification/ interruption of mosunetuzumab	50 (12.1)	25 (11.5)
Unresolved or ongoing event	10 (2.4)	8 (3.7)
Total patients with all events resolved, n (%)	104 (25.1)	52 (23.9)
Total patients with treatment received for the event [a], n (%)	83 (20.0)	44 (20.2)
Time to onset of first event (days), median (range)	42.5 (1.0–303.0)	47.5 (1.0–280.0)
Duration of event (days), median (range)	8.0 (1.0–385.0)	8.0 (1.0–314.0)

AE=adverse event; RP2D=recommended Phase II dose.

[a] Counted based on the investigator's answer to the AE Case Report Form question "Was medication given for AE?"

Source: t_aesi_bysmq_INIT_GRPBH_SE_27AUG2021_29781; t_ae_ctc_heme_INIT_GRPBH_SE_27AUG2021_29781; t_ae_dur_INIT_GRPBH_SE_27AUG2021_29781.

Thrombocytopenia/platelet count decreased:

A total of 26 events under the grouped terms of thrombocytopenia/platelet count decreased were reported in 25 of 218 patients (11.5%) in the B11 RP2D cohort.

A total of 15 bleeding events in 15 patients (3.6%) in Group B, with 9 events reported in the B11 RP2D cohort, occurred concurrently with thrombocytopenia/platelet count decreased events.

Nine bleeding events (4.1%) occurred in nine patients with thrombocytopenia in the B11 RP2D cohort.

Eight of 25 patients (32.0%) in the B11 RP2D cohort who had thrombocytopenia/platelet count decreased events received platelet transfusion. Nine bleeding events (all events were anaemia) in 9 patients (4.1%) in the B11 RP2D cohort occurred concurrently with thrombocytopenia/platelet count decreased events; all bleeding events were anemia. These anaemia events were of severity Grade 1 (4 events) and Grade 3 (5 events).

Haemorrhagic events were observed in 6% of patients. The majority of events were Grade 1-2 and non-serious. Grade 3 and serious adverse events were reported in 1.2% of patients and 1.0% of patients,

respectively. Three were CNS events (subdural hematoma in two patients, cerebrovascular accident in one patient) and one was an upper GI-bleeding in a patient with PD and in treatment with apixaban.

No fatal or life-threatening events have been reported.

Table 44 Overview of Thrombocytopenia/Platelet Count Decreased Events in Group B and B11 RP2D Cohort (CCOD: 27 August 2021), Safety-Evaluable Patients

Group/cohort No. of patients	Group B N=414	B11 RP2D Cohort N=218
Total number of events	35	26
Total number of patients with at least one, n (%)		
Event	34 (8.2)	25 (11.5)
Event of Grade 1 max. severity	9 (2.2)	7 (3.2)
Event of Grade 2 max. severity	5 (1.2)	3 (1.4)
Event of Grade 3 max. severity	7 (1.7)	7 (3.2)
Event of Grade 4 max. severity	13 (3.1)	8 (3.7)
Serious event	0	0
Event related to mosunetuzumab	15 (3.6)	12 (5.5)
Event leading to withdrawal of mosunetuzumab	0	0
Event leading to dose modification/ interruption of mosunetuzumab	5 (1.2)	4 (1.8)
Unresolved or ongoing event	14 (3.4)	10 (4.6)
Total patients with all events resolved, n (%)	20 (4.8)	15 (6.9)
Total patients with treatment received for the event [a], n (%)	8 (1.9)	6 (2.8)
Time to onset of first event (days), median (range)	14.0 (1.0–393.0)	15.0 (1.0–393.0)
Duration of event (days), median (range)	17.0 (1.0–159.0)	15.0 (1.0–152.0)

AE=adverse event; RP2D=recommended Phase II dose.

[a] Counted based on the investigator's answer to the AE Case Report Form question "Was medication given for AE?"

Source: t_aesi_bysmq_INIT_GRPBH_SE_27AUG2021_29781; t_ae_ctc_heme_INIT_GRPBH_SE_27AUG2021_29781; t_ae_dur_INIT_GRPBH_SE_27AUG2021_29781.

No DIC (disseminated intravascular coagulation) events were reported in patients in Group A and Group B.

Anaemia:

A total of 42 events under the grouped terms of anemia/hemoglobin decreased were reported in 33 of 218 patients (15.1%) in the B11 RP2D cohort. All events were reported as the PT of anemia.

The incidence of anaemia was comparable between the Group B, B11 RP2D, and B11 RP2D FL cohorts (16.4%, 15.1%, and 13.3%, respectively).

Thirteen of 33 patients (39.4%) in the B11 RP2D cohort who had anemia AEs received RBC transfusion.

Table 45 Overview of Anemia/Hemoglobin Decreased Events in Group B and B11 RP2D Cohort (CCOD: 27 August 2021), Safety-Evaluable Patients

Group/cohort No. of patients	Group B N=414	B11 RP2D Cohort N=218
Total number of events	83	42
Total number of patients with at least one, n (%)		
Event	68 (16.4)	33 (15.1)
Event of Grade 1 max. severity	15 (3.6)	7 (3.2)
Event of Grade 2 max. severity	18 (4.3)	8 (3.7)
Event of Grade 3 max. severity	35 (8.5)	18 (8.3)
Serious event	2 (0.5)	1 (0.5)
Event related to mosunetuzumab	24 (5.8)	13 (6.0)
Event leading to withdrawal of mosunetuzumab	0	0
Event leading to dose modification/ interruption of mosunetuzumab	1 (0.2)	1 (0.5)
Unresolved or ongoing event	24 (5.8)	11 (5.0)
Total patients with all events resolved, n (%)	44 (10.6)	22 (10.1)
Total patients with treatment received for the event [a], n (%)	30 (7.2)	13 (6.0)

AE=adverse event; RP2D=recommended Phase II dose.

[a] Counted based on the investigator's answer to the AE Case Report Form question "Was medication given for AE?"

Source: t_aesi_bysmq_INIT_GRPBH_SE_27AUG2021_29781; t_ae_ctc_heme_INIT_GRPBH_SE_27AUG2021_29781.

Haemophagocytic Lymphohistiocytosis

HLH events were reported in 3 patients receiving mosunetuzumab IV monotherapy as of the CCOD, including 1 of 33 patients (3.0%) in Group A and 2 of 414 patients (0.5%) in Group B (one of which was in the B11 RP2D cohort).

Tumour Lysis Syndrome

Two TLS events were reported in 2 patients in the B11 RP2D cohort. Both events (Grade 4 event in a patient with R/R FL and Grade 3 event in a patient with R/R MCL) were assessed as serious and preceded by a CRS event on the prior study day. Both patients had received allopurinol prophylaxis, and the TLS events resolved with no change in mosunetuzumab dose.

No TLS events were reported in other cohorts in Group B or in Group A.

TLS is satisfactorily described in the SmPC in sections 4.4 and 4.8.

Tumour Flare

Tumour flare events were identified by PT of tumour flare, as suspected tumour flare events, or by AESI Grade ≥2 tumour flare/tumour inflammation specific for mosunetuzumab.

Table 46 Overview of tumour in group B and B11 RP2D cohort receiving mosunetuzumab iv monotherapy CCOD 27.08.2021 Safety- evaluable patients

Group/cohort No. of patients	Group B N=414	B11 RP2D Cohort N=218
Total number of events	19	9
Total number of patients with at least one, n (%)		
Event	18 (4.3)	9 (4.1)
Event of Grade 1 max. severity	2 (0.5)	0
Event of Grade 2 max. severity	9 (2.2)	4 (1.8)
Event of Grade 3 max. severity	7 (1.7)	5 (2.3)
Serious event	5 (1.2)	4 (1.8)
Event related to mosunetuzumab	15 (3.6)	6 (2.8)
Event leading to withdrawal of mosunetuzumab	0	0
Event leading to dose modification/ interruption of mosunetuzumab	3 (0.7)	1 (0.5)
Unresolved or ongoing event	4 (1.0)	1 (0.5)
Total patients with all events resolved, n (%)	14 (3.4)	8 (3.7)
Total patients with treatment received for the event [a], n (%)	9 (2.2)	6 (2.8)
Time to onset of first event (days), median (range)	12.0 (1.0–84.0)	13.0 (5.0–84.0)
Duration of event (days), median (range)	14.0 (1.0–77.0)	10.0 (1.0–77.0)

AE=adverse event; RP2D=recommended Phase II dose.

[a] Counted based on the investigator's answer to the AE Case Report Form question "Was medication given for AE?"

