Official Title: A Phase 1b/2 Study of Tafasitamab, Tafasitamab Plus Lenalidomide, Tafasitamab Plus Parsaclisib, and Tafasitamab Plus Lenalidomide in Combination With R-CHOP in Japanese Participants With Non-Hodgkin Lymphoma (J-MIND)

NCT Number: NCT04661007

Document Date: Protocol INCMOR 0208-102 Am 8 Version 9 27 OCT 2025

Clinical Study Protocol

INCMOR 0208-102

A Phase 1b/2 Study of Tafasitamab, Tafasitamab Plus Lenalidomide, Tafasitamab Plus Parsaclisib, and Tafasitamab Plus Lenalidomide in Combination With R-CHOP in Japanese Participants With Non-Hodgkin Lymphoma (J-MIND)

Product:	**Tafasitamab (INCMOR00208)**
Phase of Study:	**Phase 1b/2**
Sponsor:	**Incyte Biosciences Japan GK** **Tokyo Midtown Hibiya** **1-1-2 Yurakucho, Chiyoda-ku** **Tokyo 100-0006, Japan**
Original Protocol:	**29 JUL 2020**
Amendment 1:	**19 SEP 2020**
Amendment 2:	**18 DEC 2020**
Amendment 3:	**07 JUL 2021**
Amendment 4:	**14 JUL 2022**
Amendment 5:	**18 OCT 2022**
Amendment 6:	**14 FEB 2024**
Amendment 7:	**16 APR 2024**
Amendment 8:	**27 OCT 2025**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations in which the study is being conducted.
The information in this document is confidential. No part of this information may be duplicated, referenced, or transmitted in any form or by any means (electronic, mechanical, photocopy, recording, or otherwise) without prior written consent.

INVESTIGATOR'S AGREEMENT

I have read the INCMOR 0208-102 Protocol (Amendment 8 dated 27 OCT 2025) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
ABC	activated B-cell
ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cell-mediated phagocytosis
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
BCL2	B-cell lymphoma 2
BCL6	B-cell lymphoma 6
BEN	bendamustine
BMS	Bristol Myers Squibb
BOIN	Bayesian optimal interval
BR	bendamustine rituximab
BTK	Bruton tyrosine kinase
CAR-T	chimeric antigen receptor T cell
CBC	complete blood count
CD	cluster of differentiation
CDA	confidential disclosure agreement
CDC	complement-dependent cytotoxicity
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma or serum concentration
CMR	complete metabolic response
CMV	cytomegalovirus
CNS	central nervous system
COO	cell of origin
COVID-19	coronavirus disease 2019
CR	complete response

Abbreviations and Special Terms	Definition
CRR	complete response rate
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trials Regulation
CYP	cytochrome P450
DCR	disease-control rate
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSMC	Data and Safety Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
EU	European Union
FAS	full analysis set
FCBP	female of childbearing potential
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FNCBP	female not of childbearing potential
GCB	germinal center B-cell
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GDPR	General Data Protection Regulation
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCL	hairy cell leukemia

Abbreviations and Special Terms	Definition
HCV	hepatitis C virus
HDC	high-dose chemotherapy
HGBL	high-grade B-cell lymphoma
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICML	International Conference on Malignant Lymphoma
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
ILD	interstitial lung disease
IMiDs	immunomodulatory drugs
iNHL	indolent non-Hodgkin lymphoma
INR	international normalized ratio
IPI	International Prognostic Index
IRB	institutional review board
IRC	independent review committee
IRR	infusion-related reaction
IV	intravenous
IWG	International Working Group
IWRS	interactive web response system
JSH	Japanese Society of Hematology
LAM	lymphoma-associated macrophages
LDH	lactate dehydrogenase
LEN	lenalidomide
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma

Abbreviations and Special Terms	Definition
NE	not evaluable
NHL	non-Hodgkin lymphoma
NK	natural killer
NR	not reached
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI	package insert
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetic(s)
PMBL	primary mediastinal (thymic) large B-cell lymphoma
PMD	progressive metabolic disease
PMDA	Pharmaceuticals and Medical Devices Agency
PMR	partial metabolic response
PO	per os, orally
PPS	per Protocol set
PPP	Pregnancy Prevention Plan
PR	partial response
PSL	prednisolone
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	once every 2 weeks
Q4W	once every 4 weeks
QD	once daily
QW	once weekly
R/R	relapsed/refractory
R-CHOP	combination regimen consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone
RP2D	recommended Phase 2 dose
RTX	rituximab
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Abbreviations and Special Terms	Definition
SLL	small lymphocytic lymphoma
SMC	safety monitoring committee
SoA	schedule of activities
SoC	standard of care
SOP	standard operating procedure
SPD	sum of the products of perpendicular diameters for multiple lesions
SPM	second primary malignancy
SpO_2	saturation of peripheral oxygen
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TSH	thyroid-stimulating hormone
TTNT	time to next treatment
ULN	upper limit of normal
US	United States
VTE	venous thromboembolism
WBC	white blood cell

1. PROTOCOL SUMMARY

Protocol Title: A Phase 1b/2 Study of Tafasitamab, Tafasitamab Plus Lenalidomide, Tafasitamab Plus Parsaclisib, and Tafasitamab Plus Lenalidomide in Combination With R-CHOP in Japanese Participants With Non-Hodgkin Lymphoma (J-MIND)

Protocol Number: INCMOR 0208-102

Objectives and Endpoints:

Table 1 presents the primary and major secondary endpoints and objectives.

Table 1: Primary and Major Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
Part 1: To assess the safety and tolerability and to determine the RP2D of single-agent tafasitamab (Group 1) in Japanese participants with R/R NHL.	Incidence and severity of TEAEs and incidence of DLTs with single-agent tafasitamab.
Parts 2 and 3: To assess the safety and tolerability and to determine the recommended clinical dose (Group 2)/RP2D (Groups 3, 4a, and 5) of the following: • Tafasitamab Q2W/Q4W dosing in combination with LEN (Group 2) in Japanese participants with R/R DLBCL. • Tafasitamab in combination with LEN (Group 3) in Japanese participants with R/R DLBCL. • Tafasitamab in combination with parsaclisib (Group 4a) in Japanese participants with R/R DLBCL. • Tafasitamab in combination with LEN plus R-CHOP (Group 5) in Japanese participants with previously untreated DLBCL.	• Incidence and severity of TEAEs with tafasitamab Q2W/Q4W in combination with LEN (Group 2). • Incidence and severity of TEAEs and incidence of DLTs with tafasitamab in combination with LEN, parsaclisib, or LEN plus R-CHOP (Groups 3, 4a, and 5).
Part 4: To evaluate the efficacy of tafasitamab in combination with LEN (Group 6) in Japanese participants with R/R DLBCL.	OR, defined as the best response of CR/CMR or PR/PMR as determined by an IRC according to the Lugano criteria (Cheson et al 2014), will be analyzed on the FAS using ORR as a population-level summary, in which ORR is defined as the percentage of participants experiencing OR.

Table 1: Primary and Major Secondary Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary	
Parts 1, 2, 3, and 4: To determine the PK of the following: • Single-agent tafasitamab (Group 1) in Japanese participants with R/R NHL. • Tafasitamab Q2W/Q4W in combination with LEN (Group 2) in Japanese participants with R/R DLBCL. • Tafasitamab in combination with LEN (Groups 3 and 6) or parsaclisib (Group 4a) in Japanese participants with R/R DLBCL. • Tafasitamab in combination with LEN plus R-CHOP in Japanese participants with previously untreated DLBCL (Group 5).	PK analysis of single-agent tafasitamab and tafasitamab as part of combination treatments. Descriptive statistics of trough (ie, predose) and C_{max} levels at different timepoints.
Part 2 (Group 2 only): To evaluate the efficacy of tafasitamab Q2W/Q4W in combination with LEN in Japanese participants with R/R DLBCL.	Tumor response as follows: • Response assessment as per investigator assessment of response according to the Lugano criteria (Cheson et al 2014). • Percent reduction in SPD in up to 6 target measurable nodes and extranodal sites assessed by CT as per investigator assessment of response according to the Lugano criteria (Cheson et al 2014).
Part 4: To further evaluate the efficacy of tafasitamab in combination with LEN (Group 6) in Japanese participants with R/R DLBCL based on additional efficacy outcomes.	• CR, defined as CR/CMR as determined by an IRC according to the Lugano criteria (Cheson et al 2014), will be analyzed on the FAS using CRR as a population-level summary, in which CRR is defined as the percentage of participants experiencing CR. • DOR, defined as the time from the first documented CR/CMR or PR/PMR as determined by an IRC according to the Lugano criteria (Cheson et al 2014) until the date of first documented disease progression or death due to any cause, whichever occurs first. DOR will be analyzed on the FAS using Kaplan-Meier–estimated median survival time as a population-level summary.

Table 1: Primary and Major Secondary Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary (continued)	
Part 4: To further evaluate the efficacy of tafasitamab in combination with LEN (Group 6) in Japanese participants with R/R DLBCL based on additional efficacy outcomes (continued).	• PFS, defined as the time from the date of first dose of study treatment until the first documented disease progression as determined by an IRC according to the Lugano criteria (Cheson et al 2014) or death due to any cause, whichever occurs first. PFS will be analyzed on the FAS using Kaplan-Meier–estimated median survival time as a population-level summary. • OS, defined as the time from the first dose of study treatment until death due to any cause. OS will be analyzed on the FAS using Kaplan-Meier–estimated median survival time as a population-level summary. • OR, CR/CMR, DOR, and PFS as per investigator assessment of response according to the Lugano criteria (Cheson et al 2014). OR and CR/CMR will be summarized by the ORR and CRR, defined as the percentage of participants experiencing OR and CR/CMR respectively.
Part 4: To assess the safety and tolerability of tafasitamab in combination with LEN in Japanese participants with R/R DLBCL.	Incidence and severity of TEAEs following treatment with tafasitamab in combination with LEN.

Overall Design:

Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 1b/2
Clinical Indications	R/R NHL, R/R DLBCL, and untreated DLBCL.
Population	Male and female participants of at least 18 years of age who have R/R NHL (Group 1), R/R DLBCL (Groups 2, 3, 4a, and 6), or previously untreated DLBCL (Group 5).
Number of Participants	Up to 125 participants will be enrolled. Part 1 will include up to approximately 12 participants (6-12 evaluable participants for Group 1). Part 2 will include up to approximately 60 participants (6 evaluable participants for Group 2 and 6 to 18 participants each for Groups 3, 4a, and 5). Part 3 was originally planned to include up to approximately 12 participants (Group 4b). Based on the sponsor's decision, participants for Part 3 Group 4b will not be recruited. Part 4 will include 41 participants who are evaluable for efficacy (Group 6).
Study Design	This is an open-label, multiple-group, Phase 1b/2 study.
Estimated Duration of Study Participation	<u>Phase 1b</u> Up to 28 days for screening. Treatment with tafasitamab and/or parsaclisib may continue as long as participants are receiving benefit and have not met any criteria for treatment withdrawal; treatment with LEN in Groups 2 and 3 can be given for up to a total of 12 cycles; and treatment with R-CHOP and LEN in Group 5 will be given for 6 cycles (participants will receive treatment on a 28-day cycle for approximately 4-12 cycles in Groups 1, 2, 3, and 4a or on a 21-day cycle for 6 cycles in Group 5), with a reporting period of 90 days after the EOT visit for safety follow-up and the EOS visit for Groups 1, 2, 3, and 4a or the EOS visit (18 months after the EOT visit) for Group 5. Disease follow-up will be conducted up to 15 months after EOT visit in Part 2 Group 5. It is estimated that an individual will participate for approximately 16 months after initiation of treatment in Groups 1, 2, 3, and 4a and for approximately 22 months after initiation of treatment in Group 5. <u>Phase 2</u> Up to 28 days for screening. Treatment with tafasitamab may continue as long as participants are receiving benefit and have not met any criteria for treatment withdrawal; treatment with LEN can be given for up to a total of 12 cycles, with a reporting period of 90 days after the EOT visit for safety follow-up. The survival follow-up will last for a maximum of 3 years from Cycle 1 Day 1 in this study in principle or until withdrawal of consent or death, whichever occurs first. It is estimated that an individual will participate for a total of approximately 24 months. After obtaining marketing authorization for tafasitamab in Japan and approval for its indication in DLBCL, participants receiving study treatment shall discontinue administration of the investigational product (EOT) and undergo safety follow-up/EOS assessments. Participants who are in the follow-up period at that time shall also terminate further follow-up and be considered to have completed participation in the study.

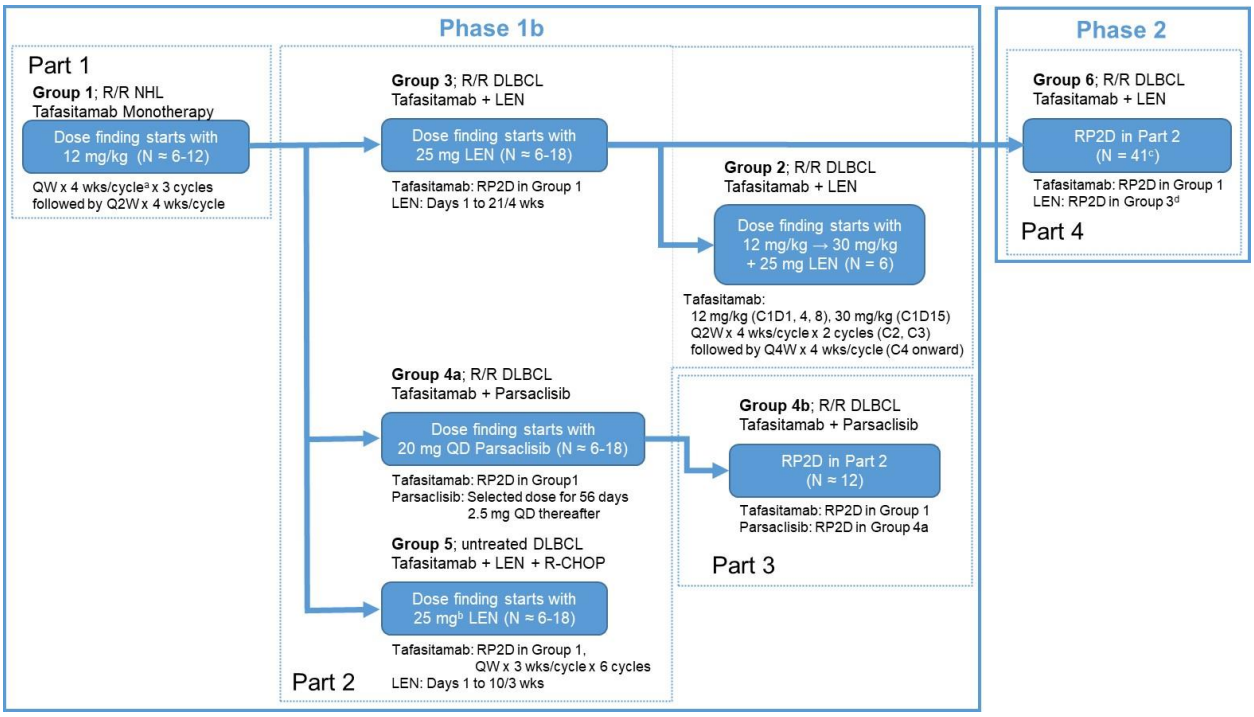
Treatment Groups and Duration:

Study INCMOR 0208-102 is a Phase 1b/2, open-label, multicenter, clinical study conducted in Japan that is designed to assess the safety and tolerability, determine the RP2Ds, and assess the PK of tafasitamab single-agent or combination therapy in Japanese participants with NHL. After the addition of the Phase 2 portion (Part 4/Group 6; see Figure 1) in Protocol Amendment 4 and the design change of the Phase 1b portion (moving Group 2 from Part 1 to Part 2) in Protocol Amendment 7, this study will consist of 4 parts and 7 groups as follows:

- Part 1 consists of tafasitamab monotherapy dose-finding to evaluate the safety and tolerability and to determine the RP2Ds of single-agent tafasitamab in Japanese participants with R/R NHL. Part 1 consists of 1 group (Group 1) to evaluate weight-based doses of tafasitamab.
- Part 2 consists of tafasitamab combination therapy dose-finding to evaluate the safety and tolerability and to determine the RP2Ds of tafasitamab when combined with LEN (Group 3) or parsaclisib (Group 4a) in participants with R/R DLBCL or LEN plus R-CHOP (Group 5) in participants with previously untreated DLBCL and to determine the recommended clinical dose of tafasitamab Q2W/Q4W when combined with LEN (Group 2) in participants with R/R DLBCL. The dose of tafasitamab will be based on the weight-based RP2D that is deemed safe and tolerable in Part 1 for Groups 3, 4a, and 5 and will be based on the weight-based RP2D that is deemed safe and tolerable in Part 1 and Part 2 Group 3 for Group 2.
- Part 3 was planned to consist of 1 dose-expansion group (Group 4b) to further evaluate the safety, tolerability, and preliminary antitumor activity of the RP2D deemed safe and tolerable in Part 2 for the combination of tafasitamab and parsaclisib. Based on the sponsor's decision, participants for Part 3 Group 4b will not be recruited.
- Part 4 consists of 1 group (Group 6) for the Phase 2 portion of the study. Part 4 will evaluate the antitumor activity as the primary objective. The safety and tolerability of the RP2D of the combination of tafasitamab and LEN that was deemed safe and tolerable in Part 2 will also be evaluated as the secondary objectives.

There are 2 different treatment cycles in this study: the cycle length is 28 days for Groups 1, 2, 3, 4a, and 6 and is 21 days for Group 5. Enrollment of Part 1 was planned to occur in a sequential manner in the order of Group 1 and Group 2, but enrollment of Group 2 was not started due to a strategic change and will be restarted as of Protocol Amendment 7 with a revised dose regimen. The enrollment of the 3 groups in Part 2 (Groups 3, 4a, and 5) was planned to occur in parallel. The enrollment of Part 2 Group 2 will occur after the completion of enrollment in Group 6. The enrollment of Part 4 will occur after the RP2D is determined in Part 2 Group 3. Treatment will be given as long as the participant is receiving benefit or until the participant meets any of the discontinuation criteria (see Section 7.1.1), whichever occurs earlier. Participants whose treatment period exceeds 2 years will move to the continued access period (see Section 4.1.4) for Parts 1 and 2 (Groups 1, 3, and 4a). The study design schema (including Group 4b, which will not be recruited) is presented in Figure 1.

Figure 1: Study Design Schema



[a] An additional loading dose of tafasitamab is to be administered on Day 4 of Cycle 1.
[b] The dose may be adjusted based on the result of First-MIND study.
[c] Evaluable for efficacy.
[d] For participants with moderate renal insufficiency (creatinine clearance ≥ 30 to < 60 mL/min), the starting dose of LEN must be reduced to 10 mg.

Adherence to the study design requirements, including those specified in the SoA (see Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9), is essential and required for study conduct.

Table 3: Schedule of Activities (Group 1)

	Screening	Treatment (1 cycle = 28 days)																Follow-Up	
		C1					C2				C3 (1 wk ± 1d After C2D22)				C4 (1 wk ± 1d After C3D22) to EOT			EOS/Safety	
Visit Day (Range)	Days −28 to −1	D1	D4	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	EOT	EOT+90d (+14d)	Notes
Administrative procedures																			
Informed consent	X																		
Inclusion/exclusion criteria	X	X																	
General and disease medical history	X																		
Disease assessment (stage, IPI or FLIPI)	X																		IPI is assessed if applicable. See Section 8.1.4.2.
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Preinfusion medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Mandatory for the initial 3 doses. See Section 6.1.
Administer tafasitamab		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Safety assessments																			
AE assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Body systems with symptoms should be physically examined.
Physical examination	C	C	C	C	C	C	D				D*				D*		C	D	C = comprehensive, D = disease specific. *D1 of C3, C5, and C7, then every 3 cycles (ie, D1 of C10, C13, etc) thereafter. See Section 8.3.2.
ECOG performance status	X	X					X				X				X		X	X	See Section 8.3.3.
Vital signs/body weight/height	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Height at screening only. See Section 8.3.4.

Table 3: Schedule of Activities (Group 1) (Continued)

	Screening	Treatment (1 cycle = 28 days)															EOT	Follow-Up	Notes
		C1					C2				C3 (1 wk ± 1d After C2D22)				C4 (1 wk ± 1d After C3D22) to EOT			EOS/Safety	
Visit Day (Range)	**Days −28 to −1**	**D1**	**D4**	**D8 (±1d)**	**D15 (±1d)**	**D22 (±1d)**	**D1 (±1d)**	**D8 (±1d)**	**D15 (±1d)**	**D22 (±1d)**	**D1 (±1d)**	**D8 (±1d)**	**D15 (±1d)**	**D22 (±1d)**	**D1 (±2d)**	**D15 (±2d)**		**EOT+90d (+14d)**	
12-lead ECG	X														X*			X	*Cycle 4 only. See Section 8.3.5.
Chest X-ray or CT/MRI (chest) for ILD screening	X																		Performed additionally for symptoms of respiratory illness. See Section 8.3.7.
Efficacy assessments																			
PET/CT	X																X		
CT/MRI											X*				X*				*Performed within 3 days before C3D1 and within 5 days before D1 of C5, C7, then approximately every 3 cycles (ie, D1 of C10, C13, etc) from the previous scan thereafter.
Tumor response assessment	X										X				X*		X		See Section 8.2 and Section 10.4.1.2. *Only on the day of PET/CT or CT/MRI.
Bone marrow aspiration & biopsy	X										X*				X*		X*		*Perform within 2 weeks from the radiologic evaluation to confirm CR. Not mandated in participants with DLBCL who undergo PET/CT. See Section 8.2.2.

Table 3: Schedule of Activities (Group 1) (Continued)

	Screening	Treatment (1 cycle = 28 days)																Follow-Up	
		C1					C2				C3 (1 wk ± 1d After C2D22)				C4 (1 wk ± 1d After C3D22) to EOT			EOS/Safety	
Visit Day (Range)	Days −28 to −1	D1	D4	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	EOT	EOT+90d (+14d)	Notes
Laboratory assessments (local)																			
Hematology and serum chemistries	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Preinfusion on the day of tafasitamab administration. See Section 8.3.8 and Table 27.
Coagulation panel	X														X*			X	*C4 only. See Table 27.
Urinalysis	X														X*			X	*C4 only. See Table 27.
Immunochemistry	X														X*			X	*C4 and every 6 cycles beyond. See Table 27.
Pregnancy testing (serum)	X																X	X	
Pregnancy testing (urine)		X					X				X				X				
Serology	X																		See Table 27.
HBV DNA (if HBcAb positive)	X	X					X				X				X		X	X	See Section 8.3.8.2.
PK and translational laboratory assessments (central)																			
PK sampling		X	X	X	X	X	X			X	X			X	X*			X	*C4 and beyond every 4 cycles (8, 12, etc). See Table 28.
ADA (preinfusion)		X			X		X				X				X*			X	*C4 and beyond: every 4 cycles. See Section 8.4.2.

Table 4: Schedule of Activities (Group 2)

Visit Day (Range)	Screening	Treatment (1 cycle = 28 days)											EOT	Follow-Up	Notes
		C1				C2		C3		C4 to C12	C12	C13 to EOT		EOS/Safety	
	Days −28 to −1	D1	D4 (±1d)	D8 (±1d)	D15 (±1d)	D1 (±1d)	D15 (±1d)	D1 (±1d)	D15 (±1d)	D1 (±2d)	D28 (±2d)	D1 (±2d)		EOT+90d (+14d)	
Administrative procedures															
Informed consent	X														
Inclusion/exclusion criteria	X	X													
General and disease medical history	X														
Disease assessment (stage, IPI)	X														See Section 8.1.4.2.
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Preinfusion medication		X	X	X	X	X	X	X	X	X		X			Mandatory for the initial 4 doses. See Section 6.1
Administer tafasitamab		X	X	X	X	X	X	X	X	X		X			
Dispense LEN		X				X		X		X					Dispense LEN on Day 1 of cycle per the PPP.
Collect LEN						X		X		X		X*	X		LEN can be collected if participants visit study sites prior to D1 of the next cycle. *C13 only.
Assess compliance			X	X	X	X	X	X	X	X		X	X		
Safety assessments															
AE assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Body systems with symptoms should be physically examined.
Physical examination	C	C	C	C	C	D		D		D*		D*	C	D	C = comprehensive, D = disease specific. *D1 of C5 and C7, then every 3 cycles (ie, D1 of C10, C13, etc) thereafter.
ECOG performance status	X	X				X		X		X		X	X		See Section 8.3.3.

Table 4: Schedule of Activities (Group 2) (Continued)

Visit Day (Range)	Screening	Treatment (1 cycle = 28 days)											EOT	Follow-Up	Notes
		C1				C2		C3		C4 to C12	C12	C13 to EOT		EOS/Safety	
	Days −28 to −1	D1	D4 (±1d)	D8 (±1d)	D15 (±1d)	D1 (±1d)	D15 (±1d)	D1 (±1d)	D15 (±1d)	D1 (±2d)	D28 (±2d)	D1 (±2d)		EOT+90d (+14d)	
Vital signs/body weight/height	X	X	X	X	X	X	X	X	X	X		X	X	X	Height at screening only. See Section 8.3.4 for vital signs.
12-lead ECG	X	X*			X*	X*		X*		X†			X		*Within 3 hours after the end of tafasitamab infusion. †Cycle 6 only. See Section 8.3.5.
Chest X-ray or CT/MRI (chest) for ILD screening	X														Performed additionally for symptoms of respiratory illness. See Section 8.3.7.
Efficacy assessments															
PET/CT	X										X	X*	X*		*PET/CT from Cycle 25 onward should be performed only if deemed necessary and not more than once per year.
CT/MRI	X*							X†		X†	X*†	X†			*A CT/MRI at baseline/C12D28 are not required if the CT portion of PET/CT is used. See Section 8.2.1. †Perform within 3 days before C3D1 and within 5 days before D1 of C5, C7, and C10 and then on C12D28 (including PET) and approximately every 3 cycles (ie, D1 of C16, C19, etc) from the previous scan thereafter.
Tumor response assessments	X							X		X	X	X	X		See Section 8.2 and Section 10.4.1.2.
Bone marrow aspiration and biopsy	X								X*	X*	X*	X*			*Perform within 2 weeks from the radiologic evaluation to confirm CR. See Section 8.2.2.

Table 4: Schedule of Activities (Group 2) (Continued)

Visit Day (Range)	Screening	Treatment (1 cycle = 28 days)											EOT	Follow-Up	Notes
		C1				C2		C3		C4 to C12	C12	C13 to EOT		EOS/Safety	
	Days −28 to −1	D1	D4 (±1d)	D8 (±1d)	D15 (±1d)	D1 (±1d)	D15 (±1d)	D1 (±1d)	D15 (±1d)	D1 (±2d)	D28 (±2d)	D1 (±2d)		EOT+90d (+14d)	
Laboratory assessments (local)															
Hematology and serum chemistries	X	X	X	X	X	X	X	X	X	X		X	X	X	Preinfusion on the day of tafasitamab administration. See Section 8.3.8 and Table 27.
Coagulation panel	X									X*				X	*Cycle 4 only.
Urinalysis	X									X*				X	*Cycle 4 only.
Immunochemistry	X									X*		X*		X	*C4, C10, and every 6 cycles beyond.
Pregnancy testing (serum)	X*												X	X	*10-14 days before LEN dosing on C1D1.
Pregnancy testing (urine)		X		X	X	X	X	X	X	X		X			Perform within 24 hours prior to the defined timepoint. See Section 8.3.8.1.1.
Serology	X														
HBV DNA (if HBcAb positive)	X	X				X		X		X		X	X	X	See Section 8.3.8.2.
PK and translational laboratory assessments (central)															
PK sampling		X	X	X	X	X	X	X	X	X*	X		X†		*Cycle 4 and beyond: every other cycles. †Will not be collected for patients receiving tafasitamab treatment beyond C12. See Table 28.
ADA (preinfusion)		X				X		X		X*	X		X†		*Cycle 4 and beyond: every other cycles. †Will not be collected for patients receiving tafasitamab treatment beyond C12. See Section 8.4.2.

Table 5: Schedule of Activities (Groups 3 and 4a)

	Screening	Treatment (1 cycle = 28 days)															Follow-Up	
		C1					C2-3				C4 (1 wk ± 1d After C3D22) to C12		C12	C13 to EOT			EOS/Safety	
Visit Day (Range)	Days −28 to −1	D1	D4	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D28 (+4d)	D1 (±2d)	D15 (±2d)	EOT	EOT+90d (+14d)	Notes
Administrative procedures																		
Informed consent	X																	
Inclusion/exclusion criteria	X	X																
General and disease medical history	X																	
Disease assessment (stage, IPI)	X																	See Section 8.1.4.2.
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Preinfusion medication		X	X	X	X	X	X	X	X	X	X	X		X	X			Mandatory for the initial 3 doses. See Section 6.1.
Administer tafasitamab		X	X	X	X	X	X	X	X	X	X	X		X	X			
Dispense LEN (in Group 3) / parsaclisib (in Group 4a)		X					X				X			X*				Dispense LEN on Day 1 of cycle per the PPP (Group 3 only). *LEN will not be dispensed after Cycle 12 (Group 3 only).
Prophylaxis for PJP (Group 4a only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Until 3 months from last parsaclisib dose.
Collect study drug							X				X			X		X		LEN can be collected on Day 22 in each cycle.
Assess compliance			X	X	X	X	X	X	X	X	X	X		X	X	X		

Table 5: Schedule of Activities (Groups 3 and 4a) (Continued)

	Screening	Treatment (1 cycle = 28 days)															Follow-Up	
		C1					C2-3				C4 (1 wk ± 1d After C3D22) to C12		C12	C13 to EOT			EOS/Safety	
Visit Day (Range)	Days −28 to −1	D1	D4	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D28 (+4d)	D1 (±2d)	D15 (±2d)	EOT	EOT+90d (+14d)	Notes
Safety assessments																		
AE assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Body systems with symptoms should be physically examined.
Physical examination	C	C	C	C	C	C	D				D*			D*		C	D	C = comprehensive, D = disease specific. *D1 of C5 and C7, then every 3 cycles (ie, D1 of C10, C13, etc) thereafter. See Section 8.3.2.
ECOG performance status	X	X					X				X			X		X	X	See Section 8.3.3.
Vital signs/body weight/height	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	Height at screening only. See Section 8.3.4 for vital signs.
12-lead ECG	X										X*						X	*Cycle 4 only. See Section 8.3.5.
Chest X-ray or CT/MRI (chest) for ILD screening	X																	Performed additionally for symptoms of respiratory illness. See Section 8.3.7.
Efficacy assessments																		
PET/CT	X												X			X		
CT/MRI							X*				X*		X*	X*				*Perform within 3 days before C3D1 and within 5 days before D1 of C5, C7, and C10. Then performed on C12D28 (+ 4 days; including PET). Approximately every 3 cycles (ie, D1 of C16, C19, etc) from the previous scan thereafter.

Table 5: Schedule of Activities (Groups 3 and 4a) (Continued)

	Screening	Treatment (1 cycle = 28 days)														Follow-Up	
		C1					C2-3				C4 (1 wk ± 1d After C3D22) to C12		C12	C13 to EOT		EOS/Safety	
Visit Day (Range)	Days −28 to −1	D1	D4	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D28 (+4d)	D1 (±2d)	D15 (±2d)	EOT	EOT+90d (+14d)	Notes
Tumor response assessments	X						X				X		X	X		X		See Section 8.2 and Section 10.4.1.2.
Bone marrow aspiration & biopsy	X						X*				X*		X*	X*		X*		*Perform within 2 weeks from the radiologic evaluation to confirm CR. Not mandated in participants who undergo PET/CT in Group 4. Mandatory in participants in Group 3 to confirm CR. See Section 8.2.2.
Laboratory assessments (local)																		
Hematology and serum chemistries	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	Preinfusion on the day of tafasitamab administration. See Section 8.3.8.
Coagulation panel	X										X*						X	*Cycle 4 only.
Urinalysis	X										X*						X	*Cycle 4 only.
Immunochemistry	X										X*			X*			X	*C4, C10, and every 6 cycles beyond.
Pregnancy testing (serum)	X*															X	X	*10-14 days before LEN dosing on C1D1 in Group 3 and 1-28 days before C1D1 in Group 4a.
Pregnancy testing (urine)		X*		X*	X*	X*	X		X*		X	X*		X				Perform within 24 hours prior to the defined timepoint. See Section 8.3.8.1.1. *Group 3 only.
Serology	X																	
HBV DNA (if HBcAb positive)	X	X					X				X			X		X	X	See Section 8.3.8.2.
CMV DNA		X					X				X			X		X		Group 4a only.

Table 5: Schedule of Activities (Groups 3 and 4a) (Continued)

	Screening	Treatment (1 cycle = 28 days)															Follow-Up	
		C1					C2-3				C4 (1 wk ± 1d After C3D22) to C12		C12	C13 to EOT			EOS/Safety	
Visit Day (Range)	Days −28 to −1	D1	D4	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D28 (+4d)	D1 (±2d)	D15 (±2d)	EOT	EOT+90d (+14d)	Notes
PK and translational laboratory assessments (central)																		
PK sampling		X	X	X	X	X	X			X	X*			X*			X	*Cycle 4 and beyond: every 4 cycles. See Table 28.
ADA (preinfusion)		X			X		X				X*			X*			X	*Cycle 4 and beyond: every 4 cycles. See Section 8.4.2.

Table 6: Schedule of Activities (Group 5)

Visit Day (Range)	Screening	Treatment (1 cycle = 21 days)							Follow-Up			Notes
		C1			C2-C6				Safety	Disease	EOS	
	Days −28 to −1	D1	D8 (±2d)	D15 (±2d)	D1 (±2d)	D8 (±2d)	D15 (±2d)	EOT	EOT + 90 d (+14d)	Every 3 mo (±2wk) After EOT up to 15 mo	18 mo After EOT (±2wk)	
Administrative procedures												
Informed consent	X											
Inclusion/exclusion criteria	X	X										
General and disease medical history	X											
Disease assessment (stage, IPI)	X											See Section 8.1.4.2.
Prior/concomitant medications	X	X	X	X	X	X	X	X	X			
Preinfusion medication		X	X	X	X	X	X					Mandatory for the initial 3 doses. See Section 6.1.
Administer tafasitamab		X	X	X	X	X	X					
Administer R-CHOP		X*			X*							*Include administration of PSL from Day 1 to Day 5.
Dispense LEN		X			X							Dispense LEN on Day 1 of cycle per the PPP.
Collect study drug					X			X				LEN is collected on Day 1 in the next cycle at the latest. The earlier collection is acceptable.
Assess compliance			X	X	X	X	X	X				
Safety assessments												
AE assessments	X	X	X	X	X	X	X	X	X			Body systems with symptoms should be physically examined.
Physical examination	C	C	C	C	D			C	D	D	D	C = comprehensive, D = disease specific. See Section 8.3.2.
ECOG performance status	X	X			X			X				See Section 8.3.3.
Vital signs/body weight/height	X	X	X	X	X	X	X	X	X			Height at screening only. See Section 8.3.4 for vital signs.
12-lead ECG	X				X*				X			*Cycle 4 only. See Section 8.3.5.
Echocardiogram	X											See Section 8.3.6.

Table 6: Schedule of Activities (Group 5) (Continued)

Visit Day (Range)	Screening	Treatment (1 cycle = 21 days)						EOT	Follow-Up			Notes
		C1			C2-C6				Safety	Disease	EOS	
	Days −28 to −1	D1	D8 (±2d)	D15 (±2d)	D1 (±2d)	D8 (±2d)	D15 (±2d)		EOT + 90 d (+14d)	Every 3 mo (±2wk) After EOT up to 15 mo	18 mo After EOT (±2wk)	
Chest X-ray or CT/MRI (chest) for ILD screening	X											Performed additionally for symptoms of respiratory illness. See Section 8.3.7.
Efficacy assessments												
PET/CT	X							X				
CT/MRI					X*					X	X	*Perform within 3 days before C4D1.
Tumor response assessments	X				X*			X		X	X	*C4D1 only.
Bone marrow aspiration and biopsy	X				X*			X*		X*	X*	*Perform within 2 weeks from the radiologic evaluation to confirm CR. Not mandated in participants who undergo PET/CT. See Section 8.2.2.
Laboratory assessments (local)												
Hematology and serum chemistries	X	X	X	X	X	X	X	X	X			Preinfusion on the day of tafasitamab administration. See Section 8.3.8 and Table 27.
Coagulation panel	X				X*				X			*Cycle 4 only. See Table 27.
Urinalysis	X				X*				X			*Cycle 4 only. See Table 27.
Immunochemistry	X				X*				X	X†		*Cycle 4 only. †6 and 12 months after EOT. See Table 27.
Pregnancy testing (serum)	X*							X	X			*10-14 days before LEN dosing on C1D1.
Pregnancy testing (urine)		X	X	X	X	X	X					Perform within 24 hours prior to the defined timepoint. See Section 8.3.8.1.1.
Serology	X											
HBV DNA (if HBcAb positive)	X	X			X			X	X	X*		*Until 12 months after the last dose. See Section 8.3.8.2.
Endocrine function	X				X*				X		X	*Cycle 4 only. See Table 27.

Table 6: Schedule of Activities (Group 5) (Continued)

Visit Day (Range)	Screening	Treatment (1 cycle = 21 days)						EOT	Follow-Up			Notes
		C1			C2-C6				Safety	Disease	EOS	
	Days −28 to −1	D1	D8 (±2d)	D15 (±2d)	D1 (±2d)	D8 (±2d)	D15 (±2d)		EOT + 90 d (+14d)	Every 3 mo (±2wk) After EOT up to 15 mo	18 mo After EOT (±2wk)	
PK and translational laboratory assessments (central)												
PK sampling		X	X	X	X				X	X*		*First visit (Disease Visit 1) only. See Table 28.
ADA (preinfusion)		X		X	X*				X	X†		*Cycles 2, 3, 4, and 6. †First visit (Disease Visit 1) only. See Section 8.4.2.

Table 7: Schedule of Activities (Group 6)

	Screening	Treatment (1 cycle = 28 days)														Follow-Up		
		C1					C2-3				C4 (1wk ± 1d After C3D22) to C12		C12	C13 to EOT		Safety		
Visit Day (Range)	Days −28 to −1	D1	D4	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D28 (+4d)	D1 (±2d)	D15 (±2d)	EOT	EOT +90d (+14d)	Disease/ Survival[a]	Notes
Administrative procedures																			
Informed consent	X																		
Inclusion/exclusion criteria	X	X																	
General and disease medical history	X																		
Disease assessment (stage, IPI)	X																		See Section 8.1.4.2.
Prior/concomitant/ post-treatment medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X*	*Post-treatment therapy only.
Preinfusion medication		X	X	X	X	X	X	X	X	X	X	X		X	X				Mandatory for the initial 3 doses. See Section 6.1.
Administer tafasitamab		X	X	X	X	X	X	X	X	X	X	X		X	X				
Dispense LEN		X					X				X								Dispense LEN on Day 1 of cycle per the PPP.
Collect LEN							X				X			X		X			LEN can be collected on D22 in each cycle.
Assess compliance			X	X	X	X	X	X	X	X	X	X		X	X	X			

Table 7: Schedule of Activities (Group 6) (Continued)

Visit Day (Range)	Screening	Treatment (1 cycle = 28 days)															Follow-Up		Notes
		C1					C2-3				C4 (1wk ± 1d After C3D22) to C12		C12	C13 to EOT			Safety		
	Days −28 to −1	D1	D4	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D28 (+4d)	D1 (±2d)	D15 (±2d)	EOT	EOT +90d (+14d)	Disease/ Survival[a]	
Safety assessments																			
AE assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Body systems with symptoms should be physically examined.
Physical examination	C	C	C	C	C	C	D				D*			D*		C	D		C = comprehensive, D = disease specific. *D1 of C5 and C7, then every 3 cycles (ie, D1 of C10, C13, etc) thereafter. See Section 8.3.2.
ECOG performance status	X	X					X				X			X		X	X		See Section 8.3.3.
Vital signs/body weight/height	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		Height at screening only. See Section 8.3.4 for vital signs.
B-symptom	X	X					X				X			X		X		X*	*Only during disease follow-up.
12-lead ECG	X	X*														X			*Only if indicated. See Section 8.3.5.
Chest X-ray or CT/MRI (chest) for ILD screening	X																		Performed additionally for symptoms of respiratory illness. See Section 8.3.7.

