21 May 2026
EMADOC-1700519818-3104033
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tepkinly

International non-proprietary name: Epcoritamab

Procedure No. EMA/VR/0000311043

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

1L	first-line
2L	second-line
2L+	second-line or higher
3L+	third-line or higher
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
aNHL	aggressive non-Hodgkin lymphoma
ASTCT	American Society for Transplantation and Cellular Therapy
BOR	best overall response
BTK	Bruton's tyrosine kinase
CAR	chimeric antigen receptor
CD	cluster of differentiation
cFL	classic FL
CI	confidence interval
CL/F	apparent clearance
CMH	Cochran-Mantel-Haenszel
CMR	complete metabolic response
CMV	cytomegalovirus
COVID-19	coronavirus disease – 2019
CR	complete response
CrCl	creatinine clearance
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTLS	clinical tumor lysis syndrome
CV	coefficient of variation
CYP	cytochrome P450
DCO	data cut-off
DILI	drug-induced liver injury
DLBCL	diffuse large B-cell lymphoma
DOCR	duration of complete response
DOR	duration of response
ECG	electrocardiogram
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
eGFR	estimated glomerular filtration rate
Epco	epcoritamab
EQ-5D-5L	EuroQol 5-dimension questionnaire, 5-level
EU	European Union
EZH2	Enhancer of Zeste Homolog 2
FACT-Lym	functional assessment of cancer therapy – lymphoma
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FL	follicular lymphoma
FLBL	follicular large B-cell lymphoma
FLIPI	follicular lymphoma international prognostic index
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GELF	Groupe d'Etude des Lymphomes Folliculaires
GLP	Good Laboratory Practices
HA	harm analysis
HR	hazard ratio
IA1	interim analysis 1
ICANS	immune cell-associated neurotoxicity syndrome
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IF	information fraction

IgG1	immunoglobulin g1
IL	interleukin
iNHL	indolent non-Hodgkin lymphoma
IR	indeterminate response
IRC	Independent Review Committee
ISR	injection site reaction
ITT	intent to treat
IV	intravenous(ly)
Km	concentration at which the rate is half maximal
LBCL	large B-cell lymphoma
LDH	lactate dehydrogenase
LFT	liver function test
LLOQ	lower limit of quantitation
LYRIC	lymphoma response to immunomodulatory therapy criteria
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRD	minimal residual disease
MRI	magnetic resonance imaging
ms	millisecond
nAb	neutralizing antibody
NALT	new anti-lymphoma therapy
NE	non evaluable
NHL	non-Hodgkin lymphoma
NK	natural killer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PFS	progression-free survival
PGIC	patient global impression of change
PGIS	patient global impression of severity
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PO	oral(ly)
POD24	progression of disease within 24 months
PR	partial response
PRO	patient-reported outcome
PT	preferred term
Q4W	every 4 weeks
QoL	quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
QW	once a week
R/R	relapsed/refractory
R2	rituximab and lenalidomide
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
SC	subcutaneous(ly)
SCT	stem cell transplant
SD	stable disease
SMQ	standardized MedDRA query
SOC	system organ class
std dev	standard deviation
SUD	step-up dosing
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TOI	trial outcome index
TTCR	time to complete response
TTNLT	time to next anti-lymphoma treatment
TTP	time to progression
TTR	time to response
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Abbvie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 10 November 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include in combination with rituximab and lenalidomide treatment of patients with relapsed/refractory follicular lymphoma (FL) for Tepkinly, based on interim results from study M20-638; this is a Phase 3, open-label study to evaluate safety and efficacy of epcoritamab in combination with rituximab and lenalidomide (R2) compared to R2 in subjects with relapsed or refractory follicular lymphoma (EPCORE FL-1). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.2.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0224/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0224/2024 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

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

Date	Reference	SAWP co-ordinators
25/06/2020	**EMEA/H/SA/4478/1/2020/III**	Adriana Andric, Alexandre Moreau
15/10/2020	**EMEA/H/SA/4478/3/2020/I**	Karin Janssen van Doorn, Paolo Foggi
15/09/2022	**EMA/SA/0000095173**	Rune Kjeken, Alexandre Moreau
12/12/2024	**EMA/SA/0000229570**	Karri Penttila, Alexandre Moreau

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

- the comparability strategy for the manufacturing changes relating to transfer and scale-up as well as on the process performance qualification (PPQ) strategy to support the potential conditional MAA filing.
- the requirement of a 3-month repeat-dose toxicity study of epcoritamab in cynomolgus monkeys, as well as the requirement for a dedicated embryofetal developmental toxicity study;
- whether an unmet medical need exists in the proposed indication of relapsed / refractory follicular lymphoma;
- the design of the aNHL expansion cohort of the ongoing Phase 1/2 Trial GCT3013-01 to support a conditional marketing authorisation (CMA), in particular the inclusion criteria, the primary and secondary endpoints, including MRD status, the statistical assumptions for the sample size calculation;
- the size of the safety database; whether the GCT3013-TBD trial of epcoritamab+R2 versus R2 alone may serve as the confirmatory trial under a specific obligation if a CMA is granted for this indication.
- the revised design of the Phase 3 Study M20-638 of epcoritamab in combination with rituximab and lenalidomide (R2) in subjects with relapsed/refractory FL, in particular the choice of patient population, comparator and planned treatment arms, secondary endpoints, statistical analysis plan, PRO measurement strategy and pharmacokinetics sampling plan;
- the proposed initiation of the pivotal trial with investigational arms for 2 different doses of epcoritamab concurrently with planned dose optimization studies;
- the proposed data package based on the iNHL expansion cohort of the Phase 1/2 Study GCT3013-01 to support a conditional marketing authorisation of epcoritamab monotherapy in relapsed/refractory follicular lymphoma and of phase 3 Study M20-638 to serve as the confirmatory trial
- whether an unmet medical need exists for patients receiving a third line of treatment in this indication and the related CMA submission strategy, including phase 3 study M20-638 design; the suitability of BOR of CR or PR and PFS as dual primary endpoints; the design and statistical analysis plan of the Phase 3 Study M20-638 to fulfil the requirements of a confirmatory study in R/R FL.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Peter Mol Co-Rapporteur: NA

Timetable	Actual dates
Submission date:	11 Nov 2025
Start of procedure:	28 Nov 2025
CHMP Rapporteur's preliminary assessment report circulated on:	22 Jan 2026
PRAC Rapporteur's preliminary assessment report circulated on:	30 Jan 2026
Updated PRAC Rapporteur's assessment report circulated on:	05 Feb 2026
PRAC Outcome:	12 Feb 2026
Updated CHMP Rapporteur's assessment report circulated on:	19 Feb 2026
CHMP Request for Supplementary Information:	26 Feb 2026
MAH's responses submitted to the CHMP on:	17 Mar 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	21 Apr 2026
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	24 Apr 2026
PRAC Outcome:	07 May 2026
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on:	13 May 2026
CHMP opinion:	21 May 2026
The CHMP adopted a report on similarity of Tepkinly with Kymriah, Lunsumio, Yescarta and Minjuvi (Appendix 1)	21 May 2026
The CHMP adopted a report on the significant clinical benefit for Tepkinly in comparison with existing therapies (Appendix 2)	21 May 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Malignant lymphoma represents a disease entity characterized by malignant transformation of the cells from lymphoid tissue. Approximately 90% of lymphomas in Western countries are of B-cell origin (Blood, 1997). The majority of B-cell lymphomas express B-cell markers, such as CD19, CD20, CD22, and CD79b (Swerdlow et al, 2016). Clinically, B-cell non-Hodgkin lymphoma (NHL) has been divided into aggressive non-Hodgkin lymphoma (aNHL) and indolent non-Hodgkin lymphoma (iNHL), which is generally more slow-growing.

Claimed therapeutic indication

The applied new therapeutic indication is: "*Tepkinly in combination with lenalidomide and rituximab is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL).*"

Epidemiology and risk factors, screening tools/prevention

Follicular lymphoma (FL) is the second most prevalent type of NHL, representing 25% of NHL cases, and is the most common type of iNHL (Swerdlow et al, 2008). The median age at diagnosis of FL is 65 years.

FL is incurable and exhibits a high degree of clinical heterogeneity, ranging from an indolent to a highly aggressive clinical course. With each successive line of therapy, patients with relapsed or refractory (R/R) disease experience significantly decreased response rates, shortened duration of response (DOR), and a higher mortality rate (Rivas-Delgado et al, 2019; Casulo et al, 2015; Link et al, 2019).

Risk factors associated with poorer outcome in patients with FL include advanced age, advanced stage disease (Ann Arbor stages III-IV), bulky disease, high FL International Prognostic Index (FLIPI) score (i.e., 3 to 5), and double refractory disease (e.g., refractory to both an anti-CD20 monoclonal antibody and an alkylating agent) (Sarkozy et al, 2019; Solal et al, 2004; Qualls et al, 2022). Two-thirds of patients who undergo second-line (2L) therapy will either be refractory to treatment or have a disease recurrence within 5 years of therapy. In addition, outcomes are particularly poor in patients who experience progression of disease within 24 months of first line therapy (POD24). This patient subgroup accounts for approximately 20% of patients who receive first-line (1L) chemoimmunotherapy and 60% of patients treated in the third-line (3L) or later setting (Salles et al, 2022). Only 35-50% of these patients remain alive at 5 years (vs approximately 90% in late relapsed FL). The prognosis after histological transformation of FL to a large cell lymphoma (occurring in 2% to 3% of patients per year; 25-35% of patients, Swerdlow et al 2017) is also extremely poor, with a median overall survival (OS) of 1 to 2 years (Relander et al, 2010; Wagner-Johnston et al, 2015).

Biologic features

NHLs comprise a heterogenous group of malignancies that arise from haematopoietic progenitor cells. B cell NHLs arise from B-lymphocytes and have the cell surface characteristics of normal B-cell differentiation. FL tumour cells are considered to be malignant counterparts of normal

germinal center B cells in the lymph nodes. Morphologically, the malignant B-cells typically forms a follicular growth pattern.

According to the WHO classification (Alaggio et al, 2022), the vast majority of FL (85%) have at least in part a follicular growth pattern, are composed of centrocytes and centroblasts and harbour the t(14;18)(q32;q21) translocation associated with IGH:: BCL2 fusion; these are now termed classic FL (cFL) and set apart from two related subtypes/groups, follicular large B-cell lymphoma (FLBL) and FL with uncommon features. In WHO-HAEM5, grading of FL, which is only pertinent to cFL, is no longer mandatory due to reproducibility of grading and on its questionable clinical significance for individual patients.

As in the majority of other mature B-cell lymphomas, FL is characterized by the expression of a surface membrane antigen, CD20. CD20 is an attractive target for anti-lymphoma therapies, being B-cell-specific, highly and stably expressed, exhibiting a low rate of internalization, and not being present on hematopoietic stem cells. The concept of targeting CD20 as an effective anti-lymphoma strategy has been validated by clinical data for the anti-CD20 monoclonal antibody rituximab, which has revolutionized the treatment of FL. The utility of CD20 as a therapeutic target has led to the continued development of improved anti-CD20 monoclonal antibodies.

Clinical presentation, diagnosis and stage/prognosis

FL is generally a slow growing type of NHL that is found more frequently in older adults and is characterized by diffuse swelling of the lymph nodes, bone marrow involvement, and an enlarged spleen. Extranodal involvement is less common. However, there is a potential for transformation to a more aggressive form, usually diffuse large B-cell lymphoma (DLBCL). Cytopenias are relatively common but constitutional symptoms of fever, night sweats, and weight loss are uncommon in the absence of transformation to DLBCL (Freedman et al, 2020). Due to its indolence, FL typically is considered more of a chronic disease rather than a curable disease; however, the disease can progress to a more aggressive form of lymphoma.

The diagnosis of FL is based on histology from a biopsy of a lymph node or other affected tissue. Incisional biopsy is preferred over needle biopsies to give adequate tissue to assign grade and assess for transformation. Immunohistochemical staining is positive in virtually all cases for cell surface CD19, CD20, CD10, and monoclonal immunoglobulin, as well as cytoplasmic expression of B-cell lymphoma-2 (bcl-2) protein (Freedman et al, 2020).

The FLIPI score uses five independent predictors of inferior survival: age > 60 years, hemoglobin < 12 g/dL, serum lactate dehydrogenase (LDH) > normal, Ann Arbor stage III/IV, and number of involved nodal areas > 4. The presence of 0-1, 2, and ≥ 3 adverse factors define low, intermediate, and high-risk disease, respectively. Other factors such as POD24 from initial chemoimmunotherapy and specific gene mutations may also be useful for prognosis. Regardless of the prognostic model used, modern therapies have demonstrably improved prognosis (Freedman et al, 2020). However, patients with refractory or early relapsing disease have an especially poor prognosis (Relander et al, 2010; Bachy et al, 2021).

The course of FL is often characterized by relapsing disease, increasing refractoriness to anti-CD20 antibodies and chemotherapy, and decreasing disease-free intervals with each subsequent therapy (Rivas-Delgado et al, 2019; Bachy et al, 2019; Marcus et al, 2017).

Management

The management of r/r FL according to the ESMO-guideline is shown in Figure 1. Treatment options include chemoimmunotherapy, anti-CD20 regimens, rituximab in combination with lenalidomide (R^2), bispecific antibodies, EZH2 inhibitors, and BTK inhibitors. Depending on the patient's specific situation and previous treatment history; other options may include radioimmunotherapy and allogeneic hematopoietic cell transplant, or, for highly refractory cases, chimeric antigen receptor (CAR) T-cell therapies.

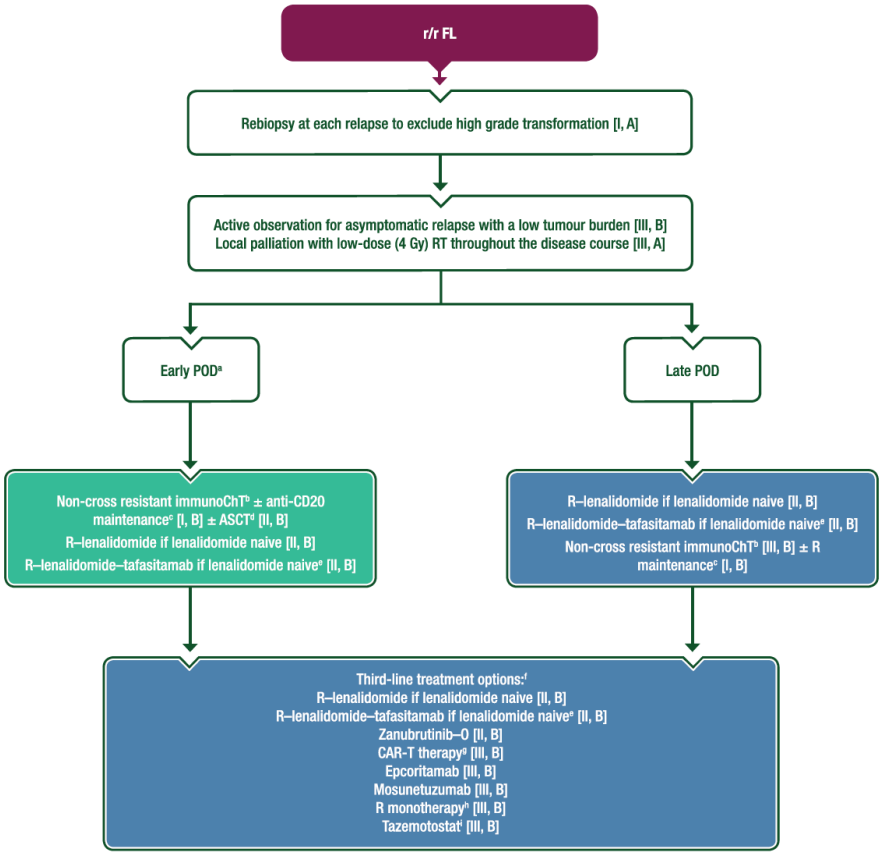


Figure 1. Management of r/r FL according to the ESMO-guideline (Eyre et al, 2025)

2.1.2. About the product

Epcoritamab is a humanised IgG1-bispecific antibody that binds to a specific extracellular epitope of CD20 on B-cells and to CD3 on T-cells. The activity of epcoritamab is dependent upon simultaneous engagement of CD20-expressing cancer cells and CD3-expressing endogenous T-cells by epcoritamab that induces specific T-cell activation and T-cell-mediated killing of CD20-expressing cells.

Epcoritamab Fc region is silenced to prevent target-independent immune effector mechanisms, such as antibody-dependent cellular cytotoxicity, complement-dependent cellular cytotoxicity (CDC), and antibody-dependent cellular phagocytosis.

Tepkinly was previously approved in the European Union in the following indications:

- Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
- Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

EMEA/H/SA/4478/1/2020/III – This advice was mainly about the suitability of the Phase 1/2 Trial GCT3013-01 to evaluate the benefit-risk profile of epcoritamab to support a CMA in the indication of R/R FL previously treated with at least 2 prior lines of therapy. Trial GCT3013-TBD of epcoritamab+ rituximab and lenalidomide (R^2) versus R^2 alone was considered acceptable as confirmatory trial under a specific obligation for the above indication. Several specific comments were made:

- Using PFS as assessed by IRC is agreed, provided that estimated treatment effects on OS ensure that there are no detrimental effects on this endpoint, regardless of the statistical significance for the PFS endpoint. For this reason the proposed interim analysis was not encouraged.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The active substance is a monoclonal antibody, which as a protein, is composed of amino-acids naturally present in the environment. The use of the medicinal product is not expected to alter the concentration or distribution of these naturally occurring substances in the environment and therefore no environmental risk assessment studies are required.

2.2.2. Conclusion on the non-clinical aspects

Previous non-clinical data supports the intended clinical use of epcoritamab. In addition, epcoritamab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

Table 1. Overview of clinical study to support the current submission

Trial Identifier and Title	Treatment(s)	Population	N* at Clinical DCO
Epcoritamab + R^2			
Study M20-638 A Phase 3, Open-Label Study to Evaluate Safety and Efficacy of	Arm A: Epcoritamab 48 mg + R^2	R/R FL	243

Epcoritamab in Combination with Rituximab and Lenalidomide (R^2) compared to R^2 in Subjects with Relapsed or Refractory Follicular Lymphoma (EPCORE™ FL-1)	Arm B: Epcoritamab 24 mg + R^2	R/R FL	61
	Arm C: R^2	R/R FL	238
Study GCT3013-02 Arm 2 A Phase 1b/2, Open-Label Trial to Assess the Safety and Preliminary Efficacy of Epcoritamab (GEN3013; DuoBody®-CD3xCD20) in Combination with Other Agents in Subjects with BNHL (supportive study)	Arm 2: Epcoritamab 24 mg + R^2	R/R FL	31
	Arm 2: Epcoritamab 48 mg + R^2	R/R FL	111

B-NHL = B-cell non-Hodgkin lymphoma; DCO = data cutoff; FL = follicular lymphoma; R/R = relapsed or refractory; R^2 = rituximab and lenalidomide
* In Safety Analysis Set.
DCO of 24 May 2025 for Study M20-638 and 21 September 2024 for Study GCT3013-02 Arm 2.

2.3.2. Pharmacokinetics

Epcoritamab is proposed to be administered by subcutaneous (SC) injection in a step-up dosing (SUD) method in treatment cycles of 28 days, with once weekly (QW) dosing in Cycles 1-3 and once every 4 weeks (Q4W) dosing in Cycles 4-12, until unacceptable toxicity or disease progression. The proposed epcoritamab 3–step SUD regimen includes an initial priming dose of 0.16 mg on Cycle 1 Day 1 (C1D1), a first intermediate dose of 0.8 mg on Cycle 1 Day 8 (C1D8), a second intermediate dose of 3 mg on Cycle 1 Day 15 (C1D15), and a full dose of 48 mg on Cycle 1 Day 22 (C1D22) and thereafter.

R^2 is administered in 28-day cycles, as detailed below:

- Rituximab 375 mg/m^2 intravenous (IV) QW during Cycle 1 (on Day 1, Day 8, Day 15, and Day 22) and Q4W during Cycles 2-5 (on Day 1)
- Lenalidomide 20 mg orally (PO) once a day from Day 1 to Day 21 during Cycles 1-12

To support the current extension of indication, the MAH submitted interim results of trials **M20-638** and **GCT3013-02** (). The drug substance and drug product used for the treatment of subjects with R/R FL in these studies were the same as those used for monotherapy treatment of subjects with R/R DLBCL and R/R FL, as noted in the previous applications.

GCT3013-02, Arm 2, is an ongoing a phase 1b/2, open-label study, which assessed safety and efficacy of epcoritamab in combination with R^2 in subjects with R/R FL. The study included two cohorts (2a and 2b), both of which used a 2-step SUD regimen for epcoritamab (0.16/0.8/24 or 48 mg) and a different frequency of dosing was studied in both cohort 2a (QW in cycle 1 to 3, Q2W in cycle 4 to 9, Q4W in cycle 10+) and 2b (QW in cycle 1 to 2, Q4W in cycle 3+) compared to the proposed posology.

Study M20-638 is an ongoing open-label, randomised, global, phase 3 study with dual primary endpoints of best overall response (BOR), complete or partial response (CR and PR) and progression-free survival (PFS). Version 1.0 of the protocol had two investigational arms with subjects randomised in a 1:1:1 ratio to epcoritamab 48 mg in combination with R^2 (Arm A), epcoritamab 24 mg in combination with R^2 (Arm B), and Arm C as the control arm (R^2). Based on the early clinical study data from Arm 2 of the Phase 1b/2 Study GCT3013-02, the recommended full dose of epcoritamab in

combination with R^2 was identified as 48 mg. Therefore, Arm B (epcoritamab 24 mg + R^2; N = 61) was closed for enrolment in Version 2.0 of the protocol and subjects had the option to switch to epcoritamab 48 mg + R^2, at the investigator's discretion. The 3-step SUD regimen for epcoritamab was introduced in Version 3.0. A full description of the studies is provided in Section 2.4.

Pharmacokinetic samples were collected at C1-12D1 pre-dose, C1-3D8 pre-dose, C1-3D15 pre-dose, C1-3D22 pre-dose and C1D16 and C1D23 (24 hours post-dose) in **M20-638**. Pharmacokinetic samples were collected at C1-13D1 pre-dose, C1-3D8 pre-dose, C1-4D15 pre-dose in **GCT3013-02 Arm 2**.

The reports of the bioanalytical method validation within studies were submitted (**PRA-NL-LML-2564, PRA-US-LML-0552** and **ANA24-026, 22BASM168**).

Methods

Immunogenicity

A titer-based acid dissociation bridging ECL immunoassay was developed and validated for the detection and characterization of anti-epcoritamab antibodies in human serum. A tiered testing principle was applied, consisting of a screening and a confirmatory assay and two titer assays for detecting anti-drug antibodies against the CD3-binding and CD20-binding arms of epcoritamab, respectively.

Population pharmacokinetic model

Aims

The objectives of the population pharmacokinetic analysis were as follows:

- Confirm PK of epcoritamab in subjects with progressive R/R B-cell lymphomas, and to determine the impact on effect of key intrinsic and extrinsic covariates on epcoritamab PK parameters and exposure. Specifically:
    - To evaluate whether a previously developed epcoritamab PopPK model can describe epcoritamab PK in combination with R2 in FL subjects from Studies M20-638 and GCT3013-02 (Arm 2).
    - To evaluate effects of intrinsic and extrinsic factors used in the previously developed PopPK model on epcoritamab PK parameters and exposure.
    - To evaluate effects of ADA on epcoritamab PK parameters and exposure.
- To derive individual exposures (e.g., AUC, Cavg, Cmin, or/and Cmax) of epcoritamab for the exposure-safety and exposure-efficacy analyses.

Data

Data from Studies M20-638 and GCT3013-02 (Arm 2) were used in the analyses. All subjects who had at least 1 post baseline quantifiable epcoritamab concentration value by the pharmacokinetic analysis cut-off date with available date and time of blood collections as well as available date and time of epcoritamab dose administrations prior to the blood collections were included in the analysis. Actual collection times of blood samples for measurement of epcoritamab concentrations were used in the population pharmacokinetic analysis without imputation. Observations below the limit of quantification (BQL) were excluded from the analysis.

In total, 446 subjects from Studies M20-638 (304 subjects) and GCT3013-02 Arm 2 (142 subjects) received at least one dose of epcoritamab. Of those 446 subjects, 8 subjects did not have quantifiable

(> lower limit of quantification [LLOQ]) post-dose PK observations. Thus, after excluding the subjects/samples above, data from 438 subjects (299 subjects from Study M20-638 and 139 subjects from Study GCT3013-02 Arm 2) contributing a total of 8243 quantifiable epcoritamab post dose concentration values were included in the analysis. Of those 438 subjects, 56 subjects were administered a full dose of 24 mg, 33 subjects started with a full dose of 24 mg and then switched to a full dose of 48 mg, and 349 subjects were administered a full dose of 48 mg. Among 299 subjects from Study M20-638, 26 subjects were administered a full dose of 24 mg, 33 subjects started with a full dose of 24 mg and then switched to a full dose of 48 mg, and 240 subjects were administered a full dose of 48 mg. Among 139 subjects from Study GCT3013-02 Arm 2, 30 subjects were administered a full dose of 24 mg and 109 subjects were administered a full dose of 48 mg.

Methods

The population pharmacokinetic analysis was conducted via nonlinear mixed-effects modelling with the NONMEM software, Version 7.5.1 (ICON Development Solutions) using the FOCE-I algorithm. Earlier analyses found that observed concentration-time data of epcoritamab were adequately described by a quasi-steady-state (QSS) approximation of a two-compartment TMDD model with first order SC absorption, see equations and Figure 2 below.

Equations:

$$\frac{dA_1}{dt} = -k_a \cdot A_1;\ A_1(0) = SC\ Dose;$$
$$\frac{dA_2}{dt} = k_a \cdot A_1 - \frac{CL}{V_C} \cdot C \cdot V_C - \frac{Q}{V_C} \cdot C \cdot V_C + \frac{Q}{V_P} \cdot A_3 - \frac{k_{int} \cdot Base \cdot C \cdot V_C}{K_{SS} + C};\ A_2(0) = 0;$$
$$\frac{dA_3}{dt} = \frac{Q}{V_C} \cdot C \cdot V_C - \frac{Q}{V_P} \cdot A_3;\ A_3(0) = 0;$$

Here

$$C = \frac{1}{2}\left(\frac{A_2}{V_C} - Base - K_{SS}\right) + \frac{1}{2}\sqrt{\left(\frac{A_2}{V_C} - Base - K_{SS}\right)^2 + 4 \cdot K_{SS} \cdot \frac{A_2}{V_C}}$$

Random effects model:

$CL = \theta_1 \cdot COV_{CL} \cdot e^{\eta 1}$; $Q = \theta_2 \cdot COV_Q$; $V_C = \theta_3 \cdot COV_{VC} \cdot e^{\eta 2}$; $V_P = \theta_4\ COV_{VP} \cdot e^{\eta 3}$;

$k_a = \theta_5 \cdot COV_{ka} \cdot e^{\eta 5}$; $BASE = \theta_6 \cdot e^{\eta 6}$; $K_{SS} = \theta_7 \cdot e^{\eta 7}$; $k_{int} = \theta_8 \cdot COV_{kint} \cdot e^{\eta 8}$; $\eta_i = N(0, \omega_i^2)$

Covariate Model:

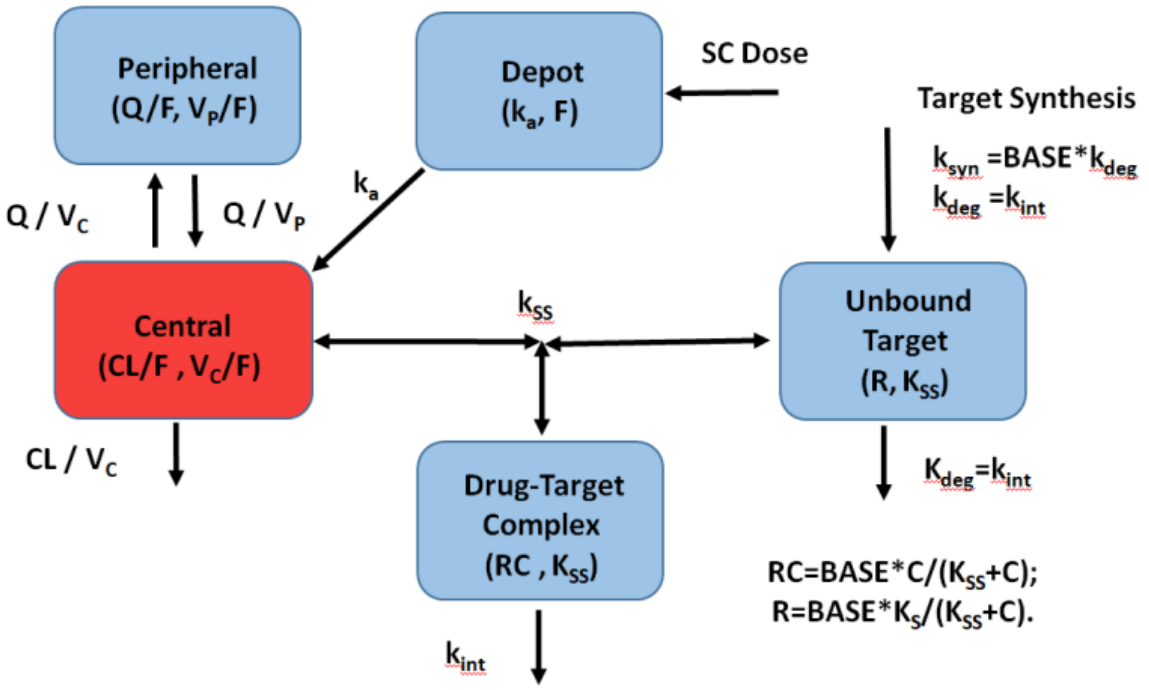
$COV_{CL} = (WT/75)^{\theta 11}$; $COV_Q = (WT/75)^{0.75;}$ $COV_{VC} = (WT/75)^{\theta 13;}$

$COV_{VP} = (WT/75)$; $COV_{ka} = (AGE/65)^{\theta 15} \cdot (BMI/25)^{\theta 16}$;

$COV_{kint} = (SUMPPD/30)^{\theta 17} \cdot (\theta_{18}\ if\ iNHL)$.

Residual Error Model:

$observed = C \cdot (1 + \sigma \cdot \varepsilon_1)$; $\varepsilon_1 = N(0,1)$; $\sigma = sqrt(C^2 \cdot \theta_9^2 + \theta_{10}^2) \cdot e^{\eta 9}$; $\eta_9 = N(0, \omega_9^2)$.



Abbreviations: K_a = absorption rate constant; K_{int} = elimination rate constant of the drug-target complex; K_{ss} = QSS constant; PK = pharmacokinetics; Q/F = apparent inter-compartmental clearance; SC = subcutaneous; Vc/F = apparent central volume of distribution; Vp/F = apparent volume of distribution in the peripheral compartment. The model was parameterized in terms of CL/F, V_c/F, Q/F, V_p/F, k_a, BASE, k_{int}, and the K_{ss}.

Figure 2. Schematic overview of population pharmacokinetic model

The model described above was evaluated using exploratory graphical analysis of Empirical Bayes Estimates (EBE) versus continuous covariates and boxplots of EBEs versus categories of categorical covariates. Potential new covariates of interest for the PopPK model were effects of concomitant administration of rituximab and lenalidomide. Standard goodness-of-fit criteria were applied for model evaluation.

Final model

The prior model with fixed parameter estimates was re-evaluated, accepted as the final model, and then used to provide individual estimates of the model parameters and exposure metrics. A prediction-corrected visual predictive check (pcVPC) is displayed in Figure 3.

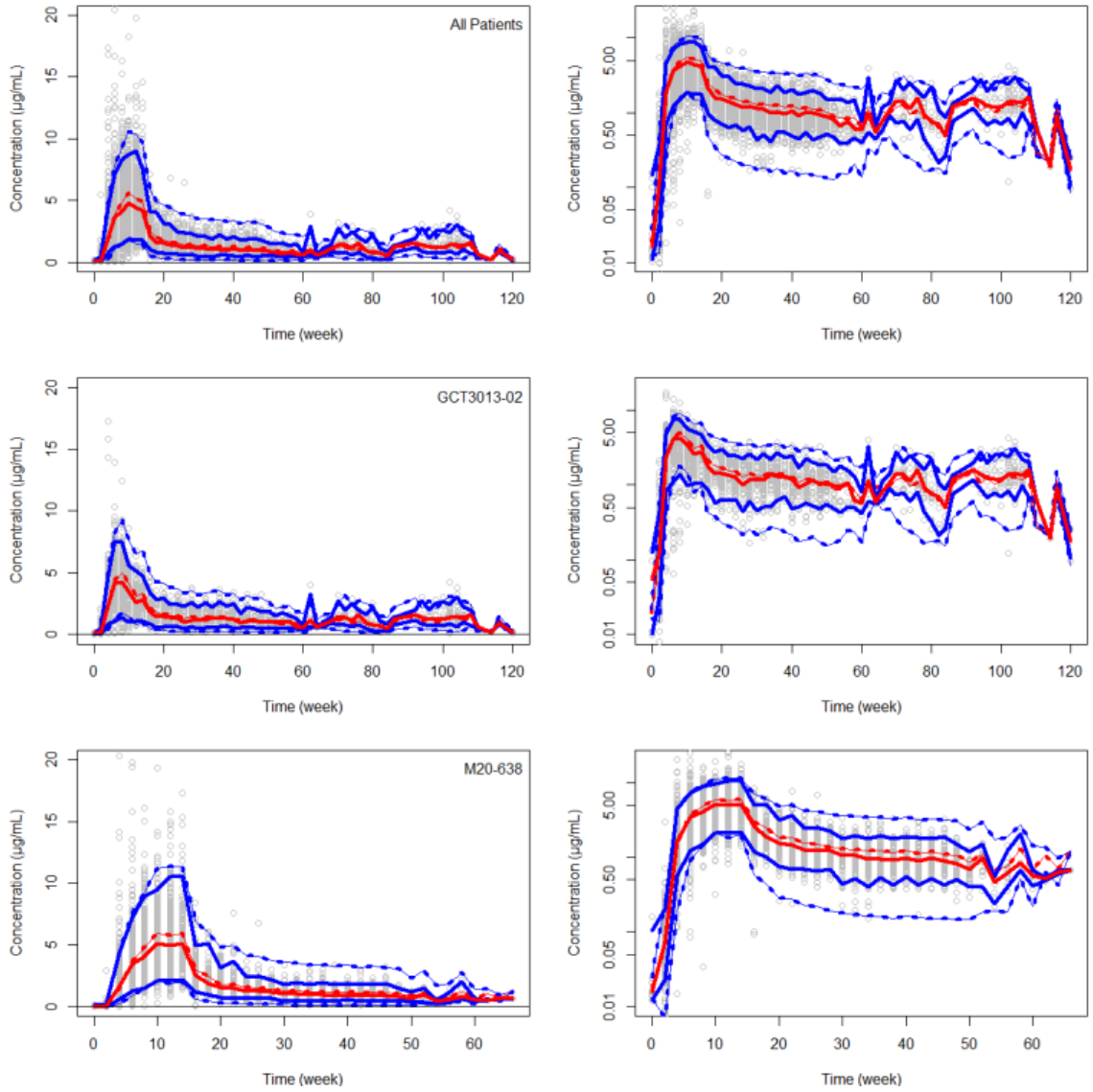
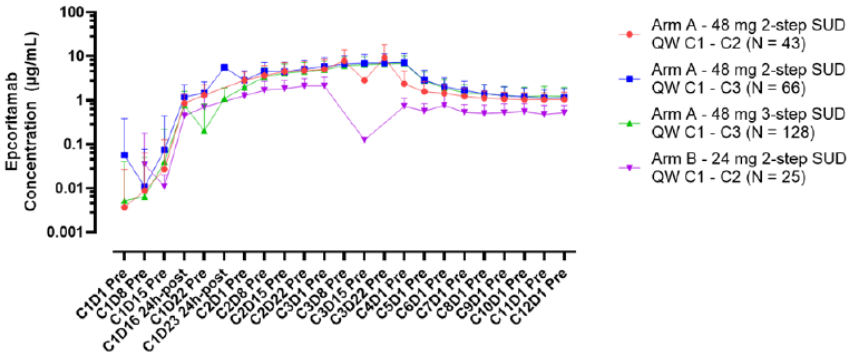


Figure 3. Prediction-corrected visual predictive check of final model

Special populations

The observed epcoritamab pharmacokinetic results in subjects with R/R FL from Studies M20-638 and GCT3013-02 Arm 2 are summarised in Figure 4**Error! Reference source not found.** and

Figure *5*. The median (range) Tmax of epcoritamab in combination with R^2 was predicted to be 3.7 (1.1 to 7) days after the first full dose and 2.2 (0.9 to 3.2) days at the end of the QW dosing regimen (end of Cycle 3). The geometric mean (%CV) Vss/F was estimated to be 27.8 L (71.9%). The population geometric mean (%CV) estimate for the CL/F for epcoritamab in combination with R^2 was estimated to be 0.566 L/day (36.4%).



C#D# = Cycle # Day #; Pre = Predose sample; Std Dev = standard deviation; QW = once weekly; SUD = step-up dosing; 24h-post = 24 h post-dose sample

Notes: The N displayed is the total number of subjects with at least one sample included in the summary; however, n values at each time point vary. Predose samples are excluded from the summary statistics if they are either collected more than 24 hours prior to dosing or if they are collected after the start of dosing.

Subjects from Arm B who started on a 24 mg full dose and switched to a 48 mg full dose or who received a 48 mg full dose from the beginning are not included in this plot.

Figure 4. Plasma Concentration of Epcoritamab (mean and standard deviation) Over Time – Log Linear in Study M20-638

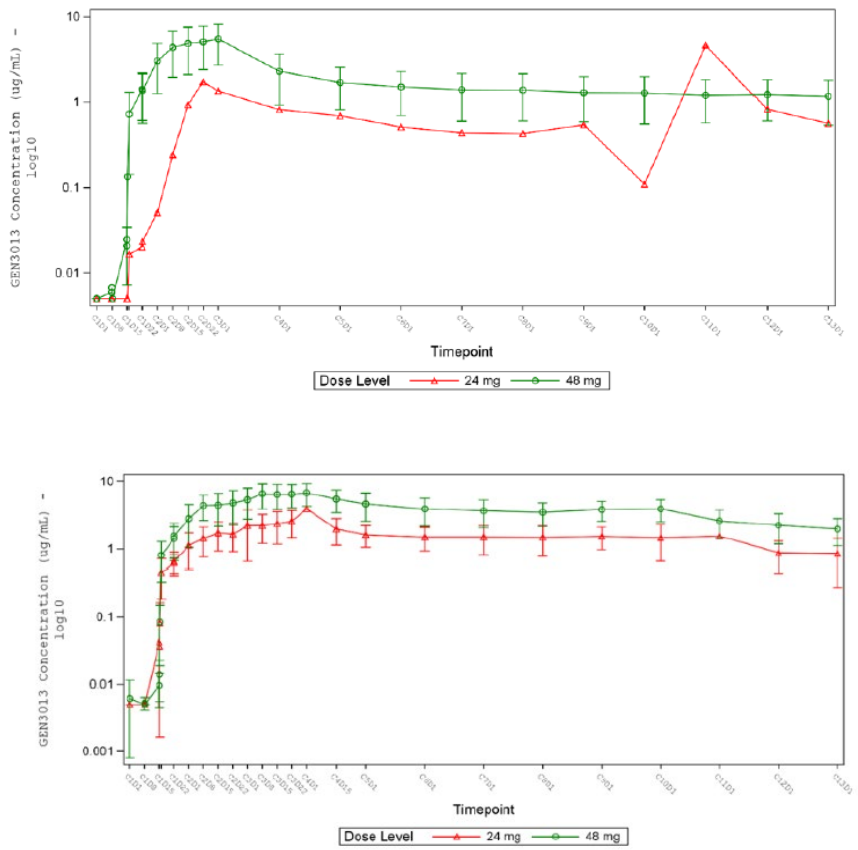


Figure 5. Plasma Concentration of Epcoritamab (mean and standard deviation) Over Time – Log Linear. Above: Cohort 2a, below: Cohort 2b

Based on the popPK model, exposure decreased with increasing weight across baseline weight categories: < 65 kg (n = 106 subjects), 65 to < 85 kg (n = 207 subjects), and ≥ 85 kg (n = 125 subjects). Among the weight groups, subjects with weight < 65 kg had the highest Cycle 1-3 geometric mean average concentration, which was 23.3 % higher than subjects with ≥ 65 to < 85 kg. Subjects with weight ≥ 85 kg had the lowest Cycle 1-3 geometric mean average concentration, which was 23.2% lower than subjects ≥ 65 to < 85 kg.

Table 2. Summary of model predicted geometric mean of the average concentration in Cycle 1-3 per covariate category

Covariate and Parameter	Level	N	Geometric Mean; µg/mL (CV)	Δ Geometric Mean (%)[a]
Age group (Significant on k_a)	< 65 years	255	4.17 (0.420)	-6.1%
	≥ 65, < 75 years	142	4.44 (0.403)	Reference
	≥ 75 years	41	5.33 (0.387)	20.0%
Weight group (Significant on CL, Q, V_C, V_P)	< 65 kg	106	5.5 (0.378)	23.3%
	≥ 65, < 85 kg	207	4.46 (0.372)	Reference
	≥ 85 kg	125	3.43 (0.376)	-23.2%
BMI group, by median (Significant on k_a)	< 25.8 kg/m^2	219	4.93 (0.413)	Reference
	≥ 25.8 kg/m^2	219	3.85 (0.378)	-22.0%
Tumor size, by median (Significant on k_{int})	< 32.8 cm^2	219	4.77 (0.400)	Reference
	≥ 32.8 cm^2	219	3.97 (0.412)	-16.7%
ADA status (Not significant)	Not Positive[b]	423	4.34 (0.417)	Reference
	Positive	15	4.85 (0.422)	11.7%

ADA = anti-drug antibody; BMI = body mass index; C_{avg} = average concentration; CV = coefficient of variation; N = number of subjects; SD = standard deviation; k_a = absorption rate constant; CL = clearance of epcoritamab; Q = inter-compartmental clearance; V_c = volume of epcoritamab central compartment; V_p = volume of epcoritamab peripheral compartment; k_{int} = elimination rate constant of the drug-target complex

a. Compared to reference category.

b. "Not Positive" indicates subjects whose ADA status was negative, indeterminate, or missing.