Hepatic Adverse Events

Hepatic AEs were identified by the High-Level Term of liver function analyses or PTs of ALT increased, AST increased, bilirubin increased, hyperbilirubinemia, blood bilirubin increased, amylase increased, and hyperamylasemia. In cohort B11 RP2D a total of 29 of 218 patients (13.3%) experienced 61 hepatic AEs following initial treatment with mosunetuzumab. Patients in Group B who potentially fulfilled Hy's law criteria for liver laboratory abnormalities and were assessed for potential DILI are addressed in the Laboratory findings section. Study GO29781 excluded patients with known hepatitis B.

Table 47 Overview of Hepatic Adverse Events in Group B and B11 RP2D Cohort (CCOD: 27 August 2021), Safety-Evaluable Patients

Group/cohort No. of patients	Group B N=414	B11 RP2D Cohort N=218
Total number of events	102	61
Total number of patients with at least one, n (%)		
Event	52 (12.6)	29 (13.3)
Event of Grade 1 max. severity	19 (4.6)	11 (5.0)
Event of Grade 2 max. severity	10 (2.4)	5 (2.3)
Event of Grade 3 max. severity	17 (4.1)	9 (4.1)
Event of Grade 4 max. severity	6 (1.4)	4 (1.8)
Serious event	4 (1.0)	3 (1.4)
Event related to mosunetuzumab	37 (8.9)	20 (9.2)
Event leading to withdrawal of mosunetuzumab	2 (0.5)	0
Event leading to dose modification/ interruption of mosunetuzumab	7 (1.7)	5 (2.3)
Unresolved or ongoing event	16 (3.9)	9 (4.1)
Total patients with all events resolved, n (%)	36 (8.7)	20 (9.2)
Total patients with treatment received for the event [a], n (%)	9 (2.2)	5 (2.3)
Time to onset of first event (days), median (range)	6.5 (1.0–399.0)	6.0 (1.0–399.0)
Duration of event (days), median (range)	8.0 (2.0–104.0)	6.5 (2.0–56.0)

AE=adverse event; RP2D=recommended Phase II dose.

[a] Counted based on the investigator's answer to the AE Case Report Form question "Was medication given for AE?"

Source: t_aesi_bysmq_INIT_GRPBH_SE_27AUG2021_29781; t_ae_dur_INIT_GRPBH_SE_27AUG2021_29781.

Table 48 Hepatic Adverse Events by Preferred Term in Group B and B11 RP2D cohort (CCOD: 27 August 2021), Safety-Evaluable Patients

	Group B N=414	B11 RP2D Cohort N=218
No. of patients with at least one AE, n (%)		
ALT increased	36 (8.7)	23 (10.6)
AST increased	27 (6.5)	15 (6.9)
GGT increased	10 (2.4)	5 (2.3)
Blood bilirubin increased	8 (1.9)	4 (1.8)
Amylase increased	3 (0.7)	1 (0.5)
Transaminase increased	2 (0.5)	2 (0.9)
Hepatic enzyme increased	1 (0.2)	1 (0.5)
Liver function test increased	1 (0.2)	0
Hyperbilirubinemia	1 (0.2)	0

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyltransferase; RP2D=recommended Phase II dose.

All AEs in Group B (N=414) and B11 RP2D cohort (N=218) are shown.

Source: t_ae_ctc_HEPT_INIT_GRPBH_SE_27AUG2021_29781.

There is a relatively high incidence of transaminase/bilirubin increases overall in B11 RP2D cohort; per NCI CTCAE classification, a Grade 2 or above transaminase is increase in >3X ULN, similar as the limit per Hy's law; for bilirubin the threshold of >2XULN is included as from Grade 2 or above. There are 17 patients in B11 RP2D who had Grade 2 or above increase in liver parameters.

Patients in Group B who fulfilled Hy's law criteria for liver laboratory abnormalities and were assessed for potential DILI are addressed in the Laboratory findings section.

Infections

Infection AEs were broadly defined as all AEs reported as PTs in the SOC of Infections and Infestations.

Table 49 Overview of Infection Events in Group B and B11 RP2D Cohort (CCOD: 27 August 2021), Safety-Evaluable Patients

Group/cohort No. of patients	Group B N=414	B11 RP2D Cohort N=218
Total number of events	359	182
Total number of patients with at least one, n (%)		
Event	195 (47.1)	102 (46.8)
Event of Grade 1 max. severity	38 (9.2)	20 (9.2)
Event of Grade 2 max. severity	92 (22.2)	49 (22.5)
Event of Grade 3 max. severity	54 (13.0)	26 (11.9)
Event of Grade 4 max. severity	7 (1.7)	5 (2.3)
Event of Grade 5 max. severity	4 (1.0)	2 (0.9)
Serious event	64 (15.5)	37 (17.0)
Event related to mosunetuzumab	46 (11.1)	28 (12.8)
Event leading to withdrawal of mosunetuzumab	7 (1.7)	2 (0.9)
Event leading to dose modification/ interruption of mosunetuzumab	47 (11.4)	25 (11.5)
Unresolved or ongoing event	47 (11.4)	26 (11.9)
Total patients with all events resolved, n (%)	148 (35.7)	76 (34.9)
Total patients with treatment received for the event [a], n (%)	170 (41.1)	90 (41.3)
Time to onset of first serious event (days), median (range)	65.5 (1.0–561.0)	50.0 (1.0–561.0)
Duration of serious event (days), median (range)	13.0 (2.0–174.0)	12.0 (2.0–174.0)

AE=adverse event; RP2D=recommended Phase II dose.

[a] Counted based on the investigator's answer to the AE Case Report Form question "Was medication given for AE?"

Source: t_aesi_bysmq_INIT_GRPBH_SE_27AUG2021_29781; t_ae_ctc_INIT_GRPBH_SE_27AUG 27AUG2021_29781; t_ae_dur_INIT_GRPBH_SE_27AUG2021_29781.

In cohort B11 RP2D 46.8% of patients experienced 182 infection adverse events (Table 66/uCSR) many of which were related to the respiratory system. SAEs were reported in 37 patients (17.0%), with pneumonia (7 patients [3.2%]) being the most frequent.

Table 50 Summary of Common (≥2%) Infection Adverse Events by Preferred Term in Group B and B11 RP2D Cohort (CCOD: 27 August 2021), Safety-Evaluable Patients

	Group B N=414	B11 RP2D Cohort N=218
No. of patients with at least one AE, n (%)		
Upper respiratory tract infection	49 (11.8)	21 (9.6)
Urinary tract infection	30 (7.2)	15 (6.9)
Pneumonia	20 (4.8)	12 (5.5)
Sinusitis	19 (4.6)	9 (4.1)
Herpes zoster	14 (3.4)	7 (3.2)
Nasopharyngitis	12 (2.9)	5 (2.3)
Bronchitis	11 (2.7)	6 (2.8)
Oral candidiasis	7 (1.7)	5 (2.3)
Rhinovirus infection	6 (1.4)	5 (2.3)

AE=adverse event; RP2D=recommended Phase II dose.

All AEs with incidence of ≥2% in Group B (N=414) and B11 RP2D cohort (N=218) are shown.

Pneumonitis/Interstitial Lung Disease

Pneumonitis/interstitial lung disease (ILD) AEs were broadly defined as all AEs reported as PTs in the Standardized MedDRA Queries Interstitial Lung Disease.

Two patients in the B11 RP2D experienced pneumonitis/ILD as SAEs (0.9%). These were both Grade 3 and both resolved.

With the updated safety data (+24 weeks) no new events of pneumonitis occurred.

Table 51 Overview of Pneumonitis/Interstitial Lung Disease Events in Group B and B11 RP2D Cohort (CCOD: 27 August 2021), Safety-Evaluable Patients

Group/cohort No. of patients	Group B N=410	B11 RP2D Cohort N=214
Total number of events	8	3
Total number of patients with at least one, n (%)		
Event	8 (2.0)	3 (1.4)
Event of Grade 1 max. severity	1 (0.2)	1 (0.5)
Event of Grade 2 max. severity	4 (1.0)	0
Event of Grade 3 max. severity	3 (0.7)	2 (0.9)
Serious event	4 (1.0)	2 (0.9)
Event related to mosunetuzumab	5 (1.2)	2 (0.9)
Event leading to withdrawal of mosunetuzumab	0	0
Event leading to dose modification/ interruption of mosunetuzumab	4 (1.0)	2 (0.9)
Unresolved or ongoing event	2 (0.5)	1 (0.5)
Total patients with all events resolved, n (%)	6 (1.5)	2 (0.9)
Total patients with treatment received for the event [a], n (%)	6 (1.5)	2 (0.9)

AE=adverse event; RP2D=recommended Phase II dose.