Table 7: Schedule of Activities (Group 6) (Continued)

Visit Day (Range)	Screening	Treatment (1 cycle = 28 days)														EOT	Follow-Up		Notes
		C1					C2-3				C4 (1wk ± 1d After C3D22) to C12		C12	C13 to EOT			Safety		
	Days −28 to −1	D1	D4	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D28 (+4d)	D1 (±2d)	D15 (±2d)		EOT +90d (+14d)	Disease/ Survival[a]	
Efficacy assessments																			
PET/CT	X												X	X*		X*			*If a radiologic CR is achieved based on CT/MRI after C12D28 but before EOT, a confirmatory PET must be performed. After the PET confirming CR, no further PET scans are necessary.
CT/MRI	X*						X†				X†		X*†	X†				X	*CT/MRI at baseline/C12D28 are not required if the CT portion of PET/CT is used for tumor measurement at baseline. See Section 8.2.1. †Perform within 3 days before C3D1 and within 5 days before D1 of C5, C7, and C10. Then performed on C12D28 (+ 4 days; including PET). Approximately every 3 cycles (ie, D1 of C16, C19, etc) from the previous scan thereafter.
Tumor response assessments	X						X				X		X	X		X		X	See Section 8.2 and Section 10.4.1.3.

Table 7: Schedule of Activities (Group 6) (Continued)

Visit Day (Range)	Screening	Treatment (1 cycle = 28 days)															Follow-Up		Notes
		C1					C2-3				C4 (1wk ± 1d After C3D22) to C12		C12	C13 to EOT			Safety		
	Days −28 to −1	D1	D4	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D28 (+4d)	D1 (±2d)	D15 (±2d)	EOT	EOT +90d (+14d)	Disease/ Survival[a]	
Bone marrow aspiration & biopsy	X						X*				X*		X*	X*		X*		X*	*Perform within 2 weeks from the radiologic evaluation to confirm CR. See Section 8.2.2.
Survival																		X	After disease progression or the start of new anticancer therapy. Can be via phone call. See Section 8.8.3.
Laboratory assessments (local)																			
Hematology and serum chemistries	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		Preinfusion on the day of tafasitamab administration. See Section 8.3.8.
Coagulation panel	X										X*						X		*Cycle 4 only.
Urinalysis	X										X*						X		*Cycle 4 only.
Immunochemistry	X										X*			X*			X		*C4, C10, and every 6 cycles beyond.
Pregnancy testing (serum)	X*															X	X		*10-14 days before LEN dosing on C1D1.
Pregnancy testing (urine)		X		X	X	X	X		X		X	X		X					Perform within 24 hours prior to the defined timepoint. See Section 8.3.8.1.1.
Serology	X																		
HBV DNA (if HBcAb positive)	X	X					X				X			X		X	X		See Section 8.3.8.2.

Table 7: Schedule of Activities (Group 6) (Continued)

Visit Day (Range)	Screening	Treatment (1 cycle = 28 days)															Follow-Up		Notes
		C1					C2-3				C4 (1wk ± 1d After C3D22) to C12		C12	C13 to EOT			Safety		
	Days −28 to −1	D1	D4	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D28 (+4d)	D1 (±2d)	D15 (±2d)	EOT	EOT +90d (+14d)	Disease/ Survival[a]	
PK and translational laboratory assessments (central)																			
PK sampling		X	X		X		X		X		X*			X*		X			*Cycle 4 and beyond: every 4 cycles. See Table 28.
ADA (preinfusion)		X			X		X				X*			X*		X			*Cycle 4 and beyond: every 4 cycles. See Section 8.4.2.

[a] Perform radiological tumor assessment Q12W (± 2 weeks) until disease progression or the start of new anticancer therapy. The survival follow-up will be performed Q12W (± 2 weeks) and last for a maximum of 3 years from Cycle 1 Day 1 or until withdrawal of consent, or death, whichever comes first.

Table 8: Schedule of Activities (Continued Access Period for Participants in Groups 1, 3, and 4a)

Visit Day (Range)	During Treatment Period Prior to or D1 of the Continued Access Period	Treatment (1 cycle = 28 days)			Follow-Up	Notes
		From Cycle Initiated After 2 Years of Treatment to EOT			EOS/Safety	
		D1 (±2d)	D15 (±2d)	EOT	EOT+90d (+14d)	
Administrative procedures						
Informed consent	X					For participants who continue the study treatment beyond 2 years only.
Prior/concomitant medications		X	X	X	X	
Preinfusion medication		X	X			See Section 6.1.
Administer tafasitamab		X	X			
Dispense parsaclisib		X				Applicable only for participants who continue parsaclisib dosing.
Prophylaxis for PJP		X	X	X	X	Applicable only for participants on parsaclisib dosing and until 3 months after the last dose of parsaclisib.
Collect parsaclisib		X		X		Applicable only for participants who continue parsaclisib dosing.
Assess compliance		X	X	X		
Safety assessments						
AE assessments		X	X	X	X	Body systems with symptoms should be physically examined.
Physical examination		D*		C	D	C = comprehensive, D = disease specific. *D1 of every 3 cycles (ie, D1 of C10, C13, etc) during the continued access period. See Section 8.3.2.
ECOG performance status		X		X	X	See Section 8.3.3.
Vital signs/body weight		X	X	X	X	See Section 8.3.4.
Efficacy assessments						
Tumor response assessments including radiographic assessment (PET/CT, CT/MRI)		X*		X		See Section 8.2. *Performed as per site standard of care.

Table 8: Schedule of Activities (Continued Access Period for Participants in Groups 1, 3, and 4a) (Continued)

Visit Day (Range)	During Treatment Period Prior to or D1 of the Continued Access Period	Treatment (1 cycle = 28 days)			Follow-Up	Notes
		From Cycle Initiated After 2 Years of Treatment to EOT			EOS/Safety	
		D1 (±2d)	D15 (±2d)	EOT	EOT+90d (+14d)	
Laboratory assessments (local)						
Hematology and serum chemistries		X		X	X	Preinfusion on the day of tafasitamab administration. See Section 8.3.8.
Coagulation panel					X	
Urinalysis					X	
Immunochemistry		X*			X	*Every 6 cycles.
Pregnancy testing (serum)				X	X	
Pregnancy testing (urine)		X				Perform within 24 hours prior to the defined timepoint. See Section 8.3.8.1.1.
HBV DNA (if HBcAb positive)		X		X	X	See Section 8.3.8.2.
CMV DNA		X		X		Group 4a only.
PK and translational laboratory assessments (central)						
PK sampling		X*		X		*Every 6 cycles. Preinfusion.
ADA (preinfusion)		X*		X		*Every 6 cycles. See Section 8.4.2.

Table 9: Schedule of Activities (All Participants After the Final Data Cutoff Date)

Visit Day (Range)	Treatment (1 cycle = 28 days) From Cycle Initiated After Data Cutoff Date to EOT D1 (±2d)	Treatment (1 cycle = 28 days) From Cycle Initiated After Data Cutoff Date to EOT D15 (±2d)[a]	EOT	Follow-Up EOS/Safety EOT+90d (+14d)	Notes
Administrative procedures					
Prior/concomitant medications	X	X	X	X	
Preinfusion medication	X	X			
Administer tafasitamab	X	X			
Safety assessments					
AE assessments	X	X	X	X	
Physical examination	To be performed as clinically indicated		X		Comprehensive physical examination at EOT.
ECOG performance status	To be performed as clinically indicated		X	X	
Vital signs/body weight	X	X	X	X	
New anticancer therapy			X	X	
Efficacy assessments					
Tumor response assessments including radiographic assessment (PET/CT, CT/MRI)	To be performed as per site standard of care				See Section 8.2.1
Laboratory assessments (local)					
Hematology and serum chemistries	X		X	X	Preinfusion on the day of tafasitamab administration. See Section 8.3.8
Coagulation panel				X	
Urinalysis				X	
Pregnancy testing (serum)			X	X	
Pregnancy testing (urine)	X				Perform within 24 hours prior to the defined timepoint. See Section 8.3.8.1.1.
HBV DNA (if HBcAb positive)	X		X	X	See Section 8.3.8.2.

[a] Not applicable for participants in Group 2.

2. INTRODUCTION

2.1. Background

2.1.1. Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma is the most common hematologic malignancy in adults. The majority of NHLs are of B-cell origin, with multiple different histologic subtypes that confer different clinical outcomes (Habermann et al 2006, Shingleton et al 2020, Swerdlow et al 2016). Apart from the pathologic classification of NHLs, they are also commonly categorized as indolent or aggressive lymphomas based on their clinical characteristics. Indolent lymphomas include various types such as FL, MZL, mucosa-associated lymphoid tissue lymphoma, and others (Sehn 2016). FL is the second most common NHL type after DLBCL and may have various clinical courses (Dada 2019). Indolent lymphomas are slowly progressing and responsive to therapy but are generally considered to be not curable. Aggressive lymphomas are rapidly progressing but responsive to therapy and often curable.

2.1.2. Diffuse Large B-Cell Lymphoma

DLBCL, an aggressive and the most common NHL, accounts for one-third of NHL. Patients with DLBCL usually present with rapidly enlarging lymphoid masses, often with symptoms both local and systemic, and fever, recurrent night sweats, and/or weight loss. Some patients also have extranodal manifestations (eg, skin, liver, gastric, CNS, and others). The current SoC for the treatment of newly diagnosed DLBCL patients with advanced-stage disease is the immune-chemotherapy regimen R-CHOP consisting of the anti-CD20 mAb rituximab (R) plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy. Following first-line therapy with R-CHOP, about 30% to 40% of patients relapse or are refractory to R-CHOP and require further treatment (Habermann et al 2006, Coiffier et al 2010).

Relapsed patients and patients with disease that fails to respond to first-line therapy (refractory patients) have a poor prognosis (Cultrera and Dalia 2012, Martelli et al 2013). Patients with relapsed/refractory disease are generally divided into 2 categories:

- Patients with chemosensitive disease who are potential candidates for HDC/ASCT
- Patients who are refractory to immuno-chemotherapy or are not medically fit for an aggressive salvage chemotherapy or CAR T-cell regimen.

For patients who are ineligible for HDC/ASCT or who relapsed after transplantation, the overall prognosis is poor and there is no global SoC established for this clinical setting.

Bendamustine in combination with rituximab (BR) demonstrated encouraging results: in a multicenter Phase 2 study, an overall response rate of 59% was observed (Fischer et al 2011). Furthermore, polatuzumab vedotin + BR and gemcitabine/oxaliplatin are recently added the list of treatment regimens recommended in the US treatment guidelines (NCCN 2021).

Although there are some candidates of salvage therapies listed in the JSH Guidelines (Ohmachi 2019), and polatuzumab vedotin in combination with BR therapy was approved recently in Japan, there is no SoC established in Japan.

In addition, a number of novel agents are undergoing evaluation for DLBCL, including immunomodulating agents, mechanistic target of rapamycin inhibitors, proteasome inhibitors, histone deacetylase inhibitors, and antiangiogenic agents.

2.1.3. Tafasitamab

Tafasitamab (also known as INCMOR00208, MOR00208, and XmAb®5574) is an Fc-engineered mAb that binds to the human B-cell surface antigen CD19 and is produced by recombinant DNA technology in Chinese hamster ovary cells. CD19 is expressed on a variety of B-cell lymphomas and normal B-cells and was shown to be expressed also in cases where rituximab is ineffective due to CD20 downregulation or other factors (Davis et al 1999, Gerber et al 2009). Due to its lineage-specific expression pattern, targeting CD19 has clinical utility as a therapeutic approach to NHL (Hammer 2012). The increased binding of tafasitamab to FcγR, due to its Fc region, significantly enhances in vitro ADCC, ADCP, and its direct cytotoxic effects (apoptosis) on the tumor cells compared with the nonengineered parental murine antibody. Tafasitamab has not been shown to mediate CDC (Awan et al 2010, Horton et al 2008).

The pharmacodynamic interactions of tafasitamab in combination with 2 standard-of-care drugs, fludarabine (Study No. MOR208P005) and BEN (Study No. MOR208P010), and 1 investigational drug, LEN (Study No. MOR208P009), used in the treatment of patients with CLL and NHL, were investigated in a human IV lymphoma model in severe combined immunodeficiency mice. This xenograft study showed a clear potentiation of the efficacy benefit of tafasitamab (3 mg/kg) and LEN (100/200 mg/kg) combination therapy compared with the respective monotherapies (1.5× increase in median lifespan).

Tafasitamab is being developed for the treatment of CD19+ lymphoid malignancies. Chronic lymphocytic leukemia, NHL, HCL, and B-precursor ALL represent tumor types that have been well-characterized in regard to expression of the CD19 antigen.

XmAB5574-01 is a first-in-human Phase 1 study in participants with R/R CLL/SLL. During the course of this study, as of the data cutoff date of 24 JAN 2013, 27 participants were treated in dose cohorts from 0.3 mg/kg (n = 1) to 12 mg/kg (n = 16) IV on a weekly schedule for 8 weeks, with an extra dose administered on Day 4. The MTD was not established, since only 1 DLT (Grade 4 neutropenia) occurred. The most frequent AE was IRR with all Grade 1 or Grade 2 in severity. MOR208C201 is a Phase 2a, open-label, multicenter study of single-agent tafasitamab in participants with R/R NHL. As of the data cutoff date of 28 SEP 2018, responses as assessed by the investigator were seen in 3 of the 4 studied subgroups: 25.7% of participants with DLBCL, 29.4% with FL, and 27.3% with other iNHLs. In a sensitivity analysis excluding participants without a postbaseline response assessment, the overall response rate was 36.0% in the DLBCL, 32.3% in the FL, and 30.0% in the other iNHL subgroups. The safety profile of tafasitamab was favorable with only 4 of 92 participants (4%) experiencing a serious adverse reaction, no treatment-related deaths, and no evidence for significant late toxicities.

Based on the results obtained from the Phase 1 and 2a studies, and based on unmet medical need considerations, further development of tafasitamab focused on clinical studies in DLBCL. Based on the data from a single-arm, open-label, multicenter Phase 2 study in participants with R/R DLBCL conducted in the US and EU (MOR208C203 [L-MIND] study; see Section 2.1.4.2 for details), tafasitamab was granted accelerated approval by the FDA on 31 JUL 2020. Tafasitamab

in combination with LEN was authorized for the treatment of adult patients with R/R DLBCL not otherwise specified, including DLBCL arising from low-grade lymphoma, and who are not eligible for ASCT. Furthermore, and based on the same data, tafasitamab was granted conditional approval in R/R DLBCL in the EU on 26 AUG 2021, in Canada on 19 AUG 2021, and in Switzerland on 22 MAR 2022.

2.1.3.1. Tafasitamab Pharmacokinetics

The PK of tafasitamab following IV administration was well-characterized by a 2-compartment linear disposition model with time-dependent elimination. Clearance was determined at 0.413 L/day, terminal elimination half-life was 16.9 days, and the total volume of distribution was 9.32 L. The PK of tafasitamab was consistent across indications.

As determined by stepwise covariate model building, body weight at baseline was found to influence tafasitamab clearance and central volume of distribution. Further covariates were serum albumin (inverse correlation with clearance), sex (lower central volume of distribution in females), and disease type (participants with NHL or ALL had a lower central volume of distribution than participants with CLL/SLL). However, the covariate effects were moderate in size and assessed as clinically not relevant, that is, not warranting dose adjustments.

2.1.3.2. Tafasitamab Immunogenicity

No treatment-emergent or treatment-boosted ADAs were detected for tafasitamab, and the pre-existing antibodies did not affect PK, safety or efficacy of tafasitamab.

2.1.4. Lenalidomide in Hematological Malignancies

Lenalidomide belongs to the class of IMiDs. Consequently, it mediates antiproliferative and antiangiogenic effects, can stimulate the activity of immune effectors such as T cells and NK cells, and induces NK-cell proliferation (Kotla et al 2009, Gribben et al 2015). Besides general activation and expansion of NK cells, LEN has also been shown to enhance their ADCC capacity (Gribben et al 2015).

Lenalidomide monotherapy was investigated in participants with R/R DLBCL and shown to result in poor outcomes (Witzig et al 2011, Czuczman et al 2017). Lenalidomide demonstrated manageable toxicity as a single agent, in combination with RTX in R/R DLBCL, or in combination with R-CHOP in R^2-CHOP regimen in untreated DLBCL (see below). It is currently unknown whether the COO has an impact on LEN efficacy in frontline DLBCL therapy. Diffuse large B-cell lymphoma risk stratification according to COO has prognostic value. Germinal center B-cell–DLBCL shows a favorable course, but ABC-DLBCL represents an aggressive form of the disease (Pasqualucci and Dalla-Favera 2018).

A dose-finding Phase 1b study of LEN (dose levels 15, 20, and 25 mg given Days 1-10) in combination with R-CHOP given every 21 days was conducted in participants with newly diagnosed DLBCL and showed that LEN did not affect dose intensity or the schedule of R-CHOP; LEN with R-CHOP was safe and associated with high response rates (100% ORR, 77% CR; Nowakowski et al 2011). Based on this study and another single-arm Phase 2 study with a different LEN dose regimen (15 mg, Days 1-14 every 21 days; Vitolo et al 2014), it was concluded that LEN can be safely combined with R-CHOP in the initial treatment of participants with DLBCL. The global Phase 3 ROBUST study (NCT02285062, EudraCT number 2013-004054-21)

was the first to compare LEN/R-CHOP (R^2-CHOP) versus placebo/R-CHOP in previously untreated, prospectively selected, CD20+ ABC-type DLBCL (Vitolo et al 2014). The results of the ROBUST study were reported at the ICML meeting in Lugano 2019, and the full manuscript has not been published to date. The primary endpoint of PFS was not met with an HR of 0.85 (95% CI: 0.63, 1.14) and p = 0.29; median PFS was not reached for either arm (median follow-up 27.1 months). The safety profile of R^2-CHOP was consistent with those of the individual compounds, and no new safety signals were identified with the combination.

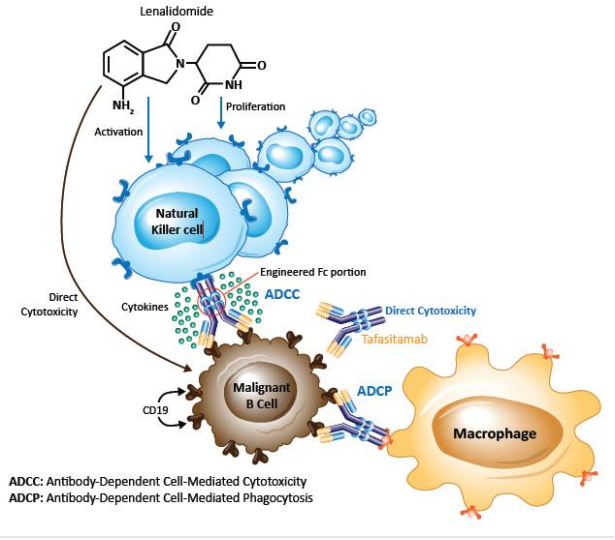
The ECOG-ACRIN1412 study is a randomized Phase 2 US intergroup study investigating R^2-CHOP versus R-CHOP in participants newly diagnosed with DLBCL (regardless of COO; Nowakowski et al 2019). The primary endpoint was PFS. Two hundred eighty participants (145 R^2-CHOP, 135 R-CHOP) were evaluable, with 94 participants being classified as ABC-DLBCL, 122 as GCB-DLBCL, and 18 designated as unclassified. Toxicity was as expected with the R-CHOP regimen. Significantly different rates of ≥ Grade 3 AEs between arms were as follows: diarrhea (6% vs 0.6% of participants, p = 0.005), febrile neutropenia (25% vs 12% of participants, p = 0.003), and thrombocytopenia (36% vs 12% of participants, p < 0.0001) in R^2-CHOP versus R-CHOP arm, respectively. A total of 86% and 85% of participants completed 6 cycles of therapy in R^2-CHOP and R-CHOP arms, respectively. The ORR and CRR were 92% and 67%, respectively, in the R-CHOP arm and 97% (p = 0.12) and 72% (p = 0.44), respectively, in the R^2-CHOP arm. With a median follow-up of 2.4 years, R^2-CHOP was associated with a 33% reduction in risk of progression or death versus R-CHOP, with an HR of 0.67 (95% CI: 0.44, 1.03) and p = 0.03 (1-sided). The 2-year OS was 87% and 80% in R^2-CHOP and R-CHOP arm, respectively.

2.1.4.1. Rationale of Tafasitamab + LEN Combination

Lenalidomide mediates antiproliferative and antiangiogenic effects, can stimulate the activity of immune effectors such as T cells and NK cells, and induces NK-cell proliferation (Kotla et al 2009, Gribben et al 2015). Besides general activation and expansion of NK cells, LEN has also been shown to enhance their ADCC capacity (Gribben et al 2015). In a preclinical study, pretreatment with LEN showed a 3- to 5-fold enhanced tafasitamab-mediated cytotoxicity by macrophages and isolated LAMs. Of note, the increased cytotoxicity was tafasitamab-specific and was neither attributable to direct cytotoxic effects of LEN nor increased CD19 expression on target cells. These results suggest that tafasitamab leverages the presence of tumor-promoting LAMs as effector cells. The inherent ADCP activity of tafasitamab can be further improved by the immunomodulatory agent LEN, potentially via reduction of SIRPα levels on macrophages (Mougiakakos et al 2019).

Thus, LEN provides tafasitamab with a larger and more potent effector cell pool for tumor cell killing. Tafasitamab and LEN in combination have demonstrated increased combinatorial antitumor effects in preclinical in vitro and in vivo experiments (Awan et al 2010, Patra et al 2020; see Figure 2).

Figure 2: Complementary Mode of Action of Tafasitamab and LEN



2.1.4.2. L-MIND Study

The L-MIND study is a Phase 2, single-arm, open-label, multicenter study designed to evaluate the efficacy and safety of tafasitamab in combination with LEN in participants with R/R DLBCL. The study enrolled 81 participants from 35 clinical sites in Europe and the US. The primary endpoint of the study is ORR, defined as the proportion of participants with CR or PR per IRC, based on response criteria per the guidelines of the IWG (Cheson et al 2007). In 80 participants with R/R DLBCL evaluable for response, the combination of tafasitamab with LEN achieved a high ORR of 60% (48/80; 95% CI: 48.4, 70.8), a CR rate of 42.5%, and a median PFS of 12.1 months (data cutoff of 30 NOV 2018; Salles et al 2020).

With a longer follow-up (data cutoff of 14 NOV 2022), the results were consistent, with a median DOR not reached (95% CI: 33.8 months, NR), median PFS of 11.6 months (95% CI: 5.7, 45.7), and median OS of 33.5 months (95% CI: 18.3, NR) in the final analysis. After the primary analysis, the best responses for 3 participants were revised based on an IRC readjudication and response deepening. The IRC-assessed ORR was 57.5% (46/80; 95% CI: 45.9, 68.5), the CRR was 41.3% (33/80; 95% CI: 30.4, 52.8), and the PR rate was 16.3% (13/80; 95% CI: 8.9, 26.2).

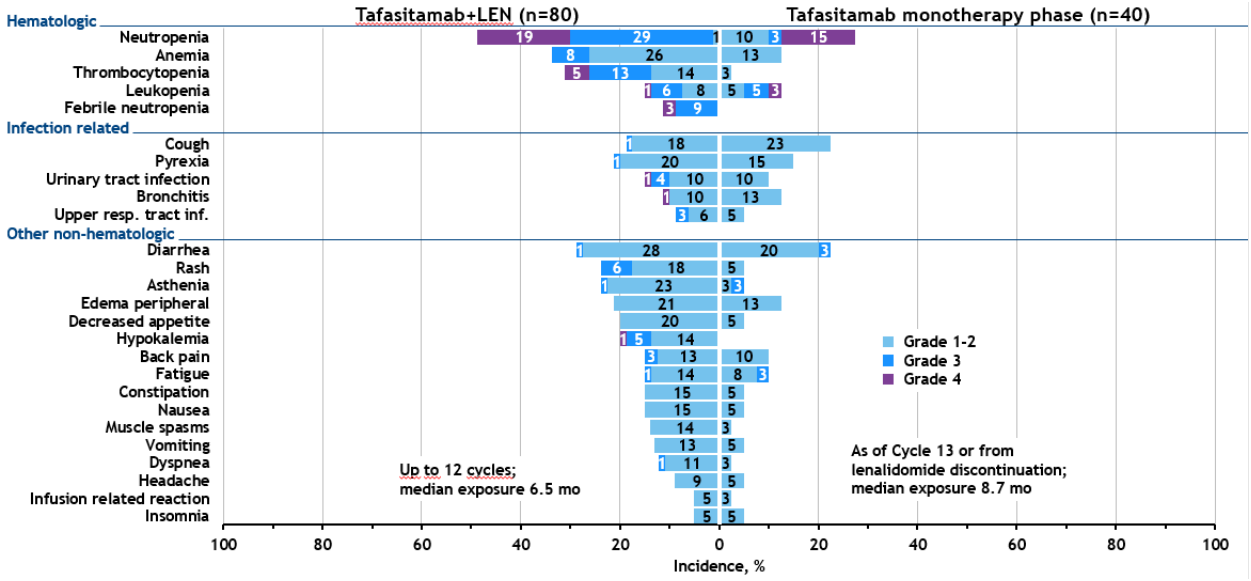
At the previous long-term data cutoff (data cutoff of 30 OCT 2020), the impact of response quality on OS was shown; among the participants with a CR, the median OS was not reached, and OS estimates were 96.9% (95% CI: 79.8, 99.6) at 18 months, 90.6% (95% CI: 73.7, 96.9) at 24 months, and 81.3% (95% CI: 62.9, 91.1) at 36 months. Among participants with a PR, the median OS was 22.5 months (95% CI: 8.6, not reached), and OS estimates were 59.8% (95% CI: 28.5, 81.0) at 18 months, 42.7% (95% CI: 15.9, 67.5) at 24 months, and 34.2% (95% CI: 10.7, 59.8) at 36 months (data cutoff of 30 OCT 2020; Duell et al 2021).

As expected, based on the mode of action of both drugs, the safety of the combination of tafasitamab plus LEN was adequately managed by clinical interventions (as of the data cutoff of 30 NOV 2019; see Figure 3). Additionally, as of 14 NOV 2022 with a longer follow-up in the final analysis, 84% of 81 participants had a study drug–related TEAE reported; 81.5% and

58.0% of the participants had a Grade 3 or higher TEAE and serious TEAE, respectively; 80.2% of participants had a TEAE that led to dose modification, dose interruption, or discontinuation of tafasitamab or LEN; and 16 participants discontinued tafasitamab, 18 participants discontinued LEN, and 10 participants discontinued both study drugs. A total of 8 participants died on study, 5 due to PD and 3 due to AEs (1 stroke, 1 sudden death, and 1 respiratory failure).

Hence, combining 2 agents with complementary mechanisms of action and with an acceptable safety profile should contribute to significantly improving outcomes in participants with R/R DLBCL as shown in L-MIND.

Figure 3: Summary of L-MIND Safety Results: Tafasitamab and Lenalidomide Combination Phase With Longer Follow-Up Versus Tafasitamab Monotherapy Phase



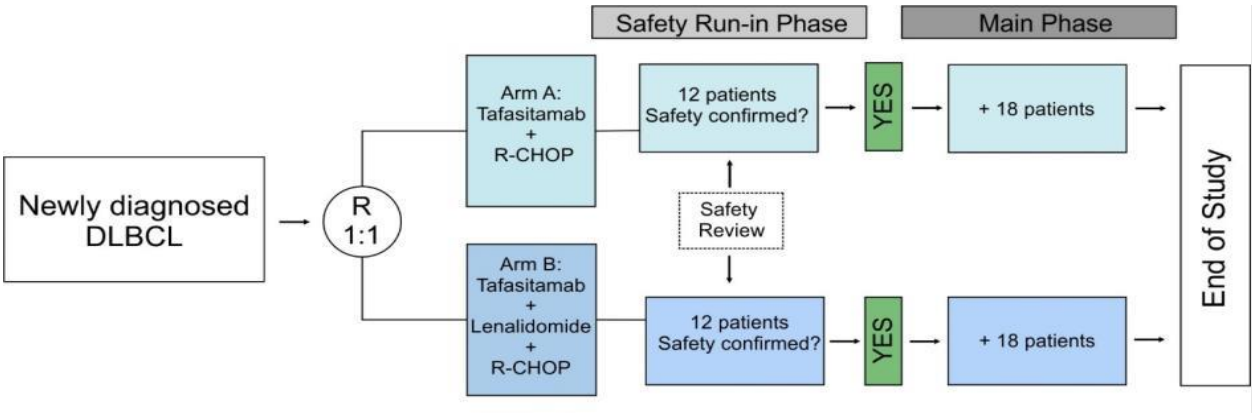
Note: Data cutoff date of 30 NOV 2019.

2.1.4.3. First-MIND Study

The First-MIND study (NCT 04134936, EudraCT number 2019-001268-31) is a Phase 1b, open-label, randomized study to assess the safety and preliminary efficacy of tafasitamab in addition to R-CHOP or tafasitamab plus LEN in addition to R-CHOP in participants with newly diagnosed DLBCL. The participant population comprises adult participants with IPI 2 to 5 (see Figure 4). The primary objective of the study is to assess safety and tolerability.

The safety and tolerability of study treatment will be evaluated by means of AE reports (nature, severity, frequency, and causality), performance status, physical examinations, ECG, and laboratory safety evaluations.

Figure 4: First-MIND Study Schema



The addition of tafasitamab to R-CHOP and tafasitamab and LEN plus R-CHOP had not previously been evaluated in a clinical study; therefore, a safety run-in phase with 12 participants in each treatment arm was performed in the First-MIND study. In order to evaluate the safety in accordance with the study stopping rules, enrollment was paused until 12 participants in each arm had been followed for 21 days after Cycle 1 Day 1. In total, 66 participants were randomized, 33 per arm.

Participants were followed for a total of 18 months after the EOT visit or early study treatment discontinuation visit. The final analyses was performed at the end of the follow-up period. The primary endpoint was safety; secondary endpoints included EOT, ORR, and CRR. All participants had ≥ 1 TEAE, mostly Grade 1 or 2. Grade 3 or higher events of neutropenia and thrombocytopenia occurred, respectively, in 57.6% and 12.1% (Arm A) and 84.8% and 36.4% (Arm B) of participants. Nonhematologic toxicities occurred at similar rates across arms. The EOT ORR was 75.8% (CRR: 72.7%) in Arm A and 81.8% (CRR: 66.7%) in Arm B; the best ORR across visits was 90.0% and 93.9%, respectively. Eighteen-month DOR and CR rates were 72.7% and 74.5% (Arm A) and 78.7% and 86.5% (Arm B); 24-month PFS and OS rates were 72.7% and 90.3% (Arm A) and 76.8% and 93.8% (Arm B). Manageable safety and promising signals of efficacy were observed in both arms (Belada et al 2023).

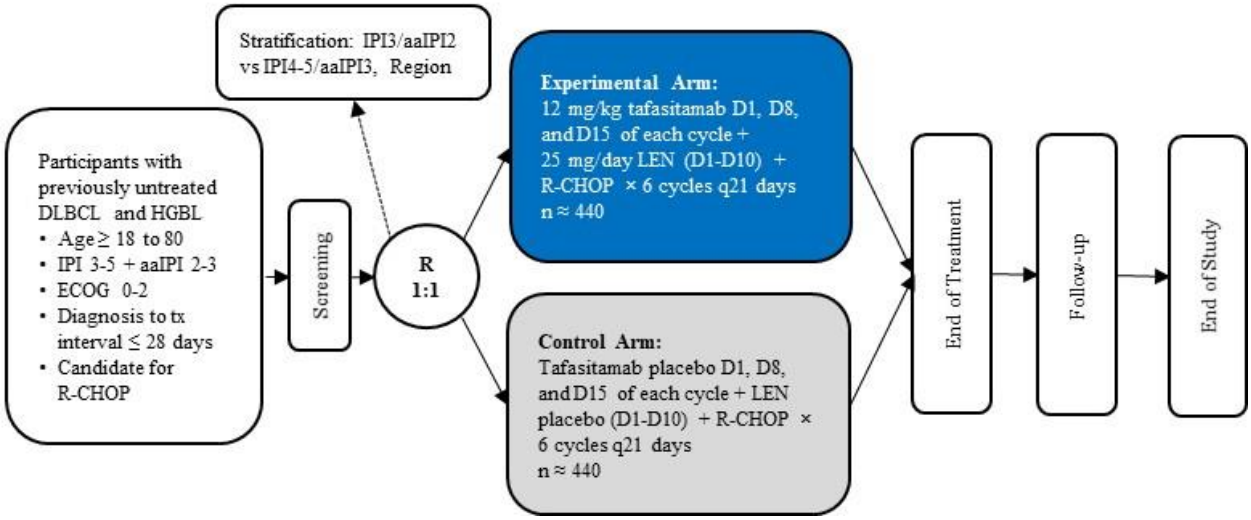
2.1.4.4. frontMIND Study

The frontMIND study (NCT04824092) is a parallel-arm, double-blind, placebo-controlled, multicenter, randomized, Phase 3 study to investigate the efficacy and safety of tafasitamab plus LEN as add-on therapy to R-CHOP (experimental arm) compared with R-CHOP (control arm) in adult participants with high-intermediate and high-risk (defined as IPI 3-5 for participants > 60 years of age and aaIPI 2-3 for participants ≤ 60 years of age) newly diagnosed, previously untreated DLBCL. This study started in 2021, and enrollment was completed with the recommendation to continue the study without any changes from the Independent Data Monitoring Committee.

Approximately 880 participants (440 in each arm) from approximately 350 study centers will be randomized in this study. In the experimental arm, participants will receive tafasitamab plus LEN in addition to R-CHOP for six 21-day cycles, and in the control arm, participants will receive tafasitamab placebo, lenalidomide placebo, and R-CHOP for six 21-day cycles (see Figure 5).

Participants will be randomized in a ratio of 1:1 to either the experimental or control arm. Permutated blocks will be employed using IPI 3 (> 60 years old)/aaIPI 2 (≤ 60 years old) versus IPI 4-5 (> 60 years old)/aaIPI 3 (≤ 60 years old), and geographical regions (Europe, US, Canada, Australia, and New Zealand versus Asia versus the Rest of World [3 groups]) as stratification factors. No crossover to the experimental arm is allowed.

Figure 5: FrontMIND Study Schema



aaIPI = age-adjusted International Prognostic Index (participants ≤ 60 years); CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; D = Day; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; HGBL = high-grade B-cell lymphoma; IPI = International Prognostic Index (participants > 60 years); LEN = lenalidomide; q = every; R = randomization; R-CHOP = rituximab-CHOP; tx = treatment.

With the confirmed safety and tolerability of tafasitamab plus LEN as add-on strategy to R-CHOP in Japanese participants with newly diagnosed DLBCL in this study (Group 5), Japan joins the frontMIND study.

2.1.4.5. MINDway Study

The MINDway study (NCT05222555) is an open-label, multicenter, Phase 1b/2 study of tafasitamab combined with LEN to evaluate the safety and PK of a modified tafasitamab dose regimen in participants with R/R DLBCL. This study was started to optimize the tafasitamab dose regimen to reduce the frequency of hospital/clinic visits for tafasitamab-treated patients with R/R DLBCL.

The primary objective is to evaluate the safety and tolerability of tafasitamab administered Q2W/Q4W in combination with LEN and to determine a recommended dose for this regimen in participants with R/R DLBCL. The secondary objectives are to evaluate the PK profile and to assess antitumor activity and the incidence of ADAs to tafasitamab after Q2W/Q4W dosing in combination with LEN.

To evaluate the tafasitamab dose regimen with approximately 50% fewer infusions, the following modifications to the currently approved dose regimen are defined:

- The dosing frequency is planned to be reduced from QW to Q2W from Cycle 1 Day 15 onward and from Q2W to Q4W from Cycle 4 Day 1 onward.
- The tafasitamab infusion at the previous dose level of 12 mg/kg is planned to be maintained for the first 3 infusions (ie, Days 1, 4, and 8), and the dose level will be increased from Cycle 1 Day 15 onward.

Taking this new dosing schedule into account (see Table 10), the existing tafasitamab population PK model was used to identify new dose levels leading to similar tafasitamab trough levels as observed in the pivotal L-MIND study (see Section 2.1.4.2) in order to maintain the previously established exposure/efficacy relationship. As a result, 24 mg/kg and 30 mg/kg administered according to the dosing schedule outlined in Table 10 are identified as potential new dose levels tested in the MINDway study.

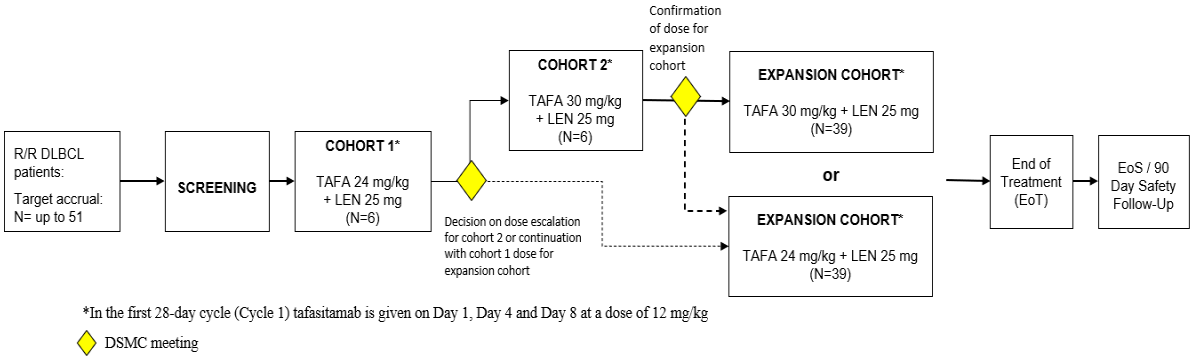
Table 10: Dosing Schedule and Frequency in the MINDway Study

Cohort	Tafasitamab[a]	LEN (up to 12 cycles)[a]
1	Cycle 1: 12 mg/kg on Days 1, 4, and 8 Cycle 1: 24 mg/kg on Day 15 Cycles 2 and 3: 24 mg/kg on Days 1 and 15 of each 28-day cycle Cycle 4 and beyond: 24 mg/kg on Day 1 of each 28-day cycle	Cycle 1-12: 25 mg on Days 1-21 of each cycle
2	Cycle 1: 12 mg/kg on Days 1, 4, and 8 Cycle 1: 30 mg/kg on Day 15 Cycles 2 and 3: 30 mg/kg on Days 1 and 15 of each 28-day cycle Cycle 4 and beyond: 30 mg/kg on Day 1 of each 28-day cycle	
Expansion	In the expansion cohort, tafasitamab will be administered according to the selected dose regimen (24 mg/kg or 30 mg/kg) for further evaluation	

[a] Each treatment cycle is 28 days.

