Official Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Tafasitamab Plus Lenalidomide in Addition to Rituximab Versus Lenalidomide in Addition to Rituximab in Patients with Relapsed/Refractory (R/R) Follicular Lymphoma Grade 1 to 3a or R/R Marginal Zone Lymphoma

NCT Number: NCT04680052

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Clinical Study Protocol

INCMOR 0208-301

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Tafasitamab Plus Lenalidomide in Addition to Rituximab Versus Lenalidomide in Addition to Rituximab in Patients With Relapsed/Refractory (R/R) Follicular Lymphoma Grade 1 to 3a or R/R Marginal Zone Lymphoma

Product:	**Tafasitamab (INCMOR00208)**
IND Number:	**152,839**
EudraCT Number:	**2020-004407-13**
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MorphoSys Reference Protocol Number:	**MOR208C311**
Phase of Study:	**3**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, Delaware 19803**
Original Protocol:	**08 OCT 2020**
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Amendment 5:	**22 OCT 2021**
Amendment 6:	**15 JUN 2022**
Amendment 7:	**18 APR 2023**

INVESTIGATOR'S AGREEMENT

I have read the INCMOR 0208-301 Protocol Amendment 7 (dated 18 APR 2023) 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
2D-ECHO	2-dimensional echocardiogram
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cell-mediated phagocytosis
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HCV	hepatitis C virus antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf}	area under the single-dose plasma or serum concentration-time curve extrapolated to time of infinity
BCL	B-cell lymphoma
BG	bendamustine + obinutuzumab
BM	bone marrow
BR	bendamustine + rituximab
C1D1	Cycle 1 Day 1
[redacted]	[redacted]
CBC	complete blood count
CFR	Code of Federal Regulations
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
[redacted]	[redacted]
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CPK	creatine phosphokinase
CR	complete response
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	Clinical Study Report

Abbreviations and Special Terms	Definition
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVP	cyclophosphamide, vincristine, prednisone/prednisolone
[redacted]	[redacted]
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
ESMO	European Society for Medical Oncology
EZH2	enhancer of zeste homolog 2
FACS	fluorescence-activated cell sorting
FAS	full analysis set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
[redacted]	[redacted]
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GDPR	General Data Protection Regulation
GELF	Groupe d'Etude des Lymphomes Folliculaires
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviations and Special Terms	Definition
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HR	hazard ratio
[redacted]	[redacted]
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	independent data monitoring committee
IEC	independent ethics committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
[redacted]	[redacted]
INV	investigator
IRB	institutional review board
IRC	independent review committee
IRR	infusion-related reaction
IRT	interactive response technology
IV	intravenous
J-GCP	Japanese Good Clinical Practice
JPI	Japanese package insert
LiHep	lithium heparin
LVEF	left-ventricular ejection fraction
mAb	monoclonal antibody
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MRD	minimal residual disease
MRI	magnetic resonance imaging
MUGA	multigated acquisition
MZL	marginal zone lymphoma
NA	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

Abbreviations and Special Terms	Definition
NE	not evaluable
NHL	non-Hodgkin lymphoma
NK	natural killer
NKCC	natural killer cell count
NR	not reached
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
[redacted]	[redacted]
PHL	potential Hy's law
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetics
[redacted]	[redacted]
PMDA	Pharmaceuticals and Medical Devices Agency
PML	progressive multifocal leukoencephalopathy
POD24	progression of disease within 24 months after initial diagnosis
PP	per protocol
PPS	per protocol set
PR	partial response
PT	prothrombin time
QD	once daily
QoL	quality of life
R^2	rituximab + lenalidomide (Revlimid®)
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone
R^2-CHOP	rituximab, lenalidomide, cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone
RNA	ribonucleic acid
R/R	relapsed/refractory
RSI	Reference Safety Information
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan

Abbreviations and Special Terms	Definition
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SPM	second primary malignancy
Study drugs	Study drugs are defined as tafasitamab/matching placebo, lenalidomide, and rituximab; tafasitamab, lenalidomide, and rituximab are regarded as IMPs (see Table 7 for the exceptions).
Study treatment	Study treatment is defined as tafasitamab plus lenalidomide in addition to rituximab (Treatment Group A [TGA]) or tafasitamab placebo plus lenalidomide in addition to rituximab (Treatment Group B [TGB]).
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
TGA	Treatment Group A
TGB	Treatment Group B
TLS	tumor lysis syndrome
TSH	thyroid-stimulating hormone
TT	thrombin time
[redacted]	[redacted]
ULN	upper limit of normal
USPI	United States prescribing information
VHP	Voluntary Harmonisation Procedure
VTE	venous thromboembolism
WBC	white blood cell
WFI	water for injection
WHO	World Health Organization
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

This Phase 3 double-blind, placebo-controlled, randomized study is designed to investigate whether tafasitamab and lenalidomide as an add-on to rituximab provides improved clinical benefit compared with lenalidomide as an add-on to rituximab alone in patients with R/R FL Grade 1 to 3a or R/R MZL.

Protocol Title:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Tafasitamab Plus Lenalidomide in Addition to Rituximab Versus Lenalidomide in Addition to Rituximab in Patients With Relapsed/Refractory (R/R) Follicular Lymphoma Grade 1 to 3a or R/R Marginal Zone Lymphoma

Protocol Number: INCMOR 0208-301

Objectives and Endpoints:

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

Table 1: Primary and Major/Key Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the efficacy of tafasitamab and lenalidomide in addition to rituximab to the efficacy of placebo and lenalidomide in addition to rituximab in terms of PFS in participants with R/R FL.	PFS by INV assessment in the FL population, using the Lugano 2014 criteria (Cheson et al 2014). PFS is defined as the time from randomization to first documented disease progression, or death from any cause, whichever occurs first.
Key Secondary	
To compare the efficacy of tafasitamab and lenalidomide in addition to rituximab versus placebo and lenalidomide in addition to rituximab in terms of PFS in the overall population (FL and MZL).	PFS by INV assessment in the overall population (FL and MZL populations).
To compare the efficacy of tafasitamab and lenalidomide in addition to rituximab versus placebo and lenalidomide in addition to rituximab in terms of PET-CR rate in FDG-avid FL participants and OS in the FL population.	• PET-CR rate by INV in the FDG-avid FL population, defined as a complete metabolic response at any time after start of treatment. • OS in the FL population.

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 3
Clinical Indication	Participants with an investigator-assessed diagnosis of R/R FL Grade 1, 2, or 3a or R/R MZL who have been previously treated with at least 1 anti-CD20 antibody containing therapy (eg, rituximab, obinutuzumab, or other).
Population	Male and female participants at least 18 years of age who have histologically confirmed Grade 1, 2 or 3a FL or histologically confirmed nodal MZL, splenic MZL, or extranodal MZL. • Must have been previously treated with at least 1 prior systemic anti-CD20 immunotherapy or chemo-immunotherapy. This includes treatments such as rituximab monotherapy or chemotherapy plus immunotherapy with rituximab or obinutuzumab, with or without maintenance. • Must have documented relapsed, refractory, or PD after treatment with systemic therapy: – Relapsed lymphoma: relapsed after initial response of CR or PR ≥ 6 months after prior therapy. – Refractory lymphoma: achieved less than PR to the last treatment or achieved a CR or PR that lasted less than 6 months. – Progressive lymphoma: PD after initial response of SD to prior therapy.
Number of Participants	A total number of 174 PFS events in the FL population are required to detect a HR of 0.65 with 80% power for the primary analysis, using a 2-sided log-rank test at an alpha level of 5% and a 1:1 randomization ratio between the 2 treatment groups. A total of 528 participants with R/R FL need to be randomized 1:1 with stratification (264 participants per treatment group), assuming a median PFS of 27.8 months for lenalidomide in addition to rituximab, 21 months of enrollment, 12 months of follow-up for PFS and 15% of dropouts. A minimum of 60 and up to 90 additional participants with R/R MZL will be randomized at a 1:1 ratio to 1 of the 2 treatment groups. The number of participants with MZL is based on an expected enrollment proportion of FL and MZL participants. Approximately 275 centers globally (Europe, Asia Pacific, North America) will be participating in this study.

Table 2: Key Study Design Elements (Continued)

Study Design	This Phase 3, multicenter, randomized, double-blind, placebo-controlled study is designed to evaluate the efficacy and safety of tafasitamab and lenalidomide in addition to rituximab versus placebo and lenalidomide in addition to rituximab in participants with R/R FL or MZL. Approximately 618 participants will be randomized, including approximately 528 participants with FL and 60 to 90 participants with MZL. Participants will be randomized 1:1 to 1 of 2 treatment groups. An IDMC will review the safety data after the first 60 participants (approximately 30 in each treatment group) have completed 2 cycles of study treatment to monitor and evaluate the safety of the combination treatment. An interim analysis for futility will be performed at approximately 20% information rate (35 PFS events approximately) in the FL population (an HR of ≥ 1.05 will be considered as a nonbinding futility boundary). An IDMC will be involved in reviewing the interim analysis and provide their recommendation as defined in the IDMC charter. FL and MZL participants will be randomized separately, based on different stratification factors. The 3 stratification factors for participants with FL include POD24 (progression of disease within 24 months after initial diagnosis; yes vs no), refractoriness to prior anti-CD20 mAb therapy (yes vs no), and the number of prior lines of therapy (< 2 vs ≥ 2). The 1 stratification factor for participants with MZL is the number of prior lines of therapy (< 2 vs ≥ 2). The primary analysis will be run when 174 PFS events are observed in the FL population. The timing of the analysis is independent of the recruitment target in the MZL population. The overall population analysis may be run concomitantly to the MZL population analysis. Recruitment will be stopped when the required 528 participants with FL for the primary analysis and at least 60 participants with MZL have been randomized. The maximum number of randomized participants with MZL is 90. An IRC will review PET and CT/MRI images to determine ORR, PFS, and DoR according to Lugano response criteria in the FL and overall populations. Details regarding the IRC constitution and procedures will be provided in a separate IRC charter.
Estimated Duration of Study Participation	The study duration for an individual participant is divided into the screening period (up to 28 days), treatment period (up to twelve 28-day cycles), and follow-up period (up to 60 months after EOT). The total duration may be up to approximately 6 years per participant.

Table 2: Key Study Design Elements (Continued)

IDMC	An IDMC will monitor data to ensure the safety of the participants enrolled in this study, and evaluate the efficacy of study treatment at a prespecified interim analysis for futility. Details regarding IDMC constitution, responsibilities, authorities, and procedures will be provided in a separate IDMC charter.
Coordinating Principal Investigator	[redacted] University of British Columbia Vancouver, Canada

Treatment Groups and Duration:

Treatment Group A:

- Tafasitamab (12 mg/kg IV), 28-day cycle
  - Cycles 1 to 3: Days 1, 8, 15, and 22
  - Cycles 4 to 12: Days 1 and 15
- Rituximab (including biosimilars; 375 mg/m^2 IV), 28-day cycle
  - Cycle 1: Days 1, 8, 15, and 22
  - Cycles 2 to 5: Day 1
- Lenalidomide (including generics; 20 mg PO once daily), 28-day cycle
  - Cycles 1 to 12: Days 1 to 21

Treatment Group B:

- Tafasitamab placebo (0.9% saline solution) IV, 28-day cycle
  - Cycles 1 to 3: Days 1, 8, 15, and 22
  - Cycles 4 to 12: Days 1 and 15
- Rituximab (including biosimilars; 375 mg/m^2 IV), 28-day cycle
  - Cycle 1: Days 1, 8, 15, and 22
  - Cycles 2 to 5: Day 1
- Lenalidomide (including generics; 20 mg PO once daily), 28-day cycle
  - Cycles 1 to 12: Days 1 to 21

Note for both treatment groups:

- Tafasitamab/placebo
  - Every effort should be made to administer on Days 1, 8, 15, and 22 of Cycles 1 to 3 and then Days 1 and 15 for Cycles 4 to 12. If delays in infusion occur, the subsequent infusion date should not be changed (eg, if the tafasitamab/placebo infusion scheduled for C2D1 is delayed to C2D4 or later, this infusion should be skipped and the next infusion should be C2D8).

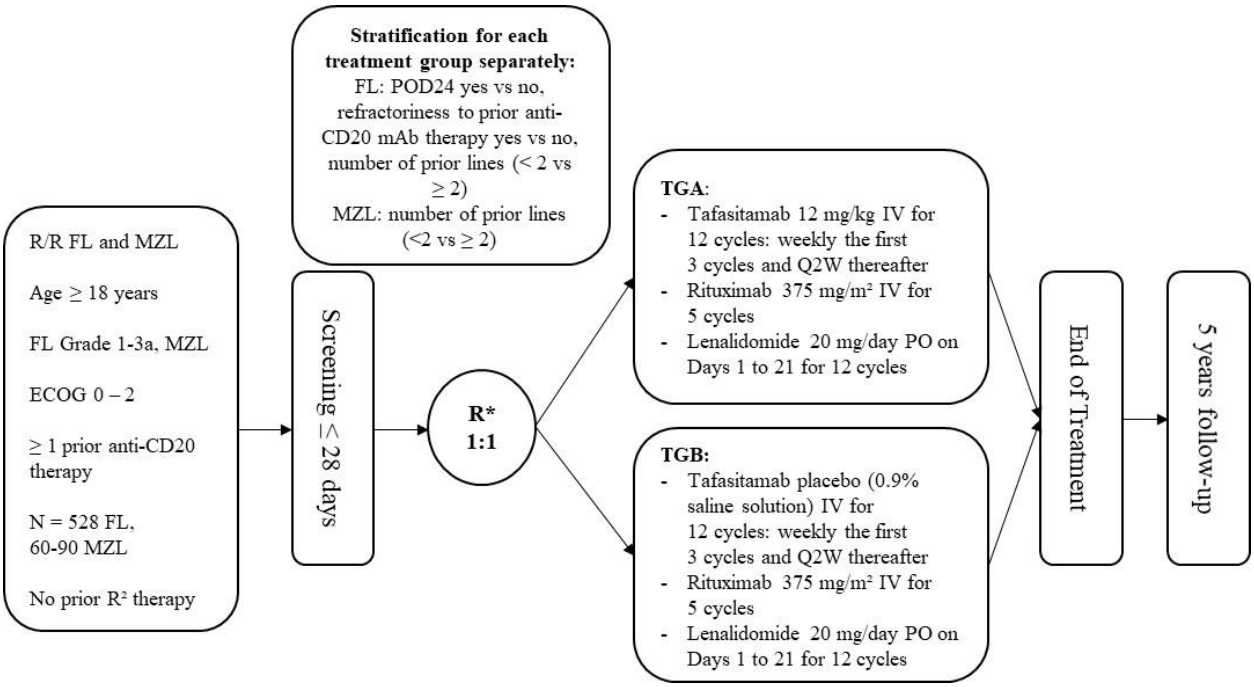
- Lenalidomide**:**
  - For participants with *moderate renal insufficiency* (creatinine clearance ≥ 30 mL/min to < 60 mL/min), the starting dose of lenalidomide must be reduced to **10 mg** QD on the same schedule. The dose of lenalidomide may be increased to 15 mg QD on Days 1 to 21 of each cycle if no Grade 3/4 lenalidomide-related toxicities occur after 2 cycles.
  - Lenalidomide should be taken at approximately the same time every day.
- Rituximab:
  - Rituximab infusion should be administered at approximately 30 minutes after tafasitamab/placebo infusion but no less than 15 minutes after the tafasitamab/placebo infusion is completed (see Section 6.1); to avoid skipping a dose, rituximab infusion is allowable the next day.

The treatment period for each participant starts with first intake of study treatment at C1D1. All subsequent treatment days and assessments are calculated from C1D1. The timing of subsequent treatment days and assessments should not change and should remain on schedule, regardless of interruptions in study drug administration.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. Figure 1 presents the study design, and Table 3 and Table 4 present the schedule of activities and laboratory assessments, respectively.

See Section 6 for additional information on tafasitamab/placebo, lenalidomide, and rituximab administration.

Figure 1: Study Design Schema



*Randomization will apply separately for FL versus MZL populations.

Table 3: Schedule of Activities

Activities	Screening Period	Treatment Period										EOT	Follow-Up Period			Notes
			Cycle 1 (± 1 day[a])			Cycles 2 and 3 (± 1 day[a])				≥ Cycle 4 (± 2 days[a])			Safety Follow-Up	Efficacy Follow-Up	Survival Follow-Up	
	Up to Day −1	C1D1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	EOT (± 2 days)	90 Days From EOT (± 7 days)		Every 12 Weeks From EOT (± 4 weeks)	
Administrative and general procedures (see Section 8.1)																
Informed consent	X															
Demography and medical history	X															
Inclusion/exclusion criteria	X	X														
Lenalidomide counseling	X	X				X				X		X				
Anticancer therapies and procedures	X												X	X	X	
IRT registration	X	X	X	X	X	X	X	X	X	X	X	X				
Treatment administration (see Section 6.1)																
Tafasitamab/placebo		X	X	X	X	X	X	X	X	X	X					Up to 12 cycles.
Lenalidomide		X				X				X						Up to 12 cycles, Day 1 to Day 21.
Rituximab		X	X	X	X	X				X						Up to 5 cycles.
Safety assessments (see Section 8.3)																
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X			
Physical examination	X*	X				X				X		X*				*Comprehensive examination at screening and EOT; targeted for all other visits.
B-symptoms	X	X				X				X		X				
ECOG performance status	X	X				X				X		X				
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X				
Body weight	X	X				X				X		X				

Table 3: Schedule of Activities (Continued)

Activities	Screening Period	Treatment Period										EOT (± 2 days)	Follow-Up Period			Notes
			Cycle 1 (± 1 day[a])			Cycles 2 and 3 (± 1 day[a])				≥ Cycle 4 (± 2 days[a])			Safety Follow-Up	Efficacy Follow-Up	Survival Follow-Up	
	Up to Day −1	C1D1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		90 Days From EOT (± 7 days)		Every 12 Weeks From EOT (± 4 weeks)	
Safety assessments (continued; see Section 8.3)																
Height	X															
12-lead ECG	X															Repeat as clinically indicated after screening.
2D-ECHO or MUGA scan	X															
Efficacy assessments (see Section 8.2)																
Bone marrow core biopsy/bone marrow aspirate* (local)	X	X*,†										X‡				*If a biopsy is not clinically feasible. an aspirate should be collected. †At the time of radiologic CR only if bone marrow is involved at screening. ‡Only if bone marrow is involved at screening and morphologic CR is not seen on treatment.
Bone marrow aspirate for central MRD assessment	X	X*										X				*At the time of radiologic CR only if bone marrow is involved at screening.
PET scan	X									X*		X*,†		X*,†		*Only to confirm radiologic CR in FDG-avid participants. †Repeat only if no prior on-treatment PET was performed.
CT/MRI	X	Year 1: every 12 weeks (3 mo, ± 2 wk) Years 2-3: every 16 weeks (4 mo, ± 2 wk) Years 4-6: every 24 weeks (6 mo, ± 3 wk)										X		X*		*Only if EOT is not due to disease progression.

Table 3: Schedule of Activities (Continued)

Activities	Screening Period	Treatment Period										EOT	Follow-Up Period			Notes
			Cycle 1 (± 1 day[a])			Cycles 2 and 3 (± 1 day[a])				≥ Cycle 4 (± 2 days[a])			Safety Follow-Up	Efficacy Follow-Up	Survival Follow-Up	
	Up to Day −1	C1D1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	EOT (± 2 days)	90 Days From EOT (± 7 days)		Every 12 Weeks From EOT (± 4 weeks)	
Efficacy assessments (continued; see Section 8.2)																
Response assessment		Year 1: every 12 weeks (3 mo, ± 2 wk) Years 2-3: every 16 weeks (4 mo, ± 2 wk) Years 4-6: every 24 weeks (6 mo, ± 3 wk)										X		X*	X†	[redacted]
Survival status															X	
Quality-of-life assessments (see Section 8.2.5)																
EORTC QLQ-C30 questionnaire		X				X				X		X		X*		*During efficacy follow-up, questionnaires must be completed at the same time as response assessment (see above).
EQ-5D-5L questionnaire		X				X				X		X		X*		
FACT-Lym questionnaire		X				X				X		X		X*		

[a] Additional visit windows will be provided in referenced sections, as appropriate.

Table 4: Schedule of Laboratory Assessments

Activities	Screening	Treatment Period										EOT	Follow-Up Period			Notes
			Cycle 1 (± 1 Day)			Cycles 2 and 3 (± 1 Day)				≥ Cycle 4 (± 2 Days)			Safety Follow-Up	Efficacy Follow-Up	Survival Follow-Up	
	Up to Day −1	C1D1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		90 Days From EOT (±7 days)		Every 12 Weeks From EOT (± 4 weeks)	
Laboratory assessments (see Section 8.3.5)																
Hematology	X	X	X	X	X	X		X		X		X				
Clinical chemistry	X	X	X	X	X	X		X		X		X				
Coagulation	X	X				X				X		X				
C-reactive protein	X	X				X				X		X				
Urinalysis	X															Repeat if clinically indicated after screening.
Creatinine clearance	X															See Appendix C.
Hepatitis virus and HIV serology	X															
IgG, IgA, and IgM	X					X*				X*		X				*Cycle 2 and every 2 cycles thereafter.
TSH	X					X*				X*		X				
Pregnancy testing	X*	X*	X	X	X	X		X†		X†		X‡	X‡			*Serum at screening and Day 1 before first dose. †Repeat monthly or biweekly on treatment; see Section 8.3.5.2. ‡Repeat monthly between EOT and safety follow-up.
[redacted]																

Table 4: Schedule of Laboratory Assessments (Continued)

	Screening	Treatment Period										Follow-Up Period			
			Cycle 1 (± 1 Day)			Cycles 2 and 3 (± 1 Day)				≥ Cycle 4 (± 2 Days)		Safety Follow-Up	Efficacy Follow-Up	Survival Follow-Up	
Activities	Up to Day −1	C1D1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	EOT	90 Days From EOT (±7 days)		Every 12 Weeks From EOT (± 4 weeks)	Notes
[redacted]																

2. INTRODUCTION

2.1. Background

2.1.1. Indolent Non-Hodgkin Lymphoma

Indolent NHL comprise approximately one-third of malignant lymphomas. Follicular lymphoma and MZL are the most common indolent NHL subtypes and account for approximately 20% to 25% and 7% of adult NHL cases, respectively (Swerdlow et al 2016). Both subtypes are considered incurable as patients usually respond to initial therapy but typically relapse over time. Current treatment outcomes have significantly improved over recent years with the inclusion of anti-CD20 immunotherapy (rituximab or obinutuzumab) to chemotherapy backbones such as bendamustine, CHOP, or CVP, often followed by anti-CD20 antibody maintenance therapy for 2 years (Monga et al 2019, NCCN 2020, O'Nions and Townsend 2019).

The incidence rate for FL ranges from 2.1/100,000 in France to 4.3/100,000 in the United States and from 0.5/100,000 in Australia to 2.6/100,000 in the United Kingdom for the MZL subtype.

2.1.2. Follicular Lymphoma

Follicular lymphoma is characterized by an indolent clinical course, a typical cell morphology, and the presence of a chromosomal translocation, t(14;18)(q32;q21) or variant in 85% of patients (Relander et al 2010), which can result in the overexpression of the BCL-2 protein, a member of a family of proteins that block apoptosis. The neoplastic lymphocytes in FL express pan-B-cell antigens CD19, CD20, CD22, and CD79a, as well as markers of the germinal center (including CD10 and BCL-6).

Histologically, the follicular form of NHL is composed mainly of centrocytes with an admixture of centroblasts. Follicular lymphoma is generally subdivided into 3 grades (Freedman 2014), which are based on the number of large transformed cells in 10 malignant follicles viewed at high power (Martinez et al 2007). Grade 3 is further divided into 2 subgroups, 3a and 3b; with 3b considered more aggressive (Hans et al 2003).

Patients with FL usually present with painless diffuse lymphadenopathy. Approximately 10% of patients present with B-symptoms (fever, drenching night sweats, loss of 10% of body weight in 6 months). The disease usually is widespread at presentation, with the involvement of multiple lymph node-bearing sites, liver, and spleen.

2.1.3. Marginal Zone Lymphoma

Marginal zone lymphoma is a heterogeneous indolent lymphoma type, further subclassified into extranodal MZL, splenic MZL, and nodal MZL (Swerdlow et al 2016).

Clinical presentation of patients with MZL is often characterized by an indolent clinical course, a slow growing lymphadenopathy, organomegaly, and cytopenia (Pileri et al 2004, Dos Santos et al 2017). Systemic B symptoms and spontaneous TLS are uncommon. However, the clinical presentation of these patients varies depending on the subtype, such as extranodal, nodal, or splenic MZL.

2.1.4. Treatment Algorithm for Indolent Non-Hodgkin Lymphoma

Both FL and MZL demonstrate a variable clinical course, with options for management ranging from active surveillance for asymptomatic patients to chemo-immunotherapy, immunotherapy, or treatment with targeted agents for those with symptomatic disease.

2.1.4.1. First-Line Therapy

Treatment guidelines in both the United States and Europe recommend chemo-immunotherapy with anti-CD20 antibodies (rituximab or obinutuzumab) and chemotherapy such as CHOP or CVP, often followed by anti-CD20 antibody maintenance therapy for 2 years (Dreyling et al 2016, NCCN 2020, O'Nions and Townsend 2019). In the GALLIUM study (NCT01332968), addition of obinutuzumab to chemotherapy (bendamustine, CHOP, or CVP) resulted in an HR for progression, relapse, or death of 0.66 (95% CI: 0.51, 0.85; p = 0.001) and a superior 3-year PFS rate of 80.0% versus 73.3%, compared with rituximab plus chemotherapy (Marcus et al 2017).

In patients with localized MZL, initial treatment depends on specific subtype and usually involves antibiotics, surgery, or radiotherapy (Zucca et al 2020, NCCN 2020). In patients with advanced stage MZL, both the NCCN and the European guidelines (ESMO) recommend chemo-immunotherapy in the first-line setting similar to those recommended for the treatment of FL patients.

