Official Title: A Phase 1b/2, Open-Label, Multicenter Study to Evaluate the Safety and Pharmacokinetics of a Modified Tafasitamab IV Dosing Regimen Combined With Lenalidomide (LEN) in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL) [MINDway]

NCT Number: NCT05222555

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CLINICAL TRIAL PROTOCOL

A Phase 1b/2, Open-Label, Multicenter Study to Evaluate the Safety and Pharmacokinetics of a Modified Tafasitamab IV Dosing Regimen Combined With Lenalidomide (LEN) in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL) [MINDway]

Clinical Trial Protocol No:	MOR208C115
Clinical Trial Protocol Name:	MINDway
Version:	CTP v7.0, 11 APR 2024
Clinical Trial Phase:	Phase 1b/2
Product Name:	Tafasitamab
Sponsor:	Incyte Corporation
Sponsor's Address:	1801 Augustine Cut-Off Wilmington, DE 19803 USA
EU CT No.:	2023-507993-42-00
IND No.:	145,009

INVESTIGATOR'S AGREEMENT

I have read the MOR208C115 CTP v7.0 (dated 11 APR 2024) 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)

PROTOCOL HISTORY

Version	Date
Amended Protocol CTP v7.0	11 APR 2024
Amended Protocol CTP v6.0	18 AUG 2023
Amended Protocol CTP v5.0	02 MAY 2023
Amended Protocol CTP v4.0	24 AUG 2022
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Amended Protocol CTP v2.0	18 OCT 2021
Original Protocol CTP v1.0	10 AUG 2021

Amended Protocol CTP v7.0 (11 APR 2024)

Overall Rationale for the Amendment:

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[redacted]

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1 PROTOCOL SYNOPSIS

Protocol title

A Phase 1b/2, Open-Label, Multicenter Study to Evaluate the Safety and Pharmacokinetics of a Modified Tafasitamab IV Dosing Regimen Combined With Lenalidomide (LEN) in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL) [MINDway]

Objectives, endpoints and estimands

The following objectives and endpoints will be evaluated in the study, see Table 1:

Table 1: Objectives and Corresponding Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of tafasitamab administered [redacted] in combination with lenalidomide in R/R DLBCL patients • To determine a recommended dose for tafasitamab [redacted] administration in combination with lenalidomide in R/R DLBCL patients	Incidence and severity of TEAEs
Secondary	
To evaluate the pharmacokinetic profile of tafasitamab after [redacted] dosing in combination with lenalidomide	Tafasitamab serum concentrations after 3 (C_{trough} and C_{max}) and 12 (C_{trough}) treatment cycles
To assess anti-tumor activity of tafasitamab after [redacted] dosing in combination with lenalidomide	• Best Objective Response Rate (ORR) by investigator assessment up to treatment Cycle 12 based on Cheson *et al*. (2007) • Duration of Response (DoR) by investigator assessment based on Cheson *et al*. (2007) • Progression-Free Survival by investigator assessment based on Cheson *et al*. (2007)
To assess the incidence of anti-drug antibodies to tafasitamab	Number and percentage of patients developing anti-tafasitamab antibodies up to treatment Cycle 12

Abbreviations: C_{max}=maximum concentration; C_{trough}=minimum concentration; DLBCL=diffuse large B-cell lymphoma; [redacted]; R/R=relapsed/refractory; TEAEs=treatment-emergent adverse events. Each treatment cycle is 28 days.

Estimands

The primary clinical question of interest is: Given a proposed [redacted] treatment [redacted] with tafasitamab [redacted], what is the observed incidence and severity of treatment emergent adverse events (TEAEs) in R/R DLBCL patients who receive [redacted]? This would allow the assessment of the safety and the tolerability of [redacted]. The primary estimand and its attributes are described in Section 4. Possible intercurrent events and strategies to capture them are described in Section 4.

Study design

MOR208C115 (MINDway) is an open-label, multicenter, phase 1b/2 study of tafasitamab combined with lenalidomide (LEN) to evaluate the safety and pharmacokinetics (PK) of a [redacted] tafasitamab [redacted] in adult patients with R/R DLBCL.

Overall, approximately 51 patients will be enrolled in the study. Patients will receive LEN in combination with tafasitamab in 28-day cycles. The [redacted] tafasitamab [redacted] will be investigated in a stepwise design with two sequential cohorts followed by an expansion cohort at the recommended dose level. Tafasitamab will be administered as intravenous infusion [redacted] (see Table 2).

LEN (25 mg) will be administered for a maximum of 12 cycles or until disease progression, unacceptable toxicity, withdrawal, death or lost to follow up, whichever comes first. After Cycle 12 or LEN discontinuation, patients will continue with tafasitamab monotherapy [redacted] until disease progression, unacceptable toxicity, withdrawal, death or lost to follow up, whichever comes first.

No follow-up for overall survival will be performed in this study after end of treatment (EOT).

A Data and Safety Monitoring Committee (DSMC), consisting of Sponsor representatives and investigators, will continuously monitor the study and can recommend to stop enrollment at any time based on emerging safety data. In addition, pre-defined DSMC meetings will take place when at least 6 patients have completed the 5-week (35 day) safety observation period in Cohort 1 and Cohort 2, respectively.

Details of specific responsibilities, composition, meeting formats and frequency of the DSMC are outlined in the DSMC Charter.

Study population

The study will enroll approximately 51 patients with histologically confirmed diagnosis of R/R DLBCL (as specified in inclusion criterion 3) based on the local pathology report.

All patients must meet below listed eligibility criteria to be enrolled in the study. Prospective approvals of deviations to eligibility criteria, also known as protocol waivers or exemptions, are not permitted.