Approximately 51 participants were planned to be enrolled in sequential cohorts. In Cohort 1, at least 6 participants receiving tafasitamab at a dose level of 24 mg/kg were planned to be enrolled. Following the recommendation from the MINDway DSMC based on review of the Cohort 1 data, thereafter at least 6 participants are planned to be enrolled in Cohort 2 at a dose level of 30 mg/kg. It was planned that the MINDway DSMC would determine the dose for the dose-expansion cohort based on evaluation of the safety and tolerability data up to Day 35 in at least 6 participants in Cohorts 1 and 2. Following the review of the safety and the PK data from Cohorts 1 and 2 by the MINDway DSMC, up to 39 additional participants at a dose of 24 mg/kg or 30 mg/kg were planned to be enrolled in the dose-expansion cohort to collect data from approximately 45 participants at the confirmed tafasitamab dosage (see Figure 6).

Figure 6: MINDway Study Schema



TAFA = tafasitamab.

The study started in 2021. At the MINDway DSMC meeting held in JUL 2023 with a cutoff date of 30 MAY 2023, it was concluded that the safety profile was similar between Cohort 1 and Cohort 2, and the preliminary PK data supported dosing at 30 mg/kg. Following the recommendation of the MINDway DSMC based on the evaluation at this meeting, it was decided that the dose level used in Cohort 2 would also be used in the dose-expansion cohort. Enrollment in the dose-expansion cohort at a dose of 30 mg/kg is ongoing as of APR 2024.

2.1.5. Parsaclisib

Parsaclisib (INCB050465) is a potent, selective inhibitor of PI3Kδ (IC_{50} value = 1.1 ± 0.5 nM), with approximately 20,000-fold selectivity for the other PI3K family members. Parsaclisib does not significantly inhibit (< 30% inhibition) a broad panel of kinases when tested at a concentration of 100 nM (refer to the parsaclisib IB). Parsaclisib is potent (IC_{50} values of ≤ 10 nM) in cell-based assays relevant to the pathogenesis of B-cell malignancies, such as PI3Kδ-mediated signaling and growth of human B-cell lines.

A Phase 1/2 study, INCB 50465-101, examined parsaclisib monotherapy dose-escalation (5-45 mg QD) and dose expansion (20 and 30 mg QD). Parsaclisib monotherapy demonstrated the vast majority (93%) of responses occurred by the first assessment (~9 weeks) in participants with R/R DLBCL (n = 23), FL (n = 14), MZL (n = 9), or MCL (n = 9), with a data cutoff of 18 AUG 2017. For these participants with NHL who received parsaclisib monotherapy, OR was achieved by 7 of 23 participants with DLBCL (30%), 10 of 14 participants with FL (71%), 7 of 9 participants with MZL (78%), and 6 of 9 of participants with MCL (67%). Among the 72 participants treated with parsaclisib monotherapy, the most common (≥ 30%) nonhematologic TEAEs of any grade were diarrhea/colitis (36%), nausea (36%), fatigue (31%), and rash (31%). New or worsened Grade 3/4 neutropenia occurred in 19% of participants based on laboratory data (Forero-Torres et al 2019).

2.1.5.1. Rationale of Tafasitamab + Parsaclisib Combination

In vitro experiments on CLL cell line MEC-1 or primary CLL cells showed synergistic potential of tafasitamab in combination with idelalisib, a PI3Kδ inhibitor (Study MOR208L018).

PI3Kδ inhibition does not significantly affect the effector mechanisms induced by anti-CD20 mAbs, RTX or obinutuzumab, and provides an effective in vivo therapeutic combination

(Palazzo et al 2018). Combination treatment of idelalisib, another PI3Kδ inhibitor, and anti-CD20 mAbs have shown clinical benefit compared with anti-CD20 mAbs alone for participants with relapsed CLL in Phase 3 studies (Jones et al 2017, Sharman et al 2019). The combination treatment of idelalisib plus RTX and duvelisib monotherapy are approved for patients with relapsed CLL in the US and EU but not in Japan.

An open-label, multicenter, Phase 2 study was performed to evaluate the safety and preliminary clinical activity of tafasitamab combined with idelalisib or venetoclax in 2 independent cohorts of participants with R/R CLL who had been pretreated with a BTK inhibitor (Study MOR208C205; NCT02639910). Tafasitamab 12 mg/kg was administered as an IV infusion weekly in Cycles 1-3 (with an additional loading dose on Day 4 in Cycle 1), every other week in Cycles 4-6, and monthly from Cycle 7 onwards (each cycle lasting 28 days).

As of the data cutoff date of 08 OCT 2019, all 11 participants treated with tafasitamab and idelalisib were included in the safety analysis set and experienced TEAEs (244 events). Most TEAEs reported were of toxicity Grade 1 or 2 (181/244 events). The most common TEAEs were anemia (63.6%), dyspnea (54.5%), and cough (54.5%). The most common ≥ Grade 3 TEAEs were hematological and included neutropenia (45.5%), anemia (27.3%), and thrombocytopenia (27.3%). Eight participants (72.7%) had serious TEAEs (19 events). The hematological serious TEAEs were anemia (1 participant, Grade 3), thrombocytopenia (1 participant, Grade 3), and pancytopenia (1 participant, Grade 2). The most common nonhematological serious TEAE was pneumonia (2 participants, ≥ Grade 3). Four participants (36.4%) had serious TEAEs (cardiac failure, acute pancreatitis, pneumonia, and arthralgia) suspected to be related to tafasitamab, and 7 participants (63.6%) had serious TEAEs (cardiac failure, pneumonia, bronchitis, septic shock, upper respiratory tract infection, acute pancreatitis, increased C-reactive protein, pancytopenia) suspected to be related to idelalisib. Tafasitamab treatment was interrupted in 10 participants (90.9%) due to TEAEs, mainly due to IRRs (in 5 participants [45.5%]). The IRRs were Grade 2 in 4 of 5 participants and Grade 3 in 1 participant. No participant discontinued tafasitamab permanently due to IRRs. Idelalisib treatment was interrupted in 9 participants (81.8%) due to TEAEs, and 5 participants (45.5%) permanently discontinued idelalisib due to TEAEs.

A best response of CR or PR in participants treated with tafasitamab and idelalisib was reached in 10 out of 11 participants (90.9%). This included CR in 1 participant (9.1%) and PR in 9 participants (81.8%).

Study INCB 50465-112 is a Phase 1, open-label, dose-finding study to evaluate the safety and tolerability of parsaclisib combined with RTX and others in participants with previously treated B-cell lymphoma. As of the data cutoff date (30 MAR 2021), 16 participants in this study received the combination of parsaclisib 20 mg QD for 8 weeks followed by 20 mg QW + RTX. Treatment-emergent AEs were reported in all 16 participants: the most frequently occurring were neutropenia (10 participants, 62.5%); diarrhea (6 participants, 37.5%); anemia (5 participants, 31.3%); increased blood creatinine (4 participants, 25.0%); and back pain, dyspnea, hyperuricemia, hypomagnesemia, IRR, pyrexia, and decreased weight (3 participants [18.8%] each). Two participants (12.5%) had fatal TEAEs that included COVID-19, COVID-19 pneumonia, and interstitial lung disease in 1 participant (6.3%) each. Serious TEAEs occurred in 6 participants (37.5%) and included diarrhea, COVID-19, and pneumonia in 2 participants (12.5%) each and neutropenia, pyrexia, contusion, abdominal sepsis, COVID-19 pneumonia,

interstitial lung disease, pneumococcal infection, pneumonia streptococcal, and renal hemorrhage in 1 participant (6.3%) each. Treatment-emergent AEs leading to discontinuation of parsaclisib occurred in 2 participants (12.5%) and included diarrhea and pneumonia streptococcal (1 participant [6.3%] each).

In summary, tafasitamab combined with a PI3Kδ inhibitor and parsaclisib combined with an anti-CD20 mAb were well-tolerated, with a manageable safety profile in participants with B-cell malignancies.

Further examination of the safety, tolerability, PK, and efficacy of the combination of tafasitamab and parsaclisib for R/R DLBCL is required and provides the rationale for this study.

2.2. Study Rationale

2.2.1. Scientific Rationale for Study Design

This study is designed to assess the safety and tolerability and to determine the RP2D of single-agent tafasitamab and 3 different combination treatments of tafasitamab with other drugs (tafasitamab + LEN; tafasitamab + parsaclisib; tafasitamab + LEN + R-CHOP) in Japanese participants with NHL. After the confirmation of the RP2D for tafasitamab monotherapy with weight-based dosing, the fixed doses of tafasitamab monotherapy and the 3 different combination therapies was planned to be assessed in parallel. This study will examine the safety and tolerability of tafasitamab plus LEN and of tafasitamab plus parsaclisib in Japanese participants with R/R DLBCL as well as the safety and tolerability of tafasitamab plus LEN as an add-on strategy to R-CHOP in Japanese participants with newly diagnosed DLBCL. As of Protocol Amendment 4, a Phase 2 extension portion for the tafasitamab plus LEN combination therapy has been added (Part 4 Group 6). As of Protocol Amendment 7, weight-based dosing of tafasitamab Q2W/Q4W in combination with LEN has been introduced (Part 2 Group 2) in Japanese participants with R/R DLBCL.

Patients with R/R DLBCL who are not eligible for HDC/ASCT have a poor prognosis, and there is no standard therapy showing OS prolongation. The treatment goal in these patients is to achieve the best response without unacceptable toxicity and to maintain the response by spacing the interval of chemotherapies in a maintenance approach (Gisselbrecht and Van Den Neste 2018).

The prognosis of patients with primary refractory DLBCL in each clinical study from which the recommended regimens in the JSH Guidelines (Ohmachi 2019) were derived is poor. The achievement of response after salvage therapy is expected to delay disease progression due to tumor shrinkage and to improve clinical symptoms and quality of life. In addition, a retrospective, observational study (Study SCHOLAR-1) in participants with refractory DLBCL who progressed on or after therapy, including first-line treatment with R-CHOP and salvage therapy, or relapsed within 12 months of ASCT reported that participants who achieved CR and PR after the last salvage therapy had longer survival than those who did not, and response to therapy was significantly associated with longer survival, especially for participants who received subsequent ASCT (Crump et al 2017).

Furthermore, it has also been reported that some patients who respond to third-line therapy can subsequently undergo HDT/ASCT, which can improve OS (Van Den Neste et al 2016).

Therefore, there is a need for novel therapies that provide high ORR with acceptable safety.

Under such circumstances, the combination of LEN and tafasitamab was approved in the US in JUL 2020 and in the EU in AUG 2021 for the treatment of adult patients with R/R DLBCL who are not eligible for HDC/ASCT and is listed in the NCCN Guidelines (2021) as one of the preferred regimens for second-line and subsequent treatment for patients with DLBCL who are not eligible for transplantation. The sponsor plans to conduct the Phase 2 portion of this study with the RP2D, which was determined in Group 3, to evaluate efficacy, safety, and tolerability in Japanese participants.

As previously discussed, the MINDway study (see Section 2.1.4.5) is ongoing with the primary objective to determine the tolerability, safety, and recommended clinical dose of a new dose regimen (Q2W/Q4W) to reduce the frequency of hospital/clinic visits for tafasitamab-treated participants with R/R DLBCL. Reducing the overall frequency of clinic visits by half is expected to reduce the patient burden and support long-term treatment compliance. Since the optimized regimen is also considered to be beneficial to Japanese patients with R/R DLBCL, the sponsor decided to assess tafasitamab Q2W/Q4W in combination with LEN in Japanese participants with R/R DLBCL as Group 2.

2.2.2. Dose Justification for Tafasitamab Monotherapy

The tafasitamab dose regimen in this study is based on the results of completed or currently ongoing clinical studies as well as a 13-week IV repeated-dose toxicity study in cynomolgus monkeys.

As a result of the dose-escalating, first-in-human study, XmAb5574-01, 12 mg/kg (ie, the highest dose tested) with an initially weekly administration scheme was identified as safe and well-tolerated (Woyach et al 2014). In this study, the MTD was not reached, and the 12 mg/kg dose level was used in all subsequent clinical studies with an initially weekly regimen for three 28-day cycles. Tafasitamab administered at 12 mg/kg with initial weekly administrations as monotherapy or in various combination therapies was generally well-tolerated and showed a manageable safety profile. It should be further mentioned that in a detailed exposure-safety assessment for participants with R/R NHL based on results of clinical studies MOR208C201 (tafasitamab monotherapy) and L-MIND (tafasitamab in combination with LEN), no obvious trends for increasing TEAEs with increasing exposure were observed (ie, C_{max} and area under the curve).

These results further support the manageable safety profile of tafasitamab as monotherapy or in combination with LEN independent of the individual tafasitamab exposure observed.

In an exposure-response assessment for efficacy, it was shown that for tafasitamab monotherapy in participants with R/R NHL (N = 92; MOR208C201), increased exposure correlated with an increased response rate and increased PFS. In contrast, in combination with LEN in participants with R/R DLBCL (N = 81; L-MIND), there was a flat-exposure response relationship for efficacy, indicating that participants were sufficiently exposed to tafasitamab. Based on these exposure-efficacy considerations, the proposed tafasitamab regimen at 12 mg/kg with initial weekly administrations is expected to be efficacious in combination with LEN, parsaclisib, or LEN + R-CHOP, as it is expected to provide similar exposures as observed previously.

Taken together, the proposed regimen at 12 mg/kg with initial weekly administrations was established in various clinical studies with tafasitamab as a safe and efficacious regimen. Consequently, in Part 1 Group 1 of this study, the starting dose of tafasitamab to be tested will be

12 mg/kg with initial weekly administrations, and a lower dose of 9 mg/kg with initial weekly administrations may be tested based on DLTs. This is expected to provide a range of tafasitamab exposures to allow comparison of tafasitamab PK in Japanese and non-Japanese participants with R/R NHL.

2.2.3. Dose Justification for Combination of Tafasitamab and LEN (Groups 3 and 6)

The expected doses to be evaluated for tafasitamab and LEN in combination are based on the global RP2D from prior studies. The selection of the combination dose to be evaluated in Part 2 Group 3 will reflect single-agent experience with tafasitamab in Part 1 as well as emerging clinical experience with these or related agents in other studies. The approved dose of LEN for Japanese patients with multiple myeloma will be initially evaluated for the combination but may be de-escalated based on DLTs.

The data from Part 2 Group 3 showed the safety and tolerability of LEN 25 mg in participants with normal renal function (serum creatinine clearance ≥ 60 mL/min), which is also the approved dose of LEN for Japanese patients with multiple myeloma, in combination with tafasitamab. Therefore, the RP2D for this combination was determined to be the same dose as used in the L-MIND study, and this dose will be used in Part 3 Group 6 for participants with normal renal function. Considering that the current data show the combination of tafasitamab 12 mg/kg plus LEN 25 mg is well tolerated in participants in Group 6 so far, and many potential participants could not be enrolled due to moderate renal insufficiency (creatinine clearance ≥ 30 to < 60 mL/min), as of Amendment 7, this population is allowed to enroll by reducing the starting dosage of LEN to 10 mg/kg QD according to the recommended dosage for patients with multiple myeloma and R/R FL who have renal impairment per the LEN PI. As this starting dosage of LEN was obtained by simulation of PK data and has been used in medical practice for the treatment of Japanese patients with R/R FL, the sponsor considered it applicable to patients with R/R DLBCL. Dose adjustment of tafasitamab is not needed for participants with moderate renal insufficiency based on available data in monotherapy studies.

2.2.4. Dose Justification for Weight-Based Dosing of Tafasitamab Q2W/Q4W in Combination With LEN (Group 2)

As described in Section 2.2.1, the design of Group 2 was changed to evaluate weight-based dosing of tafasitamab Q2W/Q4W in combination with LEN as Part 2 Group 2 in participants with R/R DLBCL. In addition, tafasitamab 30 mg/kg from Cycle 1 Day 15 was selected for the dose-expansion cohort in the MINDway study (see Section 2.1.4.5).

Evaluation of Group 3 in the current study confirmed that the RP2D of tafasitamab in combination with LEN in Japanese participants with R/R DLBCL is the same as the approved regimen in other regions, including the US, EU, United Kingdom, and Switzerland. In addition, the combination of tafasitamab and LEN has been shown to result in no major differences in tafasitamab exposure and comparable safety profiles between Japanese and non-Japanese participants, despite lower body weight in Japanese participants compared with non-Japanese participants, and no AESIs have been observed for either tafasitamab or LEN.

Among the 6 participants enrolled in Group 3, 1 participant experienced a Grade 1 IRR according to CTCAE v5.0, but no participant experienced TLS. Since the dose to be administered in the dose-expansion cohort of the MINDway study was considered acceptable for

further testing in participants in other countries, Group 2 will be evaluated using the same regimen in Japanese participants with R/R DLBCL.

2.2.5. Dose Justification for Combination of Tafasitamab and Parsaclisib (Group 4a)

The selection of the combination dose to be evaluated in Part 2 Group 4a will reflect single-agent experience with tafasitamab in Part 1 of this study, as well as emerging clinical experience with these or related agents in other studies. The recommended dose of 20 mg QD Day 1 through 56 and 2.5 mg QD thereafter from parsaclisib NHL studies will be initially evaluated for the combination but may be de-escalated based on DLTs.

2.3. Benefit/Risk Assessment

In B-cell malignancies, CD19 with its B-cell–specific expression is a proven target (Chavez et al 2019). Tafasitamab monotherapy demonstrated promising clinical activity in participants with R/R DLBCL, R/R CLL, and R/R FL, including in participants with RTX-refractory tumors. Tafasitamab as a single agent was well-tolerated in R/R B-cell lymphomas (Jurczak et al 2018). The risk assessment of tafasitamab is based on the data from completed and ongoing clinical studies. The most common study drug–related TEAEs are IRR, hematologic events such as neutropenia, febrile neutropenia, thrombocytopenia, and anemia, as well as infections including bronchitis and pneumonia. Most TEAEs have been Grades 1 and 2. Premedication is mandatory for the first 3 infusions (in Groups 1, 3, 4a, 5, and 6) or first 4 infusions (Group 2), and the guidance of infusion speed to decrease the risk of a possible IRR will be provided.

The combination of tafasitamab plus LEN is active in non-Japanese participants with R/R DLBCL, as shown in the L-MIND study. The safety profile in the L-MIND study is characterized by hematological toxicity, with the most common AE reported being neutropenia. With a median duration of 7 days, neutropenia was clinically manageable and responsive to G-CSF. Nonhematological toxicities were also of lower grade and characterized by gastrointestinal toxicities such as diarrhea, decreased appetite, constipation, nausea, or vomiting, and skin toxicity such as rash.

Based on the safety profile of tafasitamab single-agent and of the tafasitamab plus LEN combination (as demonstrated in the L-MIND study in R/R DLBCL), it is anticipated that the overall risk-benefit of tafasitamab plus LEN in combination with R-CHOP is favorable without additional major toxicities compared with treatment with R-CHOP only. Additionally, the result of MOR208C107 (First-MIND) in which untreated participants with DLBCL are treated with R-CHOP plus tafasitamab with or without LEN supported further risk-benefit assessment as discussed in Section 2.1.4.3.

In Protocol Amendment 7, the sponsor changed the dose regimen and the participant population of Group 2. With the tafasitamab dose regimen introduced in Section 2.2.4 (tafasitamab 12/30 mg/kg in combination with LEN), higher tafasitamab C_{max} levels than previously observed are expected. Based on the current nonclinical and clinical safety data, no correlation between the occurrence of AEs and exposure (including C_{max}) was observed. Nevertheless, the expected range of C_{max} values of the study dose regimens is higher than and not covered by previous clinical data. To reduce the risk of potential AEs occurring shortly after treatment initiation, such as IRRs and TLS, all participants in Group 2 will maintain a dose of 12 mg/kg at the initial 3 tafasitamab infusions prior to a dose increase to 30 mg/kg, which is the same as the regimen in

the MINDway study (see Section 2.1.4.5). The modified dose regimen will result in reduced patient burden and support long-term treatment compliance.

Both tafasitamab and parsaclisib show single-agent antilymphoma activity in vivo and in vitro. As defined by the eligibility criteria, the patient population for Group 4a in Part 2 of this study will be participants with R/R DLBCL who still have high unmet medical need. Potential risks with administration of tafasitamab plus parsaclisib are not just based on preclinical findings but also based on clinical evidence that includes lymphoid depletion (refer to the parsaclisib IB). This may result in infections including PJP, CMV, and COVID-19, fever, or cytokine release resulting in fever, chills, hypotension, wheezing, and/or rash. To reduce the risk of infection with PJP, all participants taking parsaclisib must also take a prophylactic antibiotic (see Section 6.8.4). PI3K inhibitors are associated with diarrhea/colitis, pneumonitis, severe cutaneous reactions, and neutropenia. Similar events were observed on the INCB 50465-101, INCB 50465-202, INCB 50465-203, INCB 50465-204, INCB 50465-205, and INCB 50465-111 studies.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of tafasitamab and parsaclisib may be found in the IBs (parsaclisib IB, tafasitamab IB).

3. OBJECTIVES AND ENDPOINTS

Table 11 presents the objectives and endpoints.

Table 11: Objectives and Endpoints

Objectives	Endpoints
Primary	
Part 1: To assess the safety and tolerability and to determine the RP2D of single-agent tafasitamab (Group 1) in Japanese participants with R/R NHL.	Incidence and severity of TEAEs and incidence of DLTs with single-agent tafasitamab.
Parts 2 and 3: To assess the safety, tolerability, and to determine the recommended clinical dose (Group 2)/RP2D (Groups 3, 4a, and 5) of the following: • Tafasitamab Q2W/Q4W dosing in combination with LEN (Group 2) in Japanese participants with R/R DLBCL. • Tafasitamab in combination with LEN (Group 3) in Japanese participants with R/R DLBCL. • Tafasitamab in combination with parsaclisib (Group 4a) in Japanese participants with R/R DLBCL. • Tafasitamab in combination with LEN plus R-CHOP (Group 5) in Japanese participants with previously untreated DLBCL.	• Incidence and severity of TEAEs with tafasitamab Q2W/Q4W in combination with LEN (Group 2). • Incidence and severity of TEAEs and incidence of DLTs with tafasitamab in combination with LEN, parsaclisib, or LEN plus R-CHOP (Groups 3, 4a, and 5).
Part 4: To evaluate the efficacy of tafasitamab in combination with LEN (Group 6) in Japanese participants with R/R DLBCL.	OR, defined as the best response of CR/CMR or PR/PMR as determined by an IRC according to the Lugano criteria (Cheson et al 2014), will be analyzed on the FAS using ORR as a population-level summary, in which ORR is defined as the percentage of participants experiencing OR.

Table 11: Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary	
Parts 1, 2, 3, and 4: To determine the PK of the following: • Single-agent tafasitamab (Group 1) in Japanese participants with R/R NHL. • Tafasitamab Q2W/Q4W in combination with LEN (Group 2) in Japanese participants with R/R DLBCL. • Tafasitamab in combination with LEN (Groups 3 and 6) or parsaclisib (Group 4a) in Japanese participants with R/R DLBCL. • Tafasitamab in combination with LEN plus R-CHOP in Japanese participants with previously untreated DLBCL (Group 5).	PK analysis of single-agent tafasitamab and tafasitamab as part of combination treatments. Descriptive statistics of trough (ie, predose) and C_{max} levels at different timepoints.
Part 2 (Group 2 only): To evaluate the efficacy of tafasitamab Q2W/Q4W in combination with LEN in Japanese participants with R/R DLBCL.	Tumor response as follows: • Response assessment as per investigator assessment of response according to the Lugano criteria (Cheson et al 2014). • Percent reduction in SPD in up to 6 target measurable nodes and extranodal sites assessed by CT as per investigator assessment of response according to the Lugano criteria (Cheson et al 2014).
Part 4: To further evaluate the efficacy of tafasitamab in combination with LEN (Group 6) in Japanese participants with R/R DLBCL based on additional efficacy outcomes.	• CR, defined as CR/CMR as determined by an IRC according to the Lugano criteria (Cheson et al 2014), will be analyzed on the FAS using CRR as a population-level summary, in which CRR is defined as the percentage of participants experiencing CR. • DOR, defined as the time from the first documented CR/CMR or PR/PMR as determined by an IRC according to the Lugano criteria (Cheson et al 2014) until the date of first documented disease progression or death due to any cause, whichever occurs first. DOR will be analyzed on the FAS using Kaplan-Meier–estimated median survival time as a population-level summary.

Table 11: Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary (continued)	
Part 4: To further evaluate the efficacy of tafasitamab in combination with LEN (Group 6) in Japanese participants with R/R DLBCL based on additional efficacy outcomes (continued).	• PFS, defined as the time from the date of first dose of study treatment until the first documented disease progression as determined by an IRC according to the Lugano criteria (Cheson et al 2014) or death due to any cause, whichever occurs first. PFS will be analyzed on the FAS using Kaplan-Meier–estimated median survival time as a population-level summary. • OS, defined as the time from the first dose of study treatment until death due to any cause. OS will be analyzed on the FAS using Kaplan-Meier–estimated median survival time as a population-level summary. • OR, CR/CMR, DOR, and PFS as per investigator assessment of response according to the Lugano criteria (Cheson et al 2014). OR and CR/CMR will be summarized by the ORR and CRR, defined as the percentage of participants experiencing OR and CR/CMR respectively.
Part 4: To assess the safety and tolerability of tafasitamab in combination with LEN in Japanese participants with R/R DLBCL.	Incidence and severity of TEAEs following treatment with tafasitamab in combination with LEN.
[redacted]	

Table 11: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

Table 11: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

Key elements of the study design are presented in Table 2. A high-level overview of the cohorts and study design schema are shown in Figure 1, and Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9 present the SoAs. Further details of each part are presented in Sections 4.1.1, 4.1.2, 4.1.3, 4.1.4, and 4.1.5.

INCMOR 0208-102 is a Phase 1b/2, open-label, multicenter, clinical study designed to assess the safety and tolerability, determine the RP2Ds, assess the efficacy, and assess the PK of tafasitamab in Japanese participants with NHL. This study will consist of 4 parts and 7 groups as follows:

- Part 1 consists of tafasitamab monotherapy dose-finding to evaluate the safety and tolerability and to determine the RP2Ds of single-agent tafasitamab in Japanese participants with R/R NHL. Part 1 consists of 1 group (Group 1) to evaluate weight-based doses of tafasitamab.
- Part 2 consists of tafasitamab combination therapy dose-finding to evaluate the safety and tolerability and to determine the RP2Ds of tafasitamab when combined with LEN (Group 3) or parsaclisib (Group 4a) in participants with R/R DLBCL or LEN plus R-CHOP (Group 5) in participants with previously untreated DLBCL and to determine the recommended clinical dose of tafasitamab Q2W/Q4W when combined with LEN (Group 2) in participants with R/R DLBCL. The dose of tafasitamab will be based on the weight-based RP2D that is deemed safe and tolerable in Part 1 for Groups 3, 4a, and 5 and will be based on the weight-based RP2D that is deemed safe and tolerable in Part 1 and Part 2 Group 3 for Group 2.
- Part 3 was planned to consist of 1 dose-expansion group (Group 4b) to further evaluate the safety, tolerability, and preliminary antitumor activity of the RP2D deemed safe and tolerable in Part 2 for the combination of tafasitamab and parsaclisib. Based on the sponsor's decision, participants for Part 3 Group 4b will not be recruited.
- Part 4 consists of 1 group (Group 6) for the Phase 2 portion of the study. Part 4 will evaluate the antitumor activity as the primary objective. The safety and tolerability of the RP2D of the combination of tafasitamab and LEN that was deemed safe and tolerable in Part 2 will also be evaluated as the secondary objectives.

There are 2 different treatment cycles in this study: the cycle length is 28 days for Groups 1, 2, 3, 4a, and 6 and is 21 days for Group 5. Enrollment of Part 1 was planned to occur in a sequential manner in the order of Group 1 and Group 2, but the enrollment of Group 2 was not started due to a strategic change and will be restarted as of Protocol Amendment 7 with a revised dose regimen. The enrollment of the 3 groups (Groups 3, 4a, and 5) in Part 2 was planned to occur in parallel. The enrollment of Part 2 Group 2 will occur after the completion of enrollment in Group 6. The enrollment of Part 4 will occur after the RP2D is determined in Part 2 Group 3.

In Phase 1b, it was originally determined that the treatment would be given for up to 2 years in principle as long as participants were receiving benefit and had not met any of the

discontinuation criteria (see Section 7.1.1). As of Protocol Amendment 5, the limited length of the treatment period has been removed for participants demonstrating a long-term benefit. At the discretion of the investigator, those participants will continue on tafasitamab and/or parsaclisib until meeting any of the discontinuation criteria (see Section 7.1.1), and the continued access period (see Section 4.1.4) was added for Groups 1, 3, and 4a. If the study drug is continued beyond 2 years, informed consent must be obtained again from the participant when the decision has been made by the investigator. In Phase 1b Group 2, treatment with tafasitamab may continue as long as participants are receiving benefit and have not met any discontinuation criteria; treatment with LEN can be given for up to a total of 12 cycles.

In Phase 2 Group 6, treatment with tafasitamab may continue as long as participants are receiving benefit and have not met any discontinuation criteria; treatment with LEN can be given for up to a total of 12 cycles.

The final data cutoff date will be established when the last participant in Group 2 completes Cycle 12. Participants who are still on treatment at that time can remain on treatment following the schedule of their assigned treatment group until tafasitamab obtains marketing authorization in Japan for the indication of DLBCL.

4.1.1. Part 1 – Tafasitamab Monotherapy Dose-Finding

Part 1 consists of 1 group (Group 1) of participants with R/R NHL treated with tafasitamab weight-based monotherapy. Approximately 6 to 12 evaluable participants will be enrolled.

Enrollment of Part 1 was planned to occur in a sequential manner in the order of Group 1 and Group 2, but enrollment of Group 2 was not started due to a strategic change and will be restarted as of Protocol Amendment 7 with a revised dose regimen. Dose-finding for Group 1 will proceed independently, with each group following a BOIN procedure (Liu and Yuan 2015). A cohort size of 3 evaluable participants will be used for each group. The estimated MTD for tafasitamab monotherapy in each group will be the dose at which the observed DLT rate is closest to the target DLT rate of 30%. DLTs occurring during the first cycle (28 days) of treatment will guide dose escalation/de-escalation and determination of the MTD and RP2D. In addition, participants with late-onset AEs meeting the definition of DLT or those who had intolerable, lower grade persistent toxicity determined to be attributable to study treatment will be considered in the selection of RP2D. The RP2D will be determined by the SMC as the safe and tolerable dose based on safety including number of DLT occurrence. The available data for PK and ADAs will also be reviewed by the sponsor.

In Part 1 Group 1, participants will be sequentially enrolled in cohorts of 3 participants. Each cohort will consist of 3 evaluable participants and each participant in this cohort will be observed for a DLT evaluation period of 1 cycle (28 days). After the DLT assessment is completed for a cohort and the dose escalation/de-escalation decision is made based on the observed toxicity data, the enrollment of the next cohort of 3 evaluable participants will begin. Table 29 will be used to guide dose escalation/de-escalation decisions. Participants in Group 1 must have received at least 4 doses of tafasitamab in the first cycle (28 days) of study treatment or have had a DLT to be considered evaluable. Participants who are NE will be replaced.

The starting dose of tafasitamab for Group 1 will be 12 mg/kg IV on Days 1, 8, 15, and 22 of Cycles 1 through 3 and Days 1 and 15 from Cycle 4 onwards of each 28-day cycle.

Additionally, a loading dose will be administered on Day 4 of Cycle 1. Planned weight-based dose levels to be evaluated for tafasitamab monotherapy are given in Table 12. If the starting dose of tafasitamab needs to be reduced by 1 dose level, the lower dose levels will be 9 mg/kg QW. The dose-finding procedure will stop for Group 1 if ≥ 6 evaluable participants are treated at a dose level and the observed DLT data indicate that the dose should be retained or the maximum of 12 evaluable participants are reached. Following completion of Group 1, the SMC will review available safety data to determine whether to initiate Part 2 of the study.

Table 12: Dose Levels to Be Evaluated in Dose-Finding (Part 1)

Tafasitamab Weight-Based Dose (Group 1)	
Dose Level	**Dose**
Dose Level −1	9 mg/kg QW[a]
Dose Level 1 (starting dose)	12 mg/kg QW[a]

[a] QW for Cycles 1 through 3 (plus a loading dose at C1D4); Q2W thereafter.

4.1.2. Part 2 – Tafasitamab Combination Therapy Dose-Finding/Assessing Recommended Clinical Dose

The enrollment of Part 2 except for Group 2 will be initiated after the determination of weight-based RP2D for tafasitamab monotherapy in Group 1 of Part 1. Part 2 consists of 3 groups and approximately 6 to 18 evaluable participants will be enrolled in each group:

- Group 3, tafasitamab in combination with LEN in participants with R/R DLBCL.
- Group 4a, tafasitamab in combination with parsaclisib in participants with R/R DLBCL.
- Group 5, tafasitamab plus LEN in combination with R-CHOP in participants with untreated DLBCL.

The enrollment of 3 groups in Part 2 will occur in parallel. A BOIN design (Liu and Yuan 2015) will be used to determine the MTD in each group in an independent and parallel fashion. A cohort size of 3 evaluable participants will be used for each group. The estimated MTD for tafasitamab combination treatment in each group will be the dose at which the observed DLT rate is closest to the target DLT rate of 30%. DLTs occurring during the first cycle (28 days for Groups 3 and 4a and 21 days for Group 5) of treatment will guide dose escalation/de-escalation and determination of the MTD and RP2D. In addition, participants with late-onset AEs meeting the definition of DLT or those who had intolerable, lower-grade persistent toxicity determined to be attributable to any study treatment will be considered in the selection of each combination RP2D.

The tafasitamab dose in the combination treatment groups is the selected weight-based RP2D in Group 1, and the dose of tafasitamab will not be changed in Part 2. Furthermore, doses and schedules of RTX, cyclophosphamide, doxorubicin, vincristine, and PSL (R-CHOP) will not be changed. Dose escalation/de-escalation is with regard to the daily dose of LEN (Groups 3 and 5) or parsaclisib (Group 4a). The administration of parsaclisib after Day 56 of the treatment will be 2.5 mg QD, regardless of the determined tolerable daily dose of parsaclisib.

In each group of Part 2, participants will be sequentially enrolled in cohorts of size 3. Each cohort will consist of 3 evaluable participants, and each participant in this cohort will be observed for a DLT evaluation period of 1 cycle (28 days for Groups 3 and 4a and 21 days for Group 5). After the DLT assessment is completed for a cohort and the dose escalation/de-escalation decision is made based on the observed toxicity data, the enrollment of the next cohort of 3 evaluable participants will begin. Table 29 will be used to guide dose escalation/de-escalation decisions. Any participant experiencing a DLT during Cycle 1 of combination treatment will count toward the determination of the MTD, regardless of their treatment intensity. In the case of dose interruptions or reduction (but not meeting DLT criteria) during Cycle 1, participants who met the following criteria will be considered nonevaluable for determining tolerability of the dose and will be replaced: participants who did not receive at least 17 of 21 doses of LEN or did not receive at least 4 doses of tafasitamab in the first 28 days in Group 3; participants who did not receive at least 23 of 28 doses of parsaclisib or did not receive at least 4 doses of tafasitamab in the first 28 days in Group 4a; and participants who did not receive at least 8 of 10 doses of LEN, did not receive 3 doses of tafasitamab, or did not receive any 1 or more of the component of R-CHOP in the first 21 days in Group 5.

The starting dose of LEN will be 25 mg QD on Days 1 through 21 of each 28 day-cycle in Group 3 and on Days 1 through 10 of each 21-day cycle in Group 5. The starting dose of LEN in Group 5 may be adjusted based on the result of First-MIND study. The starting dose of parsaclisib in Group 4a will be 20 mg QD on Days 1 through 56 followed by a 2.5 mg QD. Planned dose levels to be evaluated for LEN and parsaclisib are given in Table 13. If LEN needs to be reduced by 1 dose level, the lower dose levels will be as follows, depending on what the current dose level is: 25 mg QD → 20 mg QD or 20 mg QD → 15 mg QD. In case a lower starting dose of LEN is selected for Group 5 based on the result of First-MIND study, Dose Level −1 and Dose Level −2 will be 5 mg and 10 mg lower than the starting dose, respectively. If parsaclisib needs to be reduced by 1 dose level, the lower dose levels will be as follows, depending on what the current dose level is: 20 mg QD → 10 mg QD or 10 mg QD → 5 mg QD. The dose-finding procedure will stop for each group if ≥ 6 evaluable participants are treated at a dose level and the observed DLT data indicate that the dose should be retained or the maximum of 18 evaluable participants are reached.

Table 13: Dose Levels to Be Evaluated in Dose-Finding (Part 2 Except for Group 2)

Lenalidomide (Groups 3 and 5)		Parsaclisib (Group 4a)	
Dose Level	**Dose**	**Dose Level**	**Dose**
Dose Level 1 (starting dose)	25 mg QD[a,b]	Dose Level 1 (starting dose)	20 mg QD[c]
Dose Level −1	20 mg QD[b]	Dose Level −1	10 mg QD[c]
Dose Level −2	15 mg QD[b]	Dose Level −2	5 mg QD[c]

[a] The starting dose of Group 5 may be adjusted based on the result of First-MIND study. In case a lower starting dose is selected, Dose Level −1 and Dose Level −2 will be 5 mg and 10 mg lower than the starting dose, respectively.
[b] Group 3: QD on Days 1 to 21 of each 28-day cycle; Group 5: QD on Days 1 through 10 of each 21-day cycle.
[c] QD on Days 1 through 56 followed by a 2.5 mg QD.

Six evaluable participants with R/R DLBCL will be enrolled in Group 2 and treated with weight-based dosing of tafasitamab Q2W/Q4W in combination with LEN.

The recommended clinical dose will be assessed with 6 evaluable participants (see Section 6.6). Enrollment in Group 2 will be initiated after the completion of the enrollment in Group 6. The

planned dose level to be evaluated for LEN is 25 mg QD, which was established as the RP2D in Group 3.

4.1.2.1. Stopping Rules for Group 5

If the situations listed below occur, the sponsor will pause the enrollment for Group 5. The SMC (see Section 6.5.3) will convene ad hoc meetings and make recommendations on whether to stop the further enrollment and stop the treatment of ongoing participants. The sponsor will make the final decisions, taking account of these recommendations.

The situations are as follows:

If any of the events listed below occurs in ≥ 3 of the participants who have received at least 1 dose of study treatment.

- A Grade 4 or higher non-hematologic AE
- A Grade 3 or higher thrombosis/embolism suspected to be related to treatment with LEN
- A dose reduction or delay of over 7 days of R-CHOP

Note: Toxicity-related dose modifications of R-CHOP that are not thought to be related to LEN and/or tafasitamab treatment will not be considered.

4.1.3. Part 3 – Dose Expansion With the Combination of Tafasitamab and Parsaclisib

The enrollment of Part 3 was to be initiated after the confirmation of RP2D for tafasitamab in combination with parsaclisib in Group 4a of Part 2.

- Group 4b, tafasitamab in combination with parsaclisib in participants with R/R DLBCL: up to approximately 12 participants were planned to be enrolled (approximately 18 participants including Part 2 Group 4a at RP2D).

The purpose of Group 4b was to further evaluate the safety, tolerability, and preliminary antitumor activity of the selected RP2D deemed safe and tolerable for the combination of tafasitamab and parsaclisib. An interim futility analysis was planned when the first 9 participants (Part 2 Group 4a at RP2D and Part 3 Group 4b combined) had been evaluated for response or permanently discontinued the study. Part 3 Group 4b was to be terminated for futility if ≤ 3 of the 9 participants have responded (ie, CR/CMR or PR/PMR) based on assessments provided by investigators.

As of Protocol Amendment 5, the sponsor decided not to open enrollment of Group 4b of Part 3. As a result, the planned interim analysis for Groups 4a and 4b will not be run, and the efficacy and safety analyses have been updated accordingly (see Section 10.4.1 and Section 10.4.2).