2.3.3. Pharmacodynamics

Mechanism of action

Epcoritamab is a bispecific antibody, recognizing the T-cell antigen CD3 and the B-cell antigen CD20. Epcoritamab's mechanism of action is induction of T-cell-mediated cytotoxicity of CD20-expressing cells, and associated T-cell activation and proliferation, upon simultaneous binding to CD20 on target cells and CD3 on T cells.

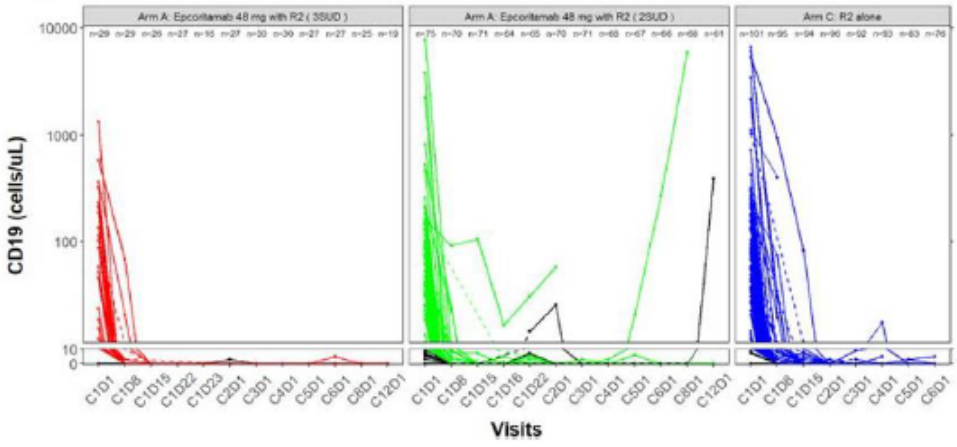
Primary and secondary pharmacology

Biomarker assessments to evaluate absolute B-cell, T-cell, natural killer (NK) cell counts using flow cytometry, and circulating cytokine levels by a sandwich immunoassay as potential safety and/or PD biomarkers were conducted in Studies M20-638 and GCT3103-02 Arm 2.

B cells

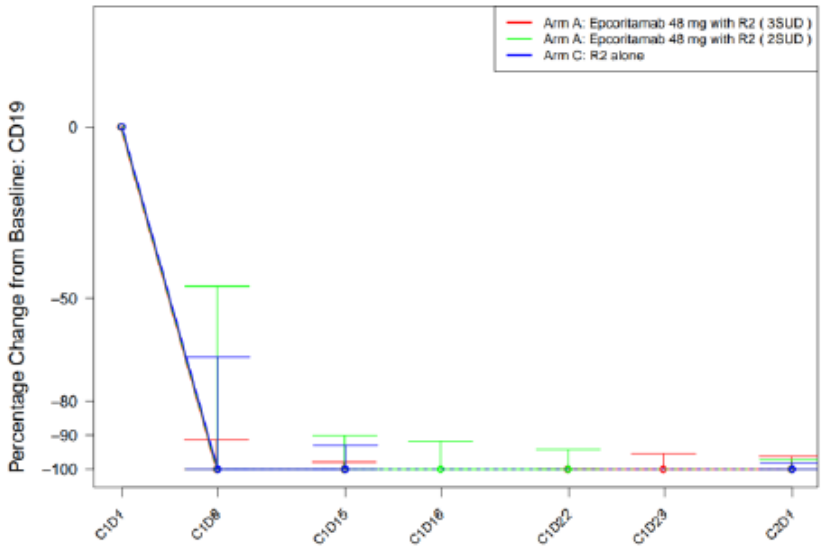
Absolute counts of circulating CD19 positive B cells were determined in the peripheral blood samples by TBNK flow cytometry analysis. A total of 205 patients had B cell counts assessed at baseline (C1D1) across Arms A and C, but only 155 patients had circulating B cells ≥10 B cells in one microliter blood at baseline. Epcoritamab 48 mg + R^2 treatment induced a rapid depletion of circulating peripheral blood B cells within the first two weeks of treatment in most patients, while in Arm C, peripheral blood B cell depletion was achieved by the end of Cycle 1 (Figure 6A). By C2D1, depletion of circulating B cells was evident in the majority of patients in the study across both arms and was sustained for the duration of treatment (Figure 6B).

A.



Each line represents one patient, n = 205 at C1D1. Black lines represent patients with < 10 B cells per µL blood at baseline and at subsequent timepoints. Dotted lines connect non-consecutive timepoints for each patient.

B. Percent Change in B Cell Absolute Counts from Baseline in Cycle 1



Percent change from baseline in B cell counts was calculated for patients with circulating B cells at baseline ≥ 10 cells/µL, 100% × (B cell counts at current timepoint - B cell counts at baseline) / (B cell counts at baseline). B cell counts at baseline with ≥ 10 cells/µL for Arm A 48 mg 3SUD, n = 22, Arm A 48 mg 2SUD, n = 55, Arm C, n = 78; total n = 155.

Figure 6. Absolute B cell counts over time

T cells

In Arm A, a transient reduction in circulating T cells was observed with epcoritamab in combination with R^2 during Cycle 1 and was most prominent after the first full dose of epcoritamab (48 mg), consistent with T-cell margination. The level of T cells rapidly returned to baseline levels by Cycle 2 and showed moderate elevation with subsequent dosing. In Arm C, T-cell counts remained stable.

NK cells

Absolute counts of circulating NK cells were determined in the peripheral blood samples from n = 216 patients using a TBNK flow cytometry panel. In Arm A, a slight decrease in NK cell numbers in Cycle 1 was observed supporting an NK cell margination event. NK cell numbers returned to baseline levels in the following cycle and continued to increase in C3 and C4 supporting an slight expansion of NK cells with epcoritamab + R^2 treatment. In Arm C, NK-cell counts remained stable. No evident difference was observed in NK cell profiles between 3-SUD and 2-SUD in Arm A.

Cytokines

The levels of inflammatory cytokines were monitored in serum samples from baseline (C1D1) through Cycle 3 across both arms of the study from n = 213 patients. IL-6, IFNγ and IL-10 concentrations at 24 hours following the first full 48 mg dose in Arm A were lower in subjects who received the 3-step SUD (C1D23) regimen than subjects who received the 2-step SUD regimen (C1D16) (Figure 7). This is consistent with the analysis of IL-6 levels across 3-SUD and 2-SUD in Arm A using the entire ITT population. TNFα levels were minimally modulated across both arms of the study.

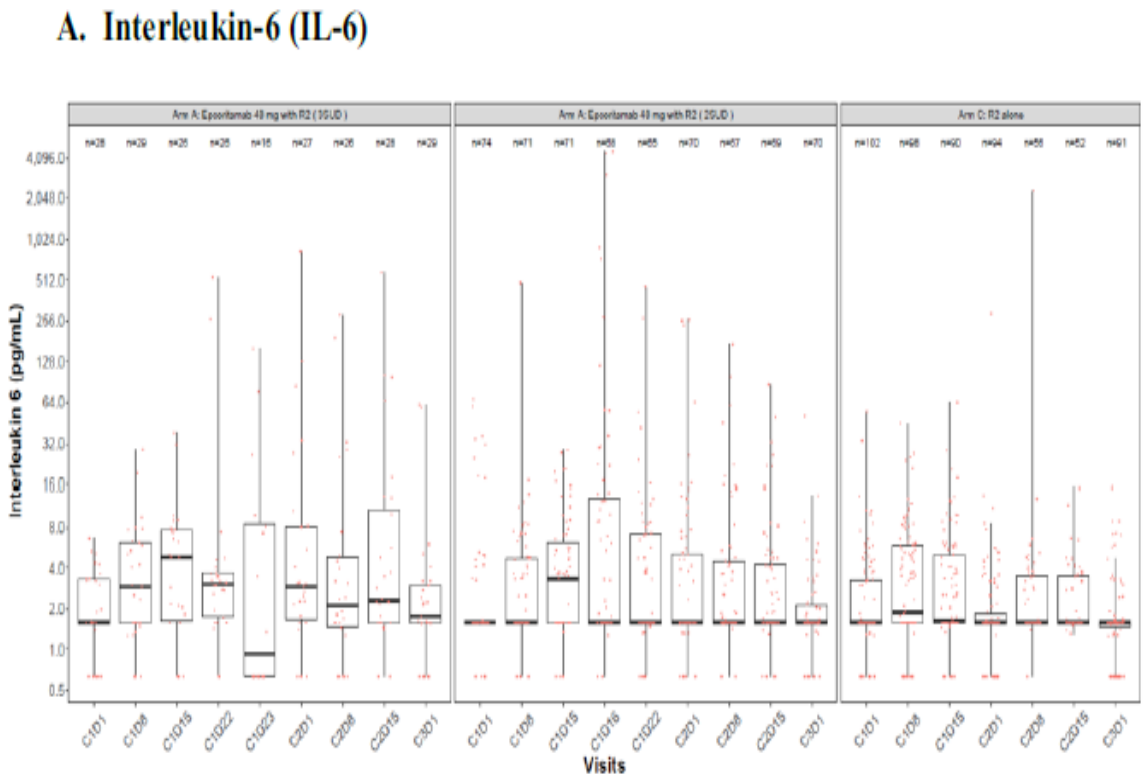


Figure 7. Changes in IL-6 Levels with Treatment

2.3.4. PK/PD modelling

The relationships between epcoritamab plasma exposures and key efficacy and safety measures in subjects with R/R FL who received epcoritamab in combination with R^2 were characterized. Efficacy analyses were conducted separately for the pivotal Study M20-638 and the supportive study GCT3013 02 Arm 2. Pooled safety E-R analyses were conducted across the two studies, in addition to separate analyses for each study. Only the results of pivotal Study M20-638 are shown here.

Exposure-efficacy

A nearly flat exposure-ORR relationship was observed for all subjects, indicating no exposure-ORR relationship. A nearly flat relationship was observed between Cycle 1-3 C_{avg} and CR rate, indicating no exposure-CR relationship.

The responders were split into 2 groups using the medians of exposure (Cycle 1-3 Cavg) in Study M20-638. The Kaplan-Meier plots for DOR are presented in Figure 8 (Cycle 1-3 Cavg). An E-R trend was observed for DOR with higher epcoritamab Cycle 1-3 Cavg exposure (approximately equivalent to 48 mg full dose exposures; 4.49µg/mL) associated with improved outcomes compared to lower exposure (approximately equivalent to 24 mg full dose exposures; 1.97 µg/mL), though the trend was not statistically significant (p-value of 0.071).

Duration of complete response (DOCR) significantly increased with Cycle 1-3 Cavg exposure (p value of 0.017). Complete responders with higher Cycle 1-3 Cavg exposure (approximately equivalent to 48 mg full dose exposures; 4.49µg/mL) exhibited longer DOCR compared to those with lower exposure (approximately equivalent to 24 mg full dose exposures; 1.97µg/mL) (KM-plot not shown).

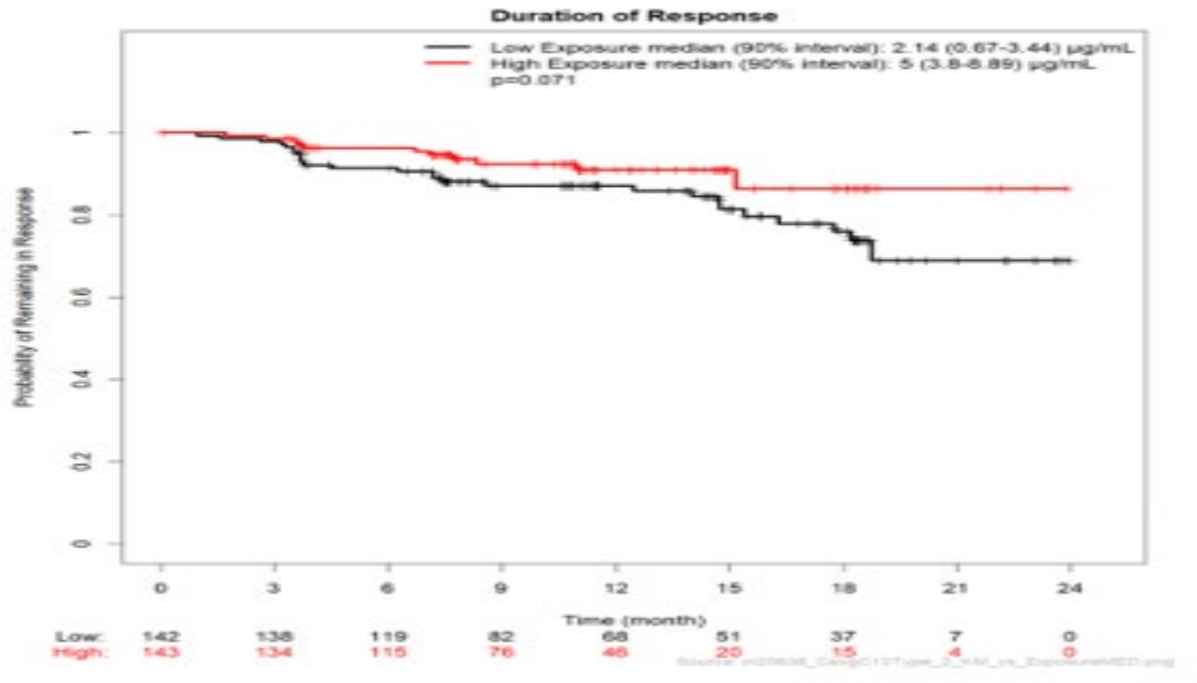


Figure 8. Kaplan-Meier Plot for Duration of Response by Median Split of Cycle 1-3 Cavg: Study M20-638. Cavg = average concentration. Low exposure: below median; high exposure: above median. P value: P value of the log-rank test.

Subjects with higher Cycle 1-3 Cavg exposure (approximately equivalent to 48 mg full dose exposures; 4.49µg/mL) exhibited longer PFS compared to those with lower exposure (approximately equivalent to 24 mg full dose exposures; 1.97µg/mL (Figure 9).

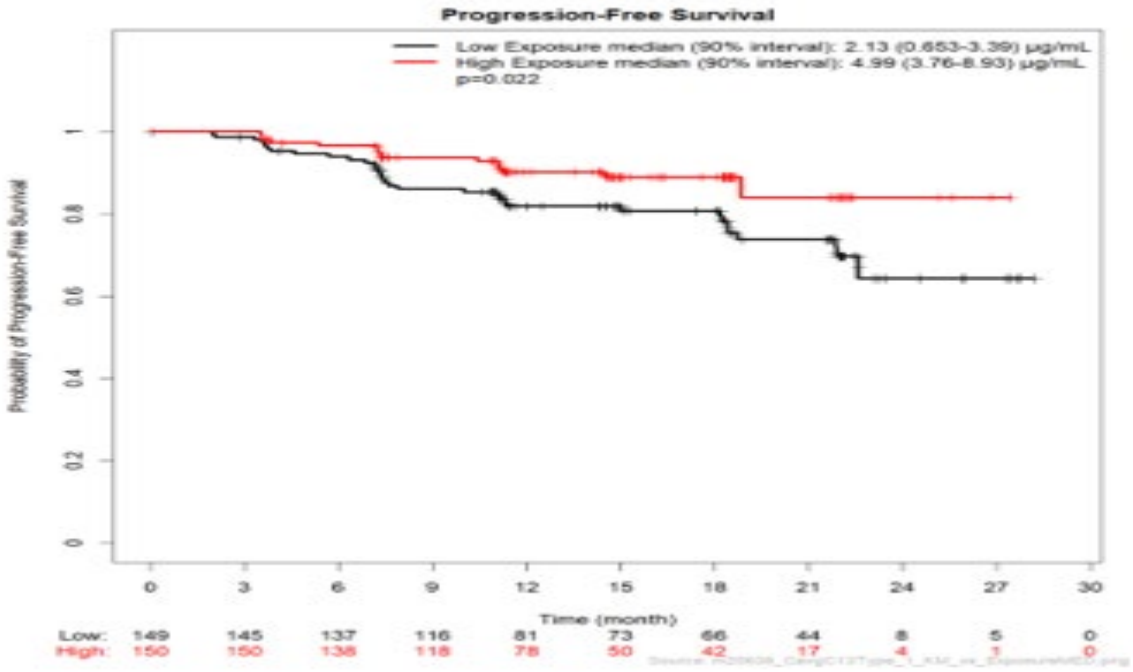


Figure 9. Kaplan-Meier Plot for PFS by Median Split of Cycle 1-3 Cavg: Study M20-638. Cavg = average concentration; PFS = progression-free survival Low exposure: below median; high exposure: above median. P value: P value of the log-rank test.

Subjects with higher exposure (approximately equivalent to 48 mg full dose exposures; 4.49µg/mL) exhibited longer OS compared to those with lower exposure (approximately equivalent to 24 mg full dose exposure; 1.97µg/mL) (KM-plot not shown).

Exposure-safety

Frequencies of TEAEs were either independent of exposure (Grades ≥ 3 TEAEs, neutropenia, TEAEs leading to dose delay or discontinuation, injection site reactions, immune cell-associated neurotoxicity syndrome [ICANS] and CTLS) or decreased with exposure (serious adverse events (SAEs), thrombocytopenia, anaemia, infections). Similar results were observed for each study (Study M20-638 and GCT3013-02 Arm 2 [Cycle 1-3 C_{avg}]).

Immunogenicity

In the immunogenicity-evaluable subjects with R/R FL treated with epcoritamab and R^2 in Study M20-638, the ADA status was evaluated up to Cycle 12. The baseline ADA status was positive for 2 subjects (1 subject in Arm A and 1 subject in Arm B). The on-treatment ADA status was positive for 5 (2.1%) out of 238 subjects with non-missing values at the 48 mg dose (Arm A), with no subject being ADA-positive at the 24 mg dose (Arm B) while on treatment. Of the 5 subjects who became ADA-positive during treatment, one subject was ADA-positive at baseline. Four subjects were confirmed ADA-positive at a single scheduled on-treatment time point: one subject at C6D1 and three subjects at C1D15. One subject was ADA-positive at C2D1 and also had two ADA-positive results at unscheduled visits; this subject was nAb-positive at one of those two unscheduled visits.

In the immunogenicity-evaluable subjects in Study GCT3013-02 Arm 2, the baseline ADA status was positive for 2 subjects in the 24 mg dose group and 1 subject in the 48 mg dose group. The on-treatment ADA status was positive for 2 (6.5%) out of 31 subjects in the 24 mg dose group and 8 (7.5%) out of 107 subjects in the 48 mg dose group. All subjects with a positive on treatment ADA

status had a titer value of < 1 (1:80 after accounting for dilutions). Among the on-treatment ADA positive subjects in the 24 mg and 48 mg dose groups, 1 out of 2 subjects and 1 out of 8 subjects were nAb positive, respectively.

2.3.5. Discussion on clinical pharmacology

In a previous procedure (EMEA/H/C/005985/II/0001), it was concluded that the clinical pharmacology of epcoritamab was sufficiently described in subjects with relapsed or refractory FL after two or more lines of systemic therapy. Also, the 0.16/0.8/3/48 mg dose was accepted. Therefore, the current assessment of the clinical pharmacology program focuses on the combined use of epcoritamab with rituximab and lenalidomide (R^2).

Pharmacokinetics

A population pharmacokinetic analysis was conducted to evaluate whether differences are present in the pharmacokinetic profile of epcoritamab with R^2 versus absence of R^2. The prediction-corrected visual predictive check plots indicate an appropriate description of the pharmacokinetic data obtained in studies **M20-638** and **GCT3013-02**. The MAH states that the pharmacokinetics in the presence of R^2 and absence of R^2 are similar. However, upon re-estimation of model parameters based on data from **Studies M20-638** and **GCT3013-02 Arm 2**, increases of 25% for the typical clearance (CL/F), 44% for the typical apparent peripheral volume (VP/F), and 30% for the typical quasi-steady-state constant (K_{ss}) compared to the monotherapy model were observed. All these parameter changes point towards a lower typical concentration-time profile. This may indicate a higher disease severity in the population included in studies **M20-638** and **GCT3013-02 Arm 2** as compared to the patients included in the monotherapy, which may be a result of the earlier treatment setting.

No drug-drug interaction studies with rituximab and lenalidomide were conducted by the MAH, but given the similarity in the observed pharmacokinetics and lack of biological grounds (other than through disease severity), this is considered acceptable.

Pharmacodynamics

Epcoritamab with R^2 induced a depletion of circulating peripheral blood B cells within the first two weeks of treatment in most patients and a small increase in T and NK cell expansion after an initial decrease as compared to the R^2 alone arm where these counts remained stable, in line with the mechanism of action of epcoritamab. These effects have already been described in the SmPC.

Exposure-response

No exposure-response relationship for efficacy for ORR and CR was observed. A significant exposure-response relationship was observed for DOCR, PFS and OS with higher exposure associated with longer DOCR/PFS/OS. No exposure-response relationship for safety was observed, in line with the previous monotherapy studies of epcoritamab.

Immunogenicity

Immunogenicity was relatively low and in line with previous monotherapy studies, with positive on-treatment ADA status for 5/238 (2.1%) of subjects, all at the 48mg dose.

2.3.6. Conclusions on clinical pharmacology

The submitted clinical pharmacology package is considered appropriate to extend the indication of epcoritamab to combined use with rituximab and lenalidomide for the treatment of adult patients with R/R FL.

2.4. Clinical efficacy

2.4.1. Dose response studies

The MAH provided rationale for the proposed posology, based on Arm 2 of Study GCT3013-02. Details for this study are reported below in the paragraph "Supportive study". The Phase 1/2 Study GCT3013-01 also influenced the proposed posology (for details reference is made to the EMEA/H/C/005985/II/0001 procedure).

Arm 2 of the ongoing Phase 1b/2 Study GCT3013-02

Based on the clinical study data from Arm 2 of the ongoing Phase 1b/2 Study GCT3013-02, the recommended dose of epcoritamab in combination with R^2 was identified as 48 mg. Additionally, epcoritamab QW dosing was implemented from Cycle 1 - Cycle 3 of Arm A instead of only in Cycle 1 and 2 followed by epcoritamab Q4W dosing.
Study GCT3013-02 Arm 2 evaluated 2 dosages for epcoritamab full dose (24 mg and 48 mg) in combination with R^2 in subjects with FL. At the 31 October 2022 DCO, a higher CR rate was observed with the 48 mg epcoritamab full dose compared to the 24 mg epcoritamab full dose. Based on the first 2 tumor assessments in subjects who had at least 3 months of follow-up in Cohort 2a, the CR rate was 92% (N = 23/25) at the 48 mg dose level compared to 77% (N = 17/22) at the 24 mg dose level. The safety profile of epcoritamab in combination with R^2 was similar among these subjects. Additionally, epcoritamab in combination with R^2 was evaluated across 2 dosing schedules (3 cycles of QW epcoritamab dosing in Cohort 2a and 2 cycles of QW epcoritamab dosing in Cohort 2b). At the epcoritamab 48 mg dose, CR rate was higher at 92% with 3 cycles of QW dosing (i.e., Cohort 2a) than with only 2 cycles of QW (i.e., Cohort 2b) at 83.1%) in Cohort 2b.

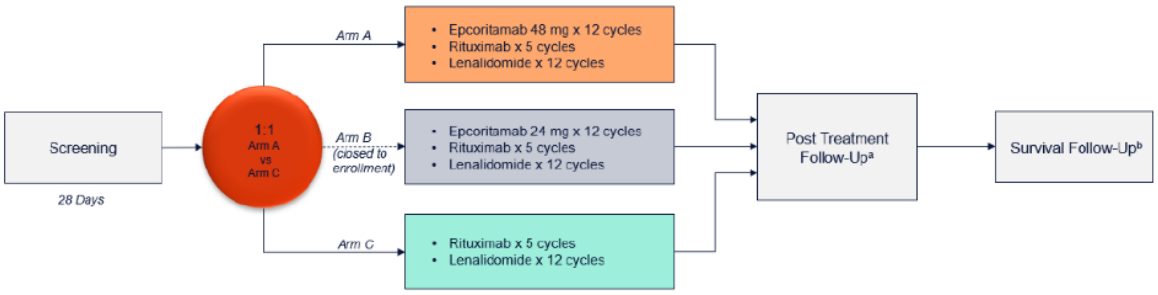
Phase 1/2 Study GCT3013-01

Based on data from the ongoing Phase 1/2 Study GCT3013-01, a 3-step SUD regimen for epcoritamab was introduced in Version 3.0 of the M20-638 protocol to reduce the incidence and severity of cytokine release syndrome (CRS). An Optimization Part including subjects with FL, was added to Study GCT3013-01 to investigate different SUD regimens to lower the Grade ≥ 2 CRS event rate, particularly CRS events observed with the first full dose. In the Optimization Part, subjects with R/R FL (hereinafter referred to as the FL optimization cohort) were treated with a 3-step SUD regimen for epcoritamab (a priming dose of 0.16 mg, a first intermediate dose of 0.8 mg on C1D8, and a second intermediate dose of 3 mg on C1D15, followed by a full dose of 48 mg on C1D22 and thereafter), along with recommendations for proper hydration and use of dexamethasone for CRS prophylaxis during Cycle 1. The incidence and severity of CRS events were lower in FL optimization cohort compared to those observed among subjects with FL in the Expansion Part of Study GCT3013-01.

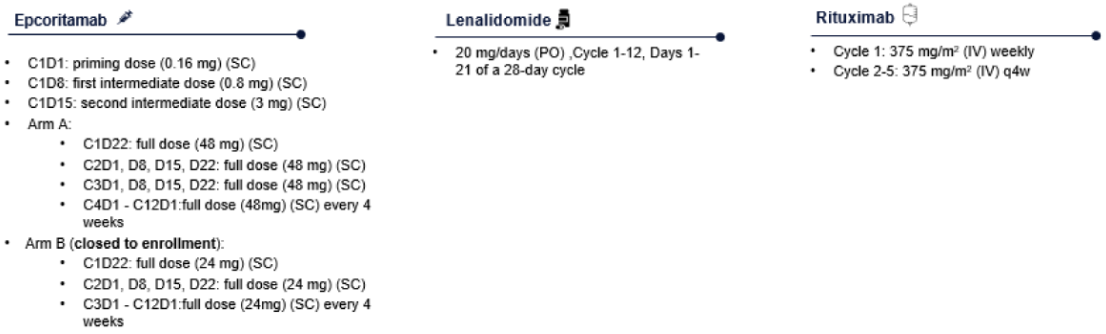
2.4.2. Main study

Pivotal Study M20-638/EPCORE™ FL-1; A Phase 3, Open-Label Study to Evaluate Safety and Efficacy of Epcoritamab in Combination with Rituximab and Lenalidomide (R2) compared to R2 in Subjects with Relapsed or Refractory Follicular Lymphoma)

A diagram of the study design and the dosing schedule is provided in Figure 10 and a tabular overview of the study is provided in Table 3. The study is still ongoing; study enrolment was completed at the time of the IA1 DCO (10 January 2025).



a. Subjects who completed treatment or discontinued treatment for reasons other than disease progression will proceed to Post-Treatment Follow-up.
b. Subjects who have confirmed disease progression, or refuse Post-Treatment Follow-up visits will proceed to Survival Follow-up.



C#D# = Cycle # Day #; IV = intravenous; PO = orally; q4w = every 4 weeks; R^2 = rituximab and lenalidomide; SC = subcutaneous
Note: Study enrolment was complete as of IA1 DCO 10 January 2025. Arm B was closed to enrolment in Protocol Version 2.0.

Figure 10. Study Design Schematic

Table 3. Description of Clinical Efficacy and Safety Studies – Pivotal Study M20-638

Study ID/ No. of Centers/ Locations/ Duration	**Enrollment Status, Enrollment Goal**	**Design Control Type**	**Study & Control Drugs Dose, Route & Regimen**	**Study Objective**	**No. of Subjects by Arm Entered[d]/ Completed[d]**	**Diagnosis Inclusion Criteria**	**Primary Endpoints**
Study M20-638 Multicenter/ Europe, North America, South America, Asia, Australia, and Africa/ Ongoing duration of approximately 2.5 years	Enrollment complete 500 subjects were planned	A Phase 3, Open-Label Study to Evaluate Safety and Efficacy of Epcoritamab in Combination with Rituximab and Lenalidomide (R^2) compared to R^2 in Subjects with Relapsed or Refractory Follicular	**All study drugs were given in 28-day cycles.** **Arm A:** epcoritamab 48 mg full dose + R^2 **Arm B[e]:** epcoritamab 24 mg full dose + R^2 **Arm C:** R^2 **Epcoritamab (SC)** **Arm A:** **Protocol V1**. 2step SUD[a] regimen, 48 mg	Primary Objective: Evaluate the efficacy, safety, and tolerability of epcoritamab 48 mg in combination with R^2 compared to R^2 alone in subjects with R/R FL. The hypotheses corresponding to the primary objectives are that: • epcoritamab 48 mg dose in	Arm A: 243 subjects entered / 44 subjects are ongoing study treatment, 132 subjects completed, and 67 subjects discontinued study treatment Arm B[e]: 61 subjects entered /41	Subjects must have had: • Histologically confirmed classic FL (previously Grade 1 to 3a FL) stage II, III, or IV with no evidence of histologic transformation to an aggressive lymphoma and CD20+ disease on the most recent representative	Dual Primary endpoints: • PFS: Duration from the date of randomization to the date of PD determined by Lugano criteria[b] (as assessed by IRC) or death. • BOR of CR or PR, determined by

Study ID/ No. of Centers/ Locations/ Duration	Enrollment Status, Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered[d]/ Completed[d]	Diagnosis Inclusion Criteria	Primary Endpoints
as of 24 May 2025		Lymphoma (EPCORE™ FL-1)	QW C1-2, Q4W C3-12 **Protocol V2**. 2step SUD[a] regimen, 48 mg QW C1-3, Q4W C412 **Protocol V3**.+ 3-step SUD[a] regimen, 48 mg QW C1-3, Q4W C412 **R^2 for Arms A and B**: All eligible subjects were assigned to receive R^2 for 12 (28-day) cycles: **Rituximab** 375 mg/m^2 IV weekly during Cycle 1 (on Day 1, Day 8, Day 15, and Day 22) and Q4W during Cycles 2 to 5 (on Day 1) **Lenalidomide** 20 mg PO once a day from Day 1 to Day 21 during Cycles 1 to 12	combination with R^2 improves rate of BOR of CR or PR compared to R^2 in subjects with R/R FL in the first 232 subjects randomized from ITT population. • epcoritamab 48 mg dose in combination with R^2 improves and PFS compared to R^2 alone in subjects with R/R FL in the ITT population. Secondary Objective: Evaluate whether epcoritamab 48 mg in combination with R^2 compared to R^2 alone can improve clinical outcomes as measured by key secondary endpoints (including CR, OS, and MRD negativity[c]) in subjects with R/R FL. The hypothesis corresponding to the secondary objective is that epcoritamab 48 mg in combination with R^2 compared to R^2 alone improves outcomes of each of the key secondary endpoints in the ITT population.	subjects completed and 20 subjects discontinued study treatment Arm C: 245 subjects entered / 32 subjects are ongoing study treatment, 97 subjects completed, and 109 subject discontinued study treatment A majority of subjects are still on study.	tumor biopsy based on the pathology report, according to the 5th edition of WHO Classification of Hematolymphoid Tumors • R/R disease after receiving treatment with at least one prior anti-lymphoma regimen that contained an anti-CD20 monoclonal antibody in combination with chemotherapy (subject who received only prior anti-CD20 monoclonal antibody monotherapy and/or radiation therapy is not eligible). • A need for treatment initiation per investigator based on symptoms and/or disease burden (GELF criteria) • One or more measurable disease site according to Lugano Classification 2014 • Eligible to receive R^2 per investigator determination.	Lugano criteria[b] as assessed by an IRC Secondary endpoints (ranked): • CR during the study, determined by Lugano criteria[b], as assessed by an IRC • OS • MRD negativity Other Secondary endpoints: • FACT-Lym • PFS, BOR, and CR during the study, determined per Lugano criteria[b] as assessed by investigator • DOR, DOCR, TTP, and CR at the end of treatment (12 cycles), TTR, TTCR, per Lugano criteria[b] as assessed by an IRC and by investigator, respectively • EFS • TTNLT[f] • Changes from baseline in PROs; including PGIS, PGIC, and EQ-5D-5L

BOR = best overall response; C = cycle; CR = complete response; D = day; DOCR = duration of complete response; DOR = duration of response; EFS = event-free survival; EQ-5D-5L = EuroQol 5-dimension questionnaire, 5-level; FACT-Lym = Functional Assessment of Cancer Therapy – Lymphoma; FL = follicular lymphoma; GELF = Groupe d'Etude des Lymphomes Folliculaires; IRC = Independent Review Committee; ITT = intent-to-treat; IV = intravenous; MRD = minimal residual disease; OS = overall survival; PFS = progression-free survival; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PD = progressive disease; PO = per os (orally); PR = partial response; PRO = patient health reported outcomes; QW = every week; Q4W = every 4 weeks; R/R = relapsed or refractory; SC = subcutaneous; SUD = step-up dosing; TTCR = time to complete response; TTNLT = time to next anti-lymphoma therapy; TTP = time to progression; TTR = time to response; WHO = world health organization.

a. **2-step SUD regimen**: Priming 0.16 mg C1D1; Intermediate 0.8 mg C1D8; Full 48 mg C1D15; QW C1-3, Q4W C4-12.

3-step SUD regimen: Priming 0.16 mg C1D1; First Intermediate 0.8 mg C1D8; Second Intermediate 3 mg C1D15; Full 48 mg C1D22; QW C1-3, Q4W C4-12.
b. Lugano criteria according to Cheson 2014, and LYRIC according to Cheson 2016.
c. As per the pre-specified hierarchical testing procedure, OS did not meet statistical significance and therefore MRD negativity analyses were not performed.
d. The 'number of subjects entered' refers to the number of subjects randomized. The 'number of subjects completed' refers to the number of subjects who completed protocol specified study treatment. The number of subjects who discontinued study treatment refers to: '1) discontinuation of all study drugs, 2) at least one study drug discontinued and rest completed'.
e. After Arm B was closed to enrolment in Version 2.0 of the protocol, 31 subjects in Arm B who received at least one full dose of 24 mg epcoritamab were switched to 48 mg epcoritamab + R^2, at investigator's discretion and 4 subjects in Arm B only received 48 mg full dose of epcoritamab.
f. Time to next anti-lymphoma therapy (TTNLT) in Study M20-638 2nd Interim CSR is synonymous with time to next anti-lymphoma therapy (TTNT) in Study GCT3013-02 Arm 2 CSR.
Note: Subjects in Arm A enrolled prior to protocol Version 2.0 received epcoritamab Q4W dosing in Cycle 3 and subjects enrolled prior to Version 3.0 received epcoritamab using a 2-step SUD regimen (0.16 mg/0.8 mg/48 mg).

Methods

Study participants

The main eligibility criteria were:

- Adult individuals, at least 18 years old
- Subject must have histologically confirmed classic FL (previously Grade 1 to 3a FL) stage II, III, or IV with no evidence of histologic transformation to an aggressive lymphoma and CD20+ disease on most recent representative tumor biopsy based on the pathology report, according to the 5th edition of WHO Classification
- Subject must have R/R disease after receiving treatment with at least one prior anti-lymphoma regimen that contained an anti-CD20 monoclonal antibody in combination with chemotherapy. (Subject who received only prior anti-CD20 monoclonal antibody monotherapy and/or radiation therapy is not eligible.)
    - Note: Relapsed disease is defined as disease that previously responded to therapy but progressed ≥6 months after completion of therapy. Refractory disease is defined as disease that either progressed during therapy, failed to achieve an objective response to prior therapy, or progressed within 6 months after completion of therapy (including maintenance therapy).
- Subject has one or more measurable disease site according to Lugano Classification 2014:
    - Fluorodeoxyglucose-positron emission tomography (FDG-PET) scan demonstrating positive lesion compatible with CT or MRI-defined anatomical tumour sites AND
    - ≥ 1 measurable nodal lesion (long axis > 1.5 cm) or ≥ 1 measurable extra-nodal lesion (long axis > 1.0 cm) on CT scan or MRI.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
- Subject must be eligible to receive R^2 per investigator determination.
- Subject must not have documented refractoriness to lenalidomide, with refractoriness defined as:
    - best response to lenalidomide of stable disease (SD) or PD, or
    - Progressive disease within 6 months of completion of lenalidomide therapy

- Subjects must not have had lenalidomide exposure within 12 months prior to randomisation.

In addition, subjects were required to have adequate renal, liver, and hematologic function laboratory values, to have available adequate fresh or paraffin-embedded tissue at Screening and to have a need for treatment initiation per investigator determination based on symptoms and/or disease burden (e.g., GELF criteria).

Subject were not to have unresolved toxicities from prior anticancer therapy, no primary CNS lymphoma or known CNS involvement, no clinically significant cardiovascular disease, no clinically significant liver disease, no active hepatitis B or C virus (HBV or HCV) infection, no active CMV disease, no HIV infection, no active infection within 2 weeks prior to randomisation, no history of other prior malignancies, no active tuberculosis, no neuropathy Grade > 1 with the exception of neuropathy related directly to lymphoma, no prior allograft, no autologous stem cell transplantation 100 days or less prior to randomisation, no current autoimmune disease requiring immunosuppressive therapy other than prednisone ≤ 20 mg daily, no active SARS-COV-2, no history of progressive multifocal leukoencephalopathy (PML) and comply with criteria for concurrent for medications.

Treatments

Epcoritamab

In Arm A, subjects were randomised to receive epcoritamab as a SC injection in a 3-step SUD regimen (C1D1, C1D8, C1D15) followed by full doses at 48 mg as described below, until up to 12 cycles (28-day cycle), PD, unacceptable toxicity, or withdrawal of consent, whichever came first.

- Cycle 1 – Day 1: priming dose (0.16 mg)
- Cycle 1 – Day 8: first intermediate dose (0.8 mg)
- Cycle 1 – Day 15: second intermediate dose (3 mg)
- Cycle 1 – Day 22: full dose (48 mg)
- Cycle 2 and 3 – Day 1, Day 8, Day 15, and Day 22: full dose (48 mg)
- Cycles 4 to 12 – Day 1: full dose (48 mg), Q4W

No dose reductions of epcoritamab on an individual subject level was allowed in this study. Dose delays were permitted, but a re-priming cycle was required if dosing was delayed beyond a specified time period, depending on the time point on treatment. A re-priming cycle consisted of a QW schedule of a priming dose, 2 intermediate doses, and 1 full dose.

Posology and study arms in different protocol versions

In version 1.0 of the protocol there were two investigational arms with subjects randomised in a 1:1:1 ratio to epcoritamab 48 mg in combination with R^2 (Arm A), epcoritamab 24 mg in combination with R^2 (Arm B), and Arm C as the control arm (R^2).
In Arm A subjects received epcoritamab using a 2-step SUD regimen (0.16 mg C1D1 /0.8 mg C1D8 /48 mg QW from C1D15 trough C2D22) followed by Q4W on Day 1 of Cycle 3 to Cycle 12.
In Arm B, subjects were assigned to receive epcoritamab in a 2-step SUD regimen (0.16 mg C1D1, 0.8 mg C1D8) followed by full doses of 24 mg epcoritamab administered QW from Cycle 1 Day 15 through Cycle 2 Day 22, followed by Q4W on Day 1 of Cycle 3 to Cycle 12.

In version 2.0 of the protocol in Arm A, epcoritamab QW dosing was implemented in Cycle 3 of Arm A, with epcoritamab QW dosing for the initial 3 cycles (Cycles 1-3) and then Q4W dosing (Cycles 4-12).

Arm B was closed to enrollment. This was based on the early clinical study data from Arm 2 of the Phase 1b/2 Study GCT3013-02, where the recommended full dose of epcoritamab in combination with R^2 was identified as 48 mg. Subjects had the option to switch to epcoritamab 48 mg + R^2, at the investigator's discretion. Subjects received the assigned study treatment up to 12 cycles (28-day cycle), or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever came first. From protocol Version 2.0, eligible subjects were randomised in a 1:1 ratio to either Arm A (epcoritamab 48 mg in combination with R^2) or Arm C (R^2).

In Version 3.0 of the protocol the 3-step SUD regimen for epcoritamab was introduced along with recommendations for proper hydration and the use of dexamethasone in Cycle 1 for CRS prophylaxis to reduce the incidence and severity of CRS. This was based on the study data from the FL optimization part of Study GCT3013-01 where the 3-step SUD regimen plus hydration recommendations were identified as significantly reducing the rate of ≥ Grade 2 CRS events in R/R FL compared to the 2-step SUD regimen without hydration recommendations. Prior to this amendment 112 and 61 subjects were enrolled to Arm A and Arm B, respectively.

Epcoritamab Premedication and CRS Prophylaxis

For each of the first 4 doses of epcoritamab of Cycle 1 or any repriming cycle, premedication with antihistamines, antipyretics, and corticosteroids on day of dosing, and additional 3 consecutive days of corticosteroids was mandatory to prevent/reduce the severity of symptoms from potential CRS. From protocol Version 3.0, dexamethasone was to be used as the first choice of corticosteroid when clinically feasible. For administration of epcoritamab beyond the fourth dose (first full dose), CRS prophylaxis with corticosteroids was optional, unless CRS Grade 2 or higher occurs, in which case, CRS prophylaxis should continue until an epcoritamab dose was given without subsequent CRS.