Inclusion criteria

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

1. Capable of giving signed informed consent as described in Appendix 2: Regulatory, Ethical, and Trial Oversight Considerations, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. Patient must be at least 18 years of age and of legal age (whichever is higher) in the jurisdiction in which the study is taking place at the time of signing the informed consent.
3. One of the following histologically confirmed diagnoses:
    - DLBCL not otherwise specified (NOS)
    - T cell/histiocyte-rich large B-cell lymphoma (THRLBCL)
    - Epstein-Barr virus (EBV) positive DLBCL of the elderly (EBV-positive DLBCL)
    - Grade 3b Follicular Lymphoma
    - Composite lymphoma with a DLBCL component with a subsequent DLBCL relapse, according to the Revised European American Lymphoma/World Health Organization (REAL/WHO) classification.

    Additionally, patients with the evidence of histological transformation to DLBCL from an earlier diagnosis of low-grade lymphoma (i.e., an indolent pathology such as follicular lymphoma, marginal zone lymphoma, chronic lymphocytic leukemia) into DLBCL with a subsequent DLBCL relapse are also eligible.
4. Tumor tissue for retrospective central pathology review must be provided as an adjunct to participation in this study. If archival formalin fixed paraffin embedded tumor tissue acquired ≤3 years prior to screening is not available, a fresh tumor tissue sample from the patient should be obtained. Archival formalin fixed- paraffin embedded tumor tissue acquired >3 years prior to screening is acceptable only in cases where a fresh tumor biopsy cannot be collected due to a safety risk, e.g., due to co-morbidity, or inaccessible tumor site.

5. Patients must have:
    a. Relapsed and/or refractory disease as defined in Appendix 3: Study Specific Definitions
    b. At least one bi-dimensionally measurable disease site. The lesion must have a greatest transverse diameter of ≥ 1.5 cm and greatest perpendicular diameter of ≥ 1.0 cm at baseline. The lesion must be positive on positron emission tomography (PET) scan (for definition see Juweid *et al.,* 2007)
    c. Received at least one, but no more than three previous systemic regimens for the treatment of DLBCL and one therapy line must have included a cluster of differentiation-20 (CD20) targeted therapy (e.g., rituximab [RTX])
    d. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
6. Patients that are not eligible to undergo intensive salvage therapy including autologous stem cell transplantation (ASCT). The reason for a patient's ineligibility must meet one of the criteria described below and documented in the patient's source data:
    a. Inadequate performance status (Karnofsky performance status ≤ 80%; see Appendix 5: Karnofsky Performance Status Scale)
    b. Disease not responsive to salvage chemotherapy. Responsiveness is defined as a tumor demonstrating either complete response (CR) or partial response (PR) to salvage chemotherapy
    c. Inadequate major organ function (any of the below):
        i. symptomatic congestive heart failure
        ii. lung function-forced vital capacity (FVC), forced expiratory volume in 1 second (FEV-1), and corrected diffusion capacity of the lung for carbon monoxide (DLCO) ≤ 60%
        iii. liver function-total serum bilirubin and transaminases > 2 x upper limit of normal (ULN)
    d. History or evidence of significant co-morbid medical or psychiatric illness which would significantly compromise the patient's clinical care and chances of survival
    e. Inability to collect adequate stem cell graft (e.g. < 1–2 x 10^6 CD34+ cells free of tumor contamination/kg recipient body weight)
7. Patients must meet the following laboratory criteria at screening:
    a. Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by recent bone marrow aspiration and bone marrow biopsy)
    b. Platelet count ≥ 75 × 10^9/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by recent bone marrow aspiration and bone marrow biopsy)
    c. Total serum bilirubin ≤ 2.5 × ULN unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma. Patients with Gilbert's syndrome or documented liver involvement by lymphoma may be included if their total bilirubin is ≤ 5 × ULN (see exclusion criterion 6g)

d. Alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) ≤ 3 × ULN or < 5 × ULN in cases of documented liver involvement
e. Serum creatinine CL must be ≥ 60 mL/minute either measured or calculated using a standard Cockcroft and Gault formula (see Appendix 6: Cockcroft-Gault Formula)

8. Patients who received previous CD19 targeted therapy (other than tafasitamab) must have CD19 positive lymphoma confirmed on a biopsy taken since completing the prior CD19 targeted therapy
9. Patients with primary refractory disease (see Appendix 3: Study Specific Definitions) who received at least one, but no more than three previous systemic regimens (including a CD20 targeted therapy) for the treatment of DLBCL are eligible.

Exclusion criteria

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

1. General provisions:
   a. Patients who are legally institutionalized, or patients under judicial protection
   b. Concurrent enrollment in another interventional clinical study
2. Patients who have:
   a. Any other histological type of lymphoma including primary mediastinal (thymic) large B-cell (PMBL) or Burkitt lymphoma
   b. Known "double/triple hit" genetics (high grade B-cell lymphoma) characterized by simultaneous detection of *MYC* with *BCL2* and/or *BCL6* translocation(s) defined by fluorescence *in situ* hybridization. *MYC*, *BCL2*, *BCL6* testing prior to study enrollment is not required
3. Patients who have:
   a. Not discontinued (within 14 days prior to Day 1 dosing): CD20 targeted therapy, chemotherapy, radiotherapy, investigational anticancer therapy or other lymphoma-specific therapy
   b. Undergone major surgery (within 4 weeks prior to Day 1 dosing) or suffered from significant traumatic injury
   c. Received live vaccines (within 4 weeks prior to Day 1 dosing) (see Appendix 7: COVID-19: Infection Prophylaxis and Vaccines)
   d. Required parenteral antimicrobial therapy for active, intercurrent infections (within 14 days prior to Day 1 dosing)
4. Patients who:
   a. Have, in the opinion of the investigator, not recovered sufficiently from the adverse toxic effects of prior therapies
   b. Were previously treated with tafasitamab or IMiDs® (e.g., thalidomide, LEN)
   c. Have a history of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, IMiDs® and/or the excipients contained in the study treatment formulations