4.1.4. Continued Access Period for Parts 1 and 2 (Groups 1, 3, and 4a only)

Participants whose treatment period exceeds 2 years may move to the continued access period if they still benefit from treatment. Participants should follow the SoA specific to the continued access period (see Table 8). In this SoA, the frequency of tumor response assessments is performed as per site standard of care, but the result of assessments should be entered into the eCRF.

4.1.5. Part 4 – Phase 2 Portion With the Combination of Tafasitamab and LEN

Part 4 Group 6 will be added after the determination of the RP2D for tafasitamab in combination with LEN in Part 2 Group 3. The purpose of Group 6 is to further evaluate the antitumor activity and safety and tolerability of the selected RP2D. Group 6 will enroll 41 participants with R/R DLBCL who are eligible for efficacy assessments.

As of Protocol Amendment 7, enrollment of participants with moderate renal insufficiency (serum creatinine clearance ≥ 30 to < 60 mL/min) is allowed for the purpose of obtaining efficacy and safety information in this population.

4.1.6. Continuation of Study Treatment Beyond the Final Data Cutoff Date

Participants who are on study treatment at the time of the final data cutoff can remain on treatment according to their assigned treatment schedule and until tafasitamab obtains marketing authorization in Japan for the indication of R/R DLBCL. Participants should follow the SoA specific to this period (see Table 9). In this SoA, the frequency of tumor response assessments is performed as per site standard of care, and the result of assessments should be entered into the eCRF as the closest visit.

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. Participants will be followed until EOS after the study treatment completion or premature discontinuation of treatment (EOT) for any reason. The study will end when the last participant (regardless of treatment group) receiving study treatment has completed the EOS visit after tafasitamab is approved for the indication of DLBCL in Japan.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator/head of study site (Japan) is to notify the IRB/IEC in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively, if, for example, upon agreement in the SMC (see Section 6.5.3). If the study is terminated prematurely, the sponsor will notify the investigators/head of the study site, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study. The head of study site will notify the investigators and the IRBs of the decision and reason for termination of the study.

5. STUDY POPULATION

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in the Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male or female Japanese participant who must be ≥ 18 years of age at the time of signing the ICF.
2. Ability to comprehend and willingness to sign a written ICF and comply with all study visits and procedures.
3. **Groups 3, 4a, and 5 only:** Biopsy-proven participants with DLBCL including one of the following diagnoses by 2016 WHO classification of lymphoid neoplasms: DLBCL, NOS including GCB type, ABC type.

   Groups 2 and 6 only: Biopsy-proven participants with DLBCL including one of the following diagnoses by 2016 WHO classification of lymphoid neoplasms:

   a. DLBCL, NOS including GCB type, ABC type.
   b. T-cell/histiocyte–rich large B-cell lymphoma, Epstein-Barr virus–positive DLBCL of the elderly.
   c. Grade 3b FL, composite lymphoma with a DLBCL component with a subsequent DLBCL relapse.
   d. Evidence of histological transformation from an earlier diagnosis of low-grade lymphoma (ie, an indolent pathology such as FL, MZL, and CLL) into DLBCL, with a subsequent DLBCL relapse.

   Note: Participants with HGBL with MYC and BCL2 and/or BCL6 rearrangements (double-hit or triple-hit lymphoma) are eligible for Group 5 only.
4. **Group 1 only:** Biopsy-proven participants with NHL including one of the subtypes described in criterion 3 or one of the following diagnoses by 2016 WHO classification of lymphoid neoplasms: FL Grade 1, 2, or 3a, and MZL (nodal, extranodal, or splenic MZL).
5. Participants must have at least 1 bidimensionally measurable lesion.

   Groups 2, 3, 4a, 5, and 6 only: Participants must have at least 1 lesion that has a greatest transverse diameter of ≥ 1.5 cm and greatest perpendicular diameter of ≥ 1.0 cm at screening and the lesion must be confirmed to be PET-positive at the latest at the time of treatment (for definition, refer to Juweid et al 2007).
6. ECOG performance status of 0 to 2.

7. Participants must have the following laboratory criteria at screening:
   a. ANC $\geq 1.5 \times 10^9$/L (in case hematologic abnormalities secondary to bone marrow involvement by DLBCL are demonstrated by recent bone marrow aspiration and bone marrow biopsy, participants with ANC $\geq 1.0 \times 10^9$/L are eligible).
   b. Platelet count $\geq 75 \times 10^9$/L (in case hematologic abnormalities secondary to bone marrow involvement by DLBCL are demonstrated by recent bone marrow aspiration and bone marrow biopsy, participants with platelet count $\geq 50 \times 10^9$/L are eligible in Groups 1 and 2).
   c. Total serum bilirubin $< 1.5 \times$ ULN unless secondary to Gilbert syndrome or documented liver involvement by lymphoma. Participants with Gilbert syndrome or documented liver involvement by lymphoma may be included if their total bilirubin is $\leq 5 \times$ ULN.
   d. ALT, AST, and alkaline phosphatase $\leq 3 \times$ ULN, or $< 5 \times$ ULN in cases of documented liver involvement.
   e. **Group 1 only:** Serum creatinine $< 2.0 \times$ ULN.
      Groups 3, 4a, and 5 only: Serum creatinine clearance must be ≥ 60 mL/min (≥ 40 mL/min for Group 4a only) either measured or calculated using a standard Cockcroft and Gault formula (Cockcroft and Gault 1976; see Appendix D).
      Group 2 only: Serum creatinine clearance must be ≥ 60 mL/min either measured or calculated using a standard Cockcroft and Gault formula (Cockcroft and Gault 1976; see Appendix D).
      Group 6 only: Serum creatinine clearance must be ≥ 30 mL/min either measured or calculated using a standard Cockcroft and Gault formula (Cockcroft and Gault 1976; see Appendix D).

8. **Group 1 only:** Participants must have the following:
   a. Relapsed or refractory NHL.
   b. Received at least 1 previous systemic therapy line for the treatment of NHL. At least 1 previous therapy line must have included a CD20-targeted therapy (eg, RTX). Additionally, there is no further effective standard anticancer therapy available (including participant refusal or intolerance of available standard therapy).
   c. Participants with DLBCL after failure of ASCT or participants considered in the opinion of the investigator currently not eligible for HDC with subsequent ASCT. Documentation of the reason for ineligibility for ASCT must be present in the participant's source data.

9. **Groups 2, 3, 4a, and 6 only:** Participants must have the following:
   a. Relapsed or refractory DLBCL.
   b. Received at least 1, but no more than 3, previous systemic therapy lines for the treatment of DLBCL. At least 1 previous therapy line for DLBCL must have included a CD20-targeted therapy (eg, RTX).

   Failed ASCT or in the opinion of the investigator currently have not been eligible for HDC with subsequent ASCT for participants with DLBCL. Documentation of the reason for ineligibility for ASCT must be present in the participant's source data.

10. **Group 5 only:** Participants must have the following:
    a. Untreated DLBCL.
    For participants with DLBCL transformed from indolent NHL, prior antilymphoma therapies are acceptable if these therapies 1) were given to treat the indolent lymphoma and 2) did not include chemotherapeutic agents or IMiDs.
    Note: Prior rituximab monotherapy or radiotherapy would be allowed in such cases.
    b. Ann Arbor Stage III to IV.
    c. IPI status of 3 to 5 or age-adjusted IPI 2-3 (in Group 5 only).
    d. Appropriate candidate for R-CHOP.
    Note: If an investigator deems a participant with a known HGBL (double- or triple-hit lymphoma) should be treated more aggressively with a chemotherapeutic regimen (eg, DA-EPOCH-R or Hyper CVAD), then this participant would be considered to be not eligible for this study.
    e. LVEF of ≥ 50%, assessed by echocardiography.
11. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Male participants with childbearing potential must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days after the last dose of study treatment and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Female participants with childbearing potential must have a negative serum pregnancy test at screening and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 90 days after the last dose of study treatment. They must also agree to regular urine pregnancy testing through the study treatment period. They must also refrain from breastfeeding and donating oocytes during the course of study and for 90 days after the last dose of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    c. Female participants without childbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 50 years of age) are eligible.
    Note: Female participants who have been amenorrheic for at least 12 months resulting from chemo/radiotherapy are considered of childbearing potential and should agree to use adequate contraceptive measures (see Appendix A).
    d. **Groups 2, 3, 5, and 6 only:** All participants must follow the Global PPP (see Appendix B).
    Note: Definition of FCBP and other requirements are in Appendix B.
12. In the opinion of investigator, the participant must:
    a. Not have a history of noncompliance in relation to medical regimens or be considered potentially unreliable and/or uncooperative.
    b. Be able to understand the reason for complying with the special conditions of the pregnancy prevention risk management plan and give written acknowledgement of this.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Any other histological type of lymphoma according to WHO 2016 classification of lymphoid neoplasms, for example, PMBL, Burkitt's lymphoma, B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma (grey-zone lymphoma); primary effusion lymphoma; primary cutaneous DLBCL, leg type; intravascular B cell lymphoma.
2. History of prior nonhematologic malignancy except for the following:
    a. Malignancy treated with curative intent and with no evidence of active disease present for more than 2 years before screening.
    b. Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer.
    c. Adequately treated carcinoma in situ without current evidence of disease.
3. Congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.
4. Participants with any of the following:
    a. Known positive test result for hepatitis C (HCV antibody serology testing) and a positive test for HCV RNA. Participants with positive serology must have been tested locally for HCV RNA and are eligible, in case of negative HCV RNA test results.
    b. Known positive test results for chronic HBV infection (defined by HBsAg positivity). Participants with occult or prior HBV infection (defined as negative HBsAg and positive total hepatitis B core antibody) may be included if HBV DNA was undetectable (local test result), provided that they are willing to undergo ongoing HBV DNA testing. Antiviral prophylaxis may be administered as per institutional guidelines. Participants who have protective titers of HBsAb after vaccination or prior but cured hepatitis B are eligible.
    c. Known seropositive for or history of active viral infection with HIV.
    d. Known active bacterial, viral, fungal, mycobacterial, or other infection at screening.
    e. Known CNS lymphoma involvement – present or past medical history.
    f. History or evidence of clinically significant cardiovascular, CNS and/or other systemic disease that would in the investigator's opinion preclude participation in the study or compromise the participant's ability to give informed consent.
    g. History or evidence of rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.
    h. History or evidence of interstitial lung disease.
    i. Vaccination with live vaccine within 21 days prior to study treatment (*Note:* throughout the study treatment period and at least 6 months after end of treatment, vaccination with live vaccines should be avoided).
    j. Major surgery within up to 30 days prior to signing the ICF, unless the participant is recovered at the time of signing the ICF.
    k. Any anticancer and/or investigational therapy within 14 days prior to the start of Cycle 1. Note: Steroid prephase is permitted only in Group 5.

l. **Groups 2, 3, 4a, 5, and 6 only:** Gastrointestinal abnormalities including the inability to take oral study treatment, requiring IV alimentation, or prior surgical procedure affecting absorption.
m. Pregnancy or lactation.
Note: Female participants who interrupt breastfeeding are able to be enrolled to the study. They must refrain from breastfeeding during the course of study and for 90 days after the last dose of study treatment.

5. **Groups 2, 3, 5, and 6 only:** Participants who have history of deep venous thrombosis/embolism, threatening thromboembolism, stroke or known thrombophilia or are at a high risk for a thromboembolic event in the opinion of the investigator and who are not willing/able to take venous thromboembolic event prophylaxis during the entire treatment period if required.

6. **Group 4a only:** Use or expected use during the study of any restricted medications (see Section 6.8.9), including potent CYP3A4 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) before the date of study treatment administration.

7. **Groups 1, 2, 3, 4a, and 6 only:** Participants who have:

a. Not discontinued CD20-targeted therapy, chemotherapy, radiotherapy, investigational anticancer therapy, or other lymphoma-specific therapy within the 14 days prior to Day 1 dosing.
b. In the opinion of the investigator, not recovered sufficiently from the adverse toxic effects of prior therapies.
c. **Groups 1, 3, and 4a only:** Previous treatment with CD19-targeted therapy (eg, CD19-CAR-T therapies, other CD19 mAbs including bispecific and ADCs).
Groups 2 and 6 only: Previous treatment with tafasitamab.
Note: Participants in Groups 2 and 6 who have received previous CD19-directed therapy (other than tafasitamab) must have CD19-positive lymphoma confirmed by a biopsy taken after completing the prior CD19-targeted therapy.
d. **Groups 2, 3, and 6 only:** Been previously treated with IMiDs (eg, thalidomide or LEN).
e. **Group 4a only:** Been previously treated with selective PI3Kδ or pan-PI3K inhibitors (eg, idelalisib, copanlisib, duvelisib) and/or Bruton's tyrosine kinase inhibitors (eg, ibrutinib).
f. A history of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, IMiDs, and/or the excipients contained in the study treatment formulations (citric acid monohydrate, polysorbate 20, sodium citrate dehydrate and trehalose dihydrate).
g. Undergone ASCT within the period ≤ 3 months before the signing of the ICF. Participants who have a more distant history of ASCT must exhibit full hematological recovery before enrolment into the study.
h. Undergone previous allogenic stem cell transplantation.
i. Concurrent treatment other anticancer or experimental treatments.

8. **Group 5 only:** Participants who have:
    a. A history of radiation therapy to ≥ 25% of the bone marrow for other diseases or history of anthracycline therapy.
    b. A history of hypersensitivity or contraindication to any component of R-CHOP, LEN, or compounds of similar biological or chemical composition as tafasitamab and/or the excipients contained in the study treatment formulations or R-CHOP.
    c. Contraindication to any of the individual components of R-CHOP.
    d. Any anticancer and/or investigational therapy within 30 days prior to the start of Cycle 1, except for permitted prephase treatment defined below.
    Note: Prephase treatment; the use of corticosteroids (eg, oral PSL 25-100 mg per day or equivalent up to a maximum of over 7 days) with or without RTX (375 mg/m^2 IV) or low-dose chemotherapy (vincristine 1 mg IV) is allowed after tumor investigations (imaging, blood samples and biopsies if applicable) for screening have been performed.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

No dietary restrictions are required.

5.3.2. Activity

All participants except for those in Groups 2 and 6 have to be hospitalized from the day before Day 1 to Day 8 in Cycle 1 in order to assess their ability to tolerate the study treatment. The investigator will judge whether or not to discharge the participant based on the outcome of physical examination, vital signs, hematology, and serum chemistries assessments scheduled on Day 8. The investigator may judge the further necessity of the hospitalization depending on the condition of the participants. There are no other restrictions on participant activities and no other requirements for participant confinement during the study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study treatment.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened maximum 3 times and, at the time of rescreening, must reconsent and be assigned a new participant number except for repeated laboratory assessments. For participants who repeat screening, the most recent test results should be used across all tests.

5.5. Replacement of Participants

In Groups 1, 3, 4a, and 5, participants may be replaced for any of the following reasons:

- Any participant who withdraws from treatment before the completion of the DLT evaluation period for any reason other than a DLT (eg, NE for DLT) may be replaced to ensure a minimum number of evaluable participants.
  - Participants who failed to receive the required doses of study treatment for DLT evaluation period (see Section 6.5.1) and did not have a DLT that was evaluable for dose tolerability will be replaced.
- Participants who were inadvertently enrolled although they do not meet the eligibility requirements of the study may be replaced.

In Group 2, 6 participants who are evaluable will be enrolled. Participants who are judged not to be evaluable will be replaced based on reasons including the following:

- Withdraws from treatment before Day 35 (relative to Cycle 1 Day 1) for any reason other than the occurrence of a prespecified AE defined in Section 6.6.1 (unless clearly attributable to causes other than study treatment).
- Fails to receive the required 5 doses of tafasitamab for any reason other than the occurrence of a prespecified AE defined in Section 6.6.1.
- Enrolled in the study even though they do not meet the eligibility requirements.

In Group 6, 41 participants who are evaluable for efficacy will be enrolled. Participants who are judged not to be evaluable for efficacy may be replaced based on reasons including the following:

- Participants who were inadvertently enrolled although they do not meet the eligibility requirements of the study.

6. STUDY TREATMENT

The following sections describe the study treatment, administration of treatment, and criteria and procedures for dose modifications of the study treatment.

6.1. Study Treatments Administered

The RP2D in weight-based dose of tafasitamab for Japanese participants will be determined in Group 1. The recommended clinical dose of a less frequent dose regimen, tafasitamab Q2W/Q4W when combined with LEN, will be determined in Group 2.

For all participants, weight measurements are to be performed at each visit for tafasitamab dosing and follow-up visit and the values are to be entered into the eCRF recording the day of the actual measurement. Measurements can be done up to 1 day before the tafasitamab infusion. The weight obtained on Day 1 of each cycle can be used for calculation of the subsequent tafasitamab dosing of the same cycle if there is no obvious change of ± 10% compared with the Day 1 visit.

Premedication for participants who do not experience any IRRs to tafasitamab during the first 3 infusions in Groups 1, 3, 4a, 5, and 6 (during the first 4 infusions in Group 2) will be optional for subsequent infusions at the discretion of the investigator. Otherwise, the premedication should be continued for subsequent administrations (see Section 6.8.1). Vital signs should be measured as outlined in Section 8.3.4. All supportive measures consistent with optimal participant care will be provided throughout the study according to institution standards. Precautions for anaphylaxis should be observed during tafasitamab infusion. Emergency resuscitation equipment and medications must be readily available. Additional supportive measures should also be available and may include but are not limited to epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen.

Prophylaxis of VTE is recommended in Groups 2, 3, 5, and 6 due to increased risk of thrombosis in participants treated with LEN without prophylaxis (see Section 6.8.3).

Participants receiving parsaclisib in Group 4a should use primary prophylaxis for PJP (see Section 6.8.4).

Prophylaxis for febrile neutropenia is mandatory in Group 5 (see Section 6.8.5).

Table 14 presents the study treatment information.

Table 14: Study Treatment Information

	Study Treatment 1	Study Treatment 2	Study Treatment 3	Study Treatment 4
Study treatment name:	Tafasitamab	Lenalidomide	Parsaclisib	R-CHOP
Dosage formulation:	200 mg in single-use 20-mL vial	5 mg, 10 mg, 15 mg, 20 mg, 25 mg oral capsules	1 mg, 2,5 mg, 5 mg, and 20 mg oral tablets	Use commercially available drugs
Unit dose strength(s)/ dosage level(s):	9 mg/kg QW, 12 mg/kg QW for Groups 1, 3, 4a, and 5 Starting dose of 12 mg/kg and then 30 mg/kg Q2W for Group 2	25 mg QD[a], 20 mg QD, 15 mg QD, 10 mg QD, 5 mg QD	20 mg QD, 10 mg QD, 2.5 mg QD, 1 mg QD	RTX 375 mg/m^2, CPA 750 mg/m^2, ADR 50 mg/m^2, VCR 1.4 mg/m^2 (max 2 mg), PSL 100 mg
Administration instructions:	Tafasitamab will be diluted into an infusion bag containing 0.9% sodium chloride for injection in 250 mL. If the weight of a participant is low, a smaller infusion bag should be used, which will result in concentrations ranging from 2 to 8 mg/mL. The infusion rate escalation schedules in this Protocol and the Drug Preparation Manual are recommendations only. If required, the investigator should use clinical judgment to optimize participant safety by administering the infusion more slowly. **Groups 1, 3, 4a, 5, and 6** For Cycle 1 Day 1, the IV infusion rate should be 70 mL/h for the first 30 minutes and subsequently increased to a rate of 125 mL/h; the total infusion duration should ideally not exceed 2.5 hours. If a 100-mL infusion bag is used, the IV infusion rate should be 30 mL/h for the first 30 minutes and subsequently increased to a rate of 50 mL/h for Cycle 1 Day 1; the total infusion duration should ideally not exceed 2.5 hours. All subsequent infusions will be administered IV at a constant rate of approximately 50 mL/h with minimal duration for a total infusion of 90 min. **Group 2** The total infusion duration should be 1.5-2.5 hours on Cycle 1 Day 1, approximately 2 hours on Cycle 1 Days 4 and 8, approximately 4 hours from Cycle 1 Day 15 to Cycle 3 Day 15, and approximately 2 hours from Cycle 4 Day 1 onward (see Table 15). If a 100-mL infusion bag is used in Cycle 1 Days 1-8, the total infusion duration should be the same as shown in Table 15.	LEN should be taken at approximately the same time each day. On days when LEN and tafasitamab are given together, LEN should be administered prior to tafasitamab in Cycle 1. If a dose is missed by more than 12 hours, the participant should skip the dose and take the next scheduled dose at the usual time.	Parsaclisib should be taken at approximately the same time each day. On days when parsaclisib and tafasitamab are given together, parsaclisib should be administered prior to tafasitamab. If a dose is missed by more than 12 hours, the participant should skip the dose and take the next scheduled dose at the usual time.	RTX is advised to be given approximately 30 minutes after the end of tafasitamab infusion, followed by the CHOP chemotherapy, which will be given approximately 30 minutes after the end of the RTX infusion.

Table 14: Study Treatment Information (Continued)

	Study Treatment 1	Study Treatment 2	Study Treatment 3	Study Treatment 4
Packaging and labeling:	Tafasitamab will be provided in a vial. Each vial will be labeled as required per country requirement.	LEN will be provided in a blister pack. Each blister will be labeled as required per country requirement.	Parsaclisib will be provided in a bottle. Each bottle will be labeled as required per country requirement.	Commercialized product will be used. Site sourced.
Storage:	Stored at 2°C to 8°C	Stored at 15°C to 30°C	Stored at 15°C to 30°C	Follow PI of each drug.
Status of treatment:	Investigational	Investigational	Investigational	Approved

ADR = doxorubicin; CPA = cyclophosphamide; PSL = prednisolone; RTX = rituximab; VCR = vincristine.

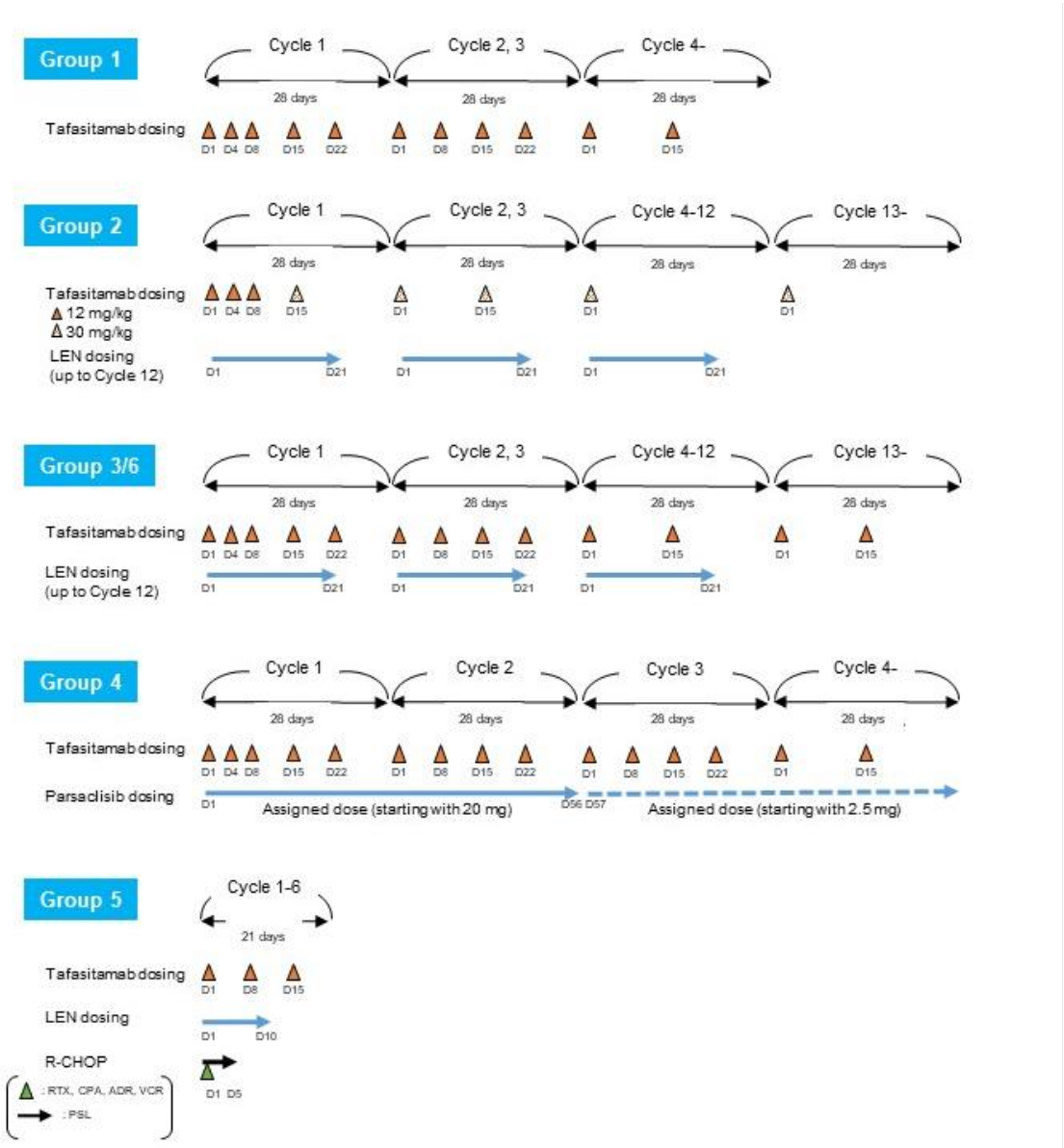
[a] The starting dose of LEN in Group 5 may be adjusted based on the result of First-MIND study. In case a lower dose is selected, the sponsor will notify the investigator site.

Table 15: Tafasitamab Infusion Duration in Group 2

Visit	Cycle l Day 1	Cycle 1 Day 4	Cycle 1 Day 8	Cycle 1 Day 15 to Cycle 3 Day 15	Cycle 4 Day 1 Onward
Tafasitamab dose	12 mg/kg			30 mg/kg	30 mg/kg
Infusion duration	1.5-2.5 h	≈ 2 h	≈ 2 h	≈ 4 h	≈ 2 h

Figure 7 shows the dosing schedule in each group. The detailed schedule of each treatment follows.

Figure 7: Scheme of Dosing Schedule in Each Group



ADR = doxorubicin; CPA = cyclophosphamide; D1 = Day 1; PSL = prednisolone; RTX = rituximab; VCR = vincristine.

As of Amendment 5, the limited length of the treatment period has been removed for participants demonstrating a long-term benefit; these participants may continue tafasitamab and/or parsaclisib at the discretion of the investigator. Participants who continue on tafasitamab and/or parsaclisib treatments at the end of the study may continue until meeting any of the discontinuation criteria (see Section 7.1.1). Participants treated in the combination group in Parts 2 (Groups 3, 4a, and 5) and 3 should generally be discontinued from both study treatments if either of the drugs is prematurely discontinued for any reason; however, exceptions will be considered on a case-by-case basis upon discussion with the sponsor's medical monitor. Participants in Part 4 Group 6 may continue only tafasitamab or LEN (up to 12 cycles) even if either of the drugs is prematurely discontinued for any reason at the physician's discretion. The follow-up period will begin once a participant has completed or prematurely discontinued study treatment. Participants will be followed up to the EOS visit in Groups 1, 2, 3, 4a, and 5 (see Section 8.8) and for a maximum of 3 years from Cycle 1 Day 1 for each participant in Group 6.

6.1.1. Tafasitamab Regimen 1: 28-Day Cycle (Groups 1, 3, 4a, and 6)

For the first 3 cycles of the study, each cycle (Cycles 1-3) will consist of a tafasitamab infusion on Days 1, 8, 15, and 22 of the cycle. Additionally, a loading dose will be administered on Day 4 of Cycle 1.

Thereafter, tafasitamab will be administered on a bi-weekly basis with infusions on Days 1 and 15 of each 28-day cycle until meeting any of discontinuation criteria (see Section 7.1.1). From Cycle 4 onwards, a delay of a dose on Day 15 due to a long holiday, bad weather, or other unforeseen circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation.

6.1.2. Tafasitamab Regimen 2: 28-Day Cycle (Group 2)

Cycle 1 will consist of a tafasitamab infusion on Days 1, 4, and 8 with 12 mg/kg and Day 15 with 30 mg/kg. Cycles 2 and 3 will consist of a tafasitamab infusion on Days 1 and 15 with 30 mg/kg.

Thereafter, tafasitamab 30 mg/kg will be administered Q4W with infusions on Day 1 of each 28-day cycle until any of the discontinuation criteria are met (see Section 7.1.1).

6.1.3. Tafasitamab Regimen 3: 21-Day Cycle (Group 5)

Each cycle (Cycles 1-6) will consist of a tafasitamab infusion on Days 1, 8, and 15 of the cycle.

6.1.4. Lenalidomide (Groups 2, 3, 5, and 6)

Participants will self-administer oral LEN daily on Days 1 through 21 of each 28-day cycle in Groups 2, 3, and 6 or Days 1 through 10 of each 21-day cycle in Group 5. Treatment with LEN may be modified in a de-escalating fashion or discontinued based upon clinical and laboratory findings except for Group 6, in which a dose increase is allowed for participants with moderate renal insufficiency who start treatment with LEN at 10 mg QD. Detailed dose modification guidelines to manage hematologic and/or other toxicities are provided in Section 6.7.5.3 and Section 6.7.6.3. Lenalidomide can be given for up to a total of 12 cycles in Groups 2, 3, and 6 and up to 6 cycles in Group 5.

Due to the potential for embryo-fetal toxicity (refer to Lenalidomide ICF Standard Risk Language for the safety profile), all participants in Groups 3, 5, and 6 who will be prescribed LEN must follow the Global PPP (see Appendix B). In accordance with the PPP, all FCBP are required to undergo specified pregnancy testing and contraception requirements in addition to counseling on the risk of teratogenicity. Furthermore, FNCBP and male participants are required to adhere to specific guidelines to ensure prevention of embryo-fetal exposure to LEN. All occurrences of pregnancy after exposure to LEN must be reported immediately to the sponsor in addition to other local reporting requirements. The sponsor will conduct pertinent follow-up of all reported pregnancies with potential exposure to LEN in alignment with the Marketing Authorization Holder's pregnancy registry protocol for LEN. Also, only prescribers and pharmacists registered with the program can prescribe and dispense LEN, and it must only be dispensed to participants who are registered and meet all the conditions of the PPP.

6.1.5. Parsaclisib (Group 4a)

Participants will self-administer oral parsaclisib daily on Days 1 through 56 followed by a dose of 2.5 mg until meeting any of discontinuation criteria (see Section 7.1.1). Treatment with parsaclisib may be modified in a de-escalating fashion or discontinued based upon clinical and laboratory findings. Detailed dose modification guidelines to manage hematologic and/or other toxicities are provided in Section 6.6.

6.1.6. R-CHOP (Group 5)

Treatment consists of following drugs for six 21-day cycles: rituximab, cyclophosphamide, doxorubicin, vincristine, and PSL. R-CHOP is considered SoC and will be given according to institutional guidelines. R-CHOP is not an investigational drug and will not be supplied by the sponsor.

R-CHOP consists of the following:

- RTX or approved biosimilar 375 mg/m^2 IV, Day 1 of every 21-day cycle.
- Cyclophosphamide 750 mg/m^2 IV, Day 1 of 21-day cycle.
- Doxorubicin 50 mg/m^2 IV, Day 1 of 21-day cycle.
- Vincristine 1.4 mg/m^2 (max 2 mg) IV, Day 1 of 21-day cycle.
- PSL 100 mg PO or IV, Days 1-5 of every 21-day cycle.

In Group 5, premedication (see Section 6.8.1) should be given approximately 30 to 60 minutes before starting each tafasitamab infusion in Cycle 1. The Day 1 corticosteroid dose (PSL) being part of CHOP can be used as the premedication for tafasitamab. R-CHOP treatment will be given according to institutional guidelines after tafasitamab infusion. Rituximab is advised to be given approximately 30 minutes after the end of tafasitamab infusion, followed by the CHOP chemotherapy.

6.2. Preparation, Handling, and Accountability

The investigator, the investigational drug storage manager, or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator, the investigational drug storage manager, and authorized site staff.

The investigator, the investigational drug storage manager, or designee is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator, the investigational drug storage manager, or designee must maintain records that document:

- Delivery of study treatment(s) to the study site.
- Inventory of study treatment(s) at the site.
- Participant use of the study treatment(s) including vial/capsule/tablet counts from each supply dispensed.
- Lot numbers and/or vial numbers of study treatment used to prepare the infusion solution. (For R-CHOP, drug accountability is managed under the investigator site's process.)
- Return of study treatment(s) to the investigator, the investigational drug storage manager, or designee by participants.

The investigational product must be used only in accordance with the Protocol. The investigator or investigational drug storage manager will also maintain records adequately documenting that the participants were provided the specified study treatment. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator, the investigational drug storage manager, or designee will be expected to collect and retain all used, unused, and partially used containers of study treatment until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator, the investigational drug storage manager, or designee will oversee shipment of any remaining study treatment back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study treatment is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

Further guidance and information for the final disposition of unused study treatments are provided in the Pharmacy Manual.

The storage condition of each study treatment is summarized in Table 14. The detailed handling procedure of tafasitamab and parsaclisib is written in the Pharmacy Manual. LEN and R-CHOP is handled in accordance with the PI.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study.

Compliance with LEN and parsaclisib will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (capsule/tablet counts). Participants will be instructed to bring all unused study treatments (including an empty bottle) with them to the study visits for site personnel to conduct capsule/tablet counts to assess study treatment accountability. The site personnel may instruct participants to keep a daily patient diary during the outpatient period to record dosing compliance. The study treatment compliance should be recorded in eCRF based on the information from the drug accountability document.

Compliance with tafasitamab infusion will be calculated by the sponsor based on infusion records documented by the site staff and monitored by the sponsor/designee.

A participant will be considered compliant with the Protocol if tafasitamab dose administered is ≥ 80% to ≤ 120% of the assigned dosage and LEN or parsaclisib dose administered is ≥ 80% to ≤ 100% of the assigned dosage during a particular cycle.

R-CHOP therapy (noninvestigational medicinal product) must be documented in the eCRF.

6.5. Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose (Groups 1, 3, 4a, and 5)

6.5.1. Definition of a Dose-Limiting Toxicity

Dose-limiting toxicity will be defined as the occurrence of any of the toxicities in Table 16 occurring up to and including Day 28 (Day 21 in Group 5 only), except those with a clear alternative explanation. All DLTs will be assessed for severity by the investigator using CTCAE v5.0. During the DLT observation period, participants who receive at least 4 of 5 doses of tafasitamab in Group 1; at least 17 of 21 doses of LEN and at least 4 of 5 doses of tafasitamab in Group 3; at least 23 of 28 doses of parsaclisib and at least 4 of 5 doses of tafasitamab in Group 4a; and at least 8 of 10 doses of LEN, 3 of 3 doses of tafasitamab, and all components of R-CHOP in Group 5 at the level assigned or participants who have a DLT will be considered evaluable for the judgment of the dose escalation and the determination of the RP2D. All safety data including the data of participants who are not evaluable for DLTs will be considered to determine the dose escalation and the RP2D.

Individual participant dose reductions may be made based on events observed at any time during treatment with study treatment; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD, decisions will be made based on events that are observed from the first day of study treatment administration through and including the final day of Cycle 1 (Day 28 in Groups 1, 3, and 4a and Day 21 in Group 5).

An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity will not be considered as DLT.

Table 16: Definition of Dose-Limiting Toxicity

Toxicity	Definition
Nonhematologic	• > Grade 3 tumor lysis syndrome or Grade 3 tumor lysis syndrome requiring dialysis. • ≥ Grade 4 fatigue lasting for ≥ 7 days. • ≥ Grade 4 IRR. • Any other ≥ Grade 3 nonhematologic toxicity except described below: – Nausea, vomiting, electrolyte abnormality, or liver function abnormality
Hematologic	• ≥ Grade 3 hematologic toxicities lasting for greater than 3 days excluding neutropenia and lymphocytopenia (also excluding thrombocytopenia in Groups 3 and 5). • Grade 4 neutropenia (ANC < 0.5×10^9/L) lasting for ≥ 7 days in participants with pretreatment ANC > 1×10^9/L under appropriate use of G-CSF (if G-CSF is required to manage neutropenia, the neutropenia is considered as a DLT in Groups 1 and 2). • Grade ≥ 4 thrombocytopenia in Groups 3 and 5. • Febrile neutropenia.
General	• Any death not clearly due to the underlying disease or extraneous causes. • Any toxicity other than described above that (in the opinion of the investigator) is potentially life-threatening and cannot be controlled with standard measures. • A drug-related AE of any grade observed during the DLT evaluation period that leads to a continuous drug interruption and that prevents a participant from receiving at least 75% of the planned cohort-specified doses of study treatment. • Any toxicity which a primary investigator and the sponsor agree on being dealt as DLT.

6.5.2. Procedures for Cohort Review and Dose Escalation/De-Escalation

The SMC (see Section 6.5.3) using web-based communication tools or in-person meeting will be scheduled by the sponsor with study investigators in order to review cohort-specific data and overall safety data, agree on dose escalation or de-escalation, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions. The attendance of an investigator who does not enroll participants to the specific cohort is not mandatory.

6.5.3. Safety Monitoring Committee (Groups 1, 3, 4a, and 5)

An independent data monitoring committee is not planned for this study, and the SMC will review the safety data. The SMC will consist of the medical monitor, the clinical scientist, and the investigators. In case any of SMC members is unavailable, each member may appoint a qualified designee in his or her place. The SMC will meet during Parts 1 and 2 (except for Group 2) of the study following completion of each dosing cohort and throughout the study to help guide any other major safety-based concerns or decisions throughout the study. In addition to the safety data throughout the study, the SMC may review the efficacy data for Group 4 (tafasitamab plus parsaclisib) of the interim analysis.

6.6. Determination of Recommended Clinical Dose (Group 2)

6.6.1. Definition of Recommended Clinical Dose

Participants who receive treatment from Cycle 1 Day 1 through Cycle 2 Day 1, complete safety assessments through Cycle 2 Day 7 (Day 35 relative to Cycle 1 Day 1), and/or experience prespecified AEs (unequivocally unrelated to study treatment) through Day 35 (regardless of treatment discontinuation or continuation as a result of the event) are considered evaluable. Participants who are considered not evaluable (eg, a participant who discontinues the study for reasons other than safety before Day 35) will be replaced (see Section 5.5).

If ≥ 34% of evaluable participants (ie, ≥ 3/6) experience a predefined AE through Day 35, the dose will be judged not to be not tolerable in Japanese participants. If the assessed dose is tolerable, the dose will be judged to be the recommended clinical dose of tafasitamab Q2W/Q4W in combination with LEN.

The predefined AEs are as follows to according to CTCAE v5.0:

- ≥ Grade 4 nonhematologic AE
- ≥ Grade 4 neutropenia lasting > 7 days, despite standard of care treatments (ie, G-CSF, others as needed)
- ≥ Grade 4 anemia
- ≥ Grade 3 neutropenia with associated fever (> 38.3 °C) lasting > 7 days, despite standard of care treatments (ie, anti-infectives, G-CSF, others as needed)
- ≥ Grade 3 IRR
- ≥ Grade 3 TLS
- ≥ Grade 3 thrombocytopenia with clinically significant bleeding
- CRS ≥ Grade 2

Adverse events that are clearly attributed to the underlying disease or LEN alone will be discussed at the SMC, and a decision will be made whether these events should be considered as a predefined AE.