[a] Counted based on the investigator's answer to the AE Case Report Form question "Was medication given for AE?"

2.6.8.4 Laboratory findings

Haematology

The most frequent (≥5% of patients) treatment-emergent Grade ≥3 worsening haematological laboratory parameter shifts in the B11 RP2D cohort were decreases in lymphocytes (the pharmacodynamic action of mosunetuzumab to deplete B-cells), neutrophils, leukocytes, hemoglobin, and platelets and are consistent with AE reporting of decreased neutropenia/neutrophil count, anemia/hemoglobin decreased, and thrombocytopenia.

The treatment-emergent haematological laboratory parameter shifts in the B11 FL cohort were similar to those reported in the B11 RP2D cohort.

Table 52 Most Frequent[a] Treatment-Emergent Hematology and Chemistry Laboratory Abnormalities (CCOD: 27 August 2021)

Laboratory abnormalities	Group B N=414 n (%)				B11 RP2D N=218 n (%)				B11 FL RP2D N=90 n (%)			
	N[b]	All Grades	Gr 3-4[c]	Gr 4	N[b]	All Grades	Gr 3-4[c]	Gr 4	N[b]	All Grades	Gr 3-4[c]	Gr 4
Hematology												
↓Lymphocytes	364	341 (93.7)	331 (90.9)	252 (69.2)	202	192 (95.0)	186 (92.1)	144 (71.3)	83	83 (100)	81 (97.6)	58 (69.9)
↓Hemoglobin	413	293 (70.9)	81 (19.6)	0	217	152 (70.0)	41 (18.9)	0	90	61 (67.8)	11 (12.2)	0
↓Leukocytes	413	254 (61.5)	92 (22.3)	27 (6.5)	217	133 (61.3)	47 (21.7)	9 (4.1)	90	54 (60.0)	12 (13.3)	0
↓Neutrophils	303	172 (56.8)	116 (38.3)	63 (20.8)	175	101 (57.7)	66 (37.7)	34 (19.4)	72	42 (58.3)	29 (40.3)	17 (23.6)
↓Platelets	413	201 (48.7)	50 (12.1)	24 (5.8)	217	97 (44.7)	26 (12.0)	11 (5.1)	90	41 (45.6)	9 (10.0)	6 (6.7)
↑Lymphocytes	364	42 (11.5)	4 (1.1)	0	202	27 (13.4)	3 (1.5)	0	83	9 (10.8)	2 (2.4)	0
Chemistry												
↑Creatinine	413	367 (88.9)	11 (2.7)	2 (0.5)	217	192 (88.5)	7 (3.2)	2 (0.9)	90	79 (87.8)	4 (4.4)	1 (1.1)
↓Phosphate	413	303 (73.4)	154 (37.3)	7 (1.7)	217	163 (75.1)	88 (40.6)	3 (1.4)	90	70 (77.8)	41 (45.6)	0
↓Albumin	412	253 (61.4)	18 (4.4)	0	216	134 (62.0)	9 (4.2)	0	89	52 (58.4)	1 (1.1)	0
↓Calcium	413	231 (55.9)	23 (5.6)	4 (1.0)	217	120 (55.3)	9 (4.1)	2 (0.9)	90	52 (57.8)	2 (2.2)	1 (1.1)
↓Sodium	413	179 (43.3)	29 (7.0)	0	217	92 (42.4)	13 (6.0)	0	90	30 (33.3)	2 (2.2)	0
↑SGOT/AST	413	175 (42.4)	18 (4.4)	5 (1.2)	217	98 (45.2)	9 (4.1)	3 (1.4)	90	35 (38.9)	4 (4.4)	2 (2.2)
↑Glucose	409	160 (39.1)	160 (39.1)	6 (1.5)	213	86 (40.4)	86 (40.4)	3 (1.4)	90	38 (42.2)	38 (42.2)	0
↓Magnesium	413	160 (38.7)	2 (0.5)	1 (0.2)	217	86 (39.6)	0	0	90	31 (34.4)	0	0
↓Potassium	413	152 (36.8)	22 (5.3)	2 (0.5)	217	71 (32.7)	10 (4.6)	1 (0.5)	90	30 (33.3)	5 (5.6)	1 (1.1)
↑GGT	408	147 (36.0)	29 (7.1)	3 (0.7)	214	81 (37.9)	16 (7.5)	1 (0.5)	90	31 (34.4)	8 (8.9)	0

Laboratory abnormalities	Group B N=414 n (%)				B11 RP2D N=218 n (%)				B11 FL RP2D N=90 n (%)			
	N[b]	All Grades	Gr 3-4[c]	Gr 4	N[b]	All Grades	Gr 3-4[c]	Gr 4	N[b]	All Grades	Gr 3-4[c]	Gr 4
↑SGPT/ALT	413	144 (34.9)	21 (5.1)	1 (0.2)	217	79 (36.4)	12 (5.5)	1 (0.5)	90	29 (32.2)	6 (6.7)	1 (1.1)
↑Alkaline phosphatase	413	107 (25.9)	6 (1.5)	0	217	53 (24.4)	3 (1.4)	0	90	23 (25.6)	0	0
↑Urate	410	83 (20.2)	83 (20.2)	25 (6.1)	214	47 (22.0)	47 (22.0)	19 (8.9)	90	20 (22.2)	20 (22.2)	9 (10.0)
↑Bilirubin	413	75 (18.2)	21 (5.1)	0	217	41 (18.9)	10 (4.6)	0	90	11 (12.2)	3 (3.3)	0
↑Potassium	413	41 (9.9)	15 (3.6)	2 (0.5)	217	35 (16.1)	6 (2.8)	1 (0.5)	90	18 (20.0)	3 (3.3)	1 (1.1)
↑Calcium	413	47 (11.4)	10 (2.4)	4 (1.0)	217	25 (11.5)	8 (3.7)	4 (1.8)	90	11 (12.2)	4 (4.4)	3 (3.3)
↓Glucose	409	42 (10.3)	1 (0.2)	0	213	16 (7.5)	1 (0.5)	0	90	9 (10.0)	1 (1.1)	0
↑Magnesium	413	41 (9.9)	15 (3.6)	2 (0.5)	217	23 (10.6)	8 (3.7)	1 (0.5)	90	8 (8.9)	2 (2.2)	0
↑Sodium	413	40 (9.7)	3 (0.7)	2 (0.5)	217	21 (9.7)	1 (0.5)	0	90	13 (14.4)	0	0

[a]Table shows any worsening grade laboratory shifts from baseline measured in ≥5% of patients in each cohort.
[b]Number of patients with a baseline and at least one post-baseline assessment for lab parameter.
[c]Includes shifts from NCI CTCAE Grade <3 to Grade ≥3, and shifts from Grade 3 to Grade 4.
Source: Table 70, Table 71, Table 73 and Table 74 of Update Interim GO29781 CSR (Report No. 1111637);
t_lb_freqabn_INITQ_3LFL_B11EXP_SE_27AUG2021_29781.

Post-Baseline IgG Level:

Summary of IgG depletion post-baseline, Initial Treatment with Mosunetuzumab, Cohort B11 Expansion, Safety-Evaluable Patients
Protocol: GO29781

	Baseline IgG	
	<5 g/L (N=35)	>=5 g/L (N=62)
Minimum IgG post-baseline		
<5 g/L	27 (77.1%)	23 (37.1%)
>=5 g/L	8 (22.9%)	39 (62.9%)

Only patients with baseline IgG level and at least one post-baseline IgG level are included in the analysis.
Data Cutoff Date - 15MAR2021

Chemistry

The treatment-emergent chemistry laboratory abnormalities in the B11 FL cohort were similar to those reported in the B11 RP2D cohort (see table above).

Hy's Law:

At least three patients experienced hepatotoxicity, which later resolved, in conjunction with CRS in Cycle 1.