d. Have undergone ASCT within the period ≤ 3 months prior to signing the ICF. Patients who have a more distant history of ASCT must exhibit full hematological recovery before enrollment into the study
e. Have undergone previous allogenic stem cell transplantation
f. Have a history of deep venous thrombosis/embolism, threatening thromboembolism or known thrombophilia or are at high risk for a thromboembolic event in the opinion of the investigator and who are not willing/able to take venous thromboembolism (VTE) prophylaxis during the entire treatment period
g. Concurrently use other anticancer or experimental treatments

5. History of other malignancy that could affect compliance with the protocol or interpretation of results. Exceptions:

a. Patients with any malignancy appropriately treated with curative intent and the malignancy has been in remission without treatment for > 2 years prior to enrollment are eligible
b. Patients with low-grade, early-stage prostate cancer (Gleason score 6 or below, Stage 1 or 2) with no requirement for therapy at any time prior to study are eligible

6. Patients with:

a. Positive hepatitis B and/or C serology (see Appendix 8: Hepatitis Virus Serology for details)
b. Known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV)
c. Central nervous system (CNS) lymphoma involvement – present or past medical history
d. 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 patient's ability to give informed consent
e. History or evidence of rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
f. Gastrointestinal (GI) abnormalities (issue with absorption) including the inability to take oral medication
g. History or evidence of severe hepatic impairment (total serum bilirubin > 3 mg/dL), jaundice unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma (see inclusion criterion 7c)
h. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical class
i. Any other medical condition which, in the investigator's opinion, makes the patient unsuitable for the study

7. Contraception provisions:

Females: Due to the teratogenic potential of LEN, FCBP must follow the rules listed below (otherwise excluded):

Applicable in all countries except the US:

a. Not be pregnant as confirmed by a negative serum pregnancy test at screening and a medically supervised urine pregnancy test prior to starting study therapy
b. Refrain from breast feeding and donating oocytes during the study and for 3 months after the last dose of study drug or according to local guidelines for LEN, whichever is longer
c. Agree to ongoing pregnancy testing during the course of the study, and after study treatment has ended. This includes pregnancy testing and counseling if a patient misses her period or if there is any abnormality in her menstrual bleeding and applies even if the patient practices complete sexual abstinence
d. Commit to continued abstinence from heterosexual intercourse if it is in accordance with her lifestyle (which must be reviewed on a monthly basis) or agree to use and be able to comply with the use of highly effective contraception without interruption at least 4 weeks prior to start of study drugs, during the study treatment and for 3 months after the last dose of study drug, or, for LEN, according to the local guidelines, whichever is longer

Applicable in the US:

e. Not be pregnant as confirmed by pregnancy tests performed before treatment initiation, within 10-14 days and again within 24 hours of initiating treatment (even if true abstinence is the chosen method of birth control)
f. Refrain from breast feeding and donating oocytes during the study and for 3 months after the last dose of study drug, or according to US guidelines for LEN, whichever is longer
g. Agree to ongoing pregnancy testing during the study (every 4 weeks in women with regular menstrual cycle and every two weeks in women with irregular menstrual cycle), and after study therapy has ended (even if true abstinence is the chosen method of birth control). This includes pregnancy testing and counseling if a patient misses her period or if there is any abnormality in her menstrual bleeding.
h. Not get pregnant while taking the study treatment and for at least 3 months after the last dose of study treatments by using at the same time 2 effective methods of contraception, at least one highly effective method and one additional effective method (see Appendix 13: Contraceptive Guidance and Collection of Pregnancy Information), each time engaging in sexual activity with a male, starting at least 4 weeks before taking the study treatment, while taking the study treatment, during breaks (dose interruptions) and for at least 3 months after stopping the study treatment, or for LEN, according to the US guidelines, whichever is longer. True abstinence from heterosexual sexual intercourse is also an acceptable method of contraception. The use of emergency contraception is also permitted

8. Due to the teratogenic potential of lenalidomide, male participants must follow the rules listed below (otherwise excluded):

Applicable in all countries except the US:

a. Use an effective barrier method of contraception without interruption if the patient is sexually active with a FCBP. Male patients should refrain from donating sperm during the study participation and for 3 months after the last dose of study treatment, or according to the local guidelines for LEN, whichever is longer

Applicable in the US:

b. Use a latex or synthetic condom each time they have sex with a FCBP. True abstinence from heterosexual sexual intercourse is also an acceptable method of contraception. The use of emergency contraception is also permitted. Male patients should refrain from donating sperm during the study participation and for 3 months after the last dose of study drug, or according to the US guidelines for LEN, whichever is longer

Statistical Analysis

A Primary analysis will be performed when all enrolled patients have either completed C3D28 or discontinued the study prior to C3D28 for any reason. Final analysis will be performed at the end of the study.

Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the clinical study report.

Details of the analyses to be performed on data from this study will be provided in a separate SAP.

End of Study

The end of the study is reached when all patients still on study treatment have been followed for at least 3 years, or when the final patient on study has completed their last visit, whichever comes first.

Patients who are receiving ongoing treatment at the end of study may continue treatment with either of the options below upon assessment of a clinical benefit of continued treatment by the investigator and in accordance with the local regulatory guidance:

- commercially available tafasitamab for the approved dose regimen locally; or
- participation in the tafasitamab extension study if above option is not available.