6.6.2. Safety Monitoring Committee Specific to Group 2

An independent data monitoring committee is not planned for this study, and the SMC will review the safety data. The SMC will consist of the medical monitor, the clinical scientist, and the investigators whose study site is included in enrollment in Group 2. The first SMC meetings will take place when 6 participants have completed the 5-week (35-day) safety observation period. The SMC will judge the recommended clinical dose of tafasitamab Q2W/Q4W in combination with LEN during the first meeting. In case any of the SMC members are unavailable, each member may appoint a qualified designee in their place. The SMC will continuously monitor the study and may recommend that an additional SMC meeting be scheduled and/or stop enrollment at any time based on emerging safety data.

6.7. Dose Modifications

6.7.1. Tafasitamab Modification for Grade 3 Infusion-Related Reaction (Groups 1, 3, 4a, and 5)

Some mAb treatments in NHL have been associated with Grade 3 IRRs during the first infusion in participants, particularly at high doses. These IRRs have been ameliorated or eliminated by fractionating the dose into 2 infusions separated by at least 24 hours.

After the first occurrence of a first-dose Grade 3 IRR, subsequent 3 infusions for this participant will be split: one-third of the dose administered on the original schedule followed by the remaining two-thirds on the next day, each infusion administered over 2 hours. If there are no IRRs with 3 consecutive split infusions, then the investigator can consider reverting to a single 2-hour infusion for the subsequent infusions. If the investigator judges a single 2-hour infusion to be appropriate, he/she may consider using the infusion speed defined in Table 14.

6.7.2. Dose Modification for Tafasitamab (All Groups)

Instructions for dose modifications for tafasitamab are outlined in Table 17, Table 18, Table 19, Table 20, Table 24, and Table 25. Individual decisions regarding dose modifications of tafasitamab should be made using clinical judgment in consultation with the medical monitor (whenever possible), taking into account relatedness of the AE to the study treatment and the participant's underlying condition. Adverse events that have a clear alternative explanation, or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms, may be exempt from dose-modification rules.

6.7.3. Management of Infusion-Related Reactions

In case a Grade 3 IRR in a cohort occurs during the first dose on Cycle 1 Day 1 in Groups 1, 3, 4a, and 5, follow Section 6.7.1.

IRRs have commonly been reported for participants with CLL or NHL treated with tafasitamab. IRRs will be defined according to the NCI CTCAE v5.0 definition of IRR and CRS. Table 17 shows intervention for each grade of IRRs for participants of all groups.

Table 17: Management of Infusion-Related Reactions

IRR Grade	CRS Grade	Interventions
2	1	The infusion should be stopped immediately. The participant should receive appropriate treatment with an antihistamine and/or acetaminophen or methylprednisolone (or equivalent) as clinically indicated. Once the symptoms have been resolved or reduced to Grade 1 according to investigator assessment, the infusion can be continued at an infusion rate of 50% of the speed so far. If, after 1 hour, the participant's symptoms do not return and vital signs are stable, the infusion rate may be increased every 30 minutes, as tolerated, to the baseline rate. In case a smaller infusion bag is used, IRR occurs within 30 minutes, or other case of need, the maximum speed may be adjusted according to the clinical judgment of the investigator. If a participant who developed a Grade 2 IRR or Grade 1 CRS receives further infusions of tafasitamab, then premedication should be given before all subsequent infusions of tafasitamab throughout the study.
3	2	The infusion should be stopped immediately. The participant must receive appropriate treatment with an antihistamine and/or acetaminophen or methylprednisolone (or equivalent) and, if necessary, further medications (ie, epinephrine, bronchodilator). Only after the complete resolution of all symptoms, and after having received appropriate prophylactic medication(s) as described above, the infusion may be resumed at an infusion rate of 25% of the speed so far. If, after 1 hour, the participant's symptoms do not return and vital signs are stable, the infusion rate may be increased to a maximum of 50% of the baseline speed. In case a smaller infusion bag is used, IRR occurs within 30 minutes, or other case of need, the maximum speed may be adjusted according to the clinical judgment of the investigator. If, after the resumption of the infusion, symptoms return (irrespective of grade), the infusion must be stopped immediately and the infusion tubing should be disconnected from the participant. Based on the investigator's decision the participant may receive further tafasitamab provided clinically appropriate precautions were undertaken. If a participant who developed a Grade 3 IRR or Grade 2 CRS receives further infusions, then premedication should be given before all subsequent infusions of tafasitamab throughout the study and follow Section 6.7.1 (Groups 1, 2, 3, 4a, and 5 only). If precluded from further tafasitamab infusions, the participant may continue treatment with LEN, parsaclisib or LEN in addition to R-CHOP.
4	3 or 4	The infusion should be stopped immediately and the infusion tubing should be disconnected from the participant. The participant must receive appropriate treatment with an antihistamine and/or acetaminophen or methylprednisolone (or equivalent) and, if necessary, further medications (ie, epinephrine, bronchodilator). The participant must not receive any further tafasitamab infusions, but may continue treatment with LEN, parsaclisib or LEN in addition to R-CHOP as per Protocol.

6.7.4. Dose Modification for Tafasitamab in Monotherapy (Group 1)

If a participant develops a tafasitamab-related Grade 3 or 4 toxicity and the toxicity has not resolved to Grade 1 or to at least the baseline grade (if the condition was pre-existing at screening) at the day of the next scheduled administration, tafasitamab administration for that visit will be postponed. Delaying the tafasitamab dosing is permitted for no more than 2 days (eg, if dosing was planned on Day 8, delaying that dose is allowed up to Day 10) except for the loading dose on Day 4 of Cycle 1. In case a participant has not recovered on Day 4 of Cycle 1, the dose should be omitted. Because B-cell depletion and a subsequent reduction of absolute lymphocyte count is an anticipated pharmacologic effect of tafasitamab, dose modification can be exempted for participants with Grade 3 or 4 lymphocytopenia related to tafasitamab with approval from the medical monitor.

If based on medical judgment, the treating physician considers a laboratory parameter change or AE not to be a study drug-related toxicity but rather to represent natural fluctuation or progression of the underlying disease, then it is up to the physician's discretion and assessment of the individual risk/benefit ratio to determine whether the participant should receive study treatment. The decision and rationale behind the decision should be documented in the source data.

Participants can only enter the next treatment cycle if the following criteria are met. If at least 1 criterion is not met (unless this is due to the fluctuation/progression of the underlying disease or infiltration of the bone marrow by the NHL), the beginning of the cycle will be postponed until resolution to Grade 1 or at least the baseline value (for pre-existing conditions at screening). If a cycle has to be postponed for more than 15 days for the same persisting study tafasitamab-related toxicity, then the participant will be discontinued from the study treatment.

- ANC $\geq 1.0 \times 10^9$/L.
- Platelet count $\geq 50 \times 10^9$/L.
- Hemoglobin ≥ 8.0 g/dL.
- Serum creatinine $< 2.0 \times$ ULN.
- Total bilirubin $\leq 2.0 \times$ ULN.
- ALT and AST $\leq 2.5 \times$ ULN.
- No tafasitamab-related Grade 3 or 4 toxicity in CNS, cardiovascular, infections, or gastrointestinal system organ class (as per the NCI CTCAE 5.0 classification). Other study treatment–related toxicity should recovered to Grade 1 or to at least the baseline grade. Individual decisions regarding entering the next treatment cycle of tafasitamab can be made using clinical judgment in consultation with the medical monitor, taking into account relatedness of the AE to the study treatment and the participant's underlying condition.

6.7.4.1. Dose Reduction for Tafasitamab in Monotherapy (Group 1)

Dose reductions are not allowed in Group 1.

6.7.5. Dose Modification in Phase 1b Combination Therapy (Groups 2, 3, 4a, and 5)

6.7.5.1. Criteria for Initiation of Cycle in Combination Therapy (Groups 2, 3, 4a, and 5)

The next cycle of treatment may begin on the scheduled Day 1 if the following criteria are met:

- ANC is $\geq 1.0 \times 10^9$/L.
- **Groups 2 and 3:** Platelet count $\geq 50 \times 10^9$/L and absence of active bleeding.
- **Groups 4a and 5**: Platelet count $\geq 75 \times 10^9$/L and absence of active bleeding.
- All other toxicities have resolved to ≤ Grade 2. Individual decisions regarding entering the next cycle can be made using clinical judgment in consultation with the medical monitor, taking into account relatedness of the AE to the study treatment and the participant's underlying condition.

If, based on medical judgment, the treating physician considers a change in laboratory parameter or AE not to be of any study treatment–related toxicity but to represent a natural fluctuation in or progression of the underlying disease, then it is at the physician's discretion and assessment of the individual risk/benefit ratio to determine whether the participant should be dosed. The decision and rationale behind the decision should be documented in the source data.

Because B-cell depletion and a subsequent reduction of absolute lymphocyte count is an anticipated pharmacologic effect of tafasitamab, dose modification can be exempted for participants with Grade 3 or 4 lymphocytopenia related to tafasitamab with approval from the medical monitor.

6.7.5.1.1. Cycle Initiation in Groups 2, 3, and 4a

If the conditions in Section 6.7.5.1 are not met on the scheduled Day 1 of new cycle, the participant will be evaluated once every 7 days and a new cycle will not be initiated until the toxicity has resolved as described above in Groups 2, 3, and 4a. The specific course of action for a given toxicity occurring in the course of the treatment cycle in Groups 2, 3, and 4a is described below.

If treatment needs to be interrupted for ≤ 28 days for the same study treatment–related toxicity in Groups 2, 3, and 4a, then the participant's treatment should continue, depending on the duration of treatment interruption, at the next Protocol-scheduled visit. No missed visits or doses of either study treatment should be made up.

If treatment with 1 study treatment needs to be interrupted for > 28 days for the same, persistent, study treatment–related toxicity in Groups 2, 3, and 4a, then the study treatment judged by the investigator to have caused the toxicity should be discontinued, and the participant should continue to be dosed with the other study treatment, as per Protocol.

If both study treatments need to be interrupted for > 28 days for the same, persistent study treatment–related toxicity in Groups 2, 3, and 4a, judged by the investigator to be related to both study treatments (LEN/parsaclisib and tafasitamab), then the EOT visit (see Section 8.7) will be performed, and the participant will enter the follow-up phase.

6.7.5.1.2. Cycle Initiation in Group 5

If the conditions in Section 6.7.5.1 are not met on the scheduled Day 1 of new cycle, the participant will be evaluated again within 7 days. If the above-mentioned criteria are met at any time within 7 days, the next treatment cycle may be initiated. If the above-mentioned criteria are still not met after 7 days delay, the next cycle should not commence. The participant will be evaluated again after another 7 days (or earlier). If the above-mentioned criteria are met at any time within another 7 days, the next treatment cycle may be initiated with the next lower dose level of LEN (see Table 21). If LEN was already at the lowest dose level, LEN treatment should be permanently discontinued.

If the above-mentioned criteria are still not met after 14 days delay, the next cycle should not commence. The CBC should be repeated at a frequency deemed appropriate by the investigator. Once the above-mentioned criteria are met in Group 5, LEN should be permanently discontinued, and tafasitamab should be interrupted in this treatment cycle while R-CHOP treatment may be resumed.

If the above-mentioned criteria are fulfilled, but the participant developed nonhematological toxicity as described in Table 20 due to LEN, tafasitamab plus R-CHOP should continue even if LEN is interrupted. LEN may be resumed at the next cycle if the criteria are met. Skipped doses of LEN will not be made up for.

If the above-mentioned criteria are fulfilled, but the participant developed nonhematological toxicity due to tafasitamab (for example Grade 4 IRR), LEN plus R-CHOP or R-CHOP should continue even if tafasitamab was permanently discontinued. Note that visits on Day 8 and Day 15 should still take place in such case for study assessments.

If delay of over 7 days of R-CHOP occurs in ≥ 3 of the participants, follow stopping rule (Section 4.1.2.1).

Any individual component of R-CHOP may be omitted (or reduced in dose) due to specific toxicities related to RTX, vincristine, doxorubicin, cyclophosphamide, or PSL in accordance with institutional guidelines.

Tafasitamab, LEN as well as R-CHOP treatment, as long as permitted by the above rules, should be started on Day 1 (within the applicable visit window) of each cycle.

6.7.5.2. Guidelines for Managing Hematological and Other Toxicities

Participants will be evaluated for AEs at each visit with NCI CTCAE v5.0 used as a guide for grading severity. The dose of study drug(s) for each participant will be interrupted and/or modified following toxicity as described below. See Table 18 for Groups 2, 3, and 4a and Table 19 for Group 5. Guidance on managing LEN- and/or tafasitamab-specific toxicities is summarized in Table 20. Table 21 shows dose levels for LEN reduction, and Table 23 shows dose levels for parsaclisib reduction. Individual decisions regarding dose interruption and reduction of LEN or parsaclisib should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study treatment and the participant's underlying condition. Even if tafasitamab is interrupted due to toxicities, scheduled visits should still take place.

Table 18: Toxicity Management Guidelines for Hematological and Other Toxicities (Groups 2, 3, and 4a)

Adverse Event	Value or Grade	Recommendation
Groups 2, 3, and 4a Grade 3/4 neutropenia judged to be related to study drugs	ANC falls to < 1.0×10^9/L for at least 7 days or ANC falls to < 1.0×10^9/L with an associated body temperature ≥ 38.5°C or ANC falls to < 0.5×10^9/L	Interrupt tafasitamab[a] and LEN or parsaclisib dosing. Follow CBC every 7 days. Growth factors (G-CSF) and antimicrobial prophylaxis are to be used, as per local guidelines.
	ANC return to ≥ 1.0×10^9/L	Provided all other criteria are fulfilled, resume dosing of tafasitamab and/or LEN/parsaclisib. LEN should be administered at the next lower dose level (see Table 21). Restart parsaclisib at the same dose; monitor as clinically indicated.
Groups 2 and 3 Grade 3/4 thrombocytopenia judged to be related to study drugs	Platelet count falls to < 50×10^9/L	Interrupt tafasitamab[a] and LEN dosing. Follow CBC every 7 days.
	Platelet count returns to ≥ 50×10^9/L	Provided all other criteria are fulfilled, resume dosing of tafasitamab and/or LEN. LEN should be administered at the next lower dose level (see Table 21).
Group 4a Grade 2-4 thrombocytopenia judged to be related to study drugs	Platelet count falls to < 75×10^9/L	Interrupt tafasitamab[a] and parsaclisib dosing. Follow CBC every 7 days.
	Platelet count returns to ≥ 75×10^9/L	Provided all other criteria are fulfilled, resume dosing of tafasitamab and/or parsaclisib. Restart parsaclisib at the same dose; monitor as clinically indicated.
Groups 2 and 3 Other clinically significant toxicities judged to be related to study drugs and not listed in Table 20 (except for lymphocytopenia; see Section 6.7.5.1)	Grade 3/4	Interrupt the administration of the study drug(s)[a] to which the toxicity is judged to be related to up to 28 days until the toxicity has resolved to ≤ Grade 2.
	Toxicities resolve to ≤ Grade 2	Provided all other criteria are fulfilled, resume dosing of study drug(s). LEN should be administered at the next lower dose level (see Table 21).
Group 4a Other clinically significant toxicities judged to be related to study drugs and not listed in Table 22 (except for lymphocytopenia; see Section 6.7.5.1)	Grade 3	Interrupt the administration of the study drug(s)[a] to which the toxicity is judged to be related to up to 28 days until the toxicity has resolved to ≤ Grade 1.
	Toxicities resolve to ≤ Grade 1	Restart tafasitamab and parsaclisib at the same doses. If assessed as related to parsaclisib, restart at next lower dose of parsaclisib (see Table 23). Monitor as clinically indicated.

Table 18: Toxicity Management Guidelines for Hematological and Other Toxicities (Groups 2, 3, and 4a) (Continued)

Adverse Event	Value or Grade	Recommendation
Group 4a Other clinically significant toxicities judged to be related to study drugs (continued)	Recurrent Grade 3 after 2 dose reduction of parsaclisib	Discontinue tafasitamab and parsaclisib administration and follow-up per Protocol. Exceptions require approval of sponsor.
	Grade 4	Discontinue tafasitamab and parsaclisib administration and follow-up per Protocol. Exceptions require approval of sponsor.

[a] If, based on medical judgment, the treating physician considers a laboratory parameter change or AE not to be a study drug-related toxicity, but to represent a natural fluctuation in or progression of the underlying disease, then it is at the physician's discretion and assessment of the individual risk/benefit ratio to determine whether the participant should be dosed. The decision and rationale behind the decision should be documented in the source data.

Table 19: Toxicity Management Guidelines for Hematological and Other Toxicities (Group 5)

Hematological Toxicity	Lenalidomide[a]	Tafasitamab
Neutropenia Grade 4	Interrupt LEN.	Continue tafasitamab infusion per Protocol.
	If neutropenia has resolved to ≤ Grade 2 within 7 days, LEN should be restarted in the subsequent cycle at the same dose. If neutropenia has not resolved to ≤ Grade 2 within 7 days, LEN should be resumed in the next cycle at the next lower dose level (see Table 21).	**Note:** Tafasitamab should not be held for asymptomatic neutropenia of any grade.
Neutropenia ≥ Grade 3 associated with infection ≥ Grade 3	Interrupt LEN.	Interrupt tafasitamab
	If infection is controlled, and neutropenia has resolved to ≤ Grade 2, LEN should be resumed in the next cycle at the next lower dose level (see Table 21).	If infection is controlled, continue tafasitamab per Protocol. If a tafasitamab infusion is delayed for 3 or more days, then this infusion should be skipped and tafasitamab treatment continued only at the next scheduled timepoint (if infection is controlled).

Table 19: Toxicity Management Guidelines for Hematological and Other Toxicities (Group 5) (Continued)

Hematological Toxicity	Lenalidomide[a]	Tafasitamab
Neutropenia < Grade 3 associated with infection ≥ Grade 3	First occurrence: Interrupt LEN. If infection is controlled, LEN should be restarted in the subsequent cycle at the same dose.	Interrupt tafasitamab. If infection is controlled, continue tafasitamab per Protocol. If a tafasitamab infusion is delayed for 3 or more days, then this infusion should be skipped and tafasitamab treatment continued only at the next scheduled timepoint (if infection is controlled).
	Reoccurrence: Interrupt LEN. If infection is controlled, LEN should be restarted in the subsequent cycle at the next lower dose level.	
Thrombocytopenia with bleeding	Interrupt VTE prophylaxis. Consider platelet transfusion for ≥ Grade 3 thrombocytopenia. If bleeding has been controlled and thrombocytopenia resolved to ≤ Grade 1, consider change of VTE prophylaxis agent (eg, change antiplatelet agent to low molecular weight heparin). VTE prophylaxis should be tailored to the participant's individual risk/benefit profile by taking into account the individual thrombotic risk and bleeding risk.	
Thrombocytopenia Grade 4	Interrupt VTE prophylaxis. Consider platelet transfusion. If thrombocytopenia has resolved to ≤ Grade 1, consider change of VTE prophylaxis agent (eg, change antiplatelet agent to low molecular weight heparin). VTE prophylaxis should be tailored to the participant's individual risk/benefit profile by taking into account the individual thrombotic risk and bleeding risk.	
	Interrupt LEN.	Continue tafasitamab infusion as per Protocol (unless thrombocytopenia is severe, see below).
	If thrombocytopenia has resolved to ≤ Grade 2 within 7 days, LEN should be restarted in the subsequent cycle at the same dose. If thrombocytopenia has not resolved to ≤ Grade 2 within 7 days, LEN should be resumed in the next cycle at the next lower dose level (see Table 21 above for LEN dosing).	Interrupt tafasitamab in case of very pronounced Grade 4 thrombocytopenia (platelets < 10,000/µL) unless platelet transfusion is administered. If a tafasitamab infusion is delayed for 3 or more days, then this infusion should be skipped and tafasitamab treatment continued only at the next scheduled timepoint.

Table 19: Toxicity Management Guidelines for Hematological and Other Toxicities (Group 5) (Continued)

Nonhematological Toxicity	Value or Grade	Recommendation
Other clinically significant toxicities judged to be related to study drugs and not listed in Table 20	Grade 3/4	Interrupt the administration of the study drug(s)[b] to which the toxicity is judged to be related to.
	Toxicities resolve to ≤ Grade 2	LEN should be administered at the next lower dose level (see Table 21). If a tafasitamab infusion is delayed for 3 or more days, then this infusion should be skipped and tafasitamab treatment continued only at the next scheduled timepoint.

[a] LEN may be given only on Day 1 to 10 of each cycle and must not be administered beyond this period.
[b] If, based on medical judgment, the treating physician considers a laboratory parameter change or AE not to be a study drug related toxicity, but to represent a natural fluctuation in or progression/relapse of the underlying disease, then it is at the physician's discretion and assessment of the individual risk/benefit ratio to determine whether the participant should be dosed. The decision and rationale behind the decision should be documented in the source data.

Table 20: Toxicity Management Guidelines for LEN- and/or Tafasitamab-Specific Nonhematological Toxicity (Groups 2, 3, and 5)

Nonhematological Toxicity	Lenalidomide[a]	Tafasitamab
Thromboembolic events Grade 3-4	Discontinue LEN permanently.	Continue tafasitamab infusion as per Protocol if clinically appropriate.
Allergic reaction or hypersensitivity Grade 2	If related to LEN then interrupt the dose.	If related to tafasitamab then interrupt the dose.
	If toxicity resolves to ≤ Grade 1, restart LEN at the next lower dose level (see Table 21 for LEN dose modifications).	If toxicity resolves to ≤ Grade 1, tafasitamab may be resumed. If tafasitamab infusion is delayed for 3 or more days, then this infusion should be skipped and tafasitamab treatment continued only at the next scheduled timepoint.
Allergic reaction or hypersensitivity ≥ Grade 3	If related to LEN then discontinue permanently.	If related to tafasitamab then discontinue permanently.
	Note: If the causality cannot be determined and the AE may be related to LEN and/or tafasitamab, discontinue both drugs permanently.	
Rash Grade 2 or 3 nondesquamating (blistering)	If related to LEN then interrupt the dose. If the AE resolves to ≤ Grade 1, restart LEN at the same level (see Table 21 for LEN dose modifications).	If related to tafasitamab then interrupt the dose. If toxicity resolves to ≤ Grade 1, tafasitamab may be resumed. If tafasitamab infusion is delayed for 3 or more days, then this infusion should be skipped and tafasitamab treatment continued only at the next scheduled timepoint.

Table 20: Toxicity Management Guidelines for LEN- and/or Tafasitamab-Specific Nonhematological Toxicity (Groups 2, 3, and 5) (Continued)

Nonhematological Toxicity	Lenalidomide[a]	Tafasitamab
Rash Desquamating (blistering) ≥ Grade 3 OR Nondesquamating Grade 4	If related to LEN then discontinue permanently.	If related to tafasitamab then discontinue permanently.
	Note: If the causality cannot be determined and the AE may be related to LEN and/or tafasitamab, discontinue both drugs permanently.	
Tumor flare reaction Grade 3-4[b]	Interrupt LEN. If the AE resolves to Grade ≤ 1, restart LEN and maintain the same dose level (see Table 21 for LEN dose modifications)	Continue tafasitamab infusion as per Protocol if clinically appropriate.
Tumor flare reaction Grade 1-2[b]	Continue LEN.	Continue tafasitamab infusion as per Protocol.
Obstipation ≥ Grade 3	Interrupt LEN. If the AE resolves to ≤ Grade 2, restart at same dose level.	Continue tafasitamab infusion as per Protocol if clinically appropriate.
Other LEN related nonhematologic AEs ≥ Grade 3	Interrupt LEN. If the AE resolves to ≤ Grade 2, restart at the next lower dose level per the investigator's discretion.	Continue tafasitamab infusion as per Protocol if clinically appropriate.

[a] LEN may be given only on Days 1 to 21 of each cycle in Group 3 and Days 1 to 10 of each cycle in Group 5 and must not be administered beyond this period.
[b] Tumor flare reaction is defined as constellation of signs and symptoms in direct relation to initiation of therapy. The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and electrolyte disturbances.

6.7.5.3. LEN Dose Modification Guidelines (Groups 2, 3, and 5)

Guidelines for dose interruption and permanent discontinuation of LEN is shown in Table 20.

If LEN dosing was interrupted during the previous cycle and was restarted with a 1-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle in Groups 3 and 5. There will be no more than 1 dose reduction from one cycle to the next. Once a participant's LEN dose has been reduced, no dose re-escalation is permitted.

The daily oral dose of LEN may be reduced successively by 1 level from the starting dose of 25 mg daily on Days 1 to 21 of each 28-day cycle in Group 3 and on Days 1 to 10 of each 21-day cycle in Group 5 (see Table 21).

In Groups 2 and 3, LEN may be interrupted within the 21-day dose period and may be restarted within this period at the same dose or at Dose Level −1 but may not be extended beyond Day 21 of this cycle. In Group 5, LEN may be interrupted for up to 2 days (eg, from Days 9-10) within the 10-day dosing period and may be restarted within this period at the same dose or at Dose Level −1 but may not be extended beyond Day 10 of this cycle.

In Group 3 and Group 5, LEN should be restarted at the same dose level during Cycle 1 after the interruption for the purpose of DLT assessment. If LEN is restarted at Dose Level −1 in Cycle 1

and the total dose in the cycle is below 75% of the planned cohort-specified doses, the participant is judged to experience DLT.

Participants who cannot tolerate Dose Level −4 are to be discontinued from LEN treatment but should continue therapy with tafasitamab in Groups 2 and 3 and tafasitamab plus R-CHOP for the total duration of 6 cycles in Group 5, if possible.

Table 21: Dose Levels of LEN (Groups 2, 3, and 5)

Dose Level	Groups 2 and 3	Group 5[a]
Starting dose	25 mg daily on Days 1-21 of each 28-day cycle	25 mg daily on Days 1-10 of each 21-day cycle
Dose Level −1	20 mg daily on Days 1-21 of each 28-day cycle	20 mg daily on Days 1-10 of each 21-day cycle
Dose Level −2	15 mg daily on Days 1-21 of each 28-day cycle	15 mg daily on Days 1-10 of each 21-day cycle
Dose Level −3	10 mg daily on Days 1-21 of each 28-day cycle	10 mg daily on Days 1-10 of each 21-day cycle
Dose Level −4	5 mg daily on Days 1-21 of each 28-day cycle	5 mg daily on Days 1-10 of each 21-day cycle

[a] The starting dose of LEN in Group 5 may be adjusted based on the result of First-MIND study. In case a lower dose is selected, the sponsor will notify the investigator site. Dose Level −1, Dose Level −2, and Dose Level −3 will be 5 mg, 10 mg, and 15 mg lower than the starting dose, respectively. Dose Level less than 5 mg leads to discontinuation.

6.7.5.4. Parsaclisib Dose Reductions, Interruption, and Discontinuation Guidelines (Group 4a)

Dose modification guidance for AEs that have been previously observed in participants receiving parsaclisib or are potential class-effect AEs are provided (see Table 22). The starting dose and dose reduction levels of parsaclisib are provided (see Table 23). Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction guidelines. Participants should be informed to immediately report to the investigator any event of diarrhea.

Table 22: Toxicity Management Guidelines for Parsaclisib (Group 4a)

Adverse Event	Recommendation
Chemistry	
AST and/or ALT is Grade 3 (> 5.0 × ULN). *Note:* In participants with liver metastasis–related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.	**Step 1:** Interrupt both tafasitamab and parsaclisib. Monitor weekly until the toxicity has resolved to ≤ Grade 1 (under 3.0 × ULN). **Step 2:** Restart tafasitamab at the same dose and parsaclisib at next lower dose with medical monitor approval. Monitor as clinically indicated.
Other toxicities	
Diarrhea (Grade 1).	**Step 1:** Treat with antimotility agents (eg, 2 mg loperamide followed by 2 mg every 4 hours or after every unformed stool) and initiate supportive care. Monitor approximately every 48 hours until resolved. If not improved after 48 hours, treat per guidance for Grade 2.
Diarrhea (Grade 2).	**Step 1:** Interrupt tafasitamab and parsaclisib. Perform work-up for infection (including CMV, *C. difficile*, etc) immediately. Initiate or continue supportive care. Monitor approximately every 48 hours until resolution. **Step 2:** If improved within 48 hours and/or infection* is confirmed, restart tafasitamab and parsaclisib at the same schedule and dose after resolved to ≤ Grade 1 and continue to monitor. *For infectious diarrhea/colitis, follow institutional standard-of-care guidelines and restart parsaclisib according to clinical judgment after resolved to ≤ Grade 1. Consult with medical monitor if needed. **Step 3:** If not improved within 48 hours and infection is ruled out, start oral steroids, or consider IV steroids if participant is being given IV fluids. If no improvement with oral steroids, switch to IV steroids. **Step 4:** When diarrhea resolves to ≤ Grade 1, continue supportive care and taper steroids according to institutional SoC. When taper is complete (eg, no steroid or ≤ 10 mg/day PSL or equivalent) and diarrhea is ≤ Grade 1, restart parsaclisib at the next lower dose with approval of the medical monitor (see Table 23 for dose levels). **Step 5:** If Grade 2 diarrhea reoccurs, treat per guidance for diarrhea (≥ Grade 3)/noninfectious colitis. **Step 6:** If ≥ Grade 2 diarrhea reoccurs a third time, permanently discontinue parsaclisib.

Table 22: Toxicity Management Guidelines for Parsaclisib (Group 4a) (Continued)

<table>
<tr><th>Adverse Event</th><th>Recommendation</th></tr>
<tr><td>Diarrhea (≥ Grade 3).
Noninfectious colitis (any grade; confirmed or suspected).</td><td>Step 1: Interrupt tafasitamab and parsaclisib. Perform work-up for infection (including CMV, C. difficile, etc) immediately. Initiate or continue supportive care. Consider colonoscopy with biopsy for diarrhea ≥ Grade 3 and/or if symptoms[a] suggestive of colitis. Monitor every 48 hours until resolution.
Step 2: If infection* is ruled out, start oral steroids, or consider IV steroids if participant is being given IV fluids. If no improvement with oral steroids within 48 hours, switch to IV steroids.
*For infectious diarrhea/colitis, follow institutional SoC guidelines and restart parsaclisib according to clinical judgment after resolved to ≤ Grade 1. Consult with medical monitor if needed.
Step 3: When diarrhea/colitis resolves to ≤ Grade 1, continue supportive care and taper steroids according to institutional SoC. When taper is complete (eg, no steroid or ≤ 10 mg/day PSL or equivalent) and diarrhea/colitis is ≤ Grade 1, restart tafasitamab and parsaclisib as described herein and with approval of the medical monitor. Continue to monitor.
<table>
<tr><th>Parsaclisib</th><th>Dose Modification</th></tr>
<tr><td>Any dose with QD dosing</td><td>20 mg QW</td></tr>
</table>
Step 4: If ≥ Grade 3 diarrhea/colitis (any grade) reoccurs, permanently discontinue parsaclisib.</td></tr>
<tr><td>Pneumonitis (Grade 1).</td><td>Step 1: Interrupt tafasitamab and parsaclisib until the toxicity has resolved.
Step 2: Restart tafasitamab at the same dose and parsaclisib at next lower dose. Monitor as clinically indicated.</td></tr>
<tr><td>Pneumonitis (≥ Grade 2).</td><td>Permanently discontinue tafasitamab and parsaclisib.</td></tr>
<tr><td>Skin toxicity (eg, rash, pruritus, etc, unless otherwise specified; Grade 2-3).</td><td>Step 1: Interrupt tafasitamab and parsaclisib until the toxicity has resolved to ≤ Grade 1.
Step 2: Restart tafasitamab and parsaclisib at same dose. If assessed as related to parsaclisib, restart at next lower dose.</td></tr>
<tr><td>Exfoliative dermatitis (Grade 1).</td><td>Step 1: Interrupt tafasitamab and parsaclisib until the toxicity has resolved.
Step 2: Restart tafasitamab at the same dose and parsaclisib at next lower dose. Monitor as clinically indicated.</td></tr>
<tr><td>Exfoliative dermatitis (≥ Grade 2).</td><td>Permanently discontinue tafasitamab and parsaclisib.</td></tr>
<tr><td>Intestinal perforation (any grade).</td><td>Permanently discontinue tafasitamab and parsaclisib.</td></tr>
</table>

Table 22: Toxicity Management Guidelines for Parsaclisib (Group 4a) (Continued)

Adverse Event	Recommendation
PJP infection.	Interrupt tafasitamab and parsaclisib. Permanently discontinue tafasitamab and parsaclisib if PJP infection is confirmed.
CMV infection.	Participants with CMV viremia without associated clinical signs of CMV infection should be carefully monitored. Consider interrupting tafasitamab and parsaclisib for participants with CMV viremia and clinical signs of infection until the infection has resolved. Restart tafasitamab at the same dose and parsaclisib reduced by 1 dose level if approved by the medical monitor.
Varicella zoster infection.	Interrupt tafasitamab and parsaclisib. Restart tafasitamab and/or parsaclisib only by approval of the medical monitor.
Any Grade 1 or Grade 2 toxicity unless otherwise specified.	Continue tafasitamab and parsaclisib. Treat the toxicity; monitor as clinically indicated.

[a] Diarrhea accompanied by abdominal pain and/or mucus or blood in stool.

Table 23: Dose Levels for Parsaclisib (Group 4a)

	Dose Up to Week 8 (Day 1-Day 56)	Dose Week 8 onward (Day 57-EOT)
Starting dose	20 mg QD	2.5 mg QD[a]
First dose reduction	10 mg QD	1 mg QD
Second dose reduction	5 mg QD	NA

[a] Participants in Group 4 will receive 2.5 mg QD at Week 8 (Day 57) regardless of prior dose level unless dose was modified due to diarrhea/colitis guidelines.

6.7.5.5. Tafasitamab Dose Reductions, Interruption, and Discontinuation (Groups 2, 3, 4a, and 5)

Dose reductions of tafasitamab are not permitted in combination therapy. Drug interruptions or discontinuation may occur in case of severe IRRs, allergic reactions, infections, febrile neutropenia or severe hematologic toxicity.

In Groups 3, 4a, and 5, delaying the tafasitamab dosing is permitted for no more than 2 days (example: if dosing was planned on Day 8, delaying that dose is allowed up to Day 10) except for the loading dose on Day 4 of Cycle 1. Alternatively, a tafasitamab infusion may be skipped completely (eg, on Day 8 or Day 15) and the next scheduled dose will be administered.

In Group 2, delaying the tafasitamab dosing is permitted for no more than 2 days during Cycle 1 and for no more than 7 days during Cycles 2 and 3. Alternatively, a tafasitamab infusion may be skipped completely and the next scheduled dose will be administered. In case 2 consecutive tafasitamab infusions are skipped during the first 3 treatment cycles due to an AE, study drugs will be discontinued and the EOT visit (see Section 8.7) will be performed.

For further details of tafasitamab interruptions, see Table 18, Table 19, and Table 20. Details of tafasitamab discontinuation and interruption due to IRR/CRS is shown in Table 17.

6.7.5.6. Dose Modification of R-CHOP (Group 5)

The toxicity management of R-CHOP will be performed at the investigator's discretion and should follow local standard R-CHOP treatment guidelines.

6.7.6. Dose Modification in Phase 2 Combination Therapy (Group 6)

6.7.6.1. Criteria for Initiation of Cycle in Combination Therapy (Group 6)

The next cycle of treatment may begin on the scheduled Day 1 if the following criteria are met:

- ANC is $\geq 1.0 \times 10^9$/L.
- Platelet count $\geq 50 \times 10^9$/L and absence of active bleeding.
- No serious organ or other toxicity present.

If, based on medical judgment, the treating physician considers a change in laboratory parameter or AE not to be of any study treatment–related toxicity but to represent a natural fluctuation in or progression of the underlying disease, then it is at the physician's discretion and assessment of the individual risk/benefit ratio to determine whether the participant should be dosed. The decision and rationale behind the decision should be documented in the source data.

Because B-cell depletion and a subsequent reduction of absolute lymphocyte count is an anticipated pharmacologic effect of tafasitamab, dose modification can be exempted for participants with Grade 3 or 4 lymphocytopenia related to tafasitamab without any approval/consultation from the medical monitor in Group 6.

6.7.6.1.1. Cycle Initiation in Group 6

If the conditions in Section 6.7.6.1 are not met on the scheduled Day 1 of new cycle, the participant will be evaluated at least once every 7 days and a new cycle will not be initiated until the toxicity has resolved as described above.

If treatment needs to be interrupted for ≤ 28 days for the same study treatment–related toxicity, then the participant's treatment should continue, depending on the duration of treatment interruption, at the next Protocol-scheduled visit. No missed visits or doses of either study treatment should be made up.

If treatment with 1 study treatment needs to be interrupted for > 28 days for the same, persistent, study treatment–related toxicity, then the study treatment judged by the investigator to have caused the toxicity should be discontinued, and the participant should continue to be dosed with the other study treatment, as per Protocol.

If both study treatments need to be interrupted for > 28 days for the same, persistent study treatment–related toxicity, judged by the investigator to be related to both study treatments (LEN and tafasitamab), then the EOT visit (see Section 8.7) will be performed, and the participant will enter the follow-up phase.

6.7.6.2. Guidelines for Managing Hematological and Other Toxicities in Group 6

Participants will be evaluated for AEs at each visit with NCI CTCAE v5.0 used as a guide for grading severity. The dose of study drug(s) for each participant will be interrupted and/or modified following toxicity as described below (see Table 24). Guidance on managing LEN- and/or tafasitamab-specific toxicities is summarized in Table 25. Table 26 shows dose levels for LEN reduction. Individual decisions regarding dose interruption and reduction of LEN should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study treatment and the participant's underlying condition. Even if tafasitamab is interrupted due to toxicities, scheduled visits should still take place.

Table 24: Toxicity Management Guidelines for Hematological and Other Toxicities (Group 6)

Adverse Event	Value or Grade	Recommendation
Grade 3/4 neutropenia judged to be related to study drugs	ANC falls to $< 1.0 \times 10^9$/L for at least 7 days or ANC falls to $< 1.0 \times 10^9$/L with an associated body temperature ≥ 38.5°C or ANC falls to $< 0.5 \times 10^9$/L	Interrupt tafasitamab[a] and LEN dosing. Follow CBC every 7 days. Growth factors (G-CSF) and antimicrobial prophylaxis are to be used, as per local guidelines.
	ANC return to $\geq 1.0 \times 10^9$/L	Provided all other criteria are fulfilled, resume dosing of tafasitamab and/or LEN. LEN should be administered at the next lower dose level (see Table 26).
Grade 3/4 thrombocytopenia judged to be related to study drugs	Platelet count falls to $< 50 \times 10^9$/L	Interrupt tafasitamab[a] and LEN dosing. Follow CBC every 7 days.
	Platelet count returns to $\geq 50 \times 10^9$/L	Provided all other criteria are fulfilled, resume dosing of tafasitamab and/or LEN. LEN should be administered at the next lower dose level (see Table 26).
Other clinically significant toxicities judged to be related to study drugs and not listed in Table 25 (except for lymphocytopenia; see Section 6.7.6.1)	Grade 3/4	Interrupt the administration of the study drug(s)[a] to which the toxicity is judged to be related to up to 28 days until the toxicity has resolved to $\leq$ Grade 2.
	Toxicities resolve to $\leq$ Grade 2	Provided all other criteria are fulfilled, resume dosing of study drug(s). LEN should be administered at the next lower dose level (see Table 26).

[a] If, based on medical judgment, the treating physician considers a laboratory parameter change or AE not to be a study drug-related toxicity, but to represent a natural fluctuation in or progression of the underlying disease, then it is at the physician's discretion and assessment of the individual risk/benefit ratio to determine whether the participant should be dosed. The decision and rationale behind the decision should be documented in the source data.