2.1.4.2. Treatment of Relapsed/Refractory Disease

Despite initial response to the first-line therapy, unfortunately most patients with FL experience relapse. Of these, approximately 20% progress within 24 months of initial diagnosis (POD24). This group of patients has a poor prognosis with a markedly impaired OS compared with those who do not progress within 24 months after initial diagnosis (5-year OS: 50% vs 90%, respectively; Casulo et al 2015).

There is no standard treatment approach for patients with relapsed indolent NHLs such as FL or MZL, and these patients are treated similarly despite being distinct entities (Dreyling et al 2016, NCCN 2020, Zucca et al 2020). Treatment choice is usually based on DoR to prior therapies, types of prior therapies, and patient comorbidities. Treatment options include radiation, rituximab monotherapy, anti-CD20–containing chemo-regimens such as BR or BG, R-CHOP, or R-CVP. In addition, the PI3K inhibitors idelalisib, copanlisib, and duvelisib are recommended in R/R patients after 2 prior therapies (NCCN 2020). However, despite improvements in treatment options for R/R FL and MZL, there is a high medical need for additional treatment options with improved outcomes and better safety profiles.

The EMA and FDA recently approved obinutuzumab in combination with bendamustine (BG), followed by obinutuzumab (G) maintenance for the treatment of patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen (NCT01059630; GADOLIN study). After a median follow-up time of 21.9 months in the obinutuzumab plus bendamustine group and 20.3 months in the bendamustine monotherapy group, PFS was significantly longer with BG (median not reached [95% CI: 22.5 months, not estimable]) than with bendamustine monotherapy (14.9 months [95% CI: 12.8, 16.6]; HR, 0.55 [95% CI: 0.40, 0.74]; p = 0.0001; Sehn et al 2016).

On 18 JUN 2020, the FDA granted accelerated approval to the EZH2 inhibitor tazemetostat for adult patients with R/R FL whose tumors are positive for an EZH2 mutation and who have received at least 2 prior systemic therapies, and for adult patients with R/R FL who have no satisfactory alternative treatment options.

2.1.4.3. Lenalidomide Plus Rituximab (R^2) in Relapsed/Refractory Follicular Lymphoma and Marginal Zone Lymphoma

It was demonstrated that immunomodulation with lenalidomide plus rituximab is a promising novel treatment approach for patients with indolent lymphoma. The positive outcome of the AUGMENT Phase 3 study comparing rituximab plus lenalidomide versus rituximab plus placebo in patients with relapsed and/or refractory FL or MZL who were considered appropriate for rituximab monotherapy has led to FDA approval (Revlimid 2019). This treatment received EU approval for the treatment of patients with previously treated FL (European Commission 2019).

- In the AUGMENT study (NCT01938001), a superiority in PFS by investigator was demonstrated in favor of the R^2 arm with a reduced risk of progression by 49% (HR, 0.51 [0.38 to 0.69], and median PFS of 25.3 months in R^2 arm [21.2 to NE] vs 14.3 [12.4 to 17.7] in the placebo arm), and an increase in median PFS by more than 2 years compared with rituximab monotherapy (39.4 months [95% CI, 22.9 months to not reached] vs 14.1 months [95% CI, 11.4 to 16.7 months]). However, the probability to remain free of progression at 2 years was 58% (95% CI: 49%, 65%) following R^2 treatment, leaving room for further improvement of the clinical outcome. Adverse events were more common in the lenalidomide plus rituximab group compared with the rituximab plus placebo group, largely due to higher rates of Grade 3/4 neutropenia, which was successfully managed through dose modifications and growth factors (Leonard et al 2019).
- The ongoing Phase 3b study MAGNIFY (NCT01996865) compares the efficacy and safety of 12 cycles of the lenalidomide plus rituximab combination for induction with later randomization to lenalidomide plus rituximab vs rituximab maintenance in patients with R/R indolent lymphoma (FL, MCL, or MZL; NCT01996865). Interim results of the R^2 induction phase were recently presented with a median PFS of 36.0 months (95% CI: 26.5, not estimable [Sharman et al 2019]).
- In the RELEVANCE study (NCT01650701), efficacy results were recently reported to be similar with the rituximab plus lenalidomide combination compared to the current standard of care, rituximab plus chemotherapy combination, in patients with previously untreated advanced FL. Grade 3/4 neutropenia and febrile neutropenia/infection rates were less common in the rituximab plus lenalidomide group than in the rituximab plus chemotherapy group, demonstrating again the importance of an immunomodulatory treatment approach (RELEVANCE study; Morschhauser et al 2018).

2.1.4.4. Tafasitamab

Tafasitamab (INCMOR00208; MOR00208/MOR208/XmAb5574/tafasitamab-cxix) is an Fc-enhanced, humanized mAb against the pan B-cell antigen CD19 and is produced by recombinant DNA technology in Chinese hamster ovary cells. CD19 is a co-receptor of the B-cell receptor, plays a key role in B-cell development and proliferation, and is expressed ubiquitously on most B cells in the B-cell maturation line, including pro-B cells. It serves as a broader target compared with CD20.

The Fc-modification led to increased binding affinity for Fc receptors on effector cells, particularly on NK cells, thereby increasing NK-cell–mediated effector functions on tumor cell lines in vitro with enhanced ADCC, ADCP, and direct cytotoxic effects (apoptosis; Horton et al 2008). Antibody-dependent cell-mediated phagocytosis and direct cytotoxic effects (apoptosis) was also increased. In preclinical studies, antitumor activity was increased versus respective monotherapy treatments when tafasitamab was combined with rituximab and different chemotherapeutic and nonchemotherapeutic drugs including lenalidomide (data on file). For the combination with rituximab or lenalidomide, increased activity was observed on NHL cell lines with respect to ADCC and inhibition of tumor cell proliferation. These data suggest a rationale and a potential clinical benefit of the tafasitamab add-on strategy to rituximab plus lenalidomide in patients with R/R FL and R/R MZL.

Tafasitamab is currently approved in the United States (Monjuvi®) and the European Union and other countries (Minjuvi®) in combination with lenalidomide, followed by tafasitamab monotherapy, for the treatment of adult patients with R/R DLBCL who are not eligible for autologous stem cell transplantation.

2.1.4.5. Tafasitamab Monotherapy in Non-Hodgkin Lymphomas

Monotherapy with tafasitamab has shown promising clinical activity and acceptable toxicity in a Phase 1 study in R/R CLL/SLL (NCT01161511; Woyach et al 2014) and a Phase 2a study in R/R NHL (NCT01685008). Treatment with tafasitamab in NHL achieved a 29% ORR in patients with FL (n = 34) and 33% ORR in patients with MZL (n = 9), with some responses (n = 4) ongoing for more than 4 years (Jurczak et al 2018, Jurczak et al 2019). Median DoR was 24 months (95% CI: 2.6, NE) in R/R FL patients and was not reached in R/R MZL patients. Median PFS was 8.8 months (95% CI: 5.4, 20.5) in FL patients and 3.5 months (95% CI: 2.0, NR) in the MZL patients. Tafasitamab as single agent is well-tolerated, and its primary side effects consist of those induced by B-cell depletion. Neutropenia ≥ Grade 3 was observed in 5.9% of FL and 9.1% of MZL patients, respectively (Jurczak et al 2018, Jurczak et al 2019).

2.1.4.6. Combination Therapy With Tafasitamab and Lenalidomide in Non-Hodgkin Lymphomas

In the single-arm, Phase 2 study in participants with R/R DLBCL (NCT02399085; L-MIND), among 80 participants evaluable for efficacy, the combination of tafasitamab plus lenalidomide achieved an ORR of 57.5% (46 of 80 participants), a CR rate of 40.0% (32 of 80 participants), and a median DoR of 34.6 months (95% CI: 26.1, NR). This combination treatment has received breakthrough therapy designation by the FDA and was recently approved (BLA 761163).

The safety data from this study indicate that tafasitamab in combination with lenalidomide is well tolerated in the population of patients with R/R DLBCL. The majority of events were CTCAE Grade 1 (840 of 1639 events) or Grade 2 (489 of 1639 events) and mild in intensity (1027 of 1639 events). The most frequently reported hematological TEAEs were neutropenia in 41 participants (50.6%), anemia in 30 participants (37%), thrombocytopenia in 25 participants (30.9%), leukopenia in 12 participants (14.8%), and febrile neutropenia in 10 participants (12.3%). Events of neutropenia were manageable with dose reduction/modification and treatment with G-CSF.

The most frequently reported nonhematological TEAEs were coded under the SOC infections and infestations (59 participants [72.8%]). The majority were Grade 1 or Grade 2 and mild in intensity. The most frequently reported TEAEs within this SOC were under the category urinary tract infection (as defined per customized MedDRA query), experienced by 18.5% of participants. Thirty participants (37.0%) experienced an event under the category rash, 10 participants (12.3%) experienced an event under the category infective pneumonia, and 4 participants (4.9%) experienced an event under the category sepsis. In total, 9 participants (11.1%) experienced AESIs during the study including tumor flare and dermatitis allergic (3 participants [3.7%] each), basal cell carcinoma (second primary malignancy; 2 participants [2.5%]), and myelodysplastic syndrome (1 participant [1.2%]). The AESIs of basal cell carcinoma (1 event; Grade 2), myelodysplastic syndrome (Grade 4), and tumor flare (1 event; Grade 3) were serious; all other AESIs were nonserious. No participants experienced Grade ≥ 3 infusion-related reaction, tumor lysis syndrome, or cytokine release syndrome. No participants reported overdose during the study. Only 5 participants experienced an infusion-related reaction; all were Grade 1 in severity. In total, 42 participants (51.9%) experienced 78 serious TEAEs during the study. The most frequently reported serious TEAEs were coded under the SOC infections and infestations (21 participants [25.9%]). The most frequently reported Grade ≥ 3 serious TEAEs were pneumonia (7 participants [8.6%]) and febrile neutropenia (5 participants [6.2%]).

Eight participants (9.9%) died while on treatment, of which 3 (3.7%) were due to AEs (sudden death, cerebrovascular accident, respiratory failure); none of these deaths were considered related to study treatment. The remaining 5 deaths were due to disease progression.

The incidence of TEAEs leading to discontinuation of both or only one of the study drugs was 24.7% (20 participants), with neutropenia being the most common reason (3 out of 20 participants [15.0%]). Ten participants (12.3%) discontinued both study drugs due to TEAEs. In total, 79 participants (98.8%) experienced a TEAE during the combination treatment phase (% of participants with a TEAE before discontinuation of lenalidomide + 7 days) compared with 37 participants (72.5%) after discontinuation of lenalidomide + 7 days. Thus, a notably reduced incidence and severity of TEAEs after cessation of lenalidomide was observed.

Review of laboratory values, vital signs, ECGs, and other safety parameters did not indicate any clinically meaningful safety findings for either the combination treatment or tafasitamab.

Refer to the IB for any additional information or findings.

2.1.4.7. Combination Therapy With Tafasitamab + Lenalidomide + Rituximab + CHOP Chemotherapy in Previously Untreated Diffuse Large B-Cell Lymphoma

The Phase 1b study MOR208C107 (First-MIND, NCT04134936) in participants with newly diagnosed DLBCL evaluates the safety and preliminary efficacy of tafasitamab or tafasitamab plus lenalidomide in addition to R-CHOP and has the primary objective to assess the safety of these combination treatments. Between DEC 2019 and AUG 2020, 66 participants were randomized into the study: 33 participants received tafasitamab + R-CHOP (Arm A), and 33 participants received tafasitamab + lenalidomide in addition to R-CHOP (Arm B). Recruitment is complete.

Preliminary data based on a data cutoff date of 09 DEC 2020 demonstrated that no new safety signals were identified in either study arm compared to data from patients with DLBCL treated with R-CHOP or R^2-CHOP. The addition of tafasitamab to R-CHOP or R^2-CHOP did not add clinically relevant side effects.

Overall, TEAEs were more frequently observed in Arm B (tafasitamab + lenalidomide + R-CHOP) versus Arm A (tafasitamab + R-CHOP). The most frequent events by system organ class were blood and lymphatic system disorders, experienced by 28 participants (84.8%) in Arm A and 29 participants (87.9%) in Arm B. Grade ≥ 3 TEAEs in Arm B were driven by a higher incidence of neutropenia (66.7% vs 54.5%) and thrombocytopenia (30.3% vs 12.1%). Grade ≥ 3 febrile neutropenia occurred in 6 participants (18.2%) in Arm A and 4 participants (12.1%) in Arm B. Grade ≥ 3 infections were reported in 6 participants (18.2%) in both treatment arms. Serious TEAEs were experienced by 31 participants (47.0%): 14 (42.4%) in Arm A and 17 (51.5%) in Arm B. Infusion-related reactions occurred in 1 participant (3.0%) in Arm A. There were 2 deaths reported in Arm A and 1 death in Arm B, which were considered unrelated to study treatment by the investigator.

These safety results are in line with previously published results of a cross-trial comparison of randomized studies comparing lenalidomide + R-CHOP versus R-CHOP: ROBUST Phase 3 (NCT02285062) and ECOG-ACRIN1412 Phase 2 (NCT01856192). Therefore, no new safety signals were identified in either arm compared with published data from patients treated with either R-CHOP or R^2-CHOP.

Based on these data and despite the more frequent hematologic TEAEs in Arm B, the preliminary data suggest that the combination of tafasitamab + lenalidomide + rituximab in addition to CHOP chemotherapy appears to be a tolerable and manageable regimen.

2.2. Study Rationale

2.2.1. Role of the Micro-Environment

The rationale for this non-chemotherapy, immunomodulatory treatment with rituximab and lenalidomide is based on the observation that the microenvironment and the interaction of the lymphoma with the microenvironment play an important role in the progression and resistance to treatment in FL, pointing to the importance of the impaired host immune response in the pathogenesis of this disease (Dave et al 2004, Federico et al 2009, Gribben 2010, Ramsay et al 2009, Solal-Céligny et al 2004). Preclinically, lenalidomide restored the response of tumor-infiltrating lymphocytes (Ramsay et al 2009) and increased NKCC and function in

peripheral blood and NK cell lines (Wu et al 2008). Adding lenalidomide to rituximab enhanced ADCC, monocyte-mediated killing (ADCP), immune synapse formation, and direct cytotoxicity against FL cells (Lagrue et al 2015, Leonard et al 2019, Ramsay et al 2009, Wu et al 2008).

2.2.2. Role of Tafasitamab

Despite progressive improvements in the availability of treatment options for patients with R/R FL and R/R MZL, there is a need to develop additional treatment options that may further improve outcomes in terms of PFS and OS, and with better tolerability profiles.

With increasing use of anti-CD20 antibodies and heterogeneity of intensity of CD20 surface expression, resistance to anti-CD20–based therapies is an increasing clinical concern. Indeed, CD20 C-terminal deletion mutations associated with loss of CD20 expression in NHL patients with disease progression after rituximab therapy was described as one of the resistance mechanisms. Moreover, the heterogeneity of CD20 expression indicates that subclones expressing lower CD20 levels are present in CD20-positive lymphoma cells and that surviving clones may cause resistance or relapse after rituximab therapy (Smith 2003, Terui et al 2009).

CD19 is a co-receptor of the B-cell receptor, plays a key role in B-cell development and proliferation, and is expressed ubiquitously on most B cells in the B-cell maturation line, including pro-B cells. It serves as an alternative target to CD20. CD19 is the earliest and most broadly expressed B-cell marker and is highly expressed on tumor cells of most patients with BCL.

2.2.3. Scientific Rationale for Study Design

The current study is an integral part of the tafasitamab development program in the FL/MZL indication. The safety profile of the tested regimen (tafasitamab + lenalidomide + rituximab) will be assessed taking into consideration also clinical data generated for this combination in studies in DLBCL participants. This clinical study's safety monitoring plan is justified and adequate from a safety standpoint in view of the following:

- The design of the safety plan permits ongoing monitoring and comparison of the safety outcomes in participants exposed to tafasitamab in addition to lenalidomide with rituximab versus in participants exposed to lenalidomide in addition to rituximab regimen only.
- The safety monitoring is secured by an unblinded IDMC.
- A safety data collection at time of the EOT permits the evaluation of late appearing adverse effects that may emerge or progress after the administration of study treatment.
- The measures used to assess safety are well-defined and reliable, and the proposed safety analyses are adequate to assess the effects of the administration of tafasitamab in addition to well know combination of lenalidomide and rituximab, as well as to assess safety of adding rituximab to already known combination of tafasitamab with lenalidomide (L-MIND).

2.2.4. Justification for Dose

2.2.4.1. Tafasitamab

Dose selection of tafasitamab for this clinical study is based on preclinical data and the results from 3 clinical studies (ie, clinical study XmAb5574-01, MOR208C201, and MOR208C203/L-MIND), which used tafasitamab at a 12 mg/kg dose. This dose is the same as approved by the FDA and EMA for tafasitamab in combination with lenalidomide for the treatment of R/R DLBCL.

Initial results on safety, tolerability, and PK were generated in a Phase 1 dose-escalation study in R/R CLL/SLL participants (XmAb5574-01). In this study, the maximum tolerated dose was not reached, and the recommended dose for further studies was defined at the highest dose tested (ie, 12 mg/kg with an initially weekly regimen; Clinical Study Report XmAb5574-01). Afterwards, this dose level was tested in 2 clinical studies in R/R NHL/DLBCL participants either as monotherapy (clinical study MOR208C201) or in combination with lenalidomide (clinical study MOR208C203/L-MIND). Based on a detailed exposure-safety assessment across these 2 studies, no trends for increasing TEAEs with increasing exposure were observed (ie, C_{max} and AUC). Thus, tafasitamab showed a manageable safety profile independent of the individual tafasitamab exposure observed.

In contrast, an exposure-response assessment for efficacy showed a direct relationship between tafasitamab monotherapy and clinical efficacy with higher exposure to tafasitamab resulting in increased ORRs and prolonged median PFS (XmAb5574-01 and MOR208C201). In combination with lenalidomide (MOR208C203/L-MIND), tafasitamab exhibited a flat exposure-response relationship, whereas ORRs increased almost 2-folds compared with tafasitamab in monotherapy (XmAb5574-01 and MOR208C201; Report MOR208L035).

According to these results, 12 mg/kg tafasitamab with initially weekly administrations is considered an appropriate regimen with a beneficial risk/benefit ratio for the intended patient population.

2.2.4.2. Lenalidomide and Rituximab

Lenalidomide 20 mg/day and rituximab 375 mg/m^2 dosing in the study is following the same treatment regimen as defined in the registration Phase 3 study AUGMENT (Leonard et al 2019). This study was the basis for FDA approval in the United States for the treatment of adult patients with previously treated FL or MZL (Revlimid 2019) and in the European Union for the treatment of adult patients with previously treated FL (Grade 1-3a).

2.3. Benefit/Risk Assessment

In this study, all eligible participants will be treated with the combination therapy lenalidomide and rituximab. In addition, participants will receive tafasitamab in TGA (experimental arm) to potentially prolong PFS and potentially improve the response rates. Participants in TGB will receive placebo instead of tafasitamab.

The risk assessment of tafasitamab is based on the data from nonclinical studies as well as on clinical experience from completed and ongoing clinical studies. Tafasitamab single agent was well-tolerated in indolent NHL patients (Jurczak et al 2018).

Clinical data on the combination treatment of tafasitamab + lenalidomide + rituximab in addition to CHOP chemotherapy in participants with previously untreated DLBCL demonstrated that no new safety signals were identified and that this combination therapy is tolerable and manageable.

The risks and most common side effects of tafasitamab and lenalidomide in addition to rituximab are IRRs, transient neutropenia, thrombocytopenia, anemia, diarrhea, pyrexia, and asthenia. Treatment-related serious AEs consist mainly of infections or neutropenic fever.

Together, the potential risks identified with tafasitamab and lenalidomide in addition to rituximab alongside with the measures in place to minimize risk to participants participating in this study are justified by the anticipated benefits that may be achieved by the add-on treatment in participants with R/R FL and MZL.

Because the combination of tafasitamab plus lenalidomide in addition to rituximab will be evaluated for the first time in a clinical study, an IDMC will evaluate the safety data from the first 60 randomized participants following the completion of at least the first 2 study treatment cycles (8 weeks) and provide recommendation whether the combination treatments are safe.

In conclusion, the potential risks identified with tafasitamab and lenalidomide as well as those with rituximab alongside with the measures in place to minimize risk to participants participating in this study are justified by the anticipated benefits that may be achieved by the add-on treatment in participants with R/R FL or R/R MZL.

The sponsor hypothesizes that the addition of tafasitamab to rituximab plus lenalidomide will not significantly alter the overall safety and tolerability profile and will improve time-to-event outcomes, response rates, and depth of response in participants with R/R FL or R/R MZL. Therefore, this prospective, randomized, double-blind, placebo-controlled Phase 3 study is designed to determine the efficacy and safety of tafasitamab as an add-on strategy to the immunomodulatory lenalidomide plus rituximab combination in this participant population.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of study treatment may be found in the IB for tafasitamab and in the SmPC, the JPI, and the USPI for both lenalidomide and rituximab (IB, MabThera® 2020, Revlimid 2020, Rituxan® 2020). The IB for tafasitamab and the SmPC (for European sites), JPI (for Japanese sites), and USPI (for US sites) for both lenalidomide and rituximab will be supplied to the clinical sites.

3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the efficacy of tafasitamab and lenalidomide in addition to rituximab to the efficacy of placebo and lenalidomide in addition to rituximab in terms of PFS in participants with R/R FL.	PFS by INV assessment in the FL population, using the Lugano 2014 criteria (Cheson et al 2014). PFS is defined as the time from randomization to first documented disease progression, or death from any cause, whichever occurs first.
Secondary	
Key Secondary Endpoints	
To compare the efficacy of tafasitamab and lenalidomide in addition to rituximab versus placebo and lenalidomide in addition to rituximab in terms of PFS in the overall population (FL and MZL).	PFS by INV assessment in the overall population (FL and MZL populations).
To compare the efficacy of tafasitamab and lenalidomide in addition to rituximab versus placebo and lenalidomide in addition to rituximab in terms of PET-CR rate in FDG-avid FL participants and OS in the FL population.	• PET-CR rate by INV in the FDG-avid FL population, defined as a complete metabolic response at any time after start of treatment. • OS in the FL population.
Other Secondary Endpoints	
To compare the efficacy of tafasitamab and lenalidomide in addition to rituximab versus placebo and lenalidomide in addition to rituximab.	• PET-CR rate by INV in the FDG-avid overall population. • MRD-negativity rate (at thresholds of 10^{-4} and 10^{-5}) at EOT in the FL and the overall populations. • ORR by INV in the FL and overall populations. • DoR by INV in the FL and overall populations. • OS in the overall population.
To compare the efficacy between treatment groups based on IRC assessment.	• PFS by IRC in the FL and overall populations. • ORR by IRC in the FL and overall populations. • DoR by IRC in the FL and overall populations.
To evaluate QoL of tafasitamab and lenalidomide in addition to rituximab versus placebo and lenalidomide in addition to rituximab in the FL and overall population.	QoL as measured by the EORTC QLQ-C30, the EQ-5D-5L, and FACT-Lym tools in the FL and overall populations.
To compare the safety of tafasitamab and lenalidomide in addition to rituximab versus placebo and lenalidomide in addition to rituximab in the FL and overall population.	Safety based on the incidence and severity of TEAEs in the FL and overall population.

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This study is a 1:1 randomized, double-blind, placebo-controlled, parallel group, multicenter, Phase 3 clinical study to compare the efficacy and safety of tafasitamab and lenalidomide in addition to rituximab versus placebo and lenalidomide in addition to rituximab in participants with R/R FL and R/R MZL. The overall study design is described in Figure 1. The study consists of the screening period (≤ 28 days), treatment period (up to twelve 28-day cycles), and a five-year follow-up period.

The overall recruitment will be considered complete once 528 participants with FL for the primary analysis and at least 60 participants with MZL are randomized. The recruitment of participants with MZL will be limited to a maximum of 90 participants. Total enrollment will be approximately 618 participants. Participants will be randomized at a 1:1 ratio to 1 of the 2 treatment groups (see Section 6). Participants with FL and MZL will be randomized separately using different stratification factors. Stratified randomization will be performed using an IRT.

Participants with FL will be stratified at the time of randomization for the following factors:

- POD24 (disease progression within 24 months after **initial** diagnosis): yes versus no
- Refractoriness to prior anti-CD20 mAb therapy: yes versus no (Note: Refractory to anti-CD20 mAb is defined as not achieving a response of CR or PR to a prior regimen containing anti-CD20 mAb, or disease progression occurring during treatment with, or relapse within 6 months after last dose of anti-CD20 mAb.)
- The number of prior lines of therapy: < 2 vs ≥ 2

Participants with MZL will be stratified at the time of randomization for the following factor:

- The number of prior lines of therapy: < 2 versus ≥ 2

Safety data will be reviewed by an IDMC, which will be convened periodically throughout this study as defined in the IDMC charter. The first safety review meeting of IDMC will be held after the first 60 participants (approximately 30 in each treatment group) have completed 2 cycles of study treatment to monitor and evaluate the safety of the combination treatment. Details on periodic safety review meetings are included in the IDMC charter.

An interim analysis for futility will be performed at approximately 20% information rate (35 PFS events approximately) in the FL population. An IDMC will be involved in reviewing the interim analysis and provide their recommendation as defined in the IDMC charter.

An IRC will review PET and CT/MRI images to determine ORR, PFS, and DoR according to the Lugano response criteria (Cheson et al 2014) in the FL and overall populations.

The study will employ safety monitoring activities that will comprise standard evaluation of AE/SAE/AESI reports (preferred term, incidence, toxicity grade, causality), performance status, physical examinations, and laboratory data assessed on an ongoing basis by the sponsor's responsible safety physicians and/or other nominated personnel to provide support in the review of safety data. Such events will be graded using the NCI CTCAE, v5.0 or higher. Laboratory safety assessments will include routine monitoring of hematology and blood chemistry and tests of immunologic parameters.