During the first cycle (i.e., the first 4 epcoritamab administrations) or any repriming cycle, the following was also recommended unless medically contraindicated:

- 2 to 3 L of orally (PO) fluid intake during the 24 hours prior to each epcoritamab administration;
- Hold antihypertensive medications for 24 hours prior to each epcoritamab administration;
- Administer 500 mL isotonic IV fluids prior to each epcoritamab administration (same day);
- AND 2 to 3 L of (PO) fluid intake during the 24 hours following each epcoritamab administration.

Hospitalization for the purpose of safety monitoring was not mandatory for any dose administration but could be implemented at the discretion of the investigator.

R^2

All eligible subjects were assigned to receive R^2 in 28-day cycles, as detailed below.

- Rituximab 375 mg/m2 IV QW during Cycle 1 (on Day 1, Day 8, Day 15, and Day 22) and Q4W during Cycles 2 to 5 (on Day 1)
- Lenalidomide 20 mg PO once a day from Day 1 to Day 21 during Cycles 1 to 12

On the days the subject was administered epcoritamab in combination with R^2, R^2 must be administered prior to epcoritamab. No dose reductions were allowed for rituximab; dose delays were permitted. A reduced initial lenalidomide dose was allowed for subjects with renal impairment, in accordance with the local label, and lenalidomide dose reductions or delays were otherwise permitted at investigator discretion.

Premedication with acetaminophen (650 to 1000 mg PO), diphenhydramine (50 to 100 mg IV or PO) and steroids, 30 to 60 minutes before starting each rituximab infusion was allowed. Aspirin prophylaxis should be administered for subjects with low or intermediate risk for thromboembolism (or as recommended per local guidelines). Prophylactic anticoagulant should be administered for subjects with high risk for a thromboembolic event.

Epcoritamab, rituximab, and lenalidomide drug products were utilized in this global clinical study that employs multiple sources of these drug products. Rituximab and lenalidomide were provided by sponsor or sourced locally if it did not conflict with local requirements. For US subjects, rituximab-abbs was US-licensed, and lenalidomide (ZELVINA) was sourced from the EU. Lenalidomide (ZELVINA) is manufactured by Adalvo and is a generic to lenalidomide (REVLIMID).

Objectives

The primary objective of this Phase 3 study is to evaluate the efficacy, safety, and tolerability of epcoritamab 48 mg in combination with R^2 compared to R^2 alone in subjects with R/R FL.

The secondary objective of this study is to evaluate whether epcoritamab 48 mg in combination with R^2 compared to R^2 alone can improve clinical outcomes, as measured by key secondary endpoints (including CR, OS, and minimal residual disease (MRD) negativity) in subjects with R/R FL.

Outcomes/endpoints

The dual primary endpoints are:

- Best overall response (BOR) of CR or PR, determined by Lugano 2014 criteria, as assessed by an IRC
- PFS: Duration from the date of randomisation to the date of any of the following (whichever occurs first):
    - Disease progression as determined by Lugano criteria 2014 (by an IRC)
    - Death

The key secondary endpoints in hierarchical order are:

- Complete Response (CR) during the study, determined by Lugano criteria, as assessed by an IRC
- OS: Duration from the date of randomisation to the date of the subject's death
- MRD negativity

Other secondary efficacy endpoints are:

- Changes from baseline in Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym)
- PFS, BOR, and CR during the study, determined per Lugano criteria, as assessed by investigator
- Duration of response (DOR), duration of complete response (DOCR), time to progression (TTP), and CR at the end of treatment (12 cycles), time to response (TTR), time to complete response (TTCR), per Lugano criteria 2014 as assessed by an IRC and by the investigator, respectively
- Event-Free Survival (EFS), defined as the duration from randomisation to the date of any of the following (whichever occurs first):

    - Disease progression determined by Lugano criteria 2014 as assessed by the investigator
    - Initiation of any non-protocol-specified new anti-lymphoma therapy for any reason
    - Death
- Time to next anti-lymphoma treatment (TTNLT)
- Changes from baseline in Patient-Reported Outcome Instruments (PROs; including Patient Global Impression of Severity [PGIS], Patient Global Impression of Change [PGIC], and EuroQol 5-dimension questionnaire, 5-level [EQ-5D-5L])

Sample size

The study was powered for the dual endpoints of BOR (CR or PR) and PFS.

For the analysis of BOR of CR or PR using ORR (arm A vs. C), the sample size of 232 subjects in the ITT population (Arm A and Arm C) was calculated assuming 93% ORR for Arm A versus 75% ORR for Arm C, with a power of 90% and one-sided significance level of 0.005.

For PFS (arm A vs. C), the target number of events was set to 181 based on a target HR of 0.6 (a 26-month increase in median PFS for Arm A relative to the control, i.e., 65 months versus 39 months, respectively), a target power of 90%, one-sided overall significance level of 0.02, an increasing accrual rate during the first 20 months to reach maximal accrual rate (56 subjects/month), an annual dropout rate of 2%, and two interim analyses for efficacy and futility. In order to observe the target number of events, 436 subjects were enrolled in arm A and C. The target number of events was expected to be observed approximately 55 months from the first subject randomised.

For key secondary outcome CR rate (arm A vs. C), a sample size of 218 subjects per arm (436 in total) would provide 87.5% power, assuming an improvement from 35% in arm C to 50% in arm B, and using a one-sided alpha of 0.02.

For key secondary outcome OS (arm A vs. C), the target number of events was set to 146 in order to achieve 80% power assuming a true HR of 0.61 (corresponding to a two-year OS rate of 84.5% in arm C vs. 90.2% in arm A) and two interim analyses for efficacy and futility.

No information was provided concerning the power for the comparison of key secondary outcome MRD negativity (arm A vs. C).

Randomisation

All subjects were assigned a unique identification number by the interactive response technology (IRT) at the Screening Visit. For subjects who rescreen, the screening number assigned by the IRT at the initial Screening Visit should be used. The IRT assigned a randomisation number that encodes the subject's treatment group assignment according to the randomisation schedule.

Randomisation was stratified by the following:

- Disease Status/History:
    - Subjects in 2L treatment: progression of disease ≤ 2 years from the date of initiation of frontline therapy (POD24)
    - Subjects in 2L treatment: progression of disease > 2 years from the date of initiation of frontline therapy

    - Subjects in 3L+ treatment: < 6 months since end of last therapy until randomisation date
    - Subjects in 3L+ treatment: ≥ 6 months since end of last therapy until randomisation date
- Region
    - United States (US) /Western Europe
    - Rest of world

Blinding (masking)

Not applicable, the study is an open-label study.

Statistical methods

Hypotheses corresponding to the objectives

The hypotheses are that epcoritamab 48 mg in combination with R^2 improves rate of best overall response (BOR) of CR or PR compared to R^2 alone in subjects with R/R FL in the first 232 subjects randomised from ITT population, and that epcoritamab 48 mg in combination with R^2 improves PFS compared to R^2 alone in subjects with R/R FL in the ITT population.

Estimand Corresponding to the Primary Objective

BOR of CR or PR was assessed for all randomised subjects with R/R FL, regardless of potential premature discontinuation of study drugs. Disease assessment after the initiation of any new anti-lymphoma therapy was not to be included in the derivation of BOR of CR or PR. The overall response rate (ORR) by an Independent Review Committee (IRC), defined as proportion of subjects with BOR of CR or PR as assessed per Lugano criteria, were derived; the treatment effect was summarized as the difference in the ORRs between epcoritamab 48 mg in combination with R^2 and R^2 alone in the first 232 randomised subjects from ITT population.

Progression-free survival was assessed for all randomised subjects with R/R FL, until disease progression as assessed per Lugano criteria by IRC regardless of potential premature discontinuation of study drugs. For PFS primary analysis, PFS was censored at last adequate disease assessment prior to the initiation of any new anti-lymphoma therapy. The PFS distributions was estimated by the Kaplan-Meier estimates. The treatment effect will be summarized as the hazard ratio (HR) using Cox proportional hazards model (epcoritamab 48 mg in combination with R^2 versus R^2 alone in the ITT population).

Estimand Corresponding to the Key Secondary Objectives

CR and MRD negativity was assessed for all randomised subjects with R/R FL, regardless of potential premature discontinuation of study drugs. Disease assessment after the initiation of any new anti-lymphoma therapy was not to be included in the derivation of CR and MRD negativity. The CR rates and MRD negativity rates will be derived; the treatment effect was summarized as the difference in the CR rates (and MRD negativity rates) between epcoritamab 48 mg in combination with R^2 and R^2 alone in the ITT population.

Overall survival (OS) was assessed for all randomised subjects with R/R FL, regardless of 1) premature discontinuation from study or 2) initiation of any non-protocol-specified new anti-lymphoma therapy. The OS distribution was estimated by the Kaplan-Meier estimates. The treatment effect was

summarized as the HR using Cox proportional hazards model (epcoritamab 48 mg in combination with R^2 versus R^2 alone in the ITT population).

Analysis of primary outcome variables

The first primary outcome variable, IRC-assessed BOR (CR or PR), was analysed using the Cochran-Mantel-Haenszel (CMH) test for common risk difference estimated by a weighted average of risk differences across strata using the Mantel-Haenszel (MH) weights, with one-sided significance level 0.005, adjusting for factors used to stratify randomisation. Estimated BOR rates per arm as well as the estimated rate difference are reported with 95% confidence intervals. The analysis is performed using data from the first 232 subjects randomised in the ITT population. In the analysis, subjects who are randomised but have no disease assessment are considered non-responders. For subjects who receive new anti-lymphoma therapy, only data prior to the start of anti-lymphoma therapies is used to determine BOR. An unstratified BOR analysis is performed as a sensitivity analysis.

The second primary outcome variable, IRC-assessed PFS, is analysed using a log-rank test stratified by stratification factors. The estimate of the hazard ratio and the corresponding 95% confidence interval are derived using a stratified Cox proportional hazards model with the treatment group as the only explanatory covariate. The Kaplan-Meier method is used to estimate the distribution and median of PFS. The analysis is performed in the ITT population. The one-sided significance level is set to 0.02 (if no significant improvement in BOR is found) or 0.025 (if the improvement in BOR is statistically significant). In the analysis, subjects without a PFS event are censored at the last adequate disease assessment date. In addition, the following censoring rules are applied: Subjects without available baseline or post-baseline disease assessments are censored at baseline; Subjects who receive new anti-lymphoma therapy are censored at the last adequate assessment date prior to start of anti-lymphoma therapy; and subjects with PD or death occurring after two or more consecutive missing/NE disease assessments are censored at the last adequate disease assessment date prior to the missing/NE assessments. For PFS, the following analyses are performed are sensitivity analyses: (1) An unstratified analysis; (2) an analysis ignoring the 2 or more consecutive missing/NE disease assessments prior to progression or death; and (3) an analysis censoring the 2 or more consecutive missing/NE disease assessments regardless of progression or death. In addition, the following supplementary analyses are performed: (1) an analysis ignoring the initiation of new anti-lymphoma therapy; (2) an analysis ignoring the 2 or more consecutive missing/NE disease assessments prior to progression or death and initiation of new anti-lymphoma therapy; (3) PFS analysis censoring for deaths due to Covid-19; and (4) a comparison between Arm A and Arm C in the mITT population.

Analysis of key secondary outcome variables:

IRC-assessed CR rate is analysed analogously to the analysis of IRC-assessed BOR (CR or PR), with the exception that the analysis is performed in the full ITT population (i.e. not restricted to the first 232 randomised subjects). An unstratified analysis is performed as a sensitivity analysis. A supplementary analysis is performed for unconfirmed IRC-assessed CR (defined as subjects with CMR/CR by imaging without confirmation of lymphoma involvement by bone marrow biopsy and aspirate).

OS is analysed using a log-rank test stratified by stratification factors. The estimate of the hazard ratio and the corresponding 95% confidence interval are derived using a stratified Cox proportional hazards model. The distribution of OS per treatment arm is estimated using the KM method. The analysis was performed in the ITT population. The comparison between arm B vs. arm C is considered descriptive. Subjects who receive new anti-lymphoma therapy are not censored. Subjects who are still alive are censored at the last known date the subject was reported to be alive. An unstratified OS analysis is performed as a sensitivity analysis. In addition, a supplementary analysis is performed censoring for deaths due to Covid-19.

MRD negativity is defined at as achieving MRD negative status at the landmark timepoint of C3D1 and is performed analogously to the analysis of the IRC-assessed CR rate. An unstratified analysis is performed as a sensitivity analysis. A supplementary analysis is performed for MRD negativity analysis at C2D1 and EOT as assessed by NGS of ctDNA in plasma or peripheral blood mononuclear cells (PBMCs) in PB and/or bone marrow.

Of note, the SAP indicates that key secondary outcomes may be performed in the mITT population.

Analysis of other secondary outcome variables

A description of other secondary efficacy endpoints is provided below:

- *PFS, BOR and CR during the study, determined per Lugano criteria as assessed by investigator* are analysed similar to the analyses based on the corresponding IRC-assessed outcomes;
- The *CR at the end of treatment (12 cycles) per Lugano criteria as assessed by an IRC/investigator* is assessed in the ITT population by means of the estimated proportions per arm as well as the rate difference, along with 95% confidence intervals. Subjects who are randomised but have no disease assessment by the end of Cycle 12 are considered non-responders. For subjects who discontinue treatment by the end of Cycle 12, all disease assessments evaluated before the cutoff date and the initiation of new anti-lymphoma therapy (whichever occurs earlier) are included.
- The *duration of response (DOR) and duration of complete response (DOCR) per Lugano criteria as assessed by an IRC/investigator* are evaluated in all randomised subjects who achieve the best response of CR or PR (for DOR) or CR (for DOCR) and is defined as the time between the first response to the earliest evidence of progressive disease (after which there is no more PR or CR assessment) or death due to any cause. KM estimates are presented per arm, and median DOR and DCOR are derived along with 95% confidence intervals. A sensitivity analysis where deaths due to Covid-19 are censored is provided. The following censoring rules are applied: Subjects with no/inadequate disease assessment after the first response are censored at the time of first response; subjects who receive new anti-lymphoma therapy are censored at the last adequate assessment date prior to start of anti-lymphoma therapy; and subjects with PD or death occurring after two or more consecutive missing/NE disease assessments are censored at the last adequate disease assessment date prior to the missing/NE assessments.
- The *time to progression (TTP) per Lugano criteria as assessed by an IRC/investigator* is defined as the time between randomisation to the date of progressive disease. Subjects who are still responding at DCO are censored. KM estimates are presented per arm, and median TTPs are derived along with 95% confidence intervals. The following censoring rules are applied: Subjects with no baseline or post-baseline disease assessment are censored at randomisation; subjects who die are censored at the time of death; subjects who receive new anti-lymphoma therapy are censored at the last adequate assessment date prior to start of anti-lymphoma therapy; and subjects with PD occurring after two or more consecutive missing/NE disease assessments are censored at the last adequate disease assessment date prior to the missing/NE assessments.
- The *time to response (TTR)* and *time to complete response (TTCR) per Lugano criteria as assessed by an IRC/investigator* is compared in the set of subjects who achieve CR or PR (or CR, for TTCR) and is defined as the time from first dose of study drug to initial CR/PR (or CR) prior to the initiation of new anti-lymphoma therapy. Descriptive statistics (mean, standard deviation, median, and range) and the 95% confidence interval of the mean are presented.

- The *event free survival (EFS) per Lugano criteria as assessed by the investigator* is defined as the time between randomisation and disease progression (determined by Lugano criteria as assessed by the investigator), initiation of any non-protocol-specified new anti-lymphoma therapy (for any reason), and death, whichever occurs first. KM estimates are presented per arm, and the median EFS times are reported along with 95% confidence intervals.
- The *time to next anti-lymphoma treatment (TTNLT)* is defined as the time between randomisation and the start of new anti-lymphoma therapy or date of death due to PD, whichever occurs first. KM estimates are presented per arm, and the median EFS times are reported along with 95% confidence intervals. The HR estimate (with 95% confidence interval) is estimated using a stratified Cox proportional hazards model with treatment group as the only explanatory variable. Subjects who were reported as not having started new non-protocol anti-lymphoma therapy are censored at the last known alive date to be free of non-protocol specified anti-lymphoma therapy. Data from subjects without any post-baseline visit are censored at the date of randomisation.
- *Change from baseline in Functional Assessment of Cancer Therapy Lymphoma (FACT-Lym) scores*, i.e. the FACT-G total score (range: 0-108), the lymphoma subscale score (LymS, range: 0-60), the FACT-Lymphoma total score (the sum of FACT-G and LymS), and FACT-Lymphoma Trial Outcome Index (TOI) (range: 0-116) are summarized per visit. Statistical comparisons of visit-specific mean change-from-baseline scores are performed using linear mixed-effects regression models with stratification factors of disease status and treatment arm as fixed factors and baseline score as a covariate using the ITT population (arm A and C) with baseline scores and at least one non-missing post-baseline score. Time and treatment-by-time interaction is included in the model. The repeated correlation structure in the timepoints is assessed by using the Bayesian Information Criterion (BIC). The following covariance structures are explored: Unstructured, compound symmetry and first-order autoregressive. In addition, the proportion of subjects classified as 'deteriorated', 'stable' or 'improved' (based on a meaningful change threshold) is provided and compared per visit. Lastly, the time to first deterioration, as well the time to first improvement, are compared using Kaplan-Meier estimates.
- *Change from baseline in Patient Global Impression of Severity (PGIS)*, *Patient Global Impression of Change (PGIC)* and *change from baseline EuroQol 5-dimension questionnaire, 5-level (EQ-5D-5L)* derived scores are summarized by visit.

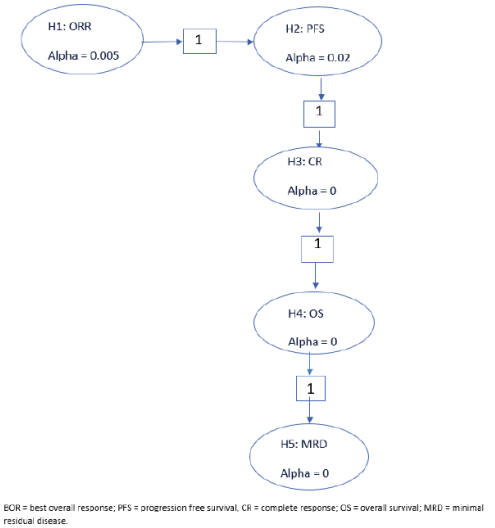
Subgroup analyses

For the primary endpoints of BOR and PFS, subgroup analyses are prespecified in (but not limited to) the following subgroups: Age categories (< 65, ≥ 65 < 75, ≥ 75 years); Sex (Male, Female); Race (White, Black or African American, Asian, Other); Ethnicity (Hispanic or Latino, Not Hispanic or Latino); Region (US/Western Europe and Rest of World (ROW)); North America (US/Canada/Puerto Rico) (Yes/No); North America/Western Europe (Yes/No); Ann Arbor stage (II, III+IV); FLIPI-1 score at diagnosis (0-1, 2, 3-5)FLIPI-1 score at baseline (0, 1-2, 3-5); FLIPI-2 score at diagnosis (0, 1-2, 3-5); FLIPI-2 score at baseline (0, 1-2, 3-5); Baseline ECOG performance status (≤ 1, > 1); Number of prior anti-lymphoma therapies (1, 2, ≥ 3); B symptoms at baseline/screening (Yes, No); Prior CAR-T (Yes, No); Prior ASCT (Yes, No); Positive bone marrow involvement (Yes, No); Presence of lymph node ≥ 7 cm at baseline/screening (Yes, No); Time since most recent anti-CD20 (< 6 months, ≥ 6 months); Progression of disease ≤ 2 years from the date of initiation of frontline therapy (POD24) vs progression of disease > 2 years from the date of initiation of frontline therapy; Prior 1L rituximab-containing chemotherapy versus prior 1L obinutuzumab containing chemotherapy; Received prior rituximab and lenalidomide (Yes, No); Refractory to 1L regimen (Yes, No); Refractory to prior regimen (Yes, No);

Double refractory (Yes, No); Prior bendamustine-containing regimen (< 9 vs ≥ 9 months, < 12 vs ≥ 12 months of starting epcoritamab); Anti-drug antibody (ADA) and neutralizing antibody (Yes, No); US only (Yes, No)

Protection of type I error across primary and key secondary endpoints

Initially, the overall alpha (0.025 one-sided) is split between two primary analyses: 0.005 for the comparison of BOR (CR or PR), and 0.02 for the comparison of PFS. If a significant improvement in BOR is observed, the allocated alpha is recycled to the PFS analysis (which then use alpha = 0.025). If no significant improvement in BOR is observed, the PFS analysis is performed using alpha = 0.02. PFS and the key secondary outcomes are then tested in a fixed sequence: If the PFS log-rank test is not significant, no further testing is performed. If a significant improvement in PFS is observed, however, the allocated alpha (0.025 or 0.02) is recycled to the first key secondary outcome. This procedure continues until all key secondary outcomes have been tested.



BOR = best overall response; PFS = progression free survival, CR = complete response; OS = overall survival; MRD = minimal residual disease

Figure 11. Hierarchical testing strategy: primary and key secondary endpoints (one-sided alpha)

Interim analyses

For PFS, two interim analyses were planned: the first was to take place approximately 12 months (48 weeks) after the 232nd subject was randomised to either arm A or C (i.e. at the same as the analysis of the analysis of IRC-assessed BOR (CR or PR). The second was to be performed when approximately 136 PFS events (75% information fraction) are observed among the subjects randomised to arm A and C. The analyses were intended to allow stopping for both efficacy and (non-binding) futility. For efficacy, O'Brien & Fleming-type stopping boundaries were derived using the Lan-DeMets alpha spending function based on the observed number of events. The futility decision is based on fixed thresholds of 1.1 and 0.9262 for the HR estimate, for the first and second interim analysis, respectively.

For OS, two interim analyses were planned: the first was to take place at the time of the second PFS interim analysis (with approximately 61 OS events in arm A and C; 42% information fraction). The second was planned to be performed at the time of the final PFS analysis (approximately 85 OS events in arm A and C; 58% information fraction). The analyses were intended to allow stopping for both efficacy and (non-binding) futility. For efficacy, O'Brien & Fleming-type stopping boundaries were

derived using the Lan-DeMets alpha spending function based on the observed number of events. The futility decision is based on fixed thresholds of 1.05 and 0.9334 for the HR estimate, for the first and second interim analysis, respectively.

In addition, for OS, three interim analysis for harm (non-binding) were planned, at the time of the first PFS interim analysis (approximately 31 OS events in arm A and C), at the time of the second PFS interim analysis/first OS interim analysis (approximately 61 OS events in arm A and C), and at the time of the final PFS analysis/second OS analysis (approximately 85 OS events in arm A and C), based on respective fixed thresholds of 1.43, 1.29, and 1.24 for the HR estimate.

Efficacy boundaries and testing strategy across interim analyses

The efficacy boundaries and testing strategy used across the interim analyses for each of the outcome variables included in the primary testing procedure are given in the table below:

Table 4. Testing sequence and alpha spending boundaries (one-sided alpha level) for primary and key secondary endpoints

Endpoints		Timing of Analyses			
Arm A vs Arm C		BOR PA/ PFS IA1 (Month 28)	PFS IA2 / OS IA1 (Month 42)	PFS FA / OS IA2 (Month 55)	OS FA (Month 94)
1	BOR*	0.005	No test	No test	No test
2	PFS (if BOR is significant)	0.0004 (IF = 40%)	0.0096 (IF = 75%)	0.0221	No test
	PFS (if BOR is not significant)	0.0002 (IF = 40%)	0.0072 (IF = 75%)	0.0178	No test
3	CR (if BOR is significant and PFS is significant)	0.025			No test
	CR (if BOR is not significant and PFS is significant)	0.02			No test
4	OS (if BOR is significant and CR is significant)	No test	0.0005 (IF = 42%)	0.0031 (IF = 58%)	0.0239
	OS (if BOR is not significant and CR is significant)	No test	0.0003 (IF = 42%)	0.0022 (IF = 58%)	0.0193
5	MRD	No test	Alpha recycled from OS analysis		

* BOR of CR or PR will be analyzed by ORR for the first 232 subjects randomized from Arm A and Arm C. ORR analysis from the ITT population will be conducted in PFS IA2 and PFS FA.

Note: The actual alpha spending for testing PFA and OS will be determined based on the actual events observed at interim analyses.

Results

Data from two data cut-offs for the pivotal study have been presented. PFS, ORR, and CR rate were statistically tested at the first interim analysis (IA) with data cutt-off (DCO) 10 January 2025. Updated efficacy outcomes at the second IA with DCO 24 May 2025 are presented for PFS, ORR and CR rate and the first OS IA was performed. The subject disposition, the conduct of the study/deviations, demographic data, other secondary efficacy endpoints, efficacy analyses in Arm B and subgroup analyses are presented from IA2.

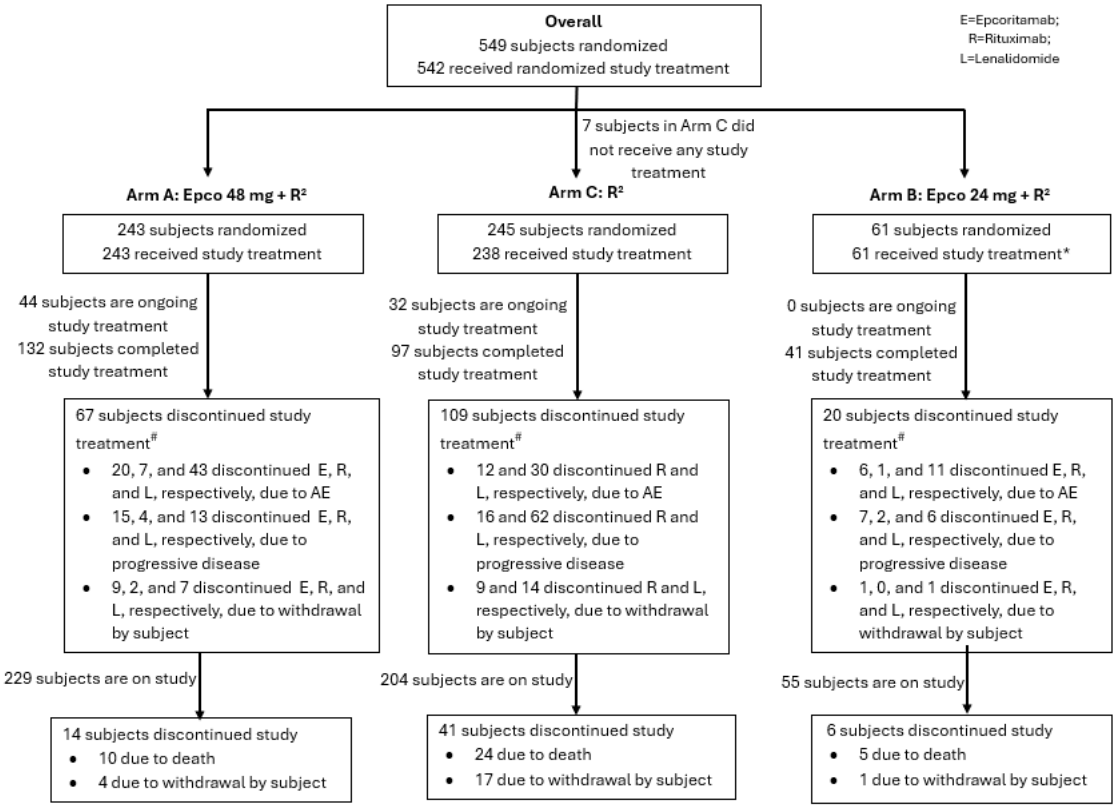
The overall median duration of study follow-up as of IA1 for the ITT population was 11.3 months (range: 0, 27) and was comparable between Arm A and Arm C at 10.4 months and 10.2 months, respectively. The median duration of study follow-up as of IA2 for the ITT population was 15.8 months

(range: 0, 31) and was comparable between Arm A and Arm C at 14.8 and 14.6 months, respectively. In Arm B, the median duration of study follow-up was 23.0 months (range; 3, 31).

Participant flow

Subject disposition in Study M20-638 is shown in Figure 12 and Table 5.

There were 119 patients with a screen failure. Of these 53 patients at least 44.6% did not meet eligibility criterion number 8 (including 8A and 8B) requiring CD20+ disease.



* Arm B was closed to enrolment with protocol version 2.0; subjects in Arm B had the option to switch to Epco 48 mg + R^2, at investigator's discretion.
\# Discontinued study treatment means 1) discontinuation of all study drugs, 2) at least one study drug discontinued and rest completed.
Data Cutoff: 24 May 2025.

Figure 12. Subject Disposition Study M20-638 CSR

In arm C, of the 7 patients that were not treated, six withdrew consent after randomization and one died due to acute respiratory failure prior to receiving study treatment.

Table 5. Subject Disposition (ITT Population)

Category	Arm A (Epco 48 mg + R²) (N=243) n (%)	Arm C# (R²) (N=245) n (%)	Arm B (Epco 24 mg + R²) (N=61) n (%)	Overall# (N=549) n (%)
Randomised				
Never received any study treatment	0	7 (2.9)	0	7 (1.3)
Received randomised study treatment	243 (100)	238 (97.1)	61 (100)	542 (98.7)
Received study treatment other than randomised	0	0	0	0
Treated	243 (100)	238 (97.1)	61 (100)	542 (98.7)
Completed Protocol-Specified Study Treatment	132 (54.3)	97 (39.6)	41 (67.2)	270 (49.2)
Completed Epcoritamab	154 (63.4)		46 (75.4)	
Completed Rituximab	226 (93.0)	199 (81.2)	58 (95.1)	483 (88.0)
Completed Lenalidomide	133 (54.7)	97 (39.6)	42 (68.9)	272 (49.5)
Ongoing Study Treatment	44 (18.1)	32 (13.1)	0	76 (13.8)
Discontinued Study Treatment*	67 (27.6)	109 (44.5)	20 (32.8)	196 (35.7)
Discontinued Epcoritamab	50 (20.6)		15 (24.6)	
Discontinued Rituximab	15 (6.2)	38 (15.5)	3 (4.9)	56 (10.2)
Discontinued Lenalidomide	69 (28.4)	109 (44.5)	19 (31.1)	197 (35.9)
Ongoing Study	229 (94.2)	204 (83.3)	55 (90.2)	488 (88.9)
Discontinued Study^	14 (5.8)	41 (16.7)	6 (9.8)	61 (11.1)
Primary reason for discontinuation				
Death	10 (4.1)	24 (9.8)	5 (8.2)	39 (7.1)
Withdrawal by subject	4 (1.6)	17 (6.9)	1 (1.6)	22 (4.0)

Arm C column and overall column will not be displayed for Epcoritamab.
* Discontinued study treatment means 1) discontinuation of all study drugs, 2) at least one study drug discontinued and rest completed.
^ There were no patients lost to follow up.
Data Cutoff: 24 May 2025.

The most frequently reported reason for treatment discontinuation of epcoritamab was adverse event (20 [8.2%] subjects) followed by progressive disease (15 [6.2%] subjects) and withdrawal by subject (9 [3.7%] subjects). The most common reasons for withdrawal by subject in Arm A were not resuming therapy after AE (3 subjects), general health status deterioration (2 subjects) and unknown (2 subjects).

The most frequently reported reason for rituximab discontinuation was adverse event (7 [2.9%] vs 12 [4.9%] subjects) followed by progressive disease (4 [1.6%] vs 16 [6.5%] and withdrawal by subject (2 [0.8%] vs 9 [3.7%] subjects, respectively). The most frequently reported reason for lenalidomide discontinuation was progressive disease (13 [5.3%] vs 62 [25.3%]), followed by adverse event (43 [17.7%] vs 30 [12.2%] subjects) and withdrawal by subject (7 [2.9%] vs 14 [15.7%] subjects, respectively).

Recruitment

The First Subject First Visit was 20 September 2022. Study M20-638 is ongoing and enrollment was complete as of the IA1 DCO of 10 January 2025, and a total of 549 subjects with R/R FL were randomised.

Conduct of the study

Protocol amendments

The original protocol (Version 1.0, 22 April 2022) had 4 amendments and 1 administrative change that was incorporated in a subsequent amendment. The key amendments are shown below.

Amendment 1, Protocol Version 2.0, 21 February 2023

- Updated epcoritamab dosing schedule to include QW dosing in Cycle 3 of Arm A (48 mg epcoritamab).
- Added that Arm B (24 mg epcoritamab) is closed to enrolment. Removed primary objectives related to 24 mg epcoritamab dosing and updated hypotheses and estimands to account for mITT population (which were all subjects randomised to Arm A after amendment 2.0 and an equal number in Arm C).
- Updated number of subjects to approximately 520.
- Removed BOR from the secondary endpoints in the hierarchical testing order to an additional efficacy endpoint and removed PFS, ORR, CR rate at end of treatment, EFS, DOR, and DOCR, TTP determined by LYRIC.
- Updated AE collection period to 30 days after discontinuation of lenalidomide or 60 days after discontinuation of epcoritamab or rituximab, whichever was later.
- Updated eligibility criteria to exclude subjects with history of PML, update definition of radiographically measurable disease, update prior therapy regimen from anti-CD20 containing regimen to include anti-lymphoma regimen that contained an antiCD20 monoclonal antibody in combination with chemotherapy
- Updated epcoritamab and lenalidomide dose modifications/premedications and added that all doses of epcoritamab must be given at least 7 days apart.

Amendment 2, Protocol Version 3.0, 30 August 2023

- Updated SUD schedule to include a second intermediate dose of 3 mg to lower the ≥ Grade 2 CRS event rate.
- Adjusted primary and secondary objectives and efficacy analyses to be performed in an ITT population on Arm A and C instead of a mITT population due to primary analysis population definition change; added that all the primary and key secondary endpoints would be performed in the mITT population as sensitivity analysis.
- Approximate number of subjects in the study was adjusted from 520 to 500 subjects.
- Replaced mentions of prednisone with dexamethasone as the preferred corticosteroid premedication for study treatment.
- Removed distinction between haematological and non-haematological Grade 3 and Grade 4 toxicities for epcoritamab dose modifications.

- Added that hydration is strongly recommended for CRS premedication.
- Added that if more than 2 separate events of Grade 3 CRS occur, even if each event resolves to Grade 2 within 72 hours, epcoritamab should be discontinued. Replaced different general guidance statements for Grade 1, Grade 2, and Grade 3 events of CRS with a common statement saying to withhold epcoritamab, manage per current practice guidelines and ensure CRS symptoms are resolved prior to the next dose of epcoritamab.
- Changed maximum trial duration from 5 to 7 years after last subject has been enrolled
- Clarified that brain MRI or CT is required at screening within 6 weeks before randomisation. Changed pretreatment tumour assessment to be performed within 6 weeks instead of 28 days before randomisation.
- Clarified that on the days the subject is administered epcoritamab in combination with R^2, R^2 must be administered prior to epcoritamab.

Amendment 3, Protocol Version 4.0, 14 August 2024

- Updated to include the dual primary efficacy endpoint of BOR of CR or PR and added TTR and TTCR as additional efficacy endpoints.
- Updated subjects numbers to 436 to have enough number of PFS and OS events in the ITT population and to accommodate dual primary endpoints of BOR of CR and PR and PFS.
- Updated ORR and PFS interim analysis details for efficacy. The final PFS analysis requirements were also updated.
- Updated family-wise Type 1 error control steps and description on how significance level 0.05 (two-sided) would be split between the dual primary endpoints. The details on recycling of significance level if the statistical testing is significant for ORR were also updated. Added testing sequence and alpha spending boundaries (two-sided alpha level) and hierarchy testing strategy for primary and ranked secondary endpoints.
- Updated the renal function eligibility criteria because the eGFR calculated by MDRD equation is more appropriate to estimate renal function for the elderly FL population.
- Updated eligibility criteria to exclude subjects with a history of post-radical prostatectomy or with active disease present.
- Clarified that secondary malignancy or second malignancy (i.e., new primary malignancy or lymphoma transformation) would be captured until the end of survival follow-up.
- Updated epcoritamab dose modification guidance for Grade 4 events. Clarified that lenalidomide may be held until complete resolution of CRS, ICANS, CTLS and other epcoritamab related AEs.

Amendment 4, Protocol Version 5.0, 20 December 2024

- Clarified ranked secondary endpoints as key secondary endpoints and listed the additional efficacy endpoints as other secondary points
- Updated to use one-sided alpha of 0.025 universally for the one-sided hypothesis tests
- Included OS harm analysis (HA) conducted at all time points where an IA is tested (e.g., PFS IA1 [BOR primary analysis (PA)], PFS IA2, PFS final analysis [FA]) and the operating characteristics regarding the harm boundary.

The number of patients treated under the different protocol versions is shown in Table 6.

Table 6. Subjects Randomised Per Protocol Version

Protocol Version	Number of Subjects Randomised (Arm A + Arm B + Arm C) (N = 549)	Arm A: 2-Step SUD (N = 112)	Arm A: 3-Step SUD (N = 131)
Version 1.0[a]	190[b]	56[c]	7[c]
Version 2.0	135	54	15
Version 3.0	217	2	107
Version 4.0	7	0	2

a. 61 subjects were randomised to Arm B. Arm B was closed to enrolment after Protocol Version 1.0 with 26 subjects who received Epco 24 mg + R^2, 31 subjects who received and switched from Epco 24 mg + R^2 to Epco 48 mg + R^2, and 4 subjects who received Epco 48 mg + R^2 only.
b. The numbers per treatment arm were; Arm A: N= 63, Arm B: N=61, Arm C: N= 66.
c. In protocol version 1.0, epcoritamab was dosed QW in cycle 1 and 2.
Note: No subjects were enrolled under Protocol Version 5.0.
Data cutoff date: 10 January 2025.

SAP

SAP version 0.1 (25 May 2022) aligns with protocol version 1.0. This version was created to support initial protocol review as a part of regulatory agency interactions but was never formally approved. Version 1.0 (05 January 2024) was created to align with protocol version 3.0, version 2.0 (28 August 2024) was created to align with protocol version 4.0, and version 3.0 (26 December 2024) was created to align with protocol version 5.0. Changes to the planned analyses after finalization of the SAP (Version 3.0; 26 December 2024) are listed below.

- As pre-specified in the SAP, at the time of the PFS IA2 for efficacy and futility, analyses for all efficacy endpoints were performed based on data maturity and appropriateness (clinically meaningfulness). Therefore, certain sensitivity analyses in the mITT population were not performed for this DCO. Sensitivity analyses in the mITT population were not performed for all primary and secondary endpoints.
- DOR/DOCR sensitivity and supplementary analyses were performed to censor for subjects with 2 or more consecutive missing/NE disease assessments regardless of progression or death.

Protocol deviations

Overall, 123/549 (22.4%) subjects reported at least 1 important protocol deviation (Table 7). In Arms A and B, there were dosing deviations specific to treatment with epcoritamab, including but not limited to:

- Instances where the interval between epcoritamab doses was less than the required 7 days;
- Cases where the toxicity management guidelines outlined in the protocol were not adhered to;
- Cases where Arm B subjects were dosed QW during Cycle 3 after the epcoritamab dose switch.

Table 7. Summary of Important Protocol Deviations (ITT Population)

Category	Arm A (Epco 48 mg + R²) (N = 243) n (%)	Arm C (R²) (N = 245) n (%)	Arm B (Epco 24 mg + R²) (N = 61) n (%)	Overall (N = 549) n (%)
Subjects with at least one protocol deviation	67 (27.6)	33 (13.5)	23 (37.7)	123 (22.4)
Subjects who entered the study even though they did not satisfy the entry criteria - Eligibility criteria not met	11 (4.5)	13 (5.3)	0	24 (4.4)
Subjects who received the wrong treatment or incorrect dose	35 (14.4)	4 (1.6)	19 (31.1)	58 (10.6)
Incorrect dose	35 (14.4)	4 (1.6)	19 (31.1)	58 (10.6)
Subjects who received an excluded concomitant treatment	17 (7.0)	13 (5.3)	4 (6.6)	34 (6.2)
Protocol compliance-IRT-incorrect entry of subject data	3 (1.2)	3 (1.2)	1 (1.6)	7 (1.3)
Protocol compliance-IP administered out of stability	2 (0.8)	0	0	2 (0.4)
Protocol compliance-study procedures	12 (4.9)	0	3 (4.9)	15 (2.7)

Note: Includes important protocol deviation categories as suggested in the ICH E3 Guideline.
Subjects are counted only once in each category for which they had a deviation. The protocol deviation is the CSR reportable protocol deviation.
Data Cutoff: 24 May 2025.

Baseline data

Key demographic characteristics for the ITT population are presented in Table 8 and baseline disease characteristics for the ITT population are presented in Table 9.