2.6.8.5 In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6 Safety in special populations

Age:

Table 53 Overview of Adverse Events by age in B11 RP2D and B11 FL Cohorts (CCOD: 15 March 2021), Safety-Evaluable Patients

MedDRA Terms	Age <65		Age 65-74		Age 75-84		Age 85+	
	B11 RP2D (N=114)	B11 FL (N=60)	B11 RP2D (N=61)	B11 FL (N=23)	B11 RP2D (N=31)	B11 FL (N=5)	B11 RP2D (N=8)	B11 FL (N=2)
Total AEs	112 (98.2)	60 (100)	59 (96.7)	23 (100)	31 (100)	5 (100)	7 (87.5)	2 (100)
Serious AEs – Total	60 (52.6)	30 (50.0)	28 (45.9)	9 (39.1)	19 (61.3)	2 (40.0)	2 (25.0)	0
- Fatal	15 (13.2)	1 (1.7)	9 (14.8)	1 (4.3)	6 (19.4)	0	1 (12.5)	0
- Hospitalization/prolong existing hospitalization	51 (44.7)	30 (50.0)	25 (41.0)	9 (39.1)	17 (54.8)	2 (40.0)	1 (12.5)	0
- Life-threatening	3 (2.6)	1 (1.7)	1 (1.6)	0	1 (3.2)	0	0	0
- Disability/incapacity	2 (1.8)	1 (1.7)	1 (1.6)	0	1 (3.2)	0	0	0
- Other (medically significant)	5 (4.4)	1 (1.7)	2 (3.3)	0	1 (3.2)	0	0	0
AE leading to drop-out	4 (3.5)	3 (5.0)	3 (4.9)	1 (4.3)	2 (6.5)	0	0	0
Psychiatric disorders	9 (7.9)	6 (10.0)	2 (3.3)	2 (8.7)	3 (9.7)	0	0	0
Nervous system disorders	60 (52.6)	39 (65.0)	33 (54.1)	16 (69.6)	16 (51.6)	3 (60.0)	6 (75.0)	2 (100)
Accidents and injuries	5 (4.4)	3 (5.0)	5 (8.2)	3 (13.0)	1 (3.2)	1 (20.0)	2 (25.0)	1 (50.0)
Cardiac disorders	10 (8.8)	7 (11.7)	10 (16.4)	2 (8.7)	5 (16.1)	1 (20.0)	1 (12.5)	0
Vascular disorders	18 (15.8)	11 (18.3)	11 (18.0)	5 (21.7)	4 (12.9)	0	2 (25.0)	1 (50.0)
Cerebrovascular disorders	0	0	0	0	0	0	0	0
Infections and infestations	50 (43.9)	32 (53.3)	30 (49.2)	11 (47.8)	18 (58.1)	2 (40.0)	2 (25.0)	1 (50.0)
Anticholinergic syndrome	0	0	0	0	0	0	0	0

MedDRA Terms	Age <65		Age 65-74		Age 75-84		Age 85+	
	B11 RP2D (N=114)	B11 FL (N=60)	B11 RP2D (N=61)	B11 FL (N=23)	B11 RP2D (N=31)	B11 FL (N=5)	B11 RP2D (N=8)	B11 FL (N=2)
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	13 (11.4)	5 (8.3)	9 (14.8)	4 (17.4)	5 (16.1)	2 (40.0)	1 (12.5)	1 (50.0)
Other AE appearing more frequently in older patients								
Fatigue	30 (26.3)	20 (33.3)	24 (39.3)	10 (43.5)	10 (32.3)	2 (40.0)	4 (50.0)	1 (50.0)
Cytokine release syndrome	54 (47.4)	31 (51.7)	23 (37.7)	8 (34.8)	13 (41.9)	2 (40.0)	2 (25.0)	0
Pyrexia	33 (28.9)	19 (31.7)	10 (16.4)	6 (26.1)	5 (16.1)	1 (20.0)	4 (50.0)	0
Hypophosphatemia	25 (21.9)	15 (25.0)	13 (21.3)	4 (17.4)	3 (9.7)	0	3 (37.5)	1 (50.0)
Rash	23 (20.2)	9 (15.0)	12 (19.7)	4 (17.4)	3 (9.7)	0	4 (50.0)	1 (50.0)

For Psychiatric Disorders: events were identified using Psychiatric Disorders SOC.
For Nervous System Disorders: events were identified using Nervous System Disorders SOC.
For Accidents and Injuries: events were identified using Accident and Injuries SMQ Narrow.
For Cardiac Disorders: events were identified using Cardiac Disorders SOC.
For Vascular Disorders: events were identified using Vascular Disorders SOC.
For Cerebrovascular Disorders: events were identified using the PT Cerebrovascular disorder.
For Infections and Infestations: events were identified using Infections and Infestations SOC.
For Anticholinergic Syndrome: events were identified using the PT Anticholinergic Syndrome.
For Quality of life decreased: events were identified using the PT Quality of life decreased.
For Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures: events were identified using the PTs Orthostatic hypotension, Fall, Loss of consciousness, Syncope, Dizziness, Ataxia, Multiple fractures.
For Other AE appearing more frequently in older patients, the 5 most frequent PTs in the older age categories (≥65 years), alongside the corresponding frequencies of these PTs in all age categories are shown.

The safety profile is comparable across the age groups. There is limited experience with mosunetuzumab in patients >85 years of age.

Race:

The two main cohorts by race in Group B were White [317 patients (77.3%)] and Asian [67 patients (16.3%)]. In the B11 RP2D cohort 23/214 patients (10.7%) were Asian and in the B11 FL cohort 8/90 (8.9%) were Asian (Table 10/uCSR, Exposure section). The only Asian country that took part in the study was the Republic of Korea, which recruited 7 patients in Group A (7/33) and 50/410 in Group B (which means that 17 Asian patients in Group B must have come from Western countries). The difference between SAEs (excluding Grade 5 PD) for Whites and Asians seem quite remarkable [136/317 (42.9%) and 14/67 (20.9%)].

Summary of Adverse Events, Race, Initial Treatment with Mosunetuzumab, Group B, Safety-Evaluable Patients
Protocol: GO29781

	WHITE (N=317)	ASIAN (N=67)	AMERICAN INDIAN OR ALASKA NATIVE (N=2)	BLACK OR AFRICAN AMERICAN (N=11)	MULTIPLE (N=1)	UNKNOWN (N=12)
Total number of patients with at least one adverse event	312 (98.4%)	65 (97.0%)	2 (100%)	11 (100%)	1 (100%)	12 (100%)
Total number of events	3448	501	32	122	7	147
Total number of deaths	143 (45.1%)	11 (16.4%)	1 (50.0%)	3 (27.3%)	1 (100%)	7 (58.3%)
Total number of patients withdrawn from initial treatment due to AE or death	14 (4.4%)	4 (6.0%)	0	1 (9.1%)	0	0
Total number of patients with at least one						
Fatal AE	51 (16.1%)	0	0	1 (9.1%)	1 (100%)	4 (33.3%)
Fatal AE (not including PD)	5 (1.6%)	0	0	1 (9.1%)	0	0
Fatal AE, Mosun related (not including PD)	2 (0.6%)	0	0	0	0	0
Serious AE	164 (51.7%)	14 (20.9%)	1 (50.0%)	5 (45.5%)	1 (100%)	6 (50.0%)
Serious AE of Grade 3-5 (excluding grade 5 PD)	90 (28.4%)	11 (16.4%)	0	4 (36.4%)	1 (100%)	3 (25.0%)
Serious AE (excluding grade 5 PD)	136 (42.9%)	14 (20.9%)	1 (50.0%)	5 (45.5%)	1 (100%)	4 (33.3%)
Serious AE (excluding Grade 5) related to Mosun	90 (28.4%)	7 (10.4%)	1 (50.0%)	3 (27.3%)	1 (100%)	4 (33.3%)
Serious AE of Grade 3-5 (excluding grade 5 PD) related to Mosun	43 (13.6%)	5 (7.5%)	0	3 (27.3%)	0	1 (8.3%)

Investigator text for AEs encoded using MedDRA version 24.0.
Only treatment emergent AEs are displayed.
Percentages are based on N in the column headings.
Total number of deaths includes events reported during both initial and retreatment periods
Data Cutoff Date - 15MAR2021

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary_GrpAB_May2021/prod/program/t_ae_summary_subgrp.sas
Output: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/CSRPrimary_GrpAB_May2021/prod/output/t_ae_summary_subgrp_RAC_INIT_GRPB_SE_15MAR2021_29781.out
24JUN2021 16:20 Page 1 of 3

Prior CAR-T therapy:

In cohort B11 FL only 3 patients had received prior CAR-T therapy. All adverse events (AEs, SAEs, PD, Grade 3-4 AEs) were seen more frequently in patients having received CAR-T therapy.

2.6.8.7 Immunological events

As of the ADA data cutoff date of 4 December 2020, no ADAs have been detected in serum samples collected at any assessment timepoint from 418 ADA-evaluable patients who received mosunetuzumab IV monotherapy treatments in Study GO29781. (See the Clinical Pharmacology section).