4.2. Overall Study Duration

The total study duration from first-patient-first-visit to last-patient-last-visit is expected to be approximately 8 years.

The study duration for an individual patient is divided into the screening period (up to 28 days), treatment period (up to 12 months), and follow-up period (up to 60 months after EOT, either completion of the last treatment cycle or treatment discontinuation). The total duration is up to approximately 6 years per participant.

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 of the study's completion or early termination in writing, 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 required by regulatory decision, or upon advice of the IDMC. The IDMC may recommend termination of the study if warranted, as described in the IDMC Charter. If the study is terminated prematurely, the sponsor will notify the investigators/head of study site (Japan), the IRBs, and regulatory bodies of the decision and reason for termination of the study. For Japan, the decision from the sponsor will be via the head of the study site(s) who will notify the investigators and the IRBs of the decision and reason for termination of the study.

The study may also be terminated by the local health authority, IRB, or IEC.

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.

At the sponsor's discretion, the sponsor may decide to use recruitment tools and vendors to support the enrollment activities. Additionally, sites will complete participant enrollment forms for all participants being considered for this study. Completed enrollment forms will be submitted to the sponsor along with completely redacted (pseudonymized) supportive documentation (eg, laboratory reports, pathology reports, imaging reports, and a brief summary of the participant's disease-specific medical history) that is necessary to confirm eligibility. The PI will be ultimately responsible for ensuring participants meet eligibility criteria.

5.1. Inclusion Criteria

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

1. Age ≥ 18 years at the time of signing the ICF.
2. Ability to comprehend and willingness to sign a written ICF for the study.

3. Histologically confirmed Grade 1, 2, or 3a FL or histologically confirmed nodal MZL, splenic MZL, or extranodal MZL as assessed locally (Swerdlow et al 2016); [redacted]

   NOTE: Participants with gastric MZL and evidence of *Helicobacter pylori* must have a *documented* nonresponse to antibiotic therapy prior to randomization.

4. Willingness to avoid pregnancy or fathering children based on the criteria below.

   a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 180 days (6 months) after the last dose of study treatment, even if they have undergone a successful vasectomy, 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. WOCBP participants:

      – Must commit either to abstain continuously from heterosexual sexual intercourse or agree to take appropriate precautions to avoid pregnancy (by using 2 different methods of birth control: one with at least 99% certainty and an additional effective [barrier] method) starting at least 4 weeks before taking the study treatment, while taking the study treatment, during breaks (dose interruptions), and for at least 180 days (6 months) after stopping the study treatment. Permitted methods that are at least 99% effective in preventing pregnancy and the permitted additional effective (barrier) methods (see Appendix A) should be communicated to the participants and their understanding confirmed.

        Note: Because of the increased risk of venous thromboembolism, combined oral contraceptive pills are not recommended. If a participant is currently using combined oral contraception, the participant should switch to one of the effective methods listed in Appendix A. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception.

      – Must have a negative **serum** pregnancy test at screening (within 10-14 days of the first study drug treatment) and before the first dose on Day 1 (within 24 hours of initiating treatment with lenalidomide).

      – Agree to ongoing pregnancy testing during the course of the study; weekly during the first month of study drug treatment, then monthly thereafter for women with regular menstrual cycles or every 2 weeks for women with irregular menstrual cycles (even if true abstinence is the chosen method of birth control) up to and including the EOT visit.

      – Must refrain from breastfeeding and donating oocytes during the course of study and for 180 days (6 months) after the last dose of study treatment.

c. A woman not considered to be of childbearing potential as defined in Appendix A is eligible.

Note: The participants should be informed about the option of donation and cryopreservation of germ cells before the study if applicable.

5. **All participants must:**
   a. Have an understanding that lenalidomide could have a potential teratogenic risk.
   b. Abstain from donating blood while on study treatment and for 28 days after discontinuation of study treatment.
   c. Not share any study medications with another person.
   d. Agree to be counseled about pregnancy precautions and risk of fetal exposure.
   e. In the opinion of the investigator, be able and willing to receive adequate mandatory prophylaxis and/or therapy for thromboembolic events (eg, aspirin 70-325 mg daily or low-molecular-weight heparin). Participants unable or unwilling to take any prophylaxis are not eligible.
   f. In the opinion of the investigator, be able to understand and comply with all study-related procedures, medication use, and evaluations.
   g. In the opinion of the investigator, not have a history of noncompliance or be considered potentially unreliable and/or uncooperative.
6. Tumor tissue sufficient for retrospective central pathology review and correlative studies must be provided to participate in this study; a new biopsy must be performed if progression or relapse of disease is within 24 months from the initial diagnosis (POD24) to exclude transformed cases and potentially misdiagnosed cases. NOTE: A more recent biopsy is preferred if clinically feasible but if not, an archival specimen is acceptable except in cases of POD24 (refer to the Laboratory Manual).
7. Must have been previously treated with at least 1 prior **systemic** anti-CD20 immunotherapy or chemo-immunotherapy. This includes treatments such as the following: rituximab monotherapy or chemotherapy plus immunotherapy with rituximab or obinutuzumab, with or without maintenance. Note: At least **4** doses of anti-CD20 immunotherapy must have been given in prior therapy. Note: Systemic therapy does not include, for example, local involved field radiotherapy for limited stage disease, HBV/HCV therapy, or *H pylori* eradication.
8. Must have **documented** relapsed, refractory, or PD after treatment with systemic therapy (a participant in remission [in CR or PR] after the last prior treatment line would not be eligible).
   a. Relapsed lymphoma: relapsed after initial response of CR or PR ≥ 6 months after prior therapy.
   b. Refractory lymphoma: achieved less than PR to the last treatment or achieved a CR or PR that lasted less than 6 months.
   c. Progressive lymphoma: PD after initial response of SD to prior therapy.
9. Must be in need of treatment for relapsed, refractory, or PD as assessed by the investigator. NOTE: For FL only, refer to GELF criteria (see Appendix G) as a guidance.

10. Participants must have at least 1 measurable disease site. A radiographically measurable lymphadenopathy is defined as at least 1 nodal lesion > 1.5 cm in longest diameter or at least 1 extranodal lesion > 1.0 cm in longest diameter (Cheson et al 2014). The lesion must be confirmed to be measurable by CT, MRI, or PET-CT, at the latest at the time of randomization.

    Note: Participants with PET-negative lesions that are measurable by CT or MRI are eligible and followed up with CT or MRI only as described in Section 8.2.4.

11. ECOG performance status of 0 to 2.
12. Participants with laboratory values at screening defined in Table 6.

Table 6: Inclusionary Laboratory Values

Laboratory Parameter		**Inclusion Criterion**
Hematology (hematological laboratory values should be considered in the absence of growth factors or transfusions)		
a	Platelets	≥ 75 × 10^9/L (unless secondary to BM involvement as demonstrated by BM biopsy).
b	ANC	≥ 1.5 × 10^9/L (unless secondary to BM involvement as demonstrated by BM biopsy).
c	Hemoglobin	≥ 8.0 g/dL (unless secondary to BM involvement as demonstrated by BM biopsy).
Hepatic		
d	ALT	≤ 3 × ULN or < 5 × ULN in cases of documented liver involvement.
e	AST	≤ 3 × ULN or < 5 × ULN in cases of documented liver involvement.
f	Total serum bilirubin	≤ 1.5 × ULN unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma. Participants with Gilbert's syndrome or documented liver involvement by lymphoma may be included if their total bilirubin is ≤ 5 × ULN.
g	Alkaline phosphatase	≤ 3 × ULN or < 5 × ULN in cases of documented liver involvement.
Renal		
h	Serum creatinine clearance	≥ 30 mL/min either measured or calculated using a standard Cockcroft and Gault formula (Cockcroft and Gault 1976).

5.2. Exclusion Criteria

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

1. Women who are pregnant or breastfeeding. For Japan, women who are breastfeeding and wish to enroll must discontinue breastfeeding at least 90 days before receiving study drug/treatment. They must also refrain from breastfeeding during the course of study and for 90 days after the last dose of study treatment.
2. History of or current histology other than FL and MZL or clinical evidence of transformed lymphoma by INV assessment.
3. History of radiation therapy to ≥ 25% of the BM for other diseases.
4. History of prior nonhematologic malignancy except for the following:
   a. Malignancy treated with curative intent and with no evidence of active disease for more than 2 years before screening.
   b. Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled nonmelanomatous skin cancer.
   c. Adequately treated carcinoma in situ without current evidence of disease.
5. Congestive heart failure (left ventricular ejection fraction of < 50%, assessed by 2D-echocardiography or MUGA scan.
6. Participants with:
   a. Known positive test result for HCV (with anti-HCV serology testing) and a positive test for HCV RNA.
      Note: Participants with positive serology must have been tested for HCV RNA and are eligible only in the case of negative HCV RNA.
   b. Known positive test result for chronic HBV infection (defined by HBsAg positivity).
      Note: Participants with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA was undetectable, provided that they are willing to undergo monthly ongoing DNA testing. Antiviral prophylaxis may be administered as per institutional guidelines. Participants who have protective titers of HBsAb (HBsAb positive, HBcAb negative, and HBsAg negative) after vaccination or previously cured hepatitis B are eligible.
   c. Seropositivity for or history of active viral infection with human immunodeficiency virus (HIV).
7. Active systemic infection (including SARS-CoV-2–positive test).
8. Participants in a severely immunocompromised state.
9. Known CNS lymphoma involvement.
10. Uncontrolled concurrent illness.
11. 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.
12. Life expectancy < 6 months.

13. History or evidence of rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.
14. Major surgery (excluding lymph node biopsy) within 28 days prior to signing the ICF unless the participant is recovered at the time of signing the ICF.
15. Any systemic antilymphoma and/or investigational therapy within 28 days prior to the start of Cycle 1.
16. Administration of a **live** vaccine within 28 days prior to the start of study treatment (Cycle 1 Day 1).
17. Prior use of lenalidomide in combination with rituximab.
18. History of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, immunomodulatory drugs, rituximab, other mAbs, and/or the excipients contained in the study drug formulations.
19. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

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

A participant can be rescreened at the discretion of the investigator under certain circumstances. Rescreening is restricted to 1 attempt per participant and can only be performed if 1 of the following criteria is met:

- The participant has already consented and met all of the inclusion and none of the exclusion criteria, and randomization was delayed due to an unexpected change in the participant's personal situation (eg, family issues).
- The participant previously failed to be eligible due to any event (eg, planned surgery, laboratory test result) that has been resolved.

Note: A participant should only be rescreened if there is a clear indication that the participant may be eligible according to the currently valid study Protocol.

If previous screening activities were discontinued and enrollment did not occur, the following procedures should be implemented:

- The eligible participant will receive a new participant number via the IRT.
- A new eCRF will be completed.
- The participant will be documented as rescreened in the source documents.
- A new ICF will be signed as per Section 8.1.1.

A rescreened participant can be randomized if all of the inclusion criteria and none of the exclusion criteria are met and all assessments have been performed as per Table 3 and Table 4.

5.5. Replacement of Participants

No participants will be replaced at any time during this study.

5.6. Independent Data Monitoring Committee

An IDMC will monitor data to ensure the safety of the participants enrolled in this study, and evaluate the efficacy of the treatment. The IDMC will consist of an independent group of clinical and statistical experts who are not involved in the management of the current study.

The IDMC will have access to unblinded aggregated interim data to make recommendations, suggest clinical study Protocol changes, or terminate the study. An unblinded, study-independent group from the CRO will support the IDMC activities. All other study personnel will have access to blinded safety and efficacy data only.

The IDMC safety review will focus on deaths, treatment discontinuations, SAEs, events ≥ Grade 3, and AESIs. The details of the analyses will be defined in the IDMC charter.

The details regarding IDMC constitution, responsibilities, authorities, and procedures and the process by which the IDMC will make recommendations and decisions are provided in the IDMC charter. The charter also defines and documents the content of the safety summaries and general procedures (including communications).

The IDMC will meet on the following schedule:

- After the first 60 randomized participants (approximately 30 in each treatment group) complete at least the first 2 study treatment cycles (8 weeks). The IDMC will review the safety data to monitor and evaluate the safety of the combination treatment and provide recommendation on whether the combination treatments are safe.
- Following the first meeting, the IDMC will meet approximately every 6 months.
- An interim analysis for nonbinding futility is planned at approximately 20% information rate (approximately 35 PFS events) in the FL population. The interim analyses for futility will be conducted by an external unblinded statistician and will be reviewed by the IDMC; the IDMC will use the guidelines provided in Section 10.5 for recommendation of either continuation or early termination of the study at the interim analysis.
- In addition, both the sponsor and the IDMC can request ad-hoc meetings for any reasons.

All AEs meeting SAE/AESI criteria will be reviewed by the sponsor's responsible safety physician on an ongoing basis and in a blinded manner to identify safety concerns. The IDMC will be informed of SUSARs according to expedited reporting rules, and about any potential safety signals.

Following each meeting, the IDMC will recommend to the sponsor whether the study should continue according to the Protocol or may suggest changes to the Protocol based on the outcome of data review. The sponsor will make the final decision for continuation or discontinuation of the study on the basis of the IDMC's recommendation.

6. STUDY TREATMENT

6.1. Study Treatments Administered

A treatment cycle is defined as 28 calendar days and includes treatment with tafasitamab/placebo, lenalidomide, and rituximab. The treatment period for each participant starts with the first administration of study treatment on Cycle 1, Day 1 (C1D1). Study drugs are tafasitamab/placebo, lenalidomide, and rituximab. Tafasitamab, lenalidomide, and rituximab are considered IMPs (see Table 7).

Tafasitamab (12 mg/kg IV) or placebo (0.9% saline solution IV)

- Administered Cycles 1 to 3 on Days 1, 8, 15, and 22, and Cycles 4 to 12 on Days 1 and 15.
- Tafasitamab will be supplied by the sponsor to an unblinded pharmacy. The placebo will be locally sourced and delivered to an unblinded pharmacy. In case of changes in body weight, tafasitamab dosing should be based on the participant's weight as assessed at the most recent treatment cycle.

Rituximab (including biosimilars; 375 mg/m^2 IV)

- Administered Cycle 1 on Days 1, 8, 15, and 22, and Cycles 2 to 5 on Day 1.
- Rituximab should be administered approximately 30 minutes after the tafasitamab/placebo infusion is completed but no less than 15 minutes. Sites have the option for the sponsor to provide rituximab via the IRT. Rituximab may also be obtained by the sites, where applicable. For logistical reasons, rituximab may be administered on the day after the tafasitamab infusion, or administration may be split over 2 consecutive days, according to local practice and the institution's standard of care.

Lenalidomide (including generics) (20 mg PO QD*)

- Administered Cycles 1 to 12 on Days 1 to 21 at approximately the same time every day. Lenalidomide will be provided by the sponsor to the sites.
- *For participants with moderate renal insufficiency (creatinine clearance ≥ 30 mL/min to < 60 mL/min), the starting dose of lenalidomide must be reduced to of 10 mg daily using the same schedule. The dose of lenalidomide may be increased to 15 mg QD on Days 1 to 21 of each cycle if no Grade 3/4 lenalidomide-related toxicities occur after 2 cycles.

Table 7 presents the study treatment information.

Table 7: Study Treatment Information

	Study Treatment 1	Study Treatment 2	Study Treatment 3
Study treatment name:	Tafasitamab	Lenalidomide	Rituximab
Mechanism of action:	Fc-enhanced, humanized mAb against the pan B-cell antigen CD19	Activates and increases number of T cells and NK cells, inhibits proinflammatory cytokines by monocytes, inhibits cell proliferation, and induces inhibition of tumor growth.	Direct effects: complement-mediated cytotoxicity and ADCC.
Dosage formulation:	Powder for concentrate for solution for infusion	Capsules for oral administration	Solution for infusion
Unit dose strength(s)/ dosage level(s):	200 mg in glass vials	Various strengths (refer to the Pharmacy Manual)	Rituximab (originator or biosimilar) will be prescribed and administered according to institutional guidelines.
Administration instructions:	Administered as an IV infusion at a dose of 12 mg/kg. First infusion: 70 mL/h for the first 30 minutes and increased to 125 mL/h; total infusion duration approximately 2.5 hours. Subsequent infusions: 125 mL/h over approximately 2-hours. Tafasitamab is NOT to be administered as an IV push or bolus.[a]	Dispensed at the beginning of each cycle. Participants will self-administer lenalidomide at a starting dose of 20 mg PO QD. Participants with renal impairment will have a starting dose of 10 mg PO QD.	Administered as an IV infusion at the dose of 375 mg/m^2 Rituximab will be administered under the direct supervision of clinical study site personnel. Rituximab will be administered until Cycle 5. Sites should follow product insert instructions for administration adjustments due to toxicity.
Packaging and labeling:	Supplied by sponsor in single-use 20 mL glass vials. Each vial will be labeled as required per country requirement.	Lenalidomide (including generic drugs) from a commercial source. Each container will be labeled as required per country requirement.	Commercial source
Storage:	Vials must be stored at 2°C to 8°C in the original package accessible only to the unblinded clinical study site pharmacy personnel.	As per the label.	As per the label.
Status of treatment in participating countries:	Investigational	Investigational Considered non-IMP in Japan	Investigational Considered non-IMP in Canada, Australia, South Korea, Taiwan, and Turkey

[a] The infusion rate escalation schedules in this Protocol and the Pharmacy Manual are recommendations. If required, the investigator should use clinical judgment to optimize participant safety by administering the infusion more slowly.

6.2. Preparation, Handling, and Accountability

6.2.1. Tafasitamab/Placebo Preparation

Reconstitution of tafasitamab vials will yield 40 mg/mL tafasitamab in 25 mM sodium citrate, 200 mM trehalose, and 0.02% (w/v) polysorbate 20 at pH 6.0. Each product vial is intended to deliver 200 mg of tafasitamab in 5 mL of reconstituted solution. The solution is colorless to slightly yellow and should be free of foreign particles; the solution may contain a few whitish product-related particles.

For administration, reconstituted tafasitamab will be diluted into a commercially available infusion container with 0.9% (w/v) sodium chloride for injection to achieve a diluted tafasitamab solution concentration between 2 and 8 mg/mL. Infusion container volumes should be 250 mL; however, participants weighing less than 42 kg or above 160 kg will require a different size infusion bag to ensure the concentration of tafasitamab is between 2 and 8 mg/mL. Refer to the Pharmacy Manual for guidance.

Tafasitamab infusion bag preparation should be prepared using an aseptic technique and administered at the clinical study site according to direction from the sponsor. Details for tafasitamab reconstitution, preparation, and infusion are included in the Pharmacy Manual.

Participants randomized to the placebo arm will receive 0.9% saline for infusion. Refer to the Pharmacy Manual for guidance.

Materials and methods for blinding the infusion bags and infusion lines are outlined in the Pharmacy Manual and in the Blinding Procedure document.

6.2.2. Handling and Accountability of Study Treatment

In the below section, the term "investigator" also represents the investigational drug storage manager for Japan as applicable.

Each investigator is responsible for ensuring that deliveries of study drugs and other clinical study materials from the sponsor are completely and correctly received, recorded, handled, and stored safely and properly in accordance with all applicable regulatory guidelines and used in accordance with this clinical study protocol.

The investigator 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 and authorized site staff.

6.2.3. Unblinded Site Staff, Handling, and Accountability

While the investigator (or designee) has ultimate responsibility for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), during the conduct of the study in order to maintain the study blind, an

unblinded team consisting of an unblinded pharmacist and an unblinded nurse/medically qualified individual to oversee the infusion administration. Blinding materials (eg, Myonex infusion bag covers and infusion line covers) are provided by the sponsor. Refer to the Blinding Procedures document for additional details.

Inventory and accountability records must be maintained by the unblinded pharmacist and only accessible by unblinded study staff members. The documents must be consistently updated by the unblinded study staff and be readily available for inspection by the unblinded study monitor and open to inspection at any time by any applicable regulatory authority. The unblinded pharmacist must maintain records that document:

- Delivery of study drugs to the study site.
- Inventory of study drugs at the site.
- Participant use of the study drugs, including lot numbers and/or vial numbers, and vial counts from each supply dispensed.
- Inventory or documentation for destruction of used vials/infusion materials.
- Return of study drugs to the unblinded pharmacist by participants (lenalidomide).

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the participants were provided the specified study drug. 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 unblinded pharmacist will be expected to collect and retain all used, unused, and partially used containers of study drugs until verified by the study monitor, unless otherwise agreed to by the sponsor based on institutional procedures. At the conclusion of the study, the unblinded pharmacist will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional procedures. If local procedures mandate on-site destruction of the investigational supply, the site should (where local procedures allow) maintain the investigational supply until the unblinded study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before unblinded monitor inspection, the unblinded monitors will rely on documentation of destruction per the institutional procedure.

Study drug/treatment will be dispensed at the study visits summarized in the SoA (see Table 3).

Returned study drug/treatment must not be redispensed to the participants.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Stratified randomization will be done through IRT using the stratification factors described below. Stratified randomization will be performed separately for participants with FL and MZL.

Participants with FL will be stratified at the time of randomization for the following factors:

- POD24 (yes vs no)
- Refractoriness to prior anti-CD20 mAb therapy (yes vs no)
- The number of prior lines of therapy (< 2 vs ≥ 2).

Participants with MZL will be stratified at the time of randomization for the following factor:

- The number of prior lines of therapy (< 2 vs ≥ 2).

Further details of procedures regarding participant randomization and treatment assignment is provided in the Suvoda IRT Site User Manual.

Block size and block permutation algorithms are specified in a separate Randomization Plan. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Details of tafasitamab/placebo treatment blinding will be outlined in the Pharmacy Manual. This is a double-blind study; therefore, participants, investigators, and the study team members will remain blinded to treatment assignment. The investigator will not be provided with randomization codes.

Data that may potentially unblind the treatment assignment (ie, study treatment concentrations) will be handled with special care to ensure that the integrity of the blind is maintained, and the potential for bias is minimized. This will include making special provisions such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and/or unblinding.

Participants, investigators, and the study team members will remain blinded to treatment assignment until the time of the primary analysis. Unblinding procedures and the control of the unblinded data are described in the IDMC charter. Examples of personnel who may be unblinded during the study are as follows:

- The IDMC and the biostatistician and statistical programmers from an independent statistical support group who are responsible for preparing interim tables, listings, and graphs for IDMC review.
- [redacted]
- The sponsor's safety team in order to fulfill regulatory reporting requirements for SUSARs.
- In case of an urgent safety concern, the clinical study site personnel and the sponsor may be unblinded if treatment assignment information is needed to determine further actions to address the urgent safety concern (eg, life-threatening event, medication error such as an accidental overdose).

6.4. Study Treatment Compliance

Compliance with study treatment administration will be calculated by the sponsor based on study drug accountability and infusion records documented by the site staff and monitored by the sponsor/designee.

Participants should receive tafasitamab/placebo under direct supervision of clinical study site unblinded personnel. Each administration volume will be checked, and the vial code and volume per administration will be recorded in each participant's eCRF as well as in the source data. Unblinded data for tafasitamab will be captured in a separate eCRF database via the IRT system and will be monitored by an unblinded CRA. Refer to the Pharmacy Manual and Suvoda IRT Site User Manual for details.

The dosing of tafasitamab or placebo will be considered appropriate if the dose administered is ≥ 80% to ≤ 120% of the assigned dose per single infusion. Overdose treatment is described in Section 9.10.

Lenalidomide will be dispensed on Day 1 of each new treatment cycle. Participants will return all unused or empty lenalidomide blister packs to the clinical study site throughout the treatment period as instructed by the investigator, and keep a record of lenalidomide doses taken at home, which will be reviewed by clinical study site personnel on an ongoing basis. The clinical site personnel will document the amount of study drug received from and returned to the sponsor and dispensed to participants in accordance with local regulatory requirements. Throughout the course of the study, drug accountability records must be maintained. A participant will be considered compliant with the Protocol if the lenalidomide dose administered is ≥ 80% to 100% of the assigned dosage. Overdose treatment is described in Section 9.10.

6.5. Dose Modifications

6.5.1. Tafasitamab/Placebo Dose Modifications

Dose reductions of tafasitamab/placebo are not permitted. Drug interruptions or discontinuation may occur in the case of severe IRRs, allergic reactions, infections, febrile neutropenia, or severe hematologic toxicity. Delaying the administration of tafasitamab/placebo is permitted for **no more than 2 days**. If the delay lasts more than 2 days, administration of tafasitamab/placebo must be skipped completely, and the next scheduled dose will be administered (eg, if an infusion is skipped on Day 8, the next dose will be administered on Day 15).

6.5.2. Criteria and Procedures for Dose Interruptions and Adjustments of Tafasitamab/Placebo

6.5.2.1. Management of Tafasitamab/Placebo Infusion-Related Reactions and Cytokine Release Syndrome

Infusion-related reactions will be defined according to the NCI CTCAE v5.0 definition of IRR and CRS (see Table 8).

Table 8: Definition of Infusion-Related Reactions and Cytokine Release Syndrome

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
IRR	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Prolonged (ie, not rapidly responsive to symptomatic medication, brief interruption of infusion, or both); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated
CRS	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to < 40% O_2[a]	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2[a]	Life-threatening consequences; urgent intervention indicated

NSAIDs = nonsteroidal anti-inflammatories.
[a] Applied, for example, via breathing mask.
Source: NCI CTCAE v5.0 (2017).

Note: An acute IRR may occur with an agent that causes cytokine release (eg, mAbs or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms of an acute IRR may include (but are not limited to) the following: allergic reaction/hypersensitivity (including drug fever), arthralgia (joint pain), bronchospasm, cough, dizziness, dyspnea, fatigue (asthenia, lethargy, malaise), headache, hypertension, hypotension, myalgia, nausea, pruritus/itching, rash/desquamation, rigors/chills, sweating (diaphoresis), tachycardia, tumor pain (onset or exacerbation of tumor pain due to treatment), urticaria (hives, welts, wheals), and vomiting.

