18 September 2025
EMA/CHMP/289782/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lunsumio

International non-proprietary name: Mosunetuzumab

Procedure No. EMEA/H/C/005680/X/0015

Note

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

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List of abbreviations

3L FL	≥ third line treatment for follicular lymphoma grade 1-3a = R/R FL
ADA	anti-drug antibody
AESI	adverse events of special interest
AUC	area under the concentration-time curve
AUC_{0-84}	AUC over 0-84 days
BTK	Bruton's tyrosine kinase
C	cycle
CAR-T	chimeric antigen receptor modified T-cell therapy
CCOD	clinical cutoff date
CIOMS	Council for International Organizations of Medical Sciences
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CO	clinical overview
COVID-19	coronavirus disease 2019
CR	complete response
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR (report nbr. 1131060)	Clinical Study Report for the F2 cohort
CSR (report nbr. 1111637)	Clinical Study Report for the B11 cohort
C_{trough}	trough concentration
$C_{troughCYC3\_OBS}$	Cycle 3 C_{trough}
CTS	clinical trial simulation
D	day
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOCR	duration of complete response
DOR	duration of response
EBE	Empirical Bayesian Estimates
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme linked immunosorbent assay
EMA	European Medicines Agency

EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-5L	EuroQol 5 Dimension-5 Level
EZH2	enhancer of zeste homolog 2
FDA U.S.	Food and Drug Administration
Fab	fragment antigen-binding
FACT-Lym	Functional Assessment of Cancer Therapy for Lymphoma
Fc	fragment crystallizable
FL	follicular lymphoma
GCP	Good Clinical Practice
GMR	geometric mean ratio
HBV	hepatitis B virus
HCV	hepatitis C virus
HLH	hemophagocytic lymphohistiocytosis
HRQoL	health-related quality of life
ICF	informed consent form
IFN-γ	interferon-gamma
Ig	immunoglobulin
IL	interleukin
IMC	Internal Monitoring Committee
IRF	independent review facility
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIDD	Model-Informed Drug Development
MRI	magnetic resonance imaging
NAE	neurologic AE
NCI CTCAE Events	National Cancer Institute Common Terminology Criteria for Adverse
NHL	non-Hodgkin’s lymphoma

ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progression of disease
PFS	progression-free survival
PI3K	phosphoinositide 3'-kinase
PK	pharmacokinetics
PK NI	pharmacokinetic non-inferiority
PO	per oral
POD24	progression of disease within 24 months of initial FL diagnosis
popPK	population PK
PPP	Per Protocol PK (analysis population)
PR	partial response
PRO	patient-reported outcome
Q3W	every 3 weeks
R/R	relapsed or refractory
RP2D	recommended Phase II dose
SAP	Statistical Analysis Plan
SC	subcutaneous
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SCT	stem cell transplant
SD	stable disease
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration
TNF-α	tumor necrosis factor-alpha
trFL	transformed FL
ULN	upper limit of normal
USPI	United States Prescribing Information

1. Background information on the procedure

1.1. Submission of the dossier

Roche Registration GmbH submitted on 22 November 2024 extensions of the marketing authorisation.

The MAH applied for addition of a new pharmaceutical form (solution for injection) associated with two new strengths (5 mg and 45 mg) and a new route of administration (subcutaneous use).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) points (c) (d) (e) - Extensions of marketing authorisations.

Lunsumio, was designated as an orphan medicinal product EU/3/21/2517 on 12 November 2021 in the following condition: treatment of follicular lymphoma.

1.3. Information on Paediatric requirements

Pursuant to Article 8 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.

At the time of submission of the application, the PIP P/0108/2020 was not yet completed as some measures were deferred.

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 MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Protocol assistance

The MAH received Protocol assistance from the CHMP on the development for the indication from the CHMP on 25 February 2021 (EMA/SA/0000049656) and 19 May 2022 (EMA/SA/0000086359). The Protocol assistance pertained to quality and clinical aspects.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Boje Kvorning Pires Ehmsen

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Mari Thorn

The application was received by the EMA on	22 November 2024
The procedure started on	27 December 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 March 2025
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	N/A
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 March 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 April 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	21 July 2025
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	19 August 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	04 September 2025
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	18 September 2025

2. Scientific discussion

2.1. Problem statement

The MAH is seeking approval for the subcutaneous use (SC) of Lunsumio (mosunetuzumab) in the same indication as currently approved: monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (R/R FL) who have received at least two prior systemic therapies.

2.2. About the product

Mosunetuzumab is a CHO-produced humanized full-length anti-CD20/CD3 T-cell-dependent bispecific (TDB) antibody of isotype immunoglobulin G1 (IgG1), which is assembled from one anti-CD20 half-antibody and one anti-CD3 half-antibody.

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 signalling, 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 Fcγ receptors will occur and, consequently, significantly reduced Fc-mediated effector function.

2.3. Type of Application and aspects on development

This application is an extension application to add a new pharmaceutical form (solution for injection) associated with two new strengths (5 mg and 45 mg) and a new route of administration (subcutaneous use) to the existing IV dosing regimen for mosunetuzumab indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (R/R FL) who have received at least two prior systemic therapies.

The application is based on the part of study GO29781 that evaluated the PK non-inferiority of mosunetuzumab SC monotherapy treatment (cohort F2 expansion R/R FL) compared to the approved mosunetuzumab IV monotherapy treatment (cohort B11 expansion R/R FL) based on the co-primary PK endpoints; $C_{troughCYC3\_OBS}$ (observed) and $AUC_{0\text{-}84}$ (model-predicted). This is also supported by the supportive study CO41942, and Model-Informed Drug Development.

The MAH sought advice from SAWP (EMA/SA/0000049656 and EMA/SA/000008635). Points related to efficacy and safety were:

- Proposed sample size of 90 patients considered appropriate to provide a similar level of evidence as for the reference IV dosing regimen; the use of the same eligibility criteria and same study sites was also supported.
- Proposed efficacy endpoints were considered acceptable with limitations linked to the lack of formal hypothesis testing. However, the timing of efficacy analysis should be revised to a minimum follow-up time of 12 months for all subjects to allow for more precise estimations of median DOR and DOCR and a more adequate assessment of efficacy non-inferiority. Longer follow-up will also allow for a better comparison of potential differences in long-term toxicities.
- In general, the assessment of safety non-inferiority was considered appropriate, also in terms of the proposed sample size, with additional recommendations to discuss the overall safety profile compared to the target population and the dose escalation cohorts at the time of submission.
- A minimum follow-up time of 12 months for all subjects was recommended to ensure data is sufficiently mature to allow adequate assessment of consistency in response rates as well as in response durability and to allow assessment of long-term safety profile.

2.4. Quality aspects

2.4.1. Introduction

Mosunetuzumab, the active substance contained in Lunsumio, is a full length, humanised anti-CD20/CD3 immunoglobulin (Ig) G1 isotype that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Lunsumio is currently authorised as concentrate for solution for infusion in glass vial, with strengths of 1 mg and 30 mg.

The scope of this line extension is to register:

- New strengths: 5 mg and 45 mg;

- A new pharmaceutical form: solution for injection;

- And a new route of administration: subcutaneous (SC) use.

The 2 new presentations subject to this line extension are glass vials. Each vial contains:

- For the 5 mg strength: 5 mg of mosunetuzumab in 0.5 mL at a concentration of 10mg/mL;

- For the 45 mg strength: 45 mg of mosunetuzumab in 1 mL at a concentration of 45 mg/mL

The SC formulation contains L-histidine, L-methionine, acetic acid, sucrose, polysorbate 20 and water for injections.

2.4.2. Active Substance

2.4.2.1. General Information

Mosunetuzumab is a recombinant humanised T-cell-engaging bispecific monoclonal antibody of the IgG1 subclass, produced in CHO cells and directed against CD3 and CD20. It is produced using knobs-into-holes technology. The anti-CD20 heavy chain carries the "knob" substitution (T366W), while the anti-CD3 heavy chain carries the "hole" substitution (T366S, L368A, and Y407V). The "knob" and "hole" substitutions in the third constant domain of the heavy chain (CH3) drive the formation of a heterodimer of one anti-CD20 half-antibody and one anti-CD3 half-antibody during the assembly step. The mosunetuzumab antibody contains the N297G amino acid substitution in the Fc region, which results in a non-glycosylated heavy chain that has minimal binding to Fc- receptors and, consequently, significantly reduced Fc-mediated effector function.

2.4.2.2. Manufacture, process controls and characterisation

The active substance process supplying the mosunetuzumab SC finished product is the approved process that also supplies the commercial mosunetuzumab IV finished product. All sites involved in manufacture and control of mosunetuzumab SC operate in accordance with EU GMP.

The manufacture of mosunetuzumab active substance for the SC version of the finished product is the same as the one currently approved for the mosunetuzumab IV version. The active substance process v1.0 has been validated (PPQ) to consistently manufacture mosunetuzumab with the expected product quality, as approved for the IV-version of the finished product. All aspects of the active substance manufacturing process and control strategy are the same for mosunetuzumab SC and mosunetuzumab IV. All previously performed studies, including the process parameter criticality and the acceptance ranges established for the approved mosunetuzumab v1.0 active substance process are directly applicable to the SC active substance.

Due to differences in route of administration and patient dosing strategy, mosunetuzumab SC-specific risk assessments were performed to demonstrate the applicability of the completed mosunetuzumab studies. No new critical process parameters (CPPs) were identified impacting the critical quality attributes (CQAs), and there was no impact to process parameter criticality, acceptance ranges and pool hold times as a result of the reassessments.

Manufacturing process development

The developmental history for the mosunetuzumab v1.0 active substance supplying mosunetuzumab SC is the same as the v1.0-derived mosunetuzumab IV**.**

To address comparability during clinical development the v1.0 active substance has been compared to pivotal clinical SC material and pivotal clinical/commercial IV material.

The comparability exercise included both quantitative and qualitative assessments of defined quality attributes. In addition, the comparability studies included a stress stability study, where changes observed under stress conditions were quantitatively and qualitatively assessed. Overall, the comparability exercise is found comprehensive and the generated data support comparability between v1.0 active substance batches compared to pivotal clinical SC and pivotal clinical/commercial active substance batches.

Characterisation

The physicochemical, biological, and immunochemical characterisation of mosunetuzumab for mosunetuzumab IV are the basis for mosunetuzumab SC, as mosunetuzumab SC has the same active ingredient, molecular properties, product-related variants, target indications, and modes of action as mosunetuzumab IV. The characterisation data has previously been reviewed during the marketing authorisation application (MAA) procedure for the IV version of mosunetuzumab.

All mosunetuzumab quality attribute classifications were reassessed to incorporate considerations specific to the SC route of administration. Two new CQAs were identified and a new high pharmacokinetic (PK) impact classification attribute was also identified. These attributes are either sufficiently controlled or classified as product variants present at levels too low to be robustly quantified, and therefore do not require specific testing.

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

The release and end-of-shelf-life specification, the analytical procedures used to test the active substance for release and/or stability, the validation of those analytical procedures and the justification of specification for v1.0 active substance used to manufacture mosunetuzumab SC are the same as for v1.0-derived mosunetuzumab IV. The container closure system for the v1.0 active substance process is the same between mosunetuzumab SC and mosunetuzumab IV and comply with Ph. Eur.

2.4.2.3. Stability

As the v1.0 active substance is stored and assigned the same shelf-life period regardless of whether it is used to produce mosunetuzumab IV or mosunetuzumab SC, all of the previously performed stability studies are directly applicable.

2.4.3. Finished Medicinal Product

2 . 4 . 3 . 1 . Description of the product and Pharmaceutical Development

Description of the product

The finished product is provided as a sterile, colourless to slightly brownish-yellow, preservative-free solution for SC injection in single use vials. The proposed to be marketed dosage form of mosunetuzumab will be 5 mg/vial and 45 mg/vial. Other ingredients are commonly used compendial (Ph. Eur.) excipients:

L-histidine, glacial acetic acid, sucrose, L-methionine, polysorbate 20 and water for injections. No novel excipients or excipients of human or animal origin are used. The finished product does not contain any overages.

Pharmaceutical Development

Mosunetuzumab SC is developed to shorten the administration time compared with the mosunetuzumab IV finished product and to improve the ease of use and patient convenience. The Applicant presented the quality target product profile (QTPP) that guided the pharmaceutical development for the line extension, including dosage form and strength required to introduce mosunetuzumab SC considering safety and efficacy of the new SC administration method.

The finished product formulation is identical to the active substance formulation with the exception of the concentration of mosunetuzumab in the finished product for SC administration. The currently approved IV formulation is identical to the SC formulation, except for the concentration of mosunetuzumab which is 1 mg/mL in mosunetuzumab IV. The mosunetuzumab IV and SC finished products are derived from the same mosunetuzumab v1.0 active substance.

Compatibility of active substance with the excipients is considered demonstrated based on formulation development studies and the long-term stability of the active substance and finished product in the formulation.

Pharmaceutical development history

A summary of the mosunetuzumab SC formulation development has been provided. Changes in mosunetuzumab concentration were made between the mosunetuzumab IV and SC formulations to support subcutaneous administration in the clinical dose range.

Formulation development studies

In order to enable SC administration of the intended clinical/commercial doses accurately and conveniently using standard needles and syringes without the use of a diluent, appropriate protein concentrations were selected for the mosunetuzumab SC formulations. Except for the protein concentration, the mosunetuzumab SC formulations are identical to the formulation approved for IV administration of mosunetuzumab, and therefore the formulation development is based on data generated during development of the IV formulation. The data generated for IV formulation during a preliminary formulation development study, representative stability and comparative stress stability studies and vial agitation studies, has been evaluated with focus on the increased protein concentration in the SC formulations as compared to IV. No formulation robustness studies were performed; however the formulation robustness study performed during development of mosunetuzumab IV covered the target formulation and the full manufacturing range for all formulation parameters for mosunetuzumab SC.

Furthermore, extractable volume studies were used to establish the minimum fill volume for both SC vial configurations.

Overall, the formulation development is found adequate and it is acceptable that the studies performed during development of the IV formulation is leveraged for the SC formulation, since excipient concentrations remain unchanged from IV.

Extended Characterisation

Extended characterisation induced measurement of subvisible particles at release and during stability testing. The data are consistent across configurations and batches, and do not exhibit a trend with storage time and temperature. Further the data are consistent with data for visible particles.

Manufacturing Process Development

Three different versions of the manufacturing process have been employed during development of mosunetuzumab finished product SC. The changes in the finished product manufacturing process are primarily intended to accommodate the proposed commercial doses and configurations established based on the pharmaceutical development. Furthermore, the changes are performed to accommodate the changes of the active substance site and finished product site during development. New sites are introduced in order to support commercial production of mosunetuzumab finished product SC in the manufacturing network. The comparability exercise includes the assessment of comparability between SC pivotal clinical finished product and to-be-commercial finished product.

2.4.3.2. Manufacture of the product and process controls

The name, address and responsibility of each site involved in the manufacturing and testing have been provided. All site involved in manufacture and control of the finished product operate in accordance with EU GMP

The manufacturing process of mosunetuzumab SC finished product is a standard process which includes thawing of active substance, sterile filtration, filling and capping, visual inspection and cold storage.

The process hold times are validated and the cumulative hold time has been evaluated using small-scale contact materials compatibility data. Furthermore, same hold-times are approved and have been implemented for routine commercial manufacturing for mosunetuzumab IV finished product and are therefore acceptable.

There are no intermediates in the process.

The overall control strategy of the quality during manufacturing process is considered adequate and the manufacturing process has been described in detail. Parameters used in all steps of the process are considered validated based on the process design studies and process performance qualifications studies.

Process validation consisted of PPQ, process design studies, environmental monitoring, shipping qualification, media fills and hold time studies.

Data from the seven most recent media fills at the manufacturing site where mosunetuzumab finished product will be produced including the mosunetuzumab SC equipment specific runs is presented. All media fills were performed with satisfactory outcome and they cover the hold times proposed by the Applicant.

Process validation included nine PPQ runs covering the commercial batch size ranges as according to the guideline EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1 *Guideline on process validation for finished products - information and data to be provided in regulatory submissions.*

Based on the data from the nine PPQ runs it can be concluded that manufacturing process is validated to ensure consistent and acceptable product quality for all quality attributes across the range of batch sizes. Moreover, it is shown that the in-process controls are suitable to monitor the manufacturing process. While operational events occurred that impacted the release of two runs, the events and remediation actions implemented do not impact the validity of the data generated from the impacted runs for PPQ.

Process design studies were performed to demonstrate process robustness and support validation of the finished product manufacturing process. Relevant CQAs for the finished product process were identified for assessment in process design studies. Process design studies were performed to evaluate the impact of CPPs on relevant CQAs. CPPs were further classified as CPPs or non-CPPs based on the observed impact on relevant CQAs and process performance in the process design studies, and acceptable ranges were defined. The ranges and values selected for the process parameters are acceptable to support commercial manufacturing.

Process design studies and the associated data have been submitted.

The mosunetuzumab SC finished product manufacturing process is highly similar to mosunetuzumab IV on the same Filling Line 2, and is derived from the same mosunetuzumab v1.0 active substance. Therefore, prior knowledge gained and process design studies completed for mosunetuzumab IV have been leveraged during mosunetuzumab SC finished product process development where appropriate.

Overall, the manufacturing process control strategy and process validation are considered adequate to deliver finished product of consistent quality.

2.4.3.3. Product specification, analytical procedures, batch analysis

The release and shelf-life specifications for mosunetuzumab finished product include control of identity, purity and impurities, potency and other general tests.

Justification of specifications

Differences in release and stability specifications between mosunetuzumab IV and SC finished product, along with the rationale of change has been provided. These justifications are considered valid.

Justification of the ACs for the finished product for each quality attribute is described in detail, and a combination of information supports the chosen ACs. Clinical experience is used for establishing ACs. Both mosunetuzumab SC and IV clinical experience are relevant for assessing the impact of individual CQAs on safety, immunogenicity, and PK. The Applicant is arguing that clinical experience from mosunetuzumab IV is applicable to mosunetuzumab SC because the same active ingredient as well as similar product variants, process-related impurities, post-translational modifications, and formulation components are present in both finished products. Therefore, setting the shelf-life ACs for mosunetuzumab SC finished product at the same ranges as those for mosunetuzumab IV (where applicable) ensures similar patient safety and product efficacy throughout shelf life. Additionally, product-specific knowledge, manufacturing experience, formulation development studies, current guidelines, the potential impact of manufacturing, shipping, and storage on an attribute is factored into the development of the ACs to ensure that the final AC will be met. Working backward from finished product shelf-life ACs, the potential storage- and process-related effects were considered for each preceding AC, in order to ensure that the final AC will be met.

Overall, the approach used to set the ACs for the finished product is accepted. The ACs set for the qualitative and quantitative attributes have been sufficiently justified and can be accepted.

Analytical procedures and reference standards

Compendial and non-compendial methods are used for release of finished product. Sufficient method descriptions have been provided. For compendial methods, references to the European Pharmacopeia monographs are provided. Majority of the analytical methods used for mosunetuzumab SC continue to be the same as the ones for mosunetuzumab IV, since the active substance is the same in these presentations.

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 and the methods are considered suitable for their intended use.

For the non-compendial analytical methods, adequate description of the methods has been provided, including the purpose of the method, procedure, equipment and materials used, preparation of samples, representative result, and system suitability criteria.

The same primary and secondary reference standards for mosunetuzumab IV are used for mosunetuzumab for subcutaneous administration (mosunetuzumab SC) which is acceptable.

Overall, the method transfer strategy and validation strategy is considered acceptable.

Batch analysis

Mosunetuzumab finished product batches have been produced at two manufacturing sites for clinical, PPQ and technical use.

Information about the mosunetuzumab SC batches manufacturing date, formulation, manufacturing site, batch size, active substance process and active substance source batch number as well as use of the finished product batches are included.

All batch analysis results meet the specifications that were in effect at the time of testing and release for each batch, with the exception of one batch, due to operational events. In addition, with the aforementioned exception, all available release data from the finished product batches produced during the PPQ campaign meet the commercial release specification acceptance criteria.

The batch data presented complies with the finished product specification and demonstrates high manufacturing consistency for the clinical and PPQ batches.

Characterisation of impurities

The assessment for elemental impurities was conducted according to ICH Q3D and showed that there are no concerns related to elemental impurities in the finished product produced at the site of commercial manufacture.

A risk assessment regarding the potential presence of nitrosamines was provided. The assessment for Lunsumio (mosunetuzumab) SC 5mg/45mg has not identified any risk for the contamination of the finished product during manufacture, shelf life or the in-use period due to the presence of nitrosating agents.

Container closure system

The container closure system for finished product consists of a 2 mL Type 1 glass vial, which is stoppered with a fluororesin-laminated rubber stopper and sealed with an aluminium flip-off seal. The primary packaging components, vial and stopper, are of compendial quality (Ph. Eur). The primary packaging components used for the 5 mg/vial and 45 mg/vial finished product are the same.

The information provided on the container closure system selected for storage of finished product is adequate and the system is considered suitable for the purpose.

2.4.3.4. Stability of the product

The proposed shelf-life of the mosunetuzumab SC finished product (5 mg/vial and 45 mg/vial) is 36 months at 2°C-8°C, protected from light. This is overall, supported by the data presented.

In general, the protocols for the stability studies provided in P.8.1 are in accordance with current guidelines.

The Applicant commits to place one batch in long-term stability per year with yearly time points and testing according to the shelf-life specification. The stability protocol provided in P.8.2 for yearly batch testing is acceptable.

Primary stability studies

To support the proposed shelf-life the Applicant submitted results of primary stability studies conducted on clinical batches and commercial PPQ batches at long-term storage conditions as well as accelerated conditions of 23°C-27°C/60% RH ±5%.

Clinical batches are included in the primary stability study. Since comparability has been established between clinical and PPQ finished product, the data submitted for the clinical batches can be considered primary stability batches. The accelerated study for the clinical batches has been concluded and long-term stability data is available for up to 36 months.

For the PPQ batches manufactured at the commercial site, three batches of each strength are included in the primary stability studies. The accelerated stability study has been concluded at 6 months. Six months of stability data has been submitted for both long term conditions.

Data from the clinical batches of both strengths, up to 36 months, met the shelf-life acceptance criteria at long-term conditions. The results show minor changes in purity tests, little or no change was observed in all other attributes tested. The submitted data for the PPQ batches manufactured at the commercial site met the shelf-life acceptance criteria and little or no change observed for all attributes tested.

6 months data from the accelerated stability study for clinical batches of both strengths show minor changes in purity tests. Little or no change was observed in all other attributes tested. The submitted data for the PPQ batches manufactured at the commercial site confirm that the results are consistent with other primary batches over the same time period.

Supportive stability studies

Supportive stability data from one clinical batch and one representative technical batch of each strength, manufactured using the same v1.0 active substance at the commercial finished product manufacturing site and stored in the same commercial container closure system and storage conditions, has been provided. Supportive stability studies have been conducted at long term, accelerated and stressed storage conditions.

The submitted stability data from the technical batches and the clinical batch at long-term conditions show that results meet shelf-life specification acceptance criteria. Further, stability trends are consistent with the primary stability batches at both long term and accelerated conditions. This supports the proposed shelf-life at recommended storage conditions.

Data from the stress stability studies confirm the degradation pathways observed at long-term and accelerated conditions. It is agreed that the changes in attributes observed over the study duration support potential excursions/time out of recommended storage conditions that may occur during manufacturing, shipping, and handling of finished product.

Additional stability studies

Furthermore, ICH Q1B photostability study have been conducted on a PPQ batch. Changes observed during the study indicate that mosunetuzumab finished product is light-sensitive after exposure to ICH-light conditions.

A temperature cycling (incl. freeze/thaw) study have been conducted with a PPQ batch. After completion of the temperature cycling events, the vials were placed at 5°C, corresponding to long-term conditions. Results to date have met the commercial stability acceptance criteria.

Overall, the proposed shelf-life of 36 months at 2°C-8°C protected from light is acceptable.

Once transferred from the vial to the syringe, Lunsumio solution for injection should be injected immediately because the medicine does not contain any antimicrobial-preservative. 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 2-8°C, unless preparation has taken place in controlled and validated aseptic conditions.

If Lunsumio solution for injection is transferred from the vial to the syringe in a controlled and validated aseptic conditions, the medicine in the capped syringe can be stored in the refrigerator at 2°C to 8°C for up to 28 days protected from light and/or at 9°C to 30°C for up to 24 hours at ambient light.

2.4.3.5. Adventitious agents

Adventitious agents safety evaluation provided for mosunetuzumab IV presentation is considered applicable for the SC presentation, given the fact that the active substance manufacturing process has not been altered. The Applicant notes that studies that evaluated impacts to host cell DNA levels, raw material clearance, virus clearance for the mosunetuzumab active substance process are directly applicable, as they were performed with criteria using doses higher than the maximum dose of 45 mg for subcutaneous administration. This is considered acceptable.

TSE-BSE Certificate specifically for mosunetuzumab SC has been provided. It includes information that the simethicone emulsion utilised in the working cell bank contains a surfactant derived from bovine tallow, which is believed to not be infectious. The raw material is compliant with the guidance for minimising the risk of transfer of TSE (EMA/410/01). This information is considered adequate.

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Mosunetuzumab SC is developed as a line extension product of the commercial mosunetuzumab for intravenous administration (mosunetuzumab IV). The dossier presented in support of the line is of good quality. Manufacturing process, process validation, specifications, justification of specifications are based also on prior knowledge gained from the mosunetuzumab IV, which is acknowledged.

The mosunetuzumab active substance process that supplies the mosunetuzumab for SC administration finished product is the same active substance process that also supplies the mosunetuzumab for IV administration finished product. Therefore, all aspects of the active substance manufacturing process and control strategy are the same for mosunetuzumab SC and the approved mosunetuzumab IV.

Comparability during clinical development is addressed and support the applicability of the finished product version applied during clinical development.

The finished product is provided as a sterile, colourless to slightly brownish-yellow, preservative-free solution for injection in single use vials. The proposed to be marketed dosage form of mosunetuzumab will be 5 mg/vial and 45 mg/vial.

Lunsumio SC finished product manufacturing process is standard and the manufacturing process description is adequate and acceptable. The submitted manufacturing process validation data document that finished product manufacturing process for Lunsumio SC (5 mg/vial and 45 mg/vial)

can be maintained within established parameters and consistently produces finished product meeting in-process acceptance criteria and release specifications.

The finished product specifications are acceptable.

A finished product shelf life of 36 months at 2-8°C, protected from light, is proposed. This is supported by the data presented.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Lunsumio is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

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

2.4.6. Recommendation(s) for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

Mosunetuzumab (Lunsumio) has already been authorised for the treatment of adult patients with relapsed or refractory follicular lymphoma following IV administration. In the current extension application, the MAH seeks to extend the use of mosunetuzumab to SC administration using the same posology as that authorised for IV administration. No new non-clinical studies have been submitted to support the current line extension application as two SC toxicology studies were already submitted with the initial MAA; a single-dose study (Study 14-1246) as well as a 4-week repeat-dose toxicity studies (Study 13-1689) in cynomolgus monkeys following IV and SC administration. These studies are assessed below under the Toxicology Section. No further assessment of other toxicological endpoints is included in the current report as this is already covered in the assessment report for the initial MAA.

2.5.2. Pharmacology

No new pharmacology studies were submitted to support the current extension MAA, which is acceptable. The pharmacology of mosunetuzumab has already been assessed in the initial authorisation of Lunsumio (IV administration) and no new pharmacology studies are required to support extension to SC administration.

2.5.3. Pharmacokinetics

No new pharmacokinetic studies were submitted to support the current extension MAA, which is acceptable. The pharmacokinetic properties of mosunetuzumab have already been assessed in the initial authorisation of Lunsumio (IV administration) and no new pharmacokinetic studies are required to support extension to SC administration.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Single-dose toxicity of mosunetuzumab was assessed in cynomolgus monkeys at doses of 0.01, 0.1 and 1 mg/kg IV or 1 mg/kg IV or SC with an observation period of 7 weeks (GLP-study, 14-1246). No test-article-related deaths were observed.

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 faeces 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

The repeat-dose toxicity of mosunetuzumab was established in the assessment of the original MAA for IV administration in 26 weeks study in cynomolgus monkeys by slow bolus injection (½-1 min) or infusion (1h). 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.

SC administration following repeated dosing in cynomolgus monkeys 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.

No changes were observed following either IV or SC administration that indicated local intolerance.

2.5.5. Ecotoxicity/environmental risk assessment

The active substance is a monoclonal antibody which will be broken down by proteolysis, the use of which will not alter the concentration or distribution of the substance in the environment. An extension of application to SC administration is not considered to pose an increased risk to the environment, and

the conclusion from the original assessment is maintained, that mosunetuzumab is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

The MAH submitted a line extension for administration of Lunsumio via SC administration. No new non-clinical studies were conducted, which is acceptable, as the pharmacological and pharmacokinetic properties were assessed in the initial MAA for IV administration. Additionally, the two SC toxicology studies were already part of the initial MAA submission. The two toxicology studies, one single dose and one repeated dose study in cynolmolgus monkeys, compare the pharmacokinetics and toxicity of the two formulations in a head-to-head study at the same dose level. Based on these studies, it appears that the SC formulation of Lunsumio at 1 mg/kg/day results in significantly reduced exposure (72-80% reduction in Cmax) and a delayed Tmax by 24 h with a corresponding reduction in cytokine levels and T-cell activation while still maintaining depletion of B-cells. 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 (males only) in the non-GLP repeat-dose study, the level of inter-animal variation and the overall mild degree of findings across dose groups.

As seen in the assessment of the initial MAA for IV administration, it was decided to derive LOAELs on basis of the findings in the non-clinical 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 potential clinical risk. Using the method for performing interspecies correlation as outlined in the original assessment report (calculation of $AUC_{0\text{-}24h}$ normalized exposure), 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, are adequately described in the SmPC and have been discussed regarding human relevance in the RMP.

2.5.7. Conclusion on the non-clinical aspects

The SC formulation did not reveal new toxicities compared to the IV formulation. On the contrary, non-clinical data could suggest a less severe toxicity profile of the SC formulation while maintaining a pharmacological response, though this is based on a limited number of male animals in a non-GLP study.

The active substance 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 clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH 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)	Population	Study Design	No of Patients	Dose, Route, and Regimen	CCOD	Median observation time	Tumor Assessment		
							Frequency	Criteria	Assessor
Study GO29781 (Phase I/II)	Patients with R/R B-cell NHL or CLL[a]	Multicenter, open-label, dose-escalation and dose-expansion study; single arm: mosunetuzumab (IV and SC) as a single agent and mosunetuzumab in combination with atezolizumab	B11 exp R/R FL cohort: 90 F2 exp R/R FL cohort: 94	B11 exp R/R FL cohort: Mosunetuzumab IV monotherapy; 1 mg on C1D1, 2 mg on C1D8, 60 mg on C1D15 and C2D1, and 30 mg on Day 1 of subsequent Q3W cycles (1/2/60/30 mg; approved dose). F2 exp R/R FL cohort: Mosunetuzumab SC monotherapy; 5 mg on C1D1, 45 mg on C1D8 and C1D15, and 45 mg on Day 1 of subsequent Q3W cycles (5/45/45 mg; proposed registrational dose). [b, c]	B11 exp R/R FL cohort: 27 August 2021 F2 exp R/R FL cohort: 1 February 2024	See Table 4	At screening and during treatment: At screening; at 3 months and 6 months following first treatment, then every 3 months.[d] In the follow-up period: Every 3 months in the first 18 months following enrollment in the study; at 24 months (timed from Cycle 1 Day 1), and then every 12 months thereafter (timed from the last tumor assessment)	Cheson et al. 2007	INV and IRF [e]

Study No (Phase)	Population	Study Design	No of Patients	Dose, Route, and Regimen	CCOD	Median observation time	Tumor Assessment		
							Frequency	Criteria	Assessor
Study CO41942 (Phase Ib/II)	Patients with R/R FL	Multicenter, open-label study, mosunetuzumab in combination with lenalidomide (Mosun + Len). Non-randomized stage: Dose escalation and expansion, two arms (IV in R/R FL and SC in 1L FL) Randomized stage: two-arm (IV vs SC in R/R FL)	IV Mosun+Len: 40 SC Mosun+Len: 80	Randomized stage:[f] IV Mosun+Len: Cycle 1 step-up IV mosunetuzumab; 1 mg on C1D1, 2 mg on C1D8, 30 mg on C1D15, and then 30 mg on Day 1 of the subsequent Q4W cycles (1/2/30 mg dosing regimen). Given in combination with lenalidomide PO; 20 mg on Days 1 to 21 of Cycles 2 to 12. SC Mosun+Len: Cycle 1 step-up SC mosunetuzumab; 5 mg on C1D1, 45 mg on C1D8, 45 mg C1D15, and 45 mg on Day 1 of subsequent Q4W cycles (5/45/45 mg dosing regimen). Given in combination with lenalidomide PO, 20 mg on Days 1 to 21 of Cycles 2 to 12.	1 February 2024	See Table 9.	At screening and during treatment: At screening; then at the end of Cycles 3, 6, 9, and 12. In the follow-up period: Every 6 months	Lugano 2014 (Cheson et al. 2014)	INV and IRC [g, h]

1L = first-line; C1D1 = Cycle 1 Day 1; C1D8 = Cycle 1 Day 8; C1D15 = Cycle 1 Day 15; CCOD = clinical cutoff date; CLL = chronic lymphocytic leukemia; CSR = Clinical Study Report; FL = follicular lymphoma; INV = investigator; IRC = Independent Review Committee; IRF = Independent Review Facility; IV = intravenous; Mosun + Len = mosunetuzumab in combination with lenalidomide; NHL = non-Hodgkin's lymphoma; PO = per os; Q3W = every 3 weeks; Q4W = every 4 weeks; R/R = relapsed / refractory; SC = subcutaneous.

[a] No patients with chronic lymphocytic leukemia (CLL) have been enrolled to date.

[b] The dose and treatment schedule of the other treatment regimens in Groups B and F, as well as Groups A, D, and E, in Study GO29781 are described in protocol v17 (Report 1131060, Appendix 16.1.1, p. 130 [Section 4.3].

[c] For patients who achieved a CR and experienced relapsed disease following completion of initial single-agent mosunetuzumab treatment, single-agent mosunetuzumab re-treatment was allowed to be initiated. Re-treatment followed the same dosing regimen described above.

[d] This included an optional early assessment at 6 weeks, at the investigator's discretion.

[e] Following protocol v4, all radiographic assessments were to be collected by an Independent Review Committee (IRF) for independent review. This change was implemented prior to the enrollment of the first patient into both B11 exp R/R FL cohort and F2 exp R/R FL cohort.

[f] The dose and treatment schedule in the non-randomized stage in Study CO41942 is described in protocol v7 (Report 1131167, Appendix 16.1.1, p. 58 [Section 4.3.2]).

[g] While Study GO29781 utilizes the term 'IRF', Study CO41942 utilizes the term 'Independent Review Committee (IRC)'. Both terms refer to equivalent independent entities responsible for reviewing and assessing study data.