Upon study closure, Incyte will notify the applicable regulatory agencies in accordance with local requirements.

End of study visit for a patient: An end of study visit for a patient is defined as the visit taking place when the patient has completed 90-day safety follow up after the last tafasitamab dose given.

2 SCHEDULE OF ASSESSMENTS (SoA)

Table 3: Schedule of Assessments

Evaluation or Procedure	Screening Period	Treatment Period (Cycle = 28 days)												Follow-Up Period
	Screening ≤28 Days prior to D1	Cycle 1				Cycle 2		Cycle 3		Cycle 4-12	Cycle 12	Cycle 13 onwards	End of Treatment Visit (EOT)[15]	90-Day Safety Follow-up Visit/ End of Study Visit[14]
Day	Screen	D1	D4 ±1 day	D8 ±1 day	D15 ±1 day	D1 ±1 day	D15 ±1 day	D1 ±1 day	D15 ±1 day	D1 ±2 days	D28 ±2 days	D1 ±2 days	Within 14 days after decision on treatment discontinuation	±7 days
Starting Evaluations and Eligibility														
Informed consent	X													
Inclusion/exclusion criteria	X	X[1]												
Demography	X													
Medical history/current medical condition	X													
Disease history/staging/Ann Arbor	X													
Disease risk assessment (IPI)	X													
Throughout Evaluations														
Prior/concomitant therapy[2]	X	X	X	X	X	X	X	X	X	X		X	X	X
Physical examination (F – full, L – limited)	F	L						L		L[3]		L[3]	F	
ECOG performance status	X	X[1]				X		X		X			X	
Body weight/height[4]		X	X	X	X	X	X	X	X	X		X	X	
B-symptoms	X	X				X		X		X		X	X	
Vital signs[16]	X	X	X	X	X	X	X	X	X	X		X	X	
12-lead resting ECG	X	X[5]			X[5]	X[5]		X[5]		X[5a]			X	
Adverse events (AEs, SAEs and AESIs)	X	X	X	X	X	X	X	X	X	X		X	X	X
Laboratory														
Urinalysis (local lab)	X	X				X		X		X			X	
Pregnancy test (FCBP)[6]	X	X[1]		X[1]	X[1]	X[1]		X[1]		X[1]		X[1]	X	
Pregnancy and risks counselling	X	X				X		X		X			X	
US only: pregnancy and risk interview	X	X				X		X		X			X	
Hematology and Serum chemistry (local lab) [7]	X	X	X	X	X	X	X	X	X	X		X	X	
Serology Hepatitis B (local lab)	X													

Evaluation or Procedure	Screening Period	Treatment Period (Cycle = 28 days)												Follow-Up Period
	Screening ≤28 Days prior to D1	Cycle 1				Cycle 2		Cycle 3		Cycle 4-12	Cycle 12	Cycle 13 onwards	End of Treatment Visit (EOT)[15]	90-Day Safety Follow-up Visit/ End of Study Visit[14]
Day	Screen	D1	D4 ±1 day	D8 ±1 day	D15 ±1 day	D1 ±1 day	D15 ±1 day	D1 ±1 day	D15 ±1 day	D1 ±2 days	D28 ±2 days	D1 ±2 days	Within 14 days after decision on treatment discontinuation	±7 days
Serology Hepatitis B, DNA, if indicated (local lab)	X[8]					X[8]		X[8]		X[8]			X[8]	
Serology Hepatitis C (local lab)	X													
Coagulation (aPTT or PTT, PT and/or INR) (local)	X									C4D1			X	
Thyroid Stimulating Hormone (TSH-local lab)[18]	X									C4D1			X	
[redacted]														
Tafasitamab ADAs		X[1]				X[1]		X[1]		X[9],	X[17]		X[15]	
PK tafasitamab		X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10a],	X[17]		X[15]	
CD19 expression[19]	X													
Imaging and Tumor Evaluation														
PET-CT or PET-MRI	X										X[11]	X[11]	X[11]	
CT or MRI								X[11a]		X[11a]		X[11a]		
Biopsy/Tissue														
Tissue sample collection for central pathology review	X													
Bone marrow aspiration & biopsy	X[12]								X[12]	X[12]	X[12]	X[12]		
Drug Administration														
[redacted]														
LEN capsules allocation (Incl. patient home intake record)		X				X		X		X				

Abbreviations: AE=adverse event; ADA=Anti-drug antibodies; AESIs=adverse events of special interest; aPTT= activated partial thromboplastin time; anti-HBc=hepatitis B core antibody; β-HCG=beta-human chorionic gonadotropin; C=cycle; CT=computed tomography; [redacted]; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOS=end of study; EOT=end of treatment; F=full physical examination; FCBP=female of childbearing potential; HBV=hepatitis B virus; INR=international normalized ratio; IPI=International Prognostic Index; IRRs=infusion-related reactions; L=limited physical examination; LEN=lenalidomide; [redacted]; MRI=magnetic resonance imaging; [redacted]; PE=physical examination; PET=positron emission tomography; PK=pharmacokinetics; PT=prothrombin time; PTT=partial thromboplastin time; SAE=serious adverse event TSH=Thyroid stimulating hormone

[1]Before study treatment administration.

[2]Previous/Concomitant therapy will be recorded as per Section 7.8. After disease progression only anticancer treatments and other relevant concomitant medications, i.e., used for treatment of an AE (at the discretion of the investigator) should be entered.

[3]A limited PE (L) will be performed on Day 1 of every other Cycle, e.g., Cycle 5, Cycle 7, Cycle 9, Cycle 11. From Cycle 13 onwards, a limited PE will only be performed at the discretion of the investigator if directed by any clinical symptoms or adverse events.