6.5.2.2. Interventions for Infusion-Related Reactions and Cytokine Release Syndrome

6.5.2.2.1. Grade 2 Infusion-Related Reactions, Grade 1 Cytokine Release Syndrome

The following should occur if a participant presents with a Grade 2 IRR or Grade 1 CRS:

- The infusion should be stopped immediately.
- The participant should receive appropriate treatment with an antihistamine and/or acetaminophen (paracetamol) or methylprednisolone (or equivalent) as clinically indicated.
- Once the symptoms have been resolved or reduced to Grade 1 (IRR) according to investigator assessment, the infusion can be continued at 50% of the last infusion rate. 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.

If a participant who developed a Grade 2 IRR or Grade 1 CRS receives further infusions of tafasitamab/placebo, then premedication should be given before all subsequent infusions of tafasitamab/placebo throughout the study.

If a participant develops an additional episode, that is, a recurrent Grade 2 IRR or Grade 1 CRS, then the participant may receive further tafasitamab/placebo based on the investigator's decision, provided clinically appropriate precautions are undertaken. Premedication must be given before all subsequent infusions of tafasitamab/placebo.

If precluded from further tafasitamab/placebo administrations, the participant may continue treatment with rituximab and/or lenalidomide.

6.5.2.2.2. Grade 3 Infusion-Related Reactions, Grade 2 Cytokine Release Syndrome

The following should occur if a participant presents with a Grade 3 IRR or Grade 2 CRS:

- The **infusion should be stopped immediately**.
- Appropriate treatment with an antihistamine and/or acetaminophen (paracetamol) 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 25% of the last infusion rate. If, after approximately 1 hour, the participant's symptoms do not return and vital signs are stable, the infusion rate may be increased every 30 minutes to a maximum of 50% of the baseline rate.
- If, after the resumption of the infusion, symptoms return (irrespective of grade), the infusion must be stopped immediately, and the infusion tubing disconnected from the participant.

Based on the investigator's decision, the participant may receive further tafasitamab/placebo provided clinically appropriate precautions are undertaken. If a participant who developed a Grade 3 IRR or Grade 2 CRS receives further infusions, then premedication will be given before all subsequent infusions of tafasitamab/placebo throughout the study.

If a participant develops another Grade 3 IRR or Grade 2 CRS, then the participant will be permanently discontinued from further tafasitamab/placebo administrations. If tafasitamab/placebo is discontinued, the participant may still continue to receive treatment with rituximab and lenalidomide.

6.5.2.2.3. Grade 4 Infusion-Related Reactions, Grade 3 to 4 Cytokine Release Syndrome

The following must occur if a participant presents with a Grade 4 infusion reaction or Grade 3 to 4 CRS:

- The infusion must be stopped immediately, and the infusion tubing disconnected from the participant.
- Appropriate treatment with an antihistamine and/or acetaminophen (paracetamol) or methylprednisolone (or equivalent) and, if necessary, further medications (ie, epinephrine, bronchodilator).
- The participant will be permanently discontinued from further tafasitamab/placebo administrations.

If tafasitamab/placebo is discontinued, the participant may continue treatment with rituximab and lenalidomide.

6.5.3. Criteria and Procedures for Dose Interruptions or Adjustments of Lenalidomide

Lenalidomide dose adjustments will be performed according to the label as described in Appendix B and in Section 6.5.5.

6.5.4. Criteria and Procedures for Dose Interruptions or Adjustments of Rituximab

Dose modifications of rituximab are not mandated unless clinically indicated as per the SmPC, the USPI, and applicable institutional guidelines (MabThera 2020, Rituxan 2020).

6.5.5. Toxicity Management Guidelines for Hematological Toxicities

In case of hematologic toxicities, tafasitamab/placebo, lenalidomide and/or rituximab treatment may need to be interrupted or discontinued according to the toxicity management guidelines provided in Table 9.

Delaying the tafasitamab/placebo dose or the rituximab dose is permitted for **no more than 2 days (≤ 2 days)**. If a tafasitamab/placebo or rituximab infusion is delayed for 3 or more days (≥ 3 days), then this infusion should be skipped and tafasitamab/placebo or rituximab treatment continued only at the next scheduled timepoint. Investigators may choose to follow their institution's standard of care for delayed dosing due to toxicity for lenalidomide and rituximab. This is acceptable and should be noted in the participant's medical record.

Dose reductions of tafasitamab/placebo or rituximab are not permitted. See Table 9 and Appendix A for guidance on dose adjustments for lenalidomide.

Table 9: Toxicity Management Guidelines for Hematological Toxicities

Adverse Event[a]	Tafasitamab/Placebo	Lenalidomide	Rituximab
Thrombocytopenia Grade 3 (platelets < 50-25 G/L) with or without bleeding	• Interrupt tafasitamab/ placebo. • Follow CBC at least every 7 days. • If thrombocytopenia has resolved to ≤ Grade 2 (platelets ≥ 50 G/L), restart tafasitamab/ placebo at the same dose. • Monitor as clinically indicated.	• Interrupt lenalidomide. • Follow CBC at least every 7 days. • If thrombocytopenia has resolved to ≤ Grade 2 (platelets ≥ 50 G/L), restart lenalidomide at the next lower dose level (see Appendix B). • Monitor as clinically indicated	• Interrupt rituximab. • Follow CBC at least every 7 days. • If thrombocytopenia has resolved to ≤ Grade 2 (platelets ≥ 50 G/L), restart rituximab at the same dose. • Monitor as clinically indicated.
Thrombocytopenia Grade 4 (platelets < 25 G/L)	• Interrupt tafasitamab/ placebo. • Follow CBC at least every 7 days. • If thrombocytopenia has resolved to ≤ Grade 2 (platelets ≥ 50 G/L), restart tafasitamab/ placebo at the same dose. • Monitor as clinically indicated.	• Interrupt lenalidomide • Follow CBC at least every 7 days. • If thrombocytopenia has resolved to ≤ Grade 2 (platelets ≥ 50 G/L), restart lenalidomide at the next lower dose level (see Appendix B). • Monitor as clinically indicated	• Interrupt rituximab. • Follow CBC at least every 7 days. • If thrombocytopenia has resolved to ≤ Grade 2 (platelets ≥ 50 G/L), restart rituximab at the same dose. • Monitor as clinically indicated.
Thrombocytopenia Grade 3-4	• Interrupt VTE prophylaxis. • Consider platelet transfusion. • Consider change of VTE prophylaxis agent (eg, change antiplatelet agent to low molecular weight heparin). • VTE prophylaxis should be tailored to the patient's individual risk/benefit profile by taking into account the individual thrombotic risk and bleeding risk.		
Neutropenia Grade 3 (ANC < 1.0 G/L) sustained < 7 days	• Interrupt tafasitamab/ placebo. • Follow CBC at least every 7 days. • Use growth factors (eg, G-CSF) and anti-microbial prophylaxis as per local guidelines. • If neutropenia has resolved to ≤ Grade 2 (ANC ≥ 1.0 G/L), restart tafasitamab/placebo at the same dose. • Monitor as clinically indicated.	• Interrupt lenalidomide. • Follow CBC at least every 7 days. • Use growth factors (eg, G-CSF) and anti-microbial prophylaxis as per local guidelines. • If neutropenia has resolved to ≤ Grade 2 (ANC ≥ 1.0 G/L), restart lenalidomide at the same dose. • Monitor as clinically indicated.	• Interrupt rituximab. • Follow CBC at least every 7 days. • Use growth factors (eg, G-CSF) and anti-microbial prophylaxis as per local guidelines. • If neutropenia has resolved to ≤ Grade 2 (ANC ≥ 1.0 G/L), restart rituximab at the same dose. • Monitor as clinically indicated.

Table 9: Toxicity Management Guidelines for Hematological Toxicities (Continued)

Adverse Event[a]	Tafasitamab/Placebo	Lenalidomide	Rituximab
Neutropenia Grade 3 (ANC < 1.0 G/L) with a temperature of ≥ 38.5°C/ 101.3°F (febrile neutropenia)	• Interrupt tafasitamab/ placebo. • Follow CBC at least every 7 days. • Use growth factors (eg, G-CSF) and antimicrobial prophylaxis as per local guidelines. • If fever is resolving (< 38.0°C/100.4°F) and neutropenia has resolved to ≤ Grade 2 (ANC ≥ 1.0 G/L), restart tafasitamab/placebo at the same dose. • Monitor as clinically indicated.	• Interrupt lenalidomide. • Follow CBC at least every 7 days. • Use growth factors (eg, G-CSF) and anti-microbial prophylaxis as per local guidelines. • If fever is resolving (< 38.0°C/100.4°F) and neutropenia has resolved to ≤ Grade 2 (ANC ≥ 1.0 G/L), restart lenalidomide at the next lower dose level (see Appendix B). • Monitor as clinically indicated.	• Interrupt rituximab. • Follow CBC at least every 7 days. • Use growth factors (eg, G-CSF) and anti-microbial prophylaxis as per local guidelines. • If fever is resolving (< 38.0°C/100.4°F) and neutropenia has resolved to ≤ Grade 2 (ANC ≥ 1.0 G/L), restart rituximab at the same dose. • Monitor as clinically indicated.
Neutropenia Grade 4 (ANC < 0.5 G/L) with or without a temperature of ≥ 38.5°C/ 101.3°F	• Interrupt tafasitamab/ placebo. • Follow CBC at least every 7 days. • Use growth factors (eg, G-CSF) and anti-microbial prophylaxis as per local guidelines. • If neutropenia has resolved to ≤ Grade 2 (ANC ≥ 1.0 G/L), restart tafasitamab/placebo at the same dose. • Monitor as clinically indicated.	• Interrupt lenalidomide. • Follow CBC at least every 7 days. • Use growth factors (eg, G-CSF) and anti-microbial prophylaxis as per local guidelines. • If neutropenia has resolved to ≤ Grade 2 (ANC ≥ 1.0 G/L), restart lenalidomide at the next lower dose level (see Appendix B). • Monitor as clinically indicated.	• Interrupt rituximab. • Follow CBC at least every 7 days. • Use growth factors (eg, G-CSF) and anti-microbial prophylaxis as per local guidelines. • If neutropenia has resolved to ≤ Grade 2 (ANC ≥ 1.0 G/L), restart rituximab at the same dose. • Monitor as clinically indicated.

Table 9: Toxicity Management Guidelines for Hematological Toxicities (Continued)

Adverse Event[a]	Tafasitamab/Placebo	Lenalidomide	Rituximab
Neutropenia Grade 3-4 sustained ≥ 7 days	• Interrupt tafasitamab/ placebo. • Follow CBC at least every 7 days. • Use growth factors (eg, G-CSF) and anti-microbial prophylaxis as per local guidelines. • If neutropenia has resolved to ≤ Grade 2 (ANC ≥ 1.0 G/L), restart tafasitamab/placebo at the same dose. • Monitor as clinically indicated.	• Interrupt lenalidomide. • Follow CBC at least every 7 days. • Use growth factors (eg, G-CSF) and anti-microbial prophylaxis as per local guidelines. • If neutropenia has resolved to ≤ Grade 2 (ANC ≥ 1.0 G/L), restart lenalidomide at the next lower dose level (see Appendix B). • Monitor as clinically indicated.	• Interrupt rituximab. • Follow CBC at least every 7 days. • Use growth factors (eg, G-CSF) and anti-microbial prophylaxis as per local guidelines. • If neutropenia has resolved to ≤ Grade 2 (ANC ≥ 1.0 G/L), restart rituximab at the same dose. • Monitor as clinically indicated.

[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.

6.5.6. Toxicity Management Guidelines for Non-Hematological Toxicities

The guidelines for toxicity management in the presence of non-hematological toxicities are described in Table 10.

Table 10: Toxicity Management Guidelines for Non-Hematological Toxicities

Adverse Event[a]	Tafasitamab/Placebo	Lenalidomide	Rituximab
Thromboembolic event ≥ Grade 3	• Continue tafasitamab/ placebo infusion as per Protocol if clinically appropriate.	• Discontinue lenalidomide permanently.	• Continue rituximab infusion as per Protocol if clinically appropriate.
Allergic or hypersensitivity reaction Grade 2	• If related to tafasitamab/placebo, interrupt/skip the dose. • If toxicity resolves to ≤ Grade 1, tafasitamab/ placebo may be resumed. • If a tafasitamab/placebo infusion is delayed for 3 or more days, then this infusion should be skipped and tafasitamab/ placebo treatment continued only at the next scheduled timepoint.	• If related to lenalidomide, interrupt/skip the dose. • If toxicity resolves to ≤ Grade 1, restart lenalidomide at the next lower dose level (see Appendix B).	• If related to rituximab, interrupt/skip the dose. • If toxicity resolves to ≤ Grade 1, rituximab may be resumed • If a rituximab infusion is delayed for 3 or more days, then this infusion should be skipped and rituximab treatment continued only at the next scheduled timepoint.
Allergic or hypersensitivity reaction ≥ Grade 3	• If related to tafasitamab/placebo, discontinue tafasitamab/placebo permanently.	• If related to lenalidomide, discontinue lenalidomide permanently.	• If related to rituximab, discontinue rituximab permanently.
	Note: If the causality cannot be determined and the AE may be related to tafasitamab/placebo and/or lenalidomide and/or rituximab, discontinue all study drugs permanently.		
Rash Grade 2 or 3 non-desquamating (blistering)	• If related to tafasitamab/placebo then interrupt the dose. • If toxicity resolves to ≤ Grade 1, tafasitamab/ placebo may be resumed. • If a tafasitamab/placebo infusion is delayed for 3 or more days, then this infusion should be skipped and tafasitamab/ placebo treatment continued only at the next scheduled timepoint.	• If related to lenalidomide, then interrupt the dose. • If the AE resolves to ≤ Grade 1, restart lenalidomide at the same level (see Appendix B).	• If related to rituximab, then interrupt the dose. • If toxicity resolves to ≤ Grade 1, rituximab may be resumed. • If a rituximab infusion is delayed for 3 or more days, then this infusion should be skipped and rituximab treatment continued only at the next scheduled timepoint.

Table 10: Toxicity Management Guidelines for Non-Hematological Toxicities (Continued)

Adverse Event[a]	Tafasitamab/Placebo	Lenalidomide	Rituximab
Rash Desquamating (blistering) ≥ Grade 3 OR Non-desquamating Grade 4	• If related to tafasitamab/ placebo, discontinue tafasitamab/placebo permanently.	• If related to lenalidomide, discontinue lenalidomide permanently.	• If related to rituximab, discontinue rituximab permanently.
	Note: If the causality cannot be determined and the AE may be related to tafasitamab/placebo and/or lenalidomide and/or rituximab, discontinue all study drugs permanently.		
Tumor flare reaction[b] Grade 1-2	• Continue tafasitamab/ placebo as per Protocol if clinically appropriate.	• Continue lenalidomide as per Protocol.	• Continue rituximab as per Protocol if clinically appropriate.
Tumor flare reaction[b] ≥ Grade 3	• Continue tafasitamab/ placebo as per Protocol if clinically appropriate.	• Interrupt lenalidomide. • If the AE resolves to ≤ Grade 1, restart lenalidomide and maintain the same dose level (see Appendix B).	• Continue rituximab as per Protocol if clinically appropriate.
Constipation ≥ Grade 3	• Continue tafasitamab/ placebo as per Protocol if clinically appropriate.	• Interrupt lenalidomide. • If the AE resolves to ≤ Grade 2, restart lenalidomide and maintain the same dose level (see Appendix B).	• Continue rituximab as per Protocol if clinically appropriate.
Other non-hematologic AEs ≥ Grade 3	• Continue tafasitamab/ placebo as per Protocol if clinically appropriate.	• Interrupt lenalidomide. • If the AE resolves to ≤ Grade 2, restart lenalidomide and maintain the same dose level (see Appendix B).	• Continue rituximab as per Protocol if clinically appropriate.

[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.

[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 (tumor flare reaction is the only AE that will be graded using NCI CTCAE v3.0).

6.5.6.1. Tumor Lysis Syndrome Prophylaxis

Participants should hydrate well (orally) during the first week of the first cycle, or for a longer period if clinically indicated. Hydration levels should be adjusted according to age and clinical status of the participant.

In addition, participants may receive TLS prophylaxis (allopurinol, rasburicase, or equivalent) as per institutional guidelines.

If clinically indicated, participants should continue with TLS prophylaxis measures by keeping hydrated and taking the TLS prophylaxis as instructed.

6.5.6.2. Hypogammaglobulinemia

Hypogammaglobulinemia induced by B-cell depletion is a potential on-target toxicity of the anti-CD19 mAb tafasitamab.

In this study, immunoglobulin levels (IgG, IgA, and IgM) are measured at screening and subsequently every 2 cycles starting from Cycle 2 until EOT. Study participants experiencing hypogammaglobulinemia should be managed according to local guidelines.

6.6. Concomitant Medications and Procedures

6.6.1. Participant Monitoring During Tafasitamab or Placebo Infusion

Vital signs should be measured as outlined in Table 3 and Section 8.3.3. All supportive measures consistent with optimal participant care will be provided throughout the study according to institutional standards.

Precautions for anaphylaxis should be observed during tafasitamab or placebo administration. 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 (paracetamol).

Vital signs are to be obtained before tafasitamab/placebo infusion and then at least 3 times during the infusion (oxygen saturation is not required during the infusion) and as clinically indicated. Participants should continue to be monitored for at least 30 minutes after completion of the tafasitamab/placebo infusion. The frequency or the length of the monitoring period may be adapted if clinically indicated.

6.6.2. Lenalidomide Counseling

Lenalidomide may cause fetal harm when administered to a pregnant woman. Male participants of reproductive potential and participants who are WOCBP may be treated with lenalidomide provided adequate precautions are taken to avoid pregnancy as described in Section 5.1.

Participants will be counseled on lenalidomide's potential risk of teratogenicity at the beginning of each treatment cycle. Additional pregnancy testing and counseling must be performed if a female participant misses her menstruation period or if there is any abnormality in menstrual bleeding.

The investigator will ensure that all participants of reproductive/childbearing potential are able to understand the reason for complying with the special conditions of the pregnancy prevention risk management plan and will also ensure written acknowledgement of participants to adhere to this plan (see Section 5.1).

6.6.3. Prior and Concomitant Therapies

Details of prior, concomitant, or procedural medication or therapy will be captured in the eCRF.

Any prior, concomitant, or procedural medications or therapy (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) given to or taken by the participant up to 4 weeks prior to enrollment and up to 90 days after the last dose of study

treatment or until the participant begins a new anticancer therapy will be recorded in the eCRF. The sponsor will encode all therapy and medication according to the WHO Drug Dictionary. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered after 90 days after the last dose of study treatment should be recorded for SAEs as defined in Section 9.4.

Corticosteroids administered/taken within 3 weeks before ICF signature will be recorded in the eCRF. Participants may continue the medications they were receiving at time of screening. Participants may receive concomitant medications that are medically indicated as standard of care 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 should be recorded in the eCRF.

6.6.4. Prophylaxis of Hepatitis B Reactivation

Participants in countries where prophylactic antiviral medications for hepatitis B reactivation are the standard of care may be treated prophylactically. Participants with occult HBV infection, defined as negative HBsAg and positive total HBcAb and negative HBV DNA, are eligible and must undergo ongoing DNA testing (irrespective of prophylactic treatment) as described in Table 4.

6.6.5. Anti-Infection Prophylaxis

Anti-infectious prophylaxis including prophylaxis of opportunistic infections can be given as per institutional guidelines.

6.6.6. Premedication for Tafasitamab or Placebo Infusions/Infusion-Related Reaction Prophylaxis

Tafasitamab or placebo infusions are to be administered to participants after premedication with oral acetaminophen (eg, 650-1000 mg), an antihistamine such as diphenhydramine hydrochloride (eg, 50-100 mg), and glucocorticosteroids (eg, 100 mg IV prednisone or prednisolone or equivalent). The premedication should be administered approximately 30 to 60 minutes prior to starting each infusion.

Premedication is mandatory for the first cycle. For participants who do not experience ≥ Grade 2 IRRs or ≥ Grade 1 CRS to tafasitamab or placebo during the first cycle, premedication will be optional for subsequent antibody infusions at the discretion of the investigator.

6.6.7. Prophylaxis of Venous Thromboembolism

Prophylaxis of VTE is mandatory for all participants due to increased risk of thrombosis in participants treated with lenalidomide without prophylaxis (Revlimid [lenalidomide] SmPC [2020]). Suggested prophylaxis treatment includes either aspirin (70-325 mg PO daily) or low molecular weight heparin. Participants with a history of VTE or thrombophilia may participate if they are willing to be on full anticoagulation during the treatment. The choice of VTE prophylaxis agent is at the 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 quality of compliance with the VTE prophylaxis.

6.6.8. Use of Growth Factors

The use of G-CSF or pegylated G-CSF is optional and should be administered as per institutional guidelines.

6.6.9. Use of Specific Medications Concomitantly With Lenalidomide

The following measurements and precautions should be considered for study participants who receive the following medications concomitantly with lenalidomide.

6.6.9.1. Digoxin

When digoxin was coadministered with multiple doses of lenalidomide (10 mg/day), the digoxin C_{max} and AUC_{inf} were increased by 14%.

Consider periodic monitoring of digoxin plasma levels as per investigator's clinical judgment and based on standard clinical practice in participants receiving this medication during administration of lenalidomide.

6.6.9.2. Concomitant Therapies That May Increase the Risk of Thrombosis

Erythropoietic agents or other agents that may increase the risk of thrombosis, such as estrogen-containing therapies, should be used with caution after making a benefit/risk assessment in study participants who receive lenalidomide.

6.6.9.3. Warfarin

Coadministration of multiple doses of lenalidomide (10 mg/day) with a single dose of warfarin (25 mg) had no effect on the PK of lenalidomide or R- and S-warfarin. Expected changes in laboratory assessments of prothrombin time and international normalized ratio were observed after warfarin administration, but these changes were not affected by concomitant lenalidomide administration. It is not known whether there is an interaction between dexamethasone and warfarin.

Close monitoring of the coagulation parameters should be conducted as described in Table 4.

6.6.10. Prohibited Medications and Procedures

6.6.10.1. Anticancer Therapies

No radiotherapy (including limited field radiotherapy) is permitted after the screening PET/CT scan for initial disease assessment has been performed.

The use of concurrent antineoplastic therapies other than study drugs 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.

Once the decision to end study treatment has been made, new anticancer treatment is permitted at the discretion of the investigator. Ideally, the safety follow-up visit should be performed prior to

initiating new anticancer therapy. Any new anticancer treatments and the associated response outcomes are to be recorded in the appropriate eCRF.

6.6.10.2. Live Vaccines

Because of the immunosuppressive effects of the study treatment, administration of any live vaccine is not recommended during the treatment period and at least 6 months after the EOT. Thereafter, the decision to administer live vaccines is at the investigator's discretion and should follow local guidelines for lenalidomide in addition to rituximab (the hematological status of individual participant, including B-cell depletion, should be considered).

Please note that this does not apply to COVID-19 vaccines which are nonlive vaccines.

6.7. Treatment After the End of the Study

'Subsequent care for study participants after the discontinuation of study treatment or completion of the study may be given per local institution standard of care.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL FROM STUDY TREATMENT

7.1. Discontinuation of Study Treatment

See Table 3 and Table 4 for data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed.

7.1.1. Reasons for Discontinuation of Study Treatment

7.1.1.1. Unacceptable Toxicity

The occurrence of unacceptable toxicity not caused by the underlying disease will require that the study treatment (ie, tafasitamab/placebo, lenalidomide, and rituximab) be permanently discontinued. Unacceptable toxicity is defined as follows:

- The occurrence of an AE that is related to study treatment that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- In case of drug delay for more than 1 month (4 weeks), the investigator will have to contact the sponsor's medical monitor.

The investigator may also discontinue the treatment to a participant if further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.

7.1.1.2. Disease Progression

Participants who demonstrate radiologic or metabolic progression of disease as per the Lugano criteria will be considered as having met criteria for disease progression. The EOT visit should be performed as soon as possible, and the participant should continue with the safety and

survival follow-up periods of the study. Any new anticancer therapy (and associated response outcomes) should be captured in the eCRFs.

7.1.1.3. Lack of Efficacy

Participants who, in the treating investigator's decision, require new anticancer therapy due to lack of sufficient response in the absence of either radiologic or metabolic progression of disease per the Lugano criteria will be considered as having met criteria for lack of efficacy. The EOT visit should be performed as soon as possible, and the participant should continue on with the safety and survival follow-up periods of the study. Any new anticancer therapy (and associated response outcomes) should be captured in the eCRFs.

7.1.1.4. Consent Withdrawal

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 the 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, disease progression, and survival per the SoA (see Table 3).

7.1.1.5. Investigator Decision

Investigator(s) also have the right to withdraw participants from the study or from study treatment in the event of illness, AEs, noncompliance, or other reasons concerning the health or well-being of the participant.

7.1.1.6. Pregnancy

Female participants who become pregnant during clinical study participation must discontinue study treatment.

7.1.1.7. Study Termination

Participants must be discontinued from study treatment if the study is terminated by the sponsor or by the local health authority, IRB, or IEC.

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 Table 3 and Table 4. 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 and in the source documents.

- The EOT visit should be performed and date recorded.
- The participant enters the follow-up period.
- The status of the participant should be updated to EOT in the IRT.
- Participants must be followed for safety until the time of the follow-up visit or until study treatment–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), 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/efficacy assessments.

7.2. Participant Withdrawal From the Study

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

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

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail 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, they 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(ies) 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 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.

A participant who is rescreened is required to sign a new ICF.