2.6.8.8 Safety related to drug-drug interactions and other interactions

Physiologically-based pharmacokinetics (PBPK) modeling and simulations based on IL-6 and CYP3A4 interaction indicated a low risk of cytokine-mediated drug-drug interaction (DDI) potential of mosunetuzumab on cytochrome P450 (CYP) enzyme expression or activity (PBPK Report No.1110241). The predicted area under the concentration-time curve (AUC) and maximum concentration (C_{max}) ratios (with mosunetuzumab coadministration/without mosunetuzumab coadministration) for midazolam, a sensitive CYP3A substrate was 1.37 and 1.37, respectively. No dose adjustment is recommended when co-dosing mosunetuzumab with small molecule drugs which are CYP3A substrates (See the Clinical Pharmacology section for an assessment of drug-drug interactions).

2.6.8.9 Discontinuation due to adverse events

B11 RP2D Cohort

Overall, 9 of 218 patients (4.1%) in the B11 RP2D cohort **discontinued** mosunetuzumab due to AEs. CRS was the only AEs that led to discontinuation in more than one patient (2 patients; 0.9%).

Overall, 73 of 218 patients (33.5%) in the B11 RP2D cohort had a **dose interruption or modification** of mosunetuzumab due to AEs. Adverse events that led to dose interruption or modification of mosunetuzumab and

occurred in ≥2% of patients in the B11 RP2D cohort were neutropenia/neutrophil count decreased (25 patients [11.5%]) and CRS (19 patients [8.7%] by Lee 2014 grading criteria; 17 patients [7.8%] by ASTCT 2019 grading criteria).

Serious adverse events led to mosunetuzumab dose modification in 3 patients (1.4%) and mosunetuzumab dose interruption in 32 patients (14.7%) in the B11 RP2D cohort.

2.6.8.10 Post marketing experience

Mosunetuzumab has not been approved for use anywhere in the world; therefore, no postmarketing data regarding its use are currently available.

2.6.9 Discussion on clinical safety

The primary safety population of 214 patients is the B11 RP2D cohort with lymphoid malignancies (DLBCL, FL, MCL) of which 90 patients had follicular lymphoma. Supportive information from an additional 196 patients having received for most patients considerably lower doses in Group B, which have been added to the primary population (N=410), has been taken into consideration. Updated safety data with the addition of 4 patients with Richter's transformation (B11 RP2D cohort n=218) and an additional 24 weeks of safety data have generally been included in the assessment report but have not led to any changes in the assessment of safety.

Safety data in patients in the intended indication is limited to 90 patients; it is unknown to what extent the safety information in Group A and Group B (all cohorts) is applicable for the intended indication. Although dataset B11 RP2D cohort (n=218) includes more patients and could provide more information on mosunetuzumab safety, it is noted that a significant proportion of the patients in this dataset have a different disease than the intended indication. Patients had follicular lymphoma (41.3%), diffuse large B-cell lymphoma/transformed follicular lymphoma (40.4%) mantle cell lymphoma (11.5%), Richter's transformation (6.4%), and other histologies (0.5%). The median number of cycles of Lunsumio received was 8 (range 1 -17), 37% of patients received 8 cycles, and 15% received more than 8 cycles up to 17 cycles. This information is included in the SmPC section 4.8.

Exposure for 6 months (corresponding to app. 8 cycles) and 1 year (approximately 17 cycles for patients who achieved a PR or maintained SD after 8 cycles) were seen for 79 and 13 patients in the primary safety population, respectively. The median observation time in cohort B11 RP2D was 14.3 months (updated safety data), and thus long-term safety is missing. The Applicant has accepted to include this as Missing information in the RMP 'Summary of safety concerns' table. This is also in line with the FU advice given by EMA.

Exposure-safety: Grade ≥2 CRS was identified as an exposure- and regimen-dependent AE where the administration of mosunetuzumab following the step-up dosing regimen was associated with a relatively low frequency but RO_{max}-dependent increase of Grade ≥2 CRS transiently during Cycle 1 following the 60 mg dose administration on Day 15. The occurrence of Grade ≥3 CRS frequency was <3%.

The key cancer history characteristics of the B11 RP2D cohort and the B11 FL were generally consistent with the overall Group B population (Table 11/CSR). One third had bulky disease (> 6 cm) and approximately half of the patients had Ann Arbor stage IV disease. In the B11 FL cohort, 18.9% had previously received PI3K inhibitor treatment, while 53.3% were doubly refractory to anti-CD20/alkylator therapy. A total of 47/90 patients (52.2%) experienced progression of disease in less than 24 months from the start of first systemic therapy. All FL patients had received at least two prior therapies (median of three) and had received both alkylator- and anti-CD20-therapy according to protocol.

In the primary safety population of 214 patients at the CCOD of 15 March 2021, almost all patients (97.7%) treated with mosunetuzumab IV monotherapy by step-up dosing in cohort B11 RP2D experienced at least one AE. Cytokine release syndrome (CRS) was the most commonly observed event (43.0% of patients based on Lee 2014 grading criteria and 39.3% by ASTCT 2019 grading criteria.

Other **common AEs** (≥20% incidence by PT) in cohort B11 RP2D were neutropenia/neutrophil count decreased, fatigue, hypophosphatemia, and pyrexia. Most AEs were Grade 1 or 2 severity except for neutropenia/neutrophil count decreased. Grade 3-4 AEs were reported in 64.6% of patients in cohort B11 RP2D. The most frequent Grade 3-4 events (≥5% incidence) were cytopenias (neutropenia/neutrophil count decreased and anemia/hemoglobin decreased) and hypophosphatemia.

Neutropenia is a well-known AE for anti-CD20 Abs and is observed with comparable frequency for mosunetuzumab: Grade 3 or 4 neutropenia/neutrophil count decreased were reported in 53 patients in cohort B11 RP2D (24.3%) with a comparable incidence for the B11 RP2D FL cohort (26.6%).

A total of 48 of 60 patients (68%) in cohort B11 RP2D and B11 FL who had neutropenia/neutrophil count decreased events received treatment with G-CSF to treat the events. This information is presented in the SmPC, which is satisfactory. Serious infections is included as an Identified risk in the RMP (see RMP).

Six deaths in Group B (1.5%), of which four occurred in cohort B11 RP2D (1.9%), were due to AEs that were not PD. Five of these were due to infections, which is not considered unexpected in this population.

Serious AEs were reported in 50.9% of patients in cohort B11 RP2D, the most frequent being CRS (22.0% of patients based on the Lee 2014 grading criteria and 20.6% by ASTCT 2019 grading criteria, predominantly Grade 1-2 events that required hospitalization). Other SAEs reported at a frequency of ≥ 2% were pyrexia (4.2%, predominantly Grade 1-2, and did not occur concurrently with CRS), and pneumonia (3.3%).

At the CCOD of 27 August 2021, adverse events in the B11 RP2D cohort infrequently led to treatment discontinuation (4.1%). CRS was the only AEs that led to discontinuation in more than one patient (2 patients; 0.9%). Overall, 73 of 218 patients (33.5%) in the B11 RP2D cohort had a dose interruption or modification of mosunetuzumab due to AEs. Adverse events that led to dose interruption or modification of mosunetuzumab and occurred in ≥2% of patients in the B11 RP2D cohort were neutropenia/neutrophil count decreased (25 patients [11.5%]) and CRS (19 patients [8.7%] by Lee 2014 grading criteria; 17 patients [7.8%] by ASTCT 2019 grading criteria).

Study GO29781 excluded patients with known hepatitis B. Anti-CD20 antibodies are known to cause reactivation of hepatitis B in some patients. Information regarding exclusion of hepatitis B-positive patients is presented in the SmPC, section 5.1.

In cohort B11 RP2D a total of 29 of 218 patients (13.3%) experienced 58 hepatic AEs following initial treatment with mosunetuzumab. ALT elevation is listed as Very common, whereas AST elevation is listed as Common in the ADR table in the SmPC, section 4.8.

The majority of the AESIs were of Grade 1-2 maximum severity, with exception of neutropenia/neutrophil count decreased events, which were most frequently reported at Grade 3-4 severity, and anemia/hemoglobin decreased events, for which approximately half of the events were Grade 3. Grade 3-4 neutropenia/neutrophil count decreased events were infrequently associated with serious infections. Serious infections such as pneumonia, bacteraemia, and sepsis or septic shock have occurred in patients receiving Lunsumio, some of which were life-threatening or fatal events (see SmPC sections 4.4 and 4.8). Febrile neutropenia was observed after receiving Lunsumio infusion.