[4]Body height will be measured at Cycle 1 Day 1 only. Body weight can be measured up to 24 hours prior to the study treatment administration.

[5]12-lead resting ECG performed within 3 hours after the end of tafasitamab infusion.

[5a]A 12-lead resting ECG will be performed (within 3 hours after the end of tafasitamab infusion.) on D1 of every third cycle until Cycle 12, i.e., Cycle 6, Cycle 9 and Cycle 12.

[6]Pregnancy tests: A serum (β-HCG)/urine pregnancy test is mandatory only for females of childbearing potential (FCBP). A serum pregnancy test will be performed locally at Screening and at the End of treatment visit. At all other indicated time points, a urine pregnancy test for FCBP will be performed locally and the result must be negative for dosing. At Cycle 1 Day 1 pregnancy test must be performed within 24 hours prior to the start of study treatment. For US only, a pregnancy test at screening must be performed within 10 to 14 days prior to the start of study treatment. For US FCBP with irregular menstrual cycle a urine pregnancy test will be performed every two weeks. A home urine pregnancy test kit and the home urine pregnancy test diary will be handed out to the US FCBP with irregular menstrual cycle on Cycle 2 Day1 to Cycle 12 Day1. Pregnancy testing and counseling must be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. Lenalidomide treatment must be discontinued during this evaluation. Patients reaching end of treatment during Cycle 1 – Cycle 12 a serum pregnancy test will be performed at-least 4 weeks after the last dose of study drug, in accordance with the Lenalidomide SmPC/USPI.

[7]Sample to be collected and evaluated in the local laboratory (can be done on the day before study treatment administration) and reviewed by study treating physician before study treatment administration.

[8]HBV-DNA to be measured at screening and re-measured at subsequent visits only if anti-HBc was positive at screening.

[9]From Cycle 4 onwards, blood samples for tafasitamab anti-drug antibodies (ADAs) will be collected pre-dose on D1 of every other cycle until Cycle 12, i.e. Cycle 4, Cycle 6, Cycle 8, Cycle 10, Cycle 12.

[10]Tafasitamab PK sample will be taken pre-dose and 30 min ± 15 min after the end of tafasitamab infusion.

[10a]Tafasitamab PK samples will be taken pre-dose and 30 min ± 15 min after the end of tafasitamab infusion on C4D1 and afterwards pre-dose on D1 of every other cycle until Cycle 12, i.e. Cycle 6, Cycle 8, Cycle 10, Cycle 12.

[11]PET-CT or PET-MRI should be performed at screening, at C12D28 (± 4 days) and at EOT visit unless disease progression was already radiologically confirmed prior to the EOT visit. If progression/relapse is suspected on the basis of clinical symptoms, PET-CT or PET-MRI should be performed to confirm disease progression. PET/CT or PET-MRI from Cycle 25 onwards should be performed only if deemed necessary, and not more than once per year.

[11a] CT or MRI should be performed within 4 days prior to C3D1, C5D1, C7D1 and C10D1. From Cycle 13-24 CT or MRI should be performed approximately every 3 months ± 2 days from the previous scan. The first assessment during this phase will take place 3 months ± 2 days after C12D28. From Cycle 25 onwards: approximately once every year ± 2 weeks from the previous scan.

[12]Repeat bone marrow biopsy only in those patients who had known bone marrow involvement at screening to confirm a CR. If repeat bone marrow biopsy is required to confirm CR, the assessment should be done at C3D15 ± 1 day and/or within 15 days after C5D1, C7D1, C10D1 and C12D28. Bone marrow assessment from Cycle 13 to 24 approximately every 3 months ± 2 weeks from the previous assessment to be performed to confirm a CR only in those patients who had known marrow involvement at screening.

[13]Tafasitamab infusions should be given after pre-medication administration 30–120 minutes prior to starting the infusion. For patients who do not experience any grade 2 or higher IRRs with their first four infusions, pre-medication at subsequent treatments may be omitted according to institutional treatment guidelines.

[14]Regardless of the reason for study treatment discontinuation, patients will have a safety follow-up visit or phone call scheduled 90 days after the last dose of the study treatment.

[15]EOT samples for PK and ADA will not be collected for patients receiving tafasitamab treatment beyond Cycle 12.

[16]Vital signs include temperature, systolic and diastolic blood pressure, pulse and respiratory rate. Vital signs are to be obtained immediately pre-tafasitamab infusion, and during infusion (15 ± 5, 30 ± 10, and then every 60 ±15 minutes), at the end of infusion (± 20 minutes) and as clinically indicated.

[17]Samples to be collected on C12D28±2 days, if overlapping with C13D1 visit, samples should be taken prior to study treatment administration on C13D1.

[18]TSH test to be performed locally at screening, C4D1 and end of treatment. Additional TSH test maybe performed as clinically indicated based on the symptoms as judged by the investigator.

[19]CD19 positive lymphoma (as per local institutional guidelines) on a biopsy taken after completing prior CD19 targeted therapy. The local pathology report indicating DLBCL diagnosis and CD19 positivity will determine a patient's eligibility for study enrollment. In this patient group, a sample of this most recent biopsy should be provided for central pathology confirmation of both DLBCL diagnosis and CD19 expression. Only the most recent biopsy needs to be provided, it is not necessary to provide tissue taken at different stages of disease.

3 INTRODUCTION

3.1 Study Rationale

3.1.1 Disease Overview

DLBCL is the most common type of non-Hodgkin lymphoma (NHL), representing approximately 30-40% of all NHLs with a median age at diagnosis of 64 years. DLBCL is an aggressive B-NHL and the majority of patients present with advanced disease. DLBCL is increasingly recognized as a heterogeneous disorder disease with distinct molecular subtypes (Lenz *et al.,* 2008; Flowers *et al.,* 2010; Vaidya and Witzig, 2014; Schmitz *et al.,* 2018).