[h] IRC assessment of response data in Study CO41942 is being performed retrospectively. Hence, IRC-assessed results will be submitted separately.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

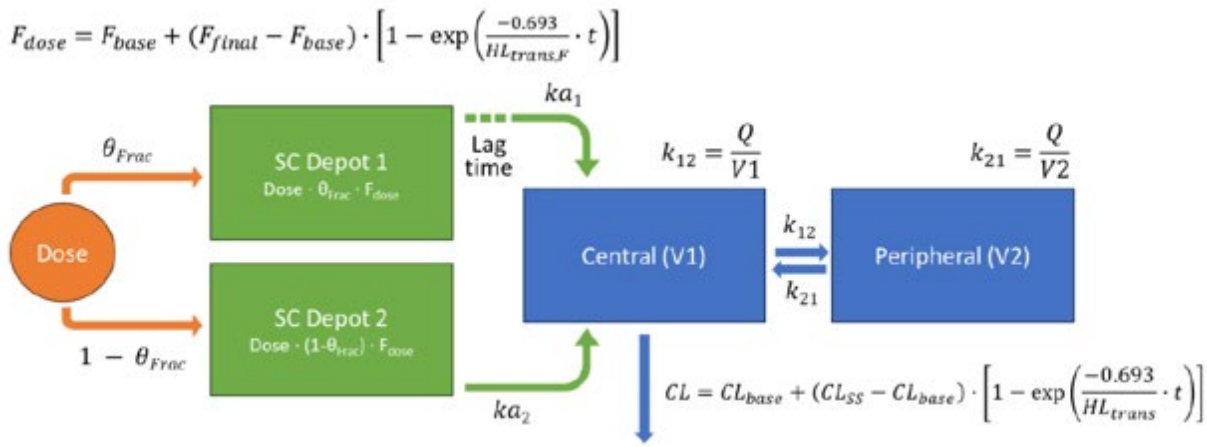
Bioanalytical methods

Mosunetuzumab in human serum samples from the SC part of the pivotal study GO29781 with the same validated ELISA method as utilized for the previously conducted mosunetuzumab IV arm of the study. Immunogenicity of mosunetuzumab in study GO29781 was also investigated with the same validated ELISA method as previously applied.

Evaluation and qualification of models

A previously-developed 2-compartment Pop PK model with time varying clearance based on IV data from cohorts A and B of Study GO29781 was extended to support SC dosing. The model structure is shown below. A total of 228 patients were treated with SC in Cohorts D and F, across a dose range of 1.6 mg to 90 mg. The final SC dataset included 3280 observations. Significant covariate effects included came from the previous IV model.

Figure 1 Schematic view of the base model for PK in patients with IV and SC dosing



The final model parameters for IV and SC dosing, are displayed along with distributions of IV and SC patients pc-VPC's for the SC dosed participants of Study GO29781.

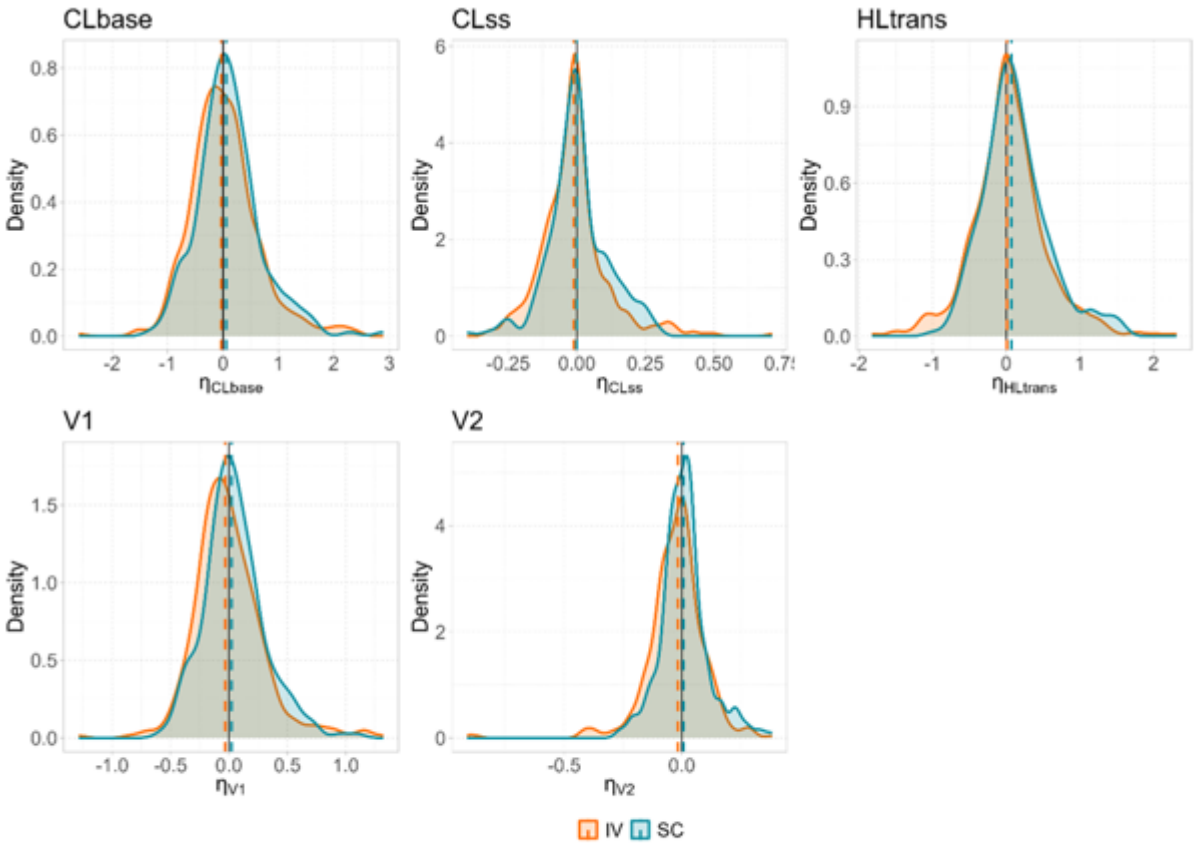
Table 2 Parameter estimates for the base model for PK in patients with IV and SC dosing

Parameter	Estimate	% RSE	95% CI[1]	Shrinkage[2]
Baseline clearance (CL_{base}, L/d)	1.08	*Fixed*	*Fixed*	-
Central volume of distribution (V1, L)	5.49	*Fixed*	*Fixed*	-
Absorption rate constant 1 (ka_1, /d)	0.181	5.73	0.161-0.202	-
Absorption rate constant 2 (ka_2, /d)	0.436	11.3	0.340-0.533	-
Stready-state clearance (CL_{SS}, L/d)	0.584	*Fixed*	*Fixed*	-
Half-life for clearance transition (HL_{trans}, d)	16.3	*Fixed*	*Fixed*	-
Peripheral volume of distribution (V2, L)	6.17	*Fixed*	*Fixed*	-
Intercompartmental clearance (Q, L/d)	1.46	*Fixed*	*Fixed*	-
Lag time ($Tlag_1$, d)	0.559	3.85	0.517-0.601	-
Baseline bioavailability (logit scale, F_{base})[3]	1.42*	12.6	1.07-1.77	-
Final bioavailability (logit scale, F_{final})[4]	4.10**	7.29	3.52-4.69	-
Half-life for bioavailability transition (HL_{transF}, d)	5.37	14.5	3.84-6.89	-
Fraction of dose allocated to depot 1 (θ_{Frac})	0.814	1.68	0.788-0.841	-
Baseline weight on CL	0.549	*Fixed*	*Fixed*	-
Baseline weight on V1	0.433	*Fixed*	*Fixed*	-
Baseline weight on V2	0.737	*Fixed*	*Fixed*	-
Baseline albumin on CL_{base}	-1.51	*Fixed*	*Fixed*	-
Baseline aCD20 on CL_{base}[5]	-0.573	*Fixed*	*Fixed*	-
Baseline SPD on CL_{SS}	0.0935	*Fixed*	*Fixed*	-
Sex on CL_{SS}	-0.128	*Fixed*	*Fixed*	-
Baseline albumin on V1	-0.481	*Fixed*	*Fixed*	-
Sex on V1	-0.126	*Fixed*	*Fixed*	-
IIV on CL_{base} ($\omega^2_{CL_{base}}$, variance)	0.426	*Fixed*	*Fixed*	9.90
CL_{base}-V1 covariance ($\omega_{CL_{base},V1}$)	0.18	*Fixed*	*Fixed*	-
IIV on V1 (ω^2_{V1}, variance)	0.0981	*Fixed*	*Fixed*	16.8
IIV on ka_1 ($\omega^2_{ka_1}$, variance)	0.275	13.1	0.204-0.346	22.2
IIV on ka_2 ($\omega^2_{ka_2}$, variance)	1.04	12.8	0.775-1.30	20.8
IIV on CL_{ss} ($\omega^2_{CL_{ss}}$, variance)	0.0343	*Fixed*	*Fixed*	40.5
CL_{ss}-HL_{trans} covariance ($\omega_{CL_{ss},HL_{trans}}$)	-0.0892	*Fixed*	*Fixed*	-
IIV on HL_{trans} ($\omega^2_{HL_{trans}}$, variance)	0.739	*Fixed*	*Fixed*	47.2
IIV on V2 (ω^2_{V2}, variance)	0.0621	*Fixed*	*Fixed*	59.6
IIV on F (ω^2_F, variance, additive on the logit scale)	2.61	25.4	1.31-3.90	32.3
Residual error (additive on the natural log scale)	0.262	0.820	0.258-0.266	12.5

Highlighted rows indicate estimated parameters.
aCD20 = anti-CD20 drug concentration, CI = confidence interval, IIV = interindividual variability, RSE = relative standard error, SPD = sum of products of diameters.
[1] CI were calculated asymptotically from NONMEM-provided standard errors.
[2] NONMEM-provided SD-shrinkage.
[3] Normal scale: 80.5%.
[4] Normal scale: 98.4%.
[5] aCD20 drug is a composite concentration of baseline rituximab and obinutuzumab concentrations.

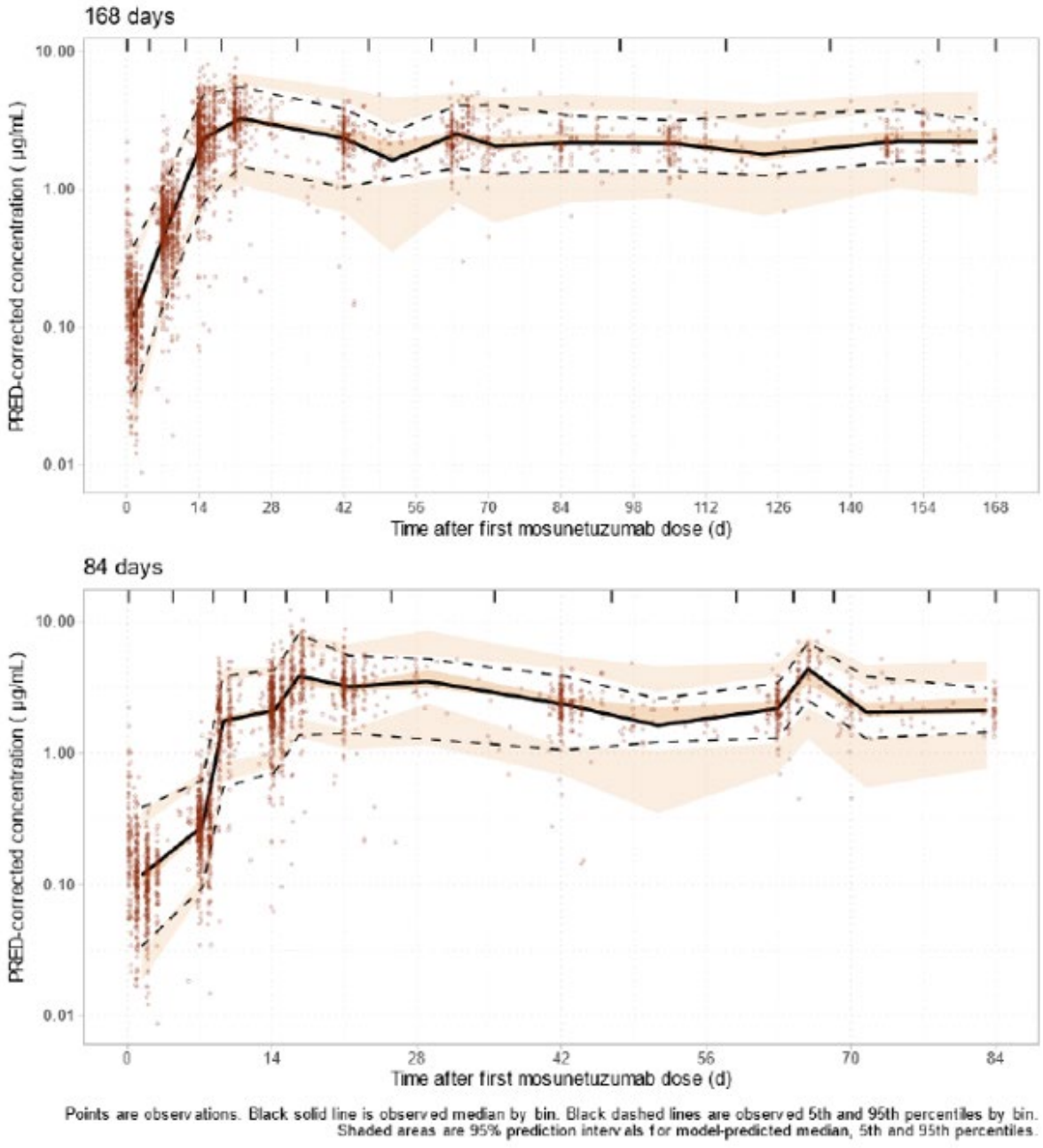
(run 086)

Figure 2 Comparison of eta distribution between IV and SC patients (study GO29781)



CL_{ss}=steady-state clearance; CL_{base}=baseline clearance; HL_{ktrans}=half-life for clearance transition;
IV = intravenous; SC = subcutaneous; V_1= central volume of distribution; V_2= peripheral volume of distribution.

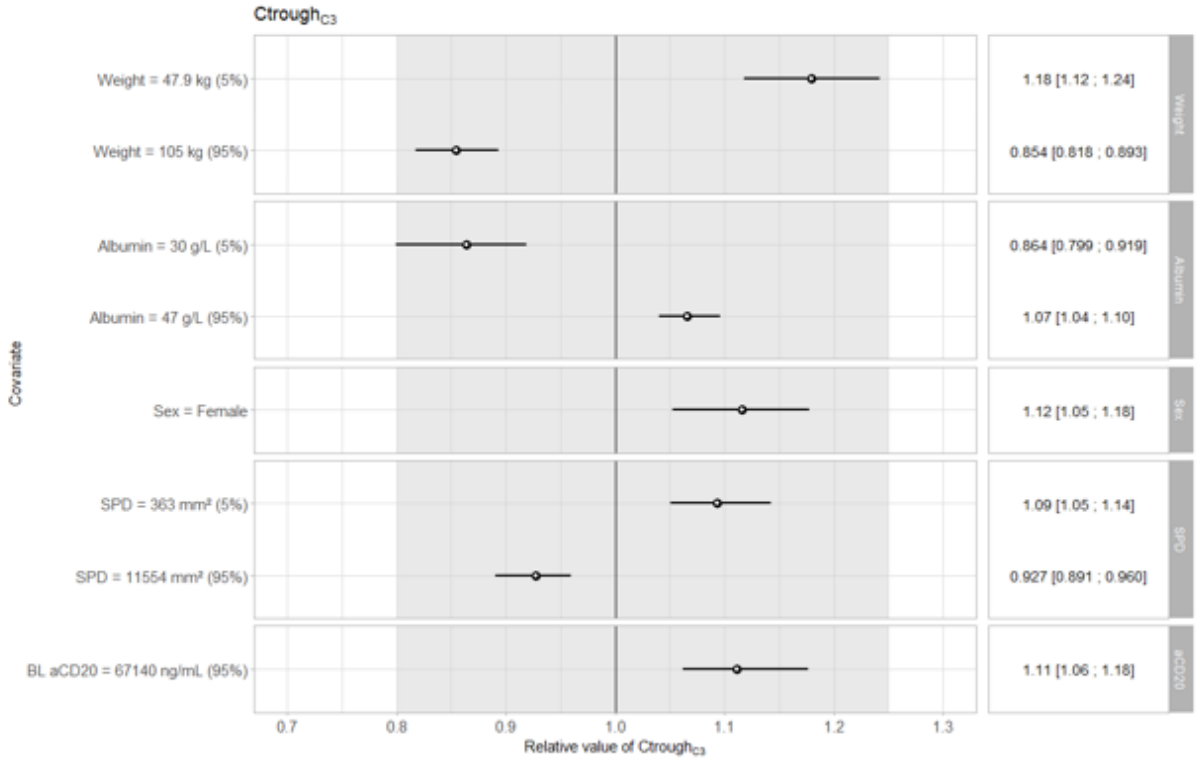
Figure 3 Prediction-corrected visual predictive checks for the base model for mosunetuzumab PK – SC patients in Study GO29781 over 168 days and 84 days



IV and SC data from supportive Study CO41942 in which mosunetuzumab was combined with lenalidomide, was used as external validation of the final SC/IV model. In addition, a non-parametric bootstrap (n=400) using resampling with replacement was performed on all non-fixed parameters in the final model.

Forest plots of the Pop PK model included covariate effects on mosunetuzumab exposure (AUC0-84, AUCss and Ctrough Cycle 3) were presented for the SC-population.

Figure 4 Forest plot for Ctrough Cycle 3



$C_{troughC3}$ = trough (pre-dose) concentration at Cycle 3.
Points are point estimates; horizontal lines are 95% confidence intervals; vertical line represents the reference case (baseline body weight=73.6 kg; baseline albumin=40 g/L; baseline SPD=2478 mm2; baseline aCD20=500 ng/mL; male); and the shaded area represents the zone of clinical interest. BL=baseline; aCD20=anti-CD20 concentration (maximal value of rituximab or obinutuzumab).

The final SC/IV population PK model for mosunetuzumab was used to simulate 1000 clinical trials comparing exposure endpoints of interest. The clinical trial simulations were performed with 90 IV and 70 SC virtual patients re-sampled from the PK population (Cohorts A, B, D and F of Study GO29781) by unique patient ID with replacement. Non-inferiority of the SC regimen relative to the IV regimen (=lower limit of the 90% CI of the GMR was ≥ 0.8) was established in 100% of the simulated trials, for both Ctrough Cycle 3 and AUC0-84.

Absorption

Study GO29781

The MAA for SC administration of mosunetuzumab is primarily supported by the clinical evidence generated in the pivotal study GO29781. Study GO29781 is an open-label, multi-center, Phase I/II study in R/R NHL and CLL patients. The study was composed of 4 study groups, two IV groups (Group A, fixed IV dosing and Group B, Step-up IV dosing) and two SC groups (Group D, fixed SC dosing and Group F, step-up SC dosing). Each group was composed of several cohorts, see clinical efficacy section for further study details. Clinical data of the two IV-groups (A and B) has provided support for approval of mosunetuzumab IV. The primary objective of the SC part of GO29871 was to demonstrate PK non-inferiority (PKNI) of SC administered mosunetuzumab vs IV administered mosunetuzumab by comparing SC cohort F2 Expansion (Exp) FL with IV cohort B11 Exp FL. The primary PK endpoints were observed Ctrough, CYC3 and Pop-PK model predicted AUC0-84 days. PKNI was demonstrated if the lower bound of the 90% CI of the GMRs was above 0.8.

Dosing:

SC F2 Exp FL cohort: Cycle 1 (step-up dosing, 21 day cycle): 5 mg D1, 45 mg D8 and 45 mg D15. Cycle 2-12: 45 mg D1.

Previously conducted IV cohort B11 Exp FL: Cycle 1 (step-up dosing, 21 day cycle): 1 mg D1, 2 mg D8 and 60 mg D15. Cycle 2-12: 30 mg D1.

PK sampling in group F: Cycle 1 day 1 (4 h, 24 h, 48h), Cycle day 8 and 15 (4 h, 24 h, 48 h, 72 h (only if patient is hospitalized or if clinically indicated)), Cycle 2, 3, 5, 6, and 8 (predose), Cycle 4 (predose and day 4), cycle 12, 16 (predose, if administered)

Exclusion criteria observed Ctrough, CYC3: 1) Patient with missing Cycle 3 Ctrough PK sample or outside of the sampling window (0-4 hours prior to the Cycle 4 Day 1 Dose) 2) Patient with a dose modification that deviates from the planned dose by >20% during either Cycles 2 or 3 3) Patient with any dose delay > 7 days during either Cycles 2 or 3, or with a total delay of > 7 days across both Cycles 2 and 3.

Exclusion criteria model predicted AUC0-84 days: Patient had less than three PK samples of the planned PK time points in Cycle 1 and one PK time point from 2 separate cycles of observed PK data (5 total PK samples).

PK results

The SC and IV cohort in study GO29781 was compared, see time-concentration profile and comparison of the PK parameters during the step-up dosing in Cycle 1.

Figure 5 Mean (SD) Mosunetuzumab Concentration-Time Profiles following IV or SC Administration in Study GO29781 (PK-Evaluable Patients, N=92 for SC and N=90 for IV), Day 1 – Day 106

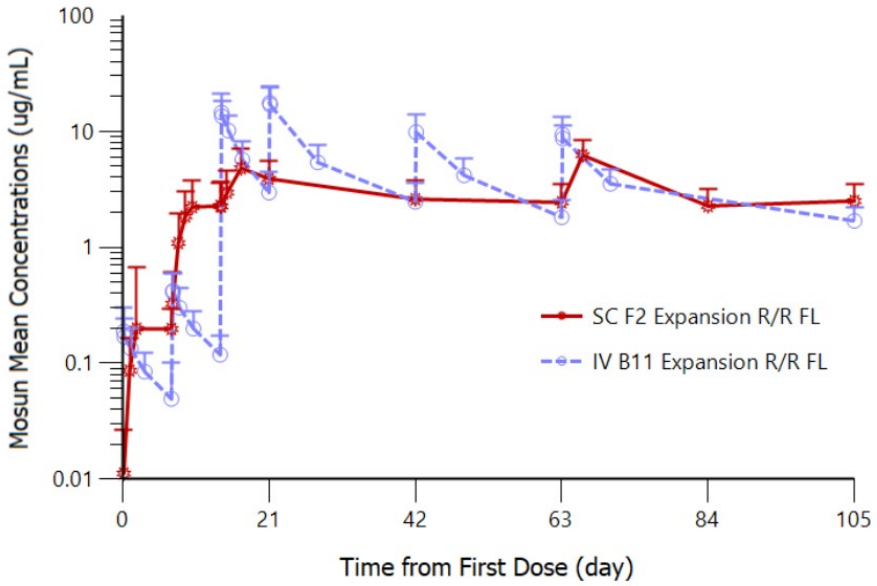


Table 3 Comparison of the Mosunetuzumab Exposure Parameters of SC versus IV During the Step-Up Dosing in Cycle 1, i.e., AUC, Cmax, and Ctrough for Dose 1 (Days 1-8), Dose 2 (Days 8-15) and Dose 3 (Days 15-22) (PPP Population)

PK parameters		***F2 exp R/R FL (SC)***		***B11 exp R/R FL (IV)***		***GMR (90%CI)***
		N	***Mean (CV%)***	***N***	***Mean (CV%)***	
Dose 1 (Day 1-Day 8)	***AUC (day µg/mL)***	68	1.1 (53.6%)	90	0.6 (37.3%)	1.69 (1.43-2.00)
	C_{max} (µg/mL)	68	0.2 (50.2%)	90	0.2 (36.1%)	0.86 (0.74-1.00)
	C_{trough} (µg/mL)	68	0.2 (48.7%)	90	0.0 (48.3%)	4.40 (3.55-5.45)
Dose 2 (Day 8-Day 15)	***AUC (day µg/mL)***	68	13.0 (47.6%)	90	1.4 (36.7%)	8.62 (7.36-10.10)
	C_{max} (µg/mL)	68	2.3 (45.5%)	90	0.5 (36.8.3%)	4.75 (4.11-5.49)
	C_{trough} (µg/mL)	68	0.1 (44.6%)	90	2.1 (44.5%)	18.29 (15.01-22.28)
Dose 3 (Day 15-Day 22)	***AUC (day µg/mL)***	68	25.8 (44.3%)	90	36.8 (31.8%)	0.66 (0.57-0.76)
	C_{max} (µg/mL)	68	4.1 (43.4%)	90	12.6 (35.9%)	0.31 (0.27-0.36)
	C_{trough} (µg/mL)	68	3.7 (43.1%)	90	3.0 (38.0%)	1.27 (1.07-1.51)

Please note that Day 1 refers to the first day of mosunetuzumab administration.

PKNI analysis

In the PKNI analysis, the PK-endpoint of SC cohort F2 Exp FL (5/45/45 mg, n=68) were retrospectively compared to the B11 Exp FL (IV, 1/2/60/30 mg, n=90), see table 4 and table 5. The analysis of secondary endpoints is shown in table 6.

Table 4 Summary of Mosunetuzumab CtroughCYC3_OBS Serum Concentration (µg/mL) in R/R FL Patients with ≥ 2 Prior Therapy in Study GO29781

	B11 Exp FL 1/2/60/30 mg (N = 90)	F2 Exp FL 5/45/45 mg (N = 68)
n	61	48
Mean (SD)	1.8 (0.6)	2.6 (1.1)
CV % Mean	34.3	41.8
Geometric Mean	1.7	2.4
CV % Geometric Mean	45.6	52.3
Median	1.8	2.5

Range	0.2-3.8		0.3-6.2
GMR [1]		1.39	
90% CI of the GMR		1.20-1.61	

[1] ratio of test treatment group (F2 Exp FL SC Patients) to reference treatment group (B11 Exp FL IV Patients).

Table 5 Summary of Mosunetuzumab Cumulative AUC over 0-84 days (day• µg/mL) in R/R FL Patients with ≥ 2 Prior Therapy in Study GO29781

	B11 Exp FL 1.0/2.0/60.0 mg w/30.0 mg on C3+ (N = 90)	***F2 Exp FL 5.0/45.0/45.0 mg (N = 68)***
n	90	68
Mean (SD)	274.2 (95.3)	286.9 (111.1)
CV % Mean	34.8	38.7
Geometric Mean	248.3	262.2
CV % Geometric Mean	57.8	50.1
Median	279.5	281.6
Range	23.9-484.1	44.8-698.6
GMR [1]		1.06
90% CI of the GMR		0.92-1.21

[1] ratio of test treatment group (F2 Exp FL SC Patients) to reference treatment group (B11 Exp FL IV Patients).

Table 6 Summary of Secondary Endpoints for Serum Mosunetuzumab PK Exposure Metrics in Per Protocol PK Analysis Populations in R/R FL Patients with ≥ 2 Prior Therapy in Study GO29781

		Model Predicted			Observed
Treatment Arm (dose)		**C2 C_{trough} (μg/mL)**	**C3 C_{trough} (μg/mL)**	**Steady state AUC (day • μg/mL)**	**C2 C_{trough} (μg/mL)**
B11 exp R/R FL (1/2/60/30 mg IV; N = 90)	N	90	90	90	55
	Mean	2.58	1.84	60.9	2.54
	CV%	42.3	40.7	33.1	39.0
	Geometric Mean	2.07	1.53	56.0	2.30
F2 exp R/R FL (5/45/45 mg SC; N = 68)	n	68	68	68	41
	Mean	2.85	2.60	77.6	2.89
	CV%	44.9	40.1	33.9	42.4
	Geometric Mean	2.50	2.37	73.0	2.55

Note that for F2 Exp R/R FL, only 68 patients received the v0.4 drug substance

Study CO41942

Subcutaneous administration of mosunetuzumab was also investigated in the supportive study CO41942. This is a Phase Ib/II, open-label, multicenter study. In the randomized open-label stage the PK-NI of mosunetuzumab SC vs mosunetuzumab IV was evaluated in addition to a comparison of the safety, tolerability, and efficacy. A mosunetuzumab SC cohort (N=80) and a mosunetuzumab IV cohort (N=40) in patients with R/R FL was included. In both cohorts, from Cycle 2 and beyond, 20 mg PO lenalidomide was co-administered. The primary PK endpoints were observed Ctrough,CYC4 and Pop-PK model predicted AUCC1-C3. PK-NI was demonstrated if the lower bound of the 90% CI of the GMRs was above 0.8.

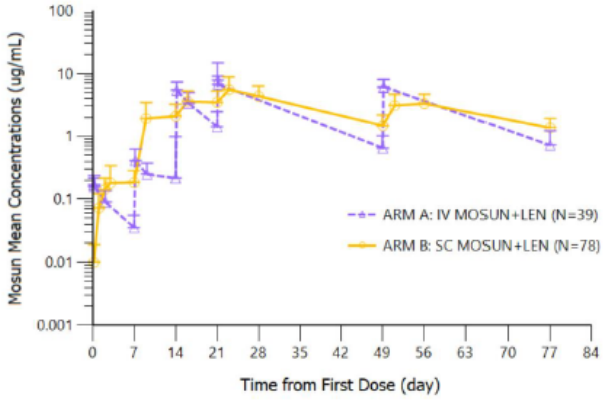
Dosing

SC cohort (Arm B): Cycle 1 (step-up dosing, 21 day cycle): 5 mg D1, 45 mg D8 and D15. Cycle 2-12 (28 day cycle): 45 mg D1.

IV cohort (Arm A): Cycle 1 (step-up dosing, 21 day cycle): 1 mg D1, 2 mg D8 and 30 mg D15. 28 day Cycle 2-12: 30 mg D1.

PK-results

Figure 6 Mean (SD) Mosunetuzumab Concentration-Time Profiles following three cycles of IV or SC Administration in Study GO29781 (PK-Evaluable Patients)



IV=intravenous; LLOQ=lower limit of quantification; Mosun=mosunetuzumab; Mosun+Len=mosunetuzumab in combination with lenalidomide; PK=pharmacokinetic; SC=subcutaneous.

Table 7 Co-Primary Endpoints for PK Non-Inferiority in Per Protocol PK Analysis Population for R/R FL Patients with ≥ 1 Prior Therapy in Study CO41942

	IV Mosun (1/2/30 mg Q4W) + Len	***SC Mosun (5/45/45 mg Q4W) + Len***
AUC_{C1-3} (day•µg/mL)		
N	39	78
Mean (SD)	117.7 (38.8)	205.8 (69.0)
CV % Mean	32.9	33.5
Geometric Mean	109.7	192.9
CV % Geometric Mean	43.8	39.4
Median	122.9	199.2
Range	28.3–213.8	62.9–341.2
GMR	1.76	
90% CI of the GMR	1.55–2.00	
$C_{trough, C4}$ (µg/mL)		
N	23	52
Mean (SD)	1.0 (0.5)	2.0 (1.3)
CV % Mean	51.1	65.0
Geometric Mean	0.9	1.8
CV % Geometric Mean	53.8	54.9
Median	0.9	1.6
Range	0.4–2.6	0.8–7.9
GMR	1.91	

90% CI of the GMR	1.54–2.36

Bioequivalence

Mosunetuzumab drug substance from two process versions were administered SC in the GO29781 study. Comparable mean PK-profile was observed with the two drug substances and drug substance was not identified as a significant covariate in Pop-PK.

Bioavailability

The bioavailability after SC administration of mosunetuzumab was estimated from the Pop-PK model derived AUCss (cycle 4) from the SC cohort F2 and IV Cohort B11 to be 0.90 (95% CI 0.83-0.98). In the Pop-PK model bioavailability was described as time-dependent.

Distribution

Distribution parameters are as previously described for mosunetuzumab IV. The mean (CV%) volume of distribution of mosunetuzumab IV and SC was 5.49 L (31%).

Elimination

Clearance parameters of mosunetuzumab SC are as previously described for mosunetuzumab IV. The geometric mean (CV%) clearance for both mosunetuzumab IV and SC at baseline and at steady state are 1.08 L/day (63%) and 0.584 L/day (18%), respectively.

Terminal beta half-lives for the SC population were derived using individual empirical Bayes estimates. The geom. mean (geom.%) terminal t1/2 at steady state after SC administration, 16.8 days (16.6%) is slightly longer than the t1/2 after IV administration, 16.1 days. Baseline t1/2 was 9.3 days, see Pop-PK model.

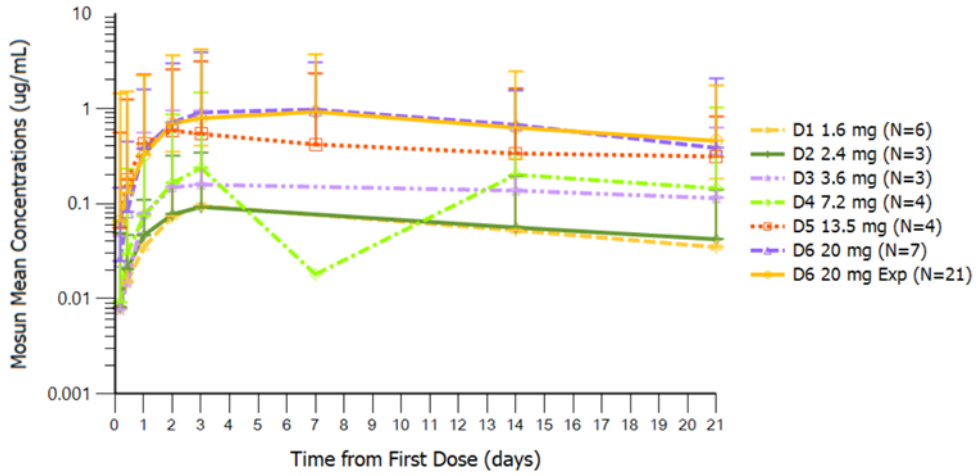
Metabolism

Metabolism (biotransformation) of mosunetuzumab SC is as previously described for mosunetuzumab IV. Mosunetuzumab is a monoclonal antibody which undergoes general proteolytic catabolism.

Dose proportionality and time dependencies

Dose-proportionality was investigated after a single dose mosunetuzumab SC, group D in study GO29781. NCA derived AUC0-21days and Cmax increased over the dose range 1.6 mg to 20 mg and tmax was 4-7 days. Furthermore, using individual Pop-PK Bayesian estimated AUCss it was demonstrated using the power method that AUCss increases in a dose-proportional manner from 1.6 mg to 45 mg mosunetuzumab SC.

Figure 7 Cycle 1 Mean (± SD) Mosunetuzumab Concentration-Time Profiles Following Administration as Fixed Dose SC Monotherapy in Dose Escalation and Expansion Cohorts in Group D in Study GO29781 (PK-Evaluable Patients)



PK after multiple-dosing of mosunetuzumab SC was investigated in study GO29781, dose expansion cohort F2. Steady-state was reached after 3-4 cycles. ADA incidence was very low so there was therefore no effect of ADA's on PK.