Table 8. Demographic Characteristics (ITT Population)

	Arm A (Epco 48 mg + R²) (N = 243)	Arm C (R²) (N = 245)	Arm B (Epco 24 mg + R²) (N = 61)	Overall (N = 549)
ECOG - n (%)				
0	166 (68.3)	170 (69.4)	41 (67.2)	377 (68.7)
1	72 (29.6)	68 (27.8)	19 (31.1)	159 (29.0)
2	5 (2.1)	7 (2.9)	1 (1.6)	13 (2.4)
Sex - n (%)				
Female	104 (42.8)	107 (43.7)	24 (39.3)	235 (42.8)
Male	139 (57.2)	138 (56.3)	37 (60.7)	314 (57.2)
Ethnicity - n (%)				
Hispanic or Latino	29 (12.2)	28 (11.5)	9 (14.8)	66 (12.2)
Not Hispanic or Latino	209 (87.8)	215 (88.5)	52 (85.2)	476 (87.8)
Missing	5	2	0	7
Race - n (%)				
American Indian/Alaska Native	0	1 (0.4)	0	1 (0.2)
Asian	63 (26.5)	54 (22.3)	5 (8.3)	122 (22.6)

	Arm A (Epco 48 mg + R²) (N = 243)	Arm C (R²) (N = 245)	Arm B (Epco 24 mg + R²) (N = 61)	Overall (N = 549)
Black or African American	6 (2.5)	2 (0.8)	1 (1.7)	9 (1.7)
White	168 (70.6)	184 (76.0)	54 (90.0)	406 (75.2)
Multiple	1 (0.4)	1 (0.4)	0	2 (0.4)
Black Or African American	1	1	0	2
White	1	1	0	2
Missing	5	3	1	9
Age (years)				
Median	60.0	63.0	64.0	61.0
Min, Max	30, 84	24, 89	35, 85	24, 89
< 65 years	155 (63.8)	139 (56.7)	31 (50.8)	325 (59.2)
65 - < 75 years	68 (28.0)	71 (29.0)	22 (36.1)	161 (29.3)
≥ 75 years	20 (8.2)	35 (14.3)	8 (13.1)	63 (11.5)
Weight at baseline (kg)				
n	243	245	61	549
Median	74.10	76.50	75.00	75.00
Region - n (%)				
United States (US)/Western Europe	58 (23.9)	60 (24.5)	16 (26.2)	134 (24.4)
Rest of world	185 (76.1)	185 (75.5)	45 (73.8)	415 (75.6)
Region 3 - n (%)				
North America/Western Europe	62 (25.5)	67 (27.3)	16 (26.2)	145 (26.4)
Not North America/Western Europe	181 (74.5)	178 (72.7)	45 (73.8)	404 (73.6)
Stratification factors per IRT Region - n (%)				
United State (US)/Western Europe	58 (23.9)	60 (24.5)	16 (26.2)	134 (24.4)
Rest of world	185 (76.1)	185 (75.5)	45 (73.8)	415 (75.6)
Baseline renal function classification by Cockcroft-Gault method (CrCl)[mL/min] - n (%)				
Normal (≥ 90)	124 (51.0)	131 (53.5)	27 (44.3)	282 (51.4)
Mildly impaired (60 - < 90)	94 (38.7)	84 (34.3)	21 (34.4)	199 (36.2)
Moderately impaired (30 - < 60)	25 (10.3)	30 (12.2)	13 (21.3)	68 (12.4)
Severe impaired (15 - < 30)	0	0	0	0
Baseline hepatic function classification - n (%)				
Normal	217 (89.3)	215 (88.1)	53 (86.9)	485 (88.5)
Mildly impaired	25 (10.3)	26 (10.7)	7 (11.5)	58 (10.6)
Moderately impaired	1 (0.4)	3 (1.2)	1 (1.6)	5 (0.9)
Severe impaired	0	0	0	0
Missing	0	1	0	1

Note: Percentages calculated on non-missing values.
Data Cutoff: 24 May 2025.

Table 9. Baseline Disease Characteristics (ITT Population)

	Arm A (Epco 48 mg + R²) (N=243)	Arm C (R²) (N=245)	Arm B (Epco 24 mg + R²) (N=61)	Overall (N=549)
Median time from initial diagnosis to randomisation (years) (min, max)	4.54 (0.2, 30.3)	5.32 (0.1, 43.0)	5.41 (0.1, 24.7)	5.06 (0.1, 43.0)
Median time since last line of therapy to randomisation (months) (min, max)	21.45 (0.2, 198.4)	17.68 (0.3, 229.5)	17.41 (0.6, 191.1)	18.96 (0.2, 229.5)
Follicular lymphoma grade - n (%)				
Grade 1	61 (25.2)	43 (17.9)	13 (21.7)	117 (21.6)
Grade 2	126 (52.1)	120 (50.0)	30 (50.0)	276 (50.9)
Grade 3a	52 (21.5)	75 (31.3)	17 (28.3)	144 (26.6)
Classical FL (Per 5th Edition WHO)	3 (1.2)	2 (0.8)	0	5 (0.9)
Missing	1	5	1	7
Ann Arbor staging - n (%)				
Stage I	0	0	0	0
Stage II	37 (15.2)	44 (18.0)	2 (3.3)	83 (15.1)
Stage III	74 (30.5)	68 (27.8)	15 (24.6)	157 (28.6)
Stage IV	132 (54.3)	133 (54.3)	44 (72.1)	309 (56.3)
FLIPI-1 score at baseline - n (%)				
0-1	63 (25.9)	56 (22.9)	5 (8.2)	124 (22.6)
2	79 (32.5)	76 (31.0)	27 (44.3)	182 (33.2)
3-5	100 (41.2)	113 (46.1)	29 (47.5)	242 (44.1)
Unknown	1 (0.4)	0	0	1 (0.2)
Bulky disease per IRC (nodal or extranodal ≥ 7 cm) - n (%)				
Yes	47 (19.7)	61 (25.7)	14 (23.3)	122 (22.8)
No	191 (80.3)	176 (74.3)	46 (76.7)	413 (77.2)
Missing	5	8	1	14
Bulky disease per IRC (nodal or extranodal > 6 cm) - n (%)				
Yes	76 (31.9)	84 (35.4)	23 (38.3)	183 (34.2)
No	162 (68.1)	153 (64.6)	37 (61.7)	352 (65.8)
Missing	5	8	1	14
Bone marrow involvement of disease at baseline - n (%)				
Positive	70 (28.8)	68 (27.8)	17 (27.9)	155 (28.2)
Negative	162 (66.7)	168 (68.6)	43 (70.5)	373 (67.9)
Unknown	11 (4.5)	9 (3.7)	1 (1.6)	21 (3.8)
Presence of extranodal disease - n (%)				
Yes	101 (41.6)	105 (42.9)	34 (55.7)	240 (43.7)
No	142 (58.4)	140 (57.1)	27 (44.3)	309 (56.3)

	Arm A (Epco 48 mg + R²) (N=243)	Arm C (R²) (N=245)	Arm B (Epco 24 mg + R²) (N=61)	Overall (N=549)
Disease status - n (%)				
2L	145 (59.7)	141 (57.6)	33 (54.1)	319 (58.1)
PD ≤ 2 years from initiation of 1L (POD24#)*	64 (44.1)	52 (37.7)	13 (39.4)	129 (40.8)
PD > 2 years from initiation of 1L*	81 (55.9)	86 (62.3)	20 (60.6)	187 (59.2)
Missing	0	3	0	3
3L+	98 (40.3)	104 (42.4)	28 (45.9)	230 (41.9)
≥ 6 months since end of last therapy until randomisation date*	77 (78.6)	74 (71.2)	20 (71.4)	171 (74.3)
< 6 months since end of last therapy until randomisation date*	21 (21.4)	30 (28.8)	8 (28.6)	59 (25.7)
Stratification factors per IRT Disease status - n (%)				
2L	157 (64.6)	159 (64.9)	39 (63.9)	355 (64.7)
PD ≤ 2 years from initiation of 1L (POD24#)*	63 (40.1)	63 (39.6)	15 (38.5)	141 (39.7)
PD > 2 years from initiation of 1L*	94 (59.9)	96 (60.4)	24 (61.5)	214 (60.3)
3L+	86 (35.4)	86 (35.1)	22 (36.1)	194 (35.3)
≥ 6 months since end of last therapy until randomisation date*	63 (73.3)	63 (73.3)	16 (72.7)	142 (73.2)
< 6 months since end of last therapy until randomisation date*	23 (26.7)	23 (26.7)	6 (27.3)	52 (26.8)

POD24 is defined as progression of disease ≤ 2 years from the date of initiation of frontline therapy.
* Percentage is based on non-missing total in each category.
Note: Percentages calculated on non-missing values.
Data Cutoff: 24 May 2025.

A summary of prior anticancer therapies by category for the ITT population is presented in Table 10.

Table 10. Summary of Prior Therapies by Category (ITT Population)

	Arm A (Epco 48 mg + R²) (N = 243)	Arm C (R²) (N = 245)	Arm B (Epco 24 mg + R²) (N = 61)	Overall (N = 549)
Prior lines of anti-lymphoma therapies				
n	243	245	61	549
Median	1.0	1.0	1.0	1.0
Min, Max	1, 7	1, 6	1, 5	1, 7
1	145 (59.7)	141 (57.6)	33 (54.1)	319 (58.1)
2	58 (23.9)	61 (24.9)	19 (31.1)	138 (25.1)
≥ 3	40 (16.5)	43 (17.6)	9 (14.8)	92 (16.8)
Prior systemic anti-lymphoma therapy	**243 (100)**	**245 (100)**	**61 (100)**	**549 (100)**
Anti-CD20 antibody	243 (100)	245 (100)	61 (100)	549 (100)
Anti-CD20 antibody containing chemotherapy	239 (98.4)	240 (98.0)	61 (100)	540 (98.4)
Alkylating agents	238 (97.9)	241 (98.4)	60 (98.4)	539 (98.2)
Anthracyclines	166 (68.3)	180 (73.5)	45 (73.8)	391 (71.2)
Antimetabolite	42 (17.3)	37 (15.1)	12 (19.7)	91 (16.6)
Corticosteroids	184 (75.7)	193 (78.8)	46 (75.4)	423 (77.0)
PI3K Inhibitors	8 (3.3)	11 (4.5)	3 (4.9)	22 (4.0)
Immunomodulatory	9 (3.7)	13 (5.3)	1 (1.6)	23 (4.2)
Vinca Alkaloids	192 (79.0)	200 (81.6)	48 (78.7)	440 (80.1)
CAR-T	1 (0.4)	1 (0.4)	0	2 (0.4)

	Arm A (Epco 48 mg + R²) (N = 243)	Arm C (R²) (N = 245)	Arm B (Epco 24 mg + R²) (N = 61)	Overall (N = 549)
POD24#	**106 (43.6)**	**93 (38.0)**	**23 (37.7)**	**222 (40.4)**
Refractory to anti-CD20 antibody	**104 (42.8)**	**103 (42.0)**	**30 (49.2)**	**237 (43.2)**
Refractory to alkylating agents	**91 (37.4)**	**96 (39.2)**	**28 (45.9)**	**215 (39.2)**
Double refractory*	**91 (37.4)**	**91 (37.1)**	**27 (44.3)**	**209 (38.1)**
Refractory to CAR-T	**1 (0.4)**	**0**	**0**	**1 (0.2)**
Received prior R² (lenalidomide and rituximab)	**8 (3.3)**	**9 (3.7)**	**1 (1.6)**	**18 (3.3)**
Refractory to R² (lenalidomide and rituximab)	1 (0.4)	1 (0.4)	0	2 (0.4)
Refractory to 1L anti-lymphoma therapy	**86 (35.4)**	**81 (33.1)**	**23 (37.7)**	**190 (34.6)**
Refractory to last line of therapy	**84 (34.6)**	**82 (33.5)**	**25 (41.0)**	**191 (34.8)**
Received prior Stem Cell Transplant (SCT)	**23 (9.5)**	**18 (7.3)**	**5 (8.2)**	**46 (8.4)**
Subject relapsed ≤ 12 months after SCT	2 (0.8)	2 (0.8)	0	4 (0.7)
Prior radiotherapy	**36 (14.8)**	**42 (17.1)**	**9 (14.8)**	**87 (15.8)**
Time from end of last-line anti-lymphoma therapy to 1st dose (months)				
n	243	238	60	541
Median	21.52	18.14	17.45	19.19
Min, Max	0.3, 198.5	0.4, 229.5	0.6, 191.1	0.3, 229.5

* Double refractory is refractory to prior anti-CD20 therapy and prior alkylator therapy. Refractory is met when a subject meets one of the either condition: the best overall response to treatment is SD or PD; progression occurs within 6 months after completion of treatment regardless of response.

POD24 is defined as progression of disease ≤ 2 years from the date of initiation of frontline therapy.

Note: All therapies with a start date prior to the first study treatment dose are included. Subjects are counted once in each row, regardless of the number of therapies they may have taken.

Data Cutoff: 24 May 2025

The most frequent subsequent anticancer therapies in Arm A and Arm C were:

- Any post treatment anti-lymphoma therapies: 15 (6.2%) in Arm A vs 78 (31.8%) in Arm C
- Anti-CD20 antibody: 12 (4.9%) in Arm A vs 36 (14.7%) in Arm C
- Alkylating agents: 8 (3.3%) in Arm A vs 18 (7.3%) in Arm C
- CAR-T: 3 (1.2%) in Arm A vs 18 (7.3%) in Arm C
- Antimetabolite: 5 (2.1%) in Arm A vs 14 (5.7%) in Arm C

Stem cell transplant as subsequent therapy was reported in 1 patient in Arm A (0.4%), in no patients in Arm C and in 1 patient (1.6%) in Arm B.

CD20 status at baseline is shown in Table 11.

Table 11. CD20 Status at Baseline (All Randomised Subjects)

	Arm A (Epco 48 mg + R²) (N = 243)	Arm C (R²) (N = 245)	Arm A + Arm C (Total) (N = 488)	Arm B (Epco 24 mg + R²) (N = 61)	Overall (N = 549)
CD20 Status at Baseline, n (%)					
Positive	242 (99.6)	241 (98.4)	483 (99.0)	61 (100)	544 (99.1)
Negative	1 (0.4)	1 (0.4)	2 (0.4)	0	2 (0.4)
Missing	0	3 (1.2)	3 (0.6)	0	3 (0.5)

Numbers analysed

Analysis sets

The following population sets were used for the analyses:

- The Intent to Treat (ITT) Population includes all randomised subjects. Efficacy analyses were conducted on Arm A and C from the ITT population. The ITT Population was used for all efficacy analyses, disposition, demographics and baseline related summaries. Subjects were included in the analysis according to the treatment groups to which they were randomised.
- The mITT Population includes all subjects randomised to Arm A and Arm C after Protocol Version 2.0 (on or after 21 February 2023). Efficacy analyses were also conducted on the mITT population.
- The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. Subjects were included in the analysis according to the study drug they actually received, in subjects randomised to Arm A and Arm C.

Per the SAP, subjects in Arm B (Arm B closed enrolment in Protocol Version 2.0) were analysed separately from Arm A and Arm C. The ITT Population for Arm B includes all randomised subjects in Arm B.

No subjects were excluded from the efficacy analyses. The ITT included N=549 patients, of which N=243 in Arm A, N=245 in Arm C and N=61 in Arm B.

Outcomes and estimation

Dual Primary Efficacy Endpoints

PFS Based on IRC Assessment as Determined by Lugano Criteria

At the IA1 with DCO of 10 January 2025 that represents the primary analysis of the dual primary endpoint of BOR and PFS, PFS per IRC analysis was analysed for both efficacy and futility. The IF for PFS was 54% (98/181 IRC-assessed PFS events), with one-sided significance level of 0.0023. Epcoritamab 48 mg + R^2 led to a statistically significantly improvement in PFS compared with R^2 alone with an HR of 0.21 (95% CI: 0.13, 0.33; P-value < 0.0001) and PFS did not cross the pre-specified futility boundary of HR > 1.1.

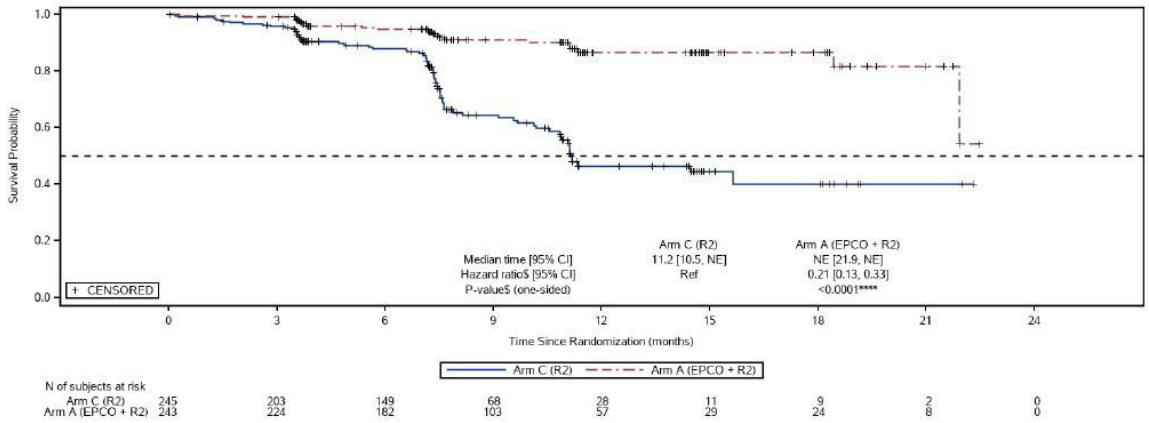
Table 12. Analysis of Progression-Free Survival Based on Lugano Criteria per IRC – ITT Population, DCO 10 Jan 2025

	Arm A (Epco 48 mg + R^2) (N=243)	**Arm C (R^2) (N=245)**
Number of subjects with events – N1 (%)	**23 (9.5)**	**75 (30.6)**
Progressive Disease	19 (82.6)	63 (84.0)
Death	4 (17.4)	12 (16.0)
Number of subjects censored – N1 (%)	**220 (90.5)**	**170 (69.4)**
No baseline assessment	15 (6.8)	22 (12.9)
No post-baseline assessment	2 (0.9)	5 (2.9)

Received NALT	3 (1.4)	21 (12.4)
Clinical cutoff	198 (90.0)	122 (71.8)
Subject withdrew consent	2 (0.9)	0
Duration of PFS (months)[a]		
Median follow up [95% CI][b]	7.7 [7.5, 11.0]	7.6 [7.4, 9.9]
25th (95% CI)[c]	21.9 [18.4, NE]	7.4 [7.2, 7.6]
Median (95% CI)[c]	NE [21.9, NE]	11.2 [10.5, NE]
75th (95% CI)[c]	NE [21.9, NE]	NE [NE, NE]
Min, Max[c]	0.03+, 22.5+	0.03+, 22.3+
KM estimate for PFS rate (%)		
4 months (95% CI)	95.8 [92.1, 97.8]	90.3 [85.4, 93.7]
8 months (95% CI)	90.9 [85.7, 94.3]	65.4 [57.1, 72.4]
12 months (95% CI)	86.7 [79.7, 91.4]	46.5 [36.8, 55.6]
16 months (95% CI)	86.7 [79.7, 91.4]	40.0 [27.9, 51.8]
Treatment comparison		
Stratified analysis[d]		
Log-rank p-value (one-sided)	<0.0001****	
Cox PH hazard ratio (95% CI)	0.21 [0.13, 0.33]	
Unstratified analysis		
Log-rank p-value (one-sided)	<0.0001****	
Cox PH hazard ratio (95% CI)	0.22 [0.14, 0.35]	

*P-value <0.05; **P-value <0.01; ***P-value <0.001; ****P-value <0.0001.

a. 25th, median, and 75th are KM estimates. If the min or max duration is a censored observation, a "+" is appended.
b. Based on reverse Kaplan-Meier estimate.
c. Based on Kaplan-Meier estimate.
d. Stratified by disease history and region. NE represents the value that is not evaluable.
The percentages under each category are calculated based on N1 of the corresponding category of each arm. Data Cutoff: 10Jan2025.



\+ Indicates censored observation.
$ Stratified by Disease Status/History (2L: PD ≤ 2 years from the date of initiation of 1L [POD24]. 2L: > 2 years from the date of initiation of 1L. 3L+: ≥ 6 months since end of last therapy. 3L: < 6 months since end of last therapy) and Region (US/Western Europe and Rest of World).
P-value is based on log-rank test. Hazard ratio is estimated using Cox proportional hazards model. Data Cutoff: 10Jan2025.

Figure 13. Kaplan-Meier Plot of Progression-Free Survival Based on Lugano Criteria per IRC Assessment by Treatment Group – ITT Population, DCO10 Jan 2025

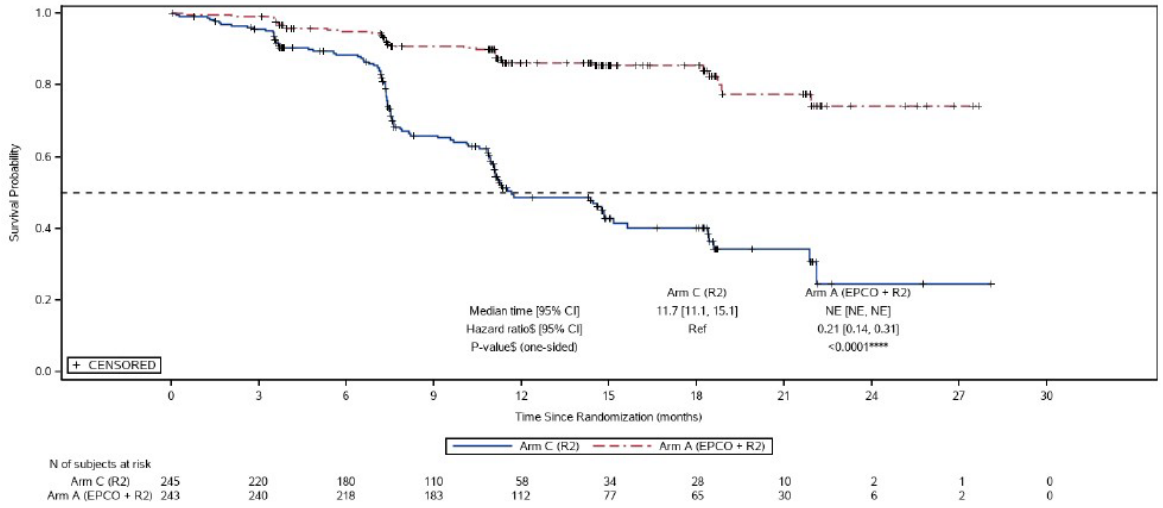
At the IA2 (DCO of 24 May 2025), epcoritamab 48 mg + R^2 demonstrated an improvement in PFS as assessed by IRC compared with R^2 alone with an HR of 0.21 (95% CI: 0.14, 0.31; nominal P-value < 0.0001; 78% information fraction). See Table 13 and *Figure 14*. PFS did not cross the pre-specified futility boundary of HR > 0.9262. Subgroup analyses are shown in Figure 16.

Table 13. Analysis of Progression-Free Survival Based on Lugano Criteria per IRC (ITT Population), DCO 24 May 2025

	Arm A (Epco 48 mg + R^2) (N = 243)	**Arm C (R^2) (N = 245)**
Progression-free survival (PFS)		
Number of subjects with events – N1 (%)	**35 (14.4)**	**106 (43.3)**
Progressive Disease	29 (82.9)	91 (85.8)
Death	6 (17.1)	15 (14.2)
Number of subjects censored – N1 (%)	**208 (85.6)**	**139 (56.7)**
No baseline assessment	0	1 (0.7)
No post baseline assessment	1 (0.5)	7 (5.0)
Received NALT	3 (1.4)	26 (18.7)
Clinical cutoff	202 (97.1)	105 (75.5)
Subject withdrew consent	2 (1.0)	0
Duration of PFS (months)[a]		
Median follow-up [95% CI][b]	14.4 [11.5, 14.8]	11.5 [11.1, 14.6]
Median [95% CI][c]	NE [NE, NE]	11.7 [11.1, 15.1]
KM estimate for PFS rate (%)		
4 months [95% CI]	95.8 [92.4, 97.7]	90.4 [85.8, 93.6]
8 months [95% CI]	90.8 [86.3, 93.9]	67.1 [60.0, 73.2]
12-months [95% CI]	86.3 [80.8, 90.3]	48.8 [40.9, 56.2]
16-months [95% CI]	85.5 [79.7, 89.7]	40.2 [31.8, 48.4]
Treatment comparison		
Stratified analysis[c]		
Log-rank p-value (one-sided)	< 0.0001****[d]	
Cox PH hazard ratio [95% CI]	0.21 [0.14, 0.31]	

a. Based on reverse KM estimate.
b. Based on KM estimate.
c. Stratified by disease history and region.
d. nominal p-value.

The percentages under each category are calculated based on N1 of the corresponding category of each arm
The unstratified analysis of PFS showed a Cox PH HR of 0.22 (95% CI 0.15, 0.32), log-rank p-value (one-sided) < 0.0001.
CI = confidence interval; IRC = independent review committee; ITT = intent to treat; KM = Kaplan-Meier; NALT = new anti-lymphoma therapy; NE = not evaluable; PFS = progression-free survival; PH = proportional hazards



\+ Indicates censored observation.
$ Stratified by Disease Status/History (2L: PD ≤ 2 years from the date of initiation of 1L [POD24]. 2L: > 2 years from the date of initiation of 1L. 3L+: ≥ 6 months since end of last therapy. 3L: < 6 months since end of last therapy) and Region (US/Western Europe and Rest of World).
*P-value <0.05; **P-value <0.01; ***P-value <0.001; ****P-value <0.0001.
P-value is based on log-rank test. Hazard ratio is estimated using Cox proportional hazards model.
Data Cutoff: 24 May 2025.

Figure 14. Kaplan-Meier Plot of Progression-Free Survival Based on Lugano Criteria per IRC Assessment by Treatment Group – ITT Population, DCO 24 May 2025

PFS sensitivity analyses were consistent to the PFS analyses at IA1 and IA2, including the PFS analysis ignoring the 2 or more consecutive missing/NE disease assessments prior to progression or death, and initiation of new anti-lymphoma therapy (at IA1); HR 0.20 [95% CI 0.13, 0.33] with a median PFS of NE [95% CI 21.9, NE] in Arm A and 11.2 [95% CI 10.5, NE] months in Arm C.

At IA1 the concordance in responder status (yes vs no) between the IRC and investigator assessments was overall 100% for Arm A, 94.0% for Arm C, and 97.0% across both. At IA 2 these numbers were 97.5%, 90.2% and 93.9%, respectively.

Overall Response Rate Based on IRC Assessment as Determined by Lugano Criteria

The primary analysis of the dual primary endpoint of BOR of CR or PR per IRC i.e., when the first 232 subjects randomised into the study (Arm A and Arm C) had at least 12 months (48 weeks) of follow-up from the date of randomisation was performed at the IA1 (DCO of 10 January 2025). ORR was significantly higher for epcoritamab 48 mg + R^2 (95.7%; 95% CI: 90.2, 98.6) compared with R^2 alone (81.0%; 95% CI: 72.7, 87.7) with a difference in rates of 14.9% (95% CI: 7.1, 22.8; P-value < 0.0001).

Reasons for NE responses were: 'Early treatment discontinuation due to AE (death, clinical progression, etc) prior to first response assessment' (arm A: 1; arm C: 4); 'Withdrew from study

without any treatment and without response assessment' (arm A: 0; arm C: 3); 'Early treatment discontinuation due to ineligibility prior to first response assessment' (arm A: 1, arm C: 2); 'Early treatment discontinuation due to second primary malignancy (confounding factor)' (arm A: 0, arm C: 1).

Table 14. Analysis of Disease Response Based on Lugano Criteria per IRC Assessment (ITT Population - First 232 Subjects from Arm A and Arm C), DCO 10 Jan 2025

	Arm A (Epco 48 mg + R^2) (N=116)	**Arm C (R^2) (N=116)**	**One-Sided p-value Arm A (Epco 48 mg + R^2) vs. Arm C (R^2)**
Overall response rate (BOR of CR + PR[a]) – n (%)	**111 (95.7)**	**94 (81.0)**	
(95% CI)[b]	[90.2, 98.6]	[72.7, 87.7]	
Diff in rates		**14.9**	**<0.0001****[c]**
(95% CI)[d]		[7.1, 22.8]	
Complete response rate (BOR of CR) – n (%)	**94 (81.0)**	**55 (47.4)**	
(95% CI)[b]	[72.7, 87.7]	[38.1, 56.9]	
Diff in rates		**33.5**	**<0.0001****[c]**
(95% CI)[d]		[22.2, 44.9]	
Best overall response (BOR) based on Lugano criteria - n (%)			
Complete response (CR)	94 (81.0)	55 (47.4)	
Partial response (PR)	17 (14.7)	39 (33.6)	
Stable disease (SD)	0	7 (6.0)	
Progressive disease (PD)	3 (2.6)	5 (4.3)	
Not evaluable (NE)[e]	2 (1.7)	10 (8.6)	
Unstratified CMH Rate difference using Mantel- Haenszel (MH) weight			
Overall response rate difference (BOR of CR + PR)		14.7	0.0002***
(95% CI)[d]		[6.6, 22.7]	
Complete response difference (BOR of CR)		33.6	<0.0001****
(95% CI)[d]		[22.1, 45.2]	
CR rate difference at the end of treatment (12 cycles)		40.5	<0.0001****
(95% CI)[d]		[28.8, 52.2]	

*P-value <0.05; **P-value <0.01; ***P-value <0.001; ****P-value <0.0001.

a. Include subjects who have best overall response of CR or PR.
b. 95% CI is from the exact binomial distribution (Clopper-Pearson exact Method).
c. P-value is from Cochran-Mantel-Haenszel test stratified by disease history and region. If a stratum sample size is less than 10, then merge it to the next higher stratum size and continue until the subsequent stratum size is 10 or more.
d. 95% CI is calculated from Mantel-Haenszel estimate and its variance.
e. Subjects with no post-baseline disease assessment are also included. Data Cutoff: 10Jan2025.

At the IA2 (DCO of 24 May 2025) in the ITT population, IRC-assessed ORR for Epcoritamab 48 mg + R^2 demonstrated an improvement compared with R^2, with a difference in rates of 16.0% (95% CI:

10.3, 21.7; nominal P-value < 0.0001 (Table 15)). Reasons for NE responses were: 'Early treatment discontinuation due to AE (death, clinical progression, etc) prior to first response assessment' (arm A: 3, arm C: 5); 'Withdrew from study without any treatment and without response assessment' (arm A: 0, arm C: 7); 'Early treatment discontinuation due to ineligibility prior to first response assessment' (arm A: 1, arm C: 3); 'Early treatment discontinuation due to hematopoietic transplant prior to first response assessment' (arm A: 0, arm C: 1); 'Early treatment discontinuation due to personal reason prior to first response assessment' (arm A: 0, arm C: 1); 'No measurable disease at baseline' (arm A: 0, arm C: 1). A forest plot of ORR for subgroup analyses is shown in Figure 17.

Table 15. Analysis of Disease Response Based on Lugano Criteria per IRC Assessment (ITT Population), DCO 24 May 2025

	Arm A (Epco 48 mg + R^2) (N = 243)	**Arm C (R^2) (N = 245)**	**One-Sided pvalue Arm A (Epco 48 mg + R^2) vs. Arm C (R^2)**
Overall response rate (BOR of CR + PR[a]) – n (%)	**231 (95.1)**	**194 (79.2)**	
[95% CI][b]	[91.5, 97.4]	[73.6, 84.1]	
Diff in rates		**16.0**	**< 0.0001**** [c]**
[95% CI][d]		[10.3, 21.7]	
Complete response rate (BOR of CR) – n (%)	**201 (82.7)**	**122 (49.8)**	
[95% CI][b]	[77.4, 87.3]	[43.4, 56.2]	
Diff in rates		**33.0**	**< 0.0001**** [c]**
[95% CI][d]		[25.3, 40.8]	
Best overall response (BOR) based on Lugano criteria - n (%)			
Complete response (CR)	201 (82.7)	122 (49.8)	
Partial response (PR)	30 (12.3)	72 (29.4)	
Stable disease (SD)	1 (0.4)	17 (6.9)	
Progressive disease (PD)	7 (2.9)	16 (6.5)	
Not evaluable (NE)[e]	4 (1.6)	18 (7.3)	

*P-value <0.05; **P-value <0.01; ***P-value <0.001; ****P-value <0.0001.
a. Include subjects who have best overall response of CR or PR.
b. 95% CI is from the exact binomial distribution (Clopper-Pearson exact Method).
c. P-value is from Cochran-Mantel-Haenszel test stratified by disease history and region. If a stratum sample size is less than 10, then merge it to the next higher stratum size and continue until the subsequent stratum size is 10 or more.
d. 95% CI is calculated from Mantel-Haenszel estimate and its variance.
e. Subjects with no post-baseline disease assessment are also included.
Data Cutoff: 24 May 2025.

Key Secondary Efficacy Endpoints

Complete Response During the Study Based on IRC Assessment

Table 16. Analysis of Disease Response Based on Lugano Criteria per IRC Assessment – ITT Population, DCO 10 Jan 2025

	Arm A (Epco 48 mg + R^2) (N=243)	**Arm C (R^2) (N=245)**	**One-Sided p-value Arm A (Epco 48 mg + R^2) vs. Arm C (R^2)**
Complete response rate (BOR of CR) – n (%)	**181 (74.5)**	**106 (43.3)**	

(95% CI)a	[68.5, 79.8]	[37.0, 49.7]	
Diff in rates		**31.3**	**<0.0001****[b]**
(95% CI)[c]		[23.1, 39.4]	
Best overall response (BOR) based on Lugano criteria - n (%)			
Complete response (CR)	181 (74.5)	106 (43.3)	
Partial response (PR)	35 (14.4)	75 (30.6)	
Stable disease (SD)	1 (0.4)	16 (6.5)	
Progressive disease (PD)	6 (2.5)	14 (5.7)	
Not evaluable[d]	20 (8.2)	34 (13.9)	

a. 95% CI is from the exact binomial distribution (Clopper-Pearson exact Method).
b. P-value is from Cochran-Mantel-Haenszel test stratified by disease history and region. If a stratum sample size is less than 10, then merge it to the next higher stratum size and continue until the subsequent stratum size is 10 or more.
c. 95% CI is calculated from Mantel-Haenszel estimate and its variance.
d. Subjects with no post-baseline disease assessment are also included. Data Cutoff: 10Jan2025.

In Table 14 the CR rate in the first 232 patients at IA1is shown and in Table 15 it is shown for IA2 in all randomised patients in Arm A and Arm C.

Overall Survival

At IA1 (DCO 10 Jan 2025) OS did not cross the pre-specified harm boundary of HR > 1.43, after a median OS follow-up of 10.4 months and 10.2 months in Arm A and Arm C, respectively.

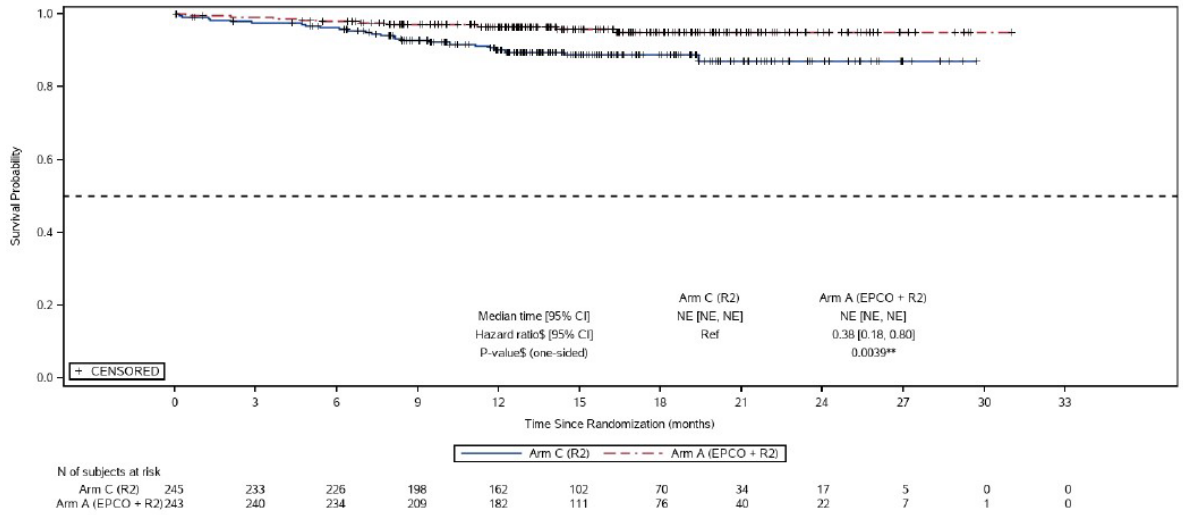
At the IA2 (DCO of 24 May 2025), the OS HR was 0.38 (95% CI: 0.18, 0.80; P-value = 0.0039) for Epcoritamab 48 mg + R^2 compared with R^2 alone (Table 17). OS did not cross the pre-specified boundary for statistical significance. OS did not cross the pre-specified futility boundary of HR > 1.05 and OS did not cross the pre-specified harm boundary of HR > 1.29.

Table 17. Analysis of Overall Survival (ITT Population), DCO 24 May 2025

	Arm A (Epco 48 mg + R^2) (N = 243)	**Arm C (R^2) (N = 245)**
Number of subjects with events – N1 (%)	**10 (4.1)**	**25 (10.2)**
Death	10 (100)	25 (100)
Number of subjects censored – N1 (%)	**233 (95.9)**	**220 (89.8)**
Alive	233 (100)	220 (100)
Time to death (months)[a]		
Median follow up [95% CI][b]	14.8 [14.0, 16.2]	14.6 [13.6, 15.6]
Median [95% CI][c]	NE [NE, NE]	NE [NE, NE]
Min, Max[c]	0.4, 31.0+	0.03+, 29.7+
KM estimate for OS rate (%)		
4 months [95% CI]	98.8 [96.2, 99.6]	97.5 [94.5, 98.9]
8 months [95% CI]	97.1 [93.9, 98.6]	94.1 [90.2, 96.4]
12 months [95% CI]	96.6 [93.2, 98.3]	90.1 [85.4, 93.4]
16 months [95% CI]	95.8 [92.0, 97.8]	88.8 [83.6, 92.4]
20 months [95% CI]	94.9 [90.3, 97.3]	87.0 [80.3, 91.5]
Treatment comparison		
Stratified analysis[d]		
Log-rank p-value (one-sided)	0.0039**	
Cox PH hazard ratio [95% CI]	0.38 [0.18, 0.80]	
Unstratified analysis		
Log-rank p-value (one-sided)	0.0035**	

	Arm A (Epco 48 mg + R²) (N = 243)	Arm C (R²) (N = 245)
Cox PH hazard ratio [95% CI]	0.38 [0.18, 0.79]	

*P-value <0.05; **P-value <0.01; ***P-value <0.001; ****P-value <0.0001.
a. 25th, median, and 75th are KM estimates. If the min or max duration is a censored observation, a "+" is appended.
b. Based on reverse Kaplan-Meier estimate.
c. Based on Kaplan-Meier estimate.
d. Stratified by disease history and region.
NE represents the value that is not evaluable.
The percentages under each category are calculated based on N1 of the corresponding category of each arm.
Data Cutoff: 24 May 2025.



+ Indicates censored observation.
$ Stratified by Disease Status/History (2L: PD ≤ 2 years from the date of initiation of 1L [POD24]. 2L: > 2 years from the date of initiation of 1L. 3L+: ≥ 6 months since end of last therapy. 3L: < 6 months since end of last therapy) and Region (US/Western Europe and Rest of World).
*P-value <0.05; **P-value <0.01; ***P-value <0.001; ****P-value <0.0001.
P-value is based on log-rank test. Hazard ratio is estimated using Cox proportional hazards model.
Figure 15 Kaplan-Meier Plot of Overall Survival by Treatment Group (ITT Population), DCO 24 May 2025

MRD

At IA2 as per the pre-specified hierarchical testing procedure, OS did not meet statistical significance and therefore MRD negativity analyses were not performed.

Other Secondary Efficacy Endpoints

Other Secondary efficacy endpoints which were IRC assessed at IA2 are shown in Table 18.

Table 18. Overview of IRC-Assessed Secondary Efficacy endpoints in Study M20-638 – ITT Population, DCO 24 May 2025

	Arm A (Epco 48 mg + R²) (N = 243)	Arm C (R²) (N = 245)
CR rate at the end of treatment (12 cycles) – n (%)	**156 (64.2)**	**68 (27.8)**
[95% CI][f]	[57.8, 70.2]	[22.2, 33.8]

	Arm A (Epco 48 mg + R²) (N = 243)	Arm C (R²) (N = 245)
Number of subjects censored – N1 (%)	**206 (89.2)**	**120 (61.9)**
Received NALT	2 (1.0)	17 (14.2)
Clinical cutoff	202 (98.1)	103 (85.8)
Subject withdrew consent	2 (1.0)	0
DOR (months)[a]		
Number of subjects who are responders	**231**	**194**
Median follow-up [95% CI][b]	10.6 [8.1, 11.0]	10.6 [7.6, 11.0]
Median [95% CI][c]	NE [NE, NE]	11.5 [8.5, 18.6]
Treatment comparison		
Stratified analysis[d]		
Log-rank p-value (one-sided)	< 0.0001****[h]	
Cox PH hazard ratio [95% CI]	0.19 [0.12, 0.30]	
Duration of complete response (DOCR)		
Number of subjects who are responders	**201**	**122**
DOCR (months)[a]		
Median follow-up [95% CI][b]	7.9 [7.6, 10.6]	7.6 [7.4, 10.7]
Treatment comparison		
Stratified analysis[d]		
Log-rank p-value (one-sided)	< 0.0001****[e]	
Cox PH hazard ratio [95% CI]	0.21 [0.11, 0.39]	
Time to response (TTR)		
Median (Range)	3.71 (1.5, 7.5)	3.68 (0.8, 7.0)
Time to complete response (TTCR)		
Median (Range)	3.75 (2.0, 22.4)	3.75 (2.4, 14.8)
Time to progression (TTP)		
Median follow-up [95% CI][b]	14.3 [11.4, 14.8]	11.3 [11.0, 14.4]
Stratified analysis[d]		
Log-rank p-value (one-sided)	< 0.0001****[e]	
Cox PH hazard ratio [95% CI]	0.19 [0.13, 0.29]	
Time to next anti-lymphoma treatment (TTNLT)		
Number of subjects with events – N1 (%)	**15 (6.2)**	**77 (31.4)**
Received new anti-lymphoma therapy	15 (100)	75 (97.4)
Death due to disease progression	0	2 (2.6)
Number of subjects censored – N1 (%)	**228 (93.8)**	**168 (68.6)**
Death due to other reasons	7 (3.1)	14 (8.3)
Alive	221 (96.9)	154 (91.7)

	Arm A (Epco 48 mg + R²) (N = 243)	Arm C (R²) (N = 245)
TTNLT (months)[a]		
Median [95% CI][c]	NE [NE, NE]	24.3 [18.2, NE]
Treatment comparison		
Stratified analysis[d]		
Log-rank p-value (one-sided)	< 0.0001****[e]	
Cox PH hazard ratio [95% CI]	0.15 [0.09, 0.27]	
Event free survival (EFS)		
Number of subjects with events – N1 (%)	**35 (14.4)**	**134 (54.7)**
Progressive disease	27 (77.1)	101 (75.4)
Death	6 (17.1)	14 (10.4)
NALT	2 (5.7)	19 (14.2)
Number of subjects censored – N1 (%)	**208 (85.6)**	**111 (45.3)**
No post-baseline assessment	1 (0.5)	8 (7.2)
Clinical cutoff	205 (98.6)	102 (91.9)
Subject withdrew consent	2 (1.0)	1 (0.9)
Event-free survival (months)[a]		
Median follow up [95% CI][b]	14.4 [11.5, 14.8]	14.6 [11.5, 14.9]
Median [95% CI][c]	NE [NE, NE]	11.0 [9.1, 12.5]
Treatment comparison		
Stratified analysis[d]		
Log-rank p-value (one-sided)	< 0.0001****	
Cox PH hazard ratio [95% CI]	0.17 [0.12, 0.25]	

BOR = best overall response; CI = confidence interval; CR = complete response; Diff = difference; IRC = independent review committee; KM = Kaplan-Meier; NALT = new anti-lymphoma therapy; PR = partial response
a. 25th, median, and 75th are KM estimates. If the min or max duration is a censored observation, a "+" is appended.
b. Based on reverse KM estimate.
c. Based on KM estimate.
d. Stratified by disease history and region.
e. nominal p-value.
f. 95% CI is from the exact binomial distribution (Clopper-Pearson exact Method).
*P-value < 0.05; **P-value < 0.01; ***P-value < 0.001; ****P-value < 0.0001.
NE represents the value that is not evaluable.
The percentages under each category are calculated based on N1 of the corresponding category of each arm.
Data Cutoff: 24 May 2025

Investigator assessed efficacy endpoints

Investigator assessed efficacy was consistent with IRC-assessed efficacy in both Ias (data not shown).