Table 25: Toxicity Management Guidelines for LEN- and/or Tafasitamab-Specific Nonhematological Toxicity (Group 6)

Nonhematological Toxicity	Lenalidomide[a]	Tafasitamab
Thromboembolic events Grade 3-4	Interrupt LEN.	Continue tafasitamab infusion as per Protocol if clinically appropriate.
	If toxicity resolves to ≤ Grade 2, restart LEN at investigator's discretion (maintain dose level).	
Allergic reaction or hypersensitivity Grade 2	If related to LEN then interrupt the dose.	If related to tafasitamab then interrupt the dose.
	If toxicity resolves to ≤ Grade 1, restart LEN at the next lower dose level (see Table 26 for LEN dose modifications).	If toxicity resolves to ≤ Grade 1, tafasitamab may be resumed. If tafasitamab infusion is delayed for 3 or more days, then this infusion should be skipped and tafasitamab treatment continued only at the next scheduled timepoint.
Allergic reaction or hypersensitivity ≥ Grade 3	If related to LEN then discontinue permanently.	If related to tafasitamab then discontinue permanently.
	Note: If the causality cannot be determined and the AE may be related to LEN and/or tafasitamab, discontinue both drugs permanently.	
Rash Grade 3 nondesquamating (blistering)	If related to LEN then interrupt the dose. If the AE resolves to ≤ Grade 1, restart LEN at the same level (see Table 26 for LEN dose modifications).	If related to tafasitamab then interrupt the dose. If toxicity resolves to ≤ Grade 1, tafasitamab may be resumed. If tafasitamab infusion is delayed for 3 or more days, then this infusion should be skipped and tafasitamab treatment continued only at the next scheduled timepoint.
Rash Desquamating (blistering) ≥ Grade 3 OR Nondesquamating Grade 4	If related to LEN then discontinue permanently.	If related to tafasitamab then discontinue permanently.
	Note: If the causality cannot be determined and the AE may be related to LEN and/or tafasitamab, discontinue both drugs permanently.	
Tumor flare reaction Grade 3-4[b]	Interrupt LEN. If the AE resolves to Grade ≤ 1, restart LEN and maintain the same dose level (see Table 26 for LEN dose modifications)	Continue tafasitamab infusion as per Protocol if clinically appropriate.
Tumor flare reaction Grade 1-2[b]	Continue LEN.	Continue tafasitamab infusion as per Protocol.
Obstipation ≥ Grade 3	Interrupt LEN. If the AE resolves to ≤ Grade 2, restart at same dose level.	Continue tafasitamab infusion as per Protocol if clinically appropriate.
Other LEN related nonhematologic AEs ≥ Grade 3	Interrupt LEN. If the AE resolves to ≤ Grade 2, restart at the next lower dose level per the investigator's discretion.	Continue tafasitamab infusion as per Protocol if clinically appropriate.

[a] LEN may be given only on Days 1 to 21 of each cycle and must not be administered beyond this period.
[b] Tumor flare reaction is defined as constellation of signs and symptoms in direct relation to initiation of therapy. The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and electrolyte disturbances.

6.7.6.3. LEN Dose Modification Guidelines (Group 6)

Guidelines for dose interruption and permanent discontinuation of LEN is shown in Table 25.

If LEN dosing was interrupted during the previous cycle and was restarted with a 1-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. There will be no more than 1 dose reduction from one cycle to the next. Once a participant's LEN dose has been reduced, no dose re-escalation is permitted.

The daily oral dose of LEN may be reduced successively by 1 level from the starting dose (see Table 26).

In Group 6, LEN may be interrupted within the 21-day dose period and may be restarted within this period at the same dose or at Dose Level −1 but may not be extended beyond Day 21 of this cycle.

Participants with normal renal function who cannot tolerate Dose Level −4 and participants with moderate renal insufficiency who cannot tolerate Dose Level −2 are to be discontinued from LEN treatment but should continue therapy with tafasitamab if possible. For participants with moderate renal insufficiency, the dose of LEN may be increased to 15 mg QD if no Grade 3 or 4 LEN-related toxicities occur after 2 cycles.

Table 26: Dose Levels of LEN (Group 6)

Dose Level	Group 6 (Creatinine Clearance ≥ 60 mL/min)	Group 6 (Creatinine Clearance ≥ 30 to < 60 mL/min)
Dose Level +1	NA	15 mg daily on Days 1-21 of each 28-day cycle
Starting dose	25 mg daily on Days 1-21 of each 28-day cycle	10 mg daily on Days 1-21 of each 28-day cycle
Dose Level −1	20 mg daily on Days 1-21 of each 28-day cycle	5 mg daily on Days 1-21 of each 28-day cycle
Dose Level −2	15 mg daily on Days 1-21 of each 28-day cycle	5 mg every other day on Days 1-21 of each 28-day cycle
Dose Level −3	10 mg daily on Days 1-21 of each 28-day cycle	Not applicable
Dose Level −4	5 mg daily on Days 1-21 of each 28-day cycle	Not applicable

6.7.6.4. Tafasitamab Dose Reductions, Interruption, and Discontinuation (Group 6)

Dose reductions of tafasitamab are not permitted in combination therapy. Drug interruptions or discontinuation may occur in case of severe IRRs, allergic reactions, infections, febrile neutropenia or severe hematologic toxicity. Delaying the tafasitamab dosing is permitted for no more than 2 days (example: if dosing was planned on Day 8, delaying that dose is allowed up to Day 10) except for the loading dose on Day 4 of Cycle 1. Alternatively, a tafasitamab infusion may be skipped completely (eg, on Day 8 or Day 15) and the next scheduled dose will be administered. For further details of tafasitamab interruptions, see Table 24 and Table 25. Details of tafasitamab discontinuation and interruption due to IRR/CRS is shown in Table 17.

6.8. Concomitant Medications and Procedures

Participants may continue the medications they were receiving at screening. Participants may receive concomitant medications that are medically indicated as SoC for the treatment of symptoms and intercurrent illnesses such as diabetes, hypertension, bronchial asthma, or chronic obstructive pulmonary disease. Participants may also receive therapy to mitigate side effects of the study treatment as clinically indicated, as well as best supportive care as per institutional guidelines. All concomitant medications and treatments must be recorded in the eCRF. Any medication participants receive from study participation (date of ICF signature) to 90 days after the last dose of study treatment, or until the participant begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered for the management of SAEs (defined in Section 9.2) should be recorded regardless of when they are provided.

6.8.1. Premedication for Tafasitamab Infusion (All Groups)

Premedication for tafasitamab is required at least during the first 3 infusions (during the first 4 infusions in Group 2) in each participant. The premedication for participants who do not experience any IRRs during the first 3 infusions (4 infusions in Group 2) will be optional for subsequent infusions at the discretion of the investigator.

Tafasitamab infusions should be administered to participants after premedication with an antipyretic analgesic such as acetaminophen, an antihistamine such as chlorpheniramine maleate and glucocorticosteroids (eg, 100 mg PSL or equivalent, PO or IV) approximately 30 to 60 minutes before the start of the infusion (unless contraindicated).

In Group 5, Day 1 corticosteroid dose being part of CHOP (100 mg PSL or equivalent, PO or IV) can be used as further component of premedication before tafasitamab infusion.

6.8.2. Prophylaxis for Tumor Lysis Syndrome (All Groups)

In participants with high risk of TLS (eg, participants with large tumor burden/bulky disease, elevated LDH, or high proliferation rate of tumor cells), TLS prophylaxis should be considered. All approaches to mitigate the risk of developing TLS, such as adequate hydration or hypouricemic agents (eg, rasburicase), may be used in high-risk participants as per institutional guidelines. Participants with high-risk of TLS should be followed closely and appropriate laboratory monitoring should be performed as per institutional guidelines.

6.8.3. Prophylaxis for Venous Thromboembolism (Groups 2, 3, 5, and 6)

Prophylaxis of VTE is recommended in Groups 2, 3, 5, and 6 due to increased risk of thrombosis in participants treated with LEN without prophylaxis. The choice of VTE prophylaxis agent is at investigator's discretion and should be tailored to the participant's individual risk/benefit profile by taking into account the individual thrombotic risk, bleeding risk, and the quality of compliance with the VTE prophylaxis. The prophylactic agent will be reimbursed by the sponsor.

6.8.4. Prophylaxis for *Pneumocystis jirovecii* (Group 4a Only)

All participants in Group 4 are required to receive a standard PJP prophylaxis regimen determined by the investigator. Examples of standard PJP prophylaxis therapies for this population include trimethoprim-sulfamethoxazole, atovaquone, diphenyl sulfone with or without pyrimethamine, and pentamidine (diphenyl sulfone and pentamidine are not approved for PJP prophylaxis in Japan; NCCN 2021). Prophylaxis should be given while participants are receiving parsaclisib treatment and should continue for 3 months after the last dose of parsaclisib.

The prophylactic agents will be obtained from commercial supplies and will be reimbursed by the sponsor. The investigators are responsible for ensuring that participants receive commercially available supplies of the selected prophylactic agents. Further details are available in the Pharmacy Manual.

6.8.5. Prophylaxis for Febrile Neutropenia (Group 5)

As per the National Comprehensive Cancer Network guidelines, CHOP belongs to chemotherapy regimens with an intermediate risk for febrile neutropenia. There is the potential for increased neutropenia risk with the addition of monoclonal antibodies such as RTX or tafasitamab, as well as LEN. To mitigate the risk of febrile neutropenia, primary neutropenia prophylaxis (eg, G-CSF or Peg-G-CSF) is mandatory in Group 5. The dose and schedule of the selected drug will be done according to local practice and institutional guidelines. The prophylactic agent will be reimbursed by the sponsor.

6.8.6. Central Nervous System Prophylaxis (Group 5)

Central nervous system prophylaxis with intrathecal chemotherapy may be given according to institutional practice. Central nervous system prophylaxis with IV methotrexate is allowed only if it was preplanned, and it may be administered only after the last treatment cycle and after the EOT tumor assessment by PET/CT.

6.8.7. Steroid Prephase (Group 5)

In participants with urgent need for a steroid prephase before initiation of therapy, the use of oral PSL 25-100 mg/day or equivalent over 7 days is allowed after tumor investigations (imaging, blood samples) for screening have been performed.

In exceptional circumstances and at the discretion of the investigator, the steroid prephase can be started prior to acquisition of PET.

Any prephase steroid use must be recorded in the eCRF and adequately documented and justified in the participant's source data.

6.8.8. Permitted Medications and Procedures

Localized radiotherapy will be permitted if administered as treatment for pain or impending compression fractures and with prior approval of the medical monitor.

Group 5 only, preplanned radiotherapy: Preplanned local radiotherapy may be administered to initial sites of bulky or extranodal disease according to institutional guidelines. Preplanned radiotherapy may be administered only after the last treatment cycle and after the EOT tumor assessment by PET/CT. In this case, the radiotherapy will not count as a next antilymphoma treatment. All unplanned radiotherapy administered to participants or a decision to switch radiotherapy to a different lesion will be considered as a next antilymphoma treatment.

Groups 1, 2, 3, 4a, and 6: Palliative use of corticosteroids before initiation of therapy is allowed at doses up to PSL 20 mg/day or equivalent.

6.8.9. Restricted Medications and Procedures (Group 4a Only)

- Use of weak or moderate inducers or inhibitors of CYP3A4 (see Appendix C) is discouraged, and investigators should seek other options where possible. Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.
- For participants receiving parsaclisib, P-glycoprotein substrates of clinical relevance should be used with caution (ie, aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan).

6.8.10. Prohibited Medications and Procedures

The use of concurrent antineoplastic therapies other than study drugs and R-CHOP, including, but not limited to, chemotherapies, hormonal therapy, immunotherapy, biological response modifiers, mAbs with or without conjugation, radioisotopic therapies, stem cell transplant and targeted small molecules are not permitted during the entire treatment period of this study.

After disease progression/relapse has been recorded or if an end-of-treatment tumor assessment indicates residual (PMR) or no metabolic response (SD), additional antineoplastic therapies are permitted at the discretion of the investigator and in accordance with the local guidelines. They should be recorded in the eCRF as next antilymphoma treatments. Participants should be encouraged to complete the follow-up period in such case and may stay in the study unless they participate in another clinical study.

Because of the immunosuppressive effects of the study treatment, exposure to a live vaccine within 21 days prior to study treatment through 6 months after the last dose is prohibited.

Use of potent inducers and inhibitors of CYP3A4 are prohibited in Group 4a (see Appendix C and consult your local pharmacist). Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole in Group 4a.

6.9. Treatment After the End of the Study

Participants who continue on tafasitamab and/or parsaclisib at the end of the study (see Section 4.2) may continue until meeting any of discontinuation criteria (see Section 7.1.1).

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

Participants **must** be discontinued from study treatment for the following reasons:

- The participant becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for safety (all groups) and/or disease status (Group 5). Participants who choose to complete the treatment when the treatment period exceeds 2 years (Phase 1b only) may also be included.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- The participant has an objective radiographic tumor response of PD/PMD.
- The incidence of SPM.
- The participant has experienced an unacceptable toxicity, including the following:
  - DLT. DLTs occurring in Dose Level 2 or 3 (see Table 12) in Part 1 Group 2 may be exceptional. However, participants who recover from the toxicity may continue study treatment with approval from the medical monitor and the participant's informed consent.
  - Persistent AE requiring a delay of cycle initiation for more than allowed duration in each group (see Section 6.7.4 and Section 6.7.5).
  - AE requiring skipping 2 consecutive tafasitamab infusions during the first 3 treatment cycles in Group 2 (see Section 6.7.5.5).
- The participant develops ILD.
- The study is terminated by the local health authority, IRB, or IEC.
- At the time of obtaining marketing authorization in Japan for tafasitamab in DLBCL, or the study is terminated by the sponsor, whichever comes first.

A participant **may** be discontinued from study treatment as follows:

- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be discontinued from study treatment.
- If a participant is noncompliant with study procedures or study drug/treatment administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in the SoAs (see Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9). The last date of the last dose of study treatment and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.
- The EOT visit should be performed and date recorded.
- The status of the participant should be updated to EOT in the IWRS.
- Participants must be followed until the time of the follow-up visit for the EOS (if study treatment–related toxicities continue, see Section 8.8.1).

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up [all groups] and/or disease assessment [Group 5] and/or disease/survival assessment [Group 6]), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety (all groups) and/or efficacy assessments (Group 5) and/or disease/survival assessments (Group 6).

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See the SoA (see Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the country in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is enrolled in the study (Cycle 1 Day 1). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility will be performed during the screening period.

Procedures conducted as part of the participant's routine clinical management (eg, laboratory analyses, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed within 28 days of Cycle 1 Day 1.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes it is needed. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to determine eligibility.

See Sections 5.4 and 5.5 for information regarding screen failures and replacement of participants, respectively.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact the IWRS to obtain the participant ID number during screening. Upon determining that the participant is eligible for enrollment, the IWRS will be contacted to register the treatment assignment by investigator or qualified designee. Additionally, the IWRS will be contacted at each regular study visit to update the study treatment supply. Additional details are provided in the IWRS Manual.

8.1.4. Demography and Medical History

8.1.4.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment that are considered to be clinically significant by the investigator.

8.1.4.2. Disease Characteristics and Treatment History

A lymphoma-targeted medical and treatment history will be collected at screening. Details regarding the participant's NHL including disease staging, date of diagnosis, relevant disease characteristics, prior treatments and ECOG performance status criteria (see Appendix E) will be recorded. In order to reflect the participant's status at the time of screening, the standard Ann Arbor staging system used for NHL reflecting the number of sites of involvement and their relation to the diaphragm, the existence of B-symptoms, and the presence of extranodal disease, will be documented. Additionally, the disease risk assessment as per IPI (see Appendix F) will be recorded for participants with DLBCL and the disease risk assessment as per FLIPI (see Appendix G) will be recorded for participants with FL or MZL.

Screening for CNS lymphoma involvement is not mandatory. Lumbar puncture with cerebrospinal fluid evaluation (cytology, flow cytometry) and/or head CT/ head MRI is recommended in participants with high-risk disease to exclude CNS lymphoma involvement.

8.2. Efficacy Assessments

Efficacy will be evaluated in terms of ORR, CRR, DOR, and PFS for each group; moreover, for Group 6, OS, TTNT, and DCR will also be evaluated. See Section 10.4.1 for definitions of efficacy terms. Additional efficacy assessments after EOT until disease progression for participants who discontinue study treatment due to a reason other than PD are preferable.

8.2.1. CT/MRI/PET-CT

Radiographic assessments will be performed at the timepoints indicated in the SoA. For participants in Groups 3 and 6, radiographic assessments will be performed following the site imaging manual. Every effort should be made to use the same scan modality for all assessments. If progression is diagnosed purely on the basis of clinical symptoms, a CT-scan or PET/CT is required within 4 weeks of clinical diagnosis. If progression of disease is judged by radiographic assessment, this assessment can be used for the EOT assessment. If participants are withdrawn from treatment for reasons other than progression of disease, radiographic assessments are only required at the EOT visit if they were not performed in the cycle before the EOT visit. Radiographic assessments will be performed as per site standard of care for participants whose treatment period exceeds 2 years and follow Table 8 in Groups 1, 3, and 4a.

In addition, for participants who continue study treatment after the final data cutoff, radiographic assessments will be performed in accordance with the standard practice of the study site (see Table 9). These images will not be required to be submitted to the central imaging laboratory (participants in Group 3 and Group 6).

CT/MRI: For all participants, all CT scans must cover neck, chest, abdomen, and pelvis as indicated in the schedule of assessments when a radiographic response assessment is performed. A CT at baseline is required. The CT portion of PET/CT will be acceptable in place of CT for tumor measurement and disease assessment *only* when the CT portion is of adequate diagnostic-quality and using adequate IV contrast. CT may be performed in lieu of PET/CT if the participant discontinues from treatment within Cycle 1. Magnetic resonance imaging may be used in lieu of CT for participants with contraindications to the administration of contrast agents or due to other medical reasons, at the same timepoints as CT, or in addition to CT, at the discretion of the investigator (in this case, MRI may be performed as/when appropriate). The method used at baseline should be used throughout the study unless otherwise medically indicated. If CT is performed within the allowance for the planned next cycle but the actual initiation of the next cycle is delayed, the event of out of allowance will not be counted as a protocol deviation if the medical monitor agrees.

PET/CT: A PET/CT is required at baseline. For participants with a PET-avid lesion at baseline, a PET/CT should be also performed at postbaseline visits indicated in the SoA but can be omitted if PET definitely would not change the response assessment according to the clinical judgment of the investigator (eg, CT already shows PD). If available and of acceptable quality, previously performed PET/CT examinations, in accordance with the SoC, that were performed up to 4 weeks before the date of informed consent may be used for a participant's baseline central radiology assessment. The Deauville 5-point scale is required to assess response (Cheson et al 2014).

Additional PET/CT or CT or MRI examinations may be performed by the investigator in the course of the study, if deemed necessary (eg, to confirm the occurrence of a PD/PMD or to make important treatment-related decisions). Whenever feasible, in such cases the investigator should seek prior approval of the sponsor for the additional imaging. If it is impossible for the participant to have their PET examination in fasted state, adequate procedures should be in place to measure and control blood glucose level.

All scans conducted in Group 3 during the study will be provided to a central imaging laboratory for independent radiological and clinical evaluation by IRC according to the guidelines of the IWG (Cheson et al 2007). All scans conducted in Group 6 during the study will be provided to a central imaging laboratory for independent radiological and clinical evaluation by IRC according to the Lugano criteria (Cheson et al 2014) and the IWG (Cheson et al 2007). For all groups, investigator's assessment for response will follow the Lugano criteria (Cheson et al 2014). Details will be given in the imaging charter.

8.2.2. Bone Marrow Biopsy and Aspiration

At the screening visit, a uni- or bilateral bone marrow aspirate and a biopsy should be obtained to assess bone marrow involvement. Results from a bone marrow examination performed within the 4 weeks before the date of informed consent will be acceptable if the participant's disease has been stable since then.

Subsequently, bone marrow examination will be performed and the sample(s) sent to a local histopathology laboratory to confirm CR, or as clinically indicated. If the bone marrow does not have lymphoma involvement at baseline, a repeat marrow examination is not required to confirm indication of CR on imaging. The repeated bone marrow examination is also not required for participants in whom bone marrow has already been cleared of the infiltrate at previous evaluation, that is, their previous response was CR. All bone marrow examinations should include a unilateral aspiration and biopsy, when feasible.

Histological examination of the bone marrow should be performed locally at the Protocol-specified timepoints (see Table 3, Table 4, Table 5, Table 6, and Table 7).

8.2.3. Health Economics

Health Economics parameters are not evaluated in this study.

8.3. Safety Assessments

See Section 6.6 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 90 days after the last dose of study treatment or until the start of new antilymphoma therapy, whichever occurs first. SPMs will be monitored as events of interest and should be included as part of the assessment of AEs throughout the course of the study. Investigators are to report any SPMs as AEs, regardless of causal relationship to the study treatments, occurring at any time, for the duration of the study, from Cycle 1 Day 1 up to and including the follow-up period. Adverse

events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study treatment. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up on AEs that are serious, considered related to the study treatment/procedures, or that caused the participant to discontinue study treatment. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits, or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AEs of special interest (as defined in Section 9.5.1), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment. Investigators should pay special attention to clinical signs related to previous serious illnesses.

At the screening, during Cycle 1 and at EOT visit, a comprehensive physical examination (indicated as "C" in the SoAs) should be conducted. The comprehensive physical examination will include assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination.

During the study, participants will be assessed by the investigator or medically qualified designee per institutional SoC as disease specific physical examination (indicated as "D" in the SoAs). These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the AE eCRF.

8.3.3. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status (Oken et al 1982; see Appendix E) will be assessed. Performance status must be assessed by a medically qualified individual and recorded in the eCRF.

8.3.4. Vital Signs, Body Weight, and Height

Vital sign measurements (to be taken before blood collection for laboratory tests), include blood pressure, pulse, SpO_2, and body temperature. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position preferably after 5 minutes of rest. Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment.

On the day of tafasitamab administration, vital signs are to be obtained before tafasitamab infusion and then at least 3 times during the infusion (SpO_2 is not required during the infusion) and as clinically indicated in Groups 1, 2, 3, 4a, and 5. Note that vital signs during the infusion are not mandatory from Cycle 13 onward in Groups 1, 3, and 4a but should be added as clinically indicated. On the day of tafasitamab administration, vital signs are to be obtained before tafasitamab infusion and as clinically indicated in Group 6. The frequency or the length of the monitoring period may be adapted if clinically indicated, for example, if in the opinion of the investigator the vital sign results at the time of event onset are clinically significant. In such a case the participant's vital sign measurements should continue to be recorded until they have returned to normal or tafasitamab levels and corresponding AEs to be recorded. Body weight will be assessed at each study visit specified in SoA (see Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9). Height is measured at screening only.

8.3.5. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Table 3, Table 4, Table 5, Table 6, and Table 7). All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

The investigator will evaluate the clinical significance of each ECG value outside the reference ranges, according to the nature and degree of the observed abnormality. Any new abnormal values or those deteriorating from baseline considered to be clinically significant should be reported as AEs.

If clinically significant abnormalities are observed or artifacts are present that result in an inability to adequately interpret the results, the ECG will be repeated.

8.3.6. Echocardiogram (Group 5 Only)

Echocardiogram will be obtained at screening in Group 5 only. The cardiac function including assessment of LVEF (data will be collected in the eCRF) is evaluated. LVEF is the fraction of chamber volume ejected in systole (stroke volume) in relation to the volume of the blood in the ventricle at the end of diastole (end-diastolic volume) and is obtained from local examination.

8.3.7. Interstitial Lung Disease Assessments

Interstitial lung disease assessments includes chest radiography, SpO_2 measurement, and auscultation. The SpO_2 measurement is included in vital signs and the auscultation is included in the physical examination. If the CT/MRI for efficacy assessment includes chest, additional assessment is not required.

8.3.8. Laboratory Assessments

See Table 27 for the list of clinical laboratory tests to be performed and the SoA (see Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9) for the timing and frequency. A certified laboratory local to the investigative site will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis). The investigative site will enter the laboratory results and laboratory normal ranges into the eCRF. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 90 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

Screening laboratory assessments must be performed within 28 days of Cycle 1 Day 1. If available, previously performed laboratory assessment that were done prior to the date of informed consent may be used for screening. If performed more than 2 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1. Laboratory samples collected on the day of tafasitamab administration must be performed before study treatment administration. After Cycle 1, predose laboratory procedures can be conducted up to 24 hours before study treatment administration (within the 1-day study window), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

Table 27: Required Laboratory Analytes

<table>
<tr><th>Chemistry</th><th>Hematology</th><th>Urinalysis</th><th>Serology</th><th>Coagulation</th></tr>
<tr><td rowspan="3">Albumin
Alkaline phosphatase
ALT
AST
Amylase
Blood urea nitrogen or urea
C-reactive protein
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase
Lipase
Phosphate
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein
Uric acid</td><td rowspan="3">Complete blood count, including:
• Hemoglobin
• Hematocrit
• Platelet count
• Red blood cell count
• WBC count

Differential count, including:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils

Absolute values must be provided for:
• WBC differential laboratory results</td><td>pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein</td><td>Hepatitis B surface antigen
Hepatitis B surface antibody
Hepatitis B core antibody
HBV DNA
(if antibody positive)
HCV antibody
HCV RNA
(if antibody positive)
HIV
CMV DNA (Group 4aonly)</td><td>PT
aPTT
INR
FDP</td></tr>
<tr><td>Immunochemistry</td><td>Endocrine Function (Group 5 only)</td><td>Pregnancy Testing</td></tr>
<tr><td>IgG
IgA
IgM</td><td>TSH
T4/FT4
T3/FT3</td><td>Female participants of childbearing potential only require a serum test at screening and EOT and a urine pregnancy test before the first dose on Cycle 1 Day 1.
Additionally, pregnancy tests (urine) will be repeated once in every cycle of treatment.</td></tr>
</table>

Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data or to rule out a diagnosis.

8.3.8.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening, at the EOT visit, and at the safety visit(s) during follow-up. Urine pregnancy tests will be performed during the treatment period. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test. Urine pregnancy tests can be replaced with serum pregnancy tests.

If the serum pregnancy test is negative after a urine test was positive, the investigator will assess the potential benefit/risk to the participant and determine whether it is in the participant's best interest to resume study treatment and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.7 for reporting requirements.

8.3.8.1.1. Requirement of Pregnancy Testing (Groups 2, 3, 5, and 6)

The timing of pregnancy testing for FCBP in Groups 2, 3, 5, and 6 must follow the timing defined in the Section 3.1 of the Global PPP (see Appendix B). Urine pregnancy tests must have a sensitivity of at least 25 mIU/mL as required in the Global PPP (see Appendix B).

An FCBP with regular menstrual cycles must undergo a pregnancy test weekly for the first 28 days and then every 28 days (± 2 days) while taking LEN, at LEN discontinuation, and 28 days after the last dose of LEN.

An FCBP with irregular menstrual cycles must undergo a pregnancy test weekly for the first 28 days and then every 14 days (± 2 days) while taking LEN, at LEN discontinuation, and 14 and 28 days after the last dose of LEN.

While taking LEN, if an additional pregnancy test is performed within the 28-day period (14 days for irregular cycles), this test result can be accepted. Pregnancy testing is to continue every 28 days (every 14 days for irregular cycles) starting from the day of the additional pregnancy test. If pregnancy testing is performed at the defined intervals, the pregnancy test does not need to be repeated on Day 1.

8.3.8.2. Serology

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 27. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

Participants with occult HBV infection, defined as negative HBsAg and positive total hepatitis B core antibody and negative HBV DNA, are eligible and must undergo ongoing DNA testing (irrespective of prophylactic treatment) as described in the SoA (see Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9).

If HBV DNA becomes detectable during treatment, participants should be prophylactically treated and followed up for potential hepatitis B reactivation as per local guideline, Japan Society of Hepatology Guidelines (2020), or institutional guidelines for CD20 antibodies such as RTX. If the HBV DNA assay is positive, then participants can only stay in the study if they are

assessed by a physician experienced in the treatment of hepatitis B and pre-emptive treatment is initiated, if deemed appropriate, and/or according to local practice/guidelines.

8.4. Pharmacokinetic Assessments

Serum samples for tafasitamab PK analysis will be collected according to the SoA as specified in Table 28. A maximum of 2 samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual.

8.4.1. Blood Sample Collection for Serum Pharmacokinetics

Timing of blood PK assessments is outlined in Table 28. The exact dates and times of the PK blood collection need to be recorded in source documents. After the tafasitamab PK sample is drawn, participants will begin the study treatment. Preinfusion is defined as within 24 hours before administration of study treatment. Adjustments to the timing of blood sampling may be made based on emerging PK data. Pharmacokinetic parameters will be determined by noncompartmental analysis using Phoenix WinNonlin v6.3 or later (Pharsight Corporation).

For participants who continue study treatment after the final data cutoff, further PK blood collection will not be required (see Table 9).

Table 28: Tafasitamab Pharmacokinetic Blood Sample Timing

Group	Study Visit	PK Timing of Sample
1, 3, and 4a	Cycle 1 Day 1	• Preinfusion • Immediately after tafasitamab infusion (≤ 10 min) • 1 hour (± 15 min) postinfusion • 4 hours (± 20 min) postinfusion
	Cycle 1 Day 2	• 24 hours (± 1 hour) postinfusion on Day 1
	Cycle 1 Days 4[a], 8[a], 15[a], and 22	• Preinfusion • 1 hour (± 15 min) postinfusion
	Cycle 2 Days 1, 22	• Preinfusion • 1 hour (± 15 min) postinfusion
	Cycle 3 Days 1, 22	• Preinfusion • 1 hour (± 15 min) postinfusion
	Cycle 4 and beyond every 4 cycles (8, 12, etc) Day 1	• Preinfusion
	Safety follow-up/EOS visit	• Untimed sample

Table 28: Tafasitamab Pharmacokinetic Blood Sample Timing (Continued)

Group	Study Visit	PK Timing of Sample
2	Cycle 1 Days 1, 4, 8, and 15	• Preinfusion • 30 min (± 15 min) postinfusion
	Cycle 2 Days 1, 15	• Preinfusion • 30 min (± 15 min) postinfusion
	Cycle 3 Days 1, 15	• Preinfusion • 30 min (± 15 min) postinfusion
	Cycle 4-12 (every other cycles, ie, Cycle 4, 6, 8, 12) Day 1	• Preinfusion • 30 min (± 15 min) postinfusion
	Cycle 12 Day 28[b]	• Untimed sample
	EOT[c]	• Untimed sample
5	Cycle 1 Day 1	• Preinfusion • Immediately after tafasitamab infusion (≤ 10 min) • 1 hour (± 15 min) postinfusion • 4 hours (± 20 min) postinfusion
	Cycle 1 Day 2	• 24 hours (± 1 hour) postinfusion on Day 1
	Cycle 1 Days 8[a], 15[a]	• Preinfusion • 1 hour (± 15 min) postinfusion
	Cycle 2 Day 1[a], Cycles 3-6 Day 1	• Preinfusion • 1 hour (± 15 min) postinfusion
	Safety follow-up	• Untimed sample
6	Cycle 1 Days 1, 4, and 15	• Preinfusion • 1 hour (± 15 min) postinfusion
	Cycle 2 Days 1 and 15	• Preinfusion • 1 hour (± 15 min) postinfusion
	Cycle 3 Days 1 and 15	• Preinfusion • 1 hour (± 15 min) postinfusion
	Cycle 4 and beyond every 4 cycles (8, 12, etc) Day 1	• Preinfusion
	EOT	• Untimed sample

[a] If a participant experiences Grade 3 IRR during the first infusion (at Cycle 1 Day 1), and the subsequent 3 infusions (Groups 1, 3, and 4a: Day 4, Day 8, Day 15; Group 2: Day 8, Day 15, Cycle 2 Day 1; Group 5: Day 8, Day 15, Cycle 2 Day 1) for the participant are split (see Section 6.7.1), the PK sampling timing for the remaining two-thirds on the next day will be the same as the initial day.

[b] Samples to be collected on Cycle 12 Day 28 (± 2 days); if overlapping with Cycle 13 Day 1 visit, samples should be taken prior to tafasitamab infusion.

[c] EOT samples will not be collected for participants treated with tafasitamab beyond Cycle 12.

8.4.2. Immunogenicity Assessments (Anti-Tafasitamab Antibodies)

Serum samples for anti-tafasitamab antibody analysis will be collected from all participants according to the SoA (see Table 3, Table 4, Table 5, Table 6, Table 7, and Table 8). Serum samples for anti-tafasitamab antibody analysis will be handled and stored as specified in the Laboratory Manual.

For participants who continue study treatment after the final data cutoff, further blood collection for immunogenicity assessments will not be required (see Table 9).

8.5. Pharmacodynamic and Translational Assessments

Not applicable.

8.6. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessment that is performed at those visits and is related to AE (eg, occurrence, recovery, severity) or change of study treatment should be recorded in the eCRF.

8.7. End of Treatment and End of Study

When the participant permanently discontinues study treatment, whether the participant is terminating the study early or the participant has completed the study, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The participant should be encouraged to return for the follow-up visit.

If a participant who intends to undergo study treatment is judged to be discontinued from the study, the assessments that were intended to be the predose assessments can be used as EOT assessments. Other assessments for EOT can take place within 7 days from the date of judgment for discontinuation. If the assessments after the last dose and within 7 days before the date of judgment for discontinuation are available, they may be used as the EOT assessment.

The EOS visit is scheduled approximately 90 days after EOT in Groups 1, 2, 3, and 4a, which is for the purpose of safety follow-up, including PK and ADA analyses. In Group 5, the EOS visit is scheduled about 18 months after EOT. The disease follow-up visit is scheduled every 3 months between EOT and EOS in Group 5. The safety assessments can be performed at the same time as the initial disease follow-up. If a participant in Group 5 experiences PD before the initial disease follow-up, only safety assessments are performed approximately 90 days after EOT. If a participant in Group 5 experiences PD during the disease follow-up period, the disease follow-up visit is finished at the time of PD and the assessments for EOS are performed.

Regardless of treatment group, participants who are continuing study treatment after marketing authorization is obtained for tafasitamab in Japan and approval for its indication in DLBCL shall discontinue administration of the investigational product (EOT) and undergo safety follow-up/EOS assessments.

The study will be considered complete after the last participant has completed the EOS visit.

8.8. Follow-Up

8.8.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 90 days after the EOT visit (or after the last dose of study treatment if the EOT visit was not performed) as described in Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9). Adverse events and SAEs must be reported up until 1) at least 90 days after the last dose of study treatment or the start of a new antilymphoma therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period. If the toxicities are deemed irreversible and the investigator considers to not further pursue them, the reason should be recorded in medical record.

If a participant is scheduled to begin a new antilymphoma therapy before the end of the safety follow-up period, the safety follow-up visit should be performed before a new antilymphoma therapy is started.

In Group 5, for participants who discontinue study treatment due to disease progression and will not move to the disease status follow-up period, the safety follow-up visit should be scheduled 90 days after the EOT visit, or before the participant begins a new antilymphoma therapy, whichever occurs first.

8.8.2. Post-Treatment Disease Follow-Up (Group 5 Only)

Participants who complete study treatment until Cycle 6 or discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should be assessed every 3 months ± 2 weeks by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until:

- The start of new anticancer therapy.
- Disease progression.
- Death.
- The end of the study (18 months after EOT).

8.8.3. Post-Treatment Disease/Survival Follow-Up (Group 6 Only)

Participants who discontinue study treatment for reasons other than disease progression will move into the disease status follow-up period and should be assessed by radiologic imaging as specified in Table 7 to monitor disease status. Every effort should be made to collect imaging information regarding disease status until the start of new anticancer therapy or disease progression. Sites are required to submit imaging tumor assessments during post-treatment disease follow-up for independent review.

Once a participant has received the last dose of study treatment and has confirmed disease progression or starts a new anticancer therapy, the participant will move into the survival follow-up period and should be contacted by telephone, email, or visit at least every 12 weeks (± 2 weeks) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

For participants who entered the survival follow-up period of the study, the site will use continuing participant records to supply data on subsequent treatment regimens, tumor assessments (if discontinued treatment for a reason other than progression), and OS in the eCRF. For participants who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases as specified in Table 7.

The disease/survival follow-up visit is scheduled every 12 weeks (± 2 weeks). The disease/survival follow-up period will last for a maximum of 3 years from Cycle 1 Day 1 for each participant.

Participants in Group 6 who are in the disease or survival follow-up period at the time of the final data cutoff will no longer be required to undergo further follow-up visits. The follow-up will be discontinued as of the data cutoff date, and the study will be terminated. An EOS visit, as specified in Table 9, will be conducted accordingly.

9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related. • An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Additional Guidance for Events <u>Meeting</u> the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study treatment administration are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dosing errors of a study treatment (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. If the condition is present before entering the study, then it should be captured as medical history. • Pre-existing diseases or conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation. • Second primary malignancies.

9.2. Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurs. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE. Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) are not considered SAEs.
d. Results in persistent or significant disability/incapacity The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is an important medical event An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse, or suspected transmission of an infectious agent via a medicinal product. Secondary malignancies should always be considered as SAEs. An event which may lead to disability is also considered an important medical event. It includes a case that is exposed to a risk of dysfunction to an extent that interferes with daily life when the adverse drug reaction occurs. It does not include an adverse drug reaction that, had the reaction been more severe, may have caused disability.

9.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. Conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Event Form in the eCRF page.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Study Reference Manual.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

To the extent possible, each AE/SAE should be evaluated to determine the following:

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit (90 days after the EOT visit).
- The action taken with regard to the study treatment as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age-appropriate activities of daily living.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. If appropriate, the relationship to the combination may be assessed as well.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the Reference Safety Information in the IB and/or Product Information, for study treatment, or marketed products, respectively, in making his/her assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • Once an AE is detected, it should be followed in the AE eCRFs until the end of safety follow-up periods. All SAEs and nonserious AESIs should be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome. • When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology. • Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. • Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study treatments, reference therapy, or study procedure), all SAEs occurring after the participant has signed the ICF through 90 days from the last dose of study treatment, or until the participant starts a new anticancer therapy must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available. This information must also be reported immediately to the head of the study site.

Investigators are not obligated to actively seek SAE information after the safety follow-up visit. If the investigator learns of any SAE, at any time during this period, and he/she considers the event to be reasonably related to the study treatment or study participation, then the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 9.5.1) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Prompt notification by the investigator to the sponsor regarding an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the tafasitamab IB, parsaclisib IB, or LEN PI for the study treatment (new occurrence) and is thought to be related to the sponsor's study treatment, the sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same treatment that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the PMDA and relevant ethics committees in accordance with national regulatory requirements in Japan.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF.
- The investigator must report within 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available. The contact information for Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual).
- In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Study Reference Manual for details and for the email address or fax number).
- Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study treatment because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.
- Contacts for SAE reporting can be found in the Study Procedures Manual.

9.5. Events of Clinical Interest

9.5.1. Adverse Events of Special Interest by eCRF (All Groups)

The following AEs will be followed as part of standard safety monitoring activities. AESIs should be captured in the eCRF.

- AESIs for tafasitamab are TLS, IRRs and allergic reactions to study treatment ≥ Grade 3, CRS, SPM, hepatitis B reactivation, progressive multifocal leukoencephalopathy.
- AESIs for LEN: Second primary malignancies.
- AESIs for parsaclisib are ALT ≥ 5 × ULN, AST ≥ 5 × ULN, colitis, diarrhea Grade ≥ 2, rash Grade ≥ 2, intestinal perforation, pneumonitis, *Pneumocystis jirovecii* infection, CMV infection, herpes simplex virus infection, varicella zoster virus infection, exfoliative dermatitis.

Adverse events of special interest should be captured in the eCRF.

9.5.2. Adverse Events of Special Interest by Category and Preferred Term (Groups 2 and 6 only)

A second method will be used to identify AESIs programmatically using standardized MedDRA queries, custom MedDRA queries, and/or selected preferred terms. The same high-level terms as described in Section 9.5.1 will be used for this analysis; refer to the SAP for further details.