Intra- and inter-individual variability

The inter-individual variability of AUCss after mosunetuzumab SC administration, was determined from Pop-PK estimated individual AUCss values, to 34.5% (moderate). SC inter-individual variability was slightly lower than IV variability. Intra-individual variability was not determined.

Special populations

No clinical studies were conducted in special populations. The PK of mosunetuzumab in special populations has been investigated by Pop-PK covariate analysis.

Based on the mosunetuzumab IV/SC population PK assessment, no clinically meaningful PK covariates were identified that warrant dose adjustment of mosunetuzumab SC. This includes intrinsic factors (e.g., baseline age, sex, baseline weight, race, hepatic and renal impairment, or NHL histology) and extrinsic factors (e.g., baseline anti-CD20 drug concentration, drug substance version, or site of administration i.e. thigh, arm and abdomen).

Impaired renal function

Renal impairment (RI) was not identified as a significant covariate in the Pop-PK model. RI was categorized using estimated creatine clearance with the Cockcroft-Gault method. The effect of RI on mosunetuzumab SC exposure was evaluated by Pop-PK and by analysis of observed Ctrough in patients in the F2 RP2D cohort, including patients with normal renal function (n=54), mild RI (n=58) and moderate RI (N=23). Mosunetuzumab SC exposure was not impacted by mild and moderate RI. Mosunetuzumab SC has not been investigated in patients with severe RI or in end stage RI including dialysis.

Impaired hepatic function

Hepatic impairment (HI) was not identified as a significant covariate in the Pop-PK model. HI was classified according to the NCI classification system for organ dysfunction. The effect of HI on mosunetuzumab SC exposure was evaluated by Pop-PK and by analysis of observed Ctrough. The effect of renal impairment was assessed in patients in the F2 RP2D cohort, including patients with

normal hepatic function (n=116), mild HI (n=21). Mosunetuzumab SC exposure parameters were not impacted by mild HI. Mosunetuzumab SC has not been investigated in patients with moderate and severe HI.

Gender

Gender was a significant covariate in the Pop-PK model, resulting in 13% lower clearance in female vs male. The effect of gender on mosunetuzumab SC exposure was evaluated by Pop-PK in addition to analysis of observed Ctrough and assessed in the F2 RP2D cohort, including 56 females and 82 males. The mean exposure was shown to be slightly higher of mosunetuzumab SC i.e. 16% for AUC0-84hr, 20% for AUCss and 14% for observed Ctrough. The higher exposure in females is considered of no clinical relevance.

Ethnic factors

In the mosunetuzumab IV/SC Pop-PK model, the effect of race was assessed as a covariate on SC specific parameters and was not found to be significant. The effect of race on mosunetuzumab SC exposure was assessed in the F2 RP2D cohort, including 111 Whites, 3 Black/African Americans and 20 Asians. The mean exposure in Asians was slightly higher than in Whites i.e. 23% for AUC0-84days, 15% for AUCss and 33% for observed Ctrough,CYC3. The higher exposure in Asians is considered of no clinical relevance, as discussed in the original IV application.

Weight

Baseline weight (BW) was not identified as a covariate for the SC absorption part of the Pop-PK model, whereas in the IV part, BW significantly impacted clearance and volume. The previous analysis for mosunetuzumab IV (EMA/CHMP/63179/2022) showed that BW extremes did not have a clinically relevant impact on mosunetuzumab exposure.

Elderly

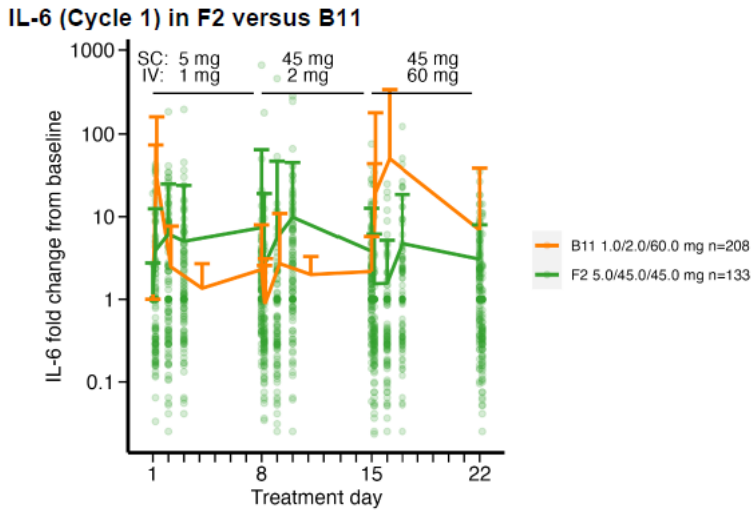
The effect of age on individual mosunetuzumab SC exposure (Pop-PK AUC estimates and observed Ctrough values) was evaluated for the F2 RP2D cohort. Baseline age range was 24 – 84 years. There was no obvious trend of mosunetuzumab SC exposure (AUC0-84, AUCss and observed-Ctrough,CYC3) vs age.

Pharmacokinetic interaction studies

CYP3A perpetrator

Mosunetuzumab causes release of the pro-inflammatory cytokines IL6 and IFN-gamma, which may suppress activity of CYP3A enzymes, resulting in increased exposure of drug metabolized by CYP3A. For mosunetuzumab IV, on the basis of the dosing period with a maximum IL-6 increase, a limited DDI was predicted for the sensitive CYP3A substrate, midazolam (C1D15, AUCR=1.37). As the IL-6 release was lower for mosunetuzumab SC in the C1D15 dosing period, it was anticipated that the CYP3A DDI would be similar or lower for mosunetuzumab SC compared to mosunetuzumab IV.

Figure 8 Arithmetic mean (± SD) in Fold Change from Baseline for IL-6 vs. Nominal Time in the RP2D Cohorts for Subcutaneous Administration (F2 cohort) and Intravenous Administration (B11 Cohort) in GO29781



Special populations

Table 8 Age ranges studied in the elderly population

	Age 65-74 yr (Older subjects number /total number)	**Age 75-84 yr (Older subjects number /total number)**	**Age 85+ yr (Older subjects number /total number)**
GO29781 **(Cohort F2)**	53/138* (38.4%)	18/138* (13.0%)	0/138* (0%)
CO41942 **Arm A: IV** **Arm B: SC**	8/39 (20.5%) 22/78 (28.2%)	1/39 (2.6%) 4/78 (5.1%)	0/39 (0%) 2/78 (2.6%)

2.6.2.2. Pharmacodynamics

Mechanism of action

Mosunetuzumab (also known as RO7030816 and BTCT4465A) is a full-length, fully humanized immunoglobulin (Ig) G1 anti-CD20/CD3 T-cell–dependent bispecific (TDB) antibody targeting both CD3 (on the surface of T cells) and CD20 (on the surface of B cells). The mechanism of action (MOA) of mosunetuzumab involves recruitment of effector T-cells via CD3 to engage with target CD20-expressing B cells, leading to T-cell activation and T-cell mediated B-cell cytolysis in a target- and dose-dependent manner. The mechanism of action was assessed in the initial MAA.

Primary and Secondary pharmacology

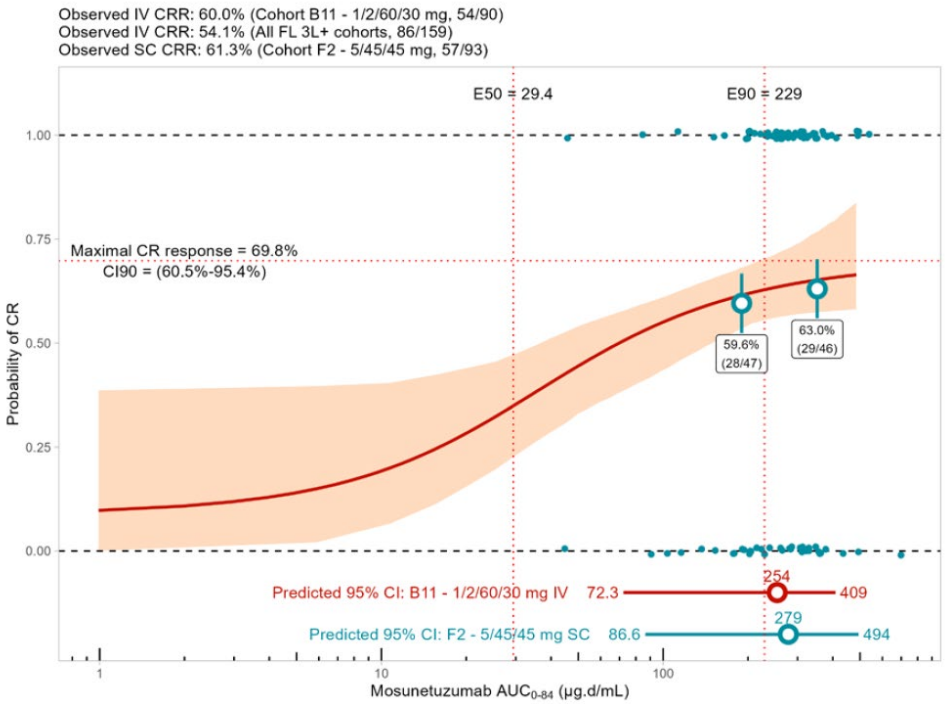
Primary and secondary pharmacology aligns with the already known effects of mosunetuzumab, although the SC use with less issues related to CRS for secondary pharmacology.

The ER analysis for efficacy was assessed using the SC R/R FL patients with ≥2 prior therapies population and available PK data (i.e., F2 exp R/R FL cohort with PK exposure; N = 93) from Study GO29781.

Median-separated bins of $AUC_{0\text{-}84}$ for the SC F2 exp R/R FL cohort patients remain on the plateau of the IV ER efficacy curves for CRR and ORR and were thus comparable between the SC and IV efficacy populations. In KM plots for PFS, the median separated bins of SC AUC_{ss} were slightly separated but the CI's overlapping. For SC $RO_{0\text{-}42}$, the median separated bins were clearly separated with non-overlapping 95% CIs, indicating lower RO in the first 1.5 months results in lower PFS over 24 months.

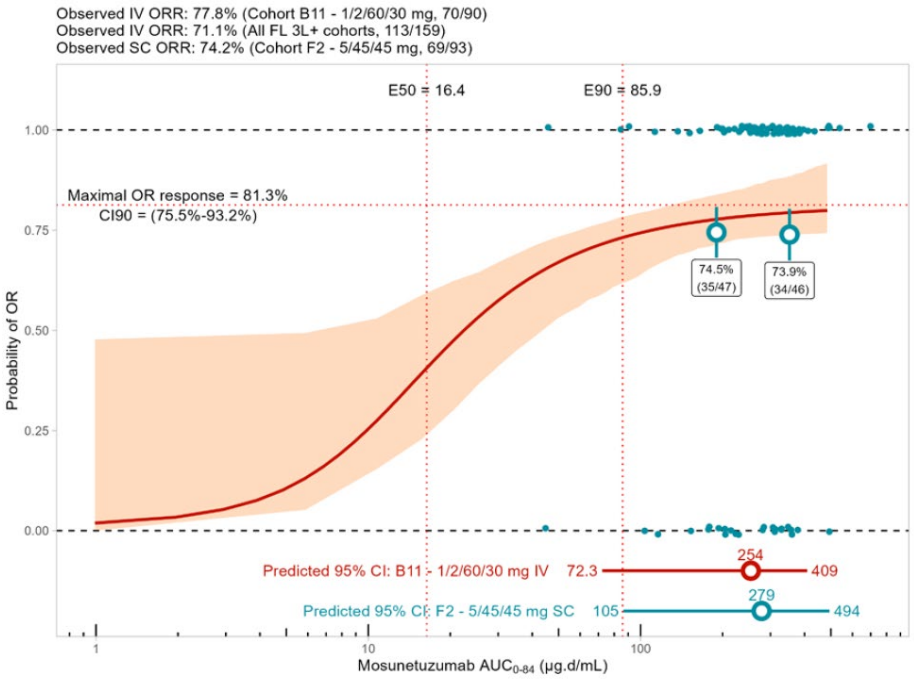
There were no clear differences between IV and SC treatment with regards to DOCR and DOR; however, the SC KM plot for DOR indicate that exposure (low/high $AUC_{0\text{-}84}$) do impact DOR. Change in tumour burden over time was similar between the IV and SC treatment.

Figure 9 Observed and predicted relationships between CR and AUC0-84 for IV and SC ER Efficacy populations in study GO29781



CI=confidence interval; CI90=90% confidence interval; CR=complete response; E50=exposure at 50% of maximal response; E90=exposure at 90% of maximal response; IV=intravenous; SC=subcutaneous. Filled points are individual exposures and response assessments (0=no event, 1=event); solid line represents the IV ER curve; shaded area represents the model-estimated 90% CI. Percentages indicate observed SC response rate (%; (x/y=x responders out of y patients) within each exposure bin. Open blue circles are the observed probability of SC patients having a clinical response by bin; error bars are the SE [sqrt(P*(1-P)/N)] at each exposure bin. Bins are median-separated groups. Horizontal lines at the bottom represent predicted AUC distributions (median with 95% CI) for IV and SC cohorts of interest; predictions are based on the population PK model EBEs.

Figure 10 Observed and predicted relationships between OR and AUC0-84 for IV and SC ER Efficacy populations in study GO29781



CI=confidence interval; CI90=90% confidence interval; OR=objective response; E50=exposure at 50% of maximal response; E90=exposure at 90% of maximal response; IV=intravenous; SC=subcutaneous. Filled points are individual exposures and response assessments (0=no event, 1=event); solid line represents the IV ER curve; shaded area represents the model-estimated 90% CI. Percentages indicate observed SC response rate (%; (x/y=x responders out of y patients) within each exposure bin. Open blue circles are the observed probability of SC patients having a clinical response by bin; error bars are the SE [sqrt(P*(1-P)/N)] at each exposure bin. Bins are median-separated groups. Horizontal lines at the bottom represent predicted AUC distributions (median with 95% CI) for IV and SC cohorts of interest; predictions are based on the population PK model EBEs.

Figure 11 Investigator – assessed PFS for the SC ER Efficacy population stratified by median separated bins of mosunetuzumab AUCss and ROavg$_{0-42}$

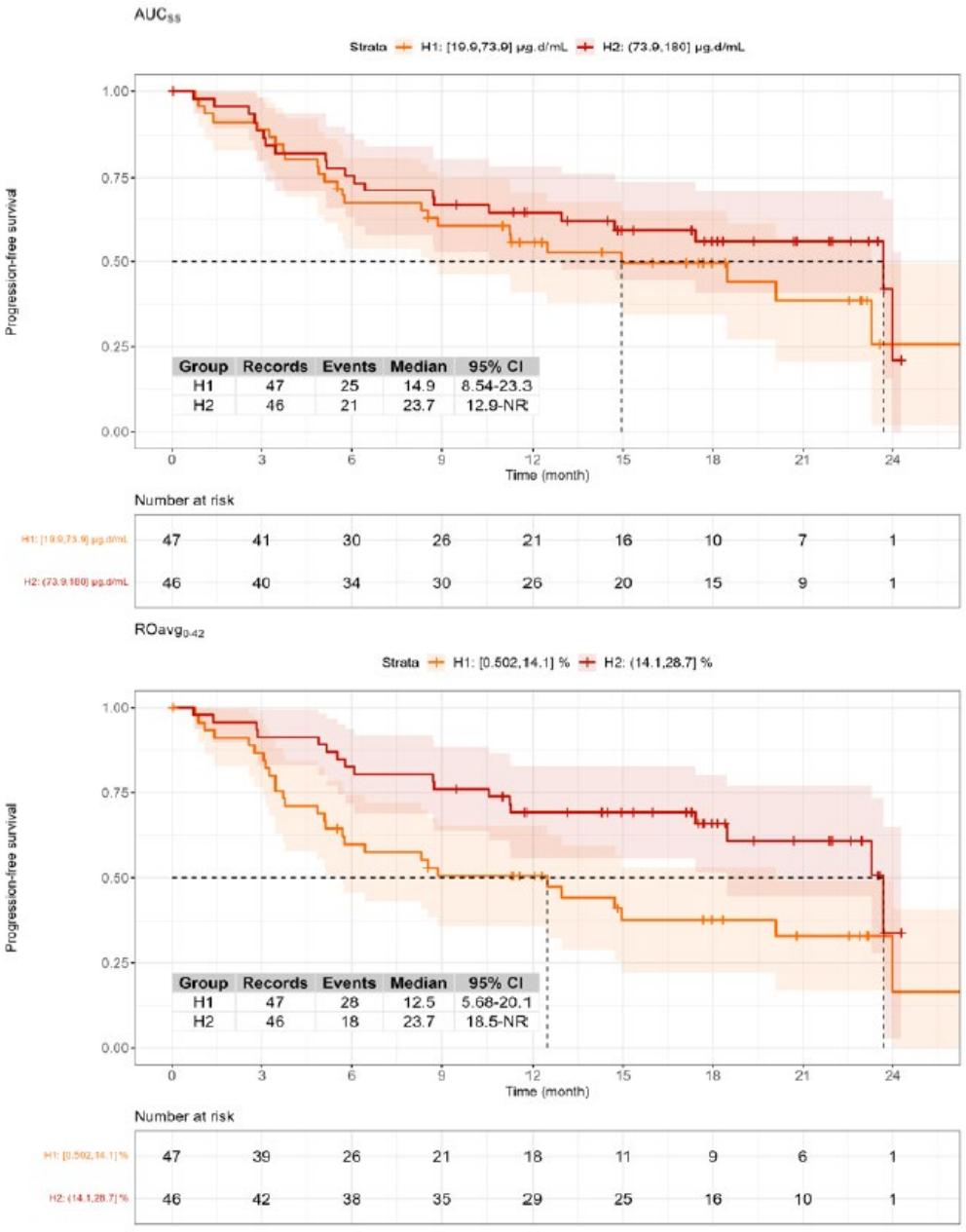
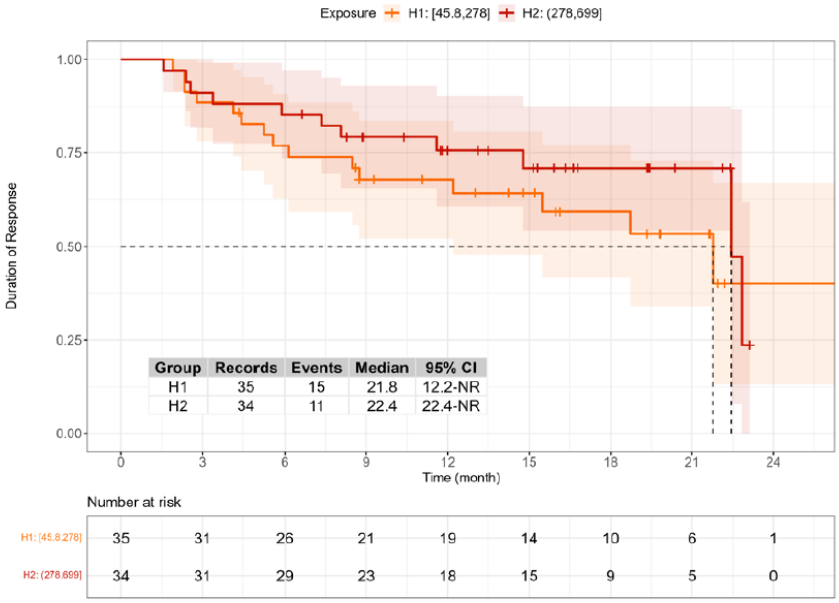


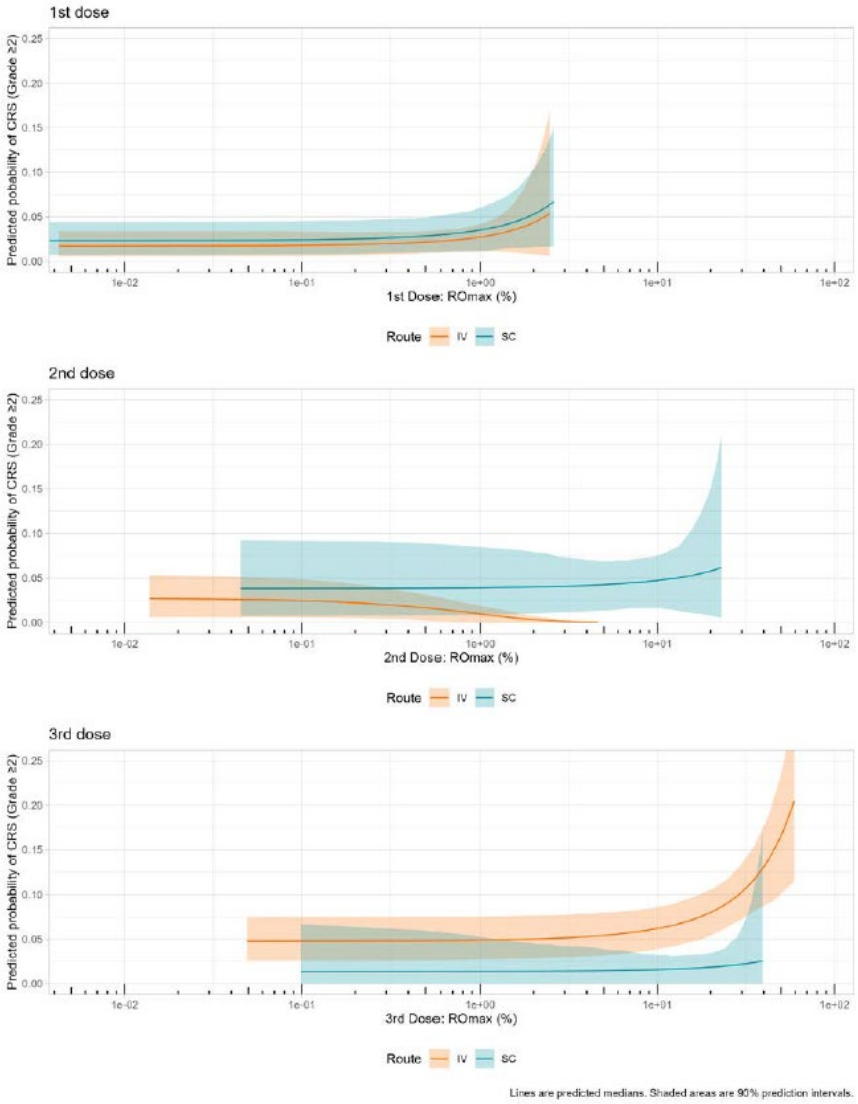
Figure 12 Investigator – assessed DOR for the SC ER Efficacy population stratified by median separated bins of mosunetuzumab AUC_{0-84}



Shaded areas are 90% CI. Dashed lines indicate median survival.
IV = intravenous; CI = confidence interval; NR = not reached; SC = subcutaneous.
One patient (PTNM=105603) withdrew consent and had no available exposure data; they were therefore excluded from the SC ER population.

The ER analysis for safety was assessed based on all Group D and Group F patients receiving SC administration of mosunetuzumab from Study GO29781 (N = 228). Selected adverse events of special interest were assessed: CRS (Grade ≥2), neutropenia (Grade ≥3), and infections (Grade ≥3) as well as adverse events; all and Grade ≥3. Results are presented in the Safety section.

Figure 13 Overlay ER plots for grade ≥2 CRS following cycle 1 doses on day 1 (1st dose), day 8 (2nd dose), and day 15 (3rd dose) in study GO29781, comparing IV and SC regimens, by dose number



There was an indication of higher probability of experiencing an AE of neutropenia in the highest exposure tertile (AUCss), meaning the highest concentration led to the highest frequency of neutropenia. For IV all tertiles were overlapping with no indication of a relation between probability for neutropenia and exposure ($AUC_{0\text{-}42}$). No clinically relevant relation to mosunetuzumab exposure following the SC treatment in the F2 Cohort was observed for any safety endpoint.

Model based ER analyses

SC data for E-R analyses came from Groups D and F of Study GO29871 and were compared to data from IV-administered patients in Study GO29781. The final IV/SC Pop PK model of mosunetuzumab was used to estimate exposure metrics and CD20 receptor occupancy. CD20 RO was estimated by a reservoir compartment which accumulated receptor occupancy over time. Rituximab and obinutuzumab bind to CD20 with higher affinity than mosunetuzumab, thus prior lines of treatment may affect efficacy and CRS incidence over early cycles and confound the use of mosunetuzumab exposure metrics. Most efficacy and safety endpoints were only evaluated graphically by Kaplan-Meier plots, except for CRR, ORR and CRS Grade≥2. Previous model predicted exposure CRR and ORR curves for IV were overlaid with binned observed CR or OR data from the SC F2 cohort and were comparable.

Of note, the model parameters of the previous CR/OR models for IV were estimated with poor precision and the simulation-based results should be interpreted with caution.

CRS Grade ≥2 was evaluated by linear logistic regression modelling using maximal RO accumulated across the first 6 weeks as the "exposure" metric. The 95% CI of the $RO_{max0-42}$ parameter contained the null hence this parameter lacks information. No other diagnostics of the RO CRS model were provided.

2.6.3. Discussion on clinical pharmacology

The current extension application is based on evidence from two clinical studies, the pivotal study GO29781 and the supportive study CO41942, and is also supported by MIDD (Model-Informed Drug Development). The bioanalysis of mosunetuzumab and immunogenicity evaluation in the pivotal study GO2971 and the supportive study CO41942 were conducted according to regulatory guidelines.

A previously developed 2-compartment Pop PK model with time varying clearance based on IV data from cohorts A and B of Study GO29781 was extended to support SC dosing. According to the MAH, re-estimation of parameters in the underlying IV model (particularly those relating to CL) improved the OFV but produced bias in the GOF plots and VPCs in the first few cycles of treatment, thus these parameters remained fixed to their previously estimated values. This is justified as density plots of eta distributions were overlapping between IV and SC dosed patients (Study GO29781).

A total of 228 patients were treated SC in Groups D and F, across a dose range of 1.6 mg to 90 mg. Cohort F2 included data from 138 participants who received the proposed SC step-up dose (RP2D). Of note, Study GO29781 IV and SC data were collected in trial cohorts conducted several years apart. The final IV/SC model was externally validated by IV and SC data from Study CO41942, in which mosunetuzumab was co-administered with lenalidomide. In Study CO41942, also the IV and SC dosing frequency was different as well as the IV step-up dosing schedule to the approved IV treatment and the proposed SC dosing schedule. Further validation of the final IV/SC model and assessment of model robustness was performed by nonparametric bootstrap (n=400) with a convergence rate of 83.4%. Albumin and body weight had large, though not considered clinically relevant, impact on mosunetuzumab exposure in the IV population. Forest plots of the model included covariate effects on mosunetuzumab SC exposure (AUC_{0-84}, AUC_{ss} and C_{trough} Cycle 3) confirmed that none of the covariates isolated resulted in clinically relevant effects.

In the pivotal Phase I/II study GO29781 with SC administration of mosunetuzumab, the PK non-inferiority (PKNI) of the proposed SC regimen to IV regimen was investigated. The study was conducted in R/R FL patients (patients treated with ≥ 2 prior therapies). The SC cohort F2 Exp FL was retrospectively compared to the previous investigated IV cohort B11 Exp FL. The less optimal non-randomized study design using a previously investigated IV study cohort was accepted by SAWP. Two primary PK endpoints were used for the PKNI analysis, observed Ctrough,CYC3 (cycle 3 pre-dose) and Bayesian Pop-PK model predicted AUC0-84d. Observed Ctrough at steady state is considered as an adequate PK-endpoint for this PK-bridging approach and the selection of AUC0-84d as PKNI endpoint has been justified. The NI criteria for GMR is adequate, consistent with the standard BE-criteria. This is consistent with the higher second SC dose of 45 mg vs IV dose of 2 mg. Safety seems not to be impacted during the step-up phase, despite the higher exposure after SC administration (see safety section).

In the supportive Phase Ib/II study CO41942 SC administration of mosunetuzumab in combination with lenalidomide was compared with mosunetuzumab IV. The study was randomized and conducted in relapsed or refractory follicular lymphoma patients (patients with ≥ 1 prior therapy). Two primary PK endpoints were used for the PKNI analysis comparing the SC and IV cohort, observed Ctrough,CYC4

and model predicted AUCC1-C3 (cumulative AUC of cycle 1 to 3) using Bayesian Pop-PK estimations on basis of GO29781 Pop-PK model. Study CO41942 is considered of less relevance for the current extension application, as the SC dosing regimen is different with regards to dosing frequency, in cycle 2 and beyond, from what is actually applied for, i.e. dosing every 28 days compared to dosing every 21 days as in the GO29781 study. Also, the IV dosing regimen is different from the approved IV regimen. The PK could be adequately simulated with the GO29781 Pop-PK model, showing as expected that mosunetuzumab PK is not impacted by lenalidomide coadministration. Overall, the PK endpoints in the SC cohort were numerically higher than those in the IV cohort and PKNI of SC vs IV administration was demonstrated. The PK results of the CO41942 study are considered as supportive for the conclusion of PKNI in study GO29781.

The bioavailability of mosunetuzumab SC was adequately estimated from AUCss to 90%. Absorption was as expected slower for SC administration, resulting in a larger tmax of 4-7 days and lower Cmax compared to IV. PK comparability of the two drug substance versions used as shown. Distribution, clearance, and metabolism of mosunetuzumab SC are as previously described for the IV product. The estimated terminal t1/2 at steady state after SC administration was slightly longer than the IV administration. Dose-proportionality of AUC was shown over the range from 1.6 mg to 45 mg mosunetuzumab SC. Steady state was reached after approximately 3-4 cycles, as for the IV product.

No clinical studies were conducted in special populations for mosunetuzumab SC. No clinically relevant PK covariates were identified in the Pop-PK model. An exposure analysis, using observed and Bayesian model predicted PK parameters, confirmed that the exposure was not significantly impacted by mild HI, moderate RI, gender, age, ethnic factors. Overall, no subpopulation requiring dose-adjustment was identified. No DDI studies were conducted. It was anticipated that the possibility of the transient CYP3A DDI would be similar or lower for mosunetuzumab SC compared to mosunetuzumab IV. Overall, the SmPC for mosunetuzumab SC related to clinical pharmacology is considered as adequate.

SC data for E-R analyses came from Cohort F2 RP2D and D SAD of Study GO29871 and were compared to data from IV-administered patients in Study GO29781. Non-inferiority assessment was partly based on Ctrough which is highly correlated to AUC,ss, one of the PK exposure metrics in the E-R analyses.

The efficacy endpoints for ER analyses: CRR, ORR, PFS, DOCR, DOR and tumour burden are acceptable. In KM plots for PFS, the median separated bins of SC AUCss were slightly separated but with CI's overlapping. For SC RO0-42, the median separated bins were clearly separated with non-overlapping 95% CIs, indicating lower RO in the first 1.5 months results in lower PFS over 24 months.

The final IV/SC Pop PK model of mosunetuzumab was used to estimate exposure metrics and CD20 receptor occupancy. Baseline albumin and body weight did not have significant impact on efficacy endpoints CR or OR, however, impact on PFS was not evaluated. Additional E-R plots for the SC ER efficacy population evaluating investigator-assessed PFS in Kaplan-Meier plots stratified by tertiles of body weight and by tertiles of baseline albumin, respectively using data from the SC F2 cohort were submitted.

The safety endpoints assessed for ER were selected adverse events of special interest: CRS (Grade ≥2), neutropenia (Grade ≥3), infections (Grade ≥3) as well as adverse events; all and Grade ≥3. No clinically relevant relation to mosunetuzumab exposure following the SC treatment in the F2 Cohort was observed for any safety endpoint.

Primary and secondary pharmacology aligns with the already known effects of mosunetuzumab, although the SC use showed less issues related to CRS for secondary pharmacology. The recommended mosunetuzumab SC 21 day-cycle regimen is: Cycle 1 (day 1, 5 mg; day 8, 45 mg; day 15, 45 mg), Cycle 2 and beyond (day 1, 45 mg), whereas the approved IV 21-day cycle regimen:

Cycle 1 (day 1, 1 mg; day 8, 2 mg; day 15, 60 mg), Cycle 2 (day 1, 60 mg) and Cycle 3 and beyond (day 1, 30 mg).

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of subcutaneous mosunetuzumab was adequately investigated in the pivotal GO29781 study, supported by the CO41942 study and by Pop-PK modelling. It was demonstrated that the PK of mosunetuzumab SC was non-inferior to the IV formulation. In conclusion, the clinical pharmacology is supportive for approval of mosunetuzumab SC.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

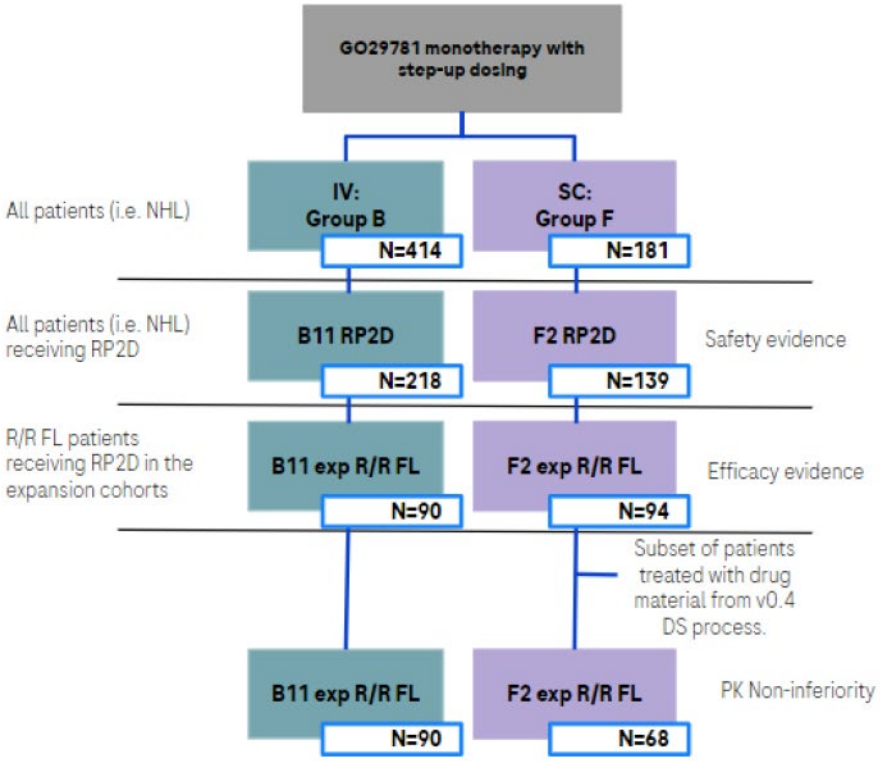
Aspects related to dose response are discussed in the pharmacology section.

2.6.5.2. Main 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 and chronic lymphocytic leukemia.

The efficacy analysis focuses on response comparisons between the R/R FL expansion cohorts receiving the respective registrational doses for SC monotherapy (F2 exp R/R FL cohort) and the IV monotherapy (B11 exp R/R FL cohort).