PROs

At IA2, a higher mean change from baseline was observed for the first 4 cycles in Arm A compared to Arm C, from C5 onward FACT-Lym scores were generally comparable between Arm A and Arm C.

Mean changes from baseline in EQ-5D-5L Index value and VAS score were generally comparable between Arm A and Arm C. PGIC and PGIS outcomes were generally comparable between Arm A and Arm C.

Efficacy analyses in the mITT

The mITT included N= 180 patients is Arm A and N=178 patients in Arm C. The PFS analyses at IA1 for the mITT showed a PFS HR of 0.17 [95% CI 0.09, 0.32] favouring Arm A with a median PFS of NE [95% CI NE, NE] in Arm A versus 10.1 [95% CI 7.6, NE] in Arm C.
At IA2 the PFS HR was 0.23 [95% CI 0.14, 0.37] with a median PFS of NE [95%CI NE, NE] in Arm A versus 11.5 [95%CI 11.0, 15.1] in Arm C.

Efficacy analyses in Arm B

A summary of the main efficacy results in Arm B at IA2 is shown in Table 19 and Table 20.

Table 19. Analysis of Disease Response Based on Lugano Criteria per IRC Assessment (ITT Population - Arm B), DCO 24 May 2025

	Arm B (Epco 24 mg + R²) (N = 61)
Overall response rate (BOR of CR + PR[a]) – n (%)	**57 (93.4)**
[95% CI][b]	[84.1, 98.2]
Complete response rate (BOR of CR) – n (%)	**49 (80.3)**
[95% CI][b]	[68.2, 89.4]
Best overall response (BOR) based on Lugano criteria - n (%)	
Complete response (CR)	49 (80.3)
Partial response (PR)	8 (13.1)
Stable disease (SD)	2 (3.3)
Progressive disease (PD)	1 (1.6)
Not evaluable (NE)[c]	1 (1.6)

a. Include subjects who have best overall response of CR or PR.
b. 95% CI is from the exact binomial distribution (Clopper-Pearson exact Method).
Data Cutoff: 24 May 2025.

Table 20. Analysis of Time to Event Endpoints Based on Lugano Criteria per IRC Assessment (ITT Population - Arm B), DCO 24 May 2025

	Arm B (Epco 24 mg + R²) (N = 61)
Progression-free survival	
Number of subjects with events – N1 (%)	15 (24.6)
Duration of PFS (months)[a]	
Median follow up [95% CI][b]	21.9 [21.6, 22.1]
Median [95% CI][c]	NE [22.6, NE]
Duration of response	
DOR (months)[a]	
Median follow up [95% CI][b]	18.2 [17.3, 18.4]
Median [95% CI][c]	NE [18.8, NE]

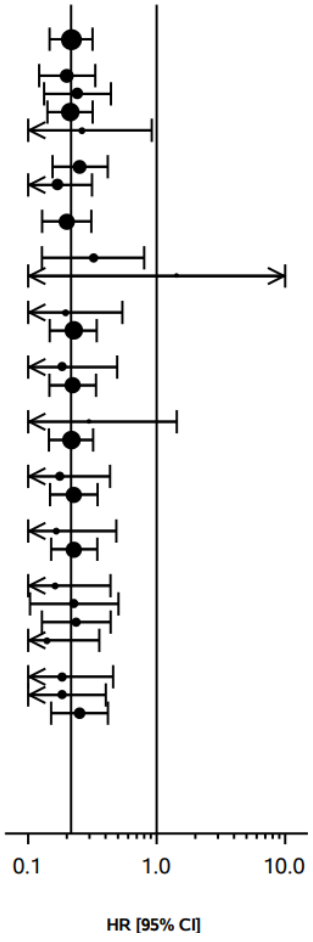
a. 25th, Median, and 75th are Kaplan-Meier estimates. If the min or max duration is a censored observation, a '+' is appended.
b. Based on reverse Kaplan-Meier estimate.
c. Based on Kaplan-Meier estimate.
NE represents the value that is not evaluable.
The percentages under each category are calculated based on N1 of the corresponding category of each arm. Data Cutoff: 24 May 2025.

After a median OS follow-up of 23.0 months, median OS was not reached (95% CI: NE, NE). The estimated percentages of subjects remaining alive at 12, 16, and 20 months were 93.4%, 93.4% and 91.6%, respectively.

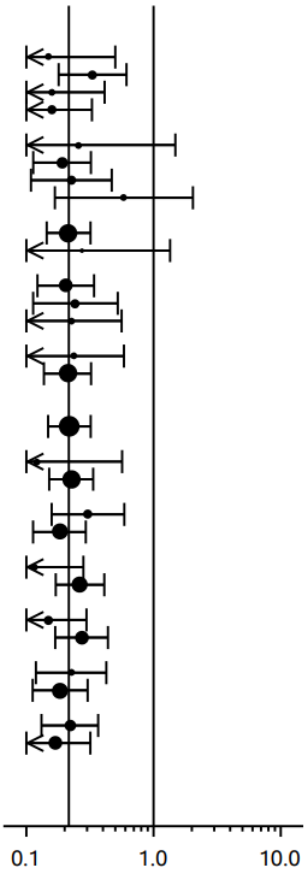
Ancillary analyses

Forest plots for subgroup analyses of PFS and ORR at IA 2are shown in Figure 16 and Figure 17, respectively.

	Arm A (EPCO + R2)		Arm C (R2)		HR [95% CI] Arm A vs. Arm C
	Event/N (%)	Median (Months) [95% CI]	Event/N (%)	Median (Months) [95% CI]	
All subjects	35/243 (14.4)	NE [NE, NE]	106/245 (43.3)	11.7 [11.1, 15.1]	0.22 [0.15, 0.32]
Age (years)					
< 65	21/155 (13.5)	NE [NE, NE]	58/139 (41.7)	11.3 [10.9, 18.6]	0.20 [0.12, 0.33]
>= 65	14/88 (15.9)	NE [18.9, NE]	48/106 (45.3)	14.5 [7.9, 18.4]	0.24 [0.13, 0.44]
< 75	32/223 (14.3)	NE [NE, NE]	91/210 (43.3)	11.3 [11.0, 15.6]	0.21 [0.14, 0.32]
>= 75	3/20 (15.0)	NE [NE, NE]	15/35 (42.9)	14.5 [7.5, NE]	0.26 [0.08, 0.92]
Sex					
Male	23/139 (16.5)	NE [NE, NE]	54/138 (39.1)	14.5 [11.1, 21.8]	0.25 [0.15, 0.42]
Female	12/104 (11.5)	NE [NE, NE]	52/107 (48.6)	11.3 [9.7, 15.1]	0.17 [0.09, 0.31]
Race					
White	26/168 (15.5)	NE [NE, NE]	88/184 (47.8)	11.3 [10.9, 14.8]	0.20 [0.13, 0.31]
Black or African American	1/6 (16.7)	NE [3.8, NE]	0/2	NE [NE, NE]	>999.999 [<0.001, NE
Asian	7/63 (11.1)	NE [14.5, NE]	14/54 (25.9)	18.4 [10.9, NE]	0.32 [0.13, 0.80]
Other	1/1 (100)	11.1 [NE, NE]	2/2 (100)	14.4 [6.8, NE]	1.41 [0.08, 23.57]
Ethnicity					
Hispanic or Latino	5/29 (17.2)	NE [18.7, NE]	15/28 (53.6)	14.8 [7.6, 18.6]	0.19 [0.07, 0.54]
Not Hispanic or Latino	29/209 (13.9)	NE [NE, NE]	90/215 (41.9)	11.7 [11.1, 18.4]	0.22 [0.15, 0.34]
Region					
US/Western Europe	5/58 (8.6)	NE [NE, NE]	18/60 (30.0)	NE [11.1, NE]	0.18 [0.07, 0.49]
Rest of World	30/185 (16.2)	NE [NE, NE]	88/185 (47.6)	11.2 [10.9, 14.8]	0.22 [0.15, 0.34]
North America (US/Canada/Puerto Rico)					
Yes	2/14 (14.3)	NE [7.3, NE]	7/19 (36.8)	8.2 [6.6, NE]	0.30 [0.06, 1.43]
No	33/229 (14.4)	NE [NE, NE]	99/226 (43.8)	11.7 [11.1, 15.6]	0.22 [0.14, 0.32]
North America/Western Europe					
Yes	6/62 (9.7)	NE [NE, NE]	23/67 (34.3)	15.1 [10.8, NE]	0.18 [0.07, 0.43]
No	29/181 (16.0)	NE [NE, NE]	83/178 (46.6)	11.3 [10.9, 14.8]	0.23 [0.15, 0.35]
Ann Arbor stage					
II	4/37 (10.8)	NE [NE, NE]	21/44 (47.7)	11.2 [9.6, NE]	0.16 [0.06, 0.49]
III+IV	31/206 (15.0)	NE [NE, NE]	85/201 (42.3)	11.7 [11.0, 18.4]	0.23 [0.15, 0.35]
FLIPI-1 score at diagnosis					
0-1	5/42 (11.9)	NE [NE, NE]	20/46 (43.5)	11.2 [10.1, 18.6]	0.16 [0.06, 0.44]
2	8/68 (11.8)	NE [NE, NE]	27/73 (37.0)	15.6 [10.9, NE]	0.23 [0.10, 0.50]
3-5	14/85 (16.5)	NE [21.9, NE]	39/85 (45.9)	14.5 [7.6, NE]	0.24 [0.13, 0.44]
Unknown	8/46 (17.4)	NE [18.2, NE]	18/36 (50.0)	11.0 [7.6, 11.7]	0.14 [0.05, 0.36]
FLIPI-1 score at baseline					
0-1	6/63 (9.5)	NE [NE, NE]	19/56 (33.9)	NE [11.1, NE]	0.18 [0.07, 0.46]
2	8/79 (10.1)	NE [18.9, NE]	30/76 (39.5)	15.1 [11.2, 21.8]	0.18 [0.08, 0.40]
3-5	21/100 (21.0)	NE [21.9, NE]	57/113 (50.4)	10.8 [7.6, 14.4]	0.25 [0.15, 0.42]
Unknown	0/1	NE [NE, NE]	0/0	NE [NE, NE]	NE [NE, NE]



	Arm A (EPCO + R2)		Arm C (R2)		HR [95% CI] Arm A vs. Arm C
	Event/N (%)	Median (Months) [95% CI]	Event/N (%)	Median (Months) [95% CI]	
FLIPI-2 score at diagnosis					
0	4/27 (14.8)	NE [NE, NE]	10/21 (47.6)	11.1 [7.2, NE]	0.15 [0.04, 0.50]
1-2	14/85 (16.5)	NE [18.7, NE]	38/91 (41.8)	14.6 [10.9, NE]	0.33 [0.18, 0.61]
3-5	5/45 (11.1)	NE [NE, NE]	29/63 (46.0)	14.4 [7.4, 21.8]	0.16 [0.06, 0.41]
Unknown	12/82 (14.6)	NE [21.9, NE]	26/62 (41.9)	11.1 [7.9, 14.8]	0.16 [0.08, 0.33]
FLIPI-2 score at baseline					
0	2/23 (8.7)	NE [NE, NE]	4/24 (16.7)	NE [10.9, NE]	0.26 [0.04, 1.48]
1-2	19/144 (13.2)	NE [NE, NE]	57/118 (48.3)	11.3 [10.8, 18.4]	0.19 [0.11, 0.32]
3-5	9/51 (17.6)	NE [18.7, NE]	40/85 (47.1)	11.3 [7.4, 15.1]	0.23 [0.11, 0.47]
Unknown	5/25 (20.0)	18.9 [18.9, NE]	5/18 (27.8)	11.7 [7.5, NE]	0.58 [0.17, 2.04]
Baseline ECOG performance status					
<= 1	33/238 (13.9)	NE [NE, NE]	99/238 (41.6)	14.4 [11.1, 18.4]	0.21 [0.14, 0.32]
> 1	2/5 (40.0)	NE [2.1, NE]	7/7 (100)	3.5 [0.2, NE]	0.28 [0.06, 1.35]
Number of prior anti-lymphoma therapies					
1	20/145 (13.8)	NE [NE, NE]	58/141 (41.1)	14.4 [10.9, 18.4]	0.20 [0.12, 0.34]
2	9/58 (15.5)	NE [NE, NE]	26/61 (42.6)	11.1 [8.1, NE]	0.24 [0.11, 0.52]
>= 3	6/40 (15.0)	NE [NE, NE]	22/43 (51.2)	11.5 [8.2, NE]	0.23 [0.09, 0.56]
B symptoms at baseline/screening					
Yes	7/34 (20.6)	NE [18.7, NE]	16/34 (47.1)	10.9 [7.3, NE]	0.24 [0.10, 0.58]
No	28/209 (13.4)	NE [NE, NE]	90/211 (42.7)	14.4 [11.1, 15.6]	0.21 [0.14, 0.32]
Prior CAR-T					
Yes	0/1	NE [NE, NE]	1/1 (100)	8.2 [NE, NE]	<0.001 [<0.001, NE]
No	35/242 (14.5)	NE [NE, NE]	105/244 (43.0)	11.7 [11.1, 15.1]	0.22 [0.15, 0.32]
Prior ASCT					
Yes	2/23 (8.7)	NE [NE, NE]	9/18 (50.0)	22.1 [7.2, NE]	0.12 [0.03, 0.57]
No	33/220 (15.0)	NE [NE, NE]	97/227 (42.7)	11.7 [11.1, 14.8]	0.23 [0.15, 0.34]
Positive bone marrow involvement					
Yes	13/69 (18.8)	NE [18.7, NE]	29/67 (43.3)	14.8 [7.9, NE]	0.31 [0.16, 0.59]
No	22/174 (12.6)	NE [NE, NE]	77/178 (43.3)	11.3 [10.9, 15.1]	0.18 [0.11, 0.29]
Bulky disease per IRC (nodal or extranodal >= 7 cm)					
Yes	6/47 (12.8)	NE [NE, NE]	31/61 (50.8)	7.6 [7.4, 11.2]	0.12 [0.05, 0.28]
No	28/191 (14.7)	NE [NE, NE]	71/176 (40.3)	14.8 [11.2, 21.8]	0.26 [0.17, 0.41]
Bulky disease per IRC (nodal or extranodal > 6 cm)					
Yes	10/76 (13.2)	NE [NE, NE]	43/84 (51.2)	10.9 [7.5, 14.8]	0.15 [0.07, 0.30]
No	24/162 (14.8)	NE [NE, NE]	59/153 (38.6)	14.6 [11.2, 22.1]	0.27 [0.17, 0.44]
Time since most recent anti-CD20					
< 6 months	15/50 (30.0)	NE [18.2, NE]	32/55 (58.2)	7.5 [6.8, 7.6]	0.22 [0.12, 0.43]
>= 6 months	20/193 (10.4)	NE [NE, NE]	73/189 (38.6)	15.1 [11.7, 21.8]	0.18 [0.11, 0.30]
POD24					
<= 2 years	22/106 (20.8)	NE [21.9, NE]	47/93 (50.5)	9.6 [7.5, 11.2]	0.22 [0.13, 0.37]
> 2 years	12/131 (9.2)	NE [NE, NE]	54/144 (37.5)	18.4 [11.7, 22.1]	0.17 [0.09, 0.32]



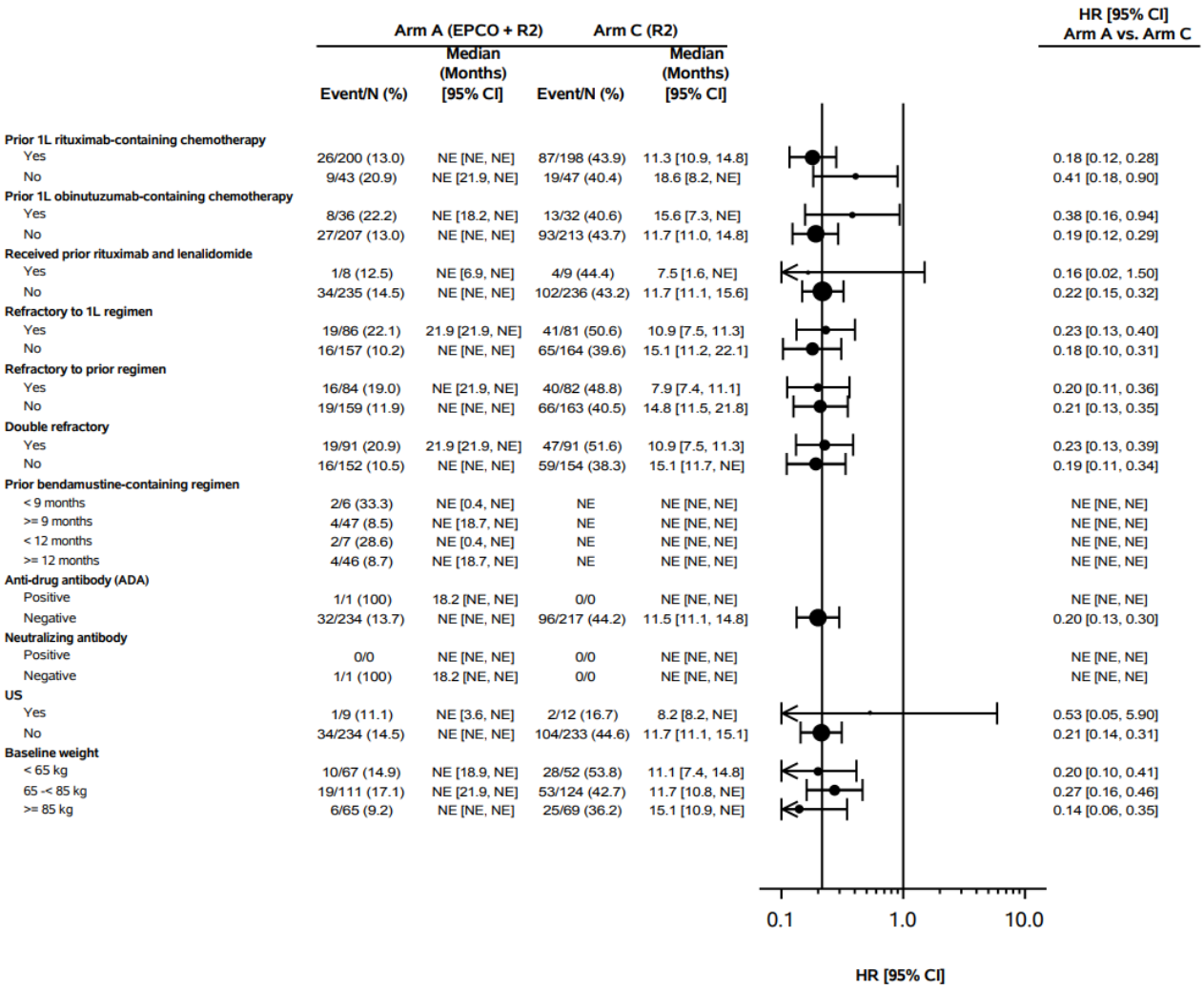
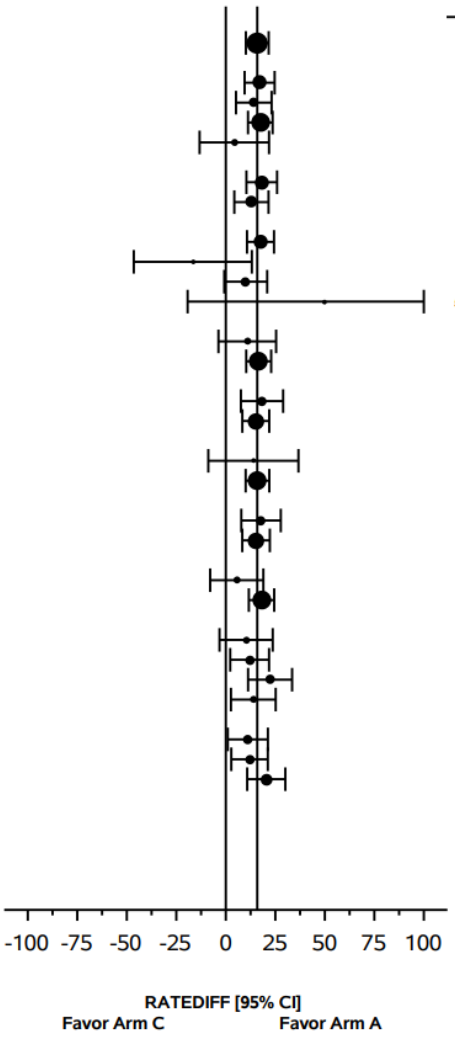
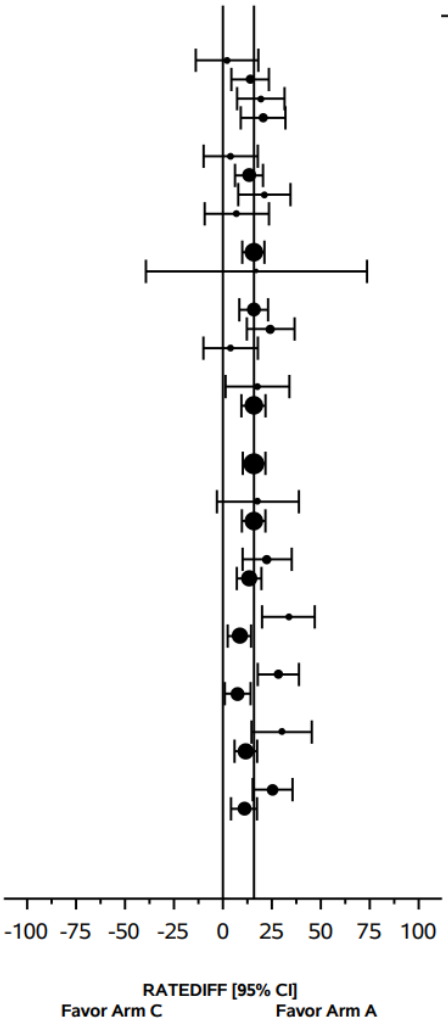


Figure 16. Forest Plot of Progression-free Survival (PFS) Based on Lugano Criteria per IRC Assessment: Hazard Ratio and 95%, DCO 24 May 2025

	Arm A (EPCO + R2) Responder/N (%)	Arm C (R2) Responder/N (%)	RATEDIFF [95% CI] Arm A vs. Arm C
All subjects	231/243 (95.1)	194/245 (79.2)	15.88 [10.11, 21.65]
Age (years)			
< 65	148/155 (95.5)	109/139 (78.4)	17.07 [9.49, 24.65]
>= 65	83/88 (94.3)	85/106 (80.2)	14.13 [5.13, 23.13]
< 75	213/223 (95.5)	164/210 (78.1)	17.42 [11.20, 23.64]
>= 75	18/20 (90.0)	30/35 (85.7)	4.29 [-13.24, 21.81]
Sex			
Male	133/139 (95.7)	107/138 (77.5)	18.15 [10.41, 25.89]
Female	98/104 (94.2)	87/107 (81.3)	12.92 [4.28, 21.56]
Race			
White	160/168 (95.2)	143/184 (77.7)	17.52 [10.70, 24.34]
Black or African American	5/6 (83.3)	2/2 (100)	-16.67 [-46.49, 13.15]
Asian	60/63 (95.2)	46/54 (85.2)	10.05 [-0.78, 20.89]
Other	1/1 (100)	1/2 (50.0)	50.00 [-19.30, 100.00]
Ethnicity			
Hispanic or Latino	28/29 (96.6)	24/28 (85.7)	10.84 [-3.73, 25.40]
Not Hispanic or Latino	198/209 (94.7)	168/215 (78.1)	16.60 [10.30, 22.90]
Region			
US/Western Europe	57/58 (98.3)	48/60 (80.0)	18.28 [7.61, 28.94]
Rest of World	174/185 (94.1)	146/185 (78.9)	15.14 [8.34, 21.93]
North America (US/Canada/Puerto Rico)			
Yes	13/14 (92.9)	15/19 (78.9)	13.91 [-8.85, 36.67]
No	218/229 (95.2)	179/226 (79.2)	15.99 [10.02, 21.97]
North America/Western Europe			
Yes	61/62 (98.4)	54/67 (80.6)	17.79 [7.82, 27.76]
No	170/181 (93.9)	140/178 (78.7)	15.27 [8.32, 22.22]
Ann Arbor stage			
II	34/37 (91.9)	38/44 (86.4)	5.53 [-7.89, 18.95]
III+IV	197/206 (95.6)	156/201 (77.6)	18.02 [11.62, 24.42]
FLIPI-1 score at diagnosis			
0-1	39/42 (92.9)	38/46 (82.6)	10.25 [-3.19, 23.69]
2	65/68 (95.6)	61/73 (83.6)	12.03 [2.22, 21.83]
3-5	79/85 (92.9)	60/85 (70.6)	22.35 [11.24, 33.46]
Unknown	46/46 (100)	31/36 (86.1)	13.89 [2.59, 25.19]
FLIPI-1 score at baseline			
0-1	61/63 (96.8)	48/56 (85.7)	11.11 [0.98, 21.25]
2	76/79 (96.2)	64/76 (84.2)	11.99 [2.77, 21.21]
3-5	93/100 (93.0)	82/113 (72.6)	20.43 [10.81, 30.06]
Unknown	1/1 (100)	0/0	NE [NE, NE]



	Arm A (EPCO + R2) Responder/N (%)	Arm C (R2) Responder/N (%)	RATEDIFF [95% CI] Arm A vs. Arm C
FLIPI-2 score at diagnosis			
0	25/27 (92.6)	19/21 (90.5)	2.12 [-13.86, 18.09]
1-2	80/85 (94.1)	73/91 (80.2)	13.90 [4.31, 23.49]
3-5	43/45 (95.6)	48/63 (76.2)	19.37 [7.25, 31.48]
Unknown	79/82 (96.3)	47/62 (75.8)	20.54 [9.13, 31.94]
FLIPI-2 score at baseline			
0	22/23 (95.7)	22/24 (91.7)	3.99 [-9.86, 17.83]
1-2	140/144 (97.2)	99/118 (83.9)	13.32 [6.17, 20.48]
3-5	45/51 (88.2)	57/85 (67.1)	21.18 [7.83, 34.52]
Unknown	24/25 (96.0)	16/18 (88.9)	7.11 [-9.31, 23.54]
Baseline ECOG performance status			
<= 1	228/238 (95.8)	191/238 (80.3)	15.55 [9.88, 21.21]
> 1	3/5 (60.0)	3/7 (42.9)	17.14 [-39.32, 73.60]
Number of prior anti-lymphoma therapies			
1	139/145 (95.9)	113/141 (80.1)	15.72 [8.38, 23.06]
2	56/58 (96.6)	44/61 (72.1)	24.42 [12.23, 36.61]
>= 3	36/40 (90.0)	37/43 (86.0)	3.95 [-9.96, 17.87]
B symptoms at baseline/screening			
Yes	32/34 (94.1)	26/34 (76.5)	17.65 [1.34, 33.95]
No	199/209 (95.2)	168/211 (79.6)	15.59 [9.44, 21.75]
Prior CAR-T			
Yes	1/1 (100)	1/1 (100)	NE [NE, NE]
No	230/242 (95.0)	193/244 (79.1)	15.94 [10.15, 21.73]
Prior ASCT			
Yes	22/23 (95.7)	14/18 (77.8)	17.87 [-3.06, 38.81]
No	209/220 (95.0)	180/227 (79.3)	15.70 [9.70, 21.71]
Positive bone marrow involvement			
Yes	64/69 (92.8)	47/67 (70.1)	22.60 [10.06, 35.15]
No	167/174 (96.0)	147/178 (82.6)	13.39 [7.10, 19.68]
Bulky disease per IRC (nodal or extranodal >= 7 cm)			
Yes	45/47 (95.7)	38/61 (62.3)	33.45 [19.99, 46.91]
No	181/191 (94.8)	152/176 (86.4)	8.40 [2.43, 14.37]
Bulky disease per IRC (nodal or extranodal > 6 cm)			
Yes	74/76 (97.4)	58/84 (69.0)	28.32 [17.80, 38.84]
No	152/162 (93.8)	132/153 (86.3)	7.55 [0.96, 14.15]
Time since most recent anti-CD20			
< 6 months	45/50 (90.0)	33/55 (60.0)	30.00 [14.61, 45.39]
>= 6 months	186/193 (96.4)	160/189 (84.7)	11.72 [5.94, 17.49]
POD24			
<= 2 years	101/106 (95.3)	65/93 (69.9)	25.39 [15.23, 35.55]
> 2 years	126/131 (96.2)	123/144 (85.4)	10.77 [4.13, 17.40]



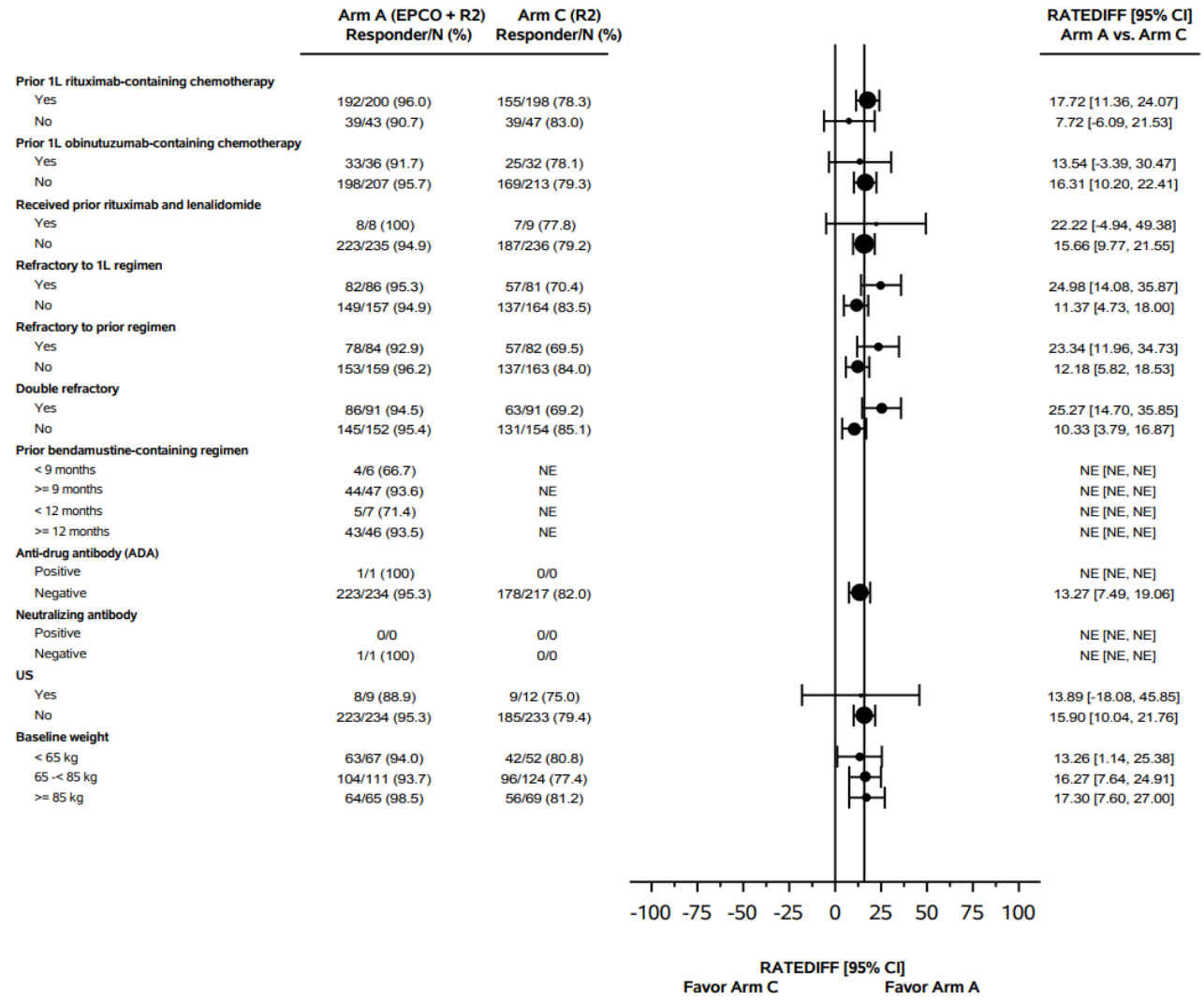


Figure 17. Forest Plot of Overall Response Rate (ORR) Based on Lugano Criteria per IRC Assessment: Rate Difference, DCO 25 Jan 2025

Summary of main study

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

Table 21. Summary of Efficacy for Study M20-638

Title: A Phase 3, Open-Label Study to Evaluate Safety and Efficacy of Epcoritamab in Combination with Rituximab and Lenalidomide (R^2) compared to R^2 in Subjects with Relapsed or Refractory Follicular Lymphoma (EPCORE™ FL-1)	
Study identifier	M20-638 EU CT 2023-505628-67
Design	Open label, randomised, Phase 3 trial of epcoritamab in combination with R^2 compared to R^2 alone in subjects with R/R FL after at least one prior anti-lymphoma regimen.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		First subject first visit: 20 September 2022 The study is still ongoing. DCO date for this submission is 24 May 2025. Not applicable
Hypothesis	Superiority		
Treatments groups	Arm A		Epcoritamab 48 mg in combination with R^2, up to 12 cycles of 28 days, N=243
	Arm B		Epcoritamab 24 mg in combination with R^2 up to 12 cycles of 28 days, N=61. Arm B was closed to enrollment with protocol version 2.0
	Arm C		R^2 alone, up to 12 cycles of 28 days, N=245
Endpoints and definitions	Dual primary endpoint: Progression free survival	PFS	Defined as the duration from the date of randomisation to the date of disease progression determined per Lugano criteria by the IRC, or death, whichever occurs first.
	Dual primary endpoint: Best overall response	BOR	ORR, defined as the proportion of subjects with BOR of CR or PR as assessed per Lugano criteria by an IRC. ORR is determined when the first 232 subjects randomised into the study (Arm A and Arm C) had at least 12 months (48 weeks) of follow-up from the date of randomization.
	Key secondary endpoint: complete response	CR	Defined as the proportion of subjects who achieve a CR determined per Lugano criteria, as assessed by the IRC prior to the initiation of subsequent anti-lymphoma therapy.
	Key secondary endpoint: overall survival	OS	Defined as the duration from the date of randomization to the date of the subject's death.
	Key secondary endpoint: MRD negativity	MRD negativity	Defined as the proportion of subjects who achieve MRD negative status prior to the initiation of subsequent anti-lymphoma therapy.
Database lock	N/A (Data cutoff for the 1st interim analysis: 10 Jan 2025)		

Results and Analysis

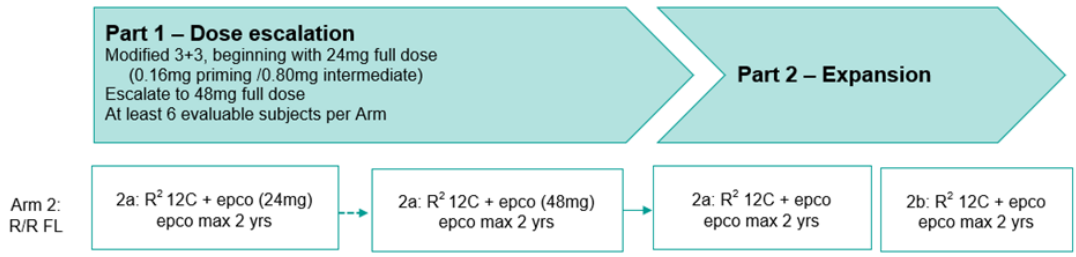
Analysis description	**Primary Analysis**		
Analysis population and time point description	For interim analysis #1 (IA1), all efficacy results except OS were assessed in the ITT population in Arm A versus Arm C. The DCO is 10 Jan 2025. OS was formally tested at IA2, DCO 24 May 2025.		
Descriptive statistics and estimate variability	Treatment group	**Arm A** **(Epco 48 mg + R^2)**	**Arm C** **(R^2)**

	Number of subjects	243	245
	Median PFS [95% CI]	NE [21.9, NE]	11.2 [10.5, NE]
	BOR rate (%) [95% CI] (in first 232 subjects)	N=116 95.7% [90.2, 98.6]	N=116 81.0% [37.0, 49.7]
	CR rate (%) [95% CI]	74.5% [68.5, 79.8]	47.4% [38.1, 56.9]
	Median OS* [95% CI]	NE [NE, NE]	NE [NE, NE]
	MRD negativity	NA	NA
Effect estimate per comparison	Dual primary endpoint PFS	Comparison groups	Arm A vs Arm C
		HR	0.21
		95%CI	[0.13, 0.33]
		P-value	< 0.0001
	Dual Primary endpoint BOR	Comparison groups	Arm A vs Arm C
		ORR difference	14.9
		95%CI	[7.1, 22.8]
		P-value	< 0.0001
	Key secondary endpoint CR rate	Comparison groups	Arm A vs Arm C
		CR rate difference	31.3
		95%CI	[23.1, 39.4]
		P-value	< 0.0001
	Key secondary endpoint OS	Comparison groups	Arm A vs Arm C
		HR	0.38
		95%CI	[0.18, 0.80]
		P-value	0.0039**
	Key secondary endpoint MRD	NA	NA

Notes	* OS was formally tested at IA2, DCO 24 May 2025 ** P-value did not cross the prespecified border. Efficacy outcomes for IA2, DCO 24 May 2025 were consistent with outcomes at IA1.

Supportive study

Study GCT3013-02 is a Phase 1b/2, open-label, trial of epcoritamab in combination with other SOC agents in subjects with B-NHL. The Dose Escalation and Expansion Parts of Arm 2 evaluated the safety and efficacy of epcoritamab + R^2 (12 cycles of epcoritamab + R^2 combination therapy followed by epcoritamab monotherapy for up to a total of 2 years) in subjects with R/R FL.



C = cycle(s); epco = epcoritamab; FL = follicular lymphoma; QW = every week; Q2W = every 2 weeks; Q4W = every 4 weeks; R^2 = rituximab and lenalidomide; R/R = relapsed or refractory
Notes: Rituximab was administered for 5 cycles and lenalidomide was administered for 12 cycles.
For Cohort 2a (Dose Escalation Part and Expansion Part), epcoritamab dosing occurred QW in C1-3, Q2W in C4-9, then Q4W in C10+ (28-day cycles) until disease progression or up to a maximum of 2 years. For Cohort 2b (Expansion Part only), epcoritamab dosing occurred QW in C1-2, then Q4W in C3+ (28-day cycles) until disease progression or up to a maximum of 2 years.

Figure 18. Study Design of Arm 2 in Study GCT3013-02

In the Dose Escalation Part, dose escalation of epcoritamab in combination with R^2 was performed using a modified 3+3 design. Epcoritamab was initially administered in combination with R^2, beginning with epcoritamab full dose of 24 mg, with escalation to the target full dose of 48 mg. Enrollment of at least 6 subjects in the Dose Escalation Part was planned.

Arm 2 of Study GCT3013-02 consists of Cohort 2a and Cohort 2b (also referred to as Arm 2a and Arm 2b) evaluating the safety and preliminary efficacy of 12 cycles of epcoritamab+R^2 combination therapy (5 cycles rituximab; 12 cycles lenalidomide) followed by up to 2 years of epcoritamab monotherapy in subjects with R/R Fl.

Arm 2 of the study enrolled subjects with R/R FL who received at least 1 prior regimen containing an anti-CD20 monoclonal antibody using similar eligibility criteria as the M20-638 study.

Cohorts 2a and 2b used a 2-step SUD regimen for epcoritamab (0.16/0.8 mg/24 or 48 mg). Cohort 2a consists of 2 parts (an escalation part and an expansion part) and Cohort 2b includes only an expansion part. For Cohort 2a (for Dose Escalation Part and Expansion Part), epcoritamab dosing occurred QW in Cycle (C)1-3, Q2W in C4-9, Q4W in C10+ (28-day cycles) until disease progression or for up to a maximum of 2 years. For Cohort 2b (for Expansion Part only), epcoritamab dosing occurred QW in C1–2, Q4W in C3+ (28-day cycles) until disease progression or for up to a maximum of 2 years.

Approximately 20 to 40 subjects in Cohort 2a and 80 to 100 subjects in Cohort 2b were planned to be enrolled in the Expansion Part.

Efficacy analyses were presented in the FAS: All subjects who received at least 1 dose of any trial drug. The FAS set was used to summarize subject information and efficacy, unless otherwise specified.