8.1.2. Screening Procedures

The screening period of a maximum of 28 days is the interval between the date of signing of informed consent and the date of randomization. The ICF must be signed before beginning any study-related assessments. Standard-of-care assessments performed on the day of consent (but before signing the ICF) do not need to be repeated solely for the purpose of screening and may be used as study data, if they meet the Protocol requirements.

Standard of care assessments that occur outside the 28-day window that are suitable for enrollment (ie, meet protocol requirements) but are not feasible to repeat may be used for determining eligibility with sponsor medical monitor approval.

During screening, each participant who signs the ICF will be allocated a unique identification number. Treatment should start within 3 days of randomization.

All participants must satisfy all the inclusion criteria and none of the exclusion criteria listed in Section 5. Signed and dated informed consent must be obtained from all participants before their entering the clinical study. Additionally, sites will complete participant enrollment forms for all participants being considered for this study. Completed enrollment forms will be submitted to the sponsor along with completely redacted (pseudonymized) supportive documentation (eg, laboratory reports, pathology reports, imaging reports, and a brief summary of the participant's disease-specific medical history) that is necessary to confirm eligibility. The PI will ultimately be responsible for ensuring participants meet eligibility criteria.

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

See Table 3 and Table 4 for the screening assessments to be performed.

8.1.3. Interactive Response Technology Procedure

Each participant is identified in the study by a unique participant number that is assigned by the IRT system when the participant is screened (ie, signs the ICF) and is retained as the primary identifier for the participant throughout their entire participation in the study.

- The participant number is unique so that each participant is numbered uniquely across the entire study.
- The investigator or designated study personnel will contact the IRT system and provide the requested identifying information for the participant to register them into the IRT system and assign a participant number.

Once assigned, the participant number must not be reused for any other participant.

All participants who fulfill all inclusion criteria and who are not barred by any of the exclusion criteria will be randomly assigned to one of the study treatment groups as defined in Section 6.1.

Randomization will be done through IRT before the participant receives any study treatment. While all inclusion and exclusion criteria need to be reviewed again before randomization, laboratory results and results of assessments obtained during the screening period or on the day of randomization may be used for determining participant eligibility for study randomization.

Additionally, the IRT will be contacted at each regular study visit to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Demography and Medical History

8.1.4.1. Demographics and General Medical History

Demographic variables to be recorded will include age, gender, race, and ethnic origin.

At the time of signing of the ICF, relevant medical history and current medical conditions should be recorded. The medical history, co-morbidities, and prior medications should be documented in detail, including all symptoms present at screening.

8.1.4.2. Disease Characteristics, Treatment History, and Pathology

A local pathology report indicating FL/MZL diagnosis is acceptable for determining a participant's eligibility for receiving the first study treatment. The participant will be enrolled in the study based on the local pathology report.

For each participant, suitable and sufficient tumor tissue material must be provided. A central pathologist will provide confirmation of the histological diagnosis of FL/MZL. A fresh biopsy is preferred, but an archival specimen is acceptable, preferably from the time of the last relapse. For archival specimens, surgically acquired tissue samples are preferred, but core biopsies are permitted. Bone marrow biopsies are not adequate for this purpose and should be performed only for disease staging. Refer to the Central Lab Manual for details. In cases where blocks cannot be provided, 15 unstained slides and 3 tissue curls should be provided. When tissue curls cannot be provided, 25 unstained slides should be provided.

Central pathology review is mandatory but will be retrospective; randomization is based on investigator assessment, and no changes will be made to treatment assignment for discordant results between the investigator and the central pathology laboratory. Differences will be highlighted in the final data analysis only.

Samples should be submitted within 30 days after randomization.

Examinations leading to the diagnosis of FL/MZL should be documented in the participant's source documents. This may include, for example, results of laboratory examinations, imaging results, or clinical symptoms related to FL/MZL. The assessment of the lymphoma should include disease staging. In order to reflect the participant's status at the time of screening, the standard staging systems for FL/MZL 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 (see Appendix E and Appendix F).

See Table 3 and Table 4 for the list of all assessments required at screening. For participants with FL, the FLIPI-1 and GELF criteria assessment will also be performed and recorded in the eCRF.

8.2. Efficacy Assessments

Efficacy assessments except OS [redacted] will be made according to the response criteria for malignant lymphoma based on the guidelines of the Lugano Classification (Cheson et al 2014; see Appendix H) and will be based on investigator assessment and IRC assessment.

Participants who experience relapse or disease progression during the study will continue to be followed for OS, [redacted], all subsequent antilymphoma therapy(ies), [redacted] according to the visit schedule until withdrawal of consent, lost to follow-up, study end, or death, whichever comes first.

8.2.1. Health Economics

Health economics parameters are not evaluated in this study.

8.2.2. Bone Marrow Biopsy and Aspirate Samples

Both bone marrow aspirate and biopsy samples are to be collected at timepoints when a bone marrow examination is indicated (see Table 3). If biopsy collection is not feasible (see Section 8.2.2.1), a bone marrow aspirate will be collected. Samples collected prior to signing the ICF may be used in lieu of collecting additional samples in discussion with the sponsor medical monitor. Please refer to the Laboratory Manual for details on sample preparation and shipment.

8.2.2.1. Bone Marrow Biopsy Sample Collection

A bone marrow biopsy is required at screening to determine if there is marrow infiltration of the underlying lymphoma. This sample will be evaluated locally unless the marrow is the only organ where disease is found. [redacted]

If a bone marrow biopsy cannot be obtained, a bone marrow aspirate must be collected for local bone marrow examination to determine disease infiltration. If a bone marrow aspirate is taken in lieu of a biopsy, the sample should contain adequate volume to support MRD analysis (see Section 8.2.2.2).

Bone marrow biopsies collected as part of standard of care that are suitable for determining eligibility may be used in lieu of collecting an additional biopsy with sponsor medical monitor approval. Bone marrow aspirates must be freshly collected samples.

If the screening bone marrow examination indicates disease infiltration in the bone marrow, a bone marrow biopsy is to be repeated within 4 weeks (± 2 weeks) of radiologic CR for evaluation of morphologic response and MRD analysis (see Section 8.2.2.2). If CR was not achieved, a repeat bone marrow biopsy must be collected at EOT.

Results from the local bone marrow examinations must be entered in the eCRF.

8.2.2.2. Bone Marrow Aspirate Sample Collection

A bone marrow aspirate must be collected at screening and EOT and sent to the central laboratory for MRD analysis regardless of marrow involvement status at baseline. A portion of

the first draw is preferable, but the second draw can be used if there is inadequate sample volume from the first draw.

An aspirate will need to be repeated and sent for central MRD analysis at the time of radiologic CR only if marrow is involved at screening.

8.2.3. Minimal Residual Disease and Mutational Analyses in Peripheral Blood

Peripheral blood samples will be collected for MRD and mutational analyses at the timepoints listed in Table 4.

8.2.4. Radiographic and Metabolic Imaging Assessments

Radiographic assessments will be performed at the timepoints indicated below and in Table 3. Additional radiographic assessments may be performed by the investigator during the course of the study if deemed clinically necessary.

Images of the radiographic assessments will be collected and centrally stored at the sponsor's central radiology vendor. The instructions are included in the Central Imaging Manual.

All CT scans (and CT parts of a combined PET-CT, if applicable) should cover the neck, chest, abdomen, and pelvis and must be of diagnostic quality, with contrast agent, if allowable based on participant contraindications and/or supply issues. An MRI with contrast should be performed if a CT scan with contrast is contraindicated as assessed by the investigator. If both a CT with contrast and an MRI with contrast are contraindicated and/or not available due to supply issues, a CT or an MRI without contrast is acceptable as radiographic assessment methodology, but should be noted in the participant's chart and eCRF. Every effort should be made to use the same assessment methodology for a participant throughout the study duration.

The CT/MRI scan assessments will be used to serve as the baseline assessments for CT/MRI response. The PET assessments will be used to serve as the baseline assessments for PET response.

Note: PET-CT hybrid scanners may be used only if the CT produced by the scanner is of diagnostic quality (ie, allows an accurate diameter measurement and, as a guidance, a slice thickness of 2-2.5 mm is adequate; refer to the Study Manual). If using a hybrid machine for both PET and CT, the PET should be performed before the CT is performed with IV contrast, so as to not compromise PET results.

If independent CT and PET-CT scanners are used, and the participant is receiving both scans on the same day, the PET-CT must be performed before the CT with IV contrast (unless contraindicated). The CT must be of diagnostic quality (ie, allows an accurate diameter measurement and, as a guidance, a slice thickness of 2 to 2.5 mm is adequate; refer to the Study Manual). Lesion measurements and other parameters relevant for the response assessment based on the Lugano classification (Cheson et al 2014; see Appendix H) will be collected in the eCRF.

At baseline:

- PET + CT or PET + MRI scans must be performed on all participants.

During the study treatment and follow-up periods:

- Participants with **negative** PET scan at **baseline** should be followed using CT or MRI imaging. Additional PET scans may be performed at the treating investigator's discretion but are not required.
- Participants with a **positive** PET scan at **baseline** (FDG-avid lymphoma) who achieve radiologic CR during treatment should be assessed by PET scan within 4 weeks (± 2 weeks) of the CT/MRI scan, noting the CR to evaluate for metabolic response. Subsequent PET scans are not required if a confirmatory PET scan is performed during treatment; otherwise, a PET scan will need to be repeated at EOT.
- CT/MRI scans are to be performed according to the following schedule:
  - Year 1: Every 12 weeks (3 months, ± 2 weeks), including the EOT visit. Circumstances where scans cannot be performed at EOT (eg, due to hospitalization, hospice care, recent per-protocol scan, etc.) must be properly documented in the eCRF
  - Years 2 to 3: Every 16 weeks (4 months, ± 2 weeks)
  - Years 4 to 6: Every 24 weeks (6 months, ± 3 weeks)
- For CT/MRI scans reporting PD, a PET-CT or PET-MRI scan should be performed within 4 weeks (± 2 weeks) for confirmation of progression.

Response assessments using Lugano criteria (Cheson et al 2014) are to be performed each time lesions are assessed.

Participants who discontinue treatment for reasons other than disease progression will enter the efficacy follow-up period (see Section 8.9.2). Lesions must followed using the same modality and schedule as was used during the treatment period until progression of disease, initiation of new anticancer therapy, death, or withdrawal of consent.

8.2.5. Quality-of-Life Assessments

Quality-of-life assessments using the EORTC QLQ-C30, EQ-5D-5L, and FACT-Lym tools will be performed at the timepoints listed in Table 3.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in Table 3 and Table 4.

The investigator(s) and the sponsor will review the safety data.

Safety will be evaluated by monitoring all AEs and clinically significant abnormalities identified through physical examinations, vital signs, and laboratory assessments. Such events and laboratory and AE toxicities will be graded according to NCI CTCAE v5.0 (or higher). Laboratory safety assessments will include routine monitoring of hematology and blood chemistry and tests of immunologic parameters.

Adverse events, pregnancies, concomitant medications, procedures, and hospitalizations will be recorded from signing the ICF until 90 days after the last dose of treatment or until the start of new anticancer therapy, whichever occurs first. Participants who relapse or progress and/or

prematurely discontinue the study treatment will continue to be followed for SPM throughout the study.

Adverse events and concomitant medications terms will be coded using MedDRA and a validated medication dictionary.

8.3.1. Adverse Events

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 the 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 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, nonserious AEs, 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).

8.3.2. Physical Examinations and Eastern Cooperative Oncology Group Performance Status

Physical examinations and ECOG performance status (see Appendix D) will be assessed according to the SoA (see Table 3).

A comprehensive physical examination will be performed by the investigator or a qualified designee during the screening and at EOT. Comprehensive physical examination should include at least cardiovascular, respiratory, abdominal, and neurologic assessment. The tumor assessment includes the evaluation of presence and degree of enlarged lymph nodes, liver, and spleen assessments.

Targeted physical examination will be guided by the individual participant's status and will include body systems associated with symptoms and/or the underlying FL/MZL disease (lymph node status, liver, spleen). Targeted physical examinations may be focused on tumor response assessment (eg, lymph nodes, liver, and spleen) and AEs per investigator discretion.

Body weight will be measured as indicated in the SoA (see Table 3) and height measured at screening only.

B-symptoms (fever, night sweat, weight loss) will be assessed at the timepoints indicated in the SoA (see Table 3).

8.3.3. Vital Signs

Vital signs include blood pressure, respiratory rate, pulse, and body temperature.

Vital signs should be measured at the timepoints described in the SoA (see Table 3). Vital signs should be obtained prior to the tafasitamab/placebo infusion, and then at least 3 times during the infusion (end of the infusion may be included as 1 of the 3 times), and/or as clinically indicated.

It is recommended that before vital signs are measured, the participant should be resting for approximately 5 minutes. If possible, vital sign assessments should be performed in the same manner at each timepoint.

8.3.4. Electrocardiograms, Echocardiograms, and/or Cardiac MUGA Scans

Standard 12-lead resting ECGs will be obtained at screening as described in the SoA (see Table 3). Electrocardiograms will be interpreted locally.

The investigator will evaluate the clinical significance of each ECG value outside the reference ranges (including QTc assessment), 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, then the ECG will be repeated.

After study start, ECGs will be performed as clinically indicated as per local practices.

The decision to include or exclude a participant or discontinue study treatment based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

Two-dimensional echocardiogram (2D-ECHO) or cardiac MUGA scan will be obtained at screening to evaluate cardiac function, including assessment of LVEF.

8.3.5. Laboratory Assessments

Any abnormal laboratory findings, regardless if centrally or locally analyzed, assessed by investigator as clinically significant will constitute an AE, and should be reported as such and followed until the outcome is known. 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.

Differences between central laboratory and local laboratory results may occur; central laboratory results will supersede local laboratory results.

Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the participant's condition (eg, ordering a WBC differential count to help characterize a high or low WBC count, or ordering a determination of RBC indices to help characterize a low hematocrit).

8.3.5.1. Central Laboratory Testing for Safety

The measurement of all safety laboratory parameters (except pregnancy testing) as indicated in this Protocol will be performed centrally. Central laboratory tests will be performed according to Table 4. Laboratory results are required for determining participant eligibility for study enrollment and will be used for the primary statistical analysis of the study results.

During screening, it is permitted to repeat the laboratory assessment of serum chemistry and hematology parameters due to the variability of the parameters and their dependence on multitude of factors (eg, hydration, muscle mass). This is valid provided no safety concerns arise and that such laboratory results might have been caused by a transient, medically plausible event, which resolved spontaneously or as result of a medical intervention in the meantime (eg, dehydration, vomiting, imaging procedure with a contrast). This procedure and the rationale behind it must be explicitly documented in source data. Such repeated assessment (once only) of the concerned parameters will not be counted as "rescreening" for that participant.

Laboratory samples may be taken as defined in Table 4. Local laboratory results may be used for taking treatment or clinically related decisions, or for the immediate safety management of a study participant; in that situation, the site will be requested to send a sample to the central laboratory for confirmation of the result(s). The investigator or designee should review laboratory results before dosing so that the administration of the study drug(s) may be adjusted or interrupted if necessary.

The laboratory results will be kept in the participant's source documentation. Any clinically significant discrepancies will be evaluated on a case-by-case basis. All blood samples will be processed and handled according to standard laboratory procedures. The time of blood collection should be documented in the source data.

Clinical laboratory parameters assessed in this clinical study are displayed in Table 11 below.

Table 11: Required Laboratory Analytes

Serum Chemistries	Hematology	Urinalysis
ALT	Hemoglobin	Glucose
Albumin	Hematocrit	Ketone
Alkaline phosphatase	Platelet count	Occult blood
Amylase	WBC count including differentials	pH
AST		Protein
Bicarbonate/CO_2 (may not be applicable in Japan)	Coagulation parameters:	Specific gravity
Bilirubin (total, direct, indirect)	aPTT	Urobilinogen
Calcium	D-dimer	
Chloride	PT	
CPK	TT	
Creatinine		
GGT	Immunological parameters:	
Glucose	CRP	
Lactate dehydrogenase		
Phosphorous		
Potassium		
Protein (total)		
Sodium		
Blood urea nitrogen/urea		
Uric acid		

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data or to rule out a diagnosis.
Note: Alternative tests (ie, CO_2 or CO_2 Combining Power or HCO_3) are also allowed as per regional standard of care.

IgA, IgG, IgM, and TSH assessments will be conducted as indicated in Table 4.

Urinalysis will be performed using a dipstick at screening and during study conduct as clinically indicated. A quantitative assessment may be required in the event of a positive or doubtful dipstick result.

8.3.5.2. Pregnancy Testing

The pregnancy tests will be performed and analyzed locally at sites.

A pregnancy test will be performed for WOCBP at various timepoints either by urine pregnancy test or beta-human chorionic gonadotropin (β-HCG) test of a serum sample. The pregnancy test assay should have a minimum sensitivity of 25 mIU/mL.

The pregnancy tests will be performed at the timepoints listed in Table 4; a serum test will be performed at screening, before the first study drug dose, and after any positive urine test; the other tests will be performed on a urine sample. Urine pregnancy tests can be replaced with serum tests.

Participants who are WOCBP must have 2 negative pregnancy tests before starting study treatment, even if true abstinence is the chosen method of birth control as defined in Section 5.1. The participant must not receive study treatment until the investigator or designee has verified that the results of these pregnancy tests are negative. Tests will be repeated weekly during the

first month and then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles until the safety follow-up visit.

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

[redacted]

8.3.5.4. Hepatitis Virus Serology

Participants will be examined according to Table 4 for viral hepatitis B and C. Hepatitis B biomarkers include HBsAg, total HBcAb, and HBsAb. Participants with a positive test for HBcAb can only be included if HBV DNA is not detected. In these HBcAb-positive participants only, HBV DNA titer should be assessed using real-time PCR at Day 1 of each cycle, and at EOT.

In the context of exclusion criteria, seropositive for or active viral infection with HBV means:

- HBsAg positive
- HBsAg negative, HBsAb positive, and/or HBcAb positive and detectable HBV DNA

Participants who are HBsAg-negative, HBcAb-positive and HBV DNA–negative are eligible.

Participants who exhibit the classical vaccination profile of HBsAb-positive, HBcAb-negative, and HBsAg-negative are eligible.

If HBV DNA becomes detectable during treatment, participants should be prophylactically treated and followed-up for potential hepatitis B reactivation as per institutional guidelines. 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. In HBcAb-positive participants, HBV DNA titer is determined using real-time PCR on Day 1 of each cycle and at least once 1 year after the last treatment cycle. Additional ad-hoc measurements may be performed as clinically indicated in consultation with the HBV specialist.

Hepatitis C serology is to be done at screening only. Hepatitis C biomarkers include anti-HCV. For participants who are positive for anti-HCV antibody, HCV RNA should be measured. A positive hepatitis C test is defined as a positive test for HCV antibodies and a positive test for HCV RNA. HCV RNA by PCR is performed only if anti-HCV Ab is positive.

8.3.5.5. Human Immunodeficiency Virus Serology

Serology for HIV is to be done at screening only (optional in the United States). HIV serology will include anti–HIV-1 and anti–HIV-2 antibodies, and seropositive participants will be excluded from the study.

[redacted]

[redacted]

8.7. Unscheduled Visits

Clinic visits or diagnostic laboratory visits not prescribed in the Protocol may be performed at any time clinically indicated at the investigator's discretion. Results of assessments performed at these visits should be entered as unscheduled visits in the eCRF. The sponsor may also request additional visits to be performed, if needed, based on emerging safety data.

8.8. End of Treatment and/or Early Treatment Discontinuation

The EOT visit will be performed at the time the decision is made to discontinue study treatment or after the participant has completed the prescribed treatment regimen (Cycle 12 Day 28). 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 visits.

See Table 3 and Table 4 for the list of assessments be performed at the EOT visit.

8.9. Follow-Up

The follow-up period is composed of 1) the safety follow-up period, 2) the efficacy follow-up, and 3) the survival follow-up period(s), as applicable.

8.9.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT date and the safety follow-up visit, which should occur 90 days (± 7 days) after the EOT visit.

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 a participant is scheduled to begin new anticancer therapy before the end of the 90-day safety follow-up period, the safety follow-up visit should be performed before new anticancer therapy is started.

Once new anticancer therapy has been started, the participant will move into the survival follow-up period.

8.9.2. Efficacy Follow-Up

Participants who discontinue study treatment for reasons other than disease progression will continue to be assessed for efficacy (eg, scans performed at regular intervals) during this period. Participants will continue to be assessed at the intervals noted in Section 8.2.4 until disease progression, initiation of new anticancer therapy, lost to follow-up, withdrawal of consent, or death is reported. Participants with PD confirmed will move into the survival follow-up phase (see Section 8.9.3).

8.9.3. Survival Follow-Up/Completion of Study

All participants will be followed for survival status every 12 weeks (± 4 weeks) until death, lost to follow-up, withdrawal of consent for survival follow-up, completion of the 5-year follow-up interval, or the end of the study.

For participants who have entered the survival follow-up period, sites will continue to collect data regarding initiation of new anticancer treatment [redacted] and report OS. For participants who do not intend to return to the study investigator for their ongoing care, follow-up will be maintained by telephone contact, patient records, and public records/databases at intervals of no longer than 12 weeks.

Additional survival assessments may be performed outside the 12-week interval if a survival update is required for an interim assessment to meet safety or regulatory needs.

8.9.4. End of Study

The end of study will occur after the last participant has completed a minimum of 5 years of post-treatment follow-up. This is expected to occur approximately 8 years after the first participant is enrolled.

The sponsor has the right to terminate the study at any time.

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

Study personnel must remain vigilant for the occurrence of AEs, particularly those that may be life-threatening. Personnel who are trained in the acute management of IRRs, CRS, anaphylaxis, and other emergencies, and who have access to appropriate clinical supplies, should be readily available.

All AEs should be treated appropriately. Such treatment may include changes in study treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an AE is detected, it should be followed up, and an assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to tafasitamab, lenalidomide or rituximab, any of the interventions required to treat it, and its outcome.

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 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 Meeting 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 test 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 surgery procedure will be collected as well. 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.

Events NOT Meeting the Adverse Event Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator.
- Efficacy endpoints as outlined in Section 3 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the cancer under study. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be transmitted to Incyte Pharmacovigilance via the EDC system within 24 hours of determination that the event is not progression of the cancer under study.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing informed consent. If present before entering the study, the condition should be captured as medical history.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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 serious adverse event 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 (these would include secondary malignancies arising during the study that are distinct from the disease[s] under study), 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 SAEs.

For Japan, an event which may lead to disability is also considered as the 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 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 or as per SAE completing guidelines.
- 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.
- The action taken with regard to 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. The relationship to each study treatment/reference therapy must be assessed (ie, for the Incyte product[s] and for the other product[s] that are used in combination with the Incyte product). 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 RSI in the IB 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 it has resolved or until it is judged to be permanent; 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, in case an autopsy was performed.
- Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (via the EDC system or via email/fax if the paper SAE form is used) 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 Incyte Pharmacovigilance within 24 hours of receipt of the information.

See Appendix I for the management of potential Hy's Law (PHL) cases.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study treatment or study procedure[s]), all SAEs occurring after the participant has signed the ICF through completion of the study ***or*** until the participant starts a new anticancer therapy (whichever occurs earlier) 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) immediately, without undue delay but not later than within 24 hours of it being available. For Japan, this information must also be reported immediately to the head of the study site in Japan.

Investigators are not obligated to actively seek SAE information after the EOT visit. If the investigator learns of any SAE, including a death, 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 towards the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the RSI of the IB or product information for study treatment (new occurrence) or marketed products, respectively, and is thought to be related to the 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 drug that this SAE has been reported. SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

The sponsor will report suspected expected deaths and life-threatening events to PMDA in Japan, as per local regulatory requirements, as applicable.

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 SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an 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 or as per the Incyte Reference Guide for Completing the Serious Adverse Event Report Form. • 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 Incyte Reference Guide for Completing the Serious Adverse Report Form or 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.

9.5. Events of Clinical Interest

An ECI is an AE that is either serious or nonserious that must be documented in a certain manner for further evaluation and assessment.

9.5.1. Adverse Events of Special Interest by eCRF

Adverse events of special interest are defined as a subset of ECIs that an investigator should urgently communicate information about the event to the sponsor/designee for further evaluation. Communication can be in the form of eCRF entry, email, or phone call to the sponsor/designee.

Adverse events of special interest for tafasitamab/placebo are TLS, IRRs and allergic reactions to study drug ≥ Grade 3, CRS, SPM, hepatitis B reactivation, and PML.

Adverse events of special interest for lenalidomide are second primary malignancy.

Adverse events of special interest will be captured in the eCRF and if any of the serious criteria is met, should be captured as an SAE as well.

Adverse events of special interest should be reported as a diagnosis and should include the symptoms of the event as 1 event term. For example, IRR with symptoms of hives, chills, and fever.

9.5.2. Adverse Events of Special Interest by Category and Preferred Term

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; please refer the SAP for further specific details.

9.6. Emergency Unblinding of Treatment Assignment

In case of a medical emergency, for a participant's safety management, the procedure for emergency unblinding is provided in the IRT or Study Reference Manual. This option may be used *only* if the participant's well-being requires the investigator to be aware of the participant's treatment assignment. If a participant's treatment assignment is unblinded, the sponsor or its designee must be notified immediately by telephone.

If an investigator, the site personnel performing assessments, or a participant is unblinded, then the participant must discontinue study treatment, unless there are ethical reasons to have the participant remain on the study treatment. In these cases, the investigator must obtain specific approval from the sponsor's (or its designee's) medical monitor for the participant to continue in the study.

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 interrupted immediately (female participants only).
- If the female participant is no longer pregnant and meets the treatment continuation criteria within 28 days of the scheduled start of a cycle study treatment may be resumed after approval has been received from the sponsor medical monitor.
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to Incyte Pharmacovigilance 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 drug 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 or Study Reference Manual.

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 drug/treatment, derived from safety information collected by the sponsor or its designee, are presented in the 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.

9.9. Product Complaints

The sponsor collects product complaints on study drugs 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.