Figure 14 Dose cohorts contributing to Clinical evidence Study GO29781



DS=drug substance; FL=follicular lymphoma; IV=intravenous(ly); NHL=Non-Hodgkin Lymphoma; RP2D=recommended Phase II dose; SC=subcutaneous(ly);
Note: B11 exp R/R FL cohort (N=90) was referred to as B11 FL RP2D in the IV dossier. CCOD for IV cohorts was 27 August 2021, and the CCOD for the SC cohorts was 01 February 2024.

The efficacy populations consist of patients with R/R FL with ≥2 prior lines of systemic therapy: 94 patients from the RP2D expansion cohort receiving mosunetuzumab monotherapy SC (F2 exp R/R FL) and 90 patients from the RP2D expansion cohort receiving mosunetuzumab monotherapy IV (B11 exp R/R FL).

The two cohorts were not enrolled at the same time so no stratification could be performed. To mitigate differences between the two cohorts the same in- and exclusion criteria were used, and patients were recruited from the same sites.

Methods

Study Participants

The B11 exp R/R FL (n=90) (IV) cohort was the population assessed for the initial MAA. Therefore, for the current extension application only the SC F2 exp R/R FL cohort was assessed and compared to the former cohort.

Patients were expected to have FL that expressed CD20. All patients had received anti-CD20 directed therapy, and could thus potentially have lost the CD20 epitope.

The schedule of efficacy assessments was the same between the B11 exp R/R FL cohort (IV) and F2 exp R/R FL cohort (SC).

Key Inclusion Criteria

- Histologically-documented Grade 1–3a FL expected to express the CD20 antigen
- Measurable disease, defined as at least one bi-dimensionally measurable nodal lesion >1.5 cm in its longest dimension, or at least one bi-dimensionally measurable extranodal lesion >1.0 cm in its longest dimension
- Patients must have relapsed after or failed to respond to ≥ 2 prior lines of systemic therapy and must have received prior treatment with an anti-CD20 directed therapy and an alkylating agent

Key Exclusion Criteria

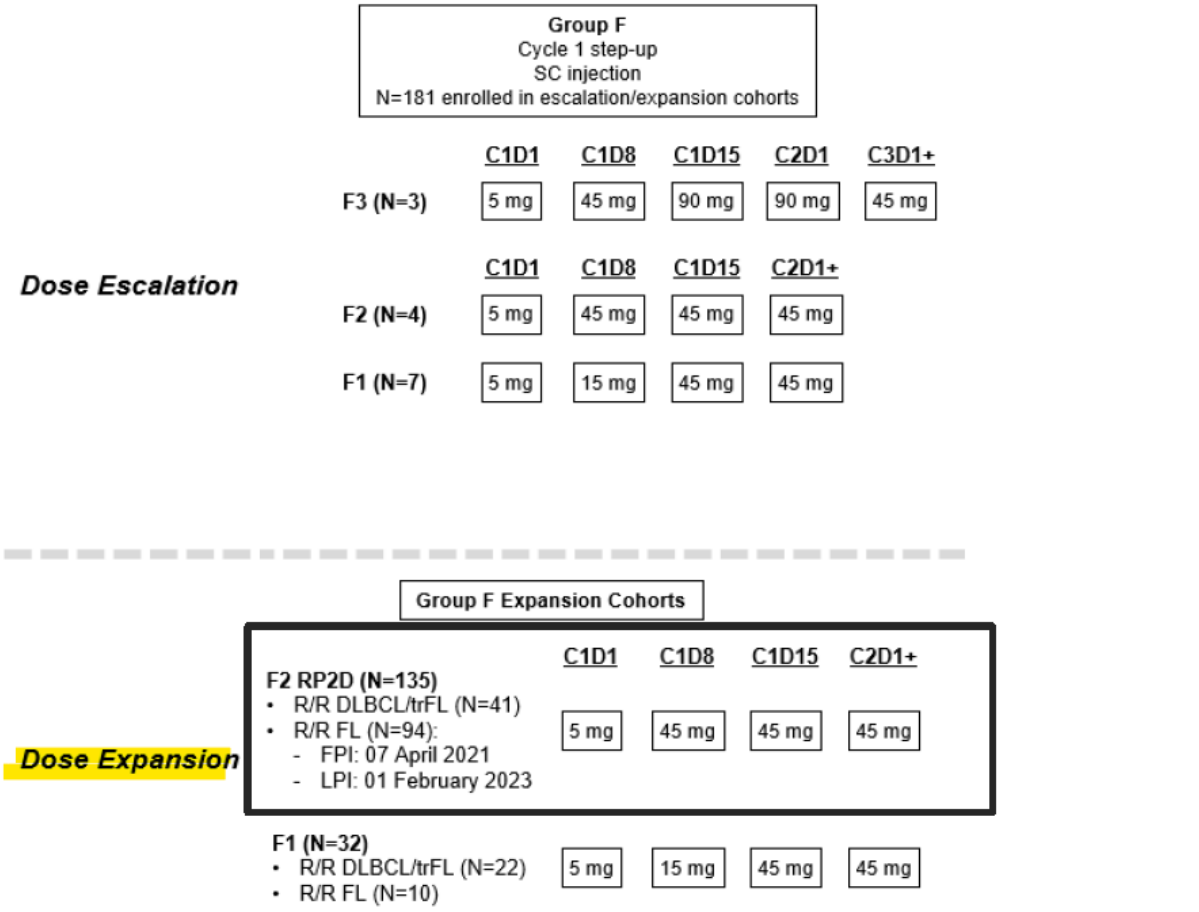
- Prior treatment with:
  - Anti-lymphoma treatment with monoclonal antibody, radioimmunoconjugate, or antibody-drug conjugate within 4 weeks before first mosunetuzumab administration
  - Systemic immunotherapeutic agents for which the mechanism of action involves T cells; including but not limited to cytokine therapy and anti-CTLA-4, anti-PD-1 and anti-PD-L1 therapeutic antibodies, within 12 weeks or five half-lives of the drug, whichever is shorter
  - Chimeric antigen receptor modified T-cell therapy within 30 days before the first mosunetuzumab administration
  - Any chemotherapeutic agent, or treatment with any other anticancer agent (investigational or otherwise) within 4 weeks or five half-lives of the drug, whichever is shorter
  - Radiotherapy within 2 weeks prior to the first mosunetuzumab administration
- Autologous stem cell transplant (SCT) within 100 days prior to the first mosunetuzumab administration
- Prior allogenic SCT, or solid organ transplant
- History of autoimmune disease

Current or past history of central nervous system (CNS) disease, CNS lymphoma, or significant cardiovascular or active pulmonary disease.

Treatments

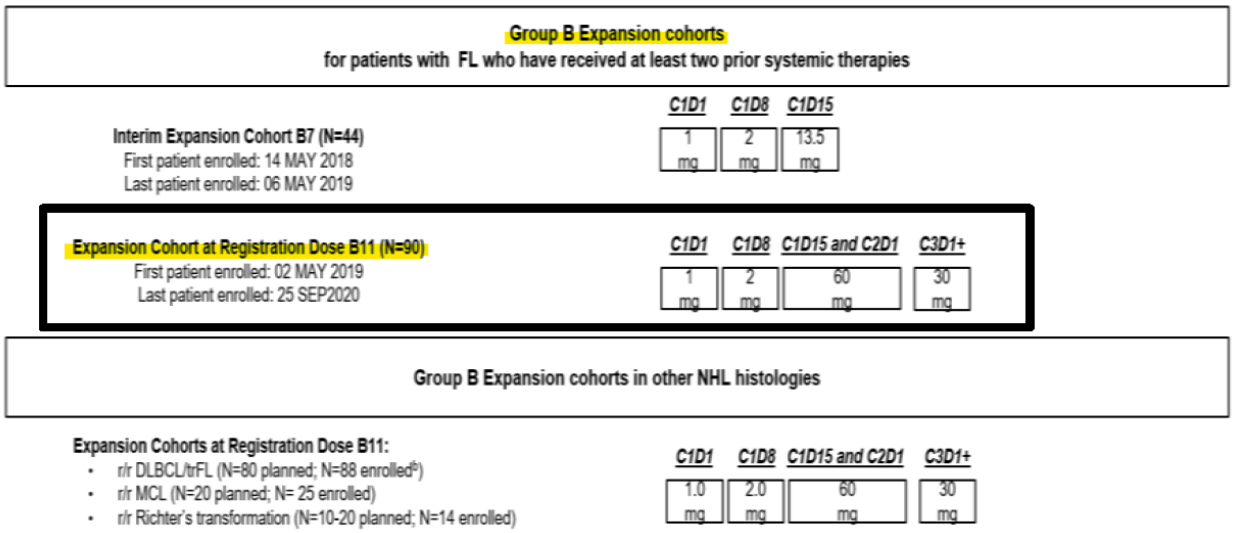
Similar to mosunetuzumab IV monotherapy, patients were treated with mosunetuzumab SC monotherapy for 8 cycles, and if CR was achieved after 8 cycles, the treatment was to be stopped. Patients who achieved a PR or maintained stable disease (SD) after 8 cycles were to continue single agent mosunetuzumab treatment for a total of 17 cycles unless relapsed disease (PD) or unacceptable toxicity was observed. For patients who achieved a CR and experienced PD following completion of initial single-agent mosunetuzumab treatment, single-agent mosunetuzumab re-treatment was allowed to be initiated. Retreatment followed the same dosing regimen described above.

Figure 15 Study design of group F, dose-escalation and dose-expansion cohorts, in Study GO29781



CCOD = clinical cutoff date; C1D1 = Cycle 1 Day 1; C1D8 = Cycle 1 Day 8; C1D15 = Cycle 1 Day 15; C2D1+ = Day 1 of Cycle 2 and beyond; C3D1+ = Day 1 of Cycle 3 and beyond; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; FPI = first patient in; LPI = last patient in; RP2D = recommended Phase II dose; R/R = relapsed/refractory; SC = subcutaneous; trFL = transformed follicular lymphoma.

Note: 'N' represents the numbers of patients enrolled as of the CCOD of 01 February 2024.



CCOD = clinical cutoff date; C1D1 = Cycle 1 Day 1; C1D8 = Cycle 1 Day 8; C1D15 = Cycle 1 Day 15; C3D1 + = Day 1 of Cycle 3 and beyond; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; R/R = relapsed/refractory; trFL = transformed follicular lymphoma.
Note: 'N' represents the numbers of patients enrolled as of the CCOD of 27 August 2021.

Concomitant and rescue therapies

For patients receiving mosunetuzumab SC, corticosteroid prophylaxis consisting of 20 mg dexamethasone (preferred) or 80 mg methylprednisolone should be administered orally or intravenously prior to mosunetuzumab administration on dosing days during Cycle 1 (i.e., Cycle 1 Days 1, 8 and 15). The administration of corticosteroid prophylaxis may be optional for Cycle 2 and beyond for patients in Groups D and F at the investigator's discretion. However, if the patient experienced CRS with prior administration of mosunetuzumab, prophylaxis with steroids must be administered for subsequent doses until no additional CRS events are observed.

In addition, premedication with oral acetaminophen or paracetamol (e.g., 500−1000 mg) and/or 50−100 mg diphenhydramine may be administered per standard institutional practice prior to administration of mosunetuzumab. Decisions to modify the prophylactic corticosteroid was based on the recommendation of the IMC.

Table 9 Management of cytokine release syndrome for patients receiving mosunetuzumab IV and SC

CRS Grade [a]	Action with Current Mosunetuzumab	Supportive Care	Anti–IL-6/Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
Grade 1 Symptoms not life-threatening and require symptomatic treatment only	• For IV mosunetuzumab, slow infusion to ≤50% or interrupt infusion until symptoms resolve; re-start at same rate. • If symptoms recur with rechallenge, interrupt study treatment, do not resume infusion, and manage per Grade 2.	• Symptomatic management of constitutional symptoms. • Consider empiric broad-spectrum antibiotics. • Consider G-CSF if neutropenic. • Maintenance IV fluids for hydration. • Consider hospitalization until symptoms completely resolve.	• For prolonged CRS (>2 days) in patients with significant symptoms and/or comorbidities (per investigator discretion, e.g., impaired cardiovascular function, reduced pulmonary reserve), consider tocilizumab and corticosteroids as per Grade 2.	• For IV mosunetuzumab, consider 50% (or lower) rate of infusion for next step-up dose in Cycle 1 or 50% rate of infusion if next dose is same dose level (beyond Cycle 1). • Consider hospitalization for next dose. • For subsequent injections/infusions, consider administration of premedication with antihistamines, anti–pyretic medications, and/or analgesics, and monitor closely for CRS (Section 4.3.2).

CRS Grade [a]	Action with Current Mosunetuzumab	Supportive Care	Anti–IL-6/Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
Grade 2 Symptoms require and respond to moderate intervention O_2 requirement <40% OR hypotension responsive to fluids or low dose of one vasopressor OR Grade 2 organ toxicity	• For IV mosunetuzumab, hold further study treatment until symptoms resolved; consider re-starting infusion at 50% rate. • If symptoms recur with rechallenge at decreased infusion rate, interrupt study treatment, do not resume, and manage per Grade 3.	• Symptomatic management of constitutional symptoms and organ toxicities. • Consider ICU admission for hemodynamic monitoring. • For hypotension: IV fluid bolus as needed; for persistent refractory hypotension (e.g., after two fluid boluses and anti-IL-6 therapy), start vasopressors and manage per Grade 3. • Rule out other inflammatory conditions that can mimic severe CRS (e.g., infections/ sepsis), undertake SARS-CoV-2 diagnostic PCR. • Consider empiric broad-spectrum antibiotics. • If no improvement within 24 hours, initiate work up and assess for signs and symptoms of HLH as described in Section 5.1.6.1.	• Consider tocilizumab [b] • For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy, consider dexamethasone 10 mg IV every 6 hours (or equivalent). • Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.	• May receive the next dose of mosunetuzumab if symptoms resolve to Grade ≤1 for 3 consecutive days • For subsequent injections/infusions, consider administration of premedication with antihistamines, anti–pyretic medications, and/or analgesics, and monitor closely for CRS. • For IV mosunetuzumab, consider 50% (or lower) rate of infusion for next step-up dose in Cycle 1 or 50% rate of infusion if next dose is same dose level (beyond Cycle 1). • Consider hospitalization for next dose.

CRS Grade [a]	Action with Current Mosunetuzumab	Supportive Care	Anti–IL-6/Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
Grade 3 Symptoms require and respond to aggressive intervention O_2 requirement ≥40% OR hypotension requiring high dose or multiple vasopressors OR Grade 3 organ toxicity or Grade 4 transaminitis	• If administered IV, stop infusion, do not resume.	• Symptomatic management of organ toxicities, admit to ICU for hemodynamic monitoring. • For hypotension: IV fluid bolus and vasopressors as needed. • Rule out other inflammatory conditions that can mimic severe CRS (e.g., infections/ sepsis), undertake SARS-CoV-2 diagnostic PCR. • Consider empiric broad-spectrum antibiotics. • If no improvement within 24 hours, initiate work up and assess for signs and symptoms of HLH as described in Section 5.1.6.1.	• Administer tocilizumab. [b] • Dexamethasone 10 mg IV every 6 hours (or equivalent). If refractory, manage as per Grade 4. [b] • Manage per Grade 4 if no improvement within 18–24 hours after second dose of tocilizumab.	• May receive the next dose of mosunetuzumab if CRS event was responsive to treatment (i.e., clinical improvement within 8–12 hours following tocilizumab/corticosteroids administration) and symptoms resolve to Grade≤1 for 3 consecutive days after discussion with the Medical Monitor: Enhanced premedications and hospitalization for next dose - For IV mosunetuzumab: ○ Decrease to 50% (or lower) rate of infusion for next dose ○ The next dose should be reduced to the next lower dose level that has been previously cleared during dose escalation; subsequent doses may not be re-escalated with signs/symptoms of Grade 3 or higher CRS at the reduced dose. [f] - For SC mosunetuzumab: ○ If Grade 3 CRS occurs after 5 mg, the next dose should be 5 mg. ○ If Grade 3 CRS occurs after other dose levels, the next dose should be reduced to the next lower dose level that has been previously cleared during dose escalation. For example, if Grade 3 CRS occurs after 45 mg, the next dose should be reduced to 20 mg. ○ If the next dose is tolerated without Grade 3 or higher CRS, the subsequent dose may be increased according to the planned dose levels. ○ If Grade 3 CRS recurs with subsequent doses, permanently discontinue mosunetuzumab. [g]

CRS Grade [a]	Action with Current Mosunetuzumab	Supportive Care	Anti–IL-6/Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
Grade 4 Life-threatening symptoms Requirement for ventilator support OR Grade 4 organ toxicity (excluding transaminitis)	• If administered IV, stop infusion, do not resume.	• ICU admission and hemodynamic monitoring. • Mechanical ventilation as needed. • IV fluids and vasopressors as needed. • Symptomatic management of organ toxicities. • Rule out other inflammatory conditions that can mimic severe CRS (e.g., Infections/sepsis), undertake SARS-CoV-2 diagnostic PCR. • Consider empiric broad-spectrum antibiotics. • If no improvement within 24 hours, initiate work up and assess for signs and symptoms of HLH as described in Section 5.1.6.1.	• Administer tocilizumab. [b] • For patients refractory to tocilizumab, consider siltuximab, anakinra, dasatinib and emapalumab, based on discretion of the investigator; management should be discussed with the Medical Monitor. [c] • Dexamethasone 10 mg IV every 6 hours (or equivalent). • If refractory, consider methylprednisolone 1000 mg/day IV. [d, e]	• Permanently discontinue mosunetuzumab. [g]

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; G-CSF = granulocyte colony stimulating factor; HLH = hemophagocytic lymphohistiocytosis; PCR = polymerase chain reaction.

[a] CRS grading per Lee et al. 2014 (Appendix 16).

[b] Tocilizumab should be administered at a dose of 8 mg/kg IV (*not* exceeding 800 mg per infusion). *If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, a second dose may be administered at least 8 hours apart (maximum 2 doses per CRS event). Within each time-period of 6 weeks of mosunetuzumab treatment, the total number of tocilizumab doses should not exceed 3 doses.* Refer to Appendix 12 for schedule of activities for tocilizumab treatment of CRS.

[c] Riegler et al. 2019.

[d] Antifungal prophylaxis should be strongly considered in patients receiving steroids for treatment of CRS.

[e] For example, methylprednisolone IV 1000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 13 hours for 2 days, and 60 mg every 12 hours for 2 days.

[f] If Grade 3 CRS occurs in the step-up dosing cohorts following mosunetuzumab administration at Cycle 1 Day 1 or Cycle 1 Day 8, the next mosunetuzumab dose should be discussed with the Medical Monitor and a dose reduction should be considered. Exceptions may be considered to repeat the same step-up dose based on individual risk-benefit assessment.

[g] Resumption of mosunetuzumab may be considered in patients who are deriving benefit and have fully recovered from the adverse event. The decision to re-challenge patients with mosunetuzumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed. Further treatment should not be considered unless all the criteria below are met:

- Individual benefit–risk assessment by Principal Investigator/treating physician favors continued treatment.
- The patient has recovered from previous toxicities and has sufficient organ function/reserve to receive subsequent doses.
- The patient has been adequately consented for risks associated with continued treatment and decides to receive subsequent doses.
- The above benefit–risk assessment and evaluation of patient's are discussed with the Sponsor.
- Subsequent doses are well planned with precautionary measures, including dose reduction, slow infusion rate at 50% or lower, mandatory hospitalizations, and enhanced premedications.

Objectives

Primary objective: To evaluate PKNI of mosunetuzumab SC RP2D (F2 expansion cohort) compared to the reference mosunetuzumab IV RP2D (B11 expansion cohort) in patients with R/R FL with at least

two prior lines of systemic therapy.

Secondary objectives:

- To further assess the PKNI of mosunetuzumab SC RP2D (Group F2 expansion cohort) compared to the reference mosunetuzumab IV RP2D (Group B11 expansion cohort) in patients with R/R FL with at least two prior lines of systemic therapy based on additional PK parameters.
- To assess impact of treatment- and disease-related symptoms on HRQoL and health status according to the EORTC QLQ-C30, the FACT-Lym subscale, and the EQ-5D-5L questionnaire in the NHL expansion cohorts
- To make a preliminary (exploratory) assessment of the anti-tumor activity of mosunetuzumab as a single agent in patients with R/R NHL (in this case R/R FL).

Outcomes/endpoints

(Co)-primary endpoints

- Observed serum C_{trough} at Cycle 3 (predose Cycle 4) (CtroughCYC3_OBS)
- Model-predicted area under the concentration-time curve (AUC) from 0 to 84 days (AUC0–84 d)

Key Secondary Pharmacokinetic Endpoints for the R/R FL Expansion Cohort at Group F RP2D

- Observed Cycle 2 serum (i.e., pre-dose Cycle 3) Ctrough concentration (CtroughCYC2_OBS)
- Model-predicted Cycle 2 (i.e., pre-dose Cycle 3) serum Ctrough concentration (CtroughCYC2), derived using EBEs, data permitting
- Model-predicted Cycle 3 (i.e., pre-dose Cycle 4) serum Ctrough concentration (CtroughCYC3), derived using EBEs, data permitting
- Model-predicted AUC at steady state (AUCSS), as approximated by AUC of Cycle 4 using EBEs, data permitting
- The safety analysis focuses on SC vs. IV comparisons for all patients treated at the registrational dose level, regardless of histology (i.e., F2 RP2D vs. B11 RP2D) (Figure 1).

The secondary efficacy outcome measures for the R/R FL Expansion Cohort at Group F RP2D

- Complete response (CR) rate, defined as the proportion of patients whose best overall response is a CR using standard criteria for NHL (Cheson et al. 2007). CR rate was assessed by an Independent Review Facility (IRF) and by the investigator. Patients included in the efficacy-evaluable population with missing or no response assessments were classified as non-complete responders.
- Objective response rate (ORR), defined as the proportion of patients whose best overall response is a partial response (PR) or CR using standard criteria for NHL (Cheson et al. 2007). ORR was assessed by the IRF and by the investigator. Patients included in the efficacy-evaluable population with missing or no response assessments were classified as non-responders.
- Duration of complete response (DOCR), defined as the time from the initial occurrence of a documented CR until documented disease progression or death due to any cause, whichever occurs first. Duration of complete response was assessed by the IRF and by the investigator, using standard criteria for NHL.

- Duration of response (DOR), defined as the time from the initial occurrence of a documented PR or CR until documented disease progression or death due to any cause, whichever occurs first. DOR was assessed by the IRF and by the investigator, using standard criteria for NHL.
- Progression-free survival (PFS), defined as the time from the first study treatment to the first occurrence of disease progression or death from any cause, whichever occurs first. PFS was assessed by the IRF and by the investigator, using standard criteria for NHL.
- Overall survival (OS), defined as the time from the first study treatment to the date of death from any cause.

Patient-Reported Outcomes

- Change from baseline in physical function, fatigue, and health-related quality of life (HRQoL) of the EORTC QLQ-C30
- Change from baseline in lymphoma symptoms of FACT-Lym subscale
- For the EQ-5D-5L, summary statistics for the health status according to the visual analog scale and changes in the index utility score from baseline were calculated

No formal hypothesis testing was formulated for these endpoints, and all analyses described in the subsequent section were considered exploratory.

Sample size

The sample size of the pivotal F2 exp R/R FL cohort (N =94) matches the sample size of the pivotal IV expansion cohort (i.e., B11 R/R FL ≥2 prior systemic therapies, N = 90).

Randomisation and blinding (masking)

Not applicable.

Statistical methods

Analysis sets for primary endpoints: The Per Protocol PK (PPP) analysis population included all of the R/R FL patients from Group B11 expansion (approximately n=90), and all of the R/R FL patients from Group F2 expansion who received the drug material created using the v0.4 drug substance process (approximately n= 64) and had at least one post-baseline measurable PK concentration. Also, patients who switched drug material prior to Cycle 4 (e.g., started on drug material created using v0.4 drug substance process and switched to v0.1 drug substance process, or vice versa) during study were excluded from the PPP population. If patients switched drug material process after Cycle 4, patients would still be included in the PPP population, grouped with the originally assigned drug material process.

A statistical testing procedure at a one-sided type I error rate of 0.05 was used to test both co-primary endpoints separately. The tests for both endpoints needed to be significant to demonstrate PK non-inferiority.

1. GMR (SC/IV) for the CtroughCYC3_OBS. If the lower bound of the 90% CI is ≥ 0.8, then the null hypothesis was rejected, and it could be concluded that the SC dose is non-inferior to the IV dose in terms of CtroughCYC3_OBS.
2. GMR (SC/IV) for AUC0-84. If the lower bound of the 90% CI is ≥0.8, then the null hypothesis would be rejected and it could be concluded that the SC dose is non-inferior to the IV dose in terms of AUC0-84.

Statistical testing was not to be performed on key secondary endpoints. Descriptive analyses for the

key secondary PK endpoints for the SC mosunetuzumab RP2D in R/R FL (Group F2 expansion) were performed to contribute to the totality of the evidence to support PK NI of mosunetuzumab SC versus IV.

Main Analytical Approach for Co-primary Endpoints

The primary analysis of CtroughCYC3_OBS was based on logarithmic values of CtroughCYC3_OBS to compensate the known skewness of its distribution. For natural logarithm (Ln) trough plasma concentration, the statistical hypothesis was tested using an analysis of covariance model

*Ln(*CtroughCYC3_OBS*)*$_{ij}$ = τ_i + ε_{ij} *(i=SC, IV; j=1, 2, …, n$_i$)*

where $i = SC$, IV and j = 1,2, … , ni with ni being the sample size in the SC or IV group; τi denotes the overall mean in the SC or IV group and ϵij is a random error variable assumed to be independently and identically normally distributed with mean zero and variance $\sigma\varepsilon^2$.

The contrast $\tau SC - \tau IV$, its 90% CIs, and the variance $\sigma\varepsilon^2$ was estimated from the model. An estimate of the treatment effects ratio and the corresponding 90% CIs for the untransformed variables was calculated by exponentiation of the estimate of contrast $\tau SC - \tau IV$ and the 90% CIs. The coefficient of variance (CV) for the untransformed primary variable was estimated using the relationship *CV*ε = *sqrt(exp(*$\sigma\varepsilon^2$*)-1)*.

If the lower confidence interval bound of

*exp(Ln[*CtroughCYC3_OBS,SC*]-Ln[*CtroughCYC3_OBS,IV*])*=CtroughCYC3_OBS*,SC/*CtroughCYC3_OBS,IV

was equal or greater than 0.8, then the null hypothesis could be rejected.

The model-predicted cumulative AUC over 0-84 days (AUC0-84) was analyzed using the same method as for CtroughCYC3_OBS.

Secondary efficacy endpoints:

Analysis set: The efficacy-evaluable population includes all enrolled R/R FL patients from Group B11 expansion and Group F2 expansion.

Analysis method

Retrospective Comparison of Efficacy for SC versus IV

Baseline characteristics were compared between R/R FL Group F expansion RP2D and R/R FL Group B11 expansion RP2D. The secondary efficacy endpoints of CR rate, ORR, DOR, DOCR, PFS, and OS was compared between efficacy evaluable R/R FL patients who received SC RP2D mosunetuzumab (Group F2 expansion) and IV RP2D mosunetuzumab (Group B11 expansion). Because the mosunetuzumab IV RP2D (Group B11 expansion) has already completed enrollment and relevant data in R/R FL patients are available, the comparisons were done retrospectively. No formal hypothesis testing was done for these analyses, and all analyses described in this section are considered exploratory. Data from only the initial treatment period was included. A sensitivity analysis excluding patients determined as negative for CD20 expression at baseline was performed and may be reported separately from the CSR. Although both the SC and IV cohorts are from the same study, imbalance of baseline characteristics may still be observed between the two cohorts due to several amendments on study conduct over the time of the study. The potential baseline imbalance may consequently introduce uncertainty when the SC cohort is retrospectively compared to the IV cohort. To address such concerns, this comparison was conducted using the following two approaches:

- Multivariate regression analysis

- Propensity score analysis

Multivariate Regression Analysis

Multivariate regression analyses with all baseline covariates adjusted simultaneously were performed. For the secondary response endpoints (CR rate, ORR), multivariate logistic regression models were used to estimate the odds ratios of SC vs. IV arm. For the secondary time-to-event endpoints (DOR, DOCR), Cox regression was implemented.

Propensity Score Analysis

The propensity score (PS) models by inverse probability of treatment weighting (Rosenbaum and Rubin 1983; Rosenbaum 1987) was used. Specifically, the propensity score for each patient in both SC and IV cohorts was calculated by performing a logistic regression of treatment assignment on the baseline covariates simultaneously. The inverse of the propensity score was incorporated in the weighted regression models to balance the baseline covariates between the two cohorts. To adhere to the intent-to-treat (ITT) principle, and also due to sample size limitations, trimming of PS weight was not to be implemented.

For the secondary response endpoints (CR rate, ORR), the weighted logistic regression model was used to estimate the odds ratios of SC vs. IV arm. For the secondary time-to-event endpoints (DOR, DOCR), weighted Cox regression was implemented.

Baseline Covariates for the Retrospective Comparison

The following covariates were used for retrospective comparisons. Patients with missing covariates were excluded from the analyses. A descriptive baseline table on the following covariates was made to compare SC R/R RP2D mosunetuzumab (Group F2 expansion) and IV R/R RP2D mosunetuzumab (Group B11 expansion).

- Age: < 65 vs. ≥ 65
- Sex: M vs. F
- Race: White vs. Asian vs. Others (Others including unknown)
- Ann Arbor Stage at Study Entry: IV/III vs I/II
- FLIPI 1 Risk at Study Entry: <3 vs. ≥ 3
- Prior lines of therapy: 2 vs. 3+
- Relapse or Refractory to Any Prior Anti-CD20 Therapy: (Refractory vs. Non-refractory)
- POD24 (Yes vs. No)

POD24 is Start of Systemic Therapy to PD <24 months (Y/N). If the model failed to converge, some covariates could be removed from the model based on their clinical relevance, where the least clinically relevant variables were removed first.

Table 10 Censoring rules for time to event endpoints

Situation	Endpoints	Date of Event/Censoring	Outcome
Death before first PD while on study	DOCR, DOR, PFS	Death	Event
Death between adequate assessment visits	DOCR, DOR, PFS	Death	Event
PD documented	DOCR, DOR, PFS	Earliest assessment of progression	Event
PD after more than 1 consecutively missed scheduled visits	DOCR, DOR, PFS	Earliest assessment of progression	Event
Death after more than 1 consecutively missed scheduled visits	DOCR, DOR, PFS	Death	Event
PD or death after the start of NALT	DOCR, DOR, PFS	Last adequate assessment of no progression prior to the start of NALT	Censored
Start of NALT	DOCR, DOR, PFS	Last adequate assessment of no progression prior to the start of NALT	Censored
No death, nor PD prior to CCOD	DOCR, DOR, PFS	Last adequate assessment of no progression	Censored
Study discontinuation prior to death or PD	DOCR, DOR, PFS	Last adequate assessment of no progression	Censored
Death	OS	Death	Event
No death prior to CCOD	OS	Last known alive date or CCOD, whichever is earlier	Censored
Death prior to start of NALT	TTNT	Death	Censored
Start of NALT prior to death	TTNT	Start of NALT	Event
No death, nor started NALT prior to CCOD	TTNT	Last known alive date or CCOD, whichever is earlier	Censored

CCOD = clinical cutoff date; DOCR = duration of complete response; DOR = duration of response; NALT = new anti-lymphoma therapy; OS = overall survival; PD = progressive disease; PFS = progression free survival; TTNT = time to next treatment.

Time to next treatment (TTNT), defined as the time from the date of initial study treatment to the start of new anti-lymphoma therapy (NALT) was an additional exploratory endpoint.

Patient reported outcomes:

According to Study GO29781 SAP Version 2 the applied analysis methods for PRO's were:

- 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

Sensitivity analyses:

All secondary efficacy endpoints, except OS, were assessed by both IRF and the investigator.

Additionally, following Covid-19 sensitivity alternative censoring was performed:

Table 11 COVID-19 sensitivity analysis Censoring rules for time to event endpoints

Situation	Endpoints	Date of Event/Censoring	Outcome
Death due to COVID-19	DOCR, DOR, OS, PFS, TTNT	Death	Censored
Treatment discontinuation due to COVID-19	DOCR, DOR, OS, PFS, TTNT	Date of treatment discontinuation	Censored

COVID-19 = coronavirus disease 2019, DOCR = duration of complete response; DOR = duration of response, OS = overall survival, PFS = progressive free survival, TTNT = time to next treatment.

Planned subgroup analyses

According to the presented SC Statistical Analysis Plan GO29781, the following subgroup analyses were performed.

Table 12 Subgroups for subgroup analyses - initial IV SAP same study (GO29781)

Subgroups for both R/R DLBCL/trFL and R/R FL	Grouping
Age	<65, ≥65
Sex	Male, Female
Ethnicity	Hispanic or Latino, Not Hispanic or Latino, Not stated or Unknown
Race	White, Black/ African American, Asian, American Indian or Alaska Native, Multiple, Unknown
Body Mass index	< median, ≥ median
Eastern Cooperative Oncology Group (ECOG) status	0, ≥1
CD20 status	Positive, negative
Prior lines of therapy	2 , 3+
R/R to last line of therapy	Refractory, non-refractory
Received prior CAR-T therapy	Yes, No
R/R to prior anti-CD20 therapy	Refractory, non-refractory
Time since last anti-CD20	3 months or less, more than 3 months

Subgroups for R/R FL only	Grouping
Double Refractory to Prior Anti-CD20 Therapy and Prior Alkylator Therapy	Yes, No
R/R to prior alkylator therapy	Refractory, non-refractory
R/R to prior PI3K inhibitor	Refractory, non-refractory
PD within 24 months of start of 1L therapy	Yes, No
FLIPI Score	Low (0-1), Intermediate (2), High (3-5)
Bulky disease (> 6cm)	Yes, No
EZH2 mutation	Mutant, Wild-type
Received prior Rituximab and Lenalidomide	Yes, No

DLBCL= Diffuse large B-cell lymphoma; GCB=Germinal center B-cell, NHL= Non-Hodgkin's lymphoma; PMBCL=primary mediastinal B-cell lymphoma; R/R= relapsed or refractory trFL=transformed follicular lymphoma

The Co-primary endpoint(s) were tested at 5% and both needed to be significant in order to demonstrate non-inferiority of mosunetuzumab SC compared to the reference mosunetuzumab IV. All other endpoints (PK and efficacy) were not tested formally and were only considered exploratory.

Results

Participant flow

Study GO29781 is an ongoing, phase I/II, open-label, multicohort study. For all cohorts, 987 patients were screened and 260 patients were screen failures. The most common reasons were: failing to meet the laboratory values criteria for study inclusion (n=50), failing to meet the historical histologically-documented haematological diagnosis criteria for study inclusion (n=43), and other (n=47).

Of the 727 patients eligible for study entry across all cohorts, 181 patients were included in group F from seven countries: United States 63 (12), Australia 36 (9), Canada 30 (3), Republic of Korea 15 (3), Spain 14 (4), Germany 13 (3), and United Kingdom 10 (3).