Results

At the DCO of 21 Sep 2024 a total of 17 subjects were treated in the Cohort 2a Dose Escalation Part; N=14 received epcoritamab 24 mg and 3 received epcoritamab 48 mg. A total of 125 subjects were treated in the Expansion Part; in cohort 2a N=17 patients received epcoritamab 24 mg and 24 received epcoritamab 48 mg. In cohort 2b 84 patients received epcoritamab 48 mg.

Among subjects who received epcoritamab 48 mg + R2 in the Expansion Part of the trial (referred to as the Cohort 2a + Cohort 2b 48 mg group; N=108), the median age was 65.0 years (range: 30, 80), with 44 (40.7%) subjects aged 65 to < 75 years and 12 (11.1%) subjects aged ≥ 75 years. Approximately half of subjects (55 [50.9%] subjects) were male. Subjects had a baseline ECOG performance status of 0 (69 [63.9%] subjects), 1 (36 [33.3%] subjects), or 2 (3 [2.8%] subjects). Most (82 [75.9%]) subjects were from regions outside of the US, 26 (24.1%) subjects were from the US, and 57 (52.8%) subjects were from North America or Western Europe.

Twenty-four (22.2%) subjects had Ann Arbor Stage III disease, and 65 (60.2%) subjects had Ann Arbor Stage IV disease. Sixty-one (56.5%) subjects had a FLIPI score of 3 to 5 and 37 (34.3%) subjects had bone marrow involvement at baseline. Twenty-nine (26.9%) subjects had bulky disease (≥ 7 cm) as per investigator assessment. The median number of prior lines of anti-lymphoma therapy was 1.0 (range: 1, 7), with 9 (8.3%) subjects each having received 3 prior lines and > 3 prior lines, respectively. Fourteen (13.0%) subjects were refractory to ≥ 2 consecutive prior lines of anti-lymphoma therapy. Thirty-nine (36.1%) subjects were refractory to the last line of antineoplastic therapy, and 69 (63.9%) subjects relapsed after the last line of antineoplastic therapy. Forty-eight (44.4%) subjects were refractory to anti-CD20, and 39 (36.1%) subjects were double refractory to both anti-CD20 and an alkylating agent. A total of 54 (50.0%) subjects progressed within 24 months (POD24) after initiation of 1L therapy.

For subjects assigned to receive epcoritamab at the full dose of 48 mg in Cohort 2a (N = 24), the median number of epcoritamab cycles initiated was 11.5 cycles (range: 1, 12), and the median duration of treatment was 11.02 months (range: 0.0, 11.7). For subjects assigned to receive epcoritamab at the full dose of 48 mg in Cohort 2b (N = 84) the median number of epcoritamab cycles initiated was 12.0 cycles (range: 3, 12), and the median duration of treatment was 11.14 months (range: 1.9, 16.6).

Response data per study part are shown in Table 22.

Table 22. Best Overall Response Determined by Lugano Criteria – Escalation and expansion Part

		24mg	**48mg**
Dose escalation part (N)		N=14	N=3
	ORR N % [95%CI]	14 100% [76.8%, 100.0%]	3 100% [29.2%, 100.0%]
	CR rate N	13	2

	% [95%CI]	92.9% [66.1%, 99.8%]	66.7% [9.4%, 99.2%]
	DOR months, [95%CI]	NR [15.6, NR]	20.7 [9.1, NR]
Dose expansion part Cohort 2a (N)		N=17	N=24
	ORR N % [95%CI]	17 100% [80.5%, 100.0%]	22 91.7% [73.0%, 99.0%]
	CR rate N % [95%CI]	16 94.1% [71.3%, 99.9%]	22 91.7% [73.0%, 99.0%]
	DOR months, [95%CI]	NR [NR, NR]	NR [21.7, NR]
Dose expansion part Cohort 2b (N)		-	N= 84
	ORR N % [95%CI]	-	82 97.6% [91.7%, 99.7%]
	CR rate N % [95%CI]	-	73 86.9% [77.8%, 93.3%]
	DOR months, [95%CI]	-	NR [27.3%, NR]

Efficacy results for the 108 subjects treated with epcoritamab 48 mg + R^2 in the Expansion Part (02 Arm 2 EXP 48 mg) with an estimated median duration of study follow-up of 28.2 months (range: 2.4+, 39.0) at the time of DCO (21 September 2024).

- Based on investigator assessment determined by Lugano criteria, the ORR and CR rate were 96.3% (95% CI: 90.8, 99.0) and 88.0% (95% CI: 80.3, 93.4), respectively.
- After a median duration of follow-up for DOR of 26.2 months, the median DOR was not reached (95% CI: 37.0, NR). The estimated percentages of subjects remaining in response at 12 and 24 months were 84.1% and 75.6%, respectively.
- After a median duration of follow-up for DOCR of 26.2 months, the median DOCR was not reached (95% CI: 37.0, NR). The estimated percentages of subjects remaining in complete response at 12 and 24 months were 90.2% and 81.9%, respectively.
- After a median duration of follow-up for PFS of 27.6 months, the median PFS was not reached (95% CI: 38.5, NR). The estimated percentage of subjects remaining progression free at 12 and 24 months was 82.5% and 75.5%, respectively.
- After a median duration of follow-up of 28.2 months, the median OS was not reached (95% CI: NR, NR), and the estimated percentages of subjects remaining alive at 12 and 24 months were 95.3% and 90.5%, respectively.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH conducted one dose finding study (Arm 2 of Study GCT3013-02) in a similar population as the pivotal study population. In this study, different epcoritamab posologies were investigated; epcoritamab full dose of 24 mg vs. 48 mg and epcoritamab dosing with 3 cycles of QW dosing (Cohort 2a) vs. only 2 cycles of QW (Cohort 2b). Generally, the design of this study is acceptable, however the method of selecting a dose was not prespecified, which is a limitation.

Dose optimalisation study GCT3013-01 was submitted during the EMEA/H/C/005985/II/0001 procedure. In this procedure it was concluded that the 3-step SUD regimen reduced the number of (Grade 2) CRS events over the 2-step SUD regime, while similar efficacy and safety were observed between the two SUD regimens in R/R FL patients. The posology in the pivotal study was amended two times following the results of the dose finding and dose optimalisation study. Amendments in ongoing studies may hinder interpretation of the data.

The randomised design of the pivotal study M20-638 is acceptable, though the open label design is considered to limit interpretation of certain endpoints (such as PROs) and is unfortunate considering the changes in the ongoing study (refer to conduct of the study). The stratification factors (time to progression/time since last therapy and region) are considered acceptable.

The pivotal study population consists of R/R confirmed FL patients stage II-IV with $CD20^+$ disease according to the 5th edition of WHO Classification, treated with at least one prior chemotherapy in combination with an anti-CD20 monoclonal antibody. Eligible patients had to be eligible to R^2 and not have had lenalidomide exposure within 12 months prior to randomisation. Patients should have had a need for treatment initiation per investigator determination based on symptoms and/or disease burden (e.g., GELF criteria). In recent approvals in FL, the CHMP has chosen to reflect the precise lymphoma classification in the indication. In these applications the 4^{th} WHO classification (or older) was used, which supports the use of grading in FL. Contrary to previous procedures, in this study the 5^{th} WHO edition is used which no longer advises grading of FL due to the poor reproducibility and the questionable clinical significance. Therefore, it is not considered appropriate to report the FL grading in the indication and the proposed wording of the indication is acceptable.
The criterium for $CD20^+$ disease was based on a representative pathology report, but $CD20^+$ disease was not confirmed on screening which does not allow to determine the predictive value of $CD20^+$ as a biomarker. This could be expected considering the nature of therapy and the fact that patients may be CD20 negative after having received anti CD20 therapy. The SmPC section 4.4 already contains a warning on treating patients with CD20 negative disease, which is also adequate for this extension of indication. The most important in- and exclusion criteria, including the need for CD20+ disease have been described in section 5.1 of the SmPC.

Epcoritamab was given as add on to standard of care R^2. R^2 is considered an acceptable comparator arm. The proposed epcoritamab posology is the same as the approved monotherapy posology in FL, except that epcoritamab is given Q4W from C4 onwards instead of from C10 onwards. The posology was amended two times during the study. In total,112 patients were treated with the 2-step SUD regimen and 131 patients with the 3-step SUD regimen. In total 180 patients in Arm A were treated under protocol version 2.0 or later; i.e. with epcoritamab QW dosing in C1-3 (of which N=56 with the 2-step SUD and N=124 with the 3-step SUD regimen). Thus, 124 patients in Arm A (51%) were treated with the proposed posology. Considering the results of the Arm 2 of Study GCT3013-02 study and the assessment of the dose optimalisation study GCT3013-01 during the II/0001 procedure, the changes in posology are not expected to lead to large differences in efficacy outcomes.

In general, the study objectives and endpoints are considered acceptable, however, the clinical relevance of BOR as dual primary endpoint is unclear. PFS and OS are considered the relevant endpoints for a B/R assessment. The issue of BOR as dual primary endpoint is not pursued as the PFS analysis was statistically significant. In scientific advice, PFS as primary endpoint was agreed provided that estimated treatment effects on OS ensure that there are no detrimental effects on this endpoint (EMEA/H/SA/4478/1/2020/III). PROs were not part of the hierarchical testing procedure and their analyses methods are considered exploratory.

With respect to the definition of the estimands, two intercurrent events were specified: 'premature study drug discontinuation' and 'initiation of any new anti-lymphoma therapy'. BOR (CR or PR) was determined regardless of potential premature study drug discontinuation. Disease assessments after the initiation of any new anti-lymphoma therapy were not included in the derivation of the outcome. The intercurrent event 'premature study drug discontinuation' was handled using a treatment-policy approach, and intercurrent event 'initiation of any new anti-lymphoma therapy' was handled using a while-on-treatment strategy. For PFS, a treatment-policy approach is used with respect to the intercurrent event 'premature study drug discontinuation'. In the analysis, subjects for whom new anti-lymphoma therapy was initiated were censored, but the targeted estimand was not explicitly defined. However, a sensitivity analysis in which a treatment-policy approach is used for this intercurrent event (in line with EMA/CHMP/27994/2008/Rev.1) was performed as well. For CR and MRD negativity, the handling of intercurrent events 'premature study drug discontinuation' and 'initiation of any new anti-lymphoma therapy' are handled as for BOR (CR or PR). For OS, a treatment-policy strategy was used for both intercurrent events.

Power/sample size considerations are in line with expectations given the presented assumptions.

Overall, the analysis methods used for the primary and secondary outcomes are considered appropriate. Factors used to stratify randomisation were taken into account. Nonetheless, for the comparison of BOR (CR or PR) and CR, the decision to treat subjects with non-evaluable (NE) outcome status as non-responders might have inflated the treatment effect estimate (given the observed imbalance with more subjects with NE status in the control arm), particularly when the reason for NE status would be withdrawal from the study early without any response assessment due to being assigned to the control arm. However, the number of subjects with NE status 'withdrew from study without any treatment and without response assessment' is limited. In addition, results for CR at IA1, and results for both BOR and CR at IA2 can be considered robust.

In the primary PFS analysis (IA1), the portion of subjects censored for the non-administrative reason of receiving NALT is fairly high in arm C. However, as the main reason is 'PD or inadequate response to treatment per investigator assessment', it is likely to underestimate the treatment effect. In addition, a portion of subjects were censored at baseline due to lack of a baseline assessment. However, in the majority of cases, the latter is a consequence of the first disease response assessment taking place after the DCO, which can be assumed non-informative (of note: in IA2, only one subject was censored at baseline for having 'no baseline assessment'). In terms of statistical testing, the alpha was split between the two primary comparisons, followed by a hierarchical testing procedure. The type I error was controlled across sequential analyses using O'Brien-Fleming-type alpha spending boundaries.

The protocol was amended multiple times with respect to key design elements: In protocol version 2, recruitment to arm B was stopped, and all comparisons related to arm B were excluded from the formal testing procedure. In addition, the analysis of BOR (CR or PR) was excluded from the hierarchical testing procedure, and efficacy analyses were to be performed in the mITT set. In protocol version 3, the primary analysis population for efficacy was changed to the ITT set (i.e. also including subjects randomised prior to protocol version 2). In protocol version 4, BOR (CR or PR) was reintroduced as an outcome in the formal testing strategy as a second primary outcome. In addition,

the target number of PFS and OS events was increased, and an additional interim analysis for PFS was added. In protocol version 5, interim analyses for harm were introduced for OS. Adjustments to the protocol in an ongoing trial may affect its validity, particularly in trials with an open-label design, because the trial may be altered to increase the chance of a positive conclusion. On the other side, the changes were motivated by external considerations, baseline characteristics by subgroups based on the most recent protocol version during enrolment and corresponding treatment effect estimates are generally consistent, and, importantly, the current conclusions of the study (i.e. a demonstrated positive effect in terms of PFS, BOR, and CR, and positive but formally inconclusive results for OS) appear to have been the same if the testing procedure in protocol version 1.0 would have been followed. Finally, the PFS endpoint has been met with a very convincing result.

There were more important protocol deviations in Arm A compared to Arm C, however this appears to be related to dosing deviations specific to epcoritamab. Without the dosing deviations, the protocol deviations are balanced between Arm A and Arm C and, therefore, the deviations are not considered to be of influence on the data interpretation.

Efficacy data and additional analyses

Dose finding study

Arm 2 of Study GCT3013-02 was used to decide on the proposed posology. Based on an interim analysis (DCO 31 Oct 2022; N=47), the recommended dose of epcoritamab was identified as 48 mg and 3 cycles of QW dosing was selected as the recommended dosing schedule. This since the CR rate was 92% at the 48 mg dose level compared to 77% at the 24 mg dose and since the CR rate of 3 cycles of QW dosing was 92% vs. 83% with only 2 cycles of QW.

Data from the DCO of 21 Sep 2024, where the sample size is larger (N=142), do not fully support the decisions on the epcoritamab full dose. At this DCO there was a numerically higher CR rate in the 24 mg group compared to 48 mg (94.1% vs 87.9% respectively). The CR rate between cohorts treated QW in C1-3 vs. QW in C1–2 is similar, but numerically slightly higher in patients treated QW in C1-3 compared to QW in C1–2 (91.7% vs 86.9% respectively), thus supporting the choice made on dosing schedules. These data indicate the importance of finalizing dose response studies prior to start of phase 3 studies. It is considered likely that the full dose of 24 mg dose would have led to similar efficacy as the 48 mg dose, however as no exposure response relation for safety has been established for epcoritamab in previous applications, and the majority of patients in the pivotal study have been treated with epcoritamab 48 mg full dose, the proposed posology is considered acceptable.

Pivotal study M20-638

PFS, ORR, and CR rate were statistically tested at the IA1 with DCO 10 January 2025 at a median study follow-up of 10.4 months in Arm A and 10.2 months in Arm C. Updated efficacy outcomes for these endpoints as well as the first OS IA were presented at IA2 with DCO 24 May 2025 with a median follow-up of 14.8 and 14.6 months, respectively.

The baseline demographic characteristics were generally balanced between Arm A and Arm C, though there is a small disbalance in median age (60 years in Arm A vs 63 years in Arm C). Compared to a general FL population this study included a large part of younger patients (63.8% vs 56.7% of the patients were younger than 65, respectively). However, the imbalance in age can be acceptable as age is not a large effect modifier of PFS in the subgroup analyses. Also, the study included only 2.5% of patients with ECOG PS of 2, thus representing a generally healthy population. Disease characteristics were generally balanced between Arm A and Arm C. The study population included a considerable part of patients with poor risk factors, e.g. POD24 was observed in 43.6% of the patients in Arm A vs. 38.0% in Arm C. There were some small differences in time since diagnosis/last therapy and POD24 status, FLIPI stage and bulky disease between Arm A and Arm C, however this does not lead to a

uniform conclusion on more aggressive disease in Arm A or Arm C. In total, two patients were CD20 negative at screening (one in Arm A and C) and 3 patients (in Arm C) had a missing CD20 status (protocol deviations), however considering the small number, this not considered to have a large influence on the data interpretation. Of note, there were at least 53 patients out of 199 screen failures that did not meet eligibility criterion requiring CD20+ disease.

At the IA1 both dual endpoints were met. The PFS HR was 0.21 (95% CI: 0.13, 0.33, p=< 0.0001 at 54% of the IF) and is considered clinically relevant, even if the IF is considered low. The median PFS was not reached in Arm A and Arm C. The KM-curve for PFS shows early separation but there is a lot of censoring in the curves. PFS is consistent in sensitivity analyses including in an EMA preferred analysis in which a treatment-policy approach is used for intercurrent events (in line with EMA/CHMP/27994/2008/Rev.1) (HR 0.20 [95% CI: 0.13, 0.33]). The PFS HR is considered convincing enough to overcome uncertainties related to small imbalances in baseline characteristics. The updated PFS analysis at IA2 with a higher IF of 78% is in line with the primary analysis (HR 0.21 [95% CI: 0.14, 0.31]). The difference in PFS KM curves appears to maintain through time, but still some censoring is observed. Results in the mITT showed a PFS HR consistent with the primary analysis (HR 0.17 [95% CI: 0.09, 0.32]).

ORR at the primary analysis (in the first 232 patients with at least 12 months of follow up) was higher in Arm A compared to Arm C (95.7% [95% CI: 90.2, 98.6] vs 81.0% ([95% CI: 72.7, 87.7]) with a statistically significant difference in rates of 14.9% (p-value < 0.0001). At IA2 ORR was tested in all randomised patients in Arm A and C and results were in line with the primary analysis (ORR of 95.1% in Arm A versus 79.2% in Arm C).

Key secondary endpoint CR rate (in the ITT) showed a statistically significant improvement of 31% in Arm A over Arm C (p=<0.0001). The CR rate was 74.5% (95% CI 68.5, 79.8) in Arm A vs 43.3% (95% CI 37.0, 49.7) in Arm C. At IA2 the CR rate was 82.7% in Arm A vs 49.8% in Arm C. Thus, the difference in ORR is mainly due to a difference in CR rate. CR rate is considered to support PFS.

The key secondary endpoint OS HR was 0.38 (95% CI: 0.18, 0.80) for Arm A compared with Arm C alone, but OS did not cross the pre-specified boundary for statistical significance. There were few OS events (4.1% vs 10.2% OS events respectively and the actual number of OS events (24% of the IF) was lower than the planned number) and OS is considered immature. The OS KM-curves are difficult to interpret due to the large amount of censoring, but the curves are separated. OS did not cross the pre-specified futility/harm boundary of HR > 1.05/>1.29. Also considering the OS point estimate and the KM-curves, no detriment to OS is currently expected. The maturity of OS and the lack of detriment is in line with regulatory precedents in R/R FL and, therefore, acceptable.

MRD negativity analyses were not performed as OS did not meet statistical significance.

Other secondary endpoints (CR rate at end of treatment, TTP, TTNLT, EFS) are in support of PFS and BOR. DO(C)R and TT(C)R are comparable between Arm A and Arm C, thus the improvement in PFS mainly relates to increased ORR and CR rate rather than an increase in the duration of response.

PROs were not formally tested, the analysis method is considered exploratory and the study was performed open-label, therefore their outcomes are considered non-reliable.

The treatment effect observed in the pivotal study is supported by the results of Arm 2 of Study GCT3013-02 and by efficacy outcomes in Arm B; these are numerically comparable with Arm A, except for a slightly wider CI for the median estimates, which may be due to smaller number of patients.

The PFS effect is generally consistent in subgroups, including high risk subgroups such as POD24 positive and double refractory patients. In some subgroups a lower treatment effect is observed, however these subgroups all have a small sample size and thus results are difficult to interpret.

Moreover, in almost all groups the HR and 95% CI still indicate a PFS improvement. There are also some subgroups with a smaller ORR difference. In these subgroups the ORR is also high in the control group, indicating that the added benefit of epcoritamab is lower in terms of response rate. This, however, generally does not translate to an effect on time-to-event endpoint PFS.

Pivotal study M20-638 was intended to serve as the confirmatory trial for the approved indication of adult patients with relapsed or refractory (R/R) FL after two or more lines of systemic therapy. Data provided in the current procedure are considered comprehensive and therefore no further SOB is imposed. In order to fulfil the ongoing SOB, the final CSR should be submitted with a due date of Q4/2034. The MAH committed to providing the final PFS and OS interim with a due date of Q1 2027 (REC).

2.4.4. Conclusions on the clinical efficacy

A clinically relevant improvement in PFS was observed with the addition of epcoritamab to R^2 versus R^2 alone in R/R FL patients. PFS is supported by ORR and CR rate and is generally consistent in sensitivity analyses and subgroup analyses including high risk subgroups. OS is not statistically significant and the OS data are immature, however considering the estimate of the OS HR, no detriment is currently expected. The observed treatment effect in the pivotal study is supported by efficacy outcomes in pivotal study Arm B and outcomes in Arm 2 of Study GCT3013-02. Overall, efficacy is considered established and data considered comprehensive.

2.5. Clinical safety

Introduction

Summary of existing safety profile

The safety profile for epcoritamab was established in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) treated with epcoritamab 0.16/0.8 mg/48 mg in GCT3013-01 study (EMA/CHMP/419797/2023). Supportive data at the time of the MAA were from B-cell non-Hodgkin lymphoma (B-NHL) patients treated with 48 mg epcoritamab in studies GCT3013-01 and GCT3013-04: 374 patients with 208 LBCL (of which 188 DLBCL), 128 indolent NHL (iNHL), and 38 mantle cell lymphoma (MCL). The most common adverse reactions (≥ 20%) were CRS, fatigue, neutropenia, injection site reactions, musculoskeletal pain, abdominal pain, pyrexia, nausea and diarrhoea. Serious adverse reactions occurred in 52% of patients. Adverse events of special interest (AESIs) were CRS (any Grade: 51% Grade 3: 3.0%. CRS of any grade occurred in 6.6% of patients after the priming dose; 13% after the intermediate dose (Cycle 1, Day 8); 44% after the first full dose (Cycle 1, Day 15), 4.6% after the second full dose (Cycle 1 Day 22) and 2.8% after the third full dose (Cycle 2 Day 1) or beyond; ICANS occurred in 6.0% of the patients (one patient (0.6%) with Grade 5 ICANS); tumor lysis syndrome (TLS) occurred in 1.8% of patients (no severe cases were seen). Important identified risks associated with epcoritamab therapy are CRS, ICANS, and (serious) infections. The latter are observed in 25% of the patients including Grade 5 events in 4.2% of the patients. Risk of overdose due to medication errors is an important potential risk and long term safety data is missing information.

The safety profile for epcoritamab was also established in patients with relapsed or refractory FL treated with epcoritamab in GCT3013-01 study (EMA/369446/2024). This study investigated both the 0.16/0.8 mg/48 mg dose in the expansion cohort and a 3-step SUD regimen (0.16/0.8/3/48mg) in the dose optimization part of the study. The 3-step SUD regimen resulted in a clinically relevant reduction in the number of (Grade 2) CRS events.

Safety evaluation

Safety data from the pivotal clinical Study M20-638 were provided. The pivotal data are supported by Arm 2 of Study GCT3013-02. The data cutoff dates are 24 May 2025 for Study M20-638 and 21 September 2024 for Study GCT3013-02 Arm 2, and both studies have completed enrollment.

AEs were coded using MedDRA Version 27.1 and graded by investigators according to NCI-CTCAE Version 5.0 (NCI, 2017), except for CRS, ICANS, and CTLS. Events of CRS and ICANS were graded according to ASTCT criteria (Lee et al, 2019). Events of CTLS were graded according to Cairo-Bishop criteria (Coiffier et al, 2008).

All adverse events reported from the time of study drug administration until 30 days after discontinuation of lenalidomide or 60 days after discontinuation of epcoritamab or rituximab, (whichever was later) or until the subject begins new anti-lymphoma therapy, whichever comes first were collected, whether solicited or spontaneously reported by the subject. After completion of study treatment (30 days for lenalidomide, and 60 days for epcoritamab or rituximab, whichever was later) and throughout the Post Treatment Period or until the subject begins new anti-lymphoma therapy only spontaneously reported SAEs were collected (nonserious AEs were not collected). Second primary malignancies were captured until the end of survival follow-up. In addition, study procedure-related serious and non-serious AEs were collected from the time the subject signs the study-specific informed consent.

Events of disease progression related to the primary malignancy were evaluated in this study (FL) and accompanying symptoms, if clearly associated with disease progression, were not collected as adverse events unless the event(s) result in death or qualified as a serious adverse event.

Safety analysis sets

The following datasets were provided for safety analysis:

- Primary safety analysis set: Study M20-638 R/R FL Arm A (N = 243) and Arm C (N = 238). This safety analysis set included all R/R FL subjects who were randomised to either the 48 mg full dose of epcoritamab + R^2 (Arm A) or R^2 alone (Arm C) and received at least 1 dose of study drug. The median follow-up is shown in Table 23. In Study M20-638, the epcoritamab 3-step SUD regimen (0.16/0.8/3/48mg) instead of a 2-step SUD regimen (0.16/0.8/48mg) was introduced at Protocol Version 3.0 to reduce the incidence and severity of cytokine release syndrome (CRS). In total, 133 subjects in Arm A received the epcoritamab 3-step SUD regimen.
- Supportive safety analysis set: All epcoritamab 24 mg or 48 mg + R^2 (Study M20-638 R/R FL + Study GCT3013-02 escalation [ESC] + expansion [EXP] Arm 2 R/R FL, hereinafter referred to as **All Epco + R^2 pool**, N = 446). This safety analysis set included all R/R FL subjects who were randomised to the 24 mg or 48 mg full dose of epcoritamab + R^2 (Study M20-638) or assigned to the 24 mg or 48 mg full dose of epcoritamab + R^2 (Study GCT3013-02 Arm 2) and received at least 1 dose of study drug.

Study drug refers to epcoritamab, rituximab, or lenalidomide. Study treatment refers to Epco 48 mg + R^2, R^2 alone, or Epco 24 mg + R^2 for Arm A, C, and B, respectively.

Table 23. Duration of Safety Follow-Up (Study M20-638 Safety Analysis Set)

	Arm A Epco 48 mg + R^2 (N = 243)	Arm C R^2 (N = 238)
Duration of safety follow-up (months)[a]		
n	243	238
Mean (Std Dev)	11.2 (3.03)	9.2 (3.37)
Median	12.3	10.1
Min, Max	< 1, 20	< 1, 14
< 3 months	243 (100%)	238 (100%)
≥ 3 months	237 (97.5%)	220 (92.4%)
≥ 6 months	223 (91.8%)	185 (77.7%)
≥ 9 months	190 (78.2%)	140 (58.8%)
≥ 12 months	161 (66.3%)	56 (23.5%)
≥ 18 months	1 (0.4%)	0
≥ 24 months	0	0

Duration of safety follow-up = Minimum of (last dose date + 60 days for epcoritamab/rituximab or 30 days for lenalidomide [whichever is later], start of new anti-lymphoma therapy, death date, data cutoff date) - first dose date + 1. Data Cutoff: 24 May 2025.

Patient exposure

Epcoritamab

Refer to Figure 12 and Table 5 (Clinical Efficacy) for the subject disposition. In Arm A, 54.3% completed protocol-specified study treatment, 27.6% discontinued at least one study drug and 18.1% were on study treatment at the DCO. In Arm C 39.6% completed protocol-specified study treatment, 44.5% discontinued at least one study drug and 13.1% were on study treatment at the DCO.

The exposure to epcoritamab in the safety analysis set is shown in Table 24.

Of note, subjects in Arm B who switched to epcoritamab 48 mg in combination with R^2 at the investigator's discretion were also captured in the N for Arm B epcoritamab dose adjustments. Additionally, the >100% RDIs for epcoritamab in the later cycles of Arm B were likely due to higher exposures from these subjects who switched to epcoritamab 48 mg. In total 31 patients (51%) switched from 24mg to 48mg in Arm B, and 4 patients (6.6%) were treated with 48mg from the start of treatment.

Table 24. Summary of Exposure to Study Drug – Epcoritamab (Safety Analysis Set). Data Cutoff: 24 May 2025

	Arm A (Epco 48 mg + R^2) (N = 243) n (%)	All Epco + R^2 pool (Epco 24 mg or 48 mg + R^2) (N = 446) n (%)#
Median number of cycles initiated	**12.0**	**12.0**
Min, Max	**1, 12**	**1, 27**
Median duration of study drug, months	**10.41**	**10.58**
Min, Max	**0.3, 15.4**	**<0.1 25.8**
Relative dose intensity (%)[a]		
Epcoritamab Cycle 1 - 3*		

	Arm A (Epco 48 mg + R²) (N = 243) n (%)	All Epco + R² pool (Epco 24 mg or 48 mg + R²) (N = 446) n (%)#
n	240	
Mean (std dev)	87.73 (19.077)	
Median	90.91	
Min, Max	14.5, 142.9	
< 50%	8 (3.3)	
50 - < 70%	33 (13.8)	
70 - < 90%	72 (30.0)	
90 - < 110%	115 (47.9)	
≥ 110%	12 (5.0)	
Missing	3	
Epcoritamab Cycle 4 - 8*		
n	233	
Mean (std dev)	93.34 (12.260)	
Median	97.22	
Min, Max	20.7, 122.0	
< 50%	6 (2.6)	
50 - < 70%	5 (2.1)	
70 - < 90%	34 (14.6)	
90 - < 110%	187 (80.3)	
≥ 110%	1 (0.4)	
Missing	10	
Epcoritamab Cycle 9 to 12		
n	186	
Mean (std dev)	94.87 (10.355)	
Median	100.00	
Min, Max	28.6, 106.7	
< 50%	1 (0.5)	
50 - < 70%	7 (3.8)	
70 - < 90%	23 (12.4)	
90 - < 110%	155 (83.3)	
≥ 110%	0	
Missing	57	
Number of subjects experiencing dose adjustment	**194 (79.8)**	**362 (81.2)**
Primary reason for adjustment [b]		
Adverse event	176 (72.4)	318 (71.3)
Physician decision based on risk/benefit assessment	17 (7.0)	
COVID-19 infection	24 (9.9)	
COVID-19 logistical restrictions	2 (0.8)	
Administration Error	5 (2.1)	
Logistical Restrictions [Non COVID-19]	31 (12.8)	
Number of Subjects with Re-priming	**66 (27.2)**	**116 (26.0)**

* For Arm A, dose intensity is summarized by Cycle 1-3 and Cycle 4-8; For Arm B, dose intensity is summarized by Cycle 1-2 and Cycle 3-8.
a. Relative dose intensity is actual dose intensity divided by planned dose intensity.
b. Subjects may experience multiple times of dose adjustments.
Due to the considerable heterogeneity in the dosing regimens within the pooled population including patients transitioning between dose levels, no relative dose intensity was calculated.

Rituximab and lenalidomide (R²)

The exposure to rituximab and lenalidomide in the safety analysis set is shown in Table 25.

Table 25. Summary of Exposure to Study Drug – R² (Safety Analysis Set). Data Cutoff: 24 May 2025.

	Arm A (Epco 48 mg + R²) (N = 243) n (%)	Arm C (R²) (N = 238) n (%)	Arm B (Epco 24 mg + R²) (N = 61) n (%)	Overall (N = 542) n (%)
Rituximab				
Median number of cycles initiated	**5.0**	**5.0**	**5.0**	**5.0**

	Arm A (Epco 48 mg + R²) (N = 243) n (%)	Arm C (R²) (N = 238) n (%)	Arm B (Epco 24 mg + R²) (N = 61) n (%)	Overall (N = 542) n (%)
Min, Max	**1, 8**	**1, 6**	**2, 5**	**1, 8**
Median duration of study drug, months	**3.94**	**3.71**	**3.78**	**3.78**
Min, Max	**0.3, 11.5**	**0.0, 5.3**	**1.9, 8.0**	**0.0, 11.5**
Relative dose intensity (%)a				
Cycle 1				
n	243	238	61	542
Mean (std dev)	102.12 (19.506)	97.03 (14.339)	100.63 (13.544)	99.71 (16.925)
Median	100.00	100.00	100.00	100.00
Min, Max	48.5, 274.3	24.9, 216.0	74.3, 149.4	24.9, 274.3
< 50%	2 (0.8)	5 (2.1)	0	7 (1.3)
50 - < 70%	1 (0.4)	3 (1.3)	0	4 (0.7)
70 - < 90%	11 (4.5)	12 (5.0)	7 (11.5)	30 (5.5)
90 - < 110%	210 (86.4)	217 (91.2)	46 (75.4)	473 (87.3)
≥ 110%	19 (7.8)	1 (0.4)	8 (13.1)	28 (5.2)
Cycle 2 - 5				
n	238	228	61	527
Mean (std dev)	101.09 (8.677)	99.77 (1.720)	100.01 (1.225)	100.39 (5.981)
Median	100.00	100.00	100.00	100.00
Min, Max	86.8, 200.9	84.6, 106.0	96.7, 105.8	84.6, 200.9
< 50%	0	0	0	0
50 - < 70%	0	0	0	0
70 - < 90%	1 (0.4)	2 (0.9)	0	3 (0.6)
90 - < 110%	231 (97.1)	226 (99.1)	61 (100)	518 (98.3)
≥ 110%	6 (2.5)	0	0	6 (1.1)
Missing	5	10	0	15
Number of subjects experiencing dose adjustment	**159 (65.4)**	**85 (35.7)**	**39 (63.9)**	**283 (52.2)**
Primary reason for adjustment b				
Adverse event	142 (58.4)	71 (29.8)	33 (54.1)	246 (45.4)
Physician decision based on risk/benefit assessment	11 (4.5)	9 (3.8)	5 (8.2)	25 (4.6)
COVID-19 infection	16 (6.6)	6 (2.5)	7 (11.5)	29 (5.4)
COVID-19 logistical restrictions	2 (0.8)	0	0	2 (0.4)
Administration Error	6 (2.5)	1 (0.4)	0	7 (1.3)
Logistical Restrictions [Non COVID-19]	10 (4.1)	8 (3.4)	1 (1.6)	19 (3.5)
Lenalidomide				
Median number of cycles initiated	**12.0**	**11.0**	**12.0**	**12.0**
Min, Max	**1, 12**	**1, 12**	**1, 12**	**1, 12**
Median duration of study drug, months	**10.91**	**9.91**	**10.87**	**10.81**
Min, Max	**0.3, 19.3**	**0.1, 13.3**	**0.6, 15.5**	**0.1, 19.3**
Relative dose intensity (%)a				
Cycle 1 -12				
n	243	236	61	540
Mean (std dev)	83.60 (21.009)	86.55 (19.369)	81.48 (20.721)	84.65 (20.317)
Median	89.88	95.90	86.31	92.86
Min, Max	27.7, 166.7	9.5, 126.2	22.6, 109.1	9.5, 166.7
< 50%	19 (7.8)	15 (6.4)	5 (8.2)	39 (7.2)
50 - < 70%	44 (18.1)	26 (11.0)	12 (19.7)	82 (15.2)
70 - < 90%	61 (25.1)	53 (22.5)	16 (26.2)	130 (24.1)
90 - < 110%	111 (45.7)	139 (58.9)	28 (45.9)	278 (51.5)
≥ 110%	8 (3.3)	3 (1.3)	0	11 (2.0)
Missing	0	2	0	2
Number of subjects experiencing dose adjustment[c]	**202 (83.1)**	**139 (58.4)**	**46 (75.4)**	**387 (71.4)**
Primary reason for adjustment[b]				
Adverse event	193 (79.4)	125 (52.5)	45 (73.8)	363 (67.0)
Physician decision based on risk/benefit assessment	17 (7.0)	20 (8.4)	6 (9.8)	43 (7.9)
COVID-19 infection	15 (6.2)	11 (4.6)	7 (11.5)	33 (6.1)
COVID-19 logistical restrictions	1 (0.4)	0	0	1 (0.2)

	Arm A (Epco 48 mg + R^2) (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)	Arm B (Epco 24 mg + R^2) (N = 61) n (%)	Overall (N = 542) n (%)
Administration Error	8 (3.3)	5 (2.1)	1 (1.6)	14 (2.6)
Logistical Restrictions [Non COVID-19]	14 (5.8)	5 (2.1)	1 (1.6)	20 (3.7)

a. Relative dose intensity is actual dose intensity divided by planned dose intensity.
b. Subjects may experience multiple times of dose adjustments.
c. Dose adjustment includes subjects who had a dose reduction, dose interruption, and a dose increase.

Adverse events

Overview

An overview of TEAEs and deaths for subjects in the Safety Analysis Set is presented in Table 26.

Table 26. Overview of TEAEs and all deaths (safety analysis set). Data Cutoff: 24 May 2025

	Arm A (Epco 48 mg + R^2) Total Arm A (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)
Subjects with any TEAE	242 (99.6)	235 (98.7)
Related to		
Any study drug	236 (97.1)	213 (89.5)
Epcoritamab	219 (90.1)	0
Rituximab	175 (72.0)	160 (67.2)
Lenalidomide	228 (93.8)	207 (87.0)
Leading to discontinuation of		
Any study drug	46 (18.9)	29 (12.2)
Epcoritamab	21 (8.6)	0
Rituximab	7 (2.9)	12 (5.0)
Lenalidomide	45 (18.5)	29 (12.2)
Treatment-related AE leading to discontinuation of any study drug	40 (16.5)	18 (7.6)
Epcoritamab-related AE leading to discontinuation of epcoritamab	16 (6.6)	0
Rituximab-related AE leading to discontinuation of rituximab	3 (1.2)	4 (1.7)
Lenalidomide-related AE leading to discontinuation of lenalidomide	37 (15.2)	17 (7.1)
AE leading to interruption of		
Any study drug	204 (84.0)	127 (53.4)
Epcoritamab#	185 (76.1)	0
Rituximab	146 (60.1)	74 (31.1)
Lenalidomide#	181 (74.5)	107 (45.0)
Treatment-related AE leading to interruption of any study drug	179 (73.7)	91 (38.2)
Epcoritamab-related AE leading to interruption of epcoritamab#	136 (56.0)	0
Rituximab-related AE leading to interruption of rituximab	83 (34.2)	42 (17.6)
Lenalidomide-related AE leading to interruption of lenalidomide#	155 (63.8)	77 (32.4)
Leading to dose reduction of lenalidomide	57 (23.5)	44 (18.5)
Lenalidomide-related AE leading to dose reduction of lenalidomide	53 (21.8)	40 (16.8)
Grade 3 or 4 AE related to	219 (90.1)	159 (66.8)
Any study drug	203 (83.5)	129 (54.2)
Epcoritamab	145 (59.7)	0
Rituximab	107 (44.0)	70 (29.4)
Lenalidomide	198 (81.5)	126 (52.9)
Serious AE related to	135 (55.6)	69 (29.0)

	Arm A (Epco 48 mg + R^2) Total Arm A (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)
Any study drug	109 (44.9)	38 (16.0)
Epcoritamab	98 (40.3)	0
Rituximab	52 (21.4)	21 (8.8)
Lenalidomide	77 (31.7)	35 (14.7)
Fatal AE related to	6 (2.5)	12 (5.0)
Any study drug	0	1 (0.4)
Epcoritamab	0	0
Rituximab	0	0
Lenalidomide	0	1 (0.4)
Fatal AE, excluding PD reported as AE	4 (1.6)	9 (3.8)
All Deaths - Primary cause of death	10 (4.1)	23 (9.7)
Disease progression	2 (0.8)	8 (3.4)
Occurring before safety follow up*	0	0
Occurring after safety follow up*	2 (0.8)	8 (3.4)
AEs	6 (2.5)	12 (5.0)
Occurring before safety follow up*	5 (2.1)	10 (4.2)
Occurring after safety follow up*	1 (0.4)	2 (0.8)
Other	2 (0.8)	3 (1.3)

\# Dose interruption is dose delay for epcoritamab and lenalidomide.
* End of safety follow up period is defined as the end of TEAEs period.
Note: Relationship to any study drug(s) as assessed by investigator.
Defining TEAEs: any AE with the onset that is the first dose of study drug date until 30 days after discontinuation of lenalidomide or 60 days after discontinuation of rituximab/epcoritamab, whichever is later or until the subject begins new anti-lymphoma therapy, whichever comes first.

Treatment-Emergent Adverse Events

TEAEs reported in ≥10% of subjects in Arm A or Arm C are shown in Table 27.

In Arm A, a total of 242 (99.6%) subjects experienced at least 1 TEAE. The most frequently reported (≥ 20%) TEAEs by PT, in descending order, were neutropenia, CRS, diarrhoea, anaemia, constipation, neutrophil count decreased, pyrexia, rash, COVID-19, injection site reaction (ISR), and upper respiratory tract infection.

Adverse events that were reported more frequently (≥ 10% difference) in Arm A versus Arm C were neutropenia (49.4% vs. 31.5%), CRS (35.0% vs. 0.4%), anaemia (27.6% vs 17.2%), pyrexia (23.9% vs 13.9%), ISR (21.8% vs 0%), hypokalaemia (19.8% vs 8.8%) hypogammaglobulinemia (19.3% vs 4.2%), pneumonia (19.3% vs 8.4%), and insomnia (14.4% vs 3.4%).