A warning has been added in section 4.4 of the SmPC regarding live and/or live-attenuated vaccines that should not be given concurrently with Lunsumio.

CRS events in the overall Group B as well as cohort B11 RP2D were predominantly Grade 1 or 2 in severity and limited primarily to Cycle 1 with decreasing frequencies in the subsequent treatment cycles. Within Cycle 1, CRS events were most frequently associated with Day 1 and Day 15 dose administrations with the highest frequency of events observed following the Day 15 administration. Twenty-two percent were graded as SAEs as they required hospitalisation.

The Applicant was requested to present and discuss the risk of CRS as a function of bone marrow involvement (including various degrees of BM involvement) given that there were less CRS in DLBCL patients (although some of these were trFL patients), who usually have less BM involvement, and that 9/10 of patients with Richter's transformation developed CRS, suggesting that BM involvement (and most likely circulating tumour lymphocytes as in CLL) is a predictor for CRS. High tumour burden is considered a risk for CRS in patients receiving CAR-T cell therapy (EBMT and JACIE Guideline). Based on the Applicant's multi-variate analysis of cytokine release syndrome (CRS) risk, bone marrow (BM) involvement and baseline tumour burden are not expected to be significant prognostic factors for mosunetuzumab-related Grade ≥2 CRS. Given the limited information regarding a possible correlation between bone marrow involvement and the risk of CRS, the data is inconclusive and thus not included in the PI.

Patients developing CRS had quite a range of time to onset and duration, which the treating physician needs to consider. This has been adequately described in the SmPC, sections 4.4 and 4.8.

CRS events were managed with steroids, antihistamines and paracetamol (obligatory for Cycle 1 and 2) and for some events supplied with tocilizumab (25.0% of patients in cohort B11 RP2D with CRS events by ASTCT 2019 grade), oxygen administration (21.8%), and vasopressors (6.0%), and were reversible, as evidenced by resolution of all CRS events.

Obligatory premedication for cycle 1 and 2 included steroids, paracetamol and antihistamine. Of 218 patients in the B11 RP2D cohort 23 patients (10.6%) received tocilizumab. In the SmPC the Applicant has provided guidance for the grading and management of CRS, which is considered satisfactory.

The prescriber must discuss the risks of Lunsumio therapy with the patient. The patient should be provided with the patient card and instructed to carry it at all times. The patient card describes the common signs and symptoms of CRS, and provides instructions on when a patient should seek medical attention (see Annex II and RMP).

Neurologic AEs (NAEs) were broadly defined as all AEs reported as primary or secondary PTs in either the SOC of Nervous System Disorders or SOC of Psychiatric Disorders and were observed in 122/218 patients in cohort B11 RP2D. Serious NAEs were reported in 14 patients (6.4%). SAEs reported in more than one patient were confusional state (3 patients; one Grade 3), subdural hematoma (2 patients; all Grade 3), and neurotoxicity (2 patients; all Grade 2)..

Twenty-six patients (11.9%) in cohort B11 RP2D experienced DI-CCNAEs (Driving-Impacting Cognition or Consciousness Neurologic Adverse Events) of which 10 patients (4.6%) experienced serious DI-CCNAEs. The median duration was 3 days, but the range was 1-259 days. In the SmPC, section 4.7 the following is stated: *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,* which is considered satisfactory.

A total of 9 of 218patients (4.1%) experienced tumour flare events following initial treatment with mosunetuzumab. Tumour flare is described in the SmPC in sections 4.4 and 4.8 and is included in the RMP Summary of safety concerns table as an Important identified risk. Manifestations included new or worsening pleural effusions, localised pain and swelling at the sites of lymphoma lesions and tumour

inflammation. Consistent with the mechanism of action of Lunsumio, tumour flare is likely due to the influx of T-cells into tumour sites following Lunsumio administration.

There are no specific risk factors for tumour flare that have been identified, however, there is a heightened risk of compromise and morbidity due to mass effect secondary to tumour flare in patients with bulky tumours located in close proximity to airways and/or a vital organ. (see section 4.4 of the SmPC).

Patients treated with Lunsumio should be monitored and evaluated for tumour flare at critical anatomical sites. Only two tumour lysis syndrome (TLS) events were reported in 2 patients in the B11 RP2D cohort. TLS is described in the SmPC.

The nature, severity, and frequency of AEs reported by patients who received mosunetuzumab at RP2D in the B11 RP2D cohort was similar to the overall Group B with a generally consistent proportion across AE categories among the four histology-specific cohorts of FL, DLBCL/trFL, MCL, and Richter's transformation.

The two main cohorts by race in Group B were White [317 patients (77.3%)] and Asian [67 patients (16.3%)]. The only Asian country that took part in the study were the Republic of Korea, which recruited 7 patients in Group A (7/33) and 50/410 in Group B. Fatal AEs (including PD) were 51/317 (16.1%) vs 0/67, for Whites vs Asians, respectively. The difference between SAEs (excluding Grade 5 PD) for Whites and Asians seem quite remarkable [136/317 (42.9%) and 14/67 (20.9%)]. The percentage of Asian patients was low, and there were differences in baseline and disease characteristics with Asian patients being generally younger, and with less tumor burden. This may at least to some degree explain the lower incidence of serious AEs (including deaths) reported in Asian compared to non-Asian patients. The Applicant states that the difference in AE reporting between Asian and non-Asian patients cannot be explained by differences in mosunetuzumab PK exposure: The impact of Asian race on mosunetuzumab PK was tested in covariate analyses of a popPK model that has been developed from PK observations from patients treated with mosunetuzumab intravenous (IV) monotherapy in Study GO29781. Asian race was not shown to be a significant covariate.

Overall deaths and SAEs were reported in a higher proportion of patients who previously received CAR-T therapy (N=48 in Group B) compared with those who had not received prior CAR-T therapy (N=362); in cohort B11 FL only 3 patients had received prior CAR-T therapy. It is agreed with the Applicant, though, that patients with prior CAR-T therapy included in this analysis appeared to have more aggressive NHL histology, heavier disease burden, worse ECOG PS at baseline, and more prior therapies received. The differences and variances in baseline characteristics likely confounded the observed safety profile, and the differences seen in the subgroups could not be attributed to prior CAR-T therapy alone. Based on the imbalances in baseline characteristics, the small sample sizes and exploratory nature of these analyses, no firm conclusions can be made regarding differences in the safety profile of patients who received prior CAR-T therapy compared to those who did not. Therefore, it is accepted not to include any information regarding potential risk to patients having received prior CAR-T cell therapy into the SmPC. Based on the uncertainty due to few patients, the Applicant has agreed to add 'Safety in patients with prior CAR-T therapy' as Missing information in the Summary of safety concerns in the Risk Management Plan. No ADAs to mosunetuzumab were detected in the ADA-evaluable patients in Group B.

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical safety

Not applicable.

Additional safety data needed in the context of a conditional MA

Given the relatively small safety population (214 in B11 RP2D at the CCOD of 15 March 2021; 90 of these with FL), the single-arm design and the short follow-up, additional safety data will be needed to address uncertainties such as known risks for other monoclonal antibodies targeting CD20 on B-cells and/or CD3 on T-cells, the long-term safety; median observation time of 14.3 months in the B11 RP2D cohort, safety in patients with prior CAR-T therapy and adverse events were seen more frequently (e.g. serious infections).

A confirmatory phase III study evaluating PFS is considered necessary and has recently commenced: Study GO42909: 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 (Study GO42909).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10 Conclusions on the clinical safety

Generally, the adverse events are manageable; in particular the risk of cytokine release syndrome requires careful training of hospital staff in relation to observation and management and furthermore easy access to an ICU. Risk minimisation measures including a patient card have been agreed (see Annex II and RMP).

The CHMP considers the following measures necessary to address the missing safety data (in particular long-term safety) in the context of a conditional MA:

In order to provide further evidence of safety of mosunetuzumab in follicular lymphoma, the MAH will provide results from Study GO42909, a randomised, open-label, multicentre trial evaluating mosunetuzumab in combination with lenalidomide in comparison to rituximab in combination with lenalidomide in patients with follicular lymphoma after at least one line of systemic therapy. The Applicant has commenced recruitment in study GO42909 (see Annex II).