Disposition for the IV cohort B11 exp R/R FL (n=90) and the SC cohort F2 exp R/R FL (N=94) were similar at the CCODs (27.08.2021 and 01.02.2024, respectively).

The main reason for study discontinuation from initial treatment was progressive disease: 27.8% in the B11 exp R/R FL cohort and 23.4% in the F2 exp R/R FL cohort; time on study was 2.4 months longer in the latter cohort (see below).

Recruitment

The SCE presents response data from N = 94 patients treated with mosunetuzumab SC monotherapy in the F2 exp R/R FL cohort (CCOD: 01 February 2024). Data from the B11 exp R/R FL cohort (N = 90, CCOD: 27 August 2021), which used the currently approved dose and schedule for mosunetuzumab IV, is included as a comparator.

Conduct of the study

Not applicable

Baseline data

Although patients in F2 exp R/R FL cohort enrolled several years after the B11 exp R/R FL cohort

(CCOD 2.5 years apart) they enrolled based on the same eligibility criteria and from the same study sites. In general, demographics in the two cohorts were comparable, although some notable differences were seen: Patients in the F2 exp R/R FL cohort were older [65 years (range: 35-84)] than the B11 exp R/R FL cohort [60 years (range 29-90)]. On the other hand, there were more patients with ECOG 0 compared to 1 in the F2 exp R/R FL cohort compared to the B11 exp R/R FL cohort (67.0% vs. 58.4%, respectively).

A higher frequency of risk factors for the F2 exp R/R FL cohort related to FLIPI and Ann Arbor stage III/IV at study entry were observed, whereas higher risk factor frequencies in the B11 exp R/R FL cohort included patients with 3L+ treatments, refractoriness to prior CD20-treatment, and POD24. The importance of these various risk factors is unclear, which the multivariate regression analysis and propensity score analysis were aiming to correct.

Table 13 Summary of demographic and baseline characteristics in IV group B (CCOD 27 August 2021) and SC group F (CCOD 01 February 2024), Safety evaluable patients

	IV Mosunetuzumab (N = 218)			SC Mosunetuzumab (N = 181)	
	B11 RP2D NHL (N = 218)	B11 RP2D FL Expansion (N = 90)	Group F NHL (N = 181)	F2 RP2D NHL (N = 139)	F2 RP2D FL Expansion (N = 94)
Age (yr)					
n	218	90	181	139	94
Mean (SD)	63.0 (12.8)	60.0 (12.0)	65.1 (10.3)	64.4 (10.5)	64.5 (9.8)
Median	64	60	66	65	65
Min - Max	24 - 96	29 - 90	24 - 88	24 - 84	35 - 84
Age group (yr)					
n	218	90	181	139	94
18-65	124 (56.9%)	62 (68.9%)	87 (48.1%)	71 (51.1%)	48 (51.1%)
> 65	94 (43.1%)	28 (31.1%)	94 (51.9%)	68 (48.9%)	46 (48.9%)
≥ 65	102 (46.8%)	30 (33.3%)	97 (53.6%)	70 (50.4%)	48 (51.1%)
Sex					
n	218	90	181	139	94
Male	145 (66.5%)	55 (61.1%)	106 (58.6%)	83 (59.7%)	53 (56.4%)
Female	73 (33.5%)	35 (38.9%)	75 (41.4%)	56 (40.3%)	41 (43.6%)
Ethnicity					
n	218	90	181	139	94
Hispanic or Latino	10 (4.6%)	7 (7.8%)	5 (2.8%)	5 (3.6%)	2 (2.1%)
Not Hispanic or Latino	198 (90.8%)	77 (85.6%)	167 (92.3%)	126 (90.6%)	88 (93.6%)
Not Stated	6 (2.8%)	5 (5.6%)	6 (3.3%)	6 (4.3%)	2 (2.1%)
Unknown	4 (1.8%)	1 (1.1%)	3 (1.7%)	2 (1.4%)	2 (2.1%)
Race					
n	218	90	181	139	94
American Indian or Alaska Native	1 (0.5%)	1 (1.1%)	0	0	0
Asian	23 (10.6%)	8 (8.9%)	26 (14.4%)	20 (14.4%)	10 (10.6%)
Black or African American	6 (2.8%)	4 (4.4%)	3 (1.7%)	3 (2.2%)	2 (2.1%)
Native Hawaiian or other Pacific Islander	0	0	1 (0.6%)	1 (0.7%)	1 (1.1%)
White	179 (82.1%)	74 (82.2%)	147 (81.2%)	111 (79.9%)	80 (85.1%)
Multiple	0	0	1 (0.6%)	1 (0.7%)	0
Unknown	9 (4.1%)	3 (3.3%)	3 (1.7%)	3 (2.2%)	1 (1.1%)
Height (cm) at baseline					
n	201	82	173	134	91
Mean (SD)	170.62 (10.16)	169.92 (10.83)	169.80 (9.80)	170.08 (9.74)	169.30 (10.04)
Median	171.3	171.45	170.2	170.95	170
Min - Max	138.0 - 195.0	138.0 - 193.0	149.9 - 192.2	150.0 - 192.2	150.0 - 188.0
ECOG at baseline					
n	218	90	181	139	94
0	100 (45.9%)	53 (58.9%)	104 (57.5%)	83 (59.7%)	63 (67.0%)
1	118 (54.1%)	37 (41.1%)	77 (42.5%)	56 (40.3%)	31 (33.0%)

	IV Mosunetuzumab (N = 218)			SC Mosunetuzumab (N = 181)	
	B11 RP2D NHL (N = 218)	B11 RP2D FL Expansion (N = 90)	Group F NHL (N = 181)	F2 RP2D NHL (N = 139)	F2 RP2D FL Expansion (N = 94)
BMI (kg/m2) at baseline					
n	201	82	170	131	88
Mean (SD)	27.45 (5.54)	28.24 (5.57)	26.42 (4.90)	26.50 (4.62)	26.37 (4.59)
Median	26.7	27.51	26.21	26.34	26.47
Min - Max	14.9 - 52.2	17.0 - 45.2	16.2 - 45.3	16.2 - 45.3	16.2 - 45.3

Percentages are based on n for each estimate
Group B Data Cutoff Date - 27AUG2021
Group F Data Cutoff Date - 01FEB2024
Source: t dm INIT B11F SE

Table 14 Summary of cancer history, B11 Exp R/R FL cohort vs. F2 Exp R/R FL cohort, study GO29781 (intent-to-treat patients)

	B11 FL RP2D 1.0/2.0/60.0 mg w/30.0 mg on C3+ (N=90)	F2 FL RP2D 5.0/45.0/45.0 mg (N=94)
Time from Initial Diagnosis to First Study Treatment (Months)		
n	90	94
Mean (SD)	94.5 (59.2)	117.4 (81.5)
Median	82.2	95.1
Range	11 - 292	15 - 424
NHL Subtype at Study Entry		
n	90	94
FL	90 (100%)	94 (100%)
NHL - Study Entry Stage (Ann Arbor Stage)		
n	90	94
STAGE I	5 (5.6%)	3 (3.2%)
STAGE II	16 (17.8%)	9 (9.6%)
STAGE III	25 (27.8%)	32 (34.0%)
STAGE IV	44 (48.9%)	50 (53.2%)
Time from Last Anti-CD20 to First Mosun Dose Date (Months)		
n	90	92
Mean (SD)	19.5 (21.3)	20.9 (19.9)
Median	13.3	12.9
Range	1 - 100	1 - 100
by category:		
< 3 months	23 (25.6%)	12 (13.0%)
>= 3 months	67 (74.4%)	80 (87.0%)
Time from Last Prior Therapy to First Mosun Dose Date (Months)		
n	90	92
Mean (SD)	14.2 (16.9)	16.5 (19.2)
Median	6.7	8.4
Range	0 - 89	0 - 100
by category:		
< 3 months	31 (34.4%)	23 (25.0%)
>= 3 months	59 (65.6%)	69 (75.0%)
SPD at Baseline (Initial Treatment)		
n	90	94
Mean (SD)	3862.6 (3164.3)	3697.2 (3518.9)
Median	3014	2560.3
Range	234 - 15799	176 - 19676
by category:		
< 3000 mm2	45 (50.0%)	57 (60.6%)
>= 3000 mm2	45 (50.0%)	37 (39.4%)
FL IPI Index 1 Risk Factors		
n	90	94
0	3 (3.3%)	4 (4.3%)
1	23 (25.6%)	10 (10.6%)
2	24 (26.7%)	27 (28.7%)
3	21 (23.3%)	30 (31.9%)
4	18 (20.0%)	14 (14.9%)
5	1 (1.1%)	9 (9.6%)
Bulky Disease (>6cm)		
n	90	94
Yes	31 (34.4%)	23 (24.5%)
No	59 (65.6%)	71 (75.5%)
Bulky Disease (>7cm)		
n	90	94
Yes	16 (17.8%)	22 (23.4%)
No	74 (82.2%)	72 (76.6%)
Bulky Disease (>10cm)		
n	90	94
Yes	2 (2.2%)	6 (6.4%)
No	88 (97.8%)	88 (93.6%)

Numbers analysed

Table 15 Dose escalation and expansion cohorts in study GO29781 contributing to safety, PK and Efficacy

Mosunetuzumab SC Monotherapy							
Group F (Cycle 1 step-up dosing)							
	Dose Escalation			**Dose Expansion**			
	F1	**F2**	**F3**	**F1**		**F2**	
Histologies	NHL	NHL	NHL	R/R DLBCL /tr FL	R/R FL	R/R DLBCL /tr FL	R/R FL
N	7	4	3	22	10	41	94 [a]
Dose	5/15/45 mg	5/45/45 mg	5/45/90/45 mg	5/15/45 mg		5/45/45 mg (RP2D)	
Group D (Non-fractionated [fixed] dosing)							
D1–D6 N = 48 1.6 mg–20 mg NHL							
Mosunetuzumab IV Monotherapy							
Group B (Cycle 1 step-up dosing)							
	B11			**B11**			
Histologies	NHL			R/R FL			
N	218			90			
Dose	1/2/60/30 mg (RP2D)			1/2/60/30 mg (RP2D)			

CCOD = clinical cut-off date; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; NHL = non-Hodgkin lymphoma; Q3W = every 3 weeks; RP2D = recommended phase 2 dose; R/R = relapsed or refractory; SC = subcutaneous(ly)

[a] There were 93 patients in the popPK and exposure response analyses as 1 patient who enrolled withdrew consent, did not have any available PK data, and thus was excluded from the analysis.

Note: Not all dose groups and cohorts will be presented in all dossier components. The content and format of the dossier was discussed in detail and was accepted by the Agency.

Dosing schedule x/y/**z** mg means, x mg on Cycle 1 Day 1, y mg on Cycle 1 Day 8, **z** mg on Cycle 1 Day 15; then from Cycle 2 onwards, **z** mg on Day 1 of Q3W cycles.

Dosing schedule w/x/y/**z** means, w mg of Cycle 1 Day 1, x mg of Cycle 1 Day 8, y mg on Cycle 1 Day 15, and Cycle 2 Day 1, **z** mg on Day 1 of subsequent Q3W cycles.

Exposure was similar between SC and IV efficacy or safety assessment populations. The median number of cycles received (SC monotherapy vs. IV monotherapy) was 8 (range: 1-17). Median treatment duration was similar and the SC efficacy cohort had slightly longer time on study compared to the IV efficacy cohort (20.7 months vs. 18.3, respectively).

Table 16 Summary of efficacy observation time, F2 Exp R/R FL and B11 Exp R/R FL cohorts, study GO29781

	B11 exp R/R FL cohort [a] (N=90)	F2 exp R/R FL cohort [b] (N=94)
Time on study (months), median (range)[c]	18.3 (2.0–27.5)	20.7 (1–34)
Survival follow-up [d] (months), median (range)	Not analyzed	21.9 (1*–34)
Duration of INV-assessed response follow-up [d] (months), median (range)	15.8 (1*–23)	16.1 (2*–27)
Duration of IRF-assessed response follow-up [d] (months), median (range)	14.9 (0–23)	16.0 (0–23)

CCOD = clinical cutoff data; Exp = expansion; FL = follicular lymphoma; INV = investigator; IRF = Independent Review Facility; R/R = relapsed / refractory.

[a] CCOD = 27 August 2021

[b] CCOD = 1 February 2024

[c] Time on study is from start of first dose to study discontinuation date, death date, or CCOD, whichever is earliest.

[d] Estimated by reverse Kaplan-Meier methodology.

* Censored observation.

Outcomes and estimation

Efficacy analyses included standalone efficacy analyses for the SC (F2 exp R/R FL) cohort, and a retrospective comparison between F2 exp R/R FL cohort and the IV (B11 exp R/R FL) cohort. No formal hypothesis testing has been done and, as such, comparisons were considered exploratory.

Primary objective in study GO29781 pertinent to this application:

To evaluate PK NI of mosunetuzumab SC RP2D (F2 expansion cohort) compared to the reference mosunetuzumab IV RP2D (B11 expansion cohort) in patients with R/R FL with at least two prior lines of systemic therapy.

Secondary objective in study GO29781 pertinent to this application:

Where evaluation of efficacy of mosunetuzumab as single agent is not a primary objective, to make a preliminary assessment of the anti-tumor activity of mosunetuzumab as a single agent in patients with R/R NHL (in this case R/R FL).

The secondary efficacy endpoint was not formally tested and can only be considered supportive of the primary objective of showing non-inferiority of exposure between the two routes of administration (SC vs IV).

The in- and exclusion criteria were the same in cohort B11 and F2, but there was no stratification between the two cohorts since F2 recruited patients at a later timepoint compared to cohort B11 (CCOD 2.5 years apart).

Table 17 Overview of Efficacy (F2 Exp R/R FL vs B11 Exp R/R FL), Study GO29781

	INV-assessed		IRF-assessed	
	B11 Exp R/R FL [a]	F2 Exp R/R FL [b]	B11 Exp R/R FL [a]	F2 Exp R/R FL [b]
Complete Response (±PET)				
Univariable Analysis				
N	90	94	90	94
Responders	54 (60.0%)	57 (60.6%)	54 (60.0%)	55 (58.5%)
95% CI	(49.13, 70.19)	(50.02, 70.56)	(49.13, 70.19)	(47.88, 68.59)
Odds ratio (95% CI)	1.03 (0.57, 1.85)		0.94 (0.52, 1.69)	
Adjusted Analyses[a]				
Propensity Score Analysis (IPTW)				
Responders	64.24%	59.57%	64.00%	58.55%
Odds Ratio (95% CI)	0.82 (0.45, 1.49)		0.79 (0.44, 1.44)	
Multivariable Regression Analysis				
Odds Ratio (95% CI)	0.81 (0.42, 1.59)		0.81 (0.42, 1.55)	
Objective Response (±PET)				
Univariable Analysis				
N	90	94	90	94
Responders	70 (77.8%)	69 (73.4%)	72 (80.0%)	70 (74.5%)
95% CI	(67.79, 85.87)	(63.29, 81.99)	(70.25, 87.69)	(64.43, 82.91)
Odds ratio (95% CI)	0.79 (0.40, 1.55)		0.73 (0.36, 1.46)	
Adjusted Analyses				
Propensity Score Analysis (IPTW)				
Responders	81.22%	71.41%	82.56%	73.64%
Odds Ratio (95% CI)	0.58 (0.29, 1.15)		0.59 (0.29, 1.20)	
Multivariable Regression Analysis				
Odds Ratio (95% CI)	0.51 (0.23, 1.10)		0.55 (0.25, 1.19)	
Duration of Complete Response (±PET)				
Univariable Analysis				
N	54	57	54	55
Patients with event (%)	12 (22.2%)	17 (29.8%)	16 (29.6%)	19 (34.5%)
PD, n	12	15	16	17
Death, n	0	2	0	2
Median, months (95% CI)	NE (17.8, NE)	21.8 (18.2, NE)	NE (14.6, NE)	20.8 (18.8, NE)
Hazard Ratio (95% CI)	1.09 (0.52, 2.28)		0.98 (0.50, 1.91)	
12-month Event-free Rate, % (95% CI)	80.37 (68.79, 91.96)	78.92 (67.76, 90.08)	71.42 (57.94, 84.90)	72.35 (59.87, 84.84)
Adjusted Analyses				
Propensity Score Analysis (IPTW)				
Median, months	NE	20.76	NE	20.76
Hazard Ratio (95% CI)	1.29 (0.62, 2.68)		1.21 (0.61, 2.38)	
Multivariable Regression Analysis				
Hazard Ratio (95% CI)	1.12 (0.51, 2.48)		1.08 (0.53, 2.19)	

	INV-assessed		IRF-assessed	
	B11 Exp R/R FL [a]	F2 Exp R/R FL [b]	B11 Exp R/R FL [a]	F2 Exp R/R FL [b]
Duration of Response (±PET)				
Univariable Analysis				
N	70	69	72	70
Patients with event (%)	27 (38.6%)	26 (37.7%)	29 (40.3%)	26 (37.1%)
PD, n	26	23	28	22
Death, n	1	3	1	4
Median, months (95% CI)	22.8 (18.7, NE)	22.4 (18.7, NE)	22.8 (9.7, NE)	22.4 (16.8, 22.8)
Hazard Ratio (95% CI)	0.87 (0.51, 1.49)		0.87 (0.51, 1.48)	
12-month Event-free Rate, % (95% CI)	64.84 (53.13, 76.54)	71.7 (60.86, 82.53)	61.83 (49.95, 73.71)	69.94 (58.52, 81.36)
Adjusted Analyses				
Propensity Score Analysis (IPTW)				
Median, months	22.77	22.44	22.77	22.44
Hazard Ratio (95% CI)	1.03 (0.60, 1.77)		1.02 (0.60, 1.75)	
Multivariable Regression Analysis				
Hazard Ratio (95% CI)	0.94 (0.53, 1.67)		0.97 (0.55, 1.71)	
Progression-free Survival (±PET)				
Univariable Analysis				
N	90	94	90	94
Patients with event (%)	41 (45.6%)	47 (50.0%)	42 (46.7%)	43 (45.7%)
PD, n	39	41	41	34
Death, n	2	6	1	9
Median, months (95% CI)	21.1 (11.8, NE)	18.5 (11.3, 24.0)	17.9 (10.1, NE)	18.5 (12.9, 24.0)
Hazard Ratio (95% CI)	1.05 (0.69, 1.60)		0.92 (0.60, 1.41)	
12-month Event-free Rate, % (95% CI)	57.57 (46.78, 68.35)	59.36 (49.24, 69.47)	57.65 (46.87, 68.43)	62.28 (52.05, 72.52)
Adjusted Analyses				
Propensity Score Analysis (IPTW)				
Median, months	21.06	18.46	21.75	18.46
Hazard Ratio (95% CI)	1.19 (0.79, 1.81)		1.05 (0.68, 1.61)	
Multivariable Regression Analysis				
Hazard Ratio (95% CI)	1.23 (0.79, 1.92)		1.03 (0.66, 1.62)	
Overall Survival	B11 Exp. R/R FL		F2 Exp. R/R FL	
Univariable Analysis				
N	90		94	
Patients with event (%)	8 (8.9%)		11 (11.7%) [c]	
Median, months (95% CI)	NE (NE)		NE (NE)	
Hazard Ratio (95% CI)	1.28 (0.51, 3.19)			
12-month Event-free Rate, % (95% CI)	92.99 (87.56, 98.41)		90.16 (84.06, 96.27)	
Adjusted Analyses				
Propensity Score Analysis (IPTW)				
Median, months	NE		NE	
Hazard Ratio (95% CI)	1.53 (0.61, 3.81)			
Multivariable Regression Analysis				
Hazard Ratio (95% CI)	1.76 (0.64, 4.83)			

CI = confidence interval; Exp. = expansion; FL = follicular lymphoma; INV = investigator; IPTW = inverse probability of treatment weighting; IRF = independent review facility; PD = progressive disease; PET = Positron Emission Tomography; R/R = relapsed/refractory; RP2D = recommended phase II dose.

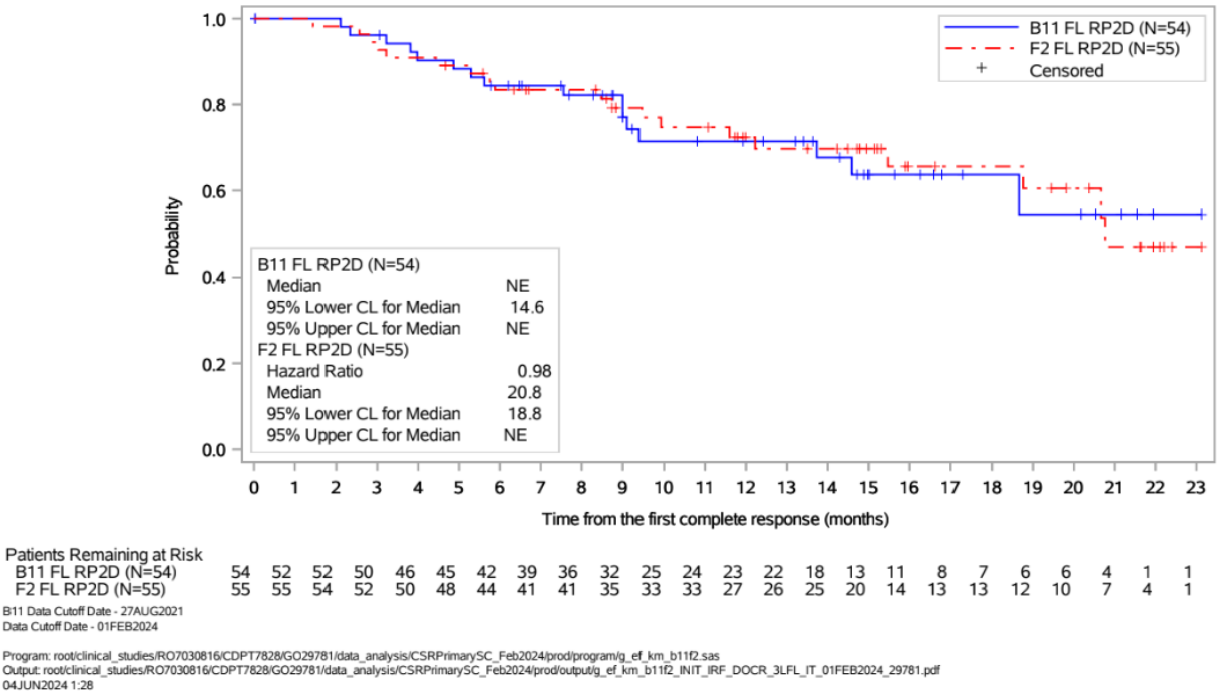
Note: Baseline covariates adjusted for in the adjusted analyses include age (≥ 65 vs. <65), sex (female vs. male), race (Asian, Other vs. White), Ann Arbor Stage (I/II vs. IV/III), FLIPI 1 Risk (≥ 3 vs. < 3), Prior lines (3 + vs. 2), R/R to anti-CD20 (Non-refractory vs. Refractory), and POD24 (No vs. Yes).

[a] CCOD = 27 August 2021

[b] CCOD = 1 February 2024

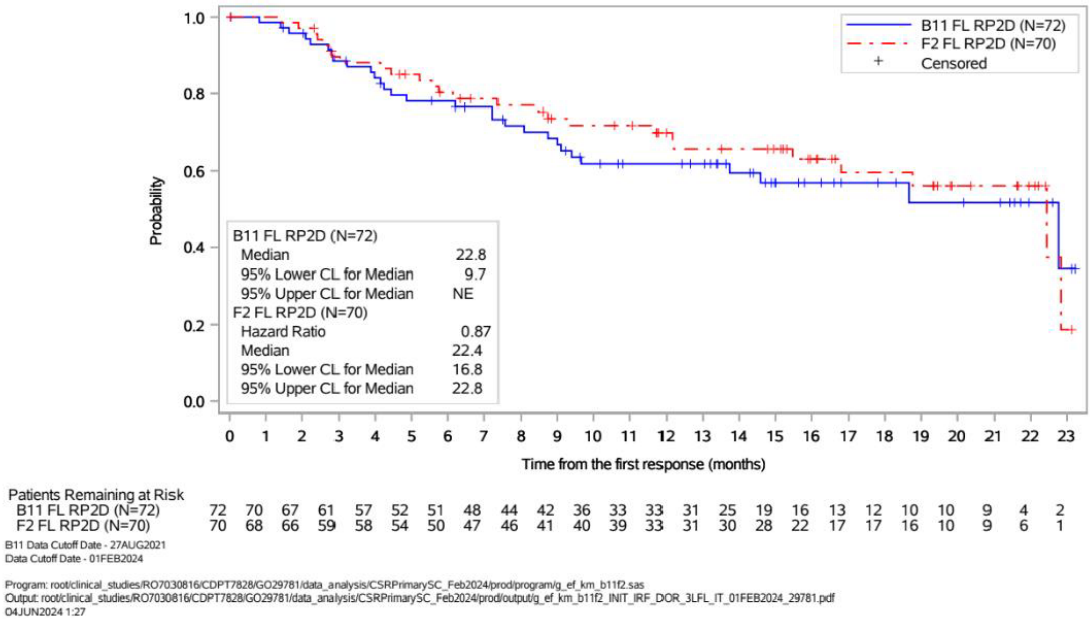
[c] One death was discovered after the CCOD but prior to the data snapshot date. The death was reported with unknown time and cause, after the patient had already withdrawn consent on Study Day 45. Because the date of death is missing completely, this event of death is not included in the time-to-event or overall survival analysis.

Figure 16 Kaplan-Meier plot of time-to-event, DOCR as assessed by IRF, F2 Exp R/R FL vs. B11 Exp R/R FL, Study GO29781 (Limited to patients with CR)



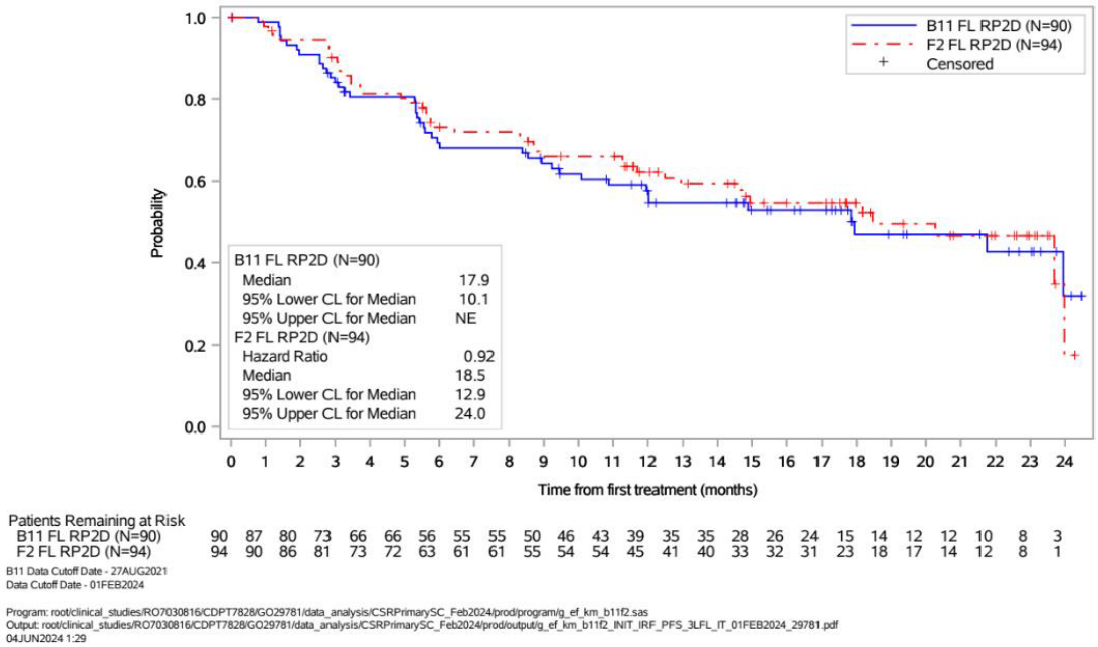
CR = complete response; DOCR = duration of complete response; Exp = expansion; FL = follicular lymphoma; IRF = Independent Review Facility; R/R = relapsed/refractory; RP2D = recommended Phase II dose.

Figure 17 Kaplan-Meier plot of time-to-event, DOR as assessed by IRF, F2 Exp R/R FL vs. B11 Exp R/R FL, Study GO29781 (Limited to patients with OR)



DOR = duration of response; Exp = expansion; FL = follicular lymphoma; IRF = Independent Review Facility; OR = overall response; R/R = relapsed/refractory; RP2D = recommended Phase II dose.

Figure 18 Kaplan-Meier plot of time-to-event, PFS as assessed by IRF, F2 Exp R/R FL vs. B11 Exp R/R FL, Study GO29781 (Intent-to-treat patients)



Exp = expansion; FL = follicular lymphoma; IRF = independent review facility; ITT = intent-to-treat; PFS = progression-free survival; R/R = relapsed/refractory; RP2D = recommended Phase II dose.

Generally, efficacy assessments favoured the IV treatment over SC treatment in R/R FL, although with wide confidence intervals thus not refuting non-inferiority. Thus, the efficacy of mosunetuzumab SC monotherapy in the F2 exp R/R FL cohort is considered comparable to the approved mosunetuzumab IV monotherapy regimen used in the B11 exp R/R FL cohort.

Ancillary analyses

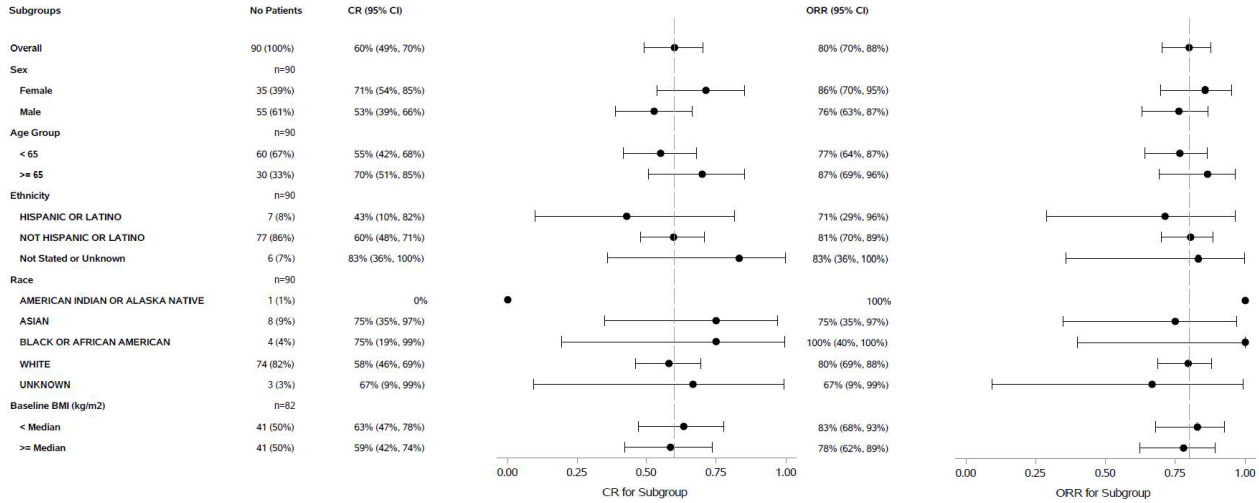
Subgroup analyses of the CR rate and ORR by IRF assessment generally demonstrated consistency of the treatment effect across relevant subpopulations:

In the F2 exp R/R FL cohort, in general the CR rate and ORR for all subgroups were consistent with the overall rates of the cohort. The ORR was numerically lower in patients that were refractory to last prior therapy (64% [95% CI: 51%, 76%]) compared to those that were not (91% [95% CI: 77%, 98%]), and in patients that were refractory to any prior anti-CD20 therapy (65% [95% CI: 52%, 77%]) compared to those that were not (94% [95% CI: 79%, 99%]). No other major differences were observed among the other subgroups.

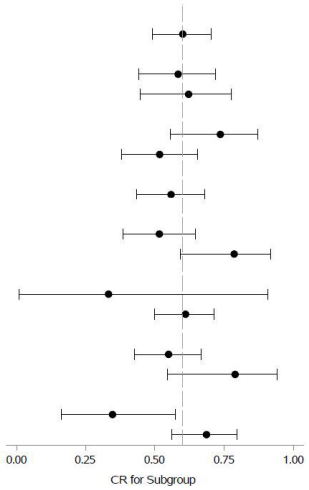
One patient that was negative for CD20 expression did not have a response to the treatment.

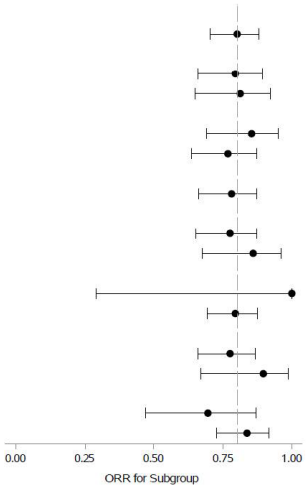
In the B11 exp R/R FL cohort, CR rate and ORR for all subgroups were consistent with the overall rates of the cohort. No major differences were observed among the subgroups.