Table 27. TEAEs Reported in ≥ 10% of subjects in Arm A or Arm C by SOC and PT (Safety Analysis Set). Data Cutoff: 24 May 2025

MedDRA 27.1 System Organ Class Preferred Term	Arm A (Epco 48 mg + R^2) (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)
Any adverse event	**242 (99.6)**	**235 (98.7)**
Infections and infestations	**188 (77.4)**	**125 (52.5)**
COVID-19	54 (22.2)	32 (13.4)
Upper respiratory tract infection	49 (20.2)	33 (13.9)
Pneumonia	47 (19.3)	20 (8.4)
Blood and lymphatic system disorders	**168 (69.1)**	**108 (45.4)**
Neutropenia	120 (49.4)	75 (31.5)
Anaemia	67 (27.6)	41 (17.2)
Thrombocytopenia	34 (14.0)	33 (13.9)
General disorders and administration site conditions	**164 (67.5)**	**101 (42.4)**
Pyrexia	58 (23.9)	33 (13.9)
Injection site reaction	53 (21.8)	0
Fatigue	48 (19.8)	31 (13.0)
Asthenia	30 (12.3)	24 (10.1)
Gastrointestinal disorders	**152 (62.6)**	**135 (56.7)**

MedDRA 27.1 System Organ Class Preferred Term	Arm A (Epco 48 mg + R^2) (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)
Diarrhoea	75 (30.9)	60 (25.2)
Constipation	67 (27.6)	51 (21.4)
Nausea	41 (16.9)	28 (11.8)
Investigations	**151 (62.1)**	**94 (39.5)**
Neutrophil count decreased	65 (26.7)	50 (21.0)
Alanine aminotransferase increased	46 (18.9)	23 (9.7)
Platelet count decreased	35 (14.4)	13 (5.5)
White blood cell count decreased	32 (13.2)	29 (12.2)
Aspartate aminotransferase increased	29 (11.9)	15 (6.3)
Skin and subcutaneous tissue disorders	**134 (55.1)**	**118 (49.6)**
Rash	58 (23.9)	53 (22.3)
Pruritus	21 (8.6)	31 (13.0)
Immune system disorders	**115 (47.3)**	**18 (7.6)**
Cytokine release syndrome	85 (35.0)	1 (0.4)
Hypogammaglobulinaemia	47 (19.3)	10 (4.2)
Metabolism and nutrition disorders	**102 (42.0)**	**66 (27.7)**
Hypokalaemia	48 (19.8)	21 (8.8)
Respiratory, thoracic and mediastinal disorders	**98 (40.3)**	**61 (25.6)**
Cough	47 (19.3)	25 (10.5)
Nervous system disorders	**90 (37.0)**	**59 (24.8)**
Headache	27 (11.1)	9 (3.8)
Musculoskeletal and connective tissue disorders	**79 (32.5)**	**76 (31.9)**
Muscle spasms	37 (15.2)	27 (11.3)
Injury, poisoning and procedural complications	**60 (24.7)**	**40 (16.8)**
Infusion related reaction	32 (13.2)	31 (13.0)
Psychiatric disorders	**46 (18.9)**	**14 (5.9)**
Insomnia	35 (14.4)	8 (3.4)

Subjects are counted once in each row within a column, regardless of the number of events they may have had.
Defining TEAEs: Any AE with the onset that is the first dose of study drug date until 30 days after discontinuation of lenalidomide or 60 days after discontinuation of rituximab/epcoritamab, whichever comes later or until the subject begins new anti-lymphoma therapy, whichever comes first.
Sort SOC by descending frequency order of Arm A (Epco 48 mg + R^2) first, then sort PT by descending frequency order of Arm A (Epco 48 mg + R^2) within SOC.

Grade 3 or 4 TEAEs Reported in ≥ 2% of Subjects in Arm A or Arm C are shown in Table 28.

Grade 3 or 4 TEAEs were reported in 90.1% and 66.8% of subjects in Arm A and Arm C, respectively, with the majority being reported in the SOC of Blood and lymphatic system disorders (53.5% and 32.8%, respectively) followed by SOC of Investigations (37.4% and 23.1%, respectively) and Infections and infestations (33.3% and 15.1%, respectively).

The most frequently reported Grade 3 or 4 events (≥ 5% of subjects) in Arm A were neutropenia, neutrophil count decreased, pneumonia, anaemia, rash, hypokalaemia, lymphocyte count decreased, thrombocytopenia, alanine aminotransferase increased, febrile neutropenia, and lymphopenia while the most frequently reported Grade 3 or 4 events (≥ 5% of subjects) in Arm C were neutropenia, neutrophil count decreased, thrombocytopenia, and white blood cell count decreased.

Grade 3 or 4 events that were reported more frequently (≥ 5% difference) in Arm A versus Arm C were neutropenia (46.1% vs. 25.6%), neutrophil count decreased (24.7% vs 16.8%), alanine aminotransferase increased (6.2% vs 0.8%), and pneumonia (11.5% vs 4.6%).

Table 28. Grade 3 or 4 TEAEs Reported in ≥ 2% of Subjects in Arm A or Arm C by SOC and PT (Safety Analysis Set). Data Cutoff: 24 May 2025

MedDRA 27.1 System Organ Class Preferred Term	Arm A (Epco 48 mg + R^2) (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)
Any adverse event	**219 (90.1)**	**159 (66.8)**
Blood and lymphatic system disorders	**130 (53.5)**	**78 (32.8)**
Neutropenia	112 (46.1)	61 (25.6)

MedDRA 27.1 System Organ Class Preferred Term	Arm A (Epco 48 mg + R^2) (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)
Anaemia	19 (7.8)	11 (4.6)
Thrombocytopenia	16 (6.6)	13 (5.5)
Febrile neutropenia	15 (6.2)	6 (2.5)
Lymphopenia	15 (6.2)	4 (1.7)
Leukopenia	7 (2.9)	3 (1.3)
Investigations	**91 (37.4)**	**55 (23.1)**
Neutrophil count decreased	60 (24.7)	40 (16.8)
Lymphocyte count decreased	16 (6.6)	6 (2.5)
Alanine aminotransferase increased	15 (6.2)	2 (0.8)
White blood cell count decreased	11 (4.5)	13 (5.5)
Platelet count decreased	8 (3.3)	2 (0.8)
Aspartate aminotransferase increased	5 (2.1)	3 (1.3)
Infections and infestations	**81 (33.3)**	**36 (15.1)**
Pneumonia	28 (11.5)	11 (4.6)
COVID-19	7 (2.9)	4 (1.7)
COVID-19 pneumonia	7 (2.9)	0
Upper respiratory tract infection	5 (2.1)	1 (0.4)
Metabolism and nutrition disorders	**30 (12.3)**	**10 (4.2)**
Hypokalaemia	16 (6.6)	6 (2.5)
Hyperglycaemia	5 (2.1)	0
Hypertriglyceridaemia	5 (2.1)	0
Skin and subcutaneous tissue disorders	**29 (11.9)**	**18 (7.6)**
Rash	19 (7.8)	9 (3.8)
Gastrointestinal disorders	**17 (7.0)**	**12 (5.0)**
Diarrhoea	10 (4.1)	7 (2.9)
General disorders and administration site conditions	**15 (6.2)**	**9 (3.8)**
Fatigue	9 (3.7)	2 (0.8)
Respiratory, thoracic and mediastinal disorders	**7 (2.9)**	**11 (4.6)**
Pleural effusion	3 (1.2)	6 (2.5)

Subjects are counted once in each row within a column, regardless of the number of events they may have had.
Defining TEAEs: Any AE with the onset that is the first dose of study drug date until 30 days after discontinuation of lenalidomide or 60 days after discontinuation of rituximab/epcoritamab, whichever comes later or until the subject begins new anti-lymphoma therapy, whichever comes first.
Sort SOC by descending frequency order of Arm A (Epco 48 mg + R^2) first, then sort PT by descending frequency order of Arm A (Epco 48 mg + R^2) within SOC.

Treatment-Emergent Adverse Events related to Epcoritamab

In total 219/243 (90.1%) of patients in Arm A had at least one TEAE which was considered treatment-related by the investigator, of which 145/243 (59.7%) were grade 3 or higher. In total 40.3% of patients in Arm A experienced a serious epcoritamab-related TEAE. There were no patients with a fatal epcoritamab-related TEAE.

TEAEs considered related to epcoritamab by the investigator and reported in > 10% of subjects included CRS (34.6%), neutropenia (25.5%), neutrophil count decreased (24.3%), ISR (21.4%), anaemia (17.7%), hypogammaglobulinemia (16.5%), alanine aminotransferase increased (15.2%), pneumonia (14.8%), pyrexia (12.3%), white blood cell count decreased (12.3%), platelet count decreased (10.3%), and upper respiratory infection (10.3%). The most frequently reported (≥ 10%) Grade 3 or 4 epcoritamab-related TEAEs were neutrophil count decreased (21.4%) and neutropenia (21.0%).

Epcoritamab-related serious TEAEs were reported in 98 (40.3%) subjects in Arm A with CRS (18.5%) being the most frequently reported followed by pneumonia (7.4%) and febrile neutropenia (3.3%)

Serious adverse event/deaths/other significant events

Serious adverse events

A summary of serious TEAEs reported in ≥ 1% of subjects in Arm A or Arm C by SOC and PT is presented in Table 29.

Serious TEAEs were reported in 55.6% and 29.0% of subjects in Arm A and Arm C, respectively. Serious TEAEs that were reported more frequently (≥ 3% difference) in Arm A versus Arm C were CRS (18.5% vs 0.4%), pneumonia (10.3% vs 5.0%), COVID-19 pneumonia (3.7% vs 0%), and febrile neutropenia (5.3% vs 2.1%). All CRS events were Grade 1-2 in severity.

The most frequently reported serious TEAEs (≥ 3% of subjects) in Arm A were CRS, pneumonia, febrile neutropenia, COVID-19, and COVID-19 pneumonia, while the most frequently reported serious TEAE (≥ 3% of subjects) in Arm C was pneumonia.

Table 29. Serious TEAEs Reported in ≥ 1% of subjects in Arm A or Arm C by SOC and PT (Safety Analysis Set). Data Cutoff: 24 May 2025.

MedDRA 27.1 System Organ Class Preferred Term	Arm A (Epco 48 mg + R^2) (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)
Any adverse event	**135 (55.6)**	**69 (29.0)**
Infections and infestations	**81 (33.3)**	**35 (14.7)**
Pneumonia	25 (10.3)	12 (5.0)
COVID-19	11 (4.5)	6 (2.5)
COVID-19 pneumonia	9 (3.7)	0
Upper respiratory tract infection	5 (2.1)	0
Influenza	4 (1.6)	0
Campylobacter gastroenteritis	3 (1.2)	0
Pneumonia fungal	3 (1.2)	0
Respiratory tract infection	3 (1.2)	0
Rhinovirus infection	3 (1.2)	0
Sepsis	1 (0.4)	3 (1.3)
Immune system disorders	**47 (19.3)**	**1 (0.4)**
Cytokine release syndrome	45 (18.5)	1 (0.4)
Blood and lymphatic system disorders	**19 (7.8)**	**10 (4.2)**
Febrile neutropenia	13 (5.3)	5 (2.1)
Neutropenia	6 (2.5)	3 (1.3)
General disorders and administration site conditions	**13 (5.3)**	**10 (4.2)**
Pyrexia	7 (2.9)	6 (2.5)
Investigations	**12 (4.9)**	**2 (0.8)**
Aspartate aminotransferase increased	5 (2.1)	0
Alanine aminotransferase increased	4 (1.6)	0
Neutrophil count decreased	4 (1.6)	0
Cardiac disorders	**9 (3.7)**	**6 (2.5)**
Atrial fibrillation	4 (1.6)	1 (0.4)
Gastrointestinal disorders	**8 (3.3)**	**6 (2.5)**
Diarrhoea	4 (1.6)	2 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**7 (2.9)**	**8 (3.4)**
Malignant neoplasm progression	2 (0.8)	4 (1.7)
Renal and urinary disorders	**7 (2.9)**	**2 (0.8)**
Acute kidney injury	3 (1.2)	0
Respiratory, thoracic and mediastinal disorders	**5 (2.1)**	**13 (5.5)**
Pulmonary embolism	2 (0.8)	4 (1.7)
Pleural effusion	1 (0.4)	6 (2.5)
Vascular disorders	**3 (1.2)**	**6 (2.5)**
Deep vein thrombosis	1 (0.4)	4 (1.7)

Subjects are counted once in each row within a column, regardless of the number of events they may have had.
Defining TEAEs: Any AE with the onset that is the first dose of study drug date until 30 days after discontinuation of lenalidomide or 60 days after discontinuation of rituximab/epcoritamab, whichever comes later or until the subject begins new anti-lymphoma therapy, whichever comes first.
Sort SOC by descending frequency order of Arm A (Epco 48 mg + R^2) first, then sort PT by descending frequency order of Arm A (Epco 48 mg + R^2) within SOC.

Deaths

As of the DCO, 10 (4.1%) subjects in Arm A and 23 (9.7%) subjects in Arm C died (*Table 26*). Six (2.5%) subjects in Arm A and 10 (4.2%) subjects in Arm C died within 60 days after the last dose of study drug.

The primary causes of death in Arm A and Arm C included AE (6 [2.5%] subjects vs. 12 [5.0%] subjects), disease progression (2 [0.8%] subjects vs 8 [3.4%] subjects), and other (2 [0.8%] subjects vs. 3 [1.3%] subjects; all deaths in the other category occurred after the safety-follow-up). Deaths due to disease progression and AEs were reported in a lower proportion of subjects in Arm A compared to Arm C.

Two subjects in Arm C died prior to receiving the first dose of any study drug and were therefore not captured as a fatal TEAE or death in the safety analysis set.

Fatal TEAEs were reported in 6 (2.5%) subjects in Arm A and 12 (5.0%) subjects in Arm C (*Table 30*). Fatal TEAEs excluding events of disease progression in Arm A included PTs of cardiac arrest, cardiac failure, myocarditis, and general physical health deterioration reported in 1 (0.4%) subject, each. Upon sponsor review, these fatal TEAEs occurred primarily in the context of concurrent infections (including COVID-19 pneumonia and sepsis), disease progression of FL, or underlying cardiovascular events. None of the fatal TEAEs in Arm A were considered related to any study drug by the investigator.

In Arm C, fatal TEAEs excluding events of disease progression included 1 (0.4%) event, each, of squamous cell carcinoma of the parotid gland, death (with unknown aetiology), sudden death, encephalitis, pneumonia, septic shock, subdural hematoma, pulmonary embolism, and hypovolemic shock; of these, the fatal TEAE of pulmonary embolism was considered related to lenalidomide by the investigator.

Table 30. TEAEs Leading to Death by SOC and PT (Safety Analysis Set). Data Cutoff: 24 May 2025

MedDRA 27.1 System Organ Class Preferred Term	Arm A (Epco 48 mg + R^2) (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)
Any adverse event	**6 (2.5)**	**12 (5.0)**
Cardiac disorders	**3 (1.2)**	**0**
Cardiac arrest	1 (0.4)	0
Cardiac failure	1 (0.4)	0
Myocarditis	1 (0.4)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (0.8)**	**4 (1.7)**
Malignant neoplasm progression	2 (0.8)	3 (1.3)
Squamous cell carcinoma of the parotid gland	0	1 (0.4)
General disorders and administration site conditions	**1 (0.4)**	**2 (0.8)**
General physical health deterioration	1 (0.4)	0
Death	0	1 (0.4)
Sudden death	0	1 (0.4)
Infections and infestations	**0**	**3 (1.3)**
Encephalitis	0	1 (0.4)
Pneumonia	0	1 (0.4)
Septic shock	0	1 (0.4)
Injury, poisoning and procedural complications	**0**	**1 (0.4)**
Subdural haematoma	0	1 (0.4)
Respiratory, thoracic and mediastinal disorders	**0**	**1 (0.4)**
Pulmonary embolism	0	1 (0.4)
Vascular disorders	**0**	**1 (0.4)**
Hypovolaemic shock	0	1 (0.4)

Adverse events of special interest

AESIs included CRS, ICANS, and CTLS. These are all considered on-target toxicities for epcoritamab, therefore this section will focus on Arm A (Epco 48 mg + R^2 arm).

Cytokine release syndrome (CRS)

In Arm A, a total of 85/243 subjects (35.0%) experienced at least 1 CRS event. In control Arm C, 1/238 (0.4%) patient experienced 5 CRS events. To reduce the incidence and severity of CRS, dosing of epcoritamab 48 mg with 3-step SUD regimen was implemented with the addition of a second intermediate dose in protocol version 3.0. CRS was reported in 35/133 subjects (26.3%) in 3-step SUD versus 50/110 subjects (45.5%) in 2-step SUD, respectively (*Table 31*). Of the patients experiencing CRS with the 2-step SUD, 70% reported one CRS event, 22% two CRS events and 8% three CRS events. Of the patients experiencing CRS with the 3-step SUD, 62.9% reported one CRS event, 28.6% two CRS events and 8.6% three CRS events.

Overall, in Arm A, none of the subjects experienced a CRS event that led to epcoritamab discontinuation; 29 (11.9%) subjects had CRS events that led to epcoritamab dose delay with a lower proportion of subjects in the 3-step SUD compared to the 2-step SUD (10.5% vs 13.6%).

For the 3-step SUD regimen, median time from the first dose of epcoritamab to the first CRS onset was 23.00 days (range: 1.0, 56.0), which correlates with the timing of first full dose of epcoritamab on C1D22. The majority of CRS events occurred during the first cycle of treatment (45/51 events; 88.2%), with the highest incidence occurring after the first full dose administration of epcoritamab. CRS occurred in 6.0% of subjects after the 0.16 mg dose on Cycle 1 Day 1, 3.8% of subjects after the 0.8 mg dose on Cycle 1 Day 8, 2.3% of subjects after the 3 mg dose on Cycle 1 Day 15, and 18.9% of subjects after the 48 mg dose on Cycle 1 Day 22. In the 35 subjects who had at least 1 CRS event, corticosteroids (beyond those administered for mandatory CRS prophylaxis) were used to treat CRS in 13 (37.1%) subjects; 9 (25.7%) subjects received tocilizumab (no other anti-cytokine therapy was used), 3 (8.6%) subjects received oxygen, and none required treatment with vasopressors. CRS resolved in 100% of patients and the median duration of CRS events was 2 days (range: 0.1 to 26 days). None of the CRS events led to epcoritamab discontinuation; 19/51 (37.3%) events led to epcoritamab dose delays.

Table 31. Cytokine Release Syndrome (Safety Analysis Set). Data Cutoff: 24 May 2025

	Arm A (Epco 48 mg + R^2)	
	2-step SUD (N = 110) n (%)	**3-step SUD (N = 133) n (%)**
Subjects with at least one CRS event a	**50 (45.5)**	**35 (26.3)**
Grade 1	40 (36.4)	28 (21.1)
Grade 2	10 (9.1)	7 (5.3)
CRS Prophylaxis b	**48 (96.0)**	**35 (100)**
IV fluid*	11 (22.0)	7 (20.0)
Dexamethasone*	23 (46.0)	25 (71.4)
IV Fluid and Dexamethasone*	27 (54.0)	25 (71.4)
Other Corticosteroids*	38 (76.0)	26 (74.3)
Time to first CRS onset from 1st dose (days)		
n	50	35
Mean (SD)	17.56 (8.954)	22.29 (14.391)
Median	16.00	23.00
Min, Max	2.0, 51.0	1.0, 56.0
Time to CRS resolution (hours)		
Subjects with resolved CRS	50 (100)	35 (100)
Mean (SD) c	77.68 (94.272)	86.47 (114.912)
Median	47.98	47.98
Min, Max	1.3, 536.9	2.0, 616.0

N/E = not estimable
* IV fluids, Dexamethasone and other corticosteroids is on the day of epcoritamab prior to dose administration.
a. Percentage calculated based on number of subjects (N). Other percentages are calculated based on subjects with at least 1 CRS event.
b. May be listed for either epcoritamab or rituximab.
c. Based on longest recorded CRS duration in subjects with > 1 CRS event.
Note: CRS events are graded according to Lee et al 2019.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

ICANS was reported in 1 (0.4%) subject in Arm A, that received the epcoritamab 3-step SUD regimen. The ICANS event was Grade 1 in severity. Time to first ICANS onset was 32 days from the first dose and 2 days after the first full dose of 48 mg epcoritamab. ICANS resolved within 3 days. The event did not lead to epcoritamab discontinuation or dose delay.

Clinical Tumour Lysis Syndrome

No subjects in Arm A or Arm C experienced a CTLS event.

Neurological events

A broad definition for neurological events that included a comprehensive search of all TEAEs coded to the SOC of Nervous System Disorders or Psychiatric Disorders was used. ICANS was included as one of the PTs in both searches and is discussed separately as an AESI.

Neurological TEAEs were reported in 44.9% and 28.2% of subjects in Arm A and Arm C, respectively. The majority of these neurological TEAEs were Grade 1-2 in severity; Grade 3 or 4 events were reported in 2.9% and 2.1% of subjects in Arm A and Arm C, respectively.

In Arm A, the most frequently reported (> 5% of subjects) neurological events were headache (11.1%), tremor (8.2%), dizziness (7.8%), and insomnia (14.4%). In Arm C, neuropathy peripheral (5.5%) was the only event reported in > 5% of subjects.

Neurological events assessed by the investigator as epcoritamab-related were reported in 37 (15.2%) subjects.

Few subjects experienced serious neurological events; 8 (3.3%) and 2 (0.8%) subjects in Arm A and Arm C, respectively. Overall, 1 (0.4%) subject in Arm A discontinued lenalidomide due to an event of peripheral sensory neuropathy; no other neurological TEAEs led to discontinuation of any study drug.

Leukopenia

Leukopenia(broad) was reported in 77.8% and 54.6% of subjects in Arm A and Arm C, respectively. Leukopenia events were mainly Grade ≥3 (72.4% versus 45.4%, respectively). The most frequently reported event in both arms was neutropenia (49.4% in Arm A and 31.5% in Arm C, respectively).

Neutropenia

Neutropenia events (grouped) (TEAEs of neutropenia and neutrophil count decreased) were reported in 74.1% and 51.7% of subjects in Arm A and Arm C, respectively. Grade 3 or 4 neutropenia (grouped) events were reported in 68.7% and 42.0% in Arm A and Arm C. In both arms, neutropenia (grouped) was most frequently in Grade 4 (41.6% and 21.4%) followed by Grade 3 (27.2% and 20.6%). Neutropenia events (grouped) were generally manageable with dose modifications and use of G-CSF. Patients in Arm A had 1 (22.2%), 2 (19.4%), 3 (17.8%) or ≥4 (40.6%) events of neutropenia. In total 83.3% required G-CSF treatment compared to 61.0% in Arm C. Overall, discontinuations of any study drug due to neutropenia (grouped) were few and reported in 2.9% and 2.1% of subjects in Arm A and

Arm C, while events leading to dose delay/interruption of any study drug were reported in 47.7% and 17.6%, respectively.

Febrile neutropenia

Febrile neutropenia was reported in 6.2% and 2.5% in Arm A and Arm C, respectively. Febrile neutropenia events in both Arm A and Arm C were most frequently Grade 3 (4.1% vs 2.1%) followed by Grade 4 (2.1% vs 0.4%); no fatal events of febrile neutropenia were reported. Overall, 1 (0.4%) subject, each, in Arm A and Arm C, experienced febrile neutropenia leading to discontinuation of any study drug, while events leading to dose delay/interruption of any study drug were reported in 5.3% and 1.7%, respectively.

Lymphopenia

Lymphopenia (grouped) was reported in 17.3% and 10.5% of subjects in Arm A and Arm C, respectively, with Grade 3 or 4 events reported in 12.8% and 4.2%, respectively. No serious events of lymphocyte count decreased, or lymphopenia were reported. One (0.4%) subject in Arm A had an event of lymphocyte count decreased that led to discontinuation of epcoritamab and lenalidomide; no subjects discontinued any study drug in Arm C due to lymphopenia (grouped) events. Overall, lymphopenia (grouped) events led to dose delay/interruption of any study drug in 3.3% and 0.4% of subjects in Arm A and Arm C, respectively.

Thrombocytopenia

Thrombocytopenia (broad) was reported in 27.6% and 18.5% of subjects in Arm A and Arm C, respectively, with Grade 3 or 4 events reported in 9.5% and 6.3%, respectively. Two (0.8%) subjects in Arm A and 1 (0.4%) subject in Arm C experienced serious thrombocytopenia (broad). Thrombocytopenia (broad) events led to discontinuation of lenalidomide in 2 (0.8%) subjects in Arm A and 1 (0.4%) subject in Arm C, while one subject in Arm A also discontinued epcoritamab. Events leading to dose delay/interruption of any study drug were reported in 9.5% and 4.2% of subjects in Arm A and Arm C, respectively; among these, lenalidomide dose delay was reported in 7.4% and 3.8%, respectively. Thrombocytopenia (broad) events were generally manageable with dose modifications. Overall, 3.7% and 2.4% of subjects in Arm A and Arm C, respectively, received on-treatment platelet transfusions.

Anaemia

Anaemia (broad) was reported in 28.0% and 17.2% of subjects in Arm A and Arm C, respectively, with Grade 3 or 4 events reported in 7.8% and 4.6%, respectively. Grade 3 anaemia events were reported in 7.8% and 4.2% in Arm A and Arm C, respectively; no Grade 4 events were reported in Arm A and 1 (0.4%) subject in Arm C experienced a Grade 4 event. Two (0.8%) subjects in each arm reported serious anaemia events. One (0.4%) subject in Arm A experienced anaemia that led to discontinuation of epcoritamab and lenalidomide; no subjects discontinued any study drug in Arm C due to anaemia (broad) events. Overall, 7.0% and 4.5% of subjects in Arm A and Arm C, respectively, received on-treatment red blood cells transfusions.

Infections

Analysis of infections included all TEAEs that coded to MedDRA PTs in the SOC of Infections and Infestations. Overall, infections occurred in 77.4% and 52.5% of subjects in Arm A and Arm C, respectively, with Grade 3 or 4 infections reported in 33.3% and 15.1%, respectively. Infections reported in > 10% of subjects in Arm A were COVID-19 (22.2%), upper respiratory tract infection (20.2%), and pneumonia (19.3%) compared to COVID-19 (13.4%) and upper respiratory tract infection (13.9%) reported in Arm C. The most frequently reported Grade 3 or 4 infection in both Arm

A and Arm C was pneumonia (11.5% and 4.6%, respectively). Infections that led to the discontinuation of epcoritamab in > 1 subject included pneumonia (4 [1.6%] subjects) and COVID-19 pneumonia (2 [0.8%] subjects).

Serious Infections

Serious infections were reported in 33.3% and 14.7% of subjects in Arm A and Arm C, respectively; with 22.6% and 5.5%, respectively, being considered related to any study drug. Serious infections that were reported more frequently (> 2% difference) in Arm A versus Arm C were pneumonia (10.3% vs 5.0%), COVID-19 pneumonia (3.7% vs 0%), and upper respiratory tract infection (2.1% vs 0%). The most frequently reported serious infections are shown in Table 32.

Table 32. Serious Infections in ≥ 1% of Subjects in Arm A or Arm C by SOC and PT (Safety Analysis Set)

MedDRA 27.1 System Organ Class Preferred Term	Arm A (Epco 48 mg + R^2) (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)
Serious infection		
Any adverse event	81 (33.3)	35 (14.7)
Infections and infestations	81 (33.3)	35 (14.7)
Pneumonia	25 (10.3)	12 (5.0)
COVID-19	11 (4.5)	6 (2.5)
COVID-19 pneumonia	9 (3.7)	0
Upper respiratory tract infection	5 (2.1)	0
Influenza	4 (1.6)	0
Campylobacter gastroenteritis	3 (1.2)	0
Pneumonia fungal	3 (1.2)	0
Respiratory tract infection	3 (1.2)	0
Rhinovirus infection	3 (1.2)	0
Sepsis	1 (0.4)	3 (1.3)

Fatal infections were infrequent with none reported in Arm A and 3 (1.3%) reported in Arm C with encephalitis, pneumonia, and septic shock being reported in 1 (0.4%) subject, each. None of the fatal infections were considered related to any study drug.

Overall, 11 (4.5%) subjects in Arm A and 3 (1.3%) subjects in Arm C discontinued a study drug due to a serious infection.

COVID-19

COVID-19 events of interest were identified using the SMQ of COVID-19 (narrow). During the timeframe the study was conducted (FSFV occurred on 20 September 2022 and a DCO of 24 May 2025), COVID-19 variants were active worldwide.

COVID-19 infections were reported in 23.9% and 13.9% of subjects in Arm A and Arm C, respectively. Grade 3 or 4 COVID-19 infections were reported in 5.8% and 1.7% of subjects in Arm A and Arm C, respectively; no fatal events of COVID-19 were reported. Serious events of COVID-19 were reported in 7.8% and 2.5% of subjects in Arm A and Arm C, respectively. COVID-19 events that led to discontinuation of any study drug were reported in 1.2% subjects in Arm A while none were reported in Arm C. COVID-19 events that led to interruption of any study drug were reported in 16.0% and 10.1% of subjects in Arm A and Arm C, respectively.

Progressive Multifocal Leukoencephalopathy

No cases of PML were observed.

Injection site reactions (ISR)

ISRs were localised reactions, all Grade 1-2 in severity, and occurred in 28.0% of subjects in Arm A, with none reported in Arm C. No serious events of ISRs were reported. In Arm A, 1 (0.4%) subject discontinued epcoritamab and lenalidomide due to ISR and 1 (0.4%) subject experienced a dose delay of epcoritamab due to ISR. The most frequently reported (in > 1% of subjects) ISRs in Arm A were injection site reaction (21.8%) followed by injection site erythema (5.3%).

Laboratory findings

Haematology

A summary of Grade ≥3 treatment-emergent haematology laboratory abnormalities is shown in Table 33. Post-baseline shifts from normal (Grade 0) baseline to worst on-treatment result of Grade 4 with incidences of > 5% were observed for neutrophils (hypo; 42.7%) and lymphocytes (hypo; 9.4%) in Arm A and for neutrophils (hypo; 20.5%) in Arm C. Post-baseline shifts from normal (Grade 0) baseline to worst on-treatment result of Grade 3 with incidences of > 10% were observed for lymphocytes (hypo; 46.8%), neutrophils (hypo; 24.9%), and leukocytes (hypo; 18.2%) in Arm A and for neutrophils (hypo; 22.8%) and leukocytes (hypo; 16.8%) in Arm C.

Table 33. Summary of Treatment-Emergent Haematology Laboratory Abnormalities Grade 3 or Higher (Safety Analysis Set)

Lab Parameter (Unit) Criteria#	Arm A (Epco 48 mg + R^2) (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)
Hemoglobin (g/L) (hyper)		
n	243	237
Grade 3	0	0
Grade 4	N/A	N/A
Grade 3 and above	0	0
Hemoglobin (g/L) (hypo)		
n	243	237
Grade 3	21 (8.6)	11 (4.6)
Grade 4	0	0
Grade 3 and above	21 (8.6)	11 (4.6)
Leukocytes (10^9/L) (hyper)		
n	243	236
Grade 3	0	1 (0.4)
Grade 4	0	0
Grade 3 and above	0	1 (0.4)
Leukocytes (10^9/L) (hypo)		
n	243	236
Grade 3	49 (20.2)	43 (18.2)
Grade 4	16 (6.6)	8 (3.4)
Grade 3 and above	65 (26.7)	51 (21.6)
Neutrophils (10^9/L) (hypo)		
n	243	236
Grade 3	61 (25.1)	53 (22.5)
Grade 4	107 (44.0)	53 (22.5)
Grade 3 and above	168 (69.1)	106 (44.9)
Lymphocytes (10^9/L) (hyper)		
n	242	235
Grade 3	3 (1.2)	2 (0.9)
Grade 4	N/A	N/A
Grade 3 and above	3 (1.2)	2 (0.9)
Lymphocytes (10^9/L) (hypo)		
n	242	235
Grade 3	120 (49.6)	29 (12.3)
Grade 4	33 (13.6)	7 (3.0)
Grade 3 and above	153 (63.2)	36 (15.3)
Platelets (10^9/L) (hypo)		
n	243	236
Grade 3	16 (6.6)	8 (3.4)
Grade 4	12 (4.9)	7 (3.0)

Lab Parameter (Unit) Criteria#	Arm A (Epco 48 mg + R^2) (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)
Grade 3 and above	28 (11.5)	15 (6.4)

Chemistry

A summary of Grade ≥3 treatment-emergent chemistry laboratory abnormalities is shown in Table 34. Post-baseline shifts from normal (Grade 0) baseline to worst on-treatment result of Grade 4 with incidences of > 2% were observed for calcium corrected (hypo) in 2.9% and 5.6% in Arm A and Arm C, respectively. Post-baseline shifts from normal (Grade 0) baseline to worst on-treatment result of Grade 3 with incidences of > 5% were observed for potassium (hypo; 7.6%), alanine aminotransferase (hyper; 6.1%) and uric acid (elevated; 12.4%) in Arm A and for uric acid (elevated; 9.7%) in Arm C.

Table 34. Summary of Treatment-Emergent Chemistry Laboratory Abnormalities Grade 3 or Higher (Safety Analysis Set)

Lab Parameter (Unit) Criteria#	Arm A (Epco 48 mg + R^2) (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)
Sodium (mmol/L) (hyper)		
n	243	235
Grade 3	0	0
Grade 4	0	0
Grade 3 and above	0	0
Sodium (mmol/L) (hypo)		
n	243	235
Grade 3	10 (4.1)	6 (2.6)
Grade 4	0	1 (0.4)
Grade 3 and above	10 (4.1)	7 (3.0)
Potassium (mmol/L) (hyper)		
n	243	234
Grade 3	1 (0.4)	1 (0.4)
Grade 4	0	0
Grade 3 and above	1 (0.4)	1 (0.4)
Potassium (mmol/L) (hypo)		
n	243	234
Grade 3	22 (9.1)	11 (4.7)
Grade 4	1 (0.4)	1 (0.4)
Grade 3 and above	23 (9.5)	12 (5.1)
Creatinine (umol/L) (hyper)		
n	243	235
Grade 3	3 (1.2)	1 (0.4)
Grade 4	0	1 (0.4)
Grade 3 and above	3 (1.2)	2 (0.9)
Glucose (mmol/L) (hypo)		
n	242	234
Grade 3	0	0
Grade 4	0	0
Grade 3 and above	0	0
Calcium Corrected (mmol/L) (hyper)		
n	217	199
Grade 3	2 (0.9)	0
Grade 4	2 (0.9)	1 (0.5)
Grade 3 and above	4 (1.8)	1 (0.5)
Calcium Corrected (mmol/L) (hypo)		
n	217	199
Grade 3	5 (2.3)	1 (0.5)
Grade 4	5 (2.3)	6 (3.0)
Grade 3 and above	10 (4.6)	7 (3.5)
Magnesium (mmol/L) (hyper)		
n	153	138
Grade 3	1 (0.7)	1 (0.7)
Grade 4	0	0
Grade 3 and above	1 (0.7)	1 (0.7)

Lab Parameter (Unit) Criteria#	Arm A (Epco 48 mg + R^2) (N = 243) n (%)	Arm C (R^2) (N = 238) n (%)
Magnesium (mmol/L) (hypo)		
n	153	138
Grade 3	2 (1.3)	1 (0.7)
Grade 4	0	0
Grade 3 and above	2 (1.3)	1 (0.7)
Albumin (g/L) (hypo)		
n	241	234
Grade 3	3 (1.2)	1 (0.4)
Grade 4	0	0
Grade 3 and above	3 (1.2)	1 (0.4)
Bilirubin (umol/L) (hyper)		
n	243	235
Grade 3	2 (0.8)	0
Grade 4	0	0
Grade 3 and above	2 (0.8)	0
Alanine Aminotransferase (U/L) (hyper)		
n	243	235
Grade 3	15 (6.2)	2 (0.9)
Grade 4	2 (0.8)	0
Grade 3 and above	17 (7.0)	2 (0.9)
Aspartate Aminotransferase (U/L) (hyper)		
n	243	234
Grade 3	6 (2.5)	2 (0.9)
Grade 4	2 (0.8)	0
Grade 3 and above	8 (3.3)	2 (0.9)
Alkaline Phosphatase (U/L) (hyper)		
n	243	235
Grade 3	0	1 (0.4)
Grade 4	0	0
Grade 3 and above	0	1 (0.4)
Uric Acid (mmol/L) (elevated)		
n	241	233
Grade 3	25 (10.4)	18 (7.7)
Grade 4	0	0
Grade 3 and above	25 (10.4)	18 (7.7)
Triglycerides (mmol/L) (hyper)		
n	232	229
Grade 3	15 (6.5)	5 (2.2)
Grade 4	2 (0.9)	0
Grade 3 and above	17 (7.3)	5 (2.2)

As of the DCO, 2 (0.8%) subjects in Arm A and 1 (0.4%) subject in Arm C had elevated LFTs that met the laboratory criteria for potential DILI or Hy's Law. Upon review of each case, no cases were identified that clinically qualified to meet the criteria for DILI or Hy's Law. All 3 subjects had potential alternative aetiologies for the elevated LFTs including septic shock, recent CRS, and other medications known to cause elevated transaminases or hepatotoxicity. One subject in Arm C died of septic shock and the 2 subjects from Arm A completed their 12 cycles of study treatment without recurrence of elevated LFTs that met the laboratory criteria for potential DILI.

Vital signs

Clinically notable vital signs that were reported more frequently (> 10% difference) in Arm A versus Arm C were body temperature < 36° C (46.5% vs 33.2%), body temperature ≥ 38.0° C (34.2% vs 4.3%), diastolic blood pressure < 50 mmHg (16.9% vs 6.0%), and systolic blood pressure < 90 mmHg (14.8% vs 3.4%).

Electrocardiograms (ECG)

Clinically significant ECG abnormalities were reported at baseline in 0.4% (Arm A) and 1.7% (Arm C) and during the overall on-treatment period in 0.8% (Arm A) and 0.4% (Arm C). All 3 subjects with on-

treatment clinically significant ECG abnormalities had an associated TEAE (ECG ST segment elevation and tricuspid valve disease in Arm A and ECG ST-T segment abnormal in Arm C).

At baseline, QTcF intervals were ≤450 ms for the majority of subjects; 95.1% and 94.1% in Arm A and Arm C, respectively; baseline QTcF values >500 ms were reported in 2 (0.8%) subjects in Arm A and 0 subjects in Arm C. During the overall on-treatment period, 1 subject in Arm A had a QTcF interval between 450 – 480 and no subjects in either arm had QTcF interval > 480 ms.

Safety in special populations

Age

In Study M20-638 Arm A, the median age of subjects was 60.0 years, and the number of subjects in < 65 years, 65 to < 75 years, and ≥ 75 years categories were 155, 68, and 20 subjects, respectively (*Table 35*). The incidences of all grade TEAEs and Grade ≥3 TEAEs were comparable (< 10% difference) among the various age groups. The incidence of CRS was 20% in the oldest age group (≥75 years) compared to 50.3% (<65 years) and 48.5% (65 - <75 years). No age-related trends in the frequency across TEAE categories were observed (Table 35).

In Study M20-638 Arm C, the median age of subjects was 63.0 years, and the number of subjects in < 65 years, 65 to < 75 years, and ≥ 75 years categories were 137, 67, and 34 subjects, respectively (Table 35). The incidences of all grade TEAEs were comparable (< 10% difference) among the various age groups. The incidence of Grade ≥3 TEAEs was higher in older age groups (Table 35).

In All Epco + R^2 pool, the incidences of all grade TEAEs and CRS by age subgroup were similar to that described above for Study M20-638 Arm A. The incidences of Grade ≥3 TEAEs was 95.2% in the oldest age group (≥75 years) compared to 83.8% (<65 years) and 89.6% (65 - <75 years).

Table 35. Treatment-Emergent Adverse Events by System Organ Class and Age

	Arm A Epco 48 mg + R^2			**Arm C R^2**		
	<65 years (N=155)	**65 to <75 years (N=68)**	**≥75 years (N=20)**	**<65 years (N=137)**	**65 to <75 years (N=67)**	**≥75 years (N=34)**
≥1 TEAE	154 (99.4%)	68 (100%)	20 (100%)	134 (97.8%)	67 (100%)	34 (100%)
TEAE Grade ≥3	136 (87.7%)	64 (94.1%)	19 (95.0%)	82 (59.9%)	52 (77.6%)	27 (79.4%)
TEAE leading to discontinuation of any study drug	24 (15.5%)	18 (26.5%)	4 (20.0%)	13 (9.5%)	7 (10.4%)	9 (26.5%)
Fatal TEAE	2 (1.3%)	3 (4.4%)	1 (5.0%)	6 (4.4%)	1 (1.5%)	5 (14.7%)
TEAE by SOC						
Infections and infestations	119 (76.8%)	55 (80.9%)	14 (70.0%)	71 (51.8%)	35 (52.2%)	19 (55.9%)
Blood and lymphatic system disorders	104 (67.1%)	53 (77.9%)	11 (55.0%)	53 (38.7%)	39 (58.2%)	16 (47.1%)
Gastrointestinal disorders	99 (63.9%)	39 (57.4%)	14 (70.0%)	79 (57.7%)	35 (52.2%)	21 (61.8%)
General disorders and administration site conditions	99 (63.9%)	48 (70.6%)	17 (85.0%)	56 (40.9%)	32 (47.8%)	13 (38.2%)
Investigations	99 (63.9%)	42 (61.8%)	10 (50.0%)	54 (39.4%)	29 (43.3%)	11 (32.4%)
Skin and subcutaneous tissue disorders	86 (55.5%)	38 (55.9%)	10 (50.0%)	62 (45.3%)	37 (55.2%)	19 (55.9%)
Immune system disorders	78 (50.3%)	33 (48.5%)	4 (20.0%)	9 (6.6%)	7 (10.4%)	2 (5.9%)
Metabolism and nutrition disorders	62 (40.0%)	29 (42.6%)	11 (55.0%)	38 (27.7%)	18 (26.9%)	10 (29.4%)
Respiratory, thoracic and mediastinal disorders	60 (38.7%)	30 (44.1%)	8 (40.0%)	33 (24.1%)	19 (28.4%)	9 (26.5%)
Nervous system disorders	56 (36.1%)	27 (39.7%)	7 (35.0%)	38 (27.7%)	15 (22.4%)	6 (17.6%)

Musculoskeletal and connective tissue disorders	46 (29.7%)	27 (39.7%)	6 (30.0%)	43 (31.4%)	22 (32.8%)	11 (32.4%)
Injury, poisoning and procedural complications	37 (23.9%)	17 (25.0%)	6 (30.0%)	23 (16.8%)	12 (17.9%)	5 (14.7%)
Psychiatric disorders	27 (17.4%)	14 (20.6%)	5 (25.0%)	9 (6.6%)	3 (4.5%)	2 (5.9%)
Vascular disorders	20 (12.9%)	12 (17.6%)	6 (30.0%)	13 (9.5%)	10 (14.9%)	5 (14.7%)
Renal and urinary disorders	17 (11.0%)	8 (11.8%)	4 (20.0%)	6 (4.4%)	7 (10.4%)	5 (14.7%)
Eye disorders	12 (7.7%)	6 (8.8%)	3 (15.0%)	9 (6.6%)	4 (6.0%)	2 (5.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (7.1%)	6 (8.8%)	0	9 (6.6%)	5 (7.5%)	3 (8.8%)
Cardiac disorders	9 (5.8%)	8 (11.8%)	4 (20.0%)	6 (4.4%)	4 (6.0%)	3 (8.8%)
Hepatobiliary disorders	8 (5.2%)	4 (5.9%)	0	1 (0.7%)	0	1 (0.7%)
Ear and labyrinth disorders	7 (4.5%)	3 (4.4%)	0	6 (4.4%)	1 (1.5%)	1 (2.9%)
Endocrine disorders	6 (3.9%)	1 (1.5%)	0	2 (1.5%)	2 (3.0%)	0
Reproductive system and breast disorders	5 (3.2%)	1 (1.5%)	0	5 (3.6^)	0	0
Congenital, familial and genetic disorders	3 (1.9%)	0	0	0	1 (1.5%)	0
Surgical and medical procedures	1 (0.6%)	1 (1.5%)	0	0	0	2 (5.9%)
Product issues	0	1 (1.5%)	0	0	0	0

Sex

In Study M20-638 Arm A, 139 subjects were male, and 104 subjects were female. The incidence of all grade TEAEs (99.5% versus 100%), Grade ≥3 TEAEs 87.8% versus93.3%), serious TEAEs (53.2% versus 58.7%), and CRS (30.9% versus 40.4%) were comparable between males and females respectively.