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a participant during maternal or paternal exposure to study treatment, the following procedures should be followed in order to ensure safety:

- The study treatment must be discontinued immediately (female participants only).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study treatment to any pregnancy outcome, as well as follow-up to the first

well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy of a study participant must be recorded on the Serious Adverse Event Report Form and submitted to the sponsor or its designee.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs (if occurring in the study participant) and must be reported as described in Section 9.4. If an abnormal pregnancy outcome is reported in a study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.8. Warnings and Precautions

Special warnings or precautions for the study treatment, derived from safety information collected by the sponsor or its designee, are presented in tafasitamab IB and parsaclisib IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

Infection with SARS-CoV-2, the coronavirus that causes COVID-19, is more frequent and severe in patients with hematologic dysfunction (Jee et al 2022). The presence of hematologic malignancy, baseline neutropenia and lymphopenia, B-cell depletion, and other factors have been identified as risk factors for loss of humoral immunity to COVID-19, poor vaccine response, viral persistence, and severe disease (Lee et al 2022, Lyudovyk et al 2022, Shree et al 2022). Targeting B-cell function, proliferation, and survival with various therapies are current strategies for improving the outcome of several hematologic malignancies. Investigators and participants need to be aware of these potential risks and consider the local standards of care and available therapies for disease prevention, vaccination, and infection management of COVID-19.

PI3K-delta inhibition with parsaclisib alone or in combination with other therapies, which may also suppress humoral immunity, has the potential to negatively impact SARS-CoV-2 infection risk, vaccine effectiveness, recovery from COVID-19, and disease severity (Cheson 2022).

9.9. Product Complaints

The sponsor collects product complaints on study treatments and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 9.3.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

Complaints associated with unapproved medical devices will be reported to the sponsor with a Medical Device Defect Report Form, and the sponsor will report medical device defects to the PMDA as per local regulatory requirements.

9.10. Treatment of Overdose

In the event of an overdose of more than 25% of tafasitamab, LEN or parsaclisib, the investigator should do the following:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

The sponsor does not recommend specific treatment for an overdose.

10. STATISTICS

10.1. Sample Size Determination

10.1.1. Sample Size Determination for Parts 1, 2, and 3

The dose-finding parts of the study (Part 1 and Part 2 except for Group 2) will follow a BOIN procedure (Liu and Yuan 2015), and the sample size will depend on the frequency of DLTs and the number of cohorts before reaching the MTD. Up to 12 evaluable participants will be treated in Part 1 Group 1 and up to 18 evaluable participants will be treated in Part 1 Group 2 and Part 2 Groups 3, 4a, and 5. The dose-finding procedure will be stopped for each group if ≥ 6 evaluable participants are treated at a dose level and the observed DLT data indicate that the dose should be retained or the maximum number of participants are reached.

The 3-point hypotheses selected for the Local BOIN design are ϕ=0.3, ϕ_1=0.6*ϕ, and ϕ_2=1.4*ϕ, where ϕ=0.3 is the target DLT rate, ϕ_1=0.6*ϕ is the highest DLT rate that is deemed subtherapeutic, and ϕ_2=1.4*ϕ is the lowest DLT rate deemed overly toxic. An equal prior probability of hypothesis being true are assigned to each of the hypotheses. The value of 0.95 is selected for the cutoff to eliminate an overly toxic dose for safety.

The estimated MTD for each group is the dose at which the observed DLT rate is closest to the target DLT rate of 30% using an isotonic method that takes the assumption of a monotonic dose-toxicity relationship into account. Table 29 will be used to guide dose escalation/de-escalation decisions. If the number of participants with DLT(s) specified in the last column is reached, that dose level and all dose levels above it will be eliminated. If the lowest dose level is eliminated, then the dose-finding will be terminated. If the number of participants with DLT(s) is between the escalation and de-escalation boundaries specified in the second and third columns in Table 29, then the dose should be retained and another cohort of 3 evaluable participants will be enrolled in the current dose level.

Table 29: Decision Boundaries

Number of Participants Treated at Current Dose	Escalate if Number of DLTs is ≤	De-Escalate if Number of DLTs is ≥	Unacceptable Toxicity if Number of DLTs ≥
3	0	2	3
6	1	3	4
9	2	4	5
12	2	5	7
15	3	6	8
18	4	7	9

The target number of evaluable participants in Part 2 Group 2 was set at 6 as the number of participants necessary for confirmation of tolerability. With a sample size of 6 evaluable participants, there is a 31% probability to observe at least 1 occurrence of a particular AE if the natural incidence of this AE is 6%.

Part 3 Group 4b could have been expanded to approximately 18 participants (including participants who were treated at RP2D in Part 2 Group 4a). If the true ORR is 65% for participants treated at RP2D in Group 4a and Group 4b, then with 18 total participants, there is approximately 85% probability of observing the lower bound of the 95% CI of ORR ≥ 30%. Based on the sponsor's decision, as of Amendment 5, Part 3 Group 4b will not be opened.

10.1.2. Sample Size Determination for Part 4

The threshold response rate in Group 6 was determined based on the ORR of 35% with rituximab monotherapy (Tobinai et al 2004). The expected response rate is set at 55%, taking into account that the ORR point estimate of the L-MIND study was 57.5% (data cutoff 30 OCT 2020; Duell et al 2021).

Assuming a threshold response rate of 35% and an expected response rate of 55%, with 41 participants evaluated for efficacy, the probability that the 90% exact binomial CI of the ORR exceeds the threshold response rate is 83% (see Table 30).

Table 30: Sample Size of Group 6

Sample Size	Probability of 90% CI Lower Bound > 0.35
39	0.736
40	0.787
41	0.831
42	0.790
43	0.833

Note: Power values were generated in base R by the "pbinom()" function, and critical values by the "qbinom()" function. The threshold rate was set at 35% and expected response rate at 55%. One-sided alpha was set to 0.05 for a 90% 2-sided CI.

10.2. Populations for Analysis

Table 31 presents the populations for analysis.

Table 31: Populations for Analysis

Population	Description
All-screened population	All participants who signed the ICF.
FAS	The FAS includes all participants who received at least 1 dose of study treatment. For Group 6, both study drugs (tafasitamab and LEN) must have been administered at least once. The FAS will be used for the summary of demographics, baseline characteristics, participants' disposition, and analyses of all efficacy data. For Group 6, participants who were inadvertently enrolled although they do not meet the eligibility requirements of the study may be excluded from the FAS (see Section 5.5).
Safety	The safety population includes all participants who received at least 1 dose of study treatment. All safety analyses will be conducted using the safety population.
DLT evaluable population (Groups 1, 3, 4a, and 5)	The DLT evaluable population will include participants who have had a DLT and as follows: • In Group 1, those who have received at least 4 doses of tafasitamab in the first cycle (28 days) • In Group 3, those who have received at least 17 of 21 doses of LEN and at least 4 doses of tafasitamab in the first 28 days • In Group 4a, those who have receive at least 23 of 28 doses of parsaclisib and at least 4 doses of tafasitamab in the first 28 days • In Group 5, those who have received at least 8 of 10 doses of LEN, 3 doses of tafasitamab, and any 1 or more of the component of R-CHOP in the first 21 days • Participants who are not evaluable will be replaced.
Evaluable for recommended clinical dose assessment (Group 2)	In Group 2, the recommended clinical dose-evaluable population will include participants who have received treatment from Cycle 1 Day 1 through Cycle 2 Day 1, completed safety assessments through Cycle 2 Day 7 (Day 35 relative to the first dose), and/or experience a prespecified AE (unequivocally unrelated to study treatment) through Day 35.
PPS	The PPS is composed of participants in the FAS who have underwent at least 1 postbaseline response assessment without having a major Protocol deviation.
Pharmacokinetic population	The PK evaluable population will include all participants who received at least 1 dose of study treatment and have at least 1 quantifiable tafasitamab serum concentration.
Immunogenicity analysis set	All participants who received at least 1 dose of study treatment and have at least 1 evaluable anti–tafasitamab antibody assessment.

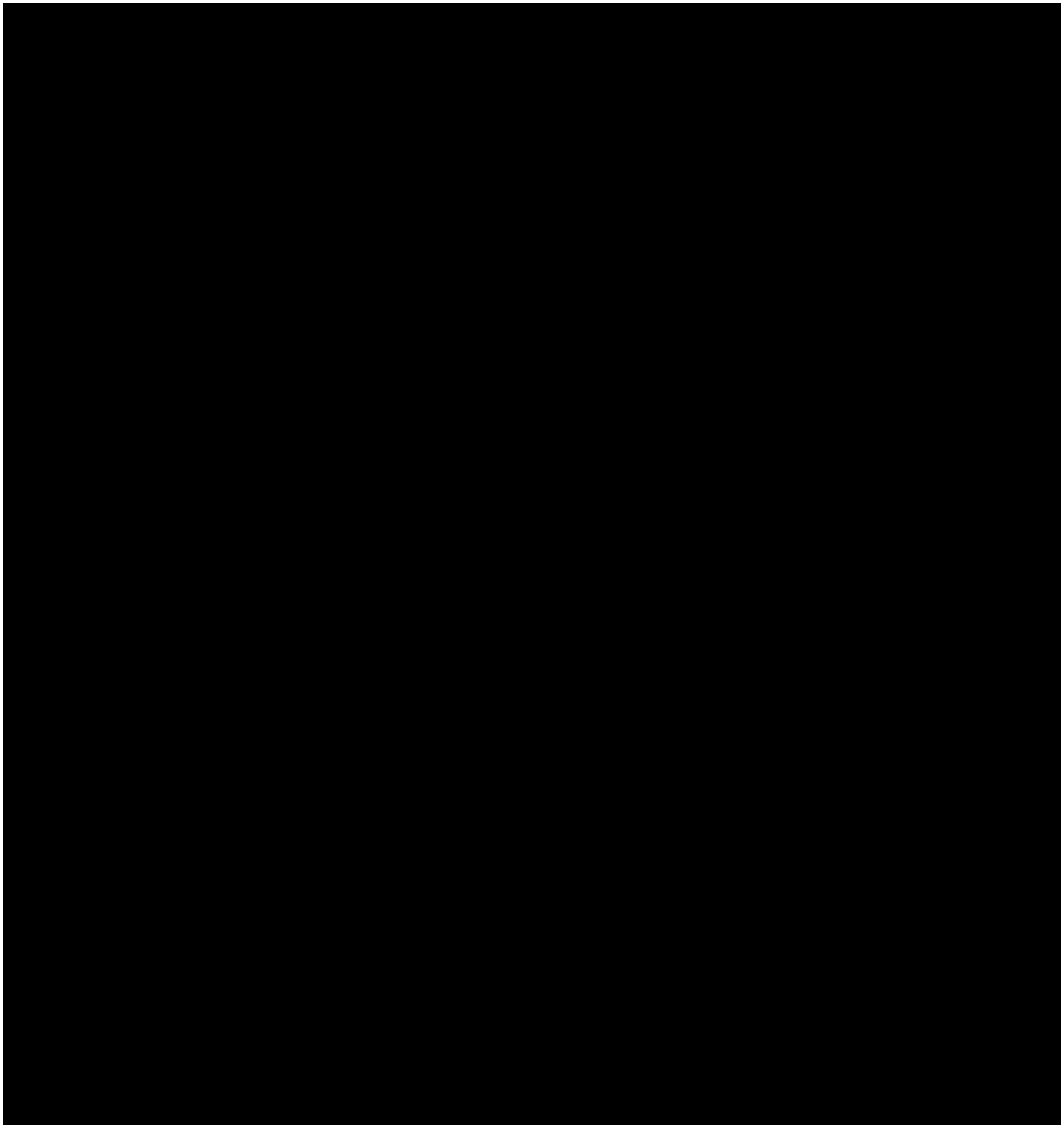
10.3. Level of Significance

This is an exploratory study, and no formal statistical tests will be performed. Unless otherwise specified, all CIs will be 95% with the exception of Group 6, where 90% CI will be displayed primarily and 95% CI will be provided as reference.

10.4. Statistical Analyses

All statistical analyses are exploratory in nature. Continuous variables will be summarized using means, medians, standard deviations, minimums, and maximums. Categorical variables will be summarized using frequency counts and percentages.

10.4.1. Efficacy Analysis





10.4.1.3. Group 6

All efficacy analyses will be conducted on the FAS; all sensitivity analyses will be run on the PPS (see Table 31).

10.4.1.3.1. Primary Analysis

For Phase 2 (Part 4 Group 6), ORR is the percentage of participants with a CR/CMR or PR/PMR as defined by the Lugano criteria (Cheson et al 2014) per IRC assessment. The ORR as determined by the IRC and its 90% exact binomial CIs will be calculated. Participants whose baseline disease assessment or on-study response assessments cannot be adequately assessed for response will be considered as nonresponders. These participants will be included in the denominators in the calculations of ORR.

10.4.1.3.2. Secondary Analyses

Complete response rate is defined as the percentage of participants experiencing a CR/CMR as determined by an IRC according to the Lugano criteria (Cheson et al 2014). The CRR as determined by IRC and its 90% exact binomial CIs will be summarized. Participants whose baseline disease assessment or on-study response assessments cannot be adequately assessed for response will be considered as nonresponders. These participants will be included in the denominators in the calculations of CRR.

Duration of response is defined as the time from the first documented evidence of CR/CMR or PR/PMR, as determined by an IRC according to the Lugano criteria (Cheson et al 2014), until the date of first documented disease progression or death due to any cause, whichever occurs first. For participants who have not progressed and are still alive at the time of the analysis, DOR will be censored on the day of last evaluable disease assessment. For participants who have discontinued study treatment or have started other antilymphoma treatment, DOR will be censored on the day of last evaluable disease assessment documenting absence of disease progression before the discontinuation or the start of the new antilymphoma treatment. Kaplan-Meier estimation of median DOR per IRC and its 90% CIs will be provided.

Progression-free survival is defined as the time from the date of the first dose of study drug to the first documented disease progression, as determined by an IRC according to the Lugano criteria (Cheson et al 2014), or death due to any cause, whichever occurs first. For participants who have not progressed and are still alive at the time of the analysis, PFS will be censored on the day of last evaluable disease assessment. For participants who have discontinued study treatment or

have started other antilymphoma treatment, PFS will be censored on the day of last evaluable disease assessment documenting absence of disease progression before the discontinuation or the start of the new antilymphoma treatment. For participants who have no baseline or no postbaseline disease assessment, PFS will be censored with duration of 1 day. For clarification, see Table 32. Kaplan-Meier estimation of median PFS per IRC and its 90% CIs will be provided.

Table 32: Censoring Rules

Participant Description	Censoring Rule
No progression; alive on final day of analysis.	Censored on day of last evaluable disease assessment.
Discontinued study treatment or started other antilymphoma treatment.	Censored on day of last evaluable disease assessment documenting absence of disease progression before the discontinuation or the start of the new antilymphoma treatment.
No baseline or no postbaseline disease assessment.	Censored with duration of 1 day.

Overall survival is defined as the time from the date of the first dose of study drug to death due to any cause. For participants who are still alive at the time of the analysis, OS will be censored on the date the participant is last known to be alive. The Kaplan-Meier estimation of median OS and its 90% CIs will be provided.

Additionally, ORR, CRR, DOR, and PFS will be analyzed as above as per investigator assessment of response according to the Lugano criteria (Cheson et al 2014).



10.4.2. Safety Analyses

10.4.2.1. DLT Safety Analysis

The primary endpoint in Part 1 Group 1 and Part 2 Groups 3, 4a, and 5 are DLTs during the DLT observation period. Analyses of DLTs are based on the DLT Evaluable Population. The occurrence of DLTs and AEs constituting DLTs during the DLT observation period will be summarized and listed by dose level for participants enrolled in Part 1 Group 1 and Part 2 Groups 3, 4a, and 5.

10.4.2.2. General Safety Analyses

Safety analyses will be conducted for the safety population. Adverse events will be coded by the MedDRA dictionary, and TEAEs (ie, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment until 90 days after the last dose of study treatment) will be tabulated by preferred term and system organ class for all events, serious events, related events, and events of Grade 3 or higher. Quantitative safety variables and their changes from baseline (laboratory, vital signs, etc) will be summarized with descriptive statistics. Abnormal values will be flagged and tabulated based on predefined criteria.

The clinical laboratory data will be analyzed using summary statistics. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE toxicity grades and tabulated.

Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. For participants exhibiting vital sign abnormalities, the abnormal values will be listed along with their assigned dose levels.

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for abnormalities according to predefined criteria (see Table 33). For participants exhibiting ECG abnormalities, the abnormal value will be listed along with their assigned dose levels.

Table 33: Normal Ranges for Electrocardiogram Intervals

Parameter	High Threshold	Low Threshold
PR	≤ 220 ms	≥ 75 ms
RR	≤ 1330 ms	≥ 600 ms
QT	≤ 500 ms	≥ 300 ms
QRS	≤ 120 ms	≥ 50 ms
QTcB, QTcF	≤ 450 ms	≥ 295 ms

QTcB = Bazett's correction; QTcF = Fridericia's correction.

Measures of exposure (eg, days of exposure, dose intensity, etc) of study treatments will be summarized.

10.4.3. Pharmacokinetic Analysis

Serum samples for determination of tafasitamab serum concentrations will be collected according to the SoA. The samples will be handled and stored as specified in the laboratory manual at the study site until shipment on dry ice to an external analytical laboratory.

Tafasitamab serum concentrations by timepoint and treatment group will be summarized using descriptive statistics and visualized in figures. Further details will be provided in the SAP.

A separate PK report will be prepared comparing the tafasitamab serum levels in Japanese participants from this study with results from previous or ongoing studies with tafasitamab.



10.5. Interim Analysis

For participants treated with tafasitamab plus parsaclisib, an interim futility analysis was originally planned when the first 9 participants (Part 2 Group 4a at RP2D and Part 3 Group 4b combined) have been evaluated for response or have permanently discontinued study. Part 3 Group 4b was supposed to be terminated for futility if ≤ 3 of the 9 participants have responded (ie, CR/CMR or PR/PMR) based on assessments provided by investigators.

Recruitment for treatment with tafasitamab plus parsaclisib was closed based on the sponsor's decision before the accrual of 9 participants, and this interim analysis will therefore not be performed.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol Amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and health authorities before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both health authorities and the IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study during the retention period without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

– All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

The record retainer (delegated by the head of the study site) will retain the J-GCP–defined essential documentation at this site until the regulatory approval of the study drug(s)/treatment or at least 3 years after the discontinuation or completion of the study conduct, whichever is later. If the sponsor requires retention of these documents for a longer period of time, the duration and method of retention will be decided upon through discussion between the sponsor and the study site. It is the responsibility of the sponsor to inform the head of the study site as to when the documents no longer need to be retained.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor medical monitor before the end of the study. As part of their responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

11.2. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol, such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and as designated by the sponsor, will have their own data flow management plans, study charters, or biomarker plans, as applicable.

The sponsor (or designee) will be responsible for the following:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Managing and reconciling the data generated and/or collected, including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for the following:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, biomarker data, photographs, diary data) or as otherwise specified in the Protocol.
- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are, in general, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.

- Sending participants' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of participants are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the participants and preserve their confidentiality) by a specially designated photography vendor prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.
- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Quality Assurance

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations). The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Further, monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues, Protocol deviations, and monitoring techniques (eg, central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.

Quality tolerance limits will be predefined in Incyte's SOPs/work instruction to identify systematic issues that can impact participants' safety, efficacy results and analysis, and/or reliability of study results. These predefined parameters will be monitored during the study and can be adjusted during the study upon data review. Important deviations from the quality tolerance limits and remedial actions taken, including reporting to IRBs/IECs and health authorities if applicable, will be summarized in the CSR.

11.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. Appropriate notice, or notice and consent (as may be required by each applicable jurisdiction), for collection, use, disclosure, and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

To ensure confidentiality of records and protect personal data, participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

In the event of a data breach involving participant data, the sponsor or its designee will follow the sponsor's incident response procedures. The precise definition of a data breach varies in accordance with applicable law but may generally be understood as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data. In accordance with its incident response procedures, the sponsor will assess the breach to consider its notification and remediation obligations under applicable law.

11.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 CFR Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure Form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research participants, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical

investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

11.6. Publication Policy

By signing the study Protocol, the investigator and their institution agree that the results of the study may be used by the sponsor, Incyte Biosciences Japan GK (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

11.7. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

When the trial is completed, the investigator should inform the head of the study site of the completion in writing and submit a written summary of the trial's outcome, and then the head of the study site should promptly inform the IRB and sponsor or designee of the completion in writing.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the Protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:
Male participants should use a condom from screening through 90 days after the end of systemic exposure. If the male participant has a partner that is of child-bearing potential, the partner should also use contraception through 90 days after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm from screening through 90 days after the end of relevant systemic exposure. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.
For female participants in the study:
The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods: • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a] – oral • Intrauterine device[b] • Intrauterine hormone-releasing system[b] • Bilateral tubal occlusion[b] • Vasectomized partner[c]
Acceptable birth control methods that result in a failure rate of more than 1% per year include: • Male condom with or without spermicide[d] • Diaphragm tubal ligation

[a] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

[b] Contraception methods that in the context of this guidance are considered to have low user dependency.

[c] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] A combination of male condom with diaphragm (double barrier methods) is also considered acceptable, but not highly effective, birth control methods.

Source: Clinical Trials Facilitation and Coordination Group 2014.

APPENDIX B. GLOBAL PPP LENALIDOMIDE ADULT

1. LENALIDOMIDE PREGNANCY PREVENTION PLAN FOR PARTICIPANTS IN CLINICAL TRIALS

The Pregnancy Prevention Plan (PPP) applies to all participants receiving LEN within a clinical trial. The following PPP documents are included:

1. The LEN Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 2) provides the following information:
   - Potential risks to the fetus associated with LEN exposure
   - Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
   - Requirements for counseling of all participants receiving LEN about pregnancy precautions and the potential risks of fetal exposure to LEN
   - Acceptable birth control methods for both female participants of childbearing potential and male participants receiving LEN in the study
   - Pregnancy testing requirements for participants receiving LEN who are FCBP
2. The LEN Education and Counseling Guidance Document for each gender (female and male; provided separately) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of LEN. A copy of this document must be maintained in the participant's records for each dispense.
3. The LEN Information Sheet (Section 5) will be given to each participant receiving LEN. The participant must read this document prior to starting LEN and each time the participant receives a new supply of LEN.

2. LENALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

2.1. Risks Associated With Pregnancy

LEN is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that LEN produced malformations in the offspring of female monkeys who received the drug during pregnancy. A teratogenic effect of LEN in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

2.1.1. Definition of FCBP

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

2.1.2. Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

2.2. Counseling

2.2.1. FCBP

For a FCBP, LEN is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of LEN):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting LEN, throughout the entire duration of LEN, during dose interruptions and for at least 28 days after the last dose of LEN
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence LEN as soon as it is dispensed following a negative pregnancy test
- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 2.4) and in the Informed Consent
- She acknowledges that she understands the hazards LEN can cause to an unborn fetus and the necessary precautions associated with the use of LEN.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

2.2.2. Females Not of Childbearing Potential

For a FNCBP, LEN is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of LEN):

- She acknowledges she understands the hazards LEN can cause to an unborn fetus and the necessary precautions associated with the use of LEN.

2.2.3. Males

Traces of LEN have been found in semen. Male participants taking LEN must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of LEN):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the participant donates semen or sperm.

2.3. Contraception

2.3.1. Female Participants of Childbearing Potential

FCBP enrolled in this protocol must agree to use two reliable forms of contraception simultaneously during the following time periods related to this study: 1) for at least 28 days before starting LEN; 2) while taking LEN; 3) during dose interruptions; and 4) for at least 28 days after the last dose of LEN.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the participant. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [eg, desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in participants with neutropenia.

2.3.2. Male Participants

Male participants must agree to use a condom during sexual contact with a pregnant female or a FCBP while taking LEN, during dose interruptions and for at least 28 days after the last dose of LEN, even if he has undergone a successful vasectomy.

2.4. Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting LEN. The first pregnancy test must be performed within 10 to 14 days prior to the start of LEN and the second pregnancy test must be performed within 24 hours prior to the start of LEN. The participant may not receive LEN until the study doctor has verified that the results of these pregnancy tests are negative.

FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking LEN, at study discontinuation, and at Day 28 following the last dose of LEN.

FCBP with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking LEN, at study discontinuation, and at Days 14 and 28 following the last dose of LEN.

The frequency of pregnancy testing during the dose LEN may be adjusted depending on the duration of treatment cycle.

2.5. Pregnancy Precautions for LEN Use

2.5.1. Before Starting LEN

2.5.1.1. Female Participants of Childbearing Potential

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting LEN. The first pregnancy test must be performed within 10 to 14 days prior to the start of LEN and the second pregnancy test must be performed within 24 hours prior to the start of LEN. The participant may not receive LEN until the study doctor has verified that the results of these pregnancy tests are negative.

FCBP must use two reliable forms of contraception simultaneously for at least 28 days before starting LEN.

2.5.1.2. Male Participants

Male participants must agree to use a condom during sexual contact with a pregnant female or a FCBP while taking LEN, during dose interruptions and for at least 28 days after the last dose of LEN, even if he has undergone a successful vasectomy.

2.5.2. During and After Study Participation

2.5.2.1. Female Participants

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking LEN, at study discontinuation, and at Day 28 following the last dose of LEN.
- FCBP with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking LEN, at study discontinuation, and at Days 14 and 28 following the last dose of LEN.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a participant, LEN must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a participant misses her period or if her pregnancy test or her menstrual bleeding is abnormal. LEN must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking LEN and for at least 28 days after the last dose of LEN.

2.5.2.2. Male Participants

- Must use a condom during sexual contact with a pregnant female or a FCBP while taking LEN, during dose interruptions and for at least 28 days after the last dose of LEN, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving LEN, during dose interruptions or for at least 28 days after the last dose of LEN.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male participant while taking LEN, the Investigator must be notified immediately.

2.5.3. Additional Precautions

- Participants should be instructed to never give LEN to another person.
- Participants should be instructed to return any unused capsules to the study doctor.
- Participants should not donate blood while receiving LEN, during dose interruptions and for at least 28 days after the last dose of LEN.
- No more than a 28-day LEN supply may be dispensed with each cycle of LEN.

3. CONTENTS OF LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE PARTICIPANTS

Format provided separately includes the contents below. It should be completed prior to each dispensing of LEN.

Protocol Number: _____

Participant Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ☐ NOT FCBP

3.1. Female of Childbearing Potential

1. I have verified and counseled the participant regarding the following:

- ☐ Potential risk of fetal exposure to LEN: A teratogenic potential of LEN in humans cannot be ruled out. If LEN is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking LEN. Females of childbearing potential must agree not to become pregnant while taking LEN.
- ☐ That the required pregnancy tests performed are negative.
- ☐ The participant confirmed that she is using TWO reliable methods of birth control at the same time (at least 28 days prior to receiving LEN, while receiving LEN, during dose interruptions and for at least 28 days after the last dose of LEN).
  One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Examples of highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [eg, desogestrel])
    - Tubal ligation
    - Partner's vasectomy

- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical cap

☐ The participant confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of LEN and at the last dose of LEN, even if the participant agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

- Two pregnancy tests will be performed prior to receiving LEN, one within 10 to 14 days, and a second within 24 hours of the start of LEN.
- Every week during the first 28 days of this study and a pregnancy test every 28 days while the participant is taking LEN if menstrual cycles are regular.
- Every week during the first 28 days of this study and a pregnancy test every 14 days while the participant is taking LEN if menstrual cycles are irregular.
- If the participant missed a period or has unusual menstrual bleeding.
- When the participant is discontinued from the study and at Day 28 after the last dose of LEN if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of LEN.

☐ The participant confirmed that she will stop taking LEN immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The participant confirmed that she has not and will not breastfeed a baby while taking LEN and for at least 28 days after the last dose of LEN.

☐ The participant has not and will never share LEN with anyone else.

☐ The participant has not and will not donate blood while taking LEN, during dose interruptions and for at least 28 days after the last dose of LEN.

☐ The participant has not and will not break, chew, or open LEN capsules at any point.

☐ The participant confirmed that she will return unused LEN capsules to the study doctor.

2. I have provided the LEN Information Sheet to the participant.

3.2. Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy)

1. I have verified and counseled the participant regarding the following:
   - ☐ Potential risk of fetal exposure to LEN: A teratogenic potential of LEN in humans cannot be ruled out. If LEN is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The participant has not and will never share LEN with anyone else.
   - ☐ The participant has not and will not donate blood while taking LEN, during dose interruptions and for at least 28 days after the last dose of LEN.
   - ☐ The participant has not and will not break, chew, or open LEN capsules at any point.
   - ☐ The participant confirmed that she will return unused LEN capsules to the study doctor.
2. I have provided the LEN Information Sheet to the participant.

Do Not Dispense LEN if:

- **The participant is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The participant states she did not use TWO reliable methods of birth control at least 28 days prior to receiving LEN, while receiving LEN and during dose interruptions.**
- **The participant stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the participant's records.

4. CONTENTS OF LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE PARTICIPANTS

Format provided separately includes the contents below. It should be completed prior to each dispensing of LEN.

Protocol Number: _____

Participant Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the participant regarding the following:

   ☐ Potential risk of fetal exposure to LEN: A teratogenic potential of LEN in humans cannot be ruled out. If LEN is taken during pregnancy, it may cause birth defects or death to any unborn baby.

   ☐ The participant confirmed that he has used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking LEN, during dose interruptions and for at least 28 days after the last dose of LEN.

   ☐ The participant confirmed that he has not impregnated his female partner while in the study.

   ☐ The participant confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male participant taking LEN confirmed that she will call her healthcare provider immediately if she becomes pregnant.

   ☐ The participant has not and will never share LEN with anyone else.

   ☐ The participant confirmed that he has not donated and will not donate semen or sperm while taking LEN or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of LEN.

   ☐ The participant has not and will not donate blood while taking LEN, during dose interruptions and for at least 28 days after the last dose of LEN.

   ☐ The participant has not and will not break, chew, or open LEN capsules at any point.

   ☐ The participant confirmed that he will return unused LEN capsules to the study doctor.

2. I have provided the LEN Information Sheet to the participant.

Do Not Dispense LEN if:

- The participant stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the participant's records.

5. LENALIDOMIDE INFORMATION SHEET

For participants enrolled in clinical research studies

Please read this LEN Information Sheet before you start taking LEN and each time you get a new supply. This LEN Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about LEN?

1. **LEN may cause birth defects (deformed babies) or death of an unborn baby.** LEN is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects.

   If you are a female who is able to become pregnant:

   - **Do not take LEN if you are pregnant or plan to become pregnant**
   - **You must use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting LEN
     - while taking LEN
     - during breaks (dose interruptions) of LEN
     - for at least 28 days after the last dose of LEN
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of LEN
     - 24 hours prior to the first dose of LEN
     - weekly for the first 28 days
     - if you have regular menstrual periods: every 28 days after the first month
     - if you have irregular menstrual periods: every 14 days after the first month
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of LEN (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking LEN if you become pregnant while taking LEN**
     - If you suspect you are pregnant at any time during the study, you must stop LEN immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to the sponsor.
   - **Do not breastfeed while taking LEN and for at least 28 days after the last dose of LEN**
   - The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to LEN, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

A small amount of LEN is found in human semen. The risk to an unborn baby in females whose male partner is receiving LEN is unknown at this time.

- Male participants (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking LEN
  - During breaks (dose interruptions) of LEN
  - For at least 28 days after the last dose of LEN
- **Male participants should not donate sperm or semen** while taking LEN, during breaks (dose interruptions) and for at least 28 days after the last dose of LEN.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to The sponsor. Your partner should call their healthcare provider immediately if they become pregnant.**

2. All participants:
   - **Do not share LEN with other people. It must be kept out of the reach of children and should never be given to any other person.**
   - **Do not donate blood** while you take LEN, during breaks (dose interruptions) and for at least 28 days after the last dose of LEN.
   - **Do not break, chew, or open LEN capsules at any point.**
   - You will get no more than a 28-day supply of LEN at one time.
   - Return unused LEN capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

APPENDIX C. CYP3A INHIBITORS AND INDUCERS

CYP3A inhibitors or inducers may alter parsaclisib concentration. These include but are not limited to the drugs listed below.

CYP3A Inhibitors

Inhibitor	Therapeutic Class
Potent CYP3A Inhibitors	
VIEKIRA PAK	Antivirals
indinavir/RIT	Protease Inhibitors
tipranavir/RIT	Protease Inhibitors
ritonavir	Protease Inhibitors
cobicistat (GS-9350)	None
ketoconazole	Antifungals
indinavir	Protease Inhibitors
troleandomycin	Antibiotics
telaprevir	Antivirals
danoprevir/RIT	Antivirals
elvitegravir/RIT	Treatments of AIDS
saquinavir/RIT	Protease Inhibitors
lopinavir/RIT	Protease Inhibitors
itraconazole	Antifungals
voriconazole	Antifungals
mibefradil	Calcium Channel Blockers
LCL161	Cancer Treatments
clarithromycin	Antibiotics
posaconazole	Antifungals
telithromycin	Antibiotics
grapefruit juice DS	Food Products
conivaptan	Diuretics
nefazodone	Antidepressants
nelfinavir	Protease Inhibitors
saquinavir	Protease Inhibitors
ribociclib	Kinase Inhibitors
idelalisib	Kinase Inhibitors
boceprevir	Antivirals

Inhibitor	Therapeutic Class
Moderate CYP3A Inhibitors	
erythromycin	Antibiotics
fluconazole	Antifungals
atazanavir/RIT	Protease Inhibitors
darunavir	Protease Inhibitors
diltiazem	Calcium Channel Blockers
darunavir/RIT	Protease Inhibitors
dronedarone	Antiarrhythmics
crizotinib	Kinase Inhibitors
atazanavir	Protease Inhibitors
letermovir	Antivirals
GSK2647544	Alzheimer's Disease & Dementia Treatments
aprepitant	Antiemetics
casopitant	Antiemetics
amprenavir	Protease Inhibitors
faldaprevir	Antivirals
imatinib	Antineoplastic Agents
verapamil	Calcium Channel Blockers
netupitant	Antiemetics
nilotinib	Kinase Inhibitors
grapefruit juice	Food Products
tofisopam	Benzodiazepines
cyclosporine	Immunosuppressants
ACT-178882	Renin Inhibitors
ciprofloxacin	Antibiotics
Magnolia vine (*Schisandra sphenanthera*)	Herbal Medications
isavuconazole	Antifungals
cimetidine	H_2-Receptor Antagonists
FK1706	Central Nervous System Agents

Inhibitor	Therapeutic Class
Weak CYP3A Inhibitors	
tabimorelin	Hormone Replacement
amlodipine	Calcium Channel Blockers
ranolazine	Cardiovascular Drugs
breviscapine	Herbal Medications
lomitapide	Other Antilipemics
fosaprepitant (IV)	Antiemetics
Seville orange (Citrus aurantium) juice	Food Products
amiodarone	Antiarrhythmics
diosmin	Herbal Medications
chlorzoxazone	Muscle Relaxants
M100240	Antihypertensive Agents
fluvoxamine	Antidepressants
ranitidine	H_2-Receptor Antagonists
goldenseal	Herbal Medications
clotrimazole	Antifungals
tacrolimus	Immunosuppressants
palbociclib	Kinase Inhibitors
cilostazol	Antiplatelets
ticagrelor	Antiplatelets
peppermint oil	Food Products
ivacaftor	Cystic Fibrosis Treatments
GSK2248761	Transcriptase Inhibitors
Guan Mai Ning	Herbal Medications
osilodrostat	Adrenal Steroidogenesis Inhibitors
AZD2327	Depression Treatments
piperine	Food Products
resveratrol	Food Products
roxithromycin	Antibiotics
suvorexant	Hypnotics – Sedatives
propiverine	Anticholinergics
isoniazid	Antibiotics
berberine	Herbal Medications
oral contraceptives	Oral Contraceptives
delavirdine	NNRTIs
daclatasvir	Antivirals
simeprevir	Protease Inhibitors

Inhibitor	Therapeutic Class
Weak CYP3A Inhibitors (continued)	
atorvastatin	HMG CoA Reductase Inhibitors (Statins)
tolvaptan	Vasopressin Antagonists
almorexant	Hypnotics – Sedatives
GSK1292263	Other Antilipemics
evacetrapib	CETP Inhibitors
linagliptin	Dipeptidyl Peptidase 4 Inhibitors
grazoprevir (*ingredient of Zepatier*)	Antivirals
lacidipine	Calcium Channel Blockers
cranberry juice	Food Products
pazopanib	Kinase Inhibitors
fostamatinib	Other
everolimus	Immunosuppressants
blueberry juice	Food Products
flibanserin	Central Nervous System Agents
lapatinib	Kinase Inhibitors
brodalumab	Immunomodulators Biologics
AMD070	Fusion Inhibitors
alprazolam	Benzodiazepines
Tong Xin Luo	Herbal Medications
glecaprevir and pibrentasvir	Antivirals
bicalutamide	Antiandrogens
sitaxentan	Endothelin Receptor Antagonists
azithromycin	Antibiotics
obeticholic acid	Miscellaneous Agents
ginkgo	Herbal Medications
teriflunomide	Other Immunomodulators

CYP3A Inducers

Inducers	Therapeutic Class
Potent Inducers	
rifampin	Antibiotics
mitotane	Other Antineoplastics
avasimibe	Other Antilipemics
rifapentine	Antibiotics
apalutamide	Antiandrogens
phenytoin	Anticonvulsants
carbamazepine	Anticonvulsants
enzalutamide	Antiandrogens
St John's wort extract	Herbal Medications
lumacaftor	Cystic Fibrosis Treatments
rifabutin	Antibiotics
phenobarbital	Anticonvulsants
Moderate Inducers	
ritonavir and St John's wort	None
semagacestat	Alzheimer's Treatments
efavirenz	NNRTIs
tipranavir and ritonavir	Protease Inhibitors
dabrafenib	Kinase Inhibitors
lesinurad	Antigout and Uricosuric Agents
bosentan	Endothelin Receptor Antagonists
genistein	Food Products
thioridazine	Antipsychotics
nafcillin	Antibiotics
talviraline	NNRTIs
lopinavir	Protease Inhibitors
modafinil	Psychostimulants
PF-06282999	Myeloperoxidase Inactivators
etravirine	NNRTIs
lersivirine	NNRTIs
telotristat ethyl	Antidiarrheals

Inducers	Therapeutic Class
Weak Inducers	
eslicarbazepine	Anticonvulsants
telaprevir	Antivirals
daclatasvir and asunaprevir and beclabuvir	Antivirals
amenamevir	Antivirals
garlic	Food Products
bexarotene	Other Antineoplastics
sarilumab	Immunomodulators Biologics
artesunate and mefloquine	Antimalarials
amprenavir (fosamprenavir)	Protease Inhibitors
raltegravir	HIV-Integrase Strand Transfer Inhibitors
vemurafenib	Kinase Inhibitors
troglitazone	Thiazolidinediones
dicloxacillin	Antibiotics
sorafenib	Kinase Inhibitors
rufinamide	Anticonvulsants
sirukumab	Immunomodulators Biologics
pleconaril	Antivirals
ginseng	Herbal Medications
boceprevir	Antivirals
sulfinpyrazone	Antigout and Uricosuric Agents
ginkgo	Herbal Medications
vinblastine	Vinca Alkaloids
nevirapine	NNRTIs
armodafinil (R-modafinil)	Psychostimulants
ticagrelor	Anticoagulants and Antiplatelets
LCL161	Cancer Treatments
vicriviroc and ritonavir	Treatments of AIDS
ritonavir	Protease Inhibitors
prednisone	Corticosteroids
oxcarbazepine	Anticonvulsants
danshen	Herbal Medications
clobazam	Benzodiazepines
echinacea	Herbal Medications
ticlopidine	Anticoagulants and Antiplatelets

Inducers	Therapeutic Class
Weak Inducers (continued)	
isavuconazole	Antifungals
brivaracetam	Anticonvulsants
Stribild	Treatments of AIDS
pioglitazone	Thiazolidinediones
VIEKIRA PAK	Antivirals
dexamethasone	Corticosteroids
terbinafine	Antifungals
quercetin	Food Products
glycyrrhizin	Herbal Medications
aprepitant	Neurokinin-1 Receptor Antagonists
pretomanid (PA-824)	Antibiotics
safinamide	MAO-B Inhibitors
oritavancin	Antibiotics
AZD 7325	Anxiolytics
methylprednisolone	Corticosteroids
topiramate	Anticonvulsants

AIDS = acquired immunodeficiency syndrome; MAO-B = monoamine oxidase B; NNRTI = non-nucleoside reverse transcriptase inhibitor; RIT = ritonavir.