Figure 19 Subgroup analysis of ORR and CR rate (IRF assessment) for Patients in the R/R FL B11 Expansion cohort (CCOD: 27 August 2021), efficacy-evaluable patients

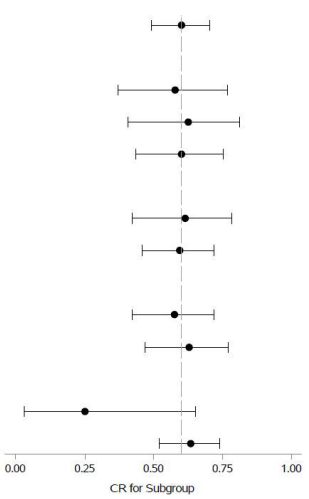


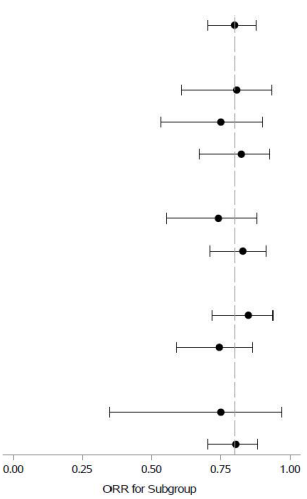
Subgroups	No Patients	CR (95% CI)	ORR (95% CI)
Overall	90 (100%)	60% (49%, 70%)	80% (70%, 88%)
Baseline ECOG	n=90		
0	53 (59%)	58% (44%, 72%)	79% (66%, 89%)
>=1	37 (41%)	62% (45%, 78%)	81% (65%, 92%)
No.of Prior Systemic Therapies	n=90		
2	34 (38%)	74% (56%, 87%)	85% (69%, 95%)
3+	56 (62%)	52% (38%, 65%)	77% (64%, 87%)
Baseline CD20	n=68		
Positive	68 (100%)	56% (43%, 68%)	78% (66%, 87%)
Relapse or Refractory to Last Prior Therapy	n=90		
Refractory	62 (69%)	52% (39%, 65%)	77% (65%, 87%)
Non-Refractory	28 (31%)	79% (59%, 92%)	86% (67%, 96%)
Received prior CAR-T therapy	n=90		
Yes	3 (3%)	33% (1%, 91%)	100% (29%, 100%)
No	87 (97%)	61% (50%, 71%)	79% (69%, 87%)
Relapse or Refr. to Any Prior Anti-CD20 Therapy	n=90		
Refractory	71 (79%)	55% (43%, 67%)	77% (66%, 87%)
Non-Refractory	19 (21%)	79% (54%, 94%)	89% (67%, 99%)
Time Since Last CD20 (Days)	n=90		
3 months or less	23 (26%)	35% (16%, 57%)	70% (47%, 87%)
More than 3 months	67 (74%)	69% (56%, 79%)	84% (73%, 92%)



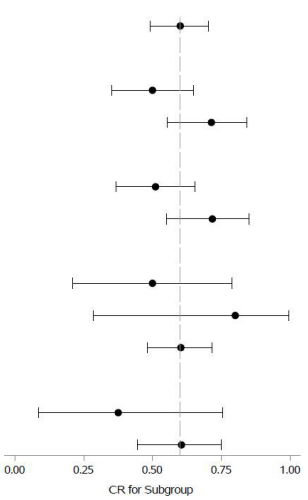


Subgroups	No Patients	CR (95% CI)	ORR (95% CI)
Overall	90 (100%)	60% (49%, 70%)	80% (70%, 88%)
FL IPI 1 Risk Factors	n=90		
Low (0-1)	26 (29%)	58% (37%, 77%)	81% (61%, 93%)
Intermediate (2)	24 (27%)	63% (41%, 81%)	75% (53%, 90%)
High (3-5)	40 (44%)	60% (43%, 75%)	83% (67%, 93%)
Bulky Disease (>6cm)	n=90		
Yes	31 (34%)	61% (42%, 78%)	74% (55%, 88%)
No	59 (66%)	59% (46%, 72%)	83% (71%, 92%)
Start Systemic Therapy < 24 months to PD	n=90		
Yes	47 (52%)	57% (42%, 72%)	85% (72%, 94%)
No	43 (48%)	63% (47%, 77%)	74% (59%, 86%)
Received Prior Rituximab & Lenalidomide Therapy	n=90		
Yes	8 (9%)	25% (3%, 65%)	75% (35%, 97%)
No	82 (91%)	63% (52%, 74%)	80% (70%, 88%)





Subgroups	No Patients	CR (95% CI)	ORR (95% CI)
Overall	90 (100%)	60% (49%, 70%)	80% (70%, 88%)
Double Refractory	n=90		
Yes	48 (53%)	50% (35%, 65%)	71% (56%, 83%)
No	42 (47%)	71% (55%, 84%)	90% (77%, 97%)
Relapse or Refractory to Any Prior ALKY Therapy	n=90		
Refractory	51 (57%)	51% (37%, 65%)	71% (56%, 83%)
Non-Refractory	39 (43%)	72% (55%, 85%)	92% (79%, 98%)
Relapse or Refractory to Any Prior PI3K Therapy	n=90		
Refractory	12 (13%)	50% (21%, 79%)	75% (43%, 95%)
Non-Refractory	5 (6%)	80% (28%, 99%)	100% (48%, 100%)
No Prior Pi3K Therapy	73 (81%)	60% (48%, 72%)	79% (68%, 88%)
EZH2 mutation	n=51		
Mutant	8 (16%)	38% (9%, 76%)	75% (35%, 97%)
Wild-type	43 (84%)	60% (44%, 75%)	79% (64%, 90%)



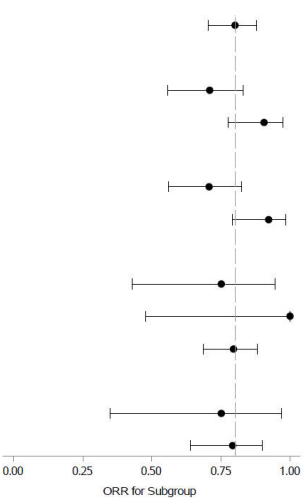
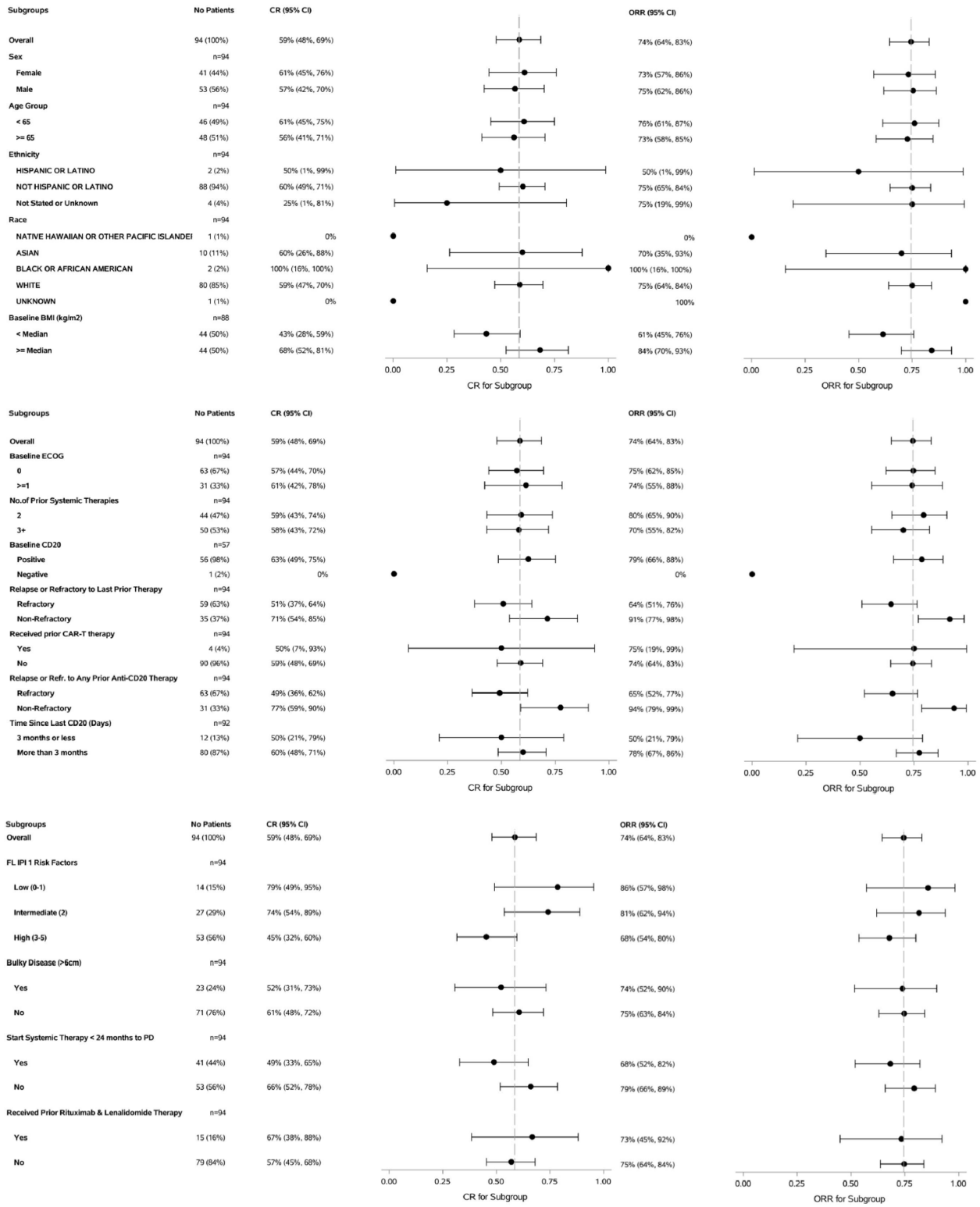
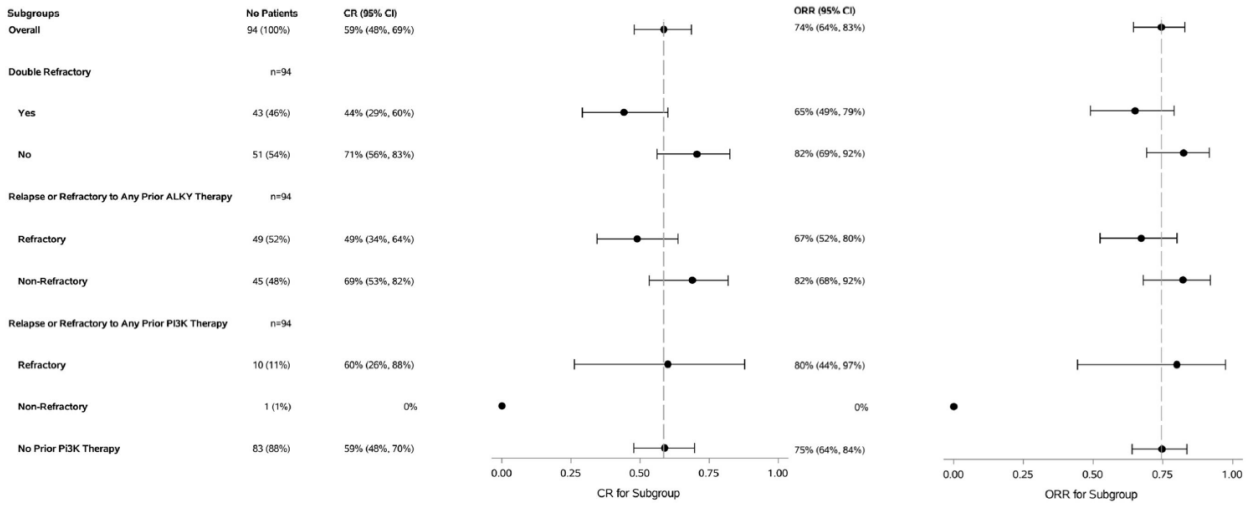


Figure 20 Subgroup analysis of ORR and CR rate (IRF assessment) for Patients in the F2 Exp R/R FL cohort, intent-to-treat patients





2.6.5.3. Clinical studies in special populations

See the *Ancillary analyses* section above.

2.6.5.4. Supportive study(ies)

The MAH submitted results from the supportive study CO41942, an ongoing Phase Ib/II, open-label, multicenter study with a non-randomized stage evaluating the safety, pharmacokinetics, and efficacy of mosunetuzumab plus lenalidomide (Mosun + Len), and a randomized stage evaluating the safety, tolerability, and pharmacokinetics of SC versus IV Mosun+Len in patients with FL.

Study CO41942 was however considered to be of limited value with regards to efficacy and safety results: The IV treatment schedule is different from study GO29781 and so is the SC treatment in that treatment is given every 4 weeks instead of every 3 weeks. In addition, lenalidomide is added in both arms.

Thus, an assessment of efficacy and safety in study C041942 was not considered relevant for the exploratory endpoint of efficacy and safety in study GO29781, where the function of these exploratory endpoints were to support the primary PK non-inferiority endpoint of SC mosunetuzumab monotherapy compared to IV treatment.

2.6.6. Discussion on clinical efficacy

Mosunetuzumab IV is currently approved for the treatment of follicular lymphoma (FL) after ≥2 prior lines of therapy. The MAH is seeking approval for SC treatment in the same indication.

Design and conduct of clinical studies

The pivotal study GO29781 is an "ongoing Phase I/II, 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 chronic lymphocytic leukemia (CLL)".

The primary objective for this part of study GO29781 was to evaluate the PK non-inferiority of mosunetuzumab SC monotherapy treatment (cohort F2 exp R/R FL) compared to the approved mosunetuzumab IV monotherapy treatment (cohort B11 exp R/R FL) based on the co-primary PK endpoints; CtroughCYC3_OBS (observed) and AUC0-84 (model-predicted). Efficacy analyses included

standalone efficacy analyses for the SC (F2 exp R/R FL) cohort, and a retrospective comparison, which was not formally tested and only supportive of the primary objective of non-inferiority, between SC (F2 exp R/R FL) cohort and the IV (B11 exp R/R FL) cohort.

In study GO29781 efficacy was assessed based on CR rate, ORR, DOR, duration of complete response, PFS, and OS. These are considered clinically relevant and match the efficacy evidence supporting the approved mosunetuzumab IV monotherapy indication. No formal statistical testing was performed for any of these endpoints.

The efficacy populations in the main study GO29781 consist of patients with R/R FL with ≥2 prior lines of systemic therapy 94 patients from the RP2D expansion cohort receiving mosunetuzumab monotherapy SC (F2 exp R/R FL) and 90 patients from the RP2D expansion cohort receiving mosunetuzumab monotherapy IV (B11 exp R/R FL). The two cohorts were not conducted at the same time and so no stratification could be performed. To mitigate differences between the two cohorts the same in- and exclusion criteria were used, and patients were recruited from the same sites.

The B11 exp R/R FL (n=90) (IV) cohort was the population assessed for the initial MAA. Therefore, only the SC F2 exp R/R FL cohort was assessed and compared to the former cohort. The schedule of efficacy assessments was the same between the B11 exp R/R FL cohort (IV) and F2 exp R/R FL cohort (SC).

Patients were expected to have FL that expressed CD20. All patients had received anti-CD20 directed therapy and could thus potentially have lost the CD20 epitope.

The analysis sets for PKNI were the Per Protocol PK (PPP) analysis population (F2 patients with adequate measurements) and for efficacy the efficacy-evaluable population includes all enrolled R/R FL patients from Group B11 expansion and Group F2 expansion.

A primary objective of the study GO29781 was to demonstrate non-inferiority of mosunetuzumab SC compared to the reference mosunetuzumab IV based on the corresponding co-primary PK endpoints being (1) observed serum C_{trough} at Cycle 3 (CtroughCYC3_OBS), and (2) model-predicted area under the concentration-time curve (AUC) from 0 to 84 days (AUC0–84). The primary objective and the related co-primary endpoints are supported and still considered clinically relevant for efficacy as both C_{trough} and AUC are considered key parameters to demonstrate similar exposure of the two formulations.

The estimand framework was not utilized for secondary efficacy endpoints. This is acceptable as these are not tested formally and only supportive of the primary objective of showing non-inferiority of exposure between the two routes of administration (SC vs IV).

During scientific advice, EMA/SA/000008635, the proposed efficacy endpoints were considered acceptable although there were limitations noted linked to the lack of formal hypothesis testing. Additionally, a minimum follow-up time of 12 months was advised which was followed by the MAH as the clinical cut-off date (CCOD) was 12 months after last patient in (1 February 2023) which allowed for a median of 16 months [95% CI: 14.8-19.4] of follow-up for duration of response.

Statistical methods of the secondary efficacy endpoints utilized logistic regression for responder analysis and survival methods for time to event endpoints. These are standard methods and endorsed. All efficacy variables except OS were both IRF and investigator assessed. Time to event endpoints included a Covid-19 sensitivity censoring. Additionally, multivariate regression analysis and propensity score analysis were implemented to account for potential imbalances of baseline characteristics. These are acceptable approaches.

For the IV formulation, the CCOD was 27 August 2021. For the SC formulation the CCOD was 1 February 2024, hence the comparison is done retrospectively. All analyses of secondary efficacy

endpoints are not formally tested and only considered exploratory.

Efficacy data and additional analyses

Participant flow:

For all cohorts of study G029781, 987 patients were screened, and 260 patients were screen failures. The most common reasons were failing to meet the laboratory values criteria for study inclusion (n=50), failing to meet the historical histologically-documented haematological diagnosis criteria for study inclusion (n=43), and other (n=47).

Disposition for the IV cohort B11 exp R/R FL (n=90) and the SC cohort F2 exp R/R FL (N=94) were similar at the CCODs (27.08.2021 and 01.02.2024, respectively).

The main reason for study discontinuation from initial treatment was progressive disease: 27.8% in the B11 exp R/R FL cohort and 23.4% in the F2 exp R/R FL cohort; time on study was 2.4 months longer in the latter cohort.

Baseline data:

There was no stratification between the two cohorts since patients in F2 exp R/R FL cohort enrolled several years after the B11 exp R/R FL cohort (CCOD 2.5 years apart) however participants were enrolled based on the same eligibility criteria and from the same study sites.

In general, demographics in the two cohorts were comparable, although some potentially notable differences were seen: Patients in the F2 exp R/R FL cohort were older [65 years (range: 35-84)] than the B11 exp R/R FL cohort [60 years (range 29-90), Table 2/SCE]. On the other hand, there were more patients with ECOG 0 compared to 1 in the F2 exp R/R FL cohort compared to the B11 exp R/R FL cohort (67.0% vs. 58.4%, respectively).

A higher frequency of risk factors for the F2 exp R/R FL cohort related to FLIPI and Ann Arbor stage III/IV at study entry were observed, whereas higher risk factor frequencies in the B11 exp R/R FL cohort included patients with 3L+ treatments, refractoriness to prior CD20-treatment, and POD24. The importance of these various risk factors is unclear, which the multivariate regression analysis and propensity score analysis were aiming to correct.

Exposure was similar between SC and IV efficacy or safety assessment populations. The median number of cycles received (SC monotherapy vs. IV monotherapy) was 8 (range: 1-17). Median treatment duration was similar and the SC efficacy cohort had slightly longer time on study compared to the IV efficacy cohort (20.7 months vs. 18.3, respectively).

Efficacy analyses included standalone efficacy analyses for the SC (F2 exp R/R FL) cohort, and a retrospective comparison between F2 exp R/R FL cohort and the IV (B11 exp R/R FL) cohort.

The efficacy endpoint (secondary) is not formally tested and can only be considered supportive of the primary objective of showing non-inferiority of exposure between the two routes of administration (SC vs IV).

The in- and exclusion criteria were the same in cohort B11 and F2, but there was no stratification between the two cohorts since F2 recruited patients at a later timepoint compared to cohort B11 (CCOD 2.5 years apart).

CR rate by IRF was comparable between the F2 exp R/R FL cohort and the B11 exp R/R FL cohort [(58.5% vs. 60.0%; odds ratio of 0.94 (95% CI: 0.52, 1.69)]. Odds ratios for the prespecified multivariate and propensity score analyses were both lower [0.81 (95% CI 0.42, 1.55) and 0.79 (95%

CI 0.44, 1.44), respectively].

Objective response (CR or PR) rate by IRF assessment was 74.5% vs. 80.0% for F2 exp R/R FL cohort vs. B11 exp R/R FL cohort. Odds ratios for the prespecified multivariable and propensity score analyses were both lower [0.55 (95% CI 0.25, 1.19) and 0.59 (95% CI 0.29, 1.20), respectively].

Among patients who had achieved CR by IRF assessment, 34.5% patients in the F2 exp R/R FL cohort and 29.6% patients in the B11 exp R/R FL cohort had subsequent disease progression (30.9% vs. 29.6%, respectively) or death (3.6% vs. 0, respectively) as the leading event. Median **DOCR** was 20.8 months (95% CI: 18.8, NE) in the F2 exp R/R FL cohort and the median was not reached in the B11 exp R/R FL cohort at the corresponding CCODs. Hazard ratio DOCR based on univariable analysis was 0.98 (95% CI: 0.50, 1.91) and higher for the prespecified multivariable and propensity score analyses [1.08 (95% CI 0.53, 2.19) and 1.12 (95% CI 0.61, 2.38), respectively]. See also the Kaplan-Meier plot comparing the DOCR as assessed by IRF for the F2 exp R/R FL cohort and B11 exp R/R FL cohorts.

Among patients with an overall response by IRF assessment, 37.1% patients in the F2 exp R/R FL cohort and 40.3% patients in the B11 exp R/R FL cohort had subsequent disease progression (31.4% vs. 38.9%) or death (5.7% vs. 1.4%) as the leading event. Median **DOR** was comparable with 22.4 months (95% CI: 16.8, 22.8) and 22.8 months (95% CI: 9.7, NE), respectively. Hazard ratio for DOR based on univariable analysis was 0.87 (95% CI: 0.51, 1.48) and higher for the prespecified multivariable and propensity score analyses [0.97 (95% CI 0.55, 1.71) and 1.02 (95% CI 0.60, 1.75), respectively]. See also the Kaplan-Meier plot comparing the DOR as assessed by IRF for the F2 exp R/R FL cohort and B11 exp R/R FL cohorts.

PFS by IRF assessment was comparable between the F2 exp R/R FL cohort and the B11 exp R/R FL cohort (median: 18.5 months [95% CI: 12.9, 24.0] vs. 17.9 months [10.1, NE], respectively). Hazard ratio for PFS based on univariable analysis was 0.92 (95% CI: 0.60, 1.41) and higher for the prespecified multivariable and propensity score analyses [1.03 (95% CI 0.66, 1.62) and 1.05 (95% CI 0.68, 1.61), respectively]. See also the Kaplan-Meier plot comparing PFS as assessed by IRF for the F2 exp R/R FL cohort and B11 exp R/R FL cohorts.

Median **OS** had not been reached in either cohort as of the respective CCODs. OS was comparable between the F2 exp R/R FL cohort and the B11 exp R/R FL cohort, with a Kaplan-Meier-estimated 12-month survival rate of 90.2% (95% CI: 84.06, 96.27) in the F2 exp R/R FL cohort and 93% (95% CI: 87.6, 98.4) in the B11 exp R/R FL cohort. Eleven patients (11.7%) had events of death by any cause in the F2 exp R/R FL cohort vs. 8 patients (8.9%) in the B11 exp R/R FL cohort. Data for OS are thus considered immature.

Generally, efficacy assessments favoured the IV treatment over SC treatment in R/R FL, although with wide confidence intervals. Thus, the efficacy of mosunetuzumab SC monotherapy in the F2 exp R/R FL cohort is considered comparable to the approved mosunetuzumab IV monotherapy regimen used in the B11 exp R/R FL cohort.

Subgroup analyses of the CR rate and ORR by IRF assessment generally demonstrated consistency of the treatment effect across relevant subpopulations:

In the F2 exp R/R FL cohort, in general the CR rate and ORR for all subgroups were consistent with the overall rates of the cohort. The ORR was numerically lower in patients that were refractory to last prior therapy (64% [95% CI: 51%, 76%]) compared to those that were not (91% [95% CI: 77%, 98%]), and in patients that were refractory to any prior anti-CD20 therapy (65% [95% CI: 52%, 77%]) compared to those that were not (94% [95% CI: 79%, 99%]). No other major differences were observed among the other subgroups. One patient that was negative for CD20 expression did not have a response to the treatment.

In the B11 exp R/R FL cohort, CR rate and ORR for all subgroups were consistent with the overall rates of the cohort. No major differences were observed among the subgroups.

The supportive study CO41942 is an ongoing Phase Ib/II, open-label, multicenter study with a non-randomized stage evaluating the safety, pharmacokinetics, and efficacy of mosunetuzumab plus lenalidomide (Mosun + Len), and a randomized stage evaluating the safety, tolerability, and pharmacokinetics of SC versus IV Mosun+Len in patients with FL.

Study CO41942 is considered to be of limited value with regards to efficacy and safety results, the IV treatment schedule is different from study GO29781 and so is the SC treatment in that treatment is given every 4 weeks instead of every 3 weeks. In addition, lenalidomide is added in both arms.

Thus, an assessment of efficacy and safety in this study is not considered relevant for the exploratory endpoint of efficacy and safety support to the primary PK non-inferiority endpoint of SC mosunetuzumab monotherapy compared to IV treatment.

2.6.7. Conclusions on the clinical efficacy

Efficacy data from the pivotal Study GO29781 showed SC mosunetuzumab to have a comparable anti-tumour activity to the IV monotherapy dosing regimen previously approved.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The primary safety pool includes the safety pool for the previously approved mosunetuzumab IV monotherapy in R/R FL patients after two or more prior systemic treatments (study GO29781, cohort B11 RP2D R/R NHL, n=218) and the safety pool for the SC treatment, which includes cohort F2 RP2D R/R NHL (n=139) also from study GO29781, amounting to a safety pool of 357 RP2D R/R NHL patients. There was a three-year difference between the conduct of the two cohorts, where the F2 cohort recruited during the COVID-19 pandemic: CCOD: B11 RP2D; 27.08.2021, F2 RP2D; 01.02.2024.

A comparison of safety between the two pools (IV and SC) is presented and discussed. Safety data collection procedures are per the initial MAA.

It should be taken into account that in study CO41942, mosunetuzumab is given in combination with lenalidomide, and although the two Mosun-Len arms can be compared, both the IV dose and SC dose are different from the dosing in study GO29781.

2.6.8.2. Adverse events

A total of 139 NHL patients (SC treated) has been added to the currently approved safety population (218 NHL IV treated patients) so that the safety database now comprises 357 patients.

Exposure is similar between the IV and SC safety population with a median number of cycles = 8 in both pools and similar dose intensity although with a shorter time on study (from start of first dose to study discontinuation date, death date or CCOD, whichever is the earliest) for the IV pool compared to the SC pool (14.3 months vs. 19.3 months, respectively).

Table 18 Summary of mosunetuzumab exposure in IV Group B (CCOD: 27 August 2021) and SC Group F (CCOD 01 February 2024) Safety evaluable patients

	IV Mosunetuzumab (N=218)		SC Mosunetuzumab (N=181)		
	B11 RP2D NHL (N=218)	B11 RP2D FL Expansion (N=90)	Group F NHL (N=181)	F2 RP2D NHL (N=139)	F2 RP2D FL Expansion (N=94)
Number of Doses Administered					
n	218	90	181	139	94
Mean (SD)	8.5 (4.6)	10.3 (4.1)	8.9 (4.1)	9.3 (4.2)	10.0 (3.7)
Median	10.0	10.0	10.0	10.0	10.0
Min - Max	1 - 21	1 - 19	1 - 21	1 - 21	3 - 21
Total Cumulative Dose (mg)					
n	218	90	181	139	94
Mean (SD)	251.2 (141.5)	303.6 (128.3)	352.8 (183.3)	374.4 (184.2)	404.4 (159.5)
Median	298.0	303.0	410.0	410.0	410.0
Min - Max	1 - 576	1 - 573	5 - 865	5 - 865	95 - 865
Number of Treatment Cycles					
n	218	90	181	139	94
Mean (SD)	6.6 (4.3)	8.2 (4.0)	6.9 (3.9)	7.2 (4.0)	7.9 (3.5)
Median	8.0	8.0	8.0	8.0	8.0
Min - Max	1 - 17	1 - 17	1 - 17	1 - 17	1 - 17
Number of Cycles					
Less than 8 cycles	105 (48.2%)	21 (23.3%)	73 (40.3%)	50 (36.0%)	21 (22.3%)
8 cycles	80 (36.7%)	53 (58.9%)	81 (44.8%)	66 (47.5%)	59 (62.8%)
9 to 16 cycles	16 (7.3%)	5 (5.6%)	18 (9.9%)	15 (10.8%)	8 (8.5%)
17 cycles	17 (7.8%)	11 (12.2%)	9 (5.0%)	8 (5.8%)	6 (6.4%)
Dose Intensity (%)					
n	218	90	181	139	94
Mean (SD)	94.2 (12.8)	93.0 (15.2)	94.0 (10.7)	93.5 (10.5)	93.3 (9.5)
Median	99.4	98.7	98.0	96.8	95.6
Min - Max	10 - 114	10 - 101	29 - 105	29 - 102	46 - 102
Patients with > 90% Dose Intensity					
Yes	178 (81.7%)	73 (81.1%)	154 (85.1%)	116 (83.5%)	79 (84.0%)
No	40 (18.3%)	17 (18.9%)	27 (14.9%)	23 (16.5%)	15 (16.0%)

	IV Mosunetuzumab (N=218)		SC Mosunetuzumab (N=181)		
	B11 RP2D NHL (N=218)	B11 RP2D FL Expansion (N=90)	Group F NHL (N=181)	F2 RP2D NHL (N=139)	F2 RP2D FL Expansion (N=94)
Treatment Duration (Days)					
n	218	90	181	139	94
Mean (SD)	127.7 (98.0)	165.2 (90.5)	135.3 (93.2)	144.7 (96.6)	159.3 (88.8)
Median	148.0	150.0	148.0	150.0	152.0
Min - Max	1 - 421	1 - 401	1 - 540	1 - 540	15 - 540
Duration of Treatment and Safety Follow-up (Months)					
n	218	90	181	139	94
Mean (SD)	6.3 (3.9)	8.0 (3.4)	6.6 (3.4)	7.0 (3.5)	7.7 (3.1)
Median	7.0	7.9	7.8	7.8	7.9
Min - Max	0 - 17	1 - 16	1 - 19	1 - 19	1 - 19
Time on Study (Months)					
n	218	90	181	139	94
Mean (SD)	14.2 (8.8)	18.2 (6.0)	18.4 (11.0)	18.5 (9.9)	19.7 (8.7)
Median	14.3	18.3	18.6	19.3	20.7
Min - Max	0 - 28	2 - 27	1 - 39	1 - 37	1 - 34

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 (Days) is time from the date of first valid dose to end of the last valid dose
Duration of Treatment and Safety Follow-up (Months) is time from first dose to end of 90 day safety follow up period or earliest of CCOD, NALT, study discontinuation or start of a re-treatment
Time on Study (Months) is from start of first dose to study discontinuation date, death date or CCOD, whichever is the earliest
Group B Data Cutoff Date - 27AUG2021
Group F Data Cutoff Date - 01FEB2024

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Baseline demographics and disease characteristics

Table 19 Summary of Demographic and baseline characteristics in IV Group B (CCOD: 27 August 2021) and SC Group F (CCOD 01 February 2024) Safety evaluable patients

	IV Mosunetuzumab (N = 218)		SC Mosunetuzumab (N = 181)		
	B11 RP2D NHL (N = 218)	B11 RP2D FL Expansion (N = 90)	Group F NHL (N = 181)	F2 RP2D NHL (N = 139)	F2 RP2D FL Expansion (N = 94)
ge (yr)					
n	218	90	181	139	94
Mean (SD)	63.0 (12.8)	60.0 (12.0)	65.1 (10.3)	64.4 (10.5)	64.5 (9.8)
Median	64	60	66	65	65
Min - Max	24 - 96	29 - 90	24 - 88	24 - 84	35 - 84
ge group (yr)					
n	218	90	181	139	94
18-65	124 (56.9%)	62 (68.9%)	87 (48.1%)	71 (51.1%)	48 (51.1%)
> 65	94 (43.1%)	28 (31.1%)	94 (51.9%)	68 (48.9%)	46 (48.9%)
≥ 65	102 (46.8%)	30 (33.3%)	97 (53.6%)	70 (50.4%)	48 (51.1%)
ex					
n	218	90	181	139	94
Male	145 (66.5%)	55 (61.1%)	106 (58.6%)	83 (59.7%)	53 (56.4%)
Female	73 (33.5%)	35 (38.9%)	75 (41.4%)	56 (40.3%)	41 (43.6%)
thnicity					
n	218	90	181	139	94
Hispanic or Latino	10 (4.6%)	7 (7.8%)	5 (2.8%)	5 (3.6%)	2 (2.1%)
Not Hispanic or Latino	198 (90.8%)	77 (85.6%)	167 (92.3%)	126 (90.6%)	88 (93.6%)
Not Stated	6 (2.8%)	5 (5.6%)	6 (3.3%)	6 (4.3%)	2 (2.1%)
Unknown	4 (1.8%)	1 (1.1%)	3 (1.7%)	2 (1.4%)	2 (2.1%)
ace					
n	218	90	181	139	94
American Indian or Alaska Native	1 (0.5%)	1 (1.1%)	0	0	0
Asian	23 (10.6%)	8 (8.9%)	26 (14.4%)	20 (14.4%)	10 (10.6%)
Black or African American	6 (2.8%)	4 (4.4%)	3 (1.7%)	3 (2.2%)	2 (2.1%)
Native Hawaiian or other Pacific Islander	0	0	1 (0.6%)	1 (0.7%)	1 (1.1%)
White	179 (82.1%)	74 (82.2%)	147 (81.2%)	111 (79.9%)	80 (85.1%)
Multiple	0	0	1 (0.6%)	1 (0.7%)	0
Unknown	9 (4.1%)	3 (3.3%)	3 (1.7%)	3 (2.2%)	1 (1.1%)
eight (cm) at baseline					
n	201	82	173	134	91
Mean (SD)	170.62 (10.16)	169.92 (10.83)	169.80 (9.80)	170.08 (9.74)	169.30 (10.04)
Median	171.3	171.45	170.2	170.95	170
Min - Max	138.0 - 195.0	138.0 - 193.0	149.9 - 192.2	150.0 - 192.2	150.0 - 188.0
COG at baseline					
n	218	90	181	139	94
0	100 (45.9%)	53 (58.9%)	104 (57.5%)	83 (59.7%)	63 (67.0%)
1	118 (54.1%)	37 (41.1%)	77 (42.5%)	56 (40.3%)	31 (33.0%)

	IV Mosunetuzumab (N = 218)		SC Mosunetuzumab (N = 181)		
	B11 RP2D NHL (N = 218)	B11 RP2D FL Expansion (N = 90)	Group F NHL (N = 181)	F2 RP2D NHL (N = 139)	F2 RP2D FL Expansion (N = 94)
BMI (kg/m2) at baseline					
n	201	82	170	131	88
Mean (SD)	27.45 (5.54)	28.24 (5.57)	26.42 (4.90)	26.50 (4.62)	26.37 (4.59)
Median	26.7	27.51	26.21	26.34	26.47
Min - Max	14.9 - 52.2	17.0 - 45.2	16.2 - 45.3	16.2 - 45.3	16.2 - 45.3

Percentages are based on n for each estimate
Group B Data Cutoff Date - 27AUG2021
Group F Data Cutoff Date - 01FEB2024
Source: t dm INIT B11F SE

Although patients in F2 exp R/R FL cohort enrolled several years after the B11 exp R/R FL cohort they enrolled based on the same eligibility criteria and from the same study sites. In general, the presented **demographics and disease characteristics** were comparable. One notable difference of possible importance for the comparison of safety between SC and IV mosunetuzumab is the higher frequency of patients with ECOG 0 at baseline in the F2 safety pool (59.7%) compared to the B11 pool (45.9%), which could skew safety in favour of the SC population. Other prognostics markers possibly affecting not only efficacy but also safety are

- Ann Arbor Stage at Study Entry: IV/III vs I/II
- Follicular Lymphoma International Prognostic Index (FLIPI) 1 Risk at Study Entry: <3 vs. ≥3
- Prior lines of therapy: 2 vs. 3+
- Relapse or Refractory to Any Prior Anti-CD20 Therapy: Refractory vs. Non-refractory
- POD24: Yes vs. No

Proportions of patients across these baseline covariates in the IV B11 RP2D and SC F2 RP2D safety population are presented below

Table 20 Patient Characteristics Related to the Baseline Covariates Requested

Covariate	IV Monotherapy		SC Monotherapy	
	B11 RP2D (N=218)	**B11 RP2D FL Exp (N=90)**	**F2 RP2D (N=139)**	**F2 RP2D FL Exp (N=94)**
ECOG PS 0 1	N=218 100 (45.9%) 118 (54.1%)	N=90 53 (58.9%) 37 (41.1%)	N=139 83 (59.7%) 56 (40.3%)	N=94 63 (67%) 31 (33%)
Ann Arbor Stage I/II III/IV	N=217 35 (16.1%) 182 (83.9%)	N=90 21 (23.3%) 69 (76.7%)	N=139 24 (17.3%) 115 (82.7%)	N=94 12 (12.8%) 82 (87.2%)
FLIPI Score <3 ≥ 3	N=91[a] 51 (56%) 40 (44%)	N=90 50 (55.6%) 40 (44.4%)	N=95 42 (44.2%) 53 (55.8%)	N=94 41 (43.6%) 53 (56.4%)
Prior Lines 2 3+	N=148 74 (50%) 74 (50%)	N=62 34 (54.8%) 28 (45.2%)	N=115 62 (53.9%) 53 (46.1%)	N=76 44 (57.9%) 32 (42.1%)
Refractory to Prior Anti-CD20 Therapy Refractory Non-refractory	N=218 175 (80.3%) 43 (19.7%)	N=90 71 (78.9%) 19 (21.1%)	N=139 104 (74.8%) 35 (25.2%)	N=94 63 (67%) 31 (33%)
POD24 Status No Yes	N=218 74 (33.9%) 144 (66.1%)	N=90 43 (47.8%) 47 (52.2%)	N=139 60 (43.2%) 79 (56.8%)	N=94 53 (56.4%) 41 (43.6%)

ECOG PS=Eastern Cooperative Oncology Group Performance Status; Exp=expansion; FL=follicular lymphoma; FLIPI= Follicular Lymphoma International Prognostic Index; IV=intravenous; POD24=progression of disease within 24 months; RP2D=recommended Phase II dose; SC=subcutaneous

a. One patient outside the R/R FL cohort with mixed histology also had a FLIPI score entered, hence N=91.