In Japan, 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

The sponsor is not recommending any specific treatment of a suspected overdose of tafasitamab, rituximab, and/or lenalidomide. In case an overdose of tafasitamab, rituximab, and/or lenalidomide happens and requires treatment, symptomatic treatment including but not limited to blood product transfusions, growth factors, antibiotics, antiemetics, and analgesics may be administered per investigator's discretion.

For purposes of this study, overdose of tafasitamab/rituximab is defined as any tafasitamab/rituximab dose above 120% of the assigned dosage per single infusion as per Protocol.

For lenalidomide the overdose is defined as any dose greater than the planned dose for a particular participant as per Protocol.

Overdose is not an SAE unless it meets the criteria of an SAE (see Section 9.2).

In the event of an overdose, the investigator should do the following:

- Contact the medical monitor immediately.

- Closely monitor the participant for any AE/SAE and laboratory abnormalities as clinically appropriate.
- 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.

10. STATISTICS

Any data analysis carried out independently by the investigator should be submitted to the sponsor before any publication or presentation.

Data from all the sites and centers will be combined in the efficacy and safety analysis.

10.1. Sample Size Determination

The primary objective of the study is to detect a statistically significant difference in PFS (INV) for the tafasitamab-lenalidomide combination in addition to rituximab relative to placebo-lenalidomide in addition to rituximab for participants with FL.

Based on the assumptions in Table 12 below, a total number of 174 PFS events in the FL population are required to detect a HR of 0.65 with 80% power at the primary analysis, using a 2-sided log-rank test at an alpha level of 5% and a 1:1 randomization ratio between the 2 treatment groups. Assuming a median PFS of 27.8 months for lenalidomide in addition to rituximab (TGB), 21 months of enrollment, 12 months of follow-up for PFS, and 15% of dropouts, 528 evaluable FL participants need to be randomized.

Table 12: Sample Size Assumptions

Primary endpoint	Progression-free survival (INV) for the FL population
Median PFS in TGA	42.8 months
Median PFS in TGB	27.8 months
Randomization ratio	1:1
Assumed HR	0.65
Alpha (2-sided)	5%
Power	80%
Enrollment duration	21 months
Follow-up for PFS (starting from last participant randomized)	12 months
Accrual rate	0.1 participant/site/month
PFS events required at primary analysis	174
Total participants (without dropout)	448
Assumed dropout rate	15%
Total randomized participants	528

A minimum of 60 and up to 90 additional participants with MZL will be randomized at a 1:1 ratio to one of the 2 treatment groups. The number of MZL participants is based on an expected enrollment proportion of FL and MZL participants.

A 2-stage design with 1 interim analysis for a potential futility stop will be applied. Information regarding the stopping boundaries at the interim and primary analyses is provided in Section 10.4 and Section 10.5.

10.2. Population for Analysis

A full description of the population for analysis is presented in Table 13.

Table 13: Analysis Population

Population	Description
All screened	All participants who sign the ICF.
FAS	All randomized participants. Treatment groups for this population are determined according to the treatment they have been assigned at the time of randomization. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy data.
PPS	The subset of the participants in the FAS who are compliant with the requirements of the clinical study Protocol. All Protocol deviations or conditions leading to exclusion from the PPS will be detailed in the Protocol Deviation Specifications. Sensitivity analyses of the primary endpoint may be performed using PPS.
SAF	All randomized participants who receive at least 1 dose of tafasitamab/placebo, lenalidomide, or rituximab. Treatment groups for this population will be determined according to the actual treatment the participant received on Cycle 1 Day 1 regardless of assigned treatment at the time of randomization. All safety analyses will be conducted using the SAF.
[redacted]	[redacted]
[redacted]	[redacted]

10.3. Level of Significance

The primary endpoint of PFS in the FL population and 3 key secondary endpoints will be tested with inferential statistics. Hypothesis testing for other secondary and exploratory endpoints may be performed for exploratory purposes. Estimates and p-values will be reported for illustrative and exploratory purpose.

Statistical tests will use a 0.05 significance level and will be 2-sided unless otherwise noted. Confidence intervals, both individual and simultaneous, will be at 95% confidence level unless stated otherwise.

In order to control the study-wise type I error due to the multiple testing of the primary and key secondary endpoints, a hierarchical order of testing will be implemented.

The primary endpoint analysis will serve as a gatekeeper:

- PFS by INV in the FL population

If the primary hypothesis is rejected, the key secondary endpoints can be tested with the following fixed order:

- PFS by INV in the overall population (FL and MZL)
- PET-CR rate by INV in the FDG-avid FL population
- OS in the FL population

If a null hypothesis is not rejected, the formal sequential testing will be stopped, and the p-values for the remaining key secondary endpoints will be reported for exploratory and illustrative purposes.

The primary analysis will be performed after approximately 174 PFS events based on INV are observed in the FL population in the FAS. The primary analysis is independent of the number of enrolled MZL participants. Recruitment will be stopped when the required 528 FL participants for the primary analysis and at least 60 MZL have been randomized. The maximum number of randomized MZL participants is 90. Formal hypothesis testing will not be performed for OS at the time of primary analysis; however, HRs may be estimated.

The final analysis will be performed at the end of the study as defined in Section 8.9.4. At the time of final analysis, the last key secondary endpoint OS will be tested.

Other secondary and exploratory endpoints will be tested using a 2-sided, 5% significance level without multiplicity adjustment. Estimates and nominal p-values will be reported for exploratory purpose. Additional follow-up analyses for safety or efficacy endpoints may be performed if needed or requested by regulatory authorities.

10.4. Statistical Analyses

10.4.1. Efficacy Analyses

All efficacy analyses will be based on FAS.

10.4.1.1. Primary Analysis for Progression-Free Survival in the Follicular Lymphoma Population

Progression-free survival as per INV is defined as the time from the date of randomization to the date of first documented disease progression, as determined by disease assessment per Lugano 2014 criteria, or death due to any cause, whichever occurs earlier.

For a given analysis, PFS will be censored if no PFS event is observed before the cutoff date or on the date that a new antilymphoma therapy is started. Censoring for PFS will follow the algorithm outlined in Table 14, which is based on the FDA Guidance (FDA 2015, FDA 2018).

Table 14: Evaluation and Censoring of Progression-Free Survival for Primary Analysis

Situation	Censoring/Event Time	Outcome	Censoring Reason
No baseline tumor assessment	Date of randomization	Censored	No baseline assessment
No valid postbaseline tumor assessment	Date of randomization	Censored	No postbaseline assessment
No PFS event observed before cutoff	Date of last adequate tumor assessment prior to cutoff date	Censored	Ongoing
Study discontinuation for undocumented progression or other reason	Date of last adequate tumor assessment prior to cutoff date	Censored	Study discontinuation
Start of a new antilymphoma treatment	Date of last adequate tumor assessment on/before start of new antilymphoma treatment	Censored	Start of new antilymphoma treatment
Death or disease progression documented after 2 or more missing or nonadequate tumor assessments	Date of last adequate tumor assessment with overall lesion response of CR, PR, or SD prior to PD	Censored	Death or PD after 2 or more missing assessments

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR, SD. In this case, the last tumor evaluation date at that assessment is used. If a PFS event is observed after a single missing or nonadequate tumor assessment, the actual date of event will be used, as per Cheson et al (2014) criteria.

The distribution of PFS as per INV will be compared between the 2 treatment groups using a stratified log-rank test at 2-sided 5% level of significance. The strata information will be based on the data obtained from the IRT that was used for randomization.

A stratified Cox proportional hazard model will be used to estimate the HR between TGA (tafasitamab-lenalidomide in addition to rituximab) versus TGB (placebo-lenalidomide in addition to rituximab), along with 2-sided 95% CI, using the same stratification factor as for randomization as mentioned in Section 4.1.

The distribution of PFS will be estimated using the Kaplan-Meier method. The median along with 2-sided 95% CIs will be presented by treatment group. In addition, investigator-assessed PFS event rates at 6, 12, 18, 24, 36, and 48 months will be provided along with the corresponding 2-sided 95% CIs for the estimates.

All analysis mentioned above will be performed for participants with FL in the FAS.

If the null hypothesis is rejected at a 2-sided significance level of 5%, the primary endpoint is met. The p-value obtained from stratified log-rank test for PFS in the FL population using the

strata information based on IRT that was used for randomization will be used for hierarchical testing.

In case of discrepancies in the diagnosis between the eCRF and the IRT, the participants will be analyzed into the population based on eCRF diagnosis.

If a participant was randomized into the MZL cohort but after randomization was confirmed by the site to have a diagnosis of FL, the eCRF-derived information for medical history will be used to derive the 2 missing stratification factors for the FL cohort: POD24 status (yes versus no) and refractoriness to prior anti-CD20 mAb therapy (please see the definition in Section 4.1). If a participant was randomized into the FL cohort but after randomization was confirmed by the site to have a diagnosis of MZL, the IRT-derived stratification factor needed for this cohort (number of prior lines of therapy: < 2 vs ≥ 2) will be used.

[redacted] Additional sensitivity analyses will be performed as mentioned in Section 10.4.1.6.

10.4.1.2. Analyses of Key Secondary Efficacy Endpoints

Hierarchical testing will be implemented for the key secondary endpoints, with the primary endpoint PFS serving as a gatekeeper. This hierarchical testing procedure will maintain the study-wise Type I error.

10.4.1.2.1. Progression-Free Survival in the Overall Population

Progression-free survival in the overall population (FL and MZL) will be compared and analyzed in the same manner as described above in Section 10.4.1.1 for the PFS in the FL population. The strata information for the stratified log-rank test will be based on the randomization factor used for both cohorts, FL and MZL: number of prior lines of therapy (< 2 vs ≥ 2).

The p-value obtained from the stratified log-rank test for PFS in the overall population using the strata information based on IRT that was used for randomization, including stratification by FL versus MZL, will be used for hierarchical testing.

[redacted] Additional sensitivity analyses will be performed as mentioned in Section 10.4.1.6.

10.4.1.2.2. Positron Emission Tomography–Complete Response Rate in the FDG-Avid Follicular Lymphoma Population

The PET-CR rate is defined as the proportion of participants who achieved a CR as per Lugano classification (Cheson et al 2014) with a PET-negative result among the participants with a positive PET scan at baseline. Participants with a positive PET scan are defined as participants with a Deauville score of 4 or 5.

Participants with no postbaseline assessment by PET or who did not achieve a PET-CR will be classified as "non CR-responder."

The CR rate will be compared between the 2 treatments groups using stratified CMH test using the same stratification factor as for randomization as for the PFS primary analysis. The odds ratio and its 95% CIs calculated from the stratified CMH test will also be presented. The number

of participants classified as PET-CR responders and the respective rates as well as 95% CIs (using Clopper-Pearson) will be presented.

Key secondary analysis of PET-CR will be performed for participants with FDG-avid FL in the FAS.

If the null hypothesis is rejected at a 2-sided significance level of 5%, this key-secondary endpoint is met. The p-value obtained from CMH test for PET-CR rate as per INV observed in the FDG-avid FL population using the strata information based on IRT that was used for randomization will be used for hierarchical testing.

[redacted] Additional sensitivity analyses will be performed as mentioned in Section 10.4.1.6.

10.4.1.2.3. Overall Survival in the Follicular Lymphoma Population

Overall survival is defined as the time from randomization until death from any cause. Participants who are not reported as a death at the time of the analysis cutoff will be censored at the date of last known alive, regardless if a new antilymphoma therapy was started.

All participants should be followed until death or until the end of study as specified in the Protocol, whichever comes first. The follow-up data should contain the date the participant was last seen alive/last known alive, the date of death, and the reason of death ("disease progression," "adverse event," or "other").

Overall survival will be compared and analyzed in the same manner as described above in Section 10.4.1.1 for the PFS.

Key secondary analysis of OS will be performed for participants with FL in the FAS. The analysis will be performed at the time of final analysis.

[redacted] Additional sensitivity analyses will be performed as mentioned in Section 10.4.1.6.

[redacted]

10.4.1.4. Analyses of Other Secondary Efficacy Endpoints

10.4.1.4.1. Positron Emission Tomography-Complete Response Rate in the Overall Population

The PET-CR rate in the overall FDG-avid population (FL and MZL) will be compared and analyzed in the same manner as described in Section 10.4.1.2.2 for the PET-CR rate in the FDG-avid FL population. The stratification factors will be those used for the PFS analysis on

the FL population and on the overall population, respectively (see Section 10.4.1.1 and Section 10.4.1.2.1).

10.4.1.4.2. Minimal Residual Disease-Negativity Rate at End of Treatment in the Follicular Lymphoma and Overall Population

The MRD-negativity rate is defined as the proportion of participants who achieved a negative MRD result at EOT. Participants with no postbaseline assessment or who did not achieve a negative MRD result will be classified as "non MRD-negative."

The MRD-negativity rate in the 2 treatment groups will be compared and analyzed in the same manner as described in Section 10.4.1.2.2 for the PET-CR rate. The stratification factors will be those used for the PFS analysis on the FL population and on the overall population, respectively (see Section 10.4.1.1 and Section 10.4.1.2.1). Analysis of the MRD-negativity rate at EOT will be performed for participants with FL and the overall population (FL and MZL) in the FAS.

[redacted]

10.4.1.4.3. Overall Response Rate in Follicular Lymphoma and Overall Populations

Overall response rate is defined as the proportion of participants who achieved a CR or PR as determined per Lugano classification (Cheson et al 2014) at any time during the study but before the first PD and before/at the start of a new antilymphoma treatment.

Overall response rate will be compared and analyzed in the same manner as described above in Section 10.4.1.2.2 for PET-CR rate in the FDG-avid FL population. The stratification factors will be those used for the PFS analysis on the FL population and on the overall population, respectively (see Section 10.4.1.1 and Section 10.4.1.2.1).

10.4.1.4.4. Duration of Response in the Follicular Lymphoma and Overall Populations

Duration of response is defined as the time from first tumor response (CR or PR as per Lugano classification [Cheson et al 2014]) until the time of first documented disease progression, or death from any cause, among participants who achieve an objective response. Participants with a response but no documented disease progression or death at the time of analysis will be censored at the date of last adequate tumor assessments.

Kaplan-Meier estimation of median DoR and its 95% CIs will be presented by treatment group for participants who achieve an objective response. No statistical comparison will be performed for this analysis.

Duration of response will be analyzed for FL and overall populations.

10.4.1.4.5. Overall Survival in Overall Population

Overall survival in the overall population (FL and MZL) will be compared and analyzed in the same manner as described in Section 10.4.1.2.3 for the OS in the FL population. The only difference will be that the strata information for the stratified log-rank test will be based on the randomization factor used for both cohorts, FL and MZL: number of prior lines of therapy (< 2 vs ≥ 2).

10.4.1.4.6. Analysis of Efficacy Endpoints by Independent Review Committee

The endpoints PFS, ORR, and DoR, as determined by IRC assessment using International Working Group 2014 response criteria (Cheson et al 2014), will be analyzed on the FL and overall populations.

They will be analyzed the same way as described for the respective efficacy endpoints by INV (see Section 10.4.1.1, Section 10.4.1.4.3, and Section 10.4.1.4.4).

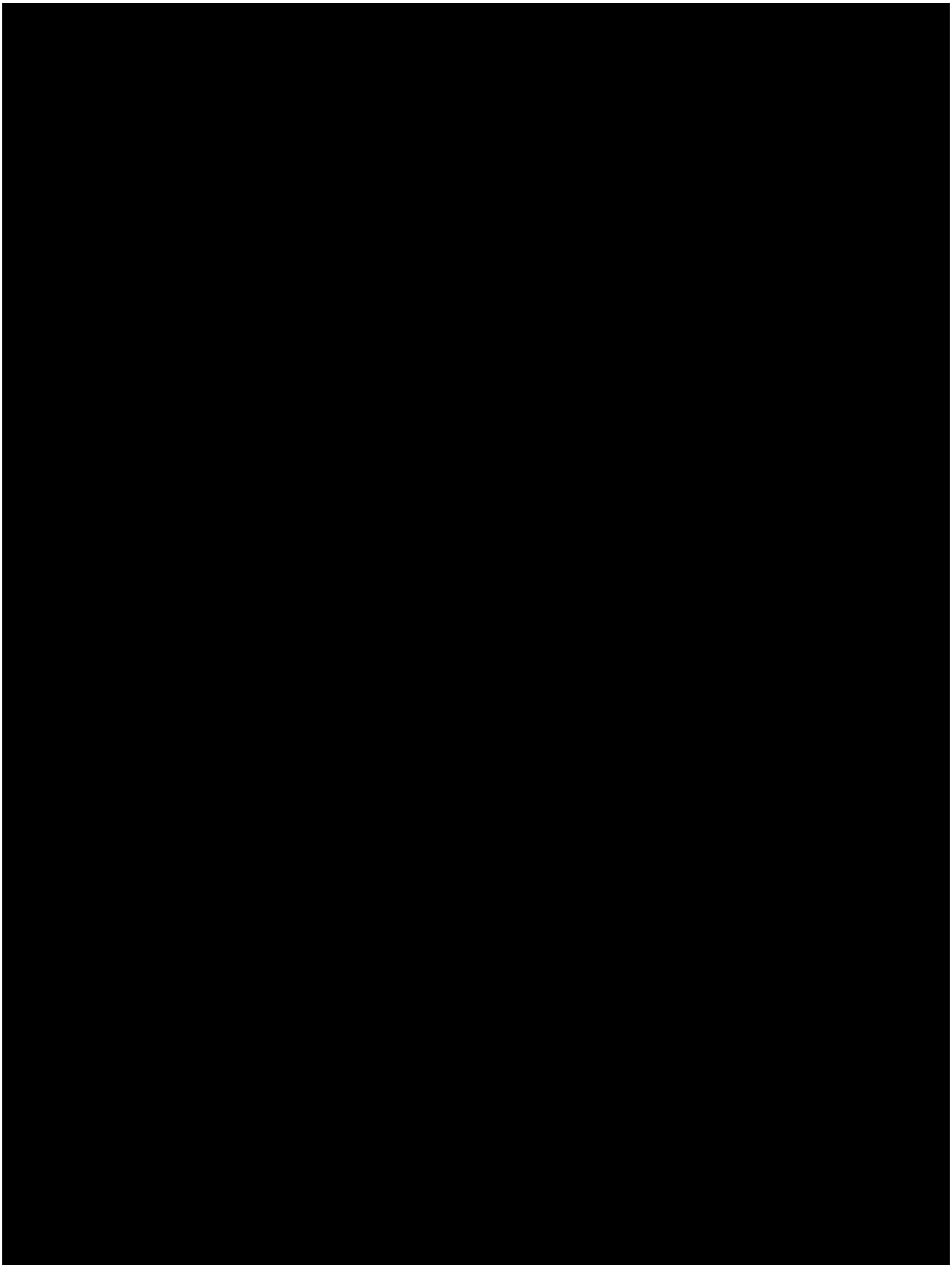
10.4.1.4.7. Response Assessment Concordance

The concordance rate represents the agreement in the best overall outcome (CR, PR, SD, PD, not evaluable, and not available) in response assessments between the IRC and INV assessment. The concordance rate is the number of concordant participants over the total number of assessed participants and will be calculated across all response categories.

10.4.1.4.8. Quality of Life Questionnaires EORTC QLQ-C30, EQ-5D-5L, and FACT-Lym in Follicular Lymphoma and Overall Populations

Quality of life will be assessed using the EORTC QLQ-C30, the EQ-5D-5L, and FACT-Lym tools. The EORTC QLQ-C30 is composed of 5 functional scales (eg, physical function, emotional functioning), 3 symptom scales (eg, fatigue), a global health status, and 6 single items (eg, dyspnea, insomnia). The EQ-5D-5L contains a participant reported score on a visual analogue scale and 5 questions on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scoring of each scale will be calculated following the respective manuals. The FACT-Lym questionnaire is composed of the FACT-General (FACT-G)—a 27-item compilation of general questions and an additional 15 items that assess patient concerns relating to lymphoma: the FACT-Lym lymphoma-specific subscale or FACT-Lym LYMS. The FACT-Lym LYMS consists of common lymphoma disease and/or treatment-related symptoms (eg, pain, fever, swelling, night sweats, insomnia, itching, weight loss, fatigue, and loss of appetite).

Descriptive statistics for each of the scores will be tabulated. Change from baseline for each score will be summarized by visit for each treatment group in the FL population and overall population.



[redacted]

10.4.1.6. Sensitivity Analysis of Efficacy Endpoints

The following sensitivity analysis will be performed:

- All primary and key secondary efficacy analyses [redacted] may be performed on the PPS.
- For time to event endpoints, the assumption of proportional hazard may be tested. If the assumption is not met, a Renyi test may be performed. Additional details will be provided in the SAP.
- For time to event endpoints, unstratified log-rank test may be performed and unadjusted HR may be obtained using unstratified Cox PH model.
- Stratified analyses may be performed using stratification factors from the eCRF.
- For binary endpoints like PET-CR rate and ORR, Fisher's exact test may be performed.
- For the primary and key secondary endpoint of PFS in the FL and overall populations, the analysis may be performed considering participants having an event after 2 or more missed visits as having a PFS event.
- For the primary and key secondary endpoint of PFS in the FL and overall populations, the analysis will correct for potential bias in the follow-up schedules for disease assessment by assigning the dates for censoring and events only at scheduled visit dates. It is the same as the primary analysis except that the date of progression is approximated as the date of the Protocol-scheduled visit immediately after the radiologic assessment of PD.
- For the primary and secondary efficacy endpoints, sensitivity analyses may be performed to evaluate the impact of subsequent antilymphoma therapy. For the PFS and DoR endpoints, sensitivity analyses may be performed per EMA guidelines to consider new antilymphoma treatment as an event or consider all disease progressions and deaths as events regardless of whether they occur after initiating new antilymphoma treatment.

Any additional sensitivity analysis will be outlined in the SAP.

10.4.2. Safety Analyses

Safety analyses will be conducted for the SAF. No formal statistical testing will be performed.

All TEAEs, clinical laboratory measurements, vital sign measurements, and abnormal ECGs will be summarized by treatment group. Quantitative safety variables and their changes from baseline (laboratory and vital signs) will be summarized with descriptive statistics. Abnormal values outside of established ranges will be flagged and tabulated based on predefined criteria.

Measures of exposure (eg, days of exposure, dose intensity) of tafasitamab/placebo, lenalidomide, and rituximab will be summarized descriptively.

Adverse events will be coded by the MedDRA dictionary and severity of AEs will be based on the NCI CTCAE v5.0 using Grades 1 through 5. A TEAE is defined as an AE either reported for the first time or worsening of a pre-existing event on or after first dose of study treatment and within 90 days of the last administration of study treatment. Number (%) of participants reporting any TEAEs, any serious TEAEs, any Grade 3 or higher TEAEs, any treatment-related TEAEs, any treatment-related serious TEAEs, any treatment-related Grade 3 or higher TEAEs, any fatal TEAEs, and any TEAEs leading to treatment interruption/delay/dose reduction/discontinuation will be tabulated by MedDRA system organ class and preferred term. Data listings will include all AEs regardless of their timing to study drug/treatment administration.

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE toxicity grades when applicable, and tabulated.

Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. The abnormal values for participants exhibiting vital sign abnormalities will be listed.

[redacted]

10.5. Interim Analysis

An interim analysis will be performed after 20% of the required PFS (INV) events (approximately 35 events) have been observed in participants with FL in the FAS population. This is expected to occur approximately 15 months after the first participant is randomized and approximately 338 (out of 528 total) participants with FL will have been randomized in the study.

An IDMC will be involved in reviewing the interim analysis results and provide their recommendation for a potential futility stop based on comparative efficacy and safety data. The PFS HR will be calculated and the IDMC may recommend to stop the study if the observed HR of tafasitamab plus lenalidomide in addition to rituximab (TGA) over placebo plus lenalidomide in addition to rituximab (TGB) is ≥1.05 for participants with FL in the FAS population (nonbinding futility boundary; see Table 15). Early stop for efficacy is not planned.

The false negative rate for a futility stop with a futility boundary of HR = 1.05 is

- Approximately 8% if the true HR is 0.65, and
- Approximately 15% if the true HR is 0.74.

The false positive rate for continuation of the study with a futility boundary of HR = 1.05 is

- Approximately 62% if the true HR is 0.95.

Table 15: Guidelines for Decisions – Progression-Free Survival

	Interim Analysis	
Projected timing	15 months	
Projected randomized participants	338 participants	
Number of PFS events	35 events	
Decision outcome	**Futility Boundary**	**Continue**
Estimated HR	≥ 1.05	< 1.05

At the interim analysis, descriptive analyses will also be provided for other efficacy endpoints, including PFS by INV in the overall population (FL + MZL), PET-CR rate at EOT by INV in the FL and overall populations, and ORR, OS, and DoR by INV in the FL and overall populations.

10.6. Independent Data Monitoring Committee

Preplanned analyses of safety and efficacy will be provided to an IDMC as specified in the IDMC charter (see Section 5.6).

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.

- For Japan, 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 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 and the unblinded pharmacist 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, [redacted], 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, [redacted], 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, or copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.

- 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 monitoring plan.

Quality tolerance limits will be predefined in the monitoring plan 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 Corporation/Incyte Biosciences International Sàrl (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.

For Japan, 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

Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required. Add FSH in the laboratory table at screening, as needed.

Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential[a]

The following methods during the Protocol-defined timeframe in Section 5.1 are highly effective:

- Condom
  - Use of a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
- Sexual abstinence[b] (sexual abstinence is not approved in Japan)
  - Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

The following are not acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method.
- Male condom with cap, diaphragm or sponge with spermicide.
- Male and female condom cannot be used together.