Standard treatment for patients with newly diagnosed DLBCL consists of immuno-chemotherapy with the anti-CD20 monoclonal antibody (mAb), RTX, and CHOP administered for 6-8 cycles (R-CHOP) (Tilly *et al.,* 2015). The addition of RTX has substantially improved the results of CHOP-chemotherapy, yielding complete and sustained remission in about 60% of cases (Coiffier *et al.,* 2002). But still approximately 30–40% of patients ultimately will relapse and are not cured by first-line therapy with R-CHOP, and approximately 10% of patients are refractory to R-CHOP as first-line therapy (primary refractory) (Coiffier *et al.,* 2010).

In patients progressing or relapsing after first-line treatment, the main consideration for further treatment is whether the patient is a candidate for HDT and ASCT. Salvage chemotherapy followed by HDT and ASCT is standard treatment for transplant-eligible patients and may offer a second chance of cure for about 30–40% of the patients (Crump *et al.,* 2017; Gisselbrecht *et al.,* 2010). However, the majority of R/R DLBCL patients are ineligible for ASCT due to comorbidities and older age. Despite recent advances, the treatment options for patients who have relapsed or progressed after second-line treatment of DLBCL, or who are not eligible for ASCT remain limited.

On 31 JUL 2020, the U.S. Food and Drug Administration (FDA) approved tafasitamab-cxix (Monjuvi®) in combination with lenalidomide for the treatment of adult patients with R/R DLBCL not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant. Furthermore tafasitamab (Minjuvi®) was granted conditional approval in R/R DLBCL in Europe on 26 AUG 2021, and thereafter in other countries (e.g., Israel, South Korea).

As per Monjuvi® United States prescribing information (USPI) (Monjuvi® 2021) and Minjuvi® Summary of product characteristics (SmPC) (Minjuvi® 2024) the recommended dose of tafasitamab is 12 mg/kg, administered as intravenous (i.v.) infusion. The current approved dosing regimen of tafasitamab in combination with LEN until disease progression or unacceptable toxicity is presented in Table 4.

Table 4: Tafasitamab in Combination With LEN Dosing Regimen as per Monjuvi® USPI in R/R DLBCL

Currently approved dosing regimen per Monjuvi® USPI			
Drug	**Route**	**Dose**	**Dosing Schedule[1]**
Tafasitamab	i.v.	12 mg/kg	Cycle 1: Days 1, 4, 8, 15, and 22
			Cycle 2 to 3: Days 1, 8, 15, and 22
			Cycle 4 and beyond: Days 1 and 15
LEN	Oral (capsule)	25 mg	Cycle 1–12: 25 mg on Days 1-21 of each cycle Administer LEN for a maximum of 12 cycles and then continue tafasitamab as monotherapy until progression or unacceptable toxicity

Abbreviations: DLBCL=diffuse large B-cell lymphoma; i.v.=intravenous; LEN=lenalidomide; R/R=relapsed/refractory; USPI=United States Prescribing Information.
[1]Each treatment cycle is 28 days.

3.1.2 Study Treatment

[redacted]

As tafasitamab [redacted] tafasitamab [redacted] in R/R DLBCL patients.

[redacted]

3.2 Non-Clinical Background Information

Tafasitamab is an Fc-modified mAb targeting CD19, a crucial component of B-cell receptor signaling. CD19 is expressed throughout normal B-cell development until terminal plasma cell differentiation and is also present on the surface of malignant hematopoietic cell. Tafasitamab possesses significantly increased tumor cytotoxicity when compared with the parental, non-engineered, murine 4G7 CD19 antibody. The increased binding of tafasitamab to Fc gamma receptors (FcγR), due to the engineered mutations, significantly enhances in vitro antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), and its direct cytotoxic effects (apoptosis) on the tumor cells compared with the non-engineered parental murine antibody (Lazar *et al.,* 2006).

Non-clinical studies with tafasitamab were designed to support human clinical trials with tafasitamab for the treatment of CD19 positive hematologic malignancies, such as chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL) and NHL.

Non-clinical studies evaluating the PK, pharmacodynamics and toxicity of tafasitamab were performed in cynomolgus monkeys. Overall, the findings in five preclinical studies were limited to the expected pharmacological effects of tafasitamab, with no reports of unanticipated toxicity.

More specifically, in the pivotal GLP-compliant, repeat-dose toxicity study, i.v. one-hour infusion of tafasitamab into sexually mature male and female cynomolgus monkeys at doses of 0, 10, 30, and 100 mg/kg once a week for 13 weeks was well-tolerated up to the highest dose tested (with no adverse effects observed) and did not affect safety pharmacology or reproductive endpoints. No mortalities occurred. There were no drug-related effects on body weights, food consumption, clinical signs, neurobehavioral observations, blood pressure, electrocardiography, respiratory rate,

ophthalmology, urinalysis, coagulation, serum chemistry or cytokine analysis. Local tolerance was assessed following each i.v. infusion and did not reveal any adverse effects at the administration sites. The reduced peripheral B-cell counts as well as the histopathological changes to several lymphatic organs (decreased cellularity of the germinal centers in lymphoid follicles of spleen, mesenteric and mandibular lymph nodes) are considered exaggerated pharmacodynamic effects. The no observed adverse effect level (NOAEL) was determined at the highest dose tested (i.e., 100 mg/kg i.v. weekly [QW]) (report MOR208P008).