2.7 Risk Management Plan

2.7.1 Safety concerns

Table 54. Summary of Safety Concerns

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

2.7.2 Pharmacovigilance plan

Table 55. 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				
Study GO42909: Phase III randomized, open-label, multicenter study evaluating efficacy and safety of mosunetuzumab in combination with lenalidomide (M+Len) in comparison to rituximab in combination with lenalidomide (R+Len) in patients with follicular lymphoma after at least one line of systemic therapy. *Ongoing*	This 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. 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	• Long-term safety	Launch of study: Projected interim analysis CSR: Projected final analysis CSR (based on primary endpoint of PFS): Projected updated final CSR after the survival follow up period:	Q4 2021 Q1 2026 Q2 2029

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
	• Tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of adverse events The exploratory safety objective for this study is to evaluate the safety of M+Len compared with R+Len from the patient's perspective, 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 National Cancer Institute's Patient-Reported Outcome Common Terminology Criteria for Adverse Events (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.			

CRS=cytokine release syndrome; CSR= clinical study report; FL = follicular lymphoma; LPI= last patient in; M + Len = mosunetuzumab in combination with lenalidomide; PFS= progression-free survival; PRO-CTCAE = Patient Reported Outcome Common Terminology Criteria for Adverse Events; R/R = relapsed/refractory; R + Len = rituxima in combination with lenalidomide.

2.7.3 Risk minimisation measures

Table 56. Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
Cytokine Release	**Routine risk-minimization measures:** **SmPC:**	**Routine pharmacovigilance activities beyond adverse**

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
Syndrome	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 mosunetuzumab Section 4 Possible side effects with mosunetuzumab **Additional risk-minimization measures:** ● Patient Card	**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 mosunetuzumab Section 4 Possible side effects with mosunetuzumab **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
Safety Concern	**Risk-Minimization Measure(s)**	**Pharmacovigilance Activities**
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 mosunetuzumab Section 4 Possible side effects with mosunetuzumab **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	**Routine pharmacovigilance activities beyond adverse**

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
	Additional risk-minimization measures: • None	**reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting**.** **Additional pharmacovigilance activities:** • **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

2.7.4 Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable.

2.8 Pharmacovigilance

2.8.1 Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2 Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The new EURD list entry will therefore use the {EBD} to determine the forthcoming Data Lock Points.

2.9 Product information

2.9.1 User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2 Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lunsumio (mosunetuzumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1 Therapeutic Context

3.1.1 Disease or condition

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

3.1.2 Available therapies and unmet medical need

For patients with FL who relapse after or are refractory to initial therapy, treatment decisions take into consideration efficacy and DOR of prior therapy, stage of disease and tumour burden at relapse, the presence of symptoms, and the age and comorbidities of the patient.

Patients who have received ≥2 prior therapies are associated with particularly poor prognosis, with a median PFS ranging from 1-1.1 years for third-line patients decreasing to 0.5 years for sixth-line patients with a corresponding median OS of 4.8-8.8 years and 1.9 years, respectively (Alperovich et al. 2016; Rivas-Delgado et al. 2019; Batlevi et al. 2020). For these patients there is no treatment considered standard of care, and options vary widely. Therefore, there is a high unmet need.

3.1.3 Main clinical studies

Study GO29781 was an open-label, multicenter, Phase I/Ib (Phase I/II per protocol v12) trial evaluating the safety, efficacy, and PK of escalating doses of mosunetuzumab (BTCT4465A) as a single agent and combined with atezolizumab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Interim Analysis (CCOD 27 August 2021).

Of the 152 patients in the Group B FL cohort, 90 patients in Group B11 had received the RP2D of 1/2/60/30 mg mosunetuzumab IV monotherapy as initial treatment during the dose expansion stage in this single-arm trial and are the main efficacy population corresponding to the indication sought.

3.2 Favourable effects

At the cut-off date of 27 Aug 2021, in the main efficacy cohort B11 FL RP2D the CR (by IRF) was 60.0% (95% CI: 49.1, 70.2) and for the supportive cohort B7 (FL), which received a lower dose, the CR rate 45.7% (95% CI: 30.9, 61.0), compared to 14% CR rate from historical controls for both cohorts.

The secondary endpoints support the primary endpoint: Agreement between IRF- and investigator-assessed response on whether a patient achieved a CR was high: 93.3% (83/89).

The results of the secondary endpoints in the B7 FL interim dose cohort receiving the lower dose of 1/2/13.5 mg were slightly lower than in the B11 FL cohort and are generally thought to support efficacy.

Of the 54 patients in the B11 FL RP2D cohort who achieved a CR as assessed by the IRF, 16 patients (29.6%) subsequently had disease progression by the time of the CCOD. The median DOCR was not estimable (Table 14/CSR). The K-M estimated event-free rates among complete responders at 12 months and 18 months after the first complete response were 71.4% and 63.7%, respectively. The median DOR is 22.8 months (95% CI: 9.7, NE). Among responders, the event-free rates at 12 and 18 months after the first response were 61.8% and 56.9%, respectively.

At the CCOD of 15 March 2021, data were immature in an indolent disease like FL with a median follow-up for DOR of 10.3 months with the proposed dosing regimen (1/2/60/30 mg). Therefore, updated data has been provided (CCOD of 27 Aug 2021), which confirmed the initial results.

3.3 Uncertainties and limitations about favourable effects

The sample size with the intended dosing regimen was limited, with 90 patients with r/r FL having received ≥2 prior lines of therapy.

Given the limitations associated with the uncontrolled single-arm design of the pivotal study and that the primary endpoint, CRR, is not an established surrogate endpoint in r/r FL, sufficiently mature DOR data are important.

The efficacy results with mosunetuzumab monotherapy have been contextualized through cross-trial indirect comparisons with alternative approved and unapproved therapies identified in a systematic literature review. Cross-trial comparisons are however associated with well-known limitations, mainly related to differences in study populations, especially in the r/r FL patient population, which are characterized by heterogeneity in terms of disease course, treatment history and prognosis. Contextualization of efficacy results is further hampered by the lack of an external real-world control, which would have partially overcome these limitations.

As discussed above the results from a single-arm trial are generally associated with a number of uncertainties, for this reason a conditional marketing authorisation is recommended with an appropriate specific obligation to submit the results from an ongoing phase III study (see section 4 and RMP).

3.4 Unfavourable effects

At the CCOD of 15 March 2021, the primary safety population of 214 patients is the B11 RP2D cohort with lymphoid malignancies (DLBCL, FL, MCL) of which 90 patients had follicular lymphoma.

Cytokine release syndrome (CRS) was the most commonly observed event (43.0% of patients based on Lee 2014 grading criteria and 39.3% by ASTCT 2019 grading criteria). CRS events were predominantly Grade 1 or 2 severity (36.4% by ASTCT 2019 grade), and limited primarily to Cycle 1, particularly D1 and D15. All CRS events resolved. CRS events were managed with steroids, antihistamines and paracetamol (obligatory for Cycle 1 and 2) and for some events supplied with tocilizumab (25.0% of patients in cohort B11 RP2D with CRS events by ASTCT 2019 grade), oxygen administration (21.8%), and vasopressors (6.0%), and were reversible, as evidenced by resolution of all CRS events. Twenty-two percent were graded as SAEs as they required hospitalisation.

Other common AEs (≥20% incidence by PT) in cohort B11 RP2D were neutropenia/neutrophil count decreased, fatigue, hypophosphatemia, and pyrexia. Most AEs were Grade 1 or 2 severity except for neutropenia/neutrophil count decreased. Grade 3-4 AEs were reported in 64.6% of patients in cohort B11 RP2D. The most frequent Grade 3-4 events (≥5% incidence) were cytopenias (neutropenia/neutrophil count decreased and anemia/hemoglobin decreased) and hypophosphatemia.

Neurologic AEs (NAEs) were broadly defined as all AEs reported as primary or secondary PTs in either the SOC of Nervous System Disorders or SOC of Psychiatric Disorders and were observed in 119/214 patients in cohort B11 RP2D. Serious NAEs were reported in 21 patients (5.1%). SAEs reported in more than one patient were confusional state (4 patients; one Grade 3), encephalopathy, syncope, and subdural hematoma (2 patients each; all Grade 3), and neurotoxicity and herpes zoster (2 patients each; all Grade 2.

Twenty-five patients (11.7%) in cohort B11 RP2D experienced DI-CCNAEs (Driving-Impacting Cognition or Consciousness Neurologic Adverse Events) of which 10 (4.7%) were SAEs. The median duration was 3 days, but the range was 1-259 days.

A total of 9 of 214 patients (4.2%) experienced tumour flare events following initial treatment with mosunetuzumab (see SmPC and RMP Summary of safety concerns).