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

For female participants who are WOCBP

The following methods during the Protocol-defined timeframe in Section 5.1 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:

- Progestogen-only hormonal contraception associated with inhibition of ovulation[c] (progesterone-only hormonal contraception is not approved in Japan, so this bullet and its sub-bullets will not apply for Japan)
  - oral
  - injectable
  - implantable[d]
- Intrauterine device[d]
- Intrauterine hormone-releasing system[d]
- Bilateral tubal occlusion[d]
- Vasectomized partner[d,e]
- Sexual abstinence (sexual abstinence is not approved in Japan).

Examples of additional effective (barrier) methods:

- Male condom
- Diaphragm
- Cervical cap

[a] If the male participant has a partner with child-bearing potential the partner should also use contraceptives.
[b] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
[c] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method; 2 methods of contraception should be used.
[d] Contraception methods that in the context of this guidance are considered to have low user dependency.
[e] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
Source: Clinical Trials Facilitation and Coordination Group 2014.

APPENDIX B. DOSE ADJUSTMENT FOR LENALIDOMIDE

Dose Reduction Steps

- *Dose reduction steps*

Starting dose	20 mg once daily on days 1-21, every 28 days
Dose Level -1	15 mg once daily on days 1-21, every 28 days
Dose Level -2	10 mg once daily on days 1-21, every 28 days
Dose Level -3	5 mg once daily on days 1-21, every 28 days

Other dose levels/dose regimens for lenalidomide may be considered after discussion and approval by the sponsor's medical monitor.

Dose Adjustments for Toxicity

Tumour lysis syndrome (TLS)
All patients should receive TLS prophylaxis (allopurinol, rasburicase or equivalent as per institutional guidelines) and be well hydrated (orally) during the first week of the first cycle or for a longer period if clinically indicated. To monitor for TLS, patients should have a chemistry panel drawn weekly during the first cycle and as clinically indicated.
Lenalidomide may be continued (maintain dose) in patients with laboratory TLS or Grade 1 clinical TLS, or at the physician's discretion, reduce dose by one level and continue lenalidomide. Vigorous intravenous hydration should be provided and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy may be needed to reduce hyperuricaemia. Hospitalisation of the patient will be at physician's discretion.
In patients with Grade 2 to 4 clinical TLS, interrupt lenalidomide and obtain a chemistry panel weekly or as clinically indicated. Vigorous intravenous hydration should be provided and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy and hospitalisation will be at physician's discretion. When the TLS resolves to Grade 0, restart lenalidomide at next lower dose per physician's discretion (see section 4.4).

Tumour flare reaction
At the physician's discretion, lenalidomide may be continued in patients with Grade 1 or 2 tumour flare reaction (TFR) without interruption or modification. At the physician's discretion, therapy with non-steroidal anti-inflammatory drugs (NSAIDs), limited duration corticosteroids, and/or narcotic analgesics may be administered. In patients with Grade 3 or 4 TFR, withhold treatment with lenalidomide and initiate therapy with NSAIDs, corticosteroids and/or narcotic analgesics. When TFR resolves to ≤ Grade 1, restart lenalidomide treatment at the same dose level for the rest of the cycle. Patients may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR (see section 4.4).

All indications
For other Grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ Grade 2 depending on the physician's discretion.

Lenalidomide interruption or discontinuation should be considered for Grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, anaphylactic reaction, Grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, and should not be resumed following discontinuation from these reactions.

For study participants experiencing a Grade 3 or higher adverse event of renal impairment, ie, a decrease of the creatinine clearance to less than 30 mL/min, the following dose modification will apply:

Renal impairment (chronic kidney disease)[a]	Grade 3: Creatinine clearance 29-15 mL/min	• Interrupt lenalidomide treatment. • Provided toxicities resolve to ≤ Grade 2, restart lenalidomide at the next lower dose level. – Restart lenalidomide at 15 mg/d (D1-21 Q28D) if participant was on 20 mg/d lenalidomide before the event. – Restart lenalidomide at 10 mg/d (D1-21 Q28D) if participant was on 15 mg/d lenalidomide before the event. – Restart lenalidomide at 5 mg/d (D1-21 Q28D) if participant was on 10 mg/d lenalidomide before the event. • Monitor as clinically indicated.
	Grade 4: Creatinine clearance < 15 mL/min	• Permanently discontinue lenalidomide treatment. • Monitor as clinically indicated.

[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.

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

Calculated Creatinine Clearance (calculated using the Cockcroft–Gault Formula)
(Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine [editorial]. Nephron 1992;62:249.)

$$\text{CrCl (men)} = \frac{(140 - \text{Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Cr (mg/dL)} \times 72}$$

$$\text{CrCl (women)} = 0.85 \times \frac{(140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Cr (mg/dL)} \times 72}$$

APPENDIX D. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	Description
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 housework or office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours.
3	Capable of only limited self-care; confined to a bed or chair > 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 E. ANN ARBOR STAGING

Grade	Description
Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)[a]
Stage II	Involvement of two or more lymph node regions or lymphatic structures on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) or limited, contiguous extralymphatic organ or site (IIIE), or both (IIIES)
Stage IV[b]	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement

Note: All cases are subclassified to indicate the absence (A) or presence (B) of the systemic B symptoms of significant unexplained fever (> 38°C), night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.

[a] The designation "E" generally refers to extranodal contiguous extension (ie, proximal or contiguous extranodal disease) that can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. A single extralymphatic site as the only site of disease should be classified as IE, rather than Stage IV.

[b] Involvement of BM at screening will always qualify for Ann Arbor Stage IV and should be recorded as extranodal involvement.

Source: Carbone et al 1971, Lister et al 1989.

APPENDIX F. FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX-1

The Follicular Lymphoma International Prognostic Index-1 (FLIPI-1) is a prognostic scoring system developed as a result of a large international cooperative effort in which clinical data was collected from 4167 patients with FL diagnosed between 1985 and 1992 (Solal-Céligny et al 2004). From this database, a prognostic index with 5 adverse factors was derived and validated. The parameters include age, Ann Arbor stage, and number of nodal sites involved, hemoglobin levels and serum lactate dehydrogenase (LDH) levels. Each of these adverse factors is assigned 1 point if positive, the points are totaled to give the final FLIPI-1 score, and lymphoma prognoses are based on this score.

The index is able to separate participants with FL into 3 distinct prognostic groups with unique survival outcomes. If the score is 0 to 1, the participant is considered "low risk" according to the FLIPI-1. Overall survival at 10 years is estimated to be 70%. If the score is 2, the participant is considered "intermediate risk" according to the FLIPI-1. Overall survival at 10 years is estimated to be 50%. If the score is ≥ 3, the participant is considered "high risk" according to the FLIPI-1. Overall survival at 10 years is estimated to be 35%.

Table A1: FLIPI-1 Criteria

Parameter	Adverse Factor
Age	≥ 60 years
Ann Arbor stage	III to IV
Hemoglobin level	< 12 g/dL
Serum LDH level	> ULN (upper limit of normal)
Number of involved nodal sites	> 4
Risk Group According to FLIPI-1 Score	**Number of Factors**
Low	0-1
Intermediate	2
High	≥ 3

APPENDIX G. THE GROUPE POUR L'ETUDE DE LYMPHOME FOLLICULAIRE CRITERIA

GELF Criteria
Involvement of ≥ 3 nodal sites, each with a diameter of > 3 cm
Any nodal or extranodal tumor mass with a diameter of > 7 cm or risk of local compressive symptoms that may result in organ compromise
B symptoms
Splenomegaly
Pleural effusions or peritoneal ascites
Cytopenias (leukocytes < 1.0×10^9/L and/or platelets < 100×10^9/L
Leukemia (> 5.0×10^9/L circulating malignant cells)

Source: GELF criteria: A guide for the need for treatment of indolent lymphoma (Chen et al 2012, Solal-Céligny et al 1998).

APPENDIX H. LUGANO RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA

Target and Nontarget Lesions

Up to 6 of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in 2 diameters should be identified from different body regions representative of the participant's overall disease burden and include mediastinal and retroperitoneal disease, if involved. At baseline, a measurable node must be > 15 mm in longest diameter (LDi). Measurable extranodal disease may be included in the 6 representative measured lesions. At baseline, measurable extranodal lesions should be > 10 mm LDi.

All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease as nontarget lesions (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites, bone, BM).

Split Lesions and Confluent Lesions

Lesions may split or may become confluent over time. In the case of split lesions, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression. In the case of confluent lesions, the PPD of the confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in PPD of the confluent mass compared with the sum of individual nodes necessary to indicate PD. The LDi and smallest diameter (SDi) are no longer needed to determine progression.

Response	Imaging	Lymph Node and Extra Lymphatic Sites	Nontarget Lesions	Liver and Spleen	Bone Marrow	New Lesion
CR	PET	Score of 1, 2 or 3[a] with our without a residual mass on 5PS.[b]	Not applicable	Not applicable	No evidence of FDG-avid disease in marrow	None
	CT	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi. No extra lymphatic site of disease.	Absent	Regress to normal	Normal by morphology; if intermediate, IHC negative	None
PR	PET	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size. At interim, these findings suggest responding disease. At end of treatment, these findings indicate residual disease.	Not applicable	Not applicable	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, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	None
	CT	≥ 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 value. When no longer visible, 0 × 0 mm. For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation.	Abnormal/ normal, regressed, but no increase	Spleen must have regressed by > 50% in length beyond normal	Not applicable	None

Response	Imaging	Lymph Node and Extra Lymphatic Sites	Nontarget Lesions	Liver and Spleen	Bone Marrow	New Lesion
SD	PET	Score 4 or 5[b] with no significant change in FDG uptake from baseline at interim or end of treatment.	Not applicable	Not applicable	No change from baseline	None
	CT	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for PD are met.	No increase consistent with progression	No increase consistent with progression	Not applicable	None
PD	PET	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment.	Not applicable	Not applicable	New or recurrent FDG-avid foci	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.
	CT	An individual node/lesion must be abnormal with LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An 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 (> 13 cm), 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 clear progression of preexisting nontarget lesions	New or recurrent splenomegaly	New or recurrent involvement	Regrowth of 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

5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; IHC =immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).
Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured; dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, BM), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] PET 5PS: 1 = no uptake above background; 2 = uptake ≤ mediastinum; 3 = uptake > mediastinum but ≤ liver; 4 = uptake moderately > liver; 5 = uptake markedly higher than liver and/or new lesions; X = new areas of uptake unlikely to be related to lymphoma.

Source: Cheson et al 2014.

APPENDIX I. MANAGEMENT OF POTENTIAL HY'S LAW CASES

INTRODUCTION

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets PHL criteria at any point during the study.

The investigator participates, in conjunction with Incyte clinical project and pharmacovigilance representatives, in the review and assessment of cases fulfilling PHL criteria to ascertain whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug.

The investigator fulfills requirements for the recording of data pertaining to PHL or Hy's law cases and AE/SAE reporting according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

For the purpose of this process, definitions are as follows:

Potential Hy's Law

An increase in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN at any point during the study. The elevations do not have to be at the same time or within a specified timeframe.

Hy's Law

An increase in AST or ALT ≥ 3 × ULN and total bilirubin > 2 × ULN, where no other reason can be found to explain the combination of increases (eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug).

ACTIONS REQUIRED IN CASES OF AST OR ALT > 3 × ULN OR TOTAL BILIRUBIN ≥ 2 × ULN

Identification and Determination of Potential Hy's Law

To identify cases of AST or ALT > 3 × ULN or total bilirubin > 2 × ULN and consequently determine whether the participant meets PHL criteria, please follow the instructions below:

- Review the laboratory report and if a participant has AST or ALT > 3 × ULN OR total bilirubin > 2 × ULN at any visit:
  - Determine without delay whether the participant meets PHL criteria by reviewing laboratory reports from all previous visits.
  - Enter the laboratory data into the laboratory eCRF as soon as possible.

Potential Hy's Law Criteria Not Met

If the participant has NOT had AST or ALT ≥ 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Perform follow-up on subsequent laboratory results according to the guidance provided in Section 8 and Section 9 of the Protocol.

Potential Hy's Law Criteria Met

If the participant has had AST or ALT ≥ 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Have participant interrupt study drug.
- Notify Incyte study team without delay.
  - The investigator, or designee, should contact the medical monitor to discuss and agree upon an approach for the study participant's follow-up and the continuous review of data.
- Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as medically indicated.
- Investigate the etiology of the event and perform any relevant diagnostic investigations as discussed with the medical monitor.
- Enter the laboratory data into the laboratory CRF as soon as possible.
- If at any time (in consultation with the medical monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

REVIEW AND ASSESSMENT

No later than 3 weeks after the biochemistry abnormality is initially detected and the criteria for PHL is met, the medical monitor, Incyte pharmacovigilance physician, and investigator will discuss and review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug. Participant matter experts will be included in the review as appropriate.

Evaluation of Alternative Causes

In order to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, the following alternative etiologies should be considered, including but not limited to:

- Active viral hepatitis
- Alcoholic and autoimmune hepatitis

- Hepatobiliary disorders
  - Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if alkaline phosphatase is increased. Malignant interruption of the biliary tract also should be considered.
- Concomitant treatment
- Other causes such as systemic infections (eg, bacterial, fungal, viral), nonalcoholic steatohepatitis, and cardiovascular diseases

Actions After Review and Assessment

According to outcome of the review and assessment, please follow the instructions below:

If there **is** an agreed alternative explanation for the AST or ALT **and** total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE.

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF if possible.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the standard study processes.
- Have participant resume study drug as per Protocol guidelines.

If it is agreed that there is no explanation that would explain the AST or ALT and total bilirubin elevations:

- Have participant permanently discontinue study drug and perform end-of-treatment procedures.
- Report an SAE (report term "Hy's Law").
  - The 'medically important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the Hy's law case, a causality assessment of related should be assigned.
- If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for a Hy's law case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made. Report an SAE (report term "Potential Hy's Law") applying serious criteria and causality assessment as per above.

ACTIONS REQUIRED FOR REPEAT EPISODES OF AST OR ALT > 3 × ULN AND/OR TOTAL BILIRUBIN > 2 × ULN

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

If the alternative cause for the previous occurrence of PHL was not chronic or progressing malignant disease, please follow the process for PHL review and assessment as described in this appendix.

If the alternative cause for the previous occurrence of PHL was chronic or progressing malignant disease, please follow the instructions below:

- Determine whether there has been a significant change* in the participant's condition.
  - If there is no significant change, no action is required.
  - If there is a significant change, follow the process described for PHL review and assessment as described in this appendix.

* A 'significant' change in the participant's condition refers to a clinically relevant change in ALT, AST, or total bilirubin, or associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

APPENDIX J. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	25 NOV 2020
Amendment 2	16 DEC 2020
Amendment 2-EU	01 MAR 2021
Amendment 2-EU2	24 MAR 2021
Amendment 3	04 MAR 2021
Amendment 4	30 JUL 2021
Amendment 5	22 OCT 2021
Amendment 6	15 JUN 2022
Amendment 7	18 APR 2023

Amendment 7 (18 APR 2023)

Overall Rationale for the Amendment:

The purpose of this amendment is to incorporate IRC review as a secondary objective, [redacted], and further clarify the timing of various study visits and procedures.

1. **Section 1, Protocol Summary (Table 1: Primary and Major/Key Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 5: Objectives and Endpoints); Section 10.3, Level of Significance; Section 10.4.1.2.2, Positron Emission Tomography–Complete Response Rate in the FDG-Avid Follicular Lymphoma Population; Section 10.4.1.4.1, Positron Emission Tomography–Complete Response Rate in the Overall Population; Section 10.4.1.4.2, Minimal Residual Disease–Negativity Rate at End of Treatment in the Follicular Lymphoma and Overall Population; Section 10.4.1.4.3, Overall Response Rate in Follicular Lymphoma and Overall Populations; Section 10.4.1.5.3, Transformation of Follicular Lymphoma Into More Aggressive State**

   Description of change: Clarified analysis of PET-CR rate and applicable populations.

   Rationale for change: The EOT component of PET-CR rate was removed; participants having a PET to confirm radiologic CR are not expected to have a repeat PET at EOT. Text was also revised to clarify that only participants with FDG-avid disease at screening will be included in the PET-CR analysis.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 3, Objectives and Endpoints (Table 5: Objectives and Endpoints); Section 4.1, Overall Design; Section 8.2, Efficacy Assessments; Section 10.4.1.4.6, Analysis of Efficacy Endpoints by Independent Review Committee; Section 10.4.1.4.7, Response Assessment Concordance**

   Description of change: Added IRC efficacy review as a secondary endpoint.

   Rationale for change: Addition of a new endpoint that will be assessed at the final analysis.

3. **Section 1, Protocol Summary**

   Description of change: Clarified that the lenalidomide schedule is Cycles 1 to 12, Days 1 to 21 in Treatment Group A.

   Rationale for change: Clarification.

4. **Section 1, Protocol Summary; Section 6.1, Study Treatments Administered**

   Description of change: Clarified that the dose of lenalidomide must be reduced to 10 mg daily for participants with moderate renal insufficiency.

   Rationale for change: Clarification.

5. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change:

   - Separated C1D1 from the rest of Cycle 1 visits as no visit window applies to C1D1.
   - Added a window to the EOT visit for participants who complete the prescribed study treatment regimen.
   - Clarified timing for the safety follow-up visit (90 days from EOT [± 7 days]).
   - Added columns clarifying the need for efficacy and survival follow-up and required assessments.
   - Clarified timing for bone marrow examination (screening and either at radiologic CR or EOT for participants with positive infiltration at screening).
   - Clarified timing for PET scan (screening, at time of radiologic CR in FDG-avid participants, or EOT).
   - [redacted]
   - Revised the QoL collection schedule to align with efficacy assessment timepoints after EOT.

   Rationale for change: Clarification and correction to align with study design.

6. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.2.2, Bone Marrow Biopsy and Aspirate Samples; Section 8.2.2.1, Bone Marrow Biopsy Sample Collection; Section 8.2.2.2, Bone Marrow Aspirate Sample Collection**

   Description of change: Revised text to ensure proper samples are being collected at the proper timepoints for bone marrow examinations and MRD analysis and allow for standard-of-care biopsies to be used for determining eligibility in certain cases.

   Rationale for change: To reduce the collection of unnecessary samples.

7. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments)**

   Description of change:

   - Separated C1D1 from the rest of Cycle 1 visits as no visit window applies to C1D1.
   - Added a window to the EOT visit for participants who complete the prescribed study treatment regimen.
   - Clarified timing for the safety follow-up visit (90 days from EOT [± 7 days]).
   - Added columns clarifying the need for efficacy and survival follow-up and required assessments.
   - Included monthly pregnancy testing between EOT and safety follow-up visit per regulatory feedback.
   - Revised collection of 6- and 12-month post-EOT sample to be an optional sample.
   - [redacted]
   - Revised MRD blood sample collection timepoints (screening, C4D1, C8D1, EOT).

   Rationale for change: Clarification of sample collection timing.

8. **Section 3, Objectives and Endpoints (Table 5: Objectives and Endpoints);** [redacted]

   Description of change: [redacted]

   Rationale for change: Limited sample availability.

9. **Section 5, Study Population; Section 8.1.2, Screening Procedures**

   Description of change: Included language regarding specific documents needed to support candidate enrollment forms and confirm that a participant's eligibility is determined by the PI.

   Rationale for change: Ethics committee request regarding eligibility review.

10. **Section 5.1, Inclusion Criteria (Inclusion Criterion 10)**

    Description of change: Clarified measurable lesion requirements (ie, lesions must be confirmed as measurable using CT, MRI, or PET-CT).

    Rationale for change: Investigator feedback and frequently asked questions.

11. **Section 5.6, Independent Data Monitoring Committee**

    Description of change: Clarified scope of interim analysis and removed stipulations regarding certain Grade 4/5 toxicities.

    Rationale for change: Clarification and alignment with IDMC charter.

12. **Section 6.5.7, Treatment After Initial Radiologic Evidence of Disease Progression**

    Description of change: Section removed.

    Rationale for change: Elimination of redundancy with other protocol sections and alignment with current sponsor protocol template.

13. **Section 6.6.10.1, Anticancer Therapies**

    Description of change: Removed redundant text.

    Rationale for change: Elimination of redundancy and alignment with current sponsor protocol template.

14. **Section 7.1, Discontinuation of Study Treatment**

    Description of change: Clarified reasons for discontinuing treatment, including that lack of efficacy and disease progression are considered mutually exclusive reasons for discontinuing treatment.

    Rationale for change: Clarification and alignment with current sponsor protocol template.

15. **Section 7.2, Participant Withdrawal From the Study**

    Description of change: Clarified reasons for withdrawing from the study.

    Rationale for change: Clarification and alignment with current sponsor protocol template.

16. **Section 7.3, Lost to Follow-Up**

    Description of change: Removed redundant paragraph.

    Rationale for change: Clarification and alignment with current sponsor protocol template.

17. **Section 8.1.2, Screening Procedures**

    Description of change: Clarified that standard of care assessments that occur outside the 28-day screening window may be used for determining eligibility with sponsor medical monitor approval.

    Rationale for change: Flexibility for determining eligibility with respect to certain procedures that cannot be practically repeated.

18. **Section 8.1.4.2.1, Central Pathology Review**

    Description of change: Incorporated relevant text into Section 8.1.4.2.

    Rationale for change: Clarification and elimination of redundancy.

19. **Section 8.2.4, Radiographic and Metabolic Imaging Assessments**

    Description of change: Revised section to ensure proper radiologic and metabolic imaging will be performed at the correct timepoints: participants with FDG nonavid disease do not require repeat PET assessments, and participants with FDG-avid disease only require 1 subsequent PET scan (either at radiologic CR or at EOT). Clarified that the schedule of radiologic imaging is to be followed while on treatment and in efficacy follow-up.

    Rationale for change: Clarification of procedural requirements and timepoints.

20. **Section 8.3.5.4, Hepatitis Virus Serology**

    Description of change: Removed collection of HBV DNA titer after EOT.

    Rationale for change: Removed unnecessary sample collection.

21. **Section 8.8, End of Treatment and/or Early Treatment Discontinuation**

    Description of change: Clarified that the EOT visit is to occur on Cycle 12 Day 28 if the participant completes the prescribed study treatment regimen or at the time the decision is made to discontinue study treatment.

    Rationale for change: To remove language related to the EOT visit occurring 90 days after the last dose because this interval only applies to the safety follow-up visit.

22. **Section 8.9.1, Safety Follow-Up**

    Description of change: Clarified that the safety follow-up visit is to occur 90 days after EOT.

    Rationale for change: Clarification of visit timings.

23. **Section 8.9.2, Efficacy Follow-up**

    Description of change: Clarified that participants who discontinue treatment for reasons other than disease progression will continue to have disease assessments until progression of disease, start of new anticancer therapy, withdrawal of consent, lost to follow-up, or death.

    Rationale for change: Clarification of visit timings.

24. **Section 8.9.3, Survival Follow-up/Completion of Study**

    Description of change: Clarified the interval and window for performing survival follow-up assessments (every 12 weeks with a ± 4-week window) [redacted]

    Rationale for change: Clarification of visit timings.

25. **Section 8.10, Appropriateness of Measurements**

    Description of change: Removed section.

    Rationale for change: Alignment with current sponsor protocol template.

26. **Section 9.4, Reporting of Serious Adverse Events**

    Description of change: Clarified previous amendment language indicating that all SAEs occurring more than 90 days after the last dose of study treatment must be reported and surveillance must continue until initiation of new anticancer therapy or end of study.

    Rationale for change: Clarification of the previous changes to reporting process.

27. **Section 9.5.1, Adverse Events of Clinical Interest by eCRF**

    Description of change: Split section to account for a second methodology that will be used for this analysis; AESIs will be identified by investigators in the clinical database but will also be accounted for programmatically (new section, Section 9.5.2).

    Rationale for change: Program-level revision to AESI reporting process.

28. **Section 10.4.1.1, Primary Analysis for Progression-Free Survival in the Follicular Lymphoma Population**

    Description of change: Added discrepancy handling process related to differences in diagnosis and/or stratification.

    Rationale for change: Process clarification and alignment with the SAP.

29. **Section 10.5, Interim Analysis**

    Description of change: Included OS as part of the data deliverables for the interim analysis.

    Rationale for change: Revision to interim analysis deliverables.

30. **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 6 (15 JUN 2022)

Overall Rationale for the Amendment:

The rationale for this amendment is to update protocol language in order to provide clarity to processes and procedures.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 2.3, Benefit/Risk Assessment; Section 4.1, Overall Design; 5.1 Inclusion Criteria; Section 5.2, Exclusion Criteria; Section 5.6, Independent Data Monitoring Committee; Section 6.1, Study Treatments Administered (Table 7: Study Treatment Information); Section 6.2.1, Tafasitamab/Placebo Preparation; Section 6.5.1, Tafasitamab/Placebo Dose Modifications; Section 6.5.2.1, Management of Tafasitamab/Placebo Infusion-Related Reactions and Cytokine Release Syndrome; Section 6.5.2.2.2, Grade 3 Infusion-Related Reactions, Grade 2 Cytokine Release Syndrome; Section 6.5.2.2.3, Grade 4 Infusion-Related Reactions, Grade 3 to 4 Cytokine Release Syndrome; Section 6.5.5, Toxicity Management Guidelines for Hematological Toxicities (Table 9: Toxicity Management Guidelines for Hematological Toxicities); Section 6.5.6.2, Hypogammaglobulinemia; Section 6.6.6, Premedication for Tafasitamab or Placebo Infusions/Infusion-Related Reaction Prophylaxis; Section 6.6.7, Prophylaxis of Venous Thromboembolism; Section 6.6.10.2, Live Vaccines; Section 7.1.1.4, Investigator Decision; Section 8.1.4.1, Demographics and General Medical History; Section 8.1.4.2, Disease Characteristics, Treatment History and Pathology; Section 8.2.2, Bone Marrow Samples; Section 8.2.3, Minimal Residual Disease Analyses; Section 8.2.4, Radiographic Imaging Assessment; Section 8.3.3, Vital Signs; Section 8.3.4, Electrocardiograms, Echocardiograms, and/or Cardiac MUGA Scans; Section 8.3.5, Laboratory Assessments; [redacted] Section 8.9.2, Efficacy Follow-Up; Section 9.5, Events of Clinical Interest; Section 9.5.1, Adverse Events of Special Interest; Section 11.2, Data Management**

   Description of change: Language has been updated/revised to align participant visits with assessment requirements and visit windows.