In the All Epco + R^2 pool TEAEs by sex subgroup were similar to that described above for Study M20-638 Arm A, except the incidence of CRS in All Epco + R^2 pool was higher in female than male subjects (46.2% vs 35.5%).

Race

Adverse events were analysed by the race of White, Asian, Black or African American, or Other. Given that the numbers of subjects in the Black or African American and Other groups were generally low, these two races were not compared for the impact of race on AEs.

In Study M20-638 Arm A, 168 subjects were White and 63 subjects were Asian. The incidences of all grade (99.4% versus 100%), Grade ≥3 TEAEs (87.5 versus 95.2) and CRS (31% versus 50.8%) were comparable between White and Asian respectively. Serious TEAEs (60.1% versus 46.0%) were more frequent in White; the higher frequency of serious TEAEs in White was also observed in Arm C (32.6% and 15.1% respectively).

In All Epco + R^2 pool, similar trends were observed as those reported in Study M20-638 Arm A.

Renal function

In Study M20-638 Arm A, 124 subjects had normal baseline renal function, 94 subjects had mildly impaired, and 25 subjects had moderately impaired renal function. The number of all grade TEAEs was 100% (normal), 98.9% (mildly impaired) and 100.0% (moderately impaired). Grade ≥3 TEAEs were reported in 85.5% (normal), 94.7% (mildly impaired) and 96.0% (moderately impaired). Serious TEAEs were observed in 50.0% (normal), 60.6% (mildly impaired) and 64.05 (moderately impaired).

In Arm C, a Grade ≥3 TEAEs and serious TEAEs were also more frequent in subjects with worse baseline renal function.

In All Epco + R^2 pool, similar trends were observed as those reported in Study M20-638 Arm A.

Other

Subgroups based on baseline weight, Ann Arbor stage, FLIPI-1 score, ECOG, ethnicity, prior lines of anti-lymphoma therapy/status and region have also been provided in the CSR, however are not reflected here.

Safety related to drug-drug interactions and other interactions

Epcoritamab causes the release of cytokines that may suppress activity of cytochrome P450 (CYP) enzymes, resulting in increased exposure of CYP substrates. Increased exposure of CYP substrates is more likely to occur after the first dose of epcoritamab on Cycle 1 Day 1 and up to 14 days after the first 48 mg dose, and during and after CRS. The 3-step SUD regimen (0.16/0.8/3/48 mg), along with adequate hydration and use of dexamethasone prophylaxis during Cycle 1, further reduced the release of cytokines, and therefore potentially the risk of drug interactions.

No new drug-drug interactions have been identified.

Discontinuation due to adverse events

Discontinuations

TEAEs leading to discontinuation of any study drug were reported in 18.9% of subjects in Arm A, with 8.6%, 2.9%, and 18.5% of subjects discontinuing epcoritamab, rituximab, and lenalidomide, respectively (*Table 26*). TEAEs leading to discontinuation of any study drug were reported in 12.2% of subjects in Arm C, with 5.0%, and 12.2% of subjects discontinuing rituximab and lenalidomide, respectively.

In Arm A, TEAEs that led to study drug discontinuation in > 1% of subjects included pneumonia (1.6%) for epcoritamab, none for rituximab, and neutropenia (2.5%), pneumonia and rash (1.6%, each), and diarrhoea (1.2%) for lenalidomide. Epcoritamab-related TEAEs leading to epcoritamab discontinuation reported in > 1 subject included pneumonia (4 [1.6%] subjects) and COVID-19 pneumonia (2 [0.8%] subjects).

In Arm C, none of the TEAEs led to rituximab discontinuation in > 1% of subjects, while neutropenia (1.3%) was the only TEAE that led to lenalidomide discontinuation in > 1% of subjects.

Dose delay/interruptions

TEAEs leading to dose delay/interruption of any study drug were reported in 84.0% of subjects in Arm A, with 76.1%, 60.1%, and 74.5% of subjects experiencing dose delays of epcoritamab, rituximab, and lenalidomide, respectively (*Table 26*). TEAEs leading to dose delay/interruption of any study drug were reported in 53.4% of subjects in Arm C, with 31.1%, and 45.0% of subjects experiencing dose delays of rituximab and lenalidomide, respectively.

Dose delays of epcoritamab were most frequent during the early treatment cycles, with 63.0% of subjects experiencing dose delays due to AEs within the first 3 months of epcoritamab exposure 35.4% during the 3 to < 6 months period, 30.0% during 6 to < 9 months, 24.7% during 9 to < 12 months, and 3.1% in the 12 to < 18 months period. Dose delays of epcoritamab due to AEs within the first 3 months were most commonly due to infections and infestations (33.7%), blood and lymphatic system

disorders (17.7%) and immune system disorders (11.9%). The incidence of dose delays due to immune system disorders in the first 3 months was higher for the 2-step SUD (13.6%) compared to the 3-step SUD (10.5%). In Arm A, the most common (in > 5% of subjects) TEAEs that led to dose delay of epcoritamab were neutropenia (27.2%), neutrophil count decreased (15.6%), COVID-19 (13.6%), CRS (11.9%), pneumonia (11.1%), and upper respiratory tract infection (10.3%). Similar events led to dose delay/interruption of R^2 in > 5% of subjects in Arm A, with the addition of rash and diarrhoea which led to dose delay of lenalidomide in 7.0% and 6.6% of subjects, respectively. Epcoritamab-related TEAEs leading to epcoritamab dose delay reported in > 5% of subjects included neutropenia (15.2%), neutrophil count decreased (14.0%), CRS (11.1%), and pneumonia (10.3%).

In Arm C, the most common (in > 5% of subjects) TEAEs that led to study drug dose delay/interruption included neutropenia (5.9%) for rituximab while for lenalidomide these included neutropenia (10.1%), COVID-19 (8.0%), and neutrophil count decreased (6.7%).

Dose reductions

Dose reductions were allowed only for lenalidomide and were reported in 57 (23.5%) and 44 (18.5%) subjects in Arm A and Arm C, respectively. The most frequently reported TEAE that led to lenalidomide dose reduction in both Arm A and Arm C was neutropenia (7.0% vs 3.8%) followed by neutrophil count decreased (2.9% vs 3.4%).

Adverse drug reactions in SmPC

The search criteria for identifying ADRs by the MAH in subjects with R/R FL treated with epcoritamab + R^2 in Study M20-638 were based on both quantitative thresholds against the comparator arm and qualitative medical assessment. Specifically, TEAEs demonstrating a between-arm difference of ≥ 5% for all-grade events or ≥ 2% for Grade 3 or 4 events were initially identified. Each event term identified through this quantitative analysis was subsequently subjected to comprehensive medical review and clinical judgment to determine its causal relationship to epcoritamab and its appropriateness for classification as an ADR.

Clinical judgment was informed by multiple considerations, including potential biological plausibility and MOA; relevant nonclinical toxicology findings; higher frequency compared with background rates in the treated population, where available; severity and clinical consequences (e.g., resulting in treatment discontinuation or other medical intervention); association with an existing ADR (including symptoms or sequelae); consistency with events reported for similar agents within the CD3×CD20 therapeutic class; and evidence of a positive dose-response or exposure-response relationship, where available. Additional factors considered include whether the event is typical of drug-induced toxicity, the presence of index cases or consistent clinical patterns, evidence of de-challenge or rechallenge, and supportive laboratory or vital sign findings, as appropriate.

The ADRs proposed for inclusion in the SmPC are provided in Table 36.

Compared to the ADRs of the approved monotherapy, the following ADRs were added:, cytomegalovirus infection (7.4% versus 0%), herpes virus infection (7.4% versus 0%), insomnia (14.4% versus 3.4%), constipation (27.6% versus 21.5%) and mucositis (9.9% versus 3.4%) and blood potassium decreased (19.8% versus 1.3%).

Table 36. ADRs proposed for inclusion in the SmPC

Immune system disorders	
Very Common	cytokine release Syndrome (26.3%)

Nervous system disorders	
Very common	neurological changes (12.3%), headache (11.1%)
Uncommon	immune effector cell-associated neurotoxicity syndrome (0.8%)
Infections and infestations	
Very Common	upper respiratory tract infections (35.44%), COVID-19 (23.9%), Pneumonia (23.5%)
Common	cytomegalovirus infection (7.4%), fungal infection (2.5%) herpes virus infection (7.4%)
Blood and lymphatic system disorders	
Very common	neutropenia (74.1%), anaemia (28.0%), thrombocytopenia (27.6%), lymphopenia (17.3%)
Common	febrile neutropenia (6.2%)
Immune system disorders	
Very common	hypogammaglobulinemia (24.7%)
Psychiatric disorders	
Very common	insomnia (14.4%)
Gastrointestinal disorders	
Very common	diarrhoea (30.9%), constipation (27.6%), nausea (16.9%)
Common	mucositis (9.9%)
Skin and subcutaneous tissue disorders	
Very common	rash (43.2%)
General disorders and administration site conditions	
Very common	fatigue (32.9%), injection site reactions (28.0%), pyrexia (23.9%)
Investigations	
Very common	blood potassium decreased (19.8%), alanine aminotransferase increased (18.9%), aspartate aminotransferase increased (11.9%)

Post marketing experience

As of 21 March 2025, epcoritamab is registered in 56 countries for R/R DLBCL and in 44 countries for adults with R/R FL after 2 or more lines of systemic therapy. The estimated cumulative post-marketing patient exposure since first approval is 1,870 Patient Treatment Years (PTY), based on available global sales data calculated through 31 March 2025.

2.5.1. Discussion on clinical safety

Safety dataset

The primary analysis set for the safety assessment of epcoritamab in combination with R^2 was based on data from the pivotal phase 3 open-label RCT M20-638. Pooling of the 2-step and 3-step SUD regimen for safety assessment is considered acceptable as the difference between these regimens in terms of total exposure is relatively minor, except for the assessment of CRS and ICANS.

A supportive safety analysis set was provided which included all patients treated with either epcoritamab 24 mg or 48 mg in combination with rituximab and lenalidomide.

The size of the safety database is considered acceptable, also considering the existing data on the safety profile of epcoritamab from the approved monotherapy indications for R/R DLBCL and R/R FL.

Exposure

The median follow-up for safety was shorter in Arm C (10.1 months) compared to Arm A (12.3 months) due to early treatment discontinuation in Arm C.

In Arm A, 18.1% of patients were on study treatment at the DCO of 24 May 2025. The median number of epcoritamab cycles was 12, corresponding to the intended number of 12 treatment cycles. Dose delays of epcoritamab were common (79.8%) and were mainly due to adverse events. Dose delays were most frequent during the first 3 months of epcoritamab, mainly due to infections and CRS. The incidence of dose delays due to immune system disorders (including CRS) in the first 3 months was higher for the 2-step SUD (13.6%) compared to the 3-step SUD (10.5%). In total 27.2% of patients needed re-priming and the guidance for re-repriming is sufficiently described in SmPC section 4.2.

The median number of rituximab cycles was the intended 5 cycles in both arms and the median number of lenalidomide cycles was 12 in Arm A and 11 in Arm C. The most frequent reason for lenalidomide discontinuation was progressive disease. Progressive disease was more common in Arm C, which might explain the lower lenalidomide exposure in Arm C.

The extent of exposure is acceptable considering the duration of treatment and disease setting. Long-term safety is included as missing information in the RMP.

Adverse events

Almost all patients in both arms experienced **TEAEs**. The most frequently reported TEAEs are all known ADRs of epcoritamab (monotherapy), rituximab and/or lenalidomide and have been added to Tepkinly's SmPC ADR table.

Adverse events that were reported more frequently (≥ 10% difference) in Arm A versus Arm C were neutropenia (49.4% vs. 31.5%), CRS (35.0% vs. 0.4%), anaemia (27.6% vs 17.2%), pyrexia (23.9% vs 13.9%), ISR (21.8% vs 0%), hypokalemia (19.8% vs 8.8%) hypogammaglobulinemia (19.3% vs 4.2%), pneumonia (19.3% vs 8.4%), and insomnia (14.4% vs 3.4%). These were all included as ADR in the SmPC, which is supported.

Grade 3 or 4 TEAEs were more common in Arm A (90.1%) compared to Arm C (66.8%) mainly driven by a higher incidence of neutropenia (46.1% vs. 25.6%). The most frequently reported Grade 3 or 4 events in Arm A were neutropenia (46.1%), neutrophil count decreased (24.7%), pneumonia (11.5%), anaemia (7.8%), rash (7.8%), hypokalemia (6.6%), lymphocyte count decreased (6.6%), thrombocytopenia (6.6%), alanine aminotransferase increased (6.2%), febrile neutropenia (6.2%), and lymphopenia (6.2%). These were all included as ADR in the SmPC, which is supported.

The overall incidence of all grade TEAEs and Grade 3 or 4 TEAEs in the supportive safety analysis set was comparable to Arm A.

The methodology to define ADRs proposed for inclusion in the SmPC was based on both quantitative thresholds against the comparator arm and medical assessment. In general, the methodology to define ADRs proposed for inclusion in the SmPC is considered acceptable. The proposed ADRs for the combination of epcoritamab with R^2 are largely in line with the ADRs for epcoritamab monotherapy, however the following ADRs were added: neurological changes (12.3% versus 5.5%), cytomegalovirus infection (3.7% versus 0%), herpes virus infection (7.4% versus 0%), hypogammaglobulinaemia (24.7% versus 4.6%), insomnia (14.4% versus 3.4%), constipation (27.6% versus 21.5%) and mucositis (9.9% versus 3.4%) and blood potassium decreased (2.5% versus 1.3%). Epcoritamab monotherapy was approved based on a single arm trial. The addition of these ADRs is agreed, as it is based on the observed higher frequency in Arm A in the pivotal RCT M20-638.

Following request, the MAH added fungal infection as ADR to SmPC section 4.8. As fungal infection was identified as an ADR for epcoritamab monotherapy, there is biological plausibility as epcoritamab is associated with a higher risk of infections and the frequency is three times higher in Arm A compared to Arm C (2.5% versus 0.8%)

Epcoritamab-related TEAEs were common (90.1%). The most frequent epcoritamab-related TEAEs were CRS, neutropenia, neutrophil count decreased and injection site reaction. The epcoritamab-related TEAEs are adequately reflected as ADRs.

Serious TEAEs were more frequent in Arm A (55.6%) compared to Arm C (29.0%). The most frequently reported serious TEAEs in Arm A were CRS (18.5%), pneumonia (10.3%), febrile neutropenia (5.3%), COVID-19 (4.5%), and COVID-19 pneumonia (3.7%), while the most frequently reported serious TEAE in Arm C was pneumonia (5.0%). These were all included as ADR in the SmPC, which is supported.

Neutropenia is known and very common ADR for epcoritamab monotherapy, rituximab and lenalidomide (SmPC epcoritamab; SmPC rituximab; SmPC lenalidomide). The combination of epcoritamab + R^2 resulted in a high frequency of neutropenia events, mainly Grade ≥3 TEAEs. The frequency of grouped neutropenia events (TEAEs of neutropenia and neutrophil count decreased) was 74.1% (Arm A) and 51.7% (Arm C), respectively. Grade 3 or 4 neutropenia (grouped) events were reported in 68.7% and 42.0% in Arm A and Arm C. Most patients in Arm A experienced multiple events of neutropenia, and 83.3% required G-CSF treatment compared to 61.0% in Arm C. **Febrile neutropenia** was more frequent with epcoritamab + R^2 (6.2% compared to 2.5%). A recommendation to consider G-CSF and a reference to the SmPC of lenalidomide are included in SmPC section 4.2. The SmPC of lenalidomide contains specific instructions for lenalidomide dose modifications in case of neutropenia (SmPC lenalidomide). Furthermore, a reference to the SmPC of rituximab is included in section 4.2 which contains recommendations regarding the determination of immunoglobin levels.

Infections were more frequently reported in Arm A (77.4%) compared to Arm C (52.5%). Serious infections were reported in 33.3% (Arm A) versus 14.7% (Arm C). There were no fatal TEAEs due to infection. The most frequent infections reported in ~20% of patients in Arm A were COVID-19, upper respiratory tract infection and pneumonia. The most frequent **serious infections** were pneumonia (10.3%), COVID-19 (4.5%) and COVID-19 pneumonia (3.7%). Study M20-638 was conducted after the Omicron peak of the COVID-19 pandemic with the first inclusion in September 2022. The study protocol included recommendations for interruption and/or discontinuations in case of (suspected) COVID-19, which were largely in line with the EHA/ESMO practice guidelines (Dreyling et al, 2020). The rates of serious COVID-19 infections and Grade 3/4 COVID-19 infections were lower compared to the rates reported for epcoritamab monotherapy in the R/R FL indication (EMA/369446/2024), however the pivotal studies for the monotherapy indication were conducted at the peak of the pandemic.

In conclusion, neutropenia and infections are known risks associated with R^2, and the addition of epcoritamab to R^2 resulted in a further increase of the risk of neutropenia and infections. This is sufficiently described in the SmPC with a warning for serious infections (section 4.4) and additional information on serious infections and neutropenia is included in the description of selected adverse events (section 4.8).

Deaths

In Arm A, 10 patients (4.4%) died due to adverse events (n=6), disease progression (n=2) and other (n=2). In Arm C, 23 (9.7%) patients died due to adverse events (n=12), disease progression (n=8) and other (n=3).

The incidence of fatal TEAEs was higher in arm C (5.0%) compared to arm A (2.5%) which is unexpected as both arms have the same backbone of R^2. After exclusion of event terms reported as disease progression, fatal TEAE rates were 3.8% (n=9) in Arm C compared to 1.6% (n=4) in Arm A. Fatal TEAEs in Arm C mainly occurred in patients with significant baseline comorbidities and intercurrent clinical events. The reason for the higher incidence of fatal TEAEs in Arm C compared to Arm A is not clear. The fatal TEAEs were not caused by a specific TEAE and the numerically small number of TEAEs hampers further assessment.

Three (1.2%) fatal TEAEs in arm A were due to cardiac disorders (cardiac arrest, cardiac failure and myocarditis) compared to zero fatal TEAEs due to cardiac disorders in arm C. In two cases the cardiac event was related to an active infection, and in one case the patient only received the step-up dose (0.16mg – 0.8mg). Therefore, there is no clear indication that epcoritamab leads to an increased risk of cardiovascular events.

All fatal TEAEs in Arm A were considered not related to the study drug by the investigator, while one fatal TEAE in Arm C (pulmonary embolism) was considered related to lenalidomide. However, in two cases the fatal TEAE was a cardiac event related to an active infection. As epcoritamab increases the risk of infections, a causal relationship between those two fatal TEAEs and epcoritamab cannot be excluded. The increased risk of infections is sufficiently addressed in the SmPC.

Adverse events of special interest

In Arm A, a total of 85/243 subjects (35.0%) experienced at least 1 **CRS** event. With the 3-step SUD regimen CRS was reported in 35/133 subjects (26.3%) compared to 50/110 subjects (45.5%) with the 2-step SUD regimen. All events with the 3-step SUD regimen were low grade (21.1% Grade 1; 5.3% Grade 2). Most events occurred during the first treatment cycle. All CRS events resolved within a median of 2 days. The frequency of CRS with the 3-step SUD regimen is lower than previously reported for epcoritamab monotherapy (EMA/369446/2024; EMA/CHMP/419797/2023) and for other bispecifics for R/R follicular lymphoma (mosunetuzumab EMA/390815/2022; odronextamab EMA/518269/2024). In addition to the 3-step SUD regimen, the mandated premedication with corticosteroids, antihistamines and antipyretics as well as recommendations for hydration potentially contributed to the relatively low frequency of CRS. The epcoritamab premedication and recommended fluid guidelines are adequately described in SmPC section 4.2.

There was only one event of **ICANS** (Grade 1). Neurological TEAEs were more frequently reported in Arm A (44.9%) compared to Arm C (28.2%) but most frequently due to headache, tremors, dizziness and insomnia. There were no events of **clinical tumor lysis syndrome** or **progressive multifocal leukoencephalopathy**.

Haematological TEAEs (lymphopenia, thrombocytopenia, anaemia) were more frequent in Arm A compared to Arm C. As a result, on-treatment platelet and red blood cells transfusions were more

common in Arm A compared to Arm C. As discussed above, infections were more frequent in Arm A and a warning for serious infections is included in SmPC section 4.4.

Discontinuations

The frequency of treatment discontinuations of any study drug was higher in Arm A compared to Arm C (18.9% versus 12.2%) The most common TEAEs resulting in discontinuation were pneumoniae (including COVID-19 pneumonia), neutropenia, rash and diarrhoea. These TEAEs are known ADRs of all three study drugs. Most often lenalidomide (18.5%) was discontinued followed by epcoritamab (8.6%) and rituximab (2.9%). TEAEs leading to discontinuation of any study drug were reported in 12.2% of subjects in Arm C, with 5.0%, and 12.2% of subjects discontinuing rituximab and lenalidomide, respectively. TEAEs leading to dose delay/interruption of any study drug were reported in 84.0% of subjects in Arm A compared to 53.4% in Arm C. In conclusion, although the tolerability of epcoritamab in combination with R^2 is lower, is comparable to the frequency of treatment discontinuations observed with epcoritamab monotherapy in the R/R FL indication (18.6%; EMA/369446/2024).

Special populations

The safety analyses to investigate safety in special populations, which included **age, sex, race** and **renal function**, did not reveal any signals of relevant differences between subgroups.

In Arm A (Epco + R^2) the incidence of all grade TEAEs and Grade ≥3 TEAEs was comparable among the various **age groups**, while in Arm C (R^2) a higher incidence of Grade ≥3 TEAEs was observed in older age groups. The frequency of TEAEs leading to treatment discontinuation and fatal TEAEs was higher in the older age group (≥75 years) of Arm C, while this trend was not observed for Arm A.

2.5.2. Conclusions on clinical safety

The overall safety profile of epcoritamab in combination with lenalidomide and rituximab was consistent with the known safety profiles of the therapeutic agents. As expected due to the mode of action of bispecifics, the addition of epcoritamab to lenalidomide and rituximab resulted in an increase in the number of Grade 3 or 4 TEAEs, SAEs and treatment delays and discontinuations. The addition of epcoritamab also resulted in a further increase of the risk of neutropenia and infections. CRS and ICANS were observed, although the incidence rates were lower than previously reported for epcoritamab monotherapy. The safety profile of epcoritamab in combination with lenalidomide and rituximab for R/R FL is considered adequately managed by the routine and additional risk minimisation measures in place for this product.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 4.0 with the following content:

Safety concerns

Table 37. Summary of safety concerns

Summary of Safety Concerns for All Indications	
Important identified risks	CRS ICANS Serious infections
Important potential risks	Risk of overdose due to medication errors
Missing information	Long-term safety

Pharmacovigilance plan

Table 38. Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional PV activities which are conditions of the marketing authorization				
Not Applicable				
Category 2 - Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
GCT3013-01: A Phase 1/2, OL, Dose-Escalation Trial of GEN3013 in Patients with R/R or Progressive BCL Ongoing	Evaluate the safety and efficacy of epcoritamab monotherapy	Long-term safety (maximum 5 years after last patient's first dose, treated until disease progression unless meet treatment discontinuation criteria)	Final CSR	Planned for Quarter 4 of 2030
GCT3013-05: Randomized, OL, Ph3 Trial of Epcoritamab vs IC Chemotherapy in R/R DLBCL Ongoing	Evaluate safety and efficacy of epcoritamab compared to SOC (R-GemOx or BR)	Long-term safety with comparator data (maximum 5 years after last patient has been randomized) CRS, ICANS, and serious infections.	Primary analysis CSR Final CSR	Planned for Quarter 2 of 2026 Planned for Quarter 1 of 2029
M20-638: A Ph3, OL Trial of Epcoritamab in Combination with R^2 compared to R^2 in R/R FL Ongoing	Evaluate the safety and efficacy of epcoritamab in combination with R^2 compared to R^2 alone	Long-term safety (maximum 7 years after last patient's first dose, subjects are treated for up to 12 cycles or until disease progression or subject withdrawal unless treatment discontinuation criteria are met) Long-term safety with comparator data (maximum 7 years after last patient randomized) CRS, ICANS, and serious infections.	Final CSR	Planned for Quarter 4 of 2034
Category 3 - Required additional PV activities				
Not Applicable				

BCL = B-cell lymphoma; BR = bendamustine + rituximab; CRS = Cytokine Release Syndrome; CSR = clinical study report; DLBCL = diffuse large B-cell lymphoma; Gen3013 = epcoritamab; IC = Investigator's choice; ICANS = Immune Effector cell-associated neurotoxicity syndrome; OL = open-label; Ph = phase; PV = pharmacovigilance; R^2 = lenalidomide and rituximab; R-GemOx = rituximab + gemcitabine-oxaliplatin; R/R= relapsed/refractory; SOC = standard of care

Risk minimisation measures

Table 39. Risk minimization measures for Tepkinly

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
CRS	Routine risk minimization measures: • SmPC Section 4.2 - Posology and method of administration includes recommended dose modifications and management of adverse reactions for CRS and CRS grading guidance • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.8 - Undesirable effects Other routine risk minimization measures: • Prescription-only medicine Additional risk minimization measure: • Patient Card	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activities: Study GCT3013-05 Study M20-638
ICANS	Routine risk minimization measures: • SmPC Section 4.2 - Posology and method of administration includes recommended dose modifications for ICANS and ICANS grading and management guidance. • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.8 - Undesirable effects Other routine risk minimization measures: • Prescription-only medicine Additional risk minimization measure: • Patient Card	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activities: Study GCT3013-05 Study M20-638
Serious Infections	Routine risk minimization measures: • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.8 - Undesirable effects Other routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activities: Study GCT3013-05 Study M20-638

	• Prescription-only medicine	
Risk of overdose due to medication errors	Routine risk minimization measures: • SmPC Section 4.2 - Posology and method of administration • SmPC Section 4.9 – Overdose • SmPC Section 6.6 – Special precautions for disposal and other handling Other routine risk minimization measures: • Prescription-only medicine	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activities: None
Long-term safety	Routine risk minimization measures: • None Other routine risk minimization measures: • Prescription-only medicine	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activities: Study GCT3013-01 Study GCT3013-05 Study M20-638

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. 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 the initial user test for Tepkinly EMEA/H/C/005985/0000. The bridging report submitted by the MAH was acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

In the current variation, Tepkinly is proposed in combination with lenalidomide and rituximab is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL).

FL is characterized by the expression of the surface membrane antigen CD20. R/R FL is incurable and exhibits a high degree of clinical heterogeneity, ranging from an indolent to a highly aggressive clinical course. The course is characterised by relapsing disease, increasing refractoriness to anti-CD20 antibodies and chemotherapy, and decreasing disease-free intervals with each subsequent therapy.

3.1.2. Available therapies and unmet medical need

Treatment options for R/R FL include chemo-immunotherapy with or without anti-CD20 regimens. For patients in 2L and beyond rituximab in combination with lenalidomide (R2) is recommended if patients are lenalidomide naïve. Recently, Minjuvi in combination with R2 was also approved for R/R FL in 2L and beyond. For patients in 3L and beyond, bispecific antibodies, CAR-T cell therapy, BTK inhibitors and rituximab monotherapy are recommended. An unmet need exists for therapies which delay recurrences and reduce toxicity.

3.1.3. Main clinical studies

The pivotal study for this application is Study M20-638, a phase 3 open-label RCT in CD20+ R/R FL patients with stage II, III, or IV disease (5th WHO classification) treated with at least one prior chemotherapy in combination with an antiCD20 monoclonal antibody. Patients should have a need for treatment initiation (e.g. by GELF criteria). From protocol version 2.0 (dated 21 Feb 2023), patients were randomised 1:1 to either epcoritamab 48 mg and R2 (Arm A; N=243) or R2 alone (Arm C; N=245). From protocol version 3.0 (dated 30 Aug 2023) a 3-step SUD regimen was introduced along with recommendations for proper hydration and the use of dexamethasone in Cycle 1 for CRS prophylaxis. A third study arm (Arm B; epcoritamab full dose of 24 mg plus R^2; N=61) was closed to enrolment after protocol version 2.0, as the recommended full dose of epcoritamab in combination with R^2 was identified as 48 mg based data from Arm 2 of the Phase 1b/2 Study GCT3013-02.

Efficacy analyses were conducted on Arm A and Arm C from the ITT population. PFS, ORR, and CR rate were statistically tested at the IA1 with DCO 10 January 2025 at a median study follow-up of 10.4 months in Arm A and 10.2 months in Arm C. Updated efficacy outcomes for these endpoints as well as the first OS IA were presented at IA2 with DCO 24 May 2025 with a median follow-up of 14.8 and 14.6 months, respectively.

3.2. Favourable effects

Epcoritamab 48 mg + R2 demonstrated an improvement in the dual primary endpoint PFS as assessed by IRC compared with R2 alone; HR 0.21 (95% CI: 0.13, 0.33), p-value < 0.0001 at an IF of 54%. The median PFS was NE [95% CI: 21.9, NE] in Arm A and 11.2 [95% CI: 10.5, NE] months in Arm C. PFS is generally consistent in subgroup analyses and in sensitivity analyses including in an EMA preferred analysis (HR 0.20 [95% CI: 0.13, 0.33]).

Dual primary endpoint BOR equivalent to ORR was tested when the first 232 subjects randomised into Arm A and C had at least 12 months of follow-up. The ORR was higher in Arm A compared to Arm C; 95.7% (95% CI: 90.2, 98.6) vs 81.0% (95% CI: 72.7, 87.7) with a difference in rates of 14.9% (95% CI: 7.1, 22.8; p-value < 0.0001).

The following key secondary endpoints were analysed in a hierarchical testing procedure:

- The CR rate was 74.5% (95% CI: 68.5, 79.8) vs 43.3% (95% CI: 37.0, 49.7), with a difference in rates of 31.3% (95% CI: 23.1, 39.4); p < 0.0001.
- The OS HR was 0.38 (95% CI: 0.18, 0.80), p=0.0039, but OS did not cross the pre-specified boundary for statistical significance. There were few OS events (4.1% vs 10.2%) and OS was considered immature (24% of the IF).

The updated efficacy outcomes at IA2 were in line with the primary analyses; the PFS (IF of 78%) HR was 0.21 (95% CI: 0.14, 0.31) (median PFS NE [95% CI: 21.9, NE] vs 11.2 [95% CI: 10.5, NE] months). The ORR in the ITT population in Arm A and Arm C was 95.1% (95% CI: 91.5, 97.4) versus

79.2 (95% CI: 73.6, 84.1). The CR rate was 82.7% (95% CI: 77.4, 87.3) vs 49.8% (95% CI: 43.4, 56.2) respectively.

The treatment effect observed in Arm A of the pivotal study is supported by the results of Arm 2 of Study GCT3013-02 and by the results in Arm B of the pivotal study.

3.3. Uncertainties and limitations about favourable effects

Adjustments to the protocol were made in an ongoing trial. Due to the open-label design these amendments may affect the validity of the trial, because the trial may be altered to increase the chance of a positive conclusion. Here, however, the impact of the protocol adjustments is considered limited, as (a) changes were motivated by external considerations, (b) baseline characteristics by subgroups based on the most recent protocol version during enrolment and corresponding treatment effect estimates are generally consistent, and, importantly, (c) the current conclusions of the study (i.e. a demonstrated positive effect in terms of PFS, BOR, and CR, and positive but formally inconclusive results for OS) appear to have been the same if the testing procedure in protocol version 1.0 had been followed.

Due to the few OS events, and frequent censoring in the OS KM- curve, OS is considered to be immature.

3.4. Unfavourable effects

The pivotal safety dataset consists of 243 patients treated with epcoritamab in combination with rituximab and lenalidomide (Arm A). The majority of patients received the intended 12 cycles of epcoritamab. TEAEs leading to discontinuation of any study drug were reported in 18.9% of subjects in Arm A compared to 12.2% of subjects in Arm C.

The most frequently reported TEAEs were neutropenia (49.4% versus 31.5%), CRS (35.0% versus 0.4%), diarrhoea (30.9% versus 25.2%), anaemia (27.6% versus 17.2%), constipation (27.6% versus 21.4%), neutrophil count decreased (26.7% versus 21.0%), pyrexia (23.9% versus 13.9%), rash (23.9% versus 22.3%), COVID-19 (22.2% versus 13.4%), injection site reaction (21.8% versus 0%), and upper respiratory tract infection (20.2% versus 13.9%) which was expected based on the known safety profile of the agents. Grade 3 or 4 TEAEs were more common in Arm A (90.1%) compared to Arm C (66.8%) mainly driven by a higher incidence of neutropenia (46.1% vs. 25.6%).

Febrile neutropenia (6.2% versus 2.5%) and infections (77.4% versus 52.5%) were more frequent in Arm A compared to Arm C. There were no fatal TEAEs due to infection. The most frequent infections reported in ~20% of patients in Arm A were COVID-19, upper respiratory tract infection and pneumonia.

Serious TEAEs were more frequent in Arm A (55.6%) compared to Arm C (29.0%). The most frequently reported serious TEAEs in Arm A were CRS (18.5%), pneumonia (10.3%), febrile neutropenia (5.3%), COVID-19 (4.5%), and COVID-19 pneumonia (3.7%), while the most frequently reported serious TEAE in Arm C was pneumonia (5.0%). Serious infections were reported in 33.3% (Arm A) versus 14.7% (Arm C).

In Arm A, 10 patients (4.4%) died due to adverse events (n=6), disease progression (n=2) and other (n=2). In Arm C (9.7%), 23 patients died due to adverse events (n=12), disease progression (n=8) and other (n=3).

In Arm A with the 3-step SUD regimen CRS was reported in 35/133 subjects (26.3%). All events with the 3-step SUD regimen were low grade (21.1% Grade 1; 5.3% Grade 2) and resolved. Most events occurred during the first treatment cycle. There was one event of ICANS (Grade 1).

The safety analyses to investigate safety in special populations, which included age, sex, race and renal function, did not reveal any signals of relevant differences between subgroups.

3.5. Uncertainties and limitations about unfavourable effects

Data on long-term safety is missing but safety information will be collected through the ongoing study M20-638

The combination regimen is associated with a high risk of (febrile) neutropenia and infections. The optimal measures to reduce risks, such as assessment of immunoglobin levels, are still unclear.

3.6. Effects Table

Table 40: Effects Table for Tepkinly in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (data cut-off: 24 May 2025)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Progression free survival	Median [95% CI]	NE [21.9, NE]	11.2 [10.5, NE]	HR 0.21 (95% CI: 0.13, 0.33), p < 0.0001 Strength: stat. significant, derived from an RCT, supported by sec. endpoints, consistent in subgroup analyses and sensitivity analyses, in line with updated PFS results. Uncertainty: 54% of the IF	Study M20-638
OS	Overall survival	Median [95% CI]	NE [NE, NE]	NE [NE, NE]	Strength: HR 0.38 (95% CI: 0.18, 0.80), not stat. significant, pre-specified futility boundary of HR > 1.05 not crossed. Uncertainty: immature	
Unfavourable Effects						
CRS	Cytokine release syndrome	% (n)	26.3% (35/133)	0.4% (1/238)	Frequency for the proposed 3-step SUD. Higher frequency with 2-step SUD (50/110, 45.5%).	Study M20-638
ICANS	Immune effector cell associated neurotoxicity syndrome	% (n)	0.8% (1/133)	0	Low incidence in the trial but known effect for epcoritamab.	
Neutropenia	Grouped neutropenia events (TEAEs of neutropenia and neutrophil count decreased)	%	74.1%	51.7%	Events of febrile neutropenia were also more common (6.2% versus 2.5%).	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Serious infections	Serious infections	%	33.3%	14.7%	Most frequent infections were COVID-19, upper respiratory tract infection and pneumonia.	

Abbreviations: CI – confidence interval; CR - Complete response rate; CRS- Cytokine Release Syndrome; HR- hazard ratio; ICANS- immune effector cell associated neurotoxicity syndrome; IF – information fraction; NE – not estimated; ORR -Overall response rate; OS - Overall survival; p – p-value; PFS - Progression free survival; RCT- randomised controlled trial; sec – secondary; stat – statistically; SUD - step-up dosing; TEAE- treatment emergent adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Considering the relapsing nature of FL, delay of progression in R/R FL patients in need of therapy is considered clinically relevant. Addition of epcoritamab to R^2 led to a relevant improvement in PFS compared to R^2 alone in R/R FL patients. PFS is supported by ORR and CR rate and is generally consistent in sensitivity analyses and in subgroup analyses including high risk subgroups such as POD24 positive and double refractory patients. The OS data are immature, but the OS HR estimate points in the right direction and OS did not cross the pre-specified futility boundary of HR > 1.05, therefore no detriment to OS is currently expected.

The overall safety profile of epcoritamab in combination with lenalidomide and rituximab was consistent with the known safety profiles of these therapeutic agents. As expected due to the mode of action of bispecific antibodies, the addition of epcoritamab to lenalidomide and rituximab resulted an increase in the number of Grade 3 or 4 TEAEs, SAEs and treatment delays and discontinuations. The addition of epcoritamab also resulted in a further increase of the risk of neutropenia and infections. CRS and ICANS were observed, although the incidence rates were lower than previously reported for epcoritamab monotherapy. The safety profile of epcoritamab in combination with lenalidomide and rituximab for R/R FL is considered acceptable.

3.7.2. Balance of benefits and risks

Addition of epcoritamab to R^2 led to a clinically relevant PFS improvement in R/R FL patients after at least one line of prior chemotherapy in combination with an anti-CD20 monoclonal antibody. No detriment to OS is currently expected. The benefits are considered to outweigh the increases in toxicity.

3.7.3. Additional considerations on the benefit-risk balance

Data provided in the current procedure are considered comprehensive and therefore no additional SOB is imposed.

3.8. Conclusions

The overall B/R of Tepkinly is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	type II	I, II, and IIIB

Extension of indication to include in combination with rituximab and lenalidomide treatment of patients with relapsed/refractory follicular lymphoma (FL) for Tepkinly, based on interim results from study M20-638; this is a Phase 3, open-label study to evaluate safety and efficacy of epcoritamab in combination with rituximab and lenalidomide (R2) compared to R2 in subjects with relapsed or refractory follicular lymphoma (EPCORE FL-1). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The 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.

In addition, 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**

Additional risk minimisation measures to minimise the important identified risks of CRS and ICANS consist of a Patient Card targeted to patients treated with epcoritamab.

Prior to the launch of epcoritamab in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the patient card, including communication media,

distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The Marketing Authorisation Holder (MAH) shall ensure that in each Member State where epcoritamab is marketed, HCPs who are expected to prescribe epcoritamab and patients treated with epcoritamab have access to/are provided with the Patient Card which will inform and explain to patients the risks of CRS and ICANS.

The Patient Card will contain the following key messages:

- Provide information on signs/symptoms of CRS and ICANS
- Alert patients to promptly contact their HCPs/emergency care if they observe any of the signs or symptoms of CRS and ICANS
- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using epcoritamab.
- Contact details of the epcoritamab prescriber

- **Obligation to conduct post-authorisation 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 confirm the safety and efficacy of epcoritamab in the treatment of R/R DLBCL after two or more lines of systemic therapy, the primary (including final OS analysis) and final CSR for study GCT3013-05 should be submitted. - Primary analysis CSR (including final OS analysis) – due date: Q2/2026 - Final CSR – due data: Q1 2029.	 Q2/2026 Q1/2029
In order to confirm the safety and efficacy of epcoritamab in the treatment of relapsed or refractory DLBCL after two or more lines of systemic therapy, the MAH should submit the final CSR for the pivotal aNHL cohort of study GCT3013-01.	Q3/2027
In order to confirm the safety and efficacy of epcoritamab in the treatment of R/R FL after two or more lines of systemic therapy, the pivotal iNHL expansion cohort of Study GCT3013-01 and the FL optimisation cohort of Study GCT3013-01 should be submitted - Final CSRs for the pivotal iNHL expansion cohort – due date: Q2/2028 - Final CSR for the FL optimisation cohort - due date: Q3 2029.	 Q2/2028 Q3/2029
In order to confirm the benefit of epcoritamab in R/R FL, the MAH is conducting a Phase 3 study (study M20-638), to evaluate the safety and efficacy of epcoritamab in combination with R2 compared to R2 alone in subjects with R/R FL after at least one prior anti-CD20 containing chemoimmunotherapy regimen. The final CSR will be submitted. Final CSR – due date: Q4 2034.	Q4/2034

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Tepkinly is not similar to Kymriah, Lunsumio, Yescarta and Minjuvi within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion EMA/VR/0000311043