Key observations across covariates are as follows:

- The SC cohort had a **lower** proportion of patients with ECOG PS 1 (40.3% vs. 54.1%, respectively) and **higher** proportion of ECOG PS 0 (59.7% vs. 45.9%, respectively) patients compared to the IV cohort.
- The distribution of Ann Arbor I/II and III/IV stages was **similar** between the SC and IV cohorts (Stage I/II: 17.3% vs. 16.1%; Stage III/IV: 82.7% vs. 83.9%, respectively).

- Among patients with FL in the F2 and B11 safety populations, a **larger** proportion of patients in the SC cohort had a FLIPI score ≥3 (55.8% vs. 44%, respectively), while a **smaller** proportion of patients had a FLIPI score <3 compared to the IV cohort.
- The proportion of patients with 2 and 3+ prior lines of therapy was **comparable** between the SC and the IV cohorts (3+ prior lines: 46.1% vs. 50%, respectively).
- The proportion of patients refractory or non-refractory to prior anti-CD20 therapy was **similar** in the SC and IV cohorts (refractory: 74.8% vs. 80.3%; non-refractory: 25.2% vs. 19.7%, respectively).
- The SC cohort had a **lower** proportion of patients with POD24 compared to the IV cohort in both the overall safety-evaluable population (56.8% vs. 66.1%, respectively) and among patients with FL (43.6% vs. 52.2%, respectively).

It was observed that the IV cohort generally experienced a numerically higher proportion of SAEs and Grade 3-4 AEs compared to the SC cohort across various subgroups. Specifically:

ECOG PS: Patients with ECOG PS 1 in the IV cohort had a higher proportion of serious (55% IV vs. 36% SC) and Grade 3-4 (70% IV vs. 55% SC) AEs compared to the SC cohort.

Ann Arbor Stage: In the IV cohort, patients with Ann Arbor Stage III/IV experienced more serious (54% IV vs. 37% SC) and Grade 3-4 (68% IV vs. 48% SC) AEs compared to the SC cohort.

FLIPI Score: In the IV cohort, patients with a FLIPI score ≥3 showed a higher proportion of serious (53% IV vs. 42% SC) and Grade 3-4 (70% IV vs. 53% SC) AEs compared to the SC cohort.

Prior Lines of Therapy: Patients in the IV cohort with 2 prior lines of therapy had a higher proportion of serious (50% IV vs. 31% SC) and Grade 3-4 (57% IV vs. 42% SC) AEs compared to the SC cohort.

Refractory to Prior Anti-CD20 Therapy: Non-refractory patients in the IV cohort experienced a higher proportion of Grade 3-4 AEs (72% IV vs. 34% SC) compared to the SC cohort.

POD24 Status: In the IV cohort, patients with no POD24 had a higher proportion of serious (53% IV vs. 35% SC) and Grade 3-4 (72% IV vs. 50% SC) AEs compared to the SC cohort. Additionally, patients with POD24 in the IV cohort also showed a higher proportion of serious (52% IV vs. 41% SC) and Grade 3-4 (64% IV vs. 51% SC) AEs compared to the SC cohort.

Key Trends in Adverse Events of Special Interest in IV and SC cohorts

CRS was consistently higher in the IV cohort compared to the SC cohort across nearly all subgroups, with the majority of these events being Grade 1/2. Similarly, neurological adverse events, particularly headache, generally occurred at higher rates in the IV cohort compared to the SC cohort across most subgroups, with the majority also being Grade 1/2.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths:

A higher frequency of **grade 5 adverse events** was observed in the SC F2 RP2D (N = 139) cohort compared with the IV B11 RP2D (N = 218) cohort: Six of nine AE-related deaths were due to COVID-19 (PD excluded), whereas there were no COVID-19-related deaths in the B11 RP2D cohort. This is presumably explained by the fact that the two studies were conducted in different time periods and

therefore differentially affected by the COVID-19 pandemic. (CCOD 01 February 2024 and 27 August 2021, respectively). The 3 remaining deaths due to AEs were due to Hemophagocytic lymphohistiocytosis, septic shock, and general physical health deterioration, whereas the 4 AE-related deaths in the B11 RP2D cohort were due to cholangitis, pneumonia, sepsis and sudden death.

Table 21 Deaths due to adverse events (other than disease progression) in B11 RP2D (CCOD 27 August 2021) and F2 RP2D cohort (CCOD 01 February 2024) Safety evaluable patients

Adverse Event	Related to Study Treatment	Study Day of Onset	Day of Last Mosunetuzumab Administration	Day of Death
IV 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
IV B11 exp R/R FL Cohort (1.0/2.0/60.0 mg with 30.0 mg on Cycle ≥3)				
Death [a]	no	60	22	60
SC F2 RP2D (5.0/45.0/45.0 mg)				
COVID-19	No	40	22	72
COVID-19 pneumonia	No	366	339	407
COVID-19 pneumonia	Yes	283	281	324
Septic shock	No	187	141	190
SC F2 exp R/R FL (5.0/45.0/45.0 mg)				
COVID-19	No	66	57	86
COVID-19 pneumonia	No	219	211	253
COVID-19 pneumonia	Yes	331	301	380
General physical health deterioration	No	68	47	113
Hemophagocytic lymphohistiocytosis	Yes	20	15	28

FL = follicular lymphoma; NHL = non-Hodgkin's lymphoma; RP2D=recommended Phase II dose; R/R = relapsed/refractory.

[a] Patient was enrolled in the B11 exp R/R FL cohort, received 2 cycles of mosunetuzumab treatment, and was found unresponsive in bed on study Day 60. Cause of death was unknown.

Serious adverse events:

The incidence of **SAEs** was lower in the SC F2 RP2D (N = 139) cohort compared to the IV B11 RP2D (N = 218) cohort; 36.7% vs 45.9%, respectively (grade 5 PD events excluded).

Serious AEs (by PT) that occurred in ≥ 2% of patients in the F2 RP2D cohort were CRS by ASTCT grading (11.5% vs. 20.6% in the B11 RP2D cohort), COVID-19 (pooled frequency of COVID-19 and COVID-19 pneumonia, 8.7% vs. 0.9%).

Table 22 Summary of serious adverse events occurring at an incidence of ≥2% in IV group B11 (CCOD 27 August 2021) and SC Group F (CCOD 01 February 2024), Safety evaluable patients

MedRA Preferred Term	IV Mosunetuzumab (N=218)		SC Mosunetuzumab (N=181)		
	B11 RP2D NHL (N=218)	B11 RP2D FL Expansion (N=90)	Group F NHL (N=181)	F2 RP2D NHL (N=139)	F2 RP2D FL Expansion (N=94)
Total number of patients with at least one adverse event	114 (52.3%)	42 (46.7%)	75 (41.4%)	53 (38.1%)	37 (39.4%)
Total number of events	229	91	126	83	61
Cytokine release syndrome (Lee 2014)	47 (21.6%)	21 (23.3%)	24 (13.3%)	17 (12.2%)	14 (14.9%)
(ASTCT 2019)	45 (20.6%)	21 (23.3%)	23 (12.7%)	16 (11.5%)	14 (14.9%)
Malignant neoplasm progression	28 (12.8%)	1 (1.1%)	11 (6.1%)	7 (5.0%)	3 (3.2%)
COVID-19 pneumonia	0	0	8 (4.4%)	8 (5.8%)	4 (4.3%)
Pyrexia	10 (4.6%)	2 (2.2%)	4 (2.2%)	2 (1.4%)	2 (2.1%)
Pneumonia	7 (3.2%)	2 (2.2%)	5 (2.8%)	2 (1.4%)	1 (1.1%)
COVID-19	2 (0.9%)	2 (2.2%)	6 (3.3%)	4 (2.9%)	2 (2.1%)
Sepsis	4 (1.8%)	1 (1.1%)	2 (1.1%)	2 (1.4%)	2 (2.1%)
Febrile neutropenia	3 (1.4%)	0	3 (1.7%)	2 (1.4%)	2 (2.1%)
Acute kidney injury	4 (1.8%)	3 (3.3%)	1 (0.6%)	0	0
Pleural effusion	4 (1.8%)	1 (1.1%)	1 (0.6%)	1 (0.7%)	1 (1.1%)
Tumour flare	2 (0.9%)	2 (2.2%)	2 (1.1%)	1 (0.7%)	0
Urinary tract infection	4 (1.8%)	3 (3.3%)	0	0	0
Cytomegalovirus infection reactivation	0	0	2 (1.1%)	2 (1.4%)	2 (2.1%)
Device related infection	0	0	2 (1.1%)	2 (1.4%)	2 (2.1%)
General physical health deterioration	0	0	2 (1.1%)	2 (1.4%)	2 (2.1%)
Hyperglycaemia	0	0	2 (1.1%)	2 (1.4%)	2 (2.1%)
Septic shock	2 (0.9%)	2 (2.2%)	1 (0.6%)	1 (0.7%)	0
Epstein-Barr viraemia	2 (0.9%)	2 (2.2%)	0	0	0

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Only treatment emergent AEs are displayed. Investigator text for AEs encoded using MedDRA version 26.1.
Percentages are based on N in the column headings.
Group B Data Cutoff Date - 27AUG2021
Group F Data Cutoff Date - 01FEB2024

Adverse Events of Special Interest and Selected Adverse Events:

Cytokine release syndrome (CRS):

Investigators reported and graded CRS events according to the Lee 2014 grading criteria in Study GO29781 only. CRS events according to the ASTCT 2019 grading criteria were derived programmatically from the reported data, based on the presence of fever and the presence and management of hypotension or hypoxia as reported in the CRS signs/symptoms eCRF.

Overall, there was a lower frequency and severity of CRS in the F2 RP2D cohort compared with the B11 RP2D cohort (25.9% vs. 39.4% overall, and for Grade 3-4 1.4% vs 2.8%, respectively).

Serious CRS events of any grade were reported in 16/139 patients (11.5%) in the F2 RP2D cohort and 45/218 patients (20.6%) in the B11 RP2D cohort.

There were no Grade 5 CRS events and all CRS events in the F2 RP2D and B11 RP2D cohorts resolved.

In the F2 RP2D cohort, all CRS events occurred in Cycle 1 and were mainly associated with Day 1 and Day 8 dose administrations, with the highest frequency of CRS of any grade observed following Day 1 dosing.

Table 23 Overview of cytokine release syndrome by ASTCT 2019 in IV group B11 (CCOD 27 August 2021) and SC Group F (CCOD 01 February 2024), Safety evaluable patients

	IV Mosunetuzumab N=218		SC Mosunetuzumab N=181		
Group/Cohort No. of Patients	**B11 RP2D NHL N=218**	**B11 RP2D FL Expansion N=90**	**Group F NHL N=181**	**F2 RP2D NHL N=139**	**F2 RP2D FL Expansion N=94**
Total number of events	123	71	62	42	32
Total number of patients with at least one, n (%)					
Event	86 (39.4%)	40 (44.4%)	52 (28.7%)	36 (25.9%)	28 (29.8%)
Event of Grade 1 max. severity	49 (22.5%)	23 (25.6%)	34 (18.8%)	24 (17.3%)	19 (20.2%)
Event of Grade 2 max. severity	31 (14.2%)	15 (16.7%)	16 (8.8%)	10 (7.2%)	7 (7.4%)
Event of Grade 3 max. severity	5 (2.3%)	1 (1.1%)	2 (1.1%)	2 (1.4%)	2 (2.1%)
Event of Grade 4 max. severity	1 (0.5%)	1 (1.1%)	0	0	0
Event related to mosunetuzumab	86 (39.4%)	40 (44.4%)	52 (28.7%)	36 (25.9%)	28 (29.8%)
Serious event	45 (20.6%)	21 (23.3%)	23 (12.7%)	16 (11.5%)	14 (14.9%)
Total patients with all events: Resolved, n (%)	86 (39.4%)	40 (44.4%)	52 (28.7%)	36 (25.9%)	28 (29.8%)
Unresolved or ongoing event	0	0	0	0	0
Duration of event (days), median (range)	3.0 (1.0 – 29.0)	3.0 (1.0 – 29.0)	2.0 (1.0 – 15.0)	2.0 (1.0 – 15.0)	2.0 (1.0 – 15.0)
Time to Onset from initial dose (days), median (range)	16.0 (1.0 – 65.0)	16.0 (1.0 – 65.0))	7.0 (1.0 – 73.0)	4.5 (1.0 – 24.0)	2.5 (1.0 – 17.0)
Time to Onset from most recent dose (days)	2.0 (1.0 – 17.0)	2.0 (1.0 – 17.0)	2.0 (1.0 – 8.0)	2.0 (1.0 – 8.0)	2.0 (1.0 – 8.0)

Source: t_aesi_bysmq_INIT_B11F_SE

Table 24 Management of CRS events among patients with CRS in Study GO29781 B11 RP2D Cohort (CCOD: 27 August 2021) and F2 RP2D Cohort (CCOD: 01 February 2024), Safety evaluable patients

	B11 RP2D NHL (N=218)					B11 Exp R/R FL (N=90)				
Patients with at least one CRS event	Any Grade N = 86	Grade 1 N = 61	Grade 2 N = 33	Grade 3 N = 5	Grade 4 N = 1	Any Grade N = 40	Grade 1 N = 32	Grade 2 N = 16	Grade 3 N = 1	Grade 4 N = 1
Tocilizumab	21 (24.4%)	7 (11.5%)	10 (30.3%)	4 (80.0%)	1 (100%)	7 (17.5%)	3 (9.4%)	3 (18.8%)	1 (100%)	1 (100%)
Fluids	23 (26.7%)	0	23 (69.7%)	0	0	11 (27.5%)	0	11 (68.8%)	0	0
Single pressor	4 (4.7%)	0	0	4 (80.0%)	0	1 (2.5%)	0	0	1 (100%)	0
Multiple pressors	1 (1.2%)	0	0	0	1 (100%)	1 (2.5%)	0	0	0	1 (100%)
Oxygen low flow	18 (20.9%)	0	16 (48.5%)	3 (60.0%)	0	8 (20.0%)	0	8 (50.0%)	0	0
Oxygen high flow	2 (2.3%)	0	0	2 (40.0%)	0	1 (2.5%)	0	0	1 (100%)	0
Corticosteroids	22 (25.6%)	9 (14.8%)	11 (33.3%)	4 (80.0%)	1 (100%)	10 (25.0%)	5 (15.6%)	5 (31.3%)	1 (100%)	1 (100%)
Corticosteroids + Tocilizumab	9 (10.5%)	2 (3.3%)	4 (12.1%)	3 (60.0%)	1 (100%)	4 (10.0%)	1 (3.1%)	2 (12.5%)	1 (100%)	1 (100%)
ICU Admission	9 (10.5%)	0	4 (12.1%)	4 (80.0%)	1 (100%)	5 (12.5%)	0	3 (18.8%)	1 (100%)	1 (100%)
Tocilizumab	8 (22.2%)	2 (8.3%)	4 (40.0%)	2 (100%)	0	8 (28.6%)	2 (10.5%)	4 (57.1%)	2 (100%)	0
Fluids	6 (16.7%)	0	6 (60.0%)	0	0	4 (14.3%)	0	4 (57.1%)	0	0
Single pressor	2 (5.6%)	0	0	2 (100%)	0	2 (7.1%)	0	0	2 (100%)	0
Multiple pressors	0	0	0	0	0	0	0	0	0	0
Oxygen low flow	7 (19.4%)	0	6 (60.0%)	1 (50.0%)	0	6 (21.4%)	0	5 (71.4%)	1 (50.0%)	0
Oxygen high flow	1 (2.8%)	0	0	1 (50.0%)	0	1 (3.6%)	0	0	1 (50.0%)	0
Corticosteroids	6 (16.7%)	5 (20.8%)	1 (10.0%)	0	0	6 (21.4%)	5 (26.3%)	1 (14.3%)	0	0
Corticosteroids + Tocilizumab	2 (5.6%)	1 (4.2%)	1 (10.0%)	0	0	2 (7.1%)	1 (5.3%)	1 (14.3%)	0	0
ICU Admission	1 (2.8%)	0	1 (10.0%)	0	0	1 (3.6%)	0	1 (14.3%)	0	0

Only treatment-emergent CRS events with a valid grade are included.
N represents the number of patients experiencing CRS events at the relevant Grade and n is the number of patients within the CRS management category.
Percentages are based on N in the column headings.
Group B Data Cutoff Date - 27AUG2021
Group F Data Cutoff Date - 01FEB2024
Source: t_crsgr_mgmt_ASTCT_INIT_B11F_SE

Table 25 Summary of adverse reactions in patients, initial treatment with mosunetuzumab, B11 RP2D and F2 patients, Safety evaluable patients (Protocol: GO29781)

SOC ADR Term	B11 RP2D (N=218) Any Grade	 Grade 3-4	F2 (N=139) Any Grade	 Grade 3-4	Total (N=357) Any Grade	 Grade 3-4
General disorders and administration site conditions						
Injection site reactions	0	0	96 (69.1%)	0	96 (26.9%)	0
Pyrexia	53 (24.3%)	4 (1.8%)	18 (12.9%)	1 (0.7%)	71 (19.9%)	5 (1.4%)
Immune system disorders						
Cytokine release syndrome	86 (39.4%)	6 (2.8%)	36 (25.9%)	2 (1.4%)	122 (34.2%)	8 (2.2%)
Haemophagocytic lymphohistiocytosis	1 (0.5%)	1 (0.5%)	1 (0.7%)	0	2 (0.6%)	1 (0.3%)

ASTCT grading is used for CRS AE grades and AEs are not included where this is set to null.

The most frequently reported CRS signs and symptoms in ≥10% of patients in the F2 RP2D cohort who experienced CRS events of any grade by ASTCT 2019 were pyrexia, hypotension, hypoxia, chills, tachycardia and headache.

Table 26 Summary of common (≥10%) CRS (ASTCT 2019) Signs and symptoms by preferred term for SC mosunetuzumab after step-up dosing – Selected dose groups - Safety evaluable patients

MedDRA System Organ Class MedDRA Preferred Term	Grade	Group F 5.0/15.0/45.0, 5.0/45.0/45.0, or 5.0/45.0/90.0/45.0 mg NHL N = 181	F2 Esc. and Exp. 5.0/45.0/45.0 mg (RP2D) NHL N = 139	F2 Expansion 5.0/45.0/45.0 mg (RP2D) DLBCL/trFL N = 41	F2 Expansion 5.0/45.0/45.0 mg (RP2D) 3L FL N = 94
No of patients with at least one CRS event		N = 52	N = 36	N = 7	N = 28
Pyrexia	Any Grade	50 (96.2%)	35 (97.2%)	7 (100%)	27 (96.4%)
	Grade 1-2	49 (94.2%)	34 (94.4%)	6 (85.7%)	27 (96.4%)
	1	34 (65.4%)	22 (61.1%)	3 (42.9%)	19 (67.9%)
	2	15 (28.8%)	12 (33.3%)	3 (42.9%)	8 (28.6%)
	Grade 3-4	1 (1.9%)	1 (2.8%)	1 (14.3%)	0
	Grade 3-5	1 (1.9%)	1 (2.8%)	1 (14.3%)	0
	3	1 (1.9%)	1 (2.8%)	1 (14.3%)	0
Chills	Any Grade	12 (23.1%)	5 (13.9%)	1 (14.3%)	3 (10.7%)
	Grade 1-2	12 (23.1%)	5 (13.9%)	1 (14.3%)	3 (10.7%)
	1	11 (21.2%)	5 (13.9%)	1 (14.3%)	3 (10.7%)
	2	1 (1.9%)	0	0	0
Hypotension	Any Grade	12 (23.1%)	8 (22.2%)	2 (28.6%)	6 (21.4%)
	Grade 1-2	9 (17.3%)	6 (16.7%)	1 (14.3%)	5 (17.9%)
	1	0	0	0	0
	2	9 (17.3%)	6 (16.7%)	1 (14.3%)	5 (17.9%)
	Grade 3-4	3 (5.8%)	2 (5.6%)	1 (14.3%)	1 (3.6%)
	Grade 3-5	3 (5.8%)	2 (5.6%)	1 (14.3%)	1 (3.6%)
	3	3 (5.8%)	2 (5.6%)	1 (14.3%)	1 (3.6%)
Hypoxia	Any Grade	8 (15.4%)	7 (19.4%)	1 (14.3%)	6 (21.4%)
	Grade 1-2	7 (13.5%)	6 (16.7%)	1 (14.3%)	5 (17.9%)
	1	0	0	0	0
	2	7 (13.5%)	6 (16.7%)	1 (14.3%)	5 (17.9%)
	Grade 3-4	1 (1.9%)	1 (2.8%)	0	1 (3.6%)
	Grade 3-5	1 (1.9%)	1 (2.8%)	0	1 (3.6%)
	3	1 (1.9%)	1 (2.8%)	0	1 (3.6%)
Tachycardia	Any Grade	6 (11.5%)	4 (11.1%)	0	4 (14.3%)
	Grade 1-2	6 (11.5%)	4 (11.1%)	0	4 (14.3%)
	1	6 (11.5%)	4 (11.1%)	0	4 (14.3%)
	2	0	0	0	0
Headache	Any Grade	7 (13.5%)	4 (11.1%)	1 (14.3%)	3 (10.7%)
	Grade 1-2	7 (13.5%)	4 (11.1%)	1 (14.3%)	3 (10.7%)
	1	5 (9.6%)	3 (8.3%)	1 (14.3%)	2 (7.1%)
	2	2 (3.8%)	1 (2.8%)	0	1 (3.6%)

Only treatment-emergent AEs are included. Investigator text for signs and symptoms encoded using MedDRA version 26.1.
Percentages are based on N in the column headings. N based on the number of patients who experience CRS
'By ASTCT Grade' refers to only including CRS signs and symptoms associated with CRS event with a valid ASTCT grade. If the CRS event did not meet ASTCT grading criteria the signs and symptoms are excluded

The actual grade displayed is the CTC grade reported for the CRS signs and symptoms
Data Cutoff Date - 01FEB2024

For the supportive study CO41942 the proportion of patients who experienced CRS was also lower in the SC Mosun-Len arm compared with the IV Mosun-Len arm (25 patients [32.1%] vs. 17 patients [43.6%]).

Neurologic Adverse Events (NAEs)/ Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) Events:

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. Neurological adverse events (NAEs) potentially consistent with ICANS were comparable between the F2 RP2D cohort and the B11 RP2D cohort (7.2% vs. 9.6%). All suspected ICANS events were low grade (Grade 1-2 maximum severity in both cohorts)

ASTCT consensus grading for ICANS (Lee et al. 2019) was not used in study GO29781. An algorithmic approach was used to capture neurologic events that may be potentially consistent with ICANS.

Subsequently, events were medically reviewed to determine whether clinical features are consistent with ICANS, which are termed 'suspected ICANS' after clinical adjudication. A total of 10/139 patients (7.2%) in the F2 RP2D cohort and 21/218 patients (9.6%) in the B11 RP2D cohort experienced a NAE potentially consistent with ICANS events following initial treatment with mosunetuzumab.

Haematological adverse events:

Neutropenia/ neutrophil count decreased was similar in the IV and SC cohorts. At the time of CCOD, the majority of the events (63 of 64 events [98.4%] in the F2 RP2D cohort and 113 of 123 events [91.9%] in the B11 RP2D cohort) had resolved. Two serious infection events in the F2 RP2D cohort and 4 serious infection events in the B11 RP2D cohort occurred concurrently with neutropenia/ neutrophil count decreased events. Frequencies for febrile neutropenia were 2/139 patients (1.4%) in the F2 RP2D cohort and 5/218 patients (2.3%). The use of G-CSF was comparable between the IV and SC safety pools: 22/33 patients (66.7%) in the F2 RP2D cohort and 41/60 patients (68.3%) in the B11 RP2D cohort.

Thrombocytopenia/platelet count decreased was similar in the IV and SC cohorts. At the time of CCOD, 15 of 18 events (83.3%) in the F2 RP2D cohort and 15 of 26 events (57.7%) in the B11 RP2D cohort had resolved. No patients in the F2 RP2D cohort or B11 RP2D cohorts reported bleeding events concurrent with thrombocytopenia/platelet count decreased events and no DIC events were observed in either cohort.

Anemia/hemoglobin decreased was similar in the IV and SC cohorts.

Haemophagocytic Lymphohistiocytosis: In the SmPC, section 4.8 the frequency is described as 4/949 patients. The dataset used for presenting HLH adverse drug reactions (ADRs; N=949) is the pooled clinical trial population in the Core Data Sheet version 4 at the time of the SC filing and includes groups from GO29781, GO40554, YO43555, GO40515, CO41942, and GO40516.

Tumour lysis syndrome (TLS): No TLS events were reported in F2 RP2D. The updated frequency of TLS in the SmPC was based on the overall frequency of TLS in the pooled safety population from B11 RP2D and F2 RP2D (2/357).

Tumour flare: Tumour flare is an important identified risk in the summary of safety concerns in the RMP. In the SmPC, section 4.8 the frequency is described as 1.4% (2/**139**), which corresponds to the SC cohort. In the B11 RP2D cohort 4.1% (9/**218**) experienced events that met the definition of tumour flare events.

There were 9 patients with AE of tumour flare in B11 RP2D (N = 218), and 2 patients with AE of tumour flare in F2 RP2D (N = 139).

Hepatic adverse events: Overall, there was a lower frequency and severity of hepatic events in the F2 RP2D cohort versus the B11 RP2D cohort. A total of 11/139 patients (7.9%) in the F2 RP2D cohort and 29/218 patients (13.3%) in the B11 RP2D cohort experienced hepatic AEs following initial treatment with mosunetuzumab. The most frequent hepatic events (reported in >5% of patients) in the F2 RP2D and/or B11 RP2D cohorts were ALT and AST increases.

Serious hepatic events were reported in 1 patient (0.7%) in the F2 RP2D cohort (Grade 3 transaminases increased) and 3 patients (1.4%) in the B11 RP2D cohort (all events were Grade 3-4 ALT and AST increased). All serious hepatic events were considered related to mosunetuzumab treatment by the investigator. At the time of CCOD, 15 of the 19 hepatic events (78.9%) in the F2 RP2D cohort and 48 of the 59 hepatic events (81.4%) in the B11 RP2D cohort had resolved.

One patient with R/R DLBCL in the B11 RP2D cohort was identified as a potential Hy's law case. Liver enzyme elevations with elevated total bilirubin were observed two days prior to confirmed disease progression with duodenal perforation related to progression of lymphoma and death on C1D7.

Infections:

Overall adverse events related to infection were of similar magnitude between the IV and SC cohorts although AEs related to COVID-19 were more frequent in the F2 RP2D cohort, which enrolled after the onset of the COVID-19 pandemic, whereas the B11 RP2D cohort were enrolled mostly prior to the pandemic.

Pneumonitis/ILD:

Pneumonitis/interstitial lung disease (ILD) AEs were broadly defined as all AEs reported as PTs in the Standardized MedDRA Queries (SMQ) Interstitial Lung Disease. There were 2 events (Grade 2 and 3) in the F2 RP2D cohort (1.4%): both events resolved after interruption/ withdrawal. There were three events (1.4%; Grade 1 and two Grade 3) in the B11 RP2D cohort.

Injection site reactions:

Injection site reactions were seen in 96/139 patients (69.1%) in the F2 RP2D cohort but were limited to Grade 1-2. No event was labelled an SAE and all but one resolved.

In study CO41942, 64.1% had injection site reactions in the SC Mosun-Len arm, all of which were Grade 1 (51.3%) or Grade 2 events (12.8%).

Rash:

The proportion of patients with rash (grouped term) was comparable between the F2 RP2D cohort (32.4%) and the B11 RP2D cohort (34.9%).

The majority of rash events in the F2 RP2D and B11 RP2D cohorts were Grade 1-2and Grade 3 rash events were reported in 4 patients (2.9%) in the F2 RP2D cohort. No Grade 4 or 5 rash events were reported.

2.6.8.4. Laboratory findings

Haematology findings are described in the AESI section.

Chemistry

Hepatic events/changes in hepatic laboratory parameters are described in the AESI section.

In the F2 RP2D cohort, the most frequent treatment-emergent Grade ≥ 3 worsening chemistry laboratory parameter shifts were increases in urate (21.6% from baseline to Grade ≥ 3; 3.6% from baseline to Grade 4), glucose (15.8% from baseline to Grade ≥ 3; 1.4% from baseline to Grade 4) and decreases in phosphate (10.1% from baseline to Grade ≥ 3; 0.7% from baseline to Grade 4) which was consistent with hypophosphatemia (5.0%), and hyperglycemia (2.4%) being among the most frequent Grade 3-4 AEs reported. When comparing the B11 RP2D cohort to the F2 RP2D cohort the changes in urate and glucose were similar but the decrease in all and Grade 3-4 phosphate was larger.

Table 27 Most frequent treatment emergent chemistry laboratory abnormalities for SC mosunetuzumab after step-up dosing – F2 RP2D cohort - Safety evaluable patients

	F2 5/45/45 mg (RP2D) NHL (N=139)			
		Worsening NCI CTCAE grade from baseline to:		
	N[a]	Any Grade	Grade≥3[b]	Grade 4
↑Creatinine	139	112 (80.6%)	2 (1.4%)	2 (1.4%)
↓Phosphate	139	62 (44.6%)	14 (10.1%)	1 (0.7%)
↓Albumin	138	60 (43.5%)	1 (0.7%)	0
↓Calcium	139	59 (42.4%)	2 (1.4%)	2 (1.4%)
↓Sodium	139	57 (41.0%)	6 (4.3%)	0
↑SGPT/ALT	139	44 (31.7%)	3 (2.2%)	0
↑GGT	138	44 (31.9%)	5 (3.6%)	2 (1.4%)
↑Alkaline phosphatase	139	42 (30.2%)	2 (1.4%)	0
↓Potassium	139	41 (29.5%)	1 (0.7%)	0
↑SGOT/AST	139	38 (27.3%)	4 (2.9%)	0
↓Magnesium	139	37 (26.6%)	2 (1.4%)	2 (1.4%)
↑Urate	139	30 (21.6%)	30 (21.6%)	5 (3.6%)
↓Glucose	139	25 (18.0%)	0	0
↑Glucose	139	22 (15.8%)	22 (15.8%)	2 (1.4%)
↑Potassium	139	22 (15.8%)	3 (2.2%)	3 (2.2%)
↑Bilirubin	139	18 (12.9%)	2 (1.4%)	0
↑Calcium	139	12 (8.6%)	2 (1.4%)	0
↑Magnesium	139	9 (6.5%)	2 (1.4%)	0
↑Sodium	139	9 (6.5%)	1 (0.7%)	1 (0.7%)

GGT=gamma glutamyl transferase; SGPT/ALT=alanine aminotransferase; SGOT/AST=aspartate aminotransferase.

Note: Table shows any worsening grade laboratory shifts from baseline measured in ≥5% of patients with any grade worsening only.

[a] Number of patients with a baseline and at least one post-baseline assessment for lab parameter.

[b] Includes shifts from NCI CTCAE Grade<3 to Grade≥3 and shifts from Grade 3 to Grade 4.

Table 28 Most frequent[a] treatment emergent chemistry laboratory abnormalities in B11 RP2D Cohort (CCOD: 27 August 2021), Safety evaluable patients

Group/cohort No. of patients	B11 RP2D Cohort N=218			
		Worsening NCI CTCAE grade from baseline to:		
	N [b]	Any Grade	Grade ≥3 [c]	Grade 4
↑Glucose	213	86 (40.4%)	86 (40.4%)	3 (1.4%)
↓Phosphate	217	163 (75.1%)	88 (40.6%)	3 (1.4%)
↑Urate	214	47 (22.0%)	47 (22.0%)	19 (8.9%)
↓Sodium	217	92 (42.4%)	13 (6.0%)	0
↑GGT	214	81 (37.9%)	16 (7.5%)	1 (0.5%)
↑SGPT/ALT	217	79 (36.4%)	12 (5.5%)	1 (0.5%)
↓Potassium	217	71 (32.7%)	10 (4.6%)	1 (0.5%)
↑Bilirubin	217	41 (18.9%)	10 (4.6%)	0
↓Calcium	217	120 (55.3%)	9 (4.1%)	2 (0.9%)
↓Albumin	216	134 (62.0%)	9 (4.2%)	0
↑SGOT/AST	217	98 (45.2%)	9 (4.1%)	3 (1.4%)
↑Magnesium	217	23 (10.6%)	8 (3.7%)	1 (0.5%)
↑Calcium	217	25 (11.5%)	8 (3.7%)	4 (1.8%)
↑Creatinine	217	192 (88.5%)	7 (3.2%)	2 (0.9%)
↑Potassium	217	35 (16.1%)	6 (2.8%)	1 (0.5%)
↑Alkaline phosphatase	217	53 (24.4%)	3 (1.4%)	0
↑Sodium	217	21 (9.7%)	1 (0.5%)	0
↓Glucose	213	16 (7.5%)	1 (0.5%)	0
↓Magnesium	217	86 (39.6%)	0	0

GGT=gamma glutamyl transferase; RP2D=recommended Phase II dose; SGPT/ALT=alanine aminotransferase; SGOT/AST=aspartate aminotransferase.

[a] Table shows any worsening grade laboratory shifts from baseline measured in ≥5% of patients with any grade worsening only.

[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.

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

The Table for AEs by age for Study GO29781 Cohort F2 RP2D is provided below. The overall safety profile was comparable across the age groups. There were no patients >85 years of age in the F2 RP2D cohort.