Following i.v. administration in cynomolgus monkey at dose levels from 0.3-100 mg/kg, tafasitamab exhibited a typical 2-compartment profile. Tafasitamab showed consistent PK parameters across studies and study groups (volume of distribution at steady state [V_{ss}] of 52.6-124.3 mL/kg; clearance [CL] of 4.31-7.37 mL/day/kg; mean terminal elimination half-life of 7.7-14.2 days). Dose linearity was observed between 2-100 mg/kg.

3.3 Clinical Background

3.3.1 Tafasitamab Clinical Development

The first-in-human trial with tafasitamab was a phase 1 dose escalation trial in patients with R/R CLL (XmAB5574-01, [NCT1161511]). Tafasitamab was administered i.v. as monotherapy in doses ranging from 0.3 mg/kg to 12 mg/kg for a total of up to seven 28-day cycles. Due to the acceptable safety profile, the 12 mg/kg dose (highest administered dose level) cohort was expanded to a total of 16 patients and was used for further development.

The Sponsor initiated a phase 2a, open-label, multicenter trial of single-agent tafasitamab in patients with R/R NHL (MOR208C201 [NCT1685008, EudraCT No. 2012-002659-41]; Jurczak *et al.,* 2018). In the DLBCL subtype, objective responses were observed in 9 (26%) of 35 patients (2 CR, 7 PR).

Based on the unmet medical need of aggressive lymphoma, further development of tafasitamab focused on clinical trials in R/R DLBCL and more recently in patients with newly diagnosed DLBCL as follows:

- A phase 2 trial (MOR208C203) in patients with R/R DLBCL (L-MIND)
- A randomized phase 2/3 trial (MOR208C204) in patients with R/R DLBCL (B-MIND; of tafasitamab + bendamustine followed by tafasitamab until progression versus RTX + bendamustine followed by RTX until progression)
- A phase 1b trial (MOR208C107) in patients with newly diagnosed DLBCL (First-MIND)
- A phase 3 trial (MOR208C310) in patients with newly diagnosed DLBCL (frontMIND)

Results from the pivotal clinical trial MOR208C203 (L-MIND) are described in the following. For additional information on all other trials, please refer to the current investigator's brochure (IB).

3.3.2 Results From L-MIND [Primary Analysis (NOV 2018) and Data Cut-Off OCT 2020]

L-MIND is an ongoing, pivotal phase 2, single-arm, open-label, multicenter trial designed to evaluate the efficacy and safety of tafasitamab plus LEN in patients with R/R DLBCL (NCT02399085; EudraCT No. 2014-004688-19). Based on the efficacy and safety data from L-MIND, tafasitamab was granted accelerated FDA approval in combination with LEN for the treatment of R/R DLBCL.

Treatment consisted of LEN and tafasitamab (12 mg/kg) administered in 28-day cycles at specified dose intervals, until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever was first. See Table 4 for treatment regimen.

The primary endpoint of the trial is objective response rate (ORR) per independent review committee (IRC) based on response criteria per the guidelines of the International Working Group (Cheson *et al*., 2007), further defined as the proportion of patients with CR or PR as best response. The primary analysis has been completed (efficacy cut-off date of NOV 2018), and the primary data were recently published (Salles *et al*., 2020).

On 30 OCT 2020, an update to the efficacy analysis was performed (FAS, N = 80, assessed by Independent Radiology/Clinical Review Committee. At the time of this data cut-off, the time from last patient enrolled until data cut-off was approximately 3 years (35 months), presenting with a longer follow up across the cohorts.

Of the 80 patients treated in the trial (excluding 1 patient who received tafasitamab only), 34 patients entered tafasitamab monotherapy after discontinuing LEN. The best objective response was CR for 32/80 (40.0%) patients and PR 14/80 (17.5%). Based on these data, the IRC-assessed best ORR was 57.5% (95% confidence interval [CI]: 45.9, 68.5). Thirteen patients (16.3%) had SD as their best objective response. Thirteen patients (16.3%) had PD as their best objective response. Eight (10.0%) patients were not evaluable, as no valid post-baseline radiological examination for response assessment was available.

An overview of updated analysis for clinical efficacy from trial L-MIND, as of cut-off date OCT 2020 is shown in Table 6, based on the FAS (N = 80 patients), assessed by Independent Radiology/Independent Review Committee (IRC).

Table 6: Updated Efficacy Analysis Results in L-MIND (Cut-Off Date OCT 2020)

Response	Tafasitamab plus LEN N = 80
Best overall response rate, n (%)	46 (57.5%)
(95% CI)	(45.9%–68.5%)
CR rate	40%
PR rate	17.5%
SD	16.3%
PD	16.3%
Not evaluable	10%
Duration of response	
Median (95% CI, months)[1]	43.9 (26.1, NR)

Abbreviations: LEN=lenalidomide.
[1]Kaplan-Meier estimates.

Overall, the efficacy results from L-MIND demonstrate that the combination of tafasitamab plus LEN provides clinical benefit for patients with R/R DLBCL. In addition, the outcomes suggest a synergistic activity of the combination in R/R DLBCL patient's ineligible for stem cell transplant, who have limited treatment options and a poor prognosis.

3.3.3 Safety Profile of Tafasitamab Plus LEN From L-MIND (Cut-Off Date OCT 2020)

In the L-MIND trial, 81 patients were treated with tafasitamab in combination therapy with lenalidomide. In Table 7, TEAEs considered related to tafasitamab reported in ≥ 3% of patients are presented, sorted by System Organ Class (SOC) and incidences (number of patients [%]).