   Rationale for change: The language in the original and previous versions of the protocol was confusing and resulted in a significant number of site errors and protocol deviations. Providing clarity will reduce errors and deviations.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities; Table 4: Schedule of Laboratory Assessments)**

   Description of change: Added column for safety follow-up period and revised headers and notes column. [redacted].

   Rationale for change: Safety follow-up column was missing in prior versions; updates to headers provide clarity regarding visit windows; revisions to the notes column deleted detail already included in the referenced sections and provided references to sections that were missing. [redacted].

[redacted]

4. **Section 5, Study Population; Section 8.1.2, Screening Procedures**

   Description of change: Participant enrollment forms will be used for all participants being considered for this study. Completed enrollment forms will be shared with the sponsor, along with completely redacted supportive documentation (eg, laboratory reports, pathology reports), to confirm eligibility.

   Rationale for change: Language was included in the clinical study manual with respect to the enrollment form and supportive documentation; however, this guidance was not included in the protocol. It is an important step in the screening process to ensure the eligibility of all randomized participants.

5. **Section 5.1, Inclusion Criteria**

   Description of change: The age requirement for the study population enrolled in Japan will be updated to indicate that participants enrolled in this study on or prior to 31 MAR 2022 must be aged ≥ 20 years; beginning 01 APR 2022, participants may be aged ≥ 18 years.

   Rationale for change: Effective 01 APR 2022, the age of adulthood in Japan changes from ≥ 20 years to ≥ 18 years.

6. **Section 6.2.1, Tafasitamab/Placebo Preparation; Section 6.2.3, Unblinded Site Staff, Handling, and Accountability; Section 6.3, Measures to Minimize Bias: Randomization and Blinding; Section 6.4, Study Treatment Compliance; Section 11.2, Data Management**

   Description of change: Language was updated and Section 6.2.3 was added to highlight the unblinded component of this study to include the responsible parties and details of the unblinded database.

   Rationale for change: This language and section was missing from previous versions of the protocol.

7. **Section 6.5.5, Toxicity Management Guidelines for Hematological Toxicities**

   Description of change: Language was added to clarify dose and schedule adjustments for study treatment compounds.

   Rationale for change: Clarification was needed due to numerous questions from sites.

8. **Section 6.6.10.1, Anticancer Therapies**

   Description of change: Language was added to clarify when anticancer therapies can start after EOT.

   Rationale for change: Clarification was needed due to errors and questions by the sites.

9. **Section 8.1.2, Screening Procedures**

   Description of change: Added language to allow for standard of care assessments to be used in screening of participant.

   Rationale for change: To provide clarity and flexibility for use of standard of care assessments to be performed before obtaining ICF signature.

10. **Section 8.1.4.2.1, Central Pathology Review**

    Description of change: Section was added to outline the central pathology review plans for this study.

    R**ationale for change:** This section was missing from previous versions of the protocol.

11. **Section 8.2.3, Minimal Residual Disease Analyses**

    Description of change: Section was added to clarify the samples needed for MRD analysis.

    Rationale for change: Language was not clear in the previous versions and a new section was needed to provide adequate details.

12. [redacted]

13. **Section 8.9.4, End of Post-Treatment Follow-Up (Study Phase Completion)**

    Description of change: The section has been removed due to it being redundant with other sections.

    Rationale for change: This section caused confusion with the clinical research associates and sites.

14. **Appendix B, Dose Adjustment for Lenalidomide**

    Description of change: Language was added to allow for other dose levels and/or dose regimens of lenalidomide after discussion and approval by the sponsor's medical monitor.

    Rationale for change: The language in the protocol was more restrictive than the product label that allows for dose adjustments lower than 5 mg once daily.

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 5 (22 OCT 2021)

Overall Rationale for the Amendment:

The rationale for this amendment is to implement updates to the background section to be in line with updated information in the IB, as per VHP request.

1. **Section 2.1.4.6, Combination Therapy With Tafasitamab and Lenalidomide in Non-Hodgkin Lymphomas**

   Description of change: The section has been updated with language from the most recent version of the IB.

   Rationale for change: Request per VHP.

2. **Section 9.4, Reporting of Serious Adverse Events**

   Description of change: The statement regarding participants enrolled in Germany has been changed to include all sites.

   Rationale for change: Request per VHP.

Amendment 4 (30 JUL 2021)

Overall Rationale for the Amendment:

The rationale for this amendment is to implement clarifications to address investigators' questions and requests, include Japanese sites in the study, and incorporate changes from previous local amendments.

1. **Section 1, Protocol Summary (Figure 1: Study Design Schema)**

   Description of change: The "TGB" part has been updated to clarify that it is composed of tafasitamab placebo (0.9% saline solution), and the mention of 12 mg/kg has been removed.

   Rationale for change: Clarification.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 2.1.3, Marginal Zone Lymphoma; Section 5.1., Inclusion Criteria (Criterion 3)**

   Description of change: Removed text indicating that extranodal MZL be of the mucosa-associated lymphoid tissue.

   Rationale for change: Clarification.

3. **Section 2.3, Benefit/Risk Assessment; Section 4.3, Study Termination; Section 5.1, Inclusion Criteria (Criterion 1); Section 5.2, Exclusion Criteria (Criterion 1); Section 6.1, Study Treatments Administered (Table 7: Study Treatment Information); Section 8.3.5, Laboratory Assessments (Table 11: Required Laboratory Analytes); Section 9.2, Definition of Serious Adverse Event; Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: Updated sections to include Japanese sites in the study.

   Rationale for change: Study sites may be located in Japan.

4. **Section 5, Study Population**

   Description of change: Added that the sponsor may decide to use recruitment tools and vendors to support the enrollment activities.

   Rationale for change: Clarification.

5. **Section 5.1, Inclusion Criteria (Inclusion Criteria 6, 7, and 8)**

   Description of change: Criterion 6 was clarified with respect to the fresh biopsy performance. Criterion 7 was changed to indicate that at least 4 doses instead of 6 doses of prior anti-CD20 immunotherapy are required for eligibility in the study. For Criterion 8, clarification was added to indicate that a participant in remission after the last prior treatment line would not be eligible.

   Rationale for change: For Criterion 6, clarification; for Criterion 7, alignment with NCCN guidelines; and for Criterion 8, clarification regarding eligibility with respect to the participant clinical status after the last prior treatment line.

6. **Section 5.1, Inclusion Criteria (Inclusion Criteria 9 and 9a)**

   Description of change: Split Criterion 9 and 9a into Criteria 9 and 10. Clarified that the GELF criteria are referenced as guidance and apply to FL participants only and that the lesion must be confirmed to be measurable by CT and/or PET (PET-negative lesions that are measureable by CT are also eligible).

   Rationale for change: Clarification and separation of 2 independent criteria.

7. **Section 6.1, Study Treatments Administered; Section 6.2.1, Tafasitamab/Placebo Preparation**

   Description of change: Guidelines were added for tafasitamab dose administration in case of changes in body weight and preparation of the tafasitamab/placebo solution for participants above 160 kg.

   Rationale for change: Clarification.

8. **Section 6.1, Study Treatments Administered (Table 7: Study Treatment Information); Section 6.2.2, Handling and Accountability of Study Treatment; Section 8.3.5.1, Central Laboratory Testing**

   Description of change: Clarification added that rituximab and lenalidomide are not considered IMPs in all countries. As a result, the statement "Study drug shall be used synonymously with IMP" has been removed.

   Rationale for change: Clarification.

9. **Section 6.6.10.1, Anticancer Therapies**

   Description of change: Sentence stating that a participant may stay in the study unless they participate in another clinical study was removed.

   Rationale for change: Participants should be encouraged to complete the follow-up period.

10. **Section 8.1.4.2, Disease Characteristics and Treatment History: Diagnostic Follicular Lymphoma/Marginal Zone Lymphoma Biopsy and Central Pathology Review; [redacted]**

    Description of change: Preferred timing for the prestudy biopsy/archival sample was added and sections were harmonized.

    Rationale for change: Clarification.

11. **Section 8.2.3, Radiographic Imaging Assessment**

    Description of change: The slide thickness guidance was updated to 2-2.5 mm. Text was added to indicate that a CT or MRI without contrast may be acceptable if neither CT with contrast nor MRI with contrast can be performed and that the baseline CT/MRI and PET assessments are used for the respective CT/MRI and PET responses.

    Rationale for change: Clarification of the requirements for the disease assessments.

12. **Section 8.3.5.1, Central Laboratory Testing (Table 11: Required Laboratory Analytes)**

    Description of change: Serum chemistry tests of CO_2 and blood urea nitrogen were added and can be measured interchangeably with bicarbonate and urea, respectively.

    Rationale for change: Clarification.

13. **Section 8.3.5.4, Hepatitis Virus Serology**

    Description of change: Updates were made to the schedule of the HBV DNA titer assessments for HBcAb-positive participants.

    Rationale for change: Clarification.

14. **Section 8.3.5.5, Human Immunodeficiency Virus Serology**

    Description of change: Added that HIV serology testing is optional in the United States.

    Rationale for change: Clarification.

15. **Section 9.1, Definition of Adverse Event; Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events; 9.7, Pregnancy**

    Description of change: Clarification added that SAEs and SAE updates must be transmitted first to Incyte Pharmacovigilance via the EDC system.

    Rationale for change: Clarification of the wording and harmonization between sections.

16. **Section 9.4, Reporting of Serious Adverse Events**

    Description of change: Text was added to indicate that, for Germany, all SAEs occurring more than 90 days after the last dose of study treatment must be reported until the participant receives a new anticancer therapy or end of the study, whichever occurs earlier.

    Rationale for change: Clarification as requested by the German Central Ethics Committee.

17. **Section 9.10, Treatment of Overdose**

    Description of change: Guidelines/definitions in case of an overdose with rituximab were added.

    Rationale for change: Clarification.

18. **Section 10.4.1.6, Sensitivity Analysis of Efficacy Endpoints**

    Description of change: The last 2 bullet points describing potential sensitivity analyses were combined and to clarify that sensitivity analyses may apply to both primary and secondary efficacy endpoints.

    Rationale for change: Clarification.

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

This amendment also includes the changes from local adaptations for the European Union (Amendment 2-EU and Amendment 2-EU2) and United States (Amendment 3), which are summarized below.

Amendment 3 (04 MAR 2021)

Overall Rationale for the Amendment:

The overall rationale for this amendment is to implement changes based on FDA requests.

1. **Section 1, Protocol Summary**

   Description of change: Removed "(FL)" and "(MZL)" from the protocol title.

   Rationale for change: Harmonization with the title on the cover page.

[redacted]

3. **Section 6.6.9, Use of Specific Medications Concomitantly With Lenalidomide**

   Description of change: Added Section 6.6.9 to describe the measurements and precautions to be implemented in the event study participants take specific medications concomitantly with lenalidomide.

   Rationale for change: Inclusion of instructions for concomitant medications due to potential drug-drug interactions as consistent with the labeling for lenalidomide.

4. **Section 10.4.1.6, Sensitivity Analysis of Efficacy Endpoints**

   Description of change: Added text regarding additional sensitivity analyses for the primary and key secondary endpoints.

   Rationale for change: Inclusion of additional sensitivity analyses to evaluate the impact of subsequent antilymphoma therapy.

5. **Section 10.5, Interim Analysis**

   Description of change: Added text to specify the efficacy endpoints to be analyzed at the PFS futility interim analysis besides the primary endpoint.

   Rationale for change: Clarification that descriptive analyses for other efficacy endpoints besides the primary endpoint will also be provided and OS will not be analyzed at the PFS interim futility analysis.

Amendment 2-EU2 (24 MAR 2021)

Overall Rationale for the Amendment:

The overall rationale for this amendment is to implement changes based on VHP requests.

1. **List of Abbreviations; Section 6.1, Study Treatments Administered (Table 7: Study Treatment Information)**

   Description of change: Clarification that rituximab is regarded as an IMP was added.

   Rationale for change: Rituximab is considered an IMP in the study.

Amendment 2-EU (01 MAR 2021)

Overall Rationale for the Amendment:

The overall rationale for this amendment is to implement changes based on VHP requests.

1. **Section 1, Protocol Summary**

   Description of change: Removed "(FL)" and "(MZL)" from the protocol title.

   Rationale for change: Harmonization with the title on the cover page.

2. **Section 1, Protocol Summary (Table 1: Primary and Major/Key Secondary Objectives and Endpoints; Table 2: Key Study Design Elements; Table 3: Schedule of Activities; Table 4: Schedule of Laboratory Assessments); Section 3, Objectives and Endpoints (Table 5: Objectives and Endpoints); Section 4.2, Overall Study Duration; Section 8.8, End of Treatment and/or Early Treatment Discontinuation; Section 8.9.1, Safety Follow-Up**

   Description of change: The EOT visit will be performed 90 days after the last dose of study treatment instead of 4 to 8 weeks after the last dose of study treatment.

   Rationale for change: Considering the elimination half-life of tafasitamab (16.9 days), the EOT visit has been changed from 4 to 8 weeks to 90 days after the last dose of study treatment.

[redacted]

4. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 5.2, Exclusion Criteria (Exclusion Criterion 6c); Section 8.3.5.5, Human Immunodeficiency Virus Serology**

   Description of change: Added HIV serology at screening and specified that all participants must be HIV-negative at baseline.

   Rationale for change: To avoid any potential safety issue with HIV-positive participants, HIV serology will be performed at screening and all participants must be HIV-negative at baseline.

5. **Section 2.1.4.7, Combination Therapy With Tafasitamab + Lenalidomide + Rituximab + CHOP Chemotherapy in Previously Untreated Diffuse Large B-Cell Lymphoma; Section 2.3, Benefit/Risk Assessment**

   Description of change: Added Section 2.1.4.7 to summarize the safety data on the combined treatment of tafasitamab + lenalidomide + rituximab + CHOP in participants with newly diagnosed DLBCL and updated Section 2.3 to reflect these changes.

   Rationale for change: Addition of the key safety findings from the MOR208C107 (First-MIND) study, presenting the safety data of the combination of tafasitamab + lenalidomide + rituximab + CHOP in participants with newly diagnosed DLBCL.

6. **Section 5.1, Inclusion Criteria (Inclusion Criterion 4b); Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: Clarified that WOCBP should use 2 different methods of birth control (one with at least 99% certainty and an additional effective [barrier] method) and that use of combined oral contraceptive pills is not recommended. Also, updated the list of highly effective birth control methods and added the permitted examples of additional effective (barrier) methods.

   Rationale for change: Alignment with the lenalidomide Pregnancy Prevention Program and the contraception guidelines in the Revlimid SmPC.

7. **Section 5.2, Exclusion Criteria (Exclusion Criterion 16)**

   Description of change: Added the exclusion criterion of administration of a live vaccine within 28 days prior to the start of the study treatment.

   Rationale for change: Due to the immunosuppressive effects of the study treatment, added exclusion of participants who have been vaccinated with a live vaccine within 4 weeks prior to the start of the study treatment.

8. **Section 5.6, Independent Data Monitoring Committee**

   Description of change: Clarified that if the IDMC identifies that a reported Grade 5 hematological ADR is related to tafasitamab, a safety review must take place immediately and further enrollment into the study must be stopped.

   Rationale for change: To extend the IDMC process and enrollment pause to include Grade 5 hematological ADRs that are identified by the IDMC.

9. **Section 6.5.6, Toxicity Management Guidelines for Hematological Toxicities (Table 9: Toxicity Management Guidelines for Hematological Toxicities)**

   Description of change: Updated the toxicity management guidelines for febrile neutropenia.

   Rationale for change: Clarification.

10. **Section 6.5.7.2, Hypogammaglobulinemia**

    Description of change: Added Section 6.5.7.2 to specify incidence data and management guideline for the potential on-target toxicity of hypogammaglobulinemia.

    Rationale for change: The primary side effects related to tafasitamab monotherapy consist of those induced by B-cell depletion, so incidence data and management guideline for the on-target toxicity hypogammaglobulinemia have been included.

11. **Section 6.6.1, Participant Monitoring During Tafasitamab or Placebo Infusion**

    Description of change: Added text regarding the timing of vital sign measurements.

    Rationale for change: Clarification of safety monitoring of participants with respect to vital sign assessments.

12. **Section 6.6.3, Prior and Concomitant Therapies; Section 8.3, Safety Assessments; Section 8.3.5, Laboratory Assessments; Section 9.4, Reporting of Serious Adverse Events; Section 10.4.2, Safety Analyses**

    Description of change: Extended the timeframe for collection of details regarding all AEs, concomitant medications, pregnancies, procedures, hospitalizations, and abnormal laboratory findings from 30 days to 90 days after the last dose of study treatment and updated the definition of TEAE.

    Rationale for change: Considering the elimination half-life of tafasitamab (16.9 days), the period for collection of details regarding AEs, concomitant medications, pregnancies, procedures, hospitalizations, and abnormal laboratory findings has been changed from 30 days to 90 days after the last dose of study treatment.

13. **Section 8.9.5, End of Study**

    Description of change: Clarified the definition of "end of study."

    Rationale for change: Clarification.

14. **Section 10.4.1.6, Sensitivity Analysis of Efficacy Endpoints**

    Description of change: Added text regarding additional sensitivity analyses for the primary and secondary endpoints.

    Rationale for change: Inclusion of additional sensitivity analyses for the PFS and DoR endpoints to apply EMA censoring rules.

Amendment 2 (16 DEC 2020)

Overall Rationale for the Amendment:

The overall rationale for this amendment is to update the TLS sections and clarify some sections.

1. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments)**

   Description of change: Blood sampling at Cycle 4 Day 1 for B-cell, T-cell, [redacted] was removed.

   Rationale for change: Clarification of the blood sampling schedule.

[redacted]

5. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 5.1, Inclusion Criteria (Criterion 6);** [redacted]

   Description of change: [redacted] Clarification that collection of tumor tissue at EOT is strongly encouraged.

   Rationale for change: Previous language regarding tumor biopsies was unclear and required clarification that tumor tissue collection at screening is not optional.

6. **Section 2.1.4.1, First-Line Therapy**

   Description of change: The words "in the first line setting ones" were removed.

   Rationale for change: Clarification of the treatment guidelines for indolent NHL in the United States and Europe.

7. **Sections 2.2.4.1, Tafasitamab; Section 3, Objectives and Endpoints (Table 5: Objectives and Endpoints); Section 10.4.1.4.3, Overall Response Rate in Follicular Lymphoma and Overall Populations**

   Description of change: Best ORR was replaced with ORR.

   Rationale for change: Editorial update to clarify wording.

8. **Section 2.3, Benefit/Risk Assessment; Section 6.5.5, Criteria and Procedures for Dose Interruptions or Adjustments of Rituximab; Section 12, References**

   Description of change: References to the USPI for lenalidomide and rituximab were added.

   Rationale for change: References added for US sites.

9. **Section 3, Objectives and Endpoints (Table 5: Objectives and Endpoints)**

   Description of change: Clarification regarding the thresholds for MRD assessments was added,

   Rationale for change: Clarification of MRD analyses.

13. [redacted]

14. **Sections 5.2, Exclusion Criteria (Criterion 7)**

    Description of change: Added clarification that the exclusion criterion of active systemic infection includes a SARS-CoV-2–positive test.

    Rationale for change: Clarification.

15. **Section 6.1, Study Treatments Administered; Section 6.2.1, Tafasitamab/Placebo Preparation**

    Description of change: If acceptable at the site, the possibility of administering the rituximab infusion the day after administering tafasitamab or of splitting the infusion over 2 consecutive days was added. Clarification that placebo will be locally sourced and delivered to an unblinded pharmacy and that sites have the option to obtain rituximab from the sponsor through the IRT system was added.

    Rationale for change: Incorporation of flexibility for rituximab infusion and clarification of the sourcing for placebo and rituximab.

16. **Section 6.5.7.1, Tumor Lysis Syndrome Prophylaxis**

    Description of change: Guidelines for the prevention of TLS were added.

    Rationale for change: Clarification of the prophylaxis to avoid TLS.

17. **Section 8.2.2, Bone Marrow Samples and Minimal Residual Disease Assessments**

    Description of change: Clarification that BM core biopsy samples should be sent to the local laboratory and BM aspirate samples should be sent to the central laboratory was added. Text was also added to indicate that the BM biopsy at EOT should be performed as clinically indicated, and to indicate that BM aspirate should be collected at time of radiological CR and as clinically indicated and pathology report results from the BM core biopsy will be entered in the eCRF.

    Rationale for change: Clarification of the sample management for MRD assessments.

18. **Section 8.2.3, Radiographic Imaging Assessments**

    Description of change: Clarification that radiographic images will be centrally stored by a vendor contracted by the sponsor.

    Rationale for change: Clarification.

19. **Section 8.3.5.2, Pregnancy Testing**

    Description of change: Correction of typographical error to indicate that the pregnancy test assays should have a minimum sensitivity of 25 mIU/mL (and not 25 IU/mL) and clarification that urine pregnancy tests can be replaced with serum ones.

    Rationale for change: Clarification.

20. [redacted]

21. **Section 10.4.2, Safety Analyses**

    Description of change: Clarification that abnormal ECGs will be summarized by treatment group.

    Rationale for change: Clarification regarding the ECG data to be analyzed.

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.

Amendment 1 (25 NOV 2020)

Overall Rationale for the Amendment:

The overall rationale for this amendment is to implement changes based on FDA comments and requests.

1. **Section 1, Protocol Summary (Table 1: Primary and Major/Key Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 5: Objectives and Endpoints); Section 10.3, Level of Significance; Section 10.4.1.2.3, Minimal Residual Disease-Negativity Rate at End of Treatment in the Follicular Lymphoma Population; Section 10.4.1.4.2, Minimal Residual Disease-Negativity Rate at End of Treatment in the Follicular Lymphoma and Overall Population;** [redacted]

   Description of change: The endpoint of "MRD-negativity rate at EOT in the FL population" was removed from the list of key secondary endpoints and demoted to a "regular" secondary endpoint that became "MRD-negativity rate (< 1 residual tumor cell per 10^4 normal cells) at EOT in the FL and the overall population." Section 10.4.1.2.3 was removed and Section 10.4.1.4.2 was updated and applied to both FL and overall populations. [redacted]

   Rationale for change: Confirmation that the key secondary endpoint of "MRD-negativity rate at EOT in the FL population" becomes a "regular" secondary endpoint.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 5.2, Exclusion Criteria; Section 8.3.4, Electrocardiograms, Echocardiograms, and Cardiac MUGA Scans**

   Description of change: "History of congestive heart failure requiring the use of ongoing maintenance therapy for life-threatening arrhythmias" was replaced by "Congestive heart failure (left ventricular ejection fraction of < 50%, assessed by 2D-echocardiography or MUGA scan," and an assessment of the left-ventricular ejection fraction by 2D-ECHO or MUGA at screening was added.

   Rationale for change: Clarification that the participants have an assessment of the left-ventricular ejection fraction by 2D-ECHO or MUGA at screening was added.

3. [redacted]

4. **Section 6.5.2.2.1, Grade 2 Infusion-Related Reactions, Grade 1 Cytokine Release Syndrome**

   Description of change: A paragraph detailing the management of tafasitamab/placebo in the event of recurrent Grade 2 IRR or Grade 1 CRS was added.

   Rationale for change: Guidelines for tafasitamab/placebo management in the event of recurrent Grade 2 IRR or Grade 1 CRS were added.

5. **Section 6.5.2.2.2, Grade 3 Infusion-Related Reactions, Grade 2 Cytokine Release Syndrome**

   Description of change: A paragraph stating that tafasitamab/placebo will be permanently discontinued in participants experiencing a recurrent Grade 3 IRR or Grade 2 CRS was added.

   Rationale for change: Guidelines for tafasitamab/placebo management in case of recurrent Grade 3 IRR or Grade 2 CSR were provided.

6. **Section 6.5.2.2.3, Grade 4 Infusion-Related Reactions, Grade 3 to 4 Cytokine Release Syndrome**

   Description of change: A paragraph stating that tafasitamab/placebo will be permanently discontinued in participants experiencing Grade 4 IRR or Grade 3 to 4 CRS was added.

   Rationale for change: Clarification that tafasitamab/placebo will be permanently discontinued if a participant experiences a Grade 4 IRR or Grade 3 or 4 CRS was added.

7. **Section 6.5.4, Criteria and Procedures for Dose Interruptions or Adjustments of Lenalidomide; Section 6.5.6, Toxicity Management Guidelines for Hematological Toxicities; Appendix B, Dose Adjustment for Lenalidomide**

   Description of change: A section describing the management of the study drugs (tafasitamab, lenalidomide, and rituximab) in the event of hematological toxicity was added, and the sections in Appendix B describing the management of lenalidomide in presence of neutropenia or thrombocytopenia were removed.

   Rationale for change: Guidelines for the management of the 3 study drugs in case of hematological toxicity were provided.

8. **Section 6.5.7, Toxicity Management Guidelines for Non-Hematological Toxicities**

   Description of change: A section describing the management of study treatment in the event of non-hematological toxicity was added.

   Rationale for change: Guidelines for study treatment management in the event of non-hematological toxicity were incorporated.

9. **Appendix B, Dose Adjustment for Lenalidomide**

   Description of change: A section describing the management of lenalidomide in participants experiencing a Grade 3 or higher adverse event of renal impairment was added.

   Rationale for change: Guidelines for lenalidomide management in the event of Grade 3 or higher adverse event of renal impairment were incorporated.

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.

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Approval Task	[redacted]
Approval Task	[redacted] Approver [redacted]
Approval Task	[redacted] Approver [redacted]
Approval Task	[redacted] Approver [redacted]
Approval Task	[redacted] Approver [redacted]

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