Overall deaths and SAEs were reported in a higher proportion of patients who previously received CAR-T therapy (N=48 in Group B) compared with those who had not received prior CAR-T therapy (N=362), and Safety in patients with prior CAR-T therapy has been included as Missing information in the Summary of safety concerns in the RMP.

In cohort B11 RP2D 46.7% of patients experienced 174 infection adverse events many of which were related to the respiratory system. SAEs were reported in 35 patients (16.4%), with pneumonia (7 patients [3.3%]) being the most frequent (see RMP).

3.5 Uncertainties and limitations about unfavourable effects

Given the relatively small safety population (214 in B11 RP2D; 90 of these with FL), the short follow-up and known risks for other monoclonal antibodies targeting CD20 on B-cells and/or CD3 on T-cells, several uncertainties remain, such as long-term safety; median observation time of 14.3 months in the B11 RP2D cohort, Safety in patients with prior CAR-T therapy and adverse events were seen more frequently (e.g. serious infections).

Furthermore, given the uncertainties of a single-arm trial, a conditional marketing authorisation is recommended and the specific obligation a confirmatory phase III study that has recently commenced (Study GO42909 - 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) will provide missing long term safety data.

3.6 Effects Table

Table 57 Effects Table for Mosunetuzumab (data cut-off: 27 August 2021)

Effect	Short Description	Unit	Treatment: Mosunetuzumab[1]	Uncertainties/ Strength of evidence	References*
Favourable Effects (Cohort B11 FL RP2D, **n=90**)					
Primary endpoint: **CR by IRF**	Complete Remission rate by Independent Review Committee (95% CI)[2]	N (%)	54/90 (60.0%) (49.1, 70.2)	Single arm trial but high CR compared to PI3K-inhibitors.	CSR
Secondary endpoints					
ORR (by IRF)	Overall response rate (CR+PR) (95% CI)[2]	N (%)	72 (80.0%) (70.3, 87.7)		CSR
DOCR (by IRF)	Duration of CR K-M 12-month event-free proportion (95% CI)[3]	%	71.4 (57.9, 84.9)	Short follow-up	CSR

Effect	Short Description	Unit	Treatment: Mosunetuzumab[1]	Uncertainties/ Strength of evidence	References*
DOR (by IRF)	Duration of response K-M 12-month event-free proportion (95% CI)[3]	%	61.8 (50.0, 73.7)	Median follow-up for DOR of 14.9 months.	CSR
Unfavourable Effects (safety population mainly cohort B11 RP2D incl. various lymphomas, **n=214, CCOD 15 March 2021**)					
Cytokine release syndrome (CRS)[4]	Any AE SAE Discontinuation	N, % N, % N, %	84 (39.3) 44 (20.6) 2 (0.9)	Mainly grade 1-2 SAEs mainly due to hospitalisation occurring mainly on C1D1 and D15.	CSR
Neurological adverse events (NAE)[5]	Any AE SAE DI-CCNAE AE DI-CCNAE SAE	N, % N, % N, % N, %	119 (55.6) 14 (6.5) 25 (11.7) 10 (4.7)		CSR
Tumour flare	Any AE SAE	N, % N, %	9 (4.2) 4 (1.9)		CSR
Neutropenia/ neutrophil count decreased	Any AE Grade 3-4 SAE	N, % N, % N, %	59 (27.6) 52 (24.3) 2 (0.9)		CSR
Infections	Any AE SAE	N, % N, %	100 (46.7) 35 (16.4)	Four events occurred concurrently with neutropenia in B11 RP2D	CSR

Abbreviations: DI-CCNAE= driving-impacting cognition or consciousness neurologic adverse event; IRF; Independent Review Committee; K-M=Kaplan-Meier

Notes:

[1]1/2/60/30 mg IV; 1 mg Cycle1Day1, 2 mg C1D8, 60 mg C1D15, 60 mg C2D1, 30 mg D1 of C3-C8 or C3-C17 depending on disease status after C8. Three-week cycles.

[2]95% CIs calculated using the Clopper-Pearson method.

[3]95% CIs calculated using the Brookmeyer-Crowley method.

[4]By ASTCT 2019 grading criteria

[5]Neurologic AEs (NAEs) were broadly defined as all AEs reported as primary or secondary PTs in either the SOC of Nervous System Disorders or SOC of Psychiatric Disorders.

3.7 Benefit-risk assessment and discussion

3.7.1 Importance of favourable and unfavourable effects

There is an unmet need for patients with R/R FL who have received ≥2 prior therapies, particularly for patients who are R/R to different classes of agents are left with limited treatment options that may have challenging safety profiles.

Results from the single-arm trial GO029781 are encouraging with a high proportion of patients with CR. Consistent response rates were also observed for subgroups with anticipated poor prognosis. Obtaining a CR, which is the disappearance of all measurable evidence of disease, can be considered relevant for the patient and indicates clinically meaningful favourable effect. Results from secondary endpoints support the primary endpoint, in particular high ORR and durability of responses, which are likely to translate into an overall survival benefit.

Most important safety concerns are CRS, serious infections, and tumour flare. The adverse events are generally manageable and acceptable in this disease population.

Indirect comparisons provided support the contextualization of the mosunetuzumab efficacy and safety results. Further, mosunetuzumab provides a novel MoA, has a potential therapeutic advantage compared to available treatments, provides clinically meaningful ORR, CR and DOR, while having a clinically manageable safety profile.

3.7.2 Balance of benefits and risks

The benefit of mosunetuzumab monotherapy in FL patients who have received ≥2 prior systemic therapies is considered to outweigh the risks.

3.7.3 Additional considerations on the benefit-risk balance

The Applicant has provided an overview of efficacy and safety results for therapies for follicular lymphoma patients having received at least 2 prior therapies. The proportion of patients who achieved CR and the durability of responses for patients with R/R FL ≥2 prior therapies treated with mosunetuzumab compare to the results of CAR-T therapy (i.e. axicabtagene ciloleucel). Overall, these indirect comparisons support the contextualization of the mosunetuzumab efficacy and safety results and suggest that the benefits to public health of the immediate availability outweigh the risks in this patient population with high unmet need.

Based on the single-arm trial design of the study, the clinical data are not considered comprehensive.

Conditional marketing authorisation

As comprehensive data on the product are not available a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease. In addition, the product is designated as an orphan medicinal product.

The product is considered to fulfil the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data: by providing results from a phase III study within a reasonable timeframe to confirm efficacy (and safety); the Applicant has recently commenced recruitment in study GO42909.
- Unmet medical needs will be addressed: Patients who have received ≥2 prior therapies are associated with particularly poor prognosis, with a median PFS ranging from 1-1.1 years for third-line patients decreasing to 0.5 years for sixth-line patients with a corresponding median OS of 4.8-8.8 years and 1.9 years, respectively. For these patients there is no treatment considered standard of care, and options vary widely (see ESMO recommendations under Introduction).

The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required: Given the positive benefit risk profile and the poor prognosis in R/R FL patients having received at least two prior systemic therapies, the benefit to public health is considered to outweigh the risks.

Based on the single-arm trial design of the study, the clinical data are not considered comprehensive.

The following measures are necessary to address the missing efficacy data in the context of a conditional MA:

In order to provide further evidence of efficacy and safety of mosunetuzumab in follicular lymphoma, the MAH will provide Study GO42909, a randomised, open-label, multicentre trial evaluating mosunetuzumab in combination with lenalidomide in comparison to rituximab in combination with lenalidomide in patients with follicular lymphoma after at least one line of systemic therapy.

3.8 Conclusions

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

is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Lunsumio is not similar to Gazyvaro within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Lunsumio is favourable in the following indication:

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

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or

as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Lunsumio is marketed, all patients/carers who are expected to use Lunsumio have access to/are provided with the Patient Card which will inform and explain to patients the risks of cytokine release syndrome (CRS). The Patient Card also includes a warning message for healthcare professionals treating the patient that the patient is receiving Lunsumio.

The patient card shall contain the following key messages:

A description of the key signs and symptoms of CRS

A description of when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS present themselves

The prescribing physician's contact details.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to provide further evidence of efficacy and safety of mosunetuzumab in follicular lymphoma, the MAH will provide results from Study GO42909, a randomised, open-label, multicentre trial evaluating mosunetuzumab in combination with lenalidomide in comparison to rituximab in combination with lenalidomide in patients with follicular lymphoma after at least one line of systemic therapy.	Q1 2026

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that mosunetuzumab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.