APPENDIX D. CALCULATION OF CREATININE CLEARANCE USING THE COCKCROFT-GAULT FORMULA

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

This formula presumes weight to be measured in kilograms and creatinine to be measured in mg/dL.

When serum creatinine is measured in µmol/L:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

where Constant is 1.23 for men and 1.04 for women.

APPENDIX E. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Eastern Cooperative Oncology Group Performance Scores

Grade	Performance Status
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al 1982.

APPENDIX F. INTERNATIONAL PROGNOSTIC INDEX

IPI Risk Factor

Ann Arbor Stage III or IV

Age > 60 years

Serum LDH > 1 × ULN

ECOG Performance status ≥ 2

Extranodal involvement ≥ 2[1]

IPI Risk Groups	Number of IPI Risk Factors
Low	0 or 1
Low-Intermediate	2
High-Intermediate	3
High	4 or 5

[1] Extranodal involvement per Cheson 2014 can include sites that have focal uptake by PET-CT (eg, spleen, liver, bone, thyroid, cutaneous, gastrointestinal (GI), bone, kidneys, pleural or pericardial effusions, ascites).

ECOG = Eastern Cooperative Oncology Group; FDG = fluorodeoxyglucose; IPI = International Prognostic Index; PET = positron emission tomography; ULN = upper limit of normal.

Source: Shipp et al 1993.

APPENDIX G. FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX

Scoring System		
Parameter	**Value**	**Point Score**
Age	> 60 years of age	1
Ann Arbor stage	Stage III or IV	1
Hemoglobin level	< 120 g/L (12.0 g/dL or 6.37 mmol/L)	1
Serum LDH level	> ULN	1
Number of nodal sites	> 5	1

Risk Group by FLIPI Total Point Score	
Risk Group	**Total Point Score**
Low	≤ 1
Intermediate	2
High	≥ 3

APPENDIX H. LUGANO CLASSIFICATION FOR RESPONSE ASSESSMENT

Site	PET-Based Response	CT-Based Response
	CMR	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on a 5-point scale.	• Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi. • No extralymphatic sites of disease.
Nonmeasured lesion	Not applicable.	Absent.
Organ enlargement	Not applicable.	Regress to normal.
New lesions	None.	None.
Bone marrow	No evidence of FDG-avid disease in marrow.	Normal by morphology; if indeterminate, immunohistochemistry negative.
	PMR	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	• Score 4 or 5a with reduced uptake compared with baseline and residual mass(es) of any size. • At interim, these findings suggest responding disease. • At EOT, these findings suggest residual disease.	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default. • When no longer visible, 0 × 0 mm. For a node > 5 mm × 5 mm but smaller than normal, use actual measurement.
Nonmeasured lesions	Not applicable.	Absent/regressed, but no increase.
Organ enlargement	Not applicable.	Spleen must have regressed by > 50% in length beyond normal.
New lesions	None.	None.
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consider further evaluation with MRI or biopsy.	Not applicable.

Site	PET-Based Response	CT-Based Response
	No metabolic response	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score of 4 or 5a with no significant change in FDG uptake from baseline at interim or EOT.	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for PD are met.
Nonmeasured lesions	Not applicable.	No increase consistent with progression.
Organ enlargement	Not applicable.	No increase consistent with progression.
New lesions	None.	None.
Bone marrow	No change from baseline.	Not applicable.
	Progressive metabolic disease	**Progressive disease (requires at least 1 of the following)**
Individual target nodes/nodal lesions	Individual target nodes/nodal lesions: • Score 4 or 5a with an increase in intensity of uptake from baseline and/or • New FDG-avid foci consistent with lymphoma at interim or EOT assessment Extranodal lesions: • New FDG-avid foci consistent with lymphoma at interim or EOT assessment New lesions: • New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered. Bone marrow: • New or recurrent FDG-avid foci	PPD progression: • An individual node/lesion must be abnormal with all of the following: – LDi > 1.5 cm. – Increase by ≥ 50% from PPD nadir. – Increase in LDi or SDi from nadir: ○ 0.5 cm for lesions ≤ 2 cm. ○ 1.0 cm for lesions > 2 cm. • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. • New or recurrent splenomegaly. • New or clear progression of pre-existing nonmeasured lesions. • Regrowth of any previously resolved lesions. • A new node > 1.5 cm in any axis. • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. • Assessable disease of any size unequivocally attributable to lymphoma. • New or recurrent involvement of the bone marrow.

CT = computed tomography; EOT = end of treatment; LDi = longest transverse diameter of lesion; MRI = magnetic resonance imaging; PPD = cross-product of the longest transverse diameter and perpendicular diameter; SDi = shortest axis perpendicular to the longest transverse diameter; SPD = sum of the product of the perpendicular diameters for multiple lesions.

APPENDIX I. PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 1:	19 SEP 2020
Amendment 2:	18 DEC 2020
Amendment 3:	07 JUL 2021
Amendment 4:	14 JUL 2022
Amendment 5:	18 OCT 2022
Amendment 6:	14 FEB 2024
Amendment 7:	16 APR 2024
Amendment 8:	27 OCT 2025

Amendment 8 (27 OCT 2025)

Overall Rationale for the Amendment:

The purpose of this amendment is to clarify the subsequent visit schedule and EOS for participants who are continuing study treatment at the time of the final data cutoff in this clinical study. Additional changes are described below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements)**

   Description of change: Removed text pertaining to a company-sponsored rollover study.

   Rationale for change: To clarify that study treatment will be discontinued upon the marketing authorization of tafasitamab for participants who are continuing treatment.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 4.2, Overall Study Duration; Section 8.7, End of Treatment and End of Study**

   Description of change: Added information on management of participants receiving study treatment after marketing authorization for tafasitamab in Japan and approval for its indication in DLBCL have been obtained.

   Rationale for change: To clarify that study treatment will be discontinued upon the marketing authorization of tafasitamab for participants who are continuing treatment.

3. **Section 1, Protocol Summary (Table 9: Schedule of Activities [All Participants After the Final Data Cutoff Date]); Section 4.1, Overall Design; Section 4.1.6, Continuation of Study Treatment Beyond the Final Data Cutoff Date; Section 8.2.1, CT/MRI/PET-CT; Section 8.4.1, Blood Sample Collection for Serum Pharmacokinetics; Section 8.4.2, Immunogenicity Assessments (Anti-Tafasitamab Antibodies); Section 8.8.3, Post-Treatment Disease/Survival Follow-Up (Group 6 Only)**

   Description of change: Defined the final data cutoff of the study and added information on the subsequent visit schedule and EOS for participants who continue study treatment at the time of the final data cutoff.

   Rationale for change: To clarify the timing of the end of study treatment and EOS as well as the assessments to be conducted.

4. **Section 7.1.1, Reasons for Discontinuation**

   Description of change: Added marketing authorization of tafasitamab for DLBCL in Japan as a reason for discontinuation of study treatment.

   Rationale for change: Clarification.

5. **Incorporation of administrative changes.** Other administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 7 (16 APR 2024)

Overall Rationale for the Amendment:

The purpose of this amendment is to optimize the dose regimen to reduce the frequency of hospital/clinic visits and to change inclusion criteria. Additional changes are described below.

1. **Section 1, Protocol Summary (Table 1: Primary and Major Secondary Objectives and Endpoints; Table 2: Key Study Design Elements; Table 4: Schedule of Activities [Group 2]); Section 2.2.1, Scientific Rationale for Study Design; Section 2.2.2, Dose Justification for Tafasitamab Monotherapy; Section 2.2.4, Dose Justification for Weight-Based Dosing of Tafasitamab Q2W/Q4W in Combination With LEN (Group 2); Section 2.3, Benefit/Risk Assessment; Section 3, Objectives and Endpoints (Table 10: Objectives and Endpoints); Section 4.1, Overall Design; Section 4.1.1, Part 1 – Tafasitamab Monotherapy Dose-Finding (Table 11: Dose Levels to Be Evaluated in Dose-Finding (Part 1); Section 4.1.2, Part 2 – Tafasitamab Combination Therapy Dose-Finding/Assessing Recommended Clinical Dose; Section 5.1, Inclusion Criteria; Section 5.2, Exclusion Criteria; Section 5.3.2, Activity; Section 5.5, Replacement of Participants; Section 6.1, Study Treatments Administered (Table 13: Study Treatment Information); Section 6.1.2, Tafasitamab Regimen 2: 28-Day Cycle (Group 2); Section 6.1.4, Lenalidomide (Groups 2, 3, 5, and 6); Section 6.5, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose (Groups 1, 3, 4a, and 5); Section 6.5.1, Definition of a Dose-Limiting Toxicity; Section 6.5.3, Safety Monitoring Committee (Groups 1, 3, 4a, and 5); Section 6.6, Determination of Recommended Clinical Dose (Group 2); Section 6.6.1, Definition of Recommended Clinical Dose; Section 6.6.2, Safety Monitoring Committee Specific to Group 2; Section 6.7.1, Tafasitamab Modification for Grade 3 Infusion-Related Reaction (Groups 1, 3, 4a, and 5); Section 6.7.3, Management of Infusion-Related Reactions; Section 6.7.4, Dose Modification for Tafasitamab in Monotherapy; Section 6.7.4,1, Dose Reduction for Tafasitamab in Monotherapy (Group 1); Section 6.7.5, Dose Modification in Phase 1b Combination Therapy (Groups 2, 3, 4a, and 5); Section 6.7.5.1, Criteria for Initiation of Cycle in Combination Therapy (Groups 2, 3, 4a, and 5); Section 6.7.5.1.1, Cycle Initiation in Groups 2, 3, and 4a; Section 6.7.5.2, Guidelines for Managing Hematological and Other Toxicities (Groups 2, 3, and 4a) (Table 17: Toxicity Management Guidelines for Hematological and Other Toxicities; Table 19: Toxicity Management Guidelines for LEN- and/or Tafasitamab-Specific Nonhematological Toxicity [Groups 2, 3, and 5]); Section 6.7.5.3, LEN Dose Modification Guidelines (Groups 2, 3, and 5) (Table 20: Dose Levels of LEN [Groups 2, 3, and 5]); Section 6.7.5.5, Tafasitamab Dose Reductions, Interruption, and Discontinuation (Groups 2, 3, 4a, and 5); Section 6.8.1, Premedication for Tafasitamab Infusion (All Groups); Section 6.8.3, Prophylaxis for Venous Thromboembolism (Groups 2, 3, 5, and 6); Section 7.1.1, Reasons for Discontinuation; Section 8.3.8.1.1, Requirement of Pregnancy Testing (Groups 2, 3, 5, and 6); Section 8.4.1, Blood Sample Collection for Serum Pharmacokinetics (Table 27: Tafasitamab Pharmacokinetic Blood Sample Timing); Section 10.1.1, Sample Size Determination for Parts 1, 2, and 3; Section 10.2, Populations for Analysis (Table 30: Populations for Analysis); Section 10.4.1.2, Groups 1, 2, 4a, and 5; Section 10.4.2.1; DLT Safety Analysis**

Description of change: Changed Group 2 from tafasitamab monotherapy in Japanese participants with R/R NHL to tafasitamab Q2W/Q4W in combination with LEN in Japanese participants with R/R DLBCL.

Rationale for change: The recommended dose for tafasitamab Q2W/Q4W administration in combination with LEN in participants with R/R DLBCL is almost established in the MINDway study; therefore, it is appropriate to test it in Japanese participants with R/R DLBCL in this study.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements)**

   Description of change: Revised the number of participants enrolled in the study and in each part.

   Rationale for change: The recommended dose determined in the MINDway study will be the only dose evaluated in Group 2.

3. **Section 2.1.4.2, L-MIND Study; Section 2.1.4.3, First-MIND Study; Section 2.1.4.4, FrontMIND Study; Section 2.1.4.5, MINDway Study**

   Description of change: Updated study status/data for the L-MIND. First-MIND, and frontMIND studies and added data for the MINDway study.

   Rationale for change: Updated data are available.

4. **Section 2.2.3, Dose Justification for Combination of Tafasitamab and LEN (Groups 3 and 6); Section 4.1.5, Part 4 – Phase 2 Portion With the Combination of Tafasitamab and LEN; Section 5.1, Inclusion Criteria (Criterion 7e); Section 6.1.4, Lenalidomide (Groups 2, 3, 5, and 6); Section 6.7.6.3, LEN Dose Modification Guidelines (Group 6) (Table 25: Dose Levels of LEN [Group 6])**

   Description of change: Allowed enrollment in Group 6 of participants who have lower serum creatinine clearance.

   Rationale for change: Modified in view of the patient population with R/R DLBCL.

5. **Section 6.7.6.2, Guidelines for Managing Hematological and Other Toxicities in Group 6 (Table 24: Toxicity Management Guidelines for LEN- and/or Tafasitamab-Specific Nonhematological Toxicity [Group 6])**

   Description of change: Modified toxicity management for LEN.

   Rationale for change: For alignment with the L-MIND study.

6. **Section 8.2.1, CT/MRI/PET-CT**

   Description of change: Clarified the requirement for radiological assessment.

   Rationale for change: Clarification.

7. **Section 8.3.8.2, Serology**

   Description of change: Added guidance if HBV DNA becomes detectable during treatment.

   Rationale for change: To define the handling of HBV reactivation during the study.

8. **Section 9.5.1, Adverse Events of Special Interest by eCRF (All Groups); Section 9.5.2, Adverse Events of Special Interest by Category and Preferred Term (Groups 2 and 6 Only)**

   Description of change: Clearly defined the method of AESI assessment to align with the program-level method.

   Rationale for change: Clarification.

9. **Incorporation of administrative changes.** Other administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 6 (14 FEB 2024)

Overall Rationale for the Amendment:

The purpose of this amendment is to change exclusion criteria in view of current approved therapies and to adjust to the changing therapy landscape in R/R DLBCL.

1. **Section 5.2, Exclusion Criteria (Criterion 1)**

   Description of change: Removed the exclusion criterion specific to Group 6.

   Rationale for change: Modified in view of current approved therapies and to adjust to the changing therapy landscape.

2. **Section 5.2, Exclusion Criteria (Criterion 7c)**

   Description of change: Divided the exclusion criterion regarding prior CD19-targeted therapy between Groups 1, 2, 3, and 4a and Group 6.

   Rationale for change: Modified in view of current approved therapies and to adjust to the changing therapy landscape.

3. **Incorporation of administrative changes.** Other administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 5 (18 OCT 2022)

Overall Rationale for the Amendment:

The purpose of this amendment is to add the sponsor's decision to not recruit participants for Group 4b in Part 3, to define the continued access period for Parts 1 and 2 (Groups 1, 3, and 4a only), to include the sponsor's recommendations regarding COVID-19 monitoring and management, to add the dosage formulation of LEN, to update the requirement for obtaining vital signs, and to update data privacy requirements in accordance with the EU CTR directive.

1. **Section 1, Protocol Summary (Table 1: Primary and Major Secondary Objectives and Endpoints; Table 2: Key Study Design Elements; Table 5: Schedule of Activities [Groups 3 and 4a]); Section 2.2.4, Dose Justification for Combination of Tafasitamab and Parsaclisib; Section 2.3, Benefit/Risk Assessment; Section 3, Objectives and Endpoints (Table 10: Objectives and Endpoints); Section 4.1, Overall Design; Section 4.1.3, Part 3 – Dose Expansion With the Combination of Tafasitamab and Parsaclisib; Section 4.2, Overall Study Duration; Section 5.1, Inclusion Criteria; Section 5.2, Exclusion Criteria; Section 5.3.2, Activity; Section 5.5, Replacement of Participants; Section 6.1, Study Treatments Administered; Section 6.1.1, Tafasitamab Regimen 1: 28-Day Cycle (Groups 1, 3, 4a, and 6); Section 6.1.5, Parsaclisib (Group 4a); Section 6.5.1, Definition of a Dose-Limiting Toxicity; Section 6.6.5, Dose Modification in Phase 1b Combination Therapy (Groups 3, 4a, and 5); Section 6.6.5.1, Criteria for Initiation of Cycle in Combination Therapy (Groups 3, 4a, and 5); Section 6.6.5.1.1, Cycle Initiation in Groups 3 and 4a; Section 6.6.5.2, Guidelines for Managing Hematological and Other Toxicities (Table 16: Toxicity Management Guidelines for Hematological and Other Toxicities [Groups 3 and 4a]); Section 6.6.5.4, Parsaclisib Dose Reductions, Interruption, and Discontinuation Guidelines (Group 4a) (Table 20: Toxicity Management Guidelines for Parsaclisib [Group 4a]; Table 21: Dose Levels for Parsaclisib [Group 4a]); Section 6.6.5.5, Tafasitamab Dose Reductions, Interruption, and Discontinuation (Groups 3, 4a, and 5); Section 6.7.4, Prophylaxis for *Pneumocystis jirovecii* (Group 4a Only); Section 6.7.8, Permitted Medications and Procedures; Section 6.7.9, Restricted Medications and Procedures (Group 4a Only); Section 6.7.10, Prohibited Medications and Procedures; Section 8.3.8, Laboratory Assessments (Table 25: Required Laboratory Analytes); Section 8.4.1, Blood Sample Collection for Serum Pharmacokinetics (Table 26: Tafasitamab Pharmacokinetic Blood Sample Timing); Section 8.7, End of Treatment and End of Study; Section 10.4.1.2, Groups 1, 2, 4a, and 5; Section 10.4.2.1, DLT Safety Analysis; Section 10.5, Interim Analysis**

   Description of change: Updated text related to Part 3 Group 4b.

   Rationale for change: Sponsor's decision to not recruit participants for Part 3 Group 4b.

2. **Section 1, Protocol Summary (Table 8: Schedule of Activities [Continued Access Period for Participants in Groups 1, 3, and 4a]); Section 4.1, Overall Design; Section 4.1.4, Continued Access Period for Parts 1 and 2 (Groups 1, 3, and 4a Only);Section 4.2, Overall Study Duration; Section 6.1, Study Treatments Administered; Section 7.1.1, Reasons for Discontinuation; Section 8.2.1, CT/MRI/PET-CT**

   Description of change: Defined the maximum treatment period as 2 years in Phase 1b and added the continued access period for Parts 1 and 2 (Groups 1, 3, and 4a).

   Rationale for change: To allow participants who are receiving benefit to continue study treatment until meeting any of the discontinuation criteria.

3. **Section 2.3, Benefit/Risk Assessment; Section 9.8, Warnings and Precautions**

   Description of change: Added text related to recommendations for COVID-19 monitoring and management in participants with hematologic malignancies.

   Rationale for change: To include recommendations arising out of ongoing safety surveillance.

4. **Section 6.1, Study Treatments Administered (Table 13: Study Treatment Information)**

   Description of change: Added the dosage formulations of 10 mg, 15 mg, 20 mg, and 25 mg to LEN capsules.

   Rationale for change: To introduce additional dose formulations to the Phase 2 portion of the study.

5. **Section 8.3.4, Vital Signs, Body Weight, and Height**

   Description of change: Updated requirement for obtaining vital signs.

   Rationale for change: To align with other studies of tafasitamab.

6. **Incorporation of administrative changes.** Other regulatory guidance and administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 4 (14 JUL 2022)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to add a Phase 2 portion to the current Phase 1b study.

1. **Title Page; Section 1, Protocol Summary; Section 2.2.1, Scientific Rationale for Study Design; Section 2.2.3, Dose Justification for Combination of Tafasitamab and LEN; Section 3, Objectives and Endpoints; Section 4.1, Overall Design; Section 4.1.4, Part 4 – Phase 2 Portion With the Combination of Tafasitamab and LEN; Section 4.2, Overall Study Duration; Section 5.1, Inclusion Criteria; Section 5.2, Exclusion Criteria; Section 5.3.2, Activity; Section 5.5, Replacement of Participants; Section 6.1, Study Treatments Administered; Section 6.1.1, Tafasitamab Regimen 1: 28-Day Cycle (Groups 1, 3, 4a, 4b, and 6); Section 6.1.4, Lenalidomide (Groups 3, 5, and 6); Section 6.6.6, Dose Modification in Combination Therapy of Phase 2 (Group 6); Section 6.7.3, Prophylaxis for Venous Thromboembolism (Groups 3, 5, and 6); Section 7.1.2, Discontinuation Procedures; Section 8.2, Efficacy Assessments; Section 8.2.1, CT/MRI/PET-CT; Section 8.3.8.1.1, Requirement of Pregnancy Testing (Groups 3, 5, and 6); Section 8.4.1, Blood Sample Collection for Serum Pharmacokinetics; Section 8.8.3, Post-Treatment Disease/Survival Follow-Up (Group 6 Only); Section 10.1.2, Sample Size Determination for Part 4; Section 10.2, Populations for Analysis; Section 10.3, Level of Significance; Section 10.4.1.3, Group 6;**

   Description of change: Added overview, details, rationale, and other procedures regarding the Phase 2 portion.

   Rationale for change: To add a Phase 2 portion (Part 4 Group 6) to the current Phase 1b study.

2. **Section 2.1.2, Diffuse Large B-Cell Lymphoma; Section 2.1.3, Tafasitamab; Section 2.1.4.2, L-MIND Study; Section 2.1.4.3, First-MIND Study; Section 2.1.4.4, FrontMIND Study; Section 2.1.5.1, Rationale of Tafasitamab + Parsaclisib Combination; Section 6.7.4, Prophylaxis for *Pneumocystis Jirovecii* (Groups 4a and 4b Only)**

   Description of change: Compound and/or study status and/or study data were updated.

   Rationale for change: Data regarding tafasitamab and NCCN guidelines have been updated since the time of the original Protocol.

3. **Section 5.1, Inclusion Criteria (Criterion 2)**

   Description of change: Deleted note regarding requirement of parent/legal guardians.

   Rationale for change: Effective 01 APR 2022, the age of adulthood in Japan changed from ≥ 20 years to ≥ 18 years.

4. **Section 6.1, Study Treatments Administered; Section 6.7.4, Prophylaxis for *Pneumocystis Jirovecii* (Groups 4a and 4b Only)**

   Description of change: Removed the specification of trimethoprim sulfamethoxazole or atovaquone as the primary PJP prophylaxis.

   Rationale for change: Potential approval status change in Japan.

5. **Section 6.6.1, Tafasitamab Modification for Grade 3 Infusion-Related Reaction (Groups 1, 2, 3, 4a, and 5); Section 6.6.3, Management of Infusion-Related Reactions**

   Description of change: Changed the applicable groups for tafasitamab modification for Grade 3 IRRs.

   Rationale for change: After reviewing the available safety information in Groups 1, 3, 4a, and 5, it was decided that the modification procedures need not apply to the expansion cohort (Group 4b) and Phase 2 part (Group 6).

6. **Section 6.7.8, Permitted Medications and Procedures**

   Description of change: Added palliative use of corticosteroids in Groups 1, 2, 3, 4a, 4b, and 6.

   Rationale for change: Clarification.

7. **Section 8.2.1, CT/MRI/PET-CT**

   Description of change: Added the requirement of the Deauville 5-point scale assessment.

   Rationale for change: Clarification.

8. **Section 9.2, Definition of Serious Adverse Event**

   Description of change: Removed inclusionary and exclusionary cases from the definition of disability.

   Rationale for change: To align with template requirement.

9. **Section 10.2, Populations for Analysis; Section 10.4.2.1, Dose-Limiting Toxicity Safety Analyses**

   Description of change: Added descriptions for the DLT evaluable population and analysis of DLTs.

   Rationale for change: Clarification of primary endpoint for Parts 1, 2, and 3.

10. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 3 (07 JUL 2021)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to clarify the eligibility of participants in Group 5. As of this amendment, study sites should no longer follow Letter of Administrative Change 1.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 3: Schedule of Activities [Group 1], Table 4: Schedule of Activities [Group 2], Table 5: Schedule of Activities [Groups 3, 4a, and 4b]; Table 6: Schedule of Activities [Group 5]); Section 4.2, Overall Study Duration; Section 6.7, Concomitant Medications and Procedures; Section 8.3.1, Adverse Events; Section 8.4.1, Blood Sample Collection for Serum Pharmacokinetics (Table 20: Tafasitamab Pharmacokinetic Blood Sample Timing); Section 8.7, End of Treatment and/or Early Termination and End of Study; Section 8.8.1, Safety Follow-Up; Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events; Section 9.4, Reporting of Serious Adverse Events; Section 10.4.2, Safety Analyses**

   Description of change: Changed the safety follow-up visit from 30 to 35 days after the EOT visit to 90 days after the EOT visit. Related to this change, visit names were revised and clarifications were added.

   Rationale for change: Treatment-emergent adverse events must be reported within 5 half-lives or within 30 days of the last administration of investigational product, whichever is longer. Because the half-life of tafasitamab is 17 days, the reporting period of TEAEs has been extended to 90 days after the EOT visit.

2. **Section 1, Protocol Summary (Table 5: Schedule of Activities [Groups 3, 4a, and 4b]; Table 6: Schedule of Activities [Group 5]); Section 8.3.8.1.1, Requirement of Pregnancy Testing (Groups 3 and 5)**

   Description of change: Updated and added the description of pregnancy testing timing.

   Rationale for change: Clarification.

3. **Section 5.1, Inclusion Criteria (Criterion 10)**

   Description of change: Added text to Criterion 10.a to clarify the definition of untreated DLBCL.

   Rationale for change: Clarification.

4. **Section 5.1, Inclusion Criteria (Criterion 11)**

   Description of change: Added a note to Criterion 11.d to clarify the definition of FCBP specific to Groups 3 and 5.

   Rationale for change: Clarification.

5. **Section 6.1, Study Treatments Administered (Table 10: Study Treatment Information)**

   Description of change: Modified administration instructions for LEN.

   Rationale for change: To improve the feasibility during the outpatient period.

6. **Section 6.4, Study Treatment Compliance**

   Description of change: Modified the upper limit of compliance for parsaclisib and LEN.

   Rationale for change: To align with the LEN Handling Manual and other tafasitamab + LEN protocols.

7. **Section 6.6.4, Dose Modification for Tafasitamab in Monotherapy (Groups 1 and 2), Section 6.6.5.2, Guidelines for Managing Hematological and Other Toxicities (Table 13: Toxicity Management Guidelines for Hematological and Other Toxicities [Groups 3, 4a, and 4b])**

   Description of change: Added exemption of lymphocytopenia.

   Rationale for change: To allow treatment continuation.

8. **Section 6.6.5.1, Criteria for Initiation of Cycle in Combination Therapy (Groups 3, 4a, 4b, and 5)**

   Description of change: Added exemption of lymphocytopenia.

   Rationale for change: To allow cycle initiation for a participant with lymphocytopenia in consultation with the medical monitor.

9. **Section 6.6.5.2, Guidelines for Managing Hematological and Other Toxicities**

   Description of change: Added description of decisions regarding dose interruption and reduction to allow flexibility in consultation with the medical monitor.

   Rationale for change: To improve the feasibility of avoiding an infusion duration that exceeds the stability of tafasitamab.

10. **Section 6.6.5.3, LEN Dose Modification Guidelines (Groups 3 and 5)**

    Description of change: Deleted the maximum days of interruption of LEN in Group 3 and added an explanation of LEN dosing during the DLT evaluation period.

    Rationale for change: To improve the feasibility for participants to continue treatment and clarification.

11. **Section 7.1.1, Reasons for Discontinuation**

    Description of change: Added description to allow treatment continuation after DLT occurrence with the medical monitor's approval.

    Rationale for change: To allow a participant who experiences DLT to continue treatment under ensuring safety and with consent from the participant.

12. **Section 8.2.1, CT/MRI/PET-CT**

    Description of change: Modified required radiological assessment at the EOT visit.

    Rationale for change: Clarification of radiographic assessments requirements at the EOT visit.

13. **Section 8.7, End of Treatment and/or Early Termination and End of Study**

    Description of change: Modified assessment requirements at the EOT visit and defined the exemption for additional safety follow-up.

    Rationale for change: Clarification.

14. **Appendix H, Lugano Classification for Response Assessment**

    Description of change: Added criteria for metabolic response based on PET.

    Rationale for change: To add missing information.

15. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 2 (18 DEC 2020)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to accommodate the requirements of the company that sources LEN. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities [Group 1] and Table 4: Schedule of Activities [Group 2]); Section 8.1.4.2, Disease Characteristics and Treatment History; Appendix G: Follicular Lymphoma International Prognostic Index**

   Description of change: Added FLIPI disease risk assessment.

   Rationale for change: To provide disease risk assessment for participants other than those with DLBCL.

2. **Section 1, Protocol Summary (Figure 1: Study Design Schema)**

   Description of change: Changed "Pa" to "parsaclisib."

   Rationale for change: Clarification.

3. **Section 1, Protocol Summary (Table 5: Schedule of Activities [Groups 3, 4a, and 4b] and Table 6: Schedule of Activities [Group 5])**

   Description of change: Changed the description the dispensing information and the timing of pregnancy testing to align with the global PPP for LEN.

   Rationale for change: To adhere to the requirements of the Global PPP, which was obtained after the CDA was executed with Celgene/BMS.

4. **Section 3, Objectives and Endpoints (Table 7: Objectives and Endpoints)**

   Description of change: [redacted]

   Rationale for change: Correction.

5. **Section 5.1, Inclusion Criteria (Criterion 3)**

   Description of change: Revised "Group 4" to include Group 4a and Group 4b.

   Rationale for change: Clarification.

6. **Section 5.1, Inclusion Criteria (Criterion 7)**

   Description of change: Added detailed criteria for participants with hematologic abnormalities secondary to bone marrow involvement by DLBCL.

   Rationale for change: Detailed criteria are needed for appropriate safety and tolerability assessment.

7. **Section 5.1, Inclusion Criteria (Criterion 11)**

   Description of change: Changed "3 months" to "90 days" and added Criterion 11.d to define the requirement for using LEN in Groups 3 and 5.

   Rationale for change: To adhere to the requirements of the Global PPP, which was obtained after the CDA was executed with Celgene/BMS.

8. **Section 5.2, Exclusion Criteria (Criterion 4.l)**

   Description of change: Added groups for which this criterion is applicable.

   Rationale for change: Groups 1 and 2 do not require oral medication; therefore, this criterion is not applicable for those groups.

9. **Section 6.1, Study Treatments Administered (Table 10: Study Treatment Information)**

   Description of change: Added administration instructions for cases in which a participant's weight could generate a tafasitamab concentration that is out of the allowed range and changed the information regarding the packaging and storage of LEN.

   Rationale for change: Some Japanese participants have low weight, in which case use of a 250 mL infusion bag may cause the required concentration of tafasitamab to be out of the accepted range. Also, the LEN information on packaging and storage was corrected.

10. **Section 6.1.1, Tafasitamab Regimen 1: 28-Day Cycle (Groups 1, 3, 4a, and 4b)**

    Description of change: Added that a delay of a dose on Day 15 from Cycle 4 onward is permitted for specific situations.

    Rationale for change: To improve feasibility.

11. **Section 6.1.4, Lenalidomide (Groups 3 and 5)**

    Description of change: Changed the information on administration of LEN in Groups 3 and 5 to follow the Global PPP.

    Rationale for change: To adhere to the requirements of the Global PPP, which was obtained after the CDA was executed with Celgene/BMS.

12. **Section 6.6.1, Tafasitamab Modification for Grade 3 Infusion-Related Reaction (All Groups)**

    Description of change: Added description to allow flexibility of infusion speed after a single 2-hour infusion is judged to be appropriate by an investigator.

    Rationale for change: To clarify the requirement of treatment continuation in participants with an AE.

13. **Section 6.6.3, Management of Infusion-Related Reactions (Table 12: Management of Infusion-Related Reactions)**

    Description of change: Added description to allow flexibility of infusion speed after a participant's condition is judged to be stable by an investigator.

    Rationale for change: To improve the feasibility of avoiding an infusion duration that exceeds the stability of tafasitamab.

14. **Section 6.6.4, Dose Modification for Tafasitamab in Monotherapy (Groups 1 and 2); Section 6.6.5.1, Criteria for Initiation of Cycle in Combination Therapy (Groups 3, 4a, 4b, and 5)**

    Description of change: Deleted exemptions for participants with hematologic abnormalities secondary to bone marrow involvement by DLBCL and modified the criteria to allow cycle initiation in participants with an AE in consultation with the medical monitor.

    Rationale for change: To remove vague criteria for exemptions for bone marrow involvement and to clarify the criteria for cycle initiation in participants with an AE.

15. **Section 8.3.8.1, Pregnancy Testing**

    Description of change: Added clarification that urine pregnancy tests can be replaced with serum pregnancy tests.

    Rationale for change: To improve feasibility.

16. **Section 8.7, End of Treatment and/or Early Termination and End of Study**

    Description of change: Added criteria for EOS assessments for Group 5 during disease follow-up.

    Rationale for change: Clarification.

17. **Appendix B, Global PPP Lenalidomide Adult**

    Description of change: Added appendix to include the Global PPP.

    Rationale for change: To adhere to the requirements of the Global PPP, which was obtained after the CDA was executed with Celgene/BMS.

18. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 1 (19 SEP 2020)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to add explanations that were requested by PMDA after the Clinical Trial Notification submission. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 5: Schedule of Activities [Group 3, 4a, and 4b])**

   Description of change: Added "X*" on Day 1 of Cycle 13 to EOT for immunochemistry.

   Rationale for change: Correction.

2. **Section 1, Protocol Summary (Table 6: Schedule of Activities [Group 5])**

   Description of change: Modified timepoints for compliance assessment.

   Rationale for change: Correction.

3. **Section 2.1.3, Tafasitamab**

   Description of change: Added text to indicate that tafasitamab is produced by recombinant DNA technology in Chinese hamster ovary cells.

   Rationale for change: PMDA's request.

4. **Section 3, Objectives and Endpoints (Table 7: Objectives and Endpoints); Section 4.1.3, Part 3 – Dose Expansion With the Combination of Tafasitamab and Parsaclisib; Section 8.2.1, CT/MRI/PET-CT; Section 10.4.1.1, Group 3; Section 10.4.1.2, Groups 1, 2, 4a, 4b, and 5; Section 10.5, Interim Analysis**

   Description of change: Objectives and endpoints of efficacy were changed. Regarding Part 2 (Group 3), the endpoints were updated to use IRC assessment according to the guidelines of the International Working Group (Cheson et al 2007), and regarding Parts 2 and 3 (Group 4a, 4b, and 5), the endpoints were updated to use investigator assessment according to response criteria of lymphoma (Cheson et al 2014).

   Rationale for change: Reconsideration of the requirement for the efficacy assessment and the budget constraint, the scope of the efficacy assessment by IRC will be for Group 3 only.

5. **Section 4.3, Study Termination; Section 9.9, Product Complaints**

   Description of change: Added Japan GCP requirements.

   Rationale for change: Inadvertently not included in the original Protocol.

6. **Section 5.1, Inclusion Criteria (Criterion 8.b)**

   Description of change: Added clarification to the criterion to indicate that no further effective standard anticancer therapy can be available to participants in Groups 1 and 2.

   Rationale for change: PMDA's request.

7. **Section 5.1, Inclusion Criteria (Criterion 10.e)**

   Description of change: Added criterion of LVEF of ≥ 50%, assessed by echocardiography.

   Rationale for change: Criterion inadvertently removed during Protocol development.

8. **Section 5.1, Inclusion Criteria (Criterion 11.c)**

   Description of change: Added note regarding female participants who have been amenorrheic for at least 12 months resulting from chemo/radiotherapy.

   Rationale for change: PMDA's request.

9. **Section 5.2, Exclusion Criteria (Criterion 4.h)**

   Description of change: Added exclusion criterion for history or evidence of interstitial lung disease

   Rationale for change: PMDA's request.

10. **Section 5.2, Exclusion Criteria (Criterion 4.m)**

    Description of change: Added note regarding breastfeeding.

    Rationale for change: PMDA's request.

11. **Section 5.2, Exclusion Criteria (Criterion 7.e)**

    Description of change: Added criterion specific to participants in Groups 4a and 4b who have been previously treated with selective PI3Kδ or pan-PI3K inhibitors and/or Bruton's tyrosine kinase inhibitors.

    Rationale for change: Added exclusion of prior therapy in consideration of the expected efficacy.

12. **Section 5.3.2, Activity**

    Description of change: Added statement that the investigator judges whether or not to discharge the participant based on the outcome of assessments scheduled on Day 8.

    Rationale for change: PMDA's request.

13. **Section 6.1, Study Treatments Administered (Table 10: Study Treatment Information)**

    Description of change: Added exception to the minimal duration for a total infusion for Dose Level 3 (1800 mg) in Group 2.

    Rationale for change: PMDA's request.

14. **Section 6.5.1, Definition of a Dose-Limiting Toxicity**

    Description of change: Added clarification that all safety data are considered in order to determine the dose escalation and the RP2D.

    Rationale for change: PMDA's request.

15. **Section 6.6.5.2, Guidelines for Managing Hematological and Other Toxicities (Table 13: Toxicity Management Guidelines for Hematological and Other Toxicities [Groups 3, 4a, and 4b])**

    Description of change: Added clarification that requires referring other dose-modification tables before judging as other toxicities and corrected the duration for dose interruption.

    Rationale for change: Clarification and correction.

16. **Section 6.6.5.3, LEN Dose Modification Guidelines (Groups 3 and 5)**

    Description of change: Modified statement regarding the acceptable interruption duration for Groups 3 and 5.

    Rationale for change: To align with the requirement defined in Section 6.4.

17. **Section 6.6.5.4, Parsaclisib Dose Reductions, Interruption, and Discontinuation Guidelines (Groups 4a and 4b)**

    Description of change: Added statement that participants should be informed to immediately report to the investigator any event of diarrhea.

    Rationale for change: To manage diarrhea appropriately.

18. **Section 6.6.5.4, Parsaclisib Dose Reductions, Interruption, and Discontinuation Guidelines (Groups 4a and 4b)**

    Description of change: Deleted statement that defined the incorrect duration of parsaclisib interruption.

    Rationale for change: In Group 3a and 3b, the longest interruption is 28 days.

19. **Section 7.1.1, Reasons for Discontinuation**

    Description of change: Added development of ILD as a reason for discontinuation.

    Rationale for change: PMDA's request.

20. **Section 8.2, Efficacy Assessments**

    Description of change: Added preference for additional efficacy assessments after EOT until disease progression.

    Rationale for change: To enable long-term follow-up of efficacy if possible.

21. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

    Description of change: Removed progestogen-only hormonal contraception associated with the inhibition of ovulation from the list of highly effective birth control methods.

    Rationale for change: PMDA's request.

22. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

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Approval Task	[redacted] nt Preparer [redacted] Clinical Research Scientist 28-Oct-2025 02:12:44 GMT+0000
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Approval Task	[redacted] [redacted] 28-Oct-2025 06:20:59 GMT+0000
Approval Task	[redacted] over [redacted] Oncology Targeted Therapeutics 28-Oct-2025 12:09:51 GMT+0000
Approval Task	[redacted] Approver [redacted] Biostatistics 28-Oct-2025 15:41:58 GMT+0000

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