Table 29 AE by Age range (<65, 65-74, 75-84, 85+), Initial Treatment with Mosunetuzumab, Cohort F2 Escalation and Expansion, Safety-Evaluable Patients

	F2 5.0/45.0/45.0 mg (N=139)				F2 RP2D FL Expansion (N=94)			
	< 65 (N=69)	**65 to 74 (N=52)**	**75 to 84 (N=18)**	**85+ (N=0)**	**< 65 (N=46)**	**65 to 74 (N=36)**	**75 to 84 (N=12)**	**85+ (N=0)**
Total AEs	749	492	202	0	528	358	140	0
Serious AEs – Total	24 (34.8%)	23 (44.2%)	6 (33.3%)	0	19 (41.3%)	15 (41.7%)	3 (25.0%)	0
- Fatal	7 (10.1%)	6 (11.5%)	3 (16.7%)	0	3 (6.5%)	4 (11.1%)	1 (8.3%)	0
- Hospitalization/prolong existing hospitalization	23 (33.3%)	23 (44.2%)	5 (27.8%)	0	19 (41.3%)	15 (41.7%)	3 (25.0%)	0
- Life-threatening	1 (1.4%)	2 (3.8%)	0	0	0	2 (5.6%)	0	0
- Disability/incapacity	2 (2.9%)	0	0	0	2 (4.3%)	0	0	0
- Other (medically significant)	1 (1.4%)	0	1 (5.6%)	0	1 (2.2%)	0	0	0
AE leading to drop-out	7 (10.1%)	2 (3.8%)	3 (16.7%)	0	4 (8.7%)	1 (2.8%)	2 (16.7%)	0
Total number of patients with at least one								
Nervous System Disorders and Psychiatric Disorders	37 (53.6%)	24 (46.2%)	7 (38.9%)	0	27 (58.7%)	18 (50.0%)	5 (41.7%)	0
Nervous System Disorders	37 (53.6%)	23 (44.2%)	6 (33.3%)	0	27 (58.7%)	17 (47.2%)	5 (41.7%)	0
Psychiatric Disorders	1 (1.4%)	2 (3.8%)	1 (5.6%)	0	0	2 (5.6%)	0	0
Accidents and injuries	7 (10.1%)	4 (7.7%)	2 (11.1%)	0	3 (6.5%)	4 (11.1%)	2 (16.7%)	0
Cardiac disorders	3 (4.3%)	1 (1.9%)	1 (5.6%)	0	3 (6.5%)	1 (2.8%)	0	0
Vascular disorders	12 (17.4%)	7 (13.5%)	5 (27.8%)	0	7 (15.2%)	5 (13.9%)	2 (16.7%)	0
Cerebrovascular disorders	0	0	0	0	0	0	0	0
Infections and infestations	40 (58.0%)	19 (36.5%)	8 (44.4%)	0	32 (69.6%)	13 (36.1%)	6 (50.0%)	0
Anticholinergic Syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	6 (8.7%)	7 (13.5%)	3 (16.7%)	0	4 (8.7%)	5 (13.9%)	2 (16.7%)	0
COVID-19 / COVID-19 pneumonia	21 (30.4%)	7 (13.5%)	3 (16.7%)	0	17 (37.0%)	5 (13.9%)	1 (8.3%)	0
Other AE appearing more frequently in older patients								
Injection site reaction	46 (66.7%)	27 (51.9%)	13 (72.2%)	0	30 (65.2%)	18 (50.0%)	9 (75.0%)	0

	F2 5.0/45.0/45.0 mg (N=139)				F2 RP2D FL Expansion (N=94)			
	< 65 (N=69)	**65 to 74 (N=52)**	**75 to 84 (N=18)**	**85+ (N=0)**	**< 65 (N=46)**	**65 to 74 (N=36)**	**75 to 84 (N=12)**	**85+ (N=0)**
Fatigue	22 (31.9%)	14 (26.9%)	6 (33.3%)	0	18 (39.1%)	10 (27.8%)	5 (41.7%)	0
ASTCT graded Cytokine Release Syndrome	19 (27.5%)	14 (26.9%)	3 (16.7%)	0	17 (37.0%)	10 (27.8%)	1 (8.3%)	0
Diarrhoea	11 (15.9%)	8 (15.4%)	5 (27.8%)	0	8 (17.4%)	7 (19.4%)	4 (33.3%)	0
Constipation	8 (11.6%)	8 (15.4%)	5 (27.8%)	0	5 (10.9%)	6 (16.7%)	2 (16.7%)	0
Nausea	8 (11.6%)	9 (17.3%)	1 (5.6%)	0	5 (10.9%)	7 (19.4%)	1 (8.3%)	0
Anaemia	10 (14.5%)	8 (15.4%)	2 (11.1%)	0	4 (8.7%)	7 (19.4%)	1 (8.3%)	0

AE=adverse event; ASTCT= American Society for Transplantation and Cellular Therapy; FL=follicular lymphoma; RP2D=recommended Phase II dose; Investigator text for AEs encoded using MedDRA version 26.1.

Only treatment emergent AEs are displayed. Percentages are based on N in the column headings. Any AE which is classified as both a Nervous System Disorder and a Psychiatric Disorder is only counted in the Nervous System Disorders row. For 'Other AE appearing more frequently in older patients', the five most frequent PTs in the older age categories (>=65 years) in either population grouping, alongside the corresponding frequencies of these PTs in all age categories, are shown.

Group F Data Cutoff Date - 01FEB2024

Pregnancy:
No pregnancies were reported in Study GO29781 Cohort F2 RP2D.

Renal Impairment:

There were no patients in the Study GO29781 Cohort F2 RP2D that met the definition of Categories G3b, G4, and G5 (KDIGO definition).

Hepatic Impairment (defined as Child Pugh B or C):
No patients with hepatic impairment were enrolled in Study GO29781.

2.6.8.7. Immunological events

N/A

2.6.8.8. Safety related to drug-drug interactions and other interactions

N/A

2.6.8.9. Discontinuation due to adverse events

AEs leading to discontinuation were more frequently observed in the F2 RP2D cohort (8.6%) compared with the B11 RP2D cohort (4.1%) mainly due to COVID-19 infections (5%) and were the only AEs leading to mosunetuzumab discontinuation in more than one patient. In the B11 RP2D cohort CRS was the only AE leading to mosunetuzumab discontinuation in more than one patient.

The proportion of patients with AEs that led to mosunetuzumab discontinuation in Study CO41942 was comparable between the SC Mosun-Len and IV Mosun-Len arms (14.1% vs. 17.9%).

Overall, 37.4% in the F2 RP2D cohort and 33.5% in the B11 RP2D cohort had an AE leading to mosunetuzumab dose modification or dose interruption. There were more CRS events leading to dose interruption/modification in the IV cohort (B11 RP2D; 8.7%) compared to the SC cohort (F2 RP2D; 2.2%), whereas COVID-19 infections were the cause in 0.9% vs 11.5%, respectively.

Table 30 Summary of adverse events leading to mosunetuzumab discontinuation by preferred term in IV Group B11 (CCOD 27 August 2021) and SC Group F (CCOD 01 February 2024), Safety-Evaluable Patients

	IV Mosunetuzumab (N=218)		SC Mosunetuzumab (N=181)		
MedRA Preferred Term	B11 RP2D NHL (N=218)	B11 RP2D FL Expansion (N=90)	Group F NHL (N=181)	F2 RP2D NHL (N=139)	F2 RP2D FL Expansion (N=94)
Total number of patients with at least one adverse event	9 (4.1%)	4 (4.4%)	15 (8.3%)	12 (8.6%)	7 (7.4%)
Total number of events	9	4	15	12	7
COVID-19 pneumonia	0	0	5 (2.8%)	5 (3.6%)	3 (3.2%)
COVID-19	0	0	4 (2.2%)	2 (1.4%)	1 (1.1%)
Cytokine release syndrome	2 (0.9%)	2 (2.2%)	0	0	0
General physical health deterioration	0	0	1 (0.6%)	1 (0.7%)	1 (1.1%)
Haemophagocytic lymphohistiocytosis	0	0	1 (0.6%)	1 (0.7%)	1 (1.1%)
Pneumonitis	0	0	1 (0.6%)	1 (0.7%)	1 (1.1%)
Epstein-Barr viraemia	1 (0.5%)	1 (1.1%)	0	0	0
Hodgkin's disease	1 (0.5%)	1 (1.1%)	0	0	0
Liver function test abnormal	0	0	1 (0.6%)	1 (0.7%)	0
Septic shock	0	0	1 (0.6%)	1 (0.7%)	0
Cholangitis	1 (0.5%)	0	0	0	0
Large intestine perforation	0	0	1 (0.6%)	0	0
Lung neoplasm malignant	1 (0.5%)	0	0	0	0
Myocardial infarction	1 (0.5%)	0	0	0	0
Sepsis	1 (0.5%)	0	0	0	0
Subdural haematoma	1 (0.5%)	0	0	0	0

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Only treatment emergent AEs are displayed. Investigator text for AEs encoded using MedDRA version 26.1.
Percentages are based on N in the column headings.
Group B Data Cutoff Date - 27AUG2021
Group F Data Cutoff Date - 01FEB2024

Program: root/clinical_studies/RO7030816/CDPT7828/GO29781/data_analysis/SCS_PoolB11F_2024/prod/program/t_ae.sas
Adapted from Output: t_ae_DSC_INIT_B11F_SE

2.6.8.10. Post marketing experience

There is no post marketing experience with the formulation of mosunetuzumab SC administered in the studies included in this submission (GO29781 and CO41942) as it is not yet approved.

2.6.9. Discussion on clinical safety

The primary safety pool as presented in the SmPC includes the safety pool for the previously approved mosunetuzumab IV monotherapy in R/R FL patients after two or more prior systemic treatments (study GO29781, cohort B11 RP2D R/R NHL, n=218) and the safety pool for the SC treatment, which includes cohort F2 RP2D R/R NHL (n=139) also from study GO29781, amounting to a safety pool of 357 RP2D R/R NHL patients, which is agreed. There was a three-year difference between the conduct of the two cohorts, where the F2 cohort recruited during the COVID-19 pandemic. CCOD: B11 RP2D; 27.08.2021, F2 RP2D; 01.02.2024. The safety database comprises 357 patients.

The MAH sought advice from SAWP (EMA/SA/0000049656 and EMA/SA/000008635). Points related to safety were:

- In general, the assessment of safety non-inferiority considered appropriate, also in terms of the proposed sample size, with additional recommendations to discuss the overall safety profile compared to the target population and the dose escalation cohorts at the time of submission.
- A minimum follow-up time of 12 months for all subjects recommended to ensure data is sufficiently mature to allow adequate assessment of consistency in response rates as well as in response durability and to allow assessment of long-term safety profile.

Exposure is similar between the IV and SC safety population with a median number of cycles = 8 in both pools and similar dose intensity although with a shorter time on study (from start of first dose to study discontinuation date, death date or CCOD, whichever is the earliest) for the IV pool compared to the SC pool (14.3 months vs. 19.3 months, respectively).

The SC cohort enrolment and treatment occurred after the onset of the coronavirus disease (COVID-

19) pandemic, whereas IV cohorts were enrolled mostly prior to the pandemic. Other differences were differences in the steroid regimen, which changed over time in the F2 cohort. Initially (protocol V11) dexamethasone 20 mg (IV or PO) was given prior to treatment only, whereas for V12 in addition it was given 1 and 2 days after each dose (C1 and C2) although in a reduced dose (10 mg). In V15 the dexamethasone dose was increased again to 20 mg but only given prior to each dose in C1 (and C2 if CRS had occurred with the previous dose). In protocol amendment V16 20 mg dexamethasone was listed as the preferred steroid [as opposed to methylprednisolone (80 mg)], and this regimen is now the recommended treatment included in the SmPC.

The impact of these differences (COVID-19 pandemic and steroid treatment differences), as well as physicians' increased familiarity with CRS on adverse events frequencies is difficult to ascertain.

Adverse events in the F2 RP2D cohort were overall comparable to the B11 RP2D cohort with the exception related to the route of administration where injection site reactions (61.9%) were seen in the F2 RP2D cohort, and a higher frequency of CRS in the B11 RP2D cohort (39.4% compared to 25.9%). Other frequent adverse events such as fatigue, neutropenia/neutrophil count decreased, and headache were of similar frequencies. In the B11 RP2D cohort, hypophosphatemia and hypokalaemia were clearly higher than in the F2 RP2D cohort (22.5% vs 9/6.5%, and 15.6% vs 7.2%, respectively).

Compared to mosunetuzumab IV monotherapy at the RP2D, SC monotherapy showed a lower frequency of Grade 3-5 AEs (54.7% vs. 72.0%) which was mainly driven by less frequent **Grade 3-4** hypophosphataemia (5.0% vs. 14.7%).

The following new **ADR**s were identified based on the higher frequency in SC and combined totality of SC and IV data that met the ADR threshold: Nausea, Injection Site Reactions, Lower Respiratory Tract Infection, Sepsis, Dizziness, and Skin Exfoliation. In addition, ICANS and HLH, which were not ADRs in the initial IV approval, have now been included in the SmPC.

A higher frequency of **grade 5 adverse events** was observed in the F2 RP2D (N = 139) cohort compared with the B11 RP2D (N = 218) cohort: Six of nine AE-related deaths were due to COVID-19 (PD excluded), whereas there were no COVID-19-related deaths in the B11 RP2D cohort (CCOD 01 February 2024 and 27 August 2021, respectively). The three remaining deaths due to AEs were due to haemophagocytic lymphohistiocytosis, septic shock, and general physical health deterioration, whereas the four AE-related deaths in the B11 RP2D cohort were due to cholangitis, pneumonia, sepsis and sudden death.

The incidence of **SAEs** was lower in the F2 RP2D (N = 139) cohort compared to the B11 RP2D (N = 218) cohort; 36.7% vs 45.9%, respectively (grade 5 PD events excluded).

Serious AEs (by PT) that occurred in ≥ 2% of patients in the F2 RP2D cohort were CRS by ASTCT grading (11.5% vs. 20.6% in the B11 RP2D cohort) and COVID-19 (8.7% vs. 0.9%).

Adverse events of special interest:

Cytokine release syndrome (CRS):

Overall, there was a lower frequency and severity of CRS in the F2 RP2D cohort compared with the B11 RP2D cohort (25.9% vs. 39.4% overall, and for Grade 3-4 1.4% vs 2.8%, respectively).

Serious CRS events of any grade were reported in 16/139 patients (11.5%) in the F2 RP2D cohort and 45/218 patients (20.6%) in the B11 RP2D cohort.

There were no Grade 5 CRS events and all CRS events in the F2 RP2D and B11 RP2D cohorts resolved.

In the F2 RP2D cohort, all CRS events occurred in Cycle 1 and were mainly associated with Day 1 and Day 8 dose administrations, with the highest frequency of CRS of any grade observed following Day 1

dosing.

The most frequently reported CRS signs and symptoms in ≥10% of patients in the F2 RP2D cohort who experienced CRS events of any grade by ASTCT 2019 were pyrexia, hypotension, hypoxia, chills, tachycardia and headache.

For the supportive study CO41942 the proportion of patients who experienced CRS was also lower in the SC Mosun-Len arm compared with the IV Mosun-Len arm (25 patients [32.1%] vs. 17 patients [43.6%]).

Neurologic Adverse Events (NAEs)/ Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) Events:

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. Neurological adverse events (NAEs) potentially consistent with ICANS were comparable between the F2 RP2D cohort and the B11 RP2D cohort (7.2% vs. 9.6%). All suspected ICANS events were low grade (Grade 1-2 maximum severity in both cohorts).

ASTCT consensus grading for ICANS (Lee et al. 2019) was not used in study GO29781. An algorithmic approach was used to capture neurologic events that may be potentially consistent with ICANS. Subsequently, events were medically reviewed to determine whether clinical features are consistent with ICANS, which are termed 'suspected ICANS' after clinical adjudication. A total of 10/139 patients (7.2%) in the F2 RP2D cohort and 21/218 patients (9.6%) in the B11 RP2D cohort experienced an NAE potentially consistent with ICANS events following initial treatment with mosunetuzumab.

Haematological adverse events:

Neutropenia/ neutrophil count decreased was similar in the IV and SC cohorts. At the time of CCOD, the majority of the events (63 of 64 events [98.4%] in the F2 RP2D cohort and 113 of 123 events [91.9%] in the B11 RP2D cohort) had resolved. Two serious infection events in the F2 RP2D cohort and 4 serious infection events in the B11 RP2D cohort occurred concurrently with neutropenia/ neutrophil count decreased events. Frequencies for febrile neutropenia were 2/139 patients (1.4%) in the F2 RP2D cohort and 5/218 patients (2.3%). In the F2 RP2D cohort, no patients had a serious infection which occurred concurrently with febrile neutropenia, whereas in the B11 RP2D cohort two serious infections occurred concurrently with febrile neutropenia.

Thrombocytopenia/platelet count decreased was similar in the IV and SC cohorts. At the time of CCOD, 15 of 18 events (83.3%) in the F2 RP2D cohort and 15 of 26 events (57.7%) in the B11 RP2D cohort) had resolved. No patients in the F2 RP2D cohort or B11 RP2D cohorts reported bleeding events concurrent with thrombocytopenia/platelet count decreased events and no DIC events were observed in either cohort.

Anemia/hemoglobin decreased was similar in the IV and SC cohorts.

Haemophagocytic Lymphohistiocytosis: In the SmPC, section 4.8 the frequency is described as 4/949 patients. The dataset used for presenting HLH adverse drug reactions (ADRs; N=949) is the pooled clinical trial population in the Core Data Sheet version 4 at the time of the SC filing.

Tumour lysis syndrome (TLS): No TLS events were reported in F2 RP2D. The updated frequency of TLS in the SmPC was based on the overall frequency of TLS in the pooled safety population from B11 RP2D and F2 RP2D (2/357).

Tumour flare: Tumour flare is an important identified risk in the summary of safety concerns in the RMP. There were 9 patients with AE of tumour flare in B11 RP2D (N = 218), and 2 patients with AE of tumour flare in F2 RP2D (N = 139). The frequency in the SmPC was updated.

Hepatic adverse events: Overall, there was a lower frequency and severity of hepatic events in the F2 RP2D cohort versus the B11 RP2D cohort. A total of 11/139 patients (7.9%) in the F2 RP2D cohort and 29/218 patients (13.3%) in the B11 RP2D cohort experienced hepatic AEs following initial treatment with mosunetuzumab. The most frequent hepatic events (reported in >5% of patients) in the F2 RP2D and/or B11 RP2D cohorts were ALT and AST increases. Serious hepatic events were reported in 1 patient (0.7%) in the F2 RP2D cohort (Grade 3 transaminases increased) and 3 patients (1.4%) in the B11 RP2D cohort (all events were Grade 3-4 ALT and AST increased). All serious hepatic events were considered related to mosunetuzumab treatment by the investigator. At the time of CCOD, 15 of the 19 hepatic events (78.9%) in the F2 RP2D cohort and 48 of the 59 hepatic events (81.4%) in the B11 RP2D cohort had resolved. One patient with R/R DLBCL in the B11 RP2D cohort was identified as a potential Hy's law case. Liver enzyme elevations with elevated total bilirubin were observed two days prior to confirmed disease progression with duodenal perforation related to progression of lymphoma and death on C1D7.

Infections:

Overall adverse events related to infection were of similar magnitude in the IV and SC cohorts although AEs related to COVID-19 were more frequent in the F2 RP2D cohort, which enrolled after the onset of the COVID-19 pandemic, whereas the B11 RP2D cohort were enrolled mostly prior to the pandemic.

Pneumonitis/ILD:

Pneumonitis/interstitial lung disease (ILD) AEs were broadly defined as all AEs reported as PTs in the Standardized MedDRA Queries (SMQ) Interstitial Lung Disease. There were 2 events (Grade 2 and 3) in the F2 RP2D cohort (1.4%): both events resolved after interruption/ withdrawal. There were three events (1.4%; Grade 1 and two Grade 3) in the B11 RP2D cohort.

Injection site reactions:

Injection site reactions were seen in 96/139 patients (69.1%) in the F2 RP2D cohort but were limited to Grade 1-2. No event was labelled an SAE and all but one resolved.

In study CO41942 64.1% had injection site reactions in the SC Mosun-Len arm, all of which were Grade 1 (51.3%) or Grade 2 events (12.8%).

Rash:

The proportion of patients with rash (grouped term) was comparable between the F2 RP2D cohort (32.4%) and the B11 RP2D cohort (34.9%). The majority of rash events in the F2 RP2D and B11 RP2D cohorts were Grade 1-2, and Grade 3 rash events were reported in 4 patients (2.9%) in the F2 RP2D cohort. No Grade 4 or 5 rash events were reported.

AEs leading to **discontinuation** were more frequently observed in the F2 RP2D cohort (8.6%) compared with the B11 RP2D cohort (4.1%) mainly due to COVID-19 infections (5%) and were the only AEs leading to mosunetuzumab discontinuation in more than one patient. In the B11 RP2D cohort CRS was the only AE leading to mosunetuzumab discontinuation in more than one patient. The proportion of patients with AEs that led to mosunetuzumab discontinuation in Study CO41942 was comparable between the SC Mosun-Len and IV Mosun-Len arms (14.1% vs. 17.9%). Overall, 37.4% in the F2 RP2D cohort and 33.5% in the B11 RP2D cohort had an AE leading to mosunetuzumab dose modification or dose interruption. There were more CRS events leading to dose interruption/modification in the IV cohort (B11 RP2D; 8.7%) compared to the SC cohort (F2 RP2D; 2.2%), whereas COVID-19 infections were the cause in 0.9% vs 11.5%, respectively.

The frequency of AEs reported in the F2 RP2D and B11 RP2D cohorts was generally similar between

patients aged < 65 years and those aged ≥ 65 years within and between cohorts: no clear pattern relating to detriment in the higher **age** category could be seen. There was a higher rate of COVID-19 infections in the < 65 year olds in the F2 RP2D, which was not seen in the B11 cohorts, as these were conducted before the pandemic.

There were more deaths due to AEs in the **prior-CAR-T treated patients**, although the number of SAEs Grade 3-5 excluding PD was comparable. Only four patients in the F2 R/R FL (n=94) had received prior CAR-T therapy.

In the F2 RP2D cohort, the most frequent treatment-emergent Grade ≥ 3 worsening chemistry laboratory parameter shifts were increases in urate (21.6% from baseline to Grade ≥ 3; 3.6% from baseline to Grade 4), glucose (15.8% from baseline to Grade ≥ 3; 1.4% from baseline to Grade 4) and decreases in phosphate (10.1% from baseline to Grade ≥ 3; 0.7% from baseline to Grade 4) which was consistent with hypophosphatemia (5.0%), and hyperglycaemia (2.4%) being among the most frequent Grade 3-4 AEs reported. When comparing the B11 RP2D cohort to the F2 RP2D cohort the changes in urate and glucose were similar but the decrease in all and Grade 3-4 phosphate was larger in the B11 RP2D cohort.

2.6.10. Conclusions on the clinical safety

Safety of mosunetuzumab is generally considered comparable between the SC and IV formulations with no new ADR identified. A lower frequency and severity of CRS was observed in favour of the SC formulation.

2.7. Risk Management Plan

2.7.1. Safety concerns

No new safety concerns were identified based on data from patients treated with mosunetuzumab SC in Study GO29781 (Group F).

Table 31: Summary of safety concerns

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

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

2.7.2. Pharmacovigilance plan

Table 32: On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk-minimization activities				
PASS GO42909: Phase III randomized, open-label, multicenter study evaluating efficacy and safety of mosunetuzumab in combination with lenalidomide in comparison to rituximab in combination with lenalidomide with a non-randomized, single arm, US extension of mosunetuzumab in combination with lenalidomide in patients with follicular lymphoma after at least one line of systemic therapy. *Ongoing*	The randomized phase of the study will evaluate the efficacy and safety of M+Len compared with R+Len in patients with R/R FL who were treated with at least one prior systemic therapy. The non-randomized extension arm will further evaluate efficacy and safety of M+Len in U.S. patient populations with FL. Safety objectives for the randomized phase and non-randomized extension arm will be assessed on the basis of the following endpoints: • Incidence and severity of adverse events, with severity determined according to the NCI CTCAE Version 5.0, including CRS, with severity determined according to the ASTCT CRS grading criteria • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory tests • Tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of adverse events The exploratory safety objective for the randomized phase and non-randomized extension arm will be assessed on the basis of the following endpoints: • Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities as assessed through use of the NCI PRO-CTCAE • Change from baseline in symptomatic treatment toxicities, as assessed through use of the PRO–CTCAE Long-Term Follow-Up visit will occur every 3 months (±14 days) for 5 years from the time of randomization. Survival follow-up will continue for 5 years after LPI.	• Long-term safety	Launch of study: Final analysis CSR (based on primary endpoint of PFS) (projected): Updated final CSR after the survival follow up period (projected):	Q4 2021 Q3 2026 Q1 2030

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

2.7.3. Risk minimisation measures

Table 33 Summary table of pharmacovigilance activities and risk-minimisation activities by safety concern

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

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
ICANS	**Routine risk minimization measures:** **SmPC:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.7 Effects on ability to drive and use machines Section 4.8 Undesirable effects **Package Leaflet:** Section 2 What you need to know before you use Lunsumio® Section 4 Possible side effects **Additional risk minimization measures:** Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting. **Additional pharmacovigilance activities:** None
Serious Infections	**Routine risk-minimization measures:** **SmPC:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Package Leaflet:** Section 2 What you need to know before you use Lunsumio® Section 4 Possible side effects **Additional risk-minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting. **Additional pharmacovigilance activities:** None
Long-term safety	**Routine risk minimization measures:** • None **Additional risk-minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting. **Additional pharmacovigilance activities:** • PASS Category 3 Study GO42909
Safety in patients with prior CAR-T therapy	**Routine risk minimization measures:** • None **Additional risk-minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** None

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

2.7.4. Conclusion

The CHMP considered that the risk management plan version 3.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH 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 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.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Lunsumio IV. The bridging report submitted by the MAH was considered acceptable.

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 is approved under a conditional marketing authorisation [REG Art 14-a].

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

Mosunetuzumab is approved for intravenous use as monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies. The MAH is seeking approval for a subcutaneous dose regimen (supported by a new pharmaceutical form and two new strengths) in the same indication.

3.1.2. Available therapies and unmet medical need

The therapeutic context is unchanged from the approved IV mosunetuzumab treatment for follicular lymphoma after two or more therapies.

For patients with FL who relapse after or are refractory to initial therapy, treatment decisions take into consideration efficacy and duration of response 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 at least 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 still a high unmet need.

3.1.3. Main clinical studies

The application is based on the pivotal study GO29781, an "ongoing Phase I/II, 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 hematological malignancies expected to express CD20, including B-cell NHL and chronic lymphocytic leukemia (CLL)".

In that study, the PK non-inferiority (PKNI) of the proposed SC regimen to IV regimen was investigated in R/R FL patients (patients treated with ≥ 2 prior therapies). The SC cohort of interest (Cohort F2 Exp FL) was retrospectively compared to the previous investigated IV cohort B11 Exp FL.

The primary objective for this part of study GO29781 was to evaluate the PK non-inferiority of mosunetuzumab SC monotherapy treatment (cohort F2 exp R/R FL) compared to the approved mosunetuzumab IV monotherapy treatment (cohort B11 exp R/R FL) based on the co-primary PK endpoints; $C_{troughCYC3\_OBS}$ (observed) and $AUC_{0\text{-}84}$ (model-predicted). Efficacy analyses include standalone efficacy analyses for the SC (F2 exp R/R FL) cohort, and a retrospective comparison, which was not formally tested and only supportive of the primary objective of PK non-inferiority, between SC (F2 exp R/R FL) cohort and the IV (B11 exp R/R FL) cohort.

In study GO29781, efficacy was assessed based on CR rate, ORR, DOR, duration of complete response, PFS, and OS. No formal statistical testing was performed for any of these endpoints. The efficacy populations consist of patients with R/R FL with ≥2 prior lines of systemic therapy: 94 patients from the RP2D expansion cohort receiving mosunetuzumab monotherapy SC (F2 exp R/R FL) and 90 patients from the RP2D expansion cohort receiving mosunetuzumab monotherapy IV (B11 exp R/R FL). The two cohorts were not conducted at the same time so no stratification could be performed. To minimize potential differences between the two cohorts, the same eligibility criteria were used, and patients were recruited from the same sites.

3.2. Favourable effects

The pharmacokinetics of subcutaneous mosunetuzumab was adequately investigated in the pivotal GO29781 study, supported by the CO41942 study and by Pop-PK modelling. It was demonstrated that the PK of mosunetuzumab SC was non-inferior to the IV product.

CR rate by IRF was comparable between the F2 exp R/R FL cohort and the B11 exp R/R FL cohort [(58.5% vs. 60.0%; odds ratio of 0.94 (95% CI: 0.52, 1.69)]. Odds ratios for the prespecified multivariate and propensity score analyses were both lower [0.81 (95% CI 0.42, 1.55) and 0.79 (95%

CI 0.44, 1.44), respectively]. **Objective response (CR or PR) rate** by IRF assessment was 74.5% vs. 80.0% for F2 exp R/R FL cohort vs. B11 exp R/R FL cohort. Odds ratios for the prespecified multivariable and propensity score analyses were both lower [0.55 (95% CI 0.25, 1.19) and 0.59 (95% CI 0.29, 1.20), respectively]. Median **DOCR** was 20.8 months (95% CI: 18.8, NE) in the F2 exp R/R FL cohort and the median was not reached in the B11 exp R/R FL cohort at the corresponding CCODs. Median **DOR** was comparable with 22.4 months (95% CI: 16.8, 22.8) in the F2 exp R/R FL cohort and 22.8 months (95% CI: 9.7, NE) in the B11 exp R/R FL cohort. These are considered clinically relevant and match the efficacy evidence supporting the approved mosunetuzumab IV monotherapy indication.

3.3. Uncertainties and limitations about favourable effects

Efficacy results are based on few patients and no formal statistical testing was performed for any of the efficacy endpoints, however the main purpose of the study was to demonstrate PK non-inferiority.

3.4. Unfavourable effects

Adverse events in the SC F2 RP2D cohort were overall comparable to the IV B11 RP2D cohort with the exception related to the route of administration where injection site reactions (61.9%) were seen in the SC F2 RP2D cohort, and a higher frequency of CRS in the IV B11 RP2D cohort (39.4% compared to 25.9%).

Compared to mosunetuzumab IV monotherapy, SC monotherapy showed a lower frequency of Grade 3-5 AEs (54.7% vs. 72.0%) which was mainly driven by less frequent **Grade 3-4** hypophosphataemia (5.0% vs. 14.7%). A higher frequency of **grade 5 adverse events** was observed in the F2 RP2D (N = 139) cohort compared with the B11 RP2D (N = 218) cohort: six of nine AE-related deaths were due to COVID-19 (PD excluded), whereas there were no COVID-19-related deaths in the B11 RP2D cohort (CCOD 01 February 2024 and 27 August 2021, respectively). The three remaining deaths due to AEs were due to haemophagocytic lymphohistiocytosis, septic shock, and general physical health deterioration, whereas the four AE-related deaths in the B11 RP2D cohort were due to cholangitis, pneumonia, sepsis and sudden death (found dead in bed). The incidence of **SAEs** was lower in the F2 RP2D (N = 139) cohort compared to the B11 RP2D (N = 218) cohort; 36.7% vs 45.9%, respectively (grade 5 PD events excluded). Overall, there was a lower frequency and severity of CRS in the F2 RP2D cohort compared with the B11 RP2D cohort (25.9% vs. 39.4% overall, and for Grade 3-4 1.4% vs 2.8%, respectively). Neutropenia/neutrophil count decreased was similar in the IV and SC cohorts. Overall adverse events related to infection were of similar magnitude in the IV and SC cohorts although AEs related to COVID-19 were more frequent in the F2 RP2D cohort, which enrolled after the onset of the COVID-19 pandemic, whereas the B11 RP2D cohort were enrolled mostly prior to the pandemic. Injection site reactions were seen in 96/139 patients (69.1%) in the F2 RP2D cohort but were limited to Grade 1-2. No event was labelled an SAE and all but one resolved.

3.5. Uncertainties and limitations about unfavourable effects

The safety database remains relatively small overall (n=357) and uncertainties remain in relation to long-term safety of mosunetuzumab regardless of route of administration. Lunsumio is still under conditional approval, therefore additional data are expected through the submission of post authorisation specific obligations.

3.6. Effects Table

Not applicable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The application is based on evidence from two clinical studies, the pivotal study GO29781 and the supportive study CO41942, and is also supported by model-informed drug development. In study GO29781, the primary objective was to show non-inferiority of mosunetuzumab SC compared to mosunetuzumab IV from a PK perspective, and secondary objectives included efficacy and safety endpoints, although these were not formally tested and only supportive of the primary objective.

The bioavailability of mosunetuzumab SC was adequately estimated from AUC_{ss} to 90%. Absorption was as expected slower for SC administration, resulting in a larger t_{max} of 4-7 days and lower C_{max} compared to IV. Distribution, clearance, and metabolism of mosunetuzumab SC are as previously described for the IV product. The estimated terminal $t_{1/2}$ at steady state was slightly longer at 16.8 days. Dose-proportionality of AUC was shown over the range from 1.6 mg to 45 mg mosunetuzumab SC. Steady state was reached after approximately 3-4 cycles, consistent with the IV product. The PK of mosunetuzumab SC was non-inferior to the IV product. Efficacy and safety data presented supported the demonstration of PK non-inferiority.

3.7.2. Balance of benefits and risks

PK non-inferiority of SC vs IV mosunetuzumab, the primary objective of pivotal study GO29781, is considered established. Furthermore, the efficacy of SC and IV mosunetuzumab appears to be comparable based on observed CR, ORR, DoCR, DoR, PFS and OS. No new safety signals were observed, and the safety profiles of both dosing regimens were similar with the exception of an increase in injection site reactions (grade 1-2) and decrease in the incidence and severity of CRS in patients treated with the SC dosing regimen. The benefit-risk ratio for SC mosunetuzumab monotherapy in FL patients is considered positive as for the IV formulation.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

Lunsumio is approved as a CMA, and the submitted data is not part of any specific obligation related to the existing CMA.

The specific obligation to complete post-authorisation measure for the CMA with the due date in Q1 2026 remains unchanged:

- In order to provide further evidence of efficacy and safety of mosunetuzumab in follicular lymphoma, the Marketing Authorisation Holder (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.

3.8. Conclusions

The overall benefit/risk balance of Lunsumio is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Lunsumio is not similar to Gazyvaro, Kymriah and Yescarta within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

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 5 mg and 45 mg solution for injection for sc administration 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 extension of the marketing authorisation for Lunsumio 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).

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) and immune effector cell-associated neurotoxicity syndrome (ICANS).

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 the key signs and symptoms of ICANS
- A description of when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS or ICANS 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.	Q3 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.

These conditions fully reflect the advice received from the PRAC.