Table 7: Adverse Drug Reactions Observed in L-MIND (Tafasitamab – Lenalidomide Combination Therapy in Patients With DLBCL) in ≥ 3.0% Patients[b]

Adverse Reaction Related to Tafasitamab	Incidence[a] Total N=81 (%)
System Organ Class **Preferred Term**	**Any Grade**
Blood and lymphatic system disorders	
Neutropenia	30 (37.0%)
Anaemia	13 (16.0%)
Thrombocytopenia	10 (12.3%)
Leukopenia	6 (7.4%)
Febrile neutropenia	5 (6.2%)
Lymphopenia	3 (3.7%)
Gastrointestinal disorders	
Nausea	6 (7.4%)
Constipation	6 (7.4%)
Vomiting	5 (6.2%)
Diarrhoea	4 (4.9%)
General disorders and administration site conditions	
Pyrexia	10 (12.3%)
Asthenia	7 (8.6%)
Fatigue	7 (8.6%)
Infections and infestations	
Pneumonia	6 (7.4%)
Bronchitis	5 (6.2%)
Respiratory tract infection	4 (4.9%)
Sepsis[c]	3 (3.7%)
Investigations	
Alanine aminotransferase increased	3 (3.7%)
C-reactive protein increased	3 (3.7%)
Respiratory, thoracic and mediastinal disorders	
Cough	6 (7.4%)
Metabolism and nutrition disorders	
Hypomagnesaemia	3 (3.7%)
Injury, poisoning and procedural complications	
Infusion related reaction	5 (6.2%)
Immune system disorders	
Hypogammaglobulinaemia	3 (3.7%)

N=number of patients
[a]Incidence: number and percentage of patients
[b]Data cut-off OCT 2020
[c]Includes the following MedDRA Preferred Terms: sepsis, streptococcal sepsis, neutropenic sepsis

3.3.4 Clinical Pharmacokinetics of Tafasitamab

[redacted]

For more detailed non-clinical pharmacology, PK and toxicology results of tafasitamab, please refer to the current version of the IB.

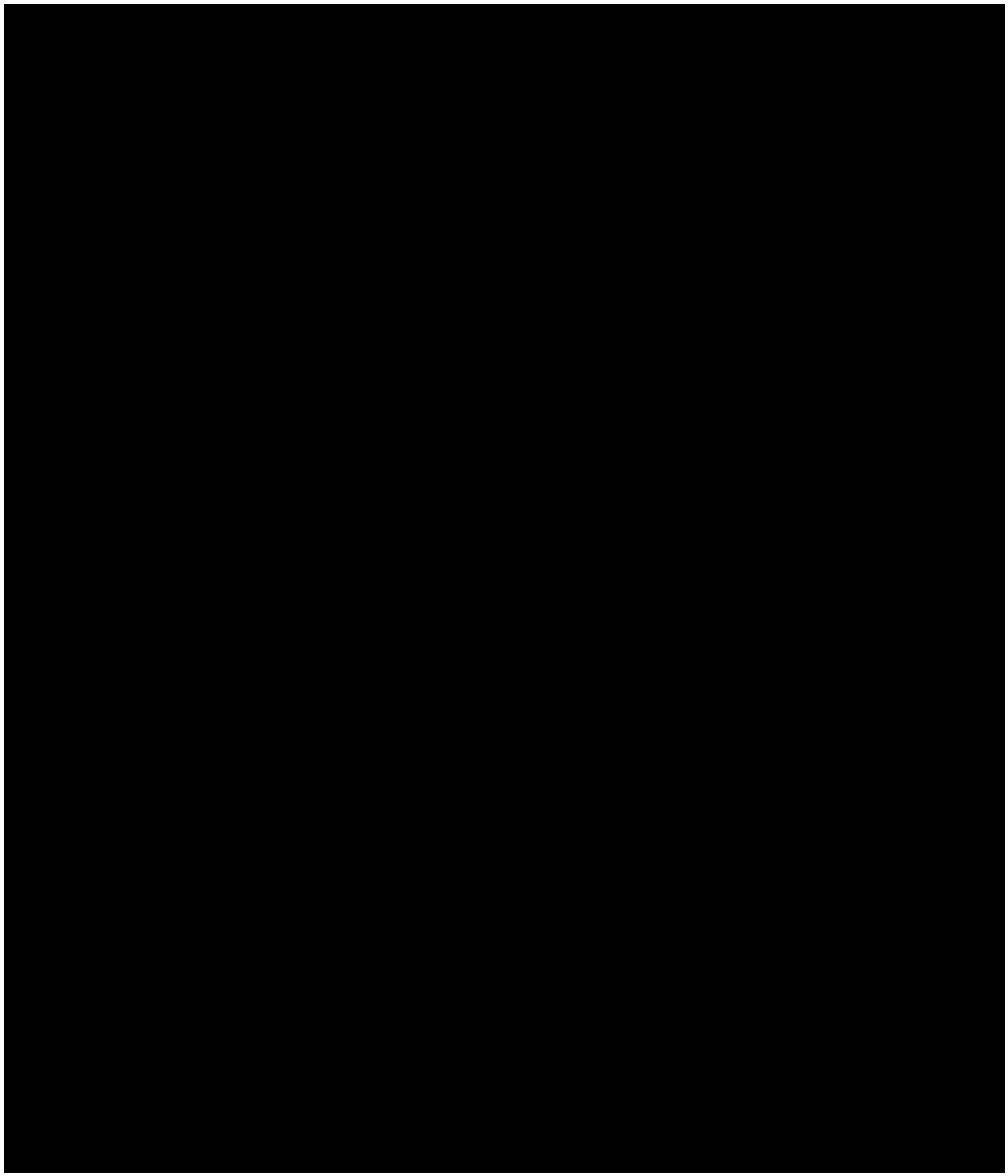
3.4 Justification for Dose

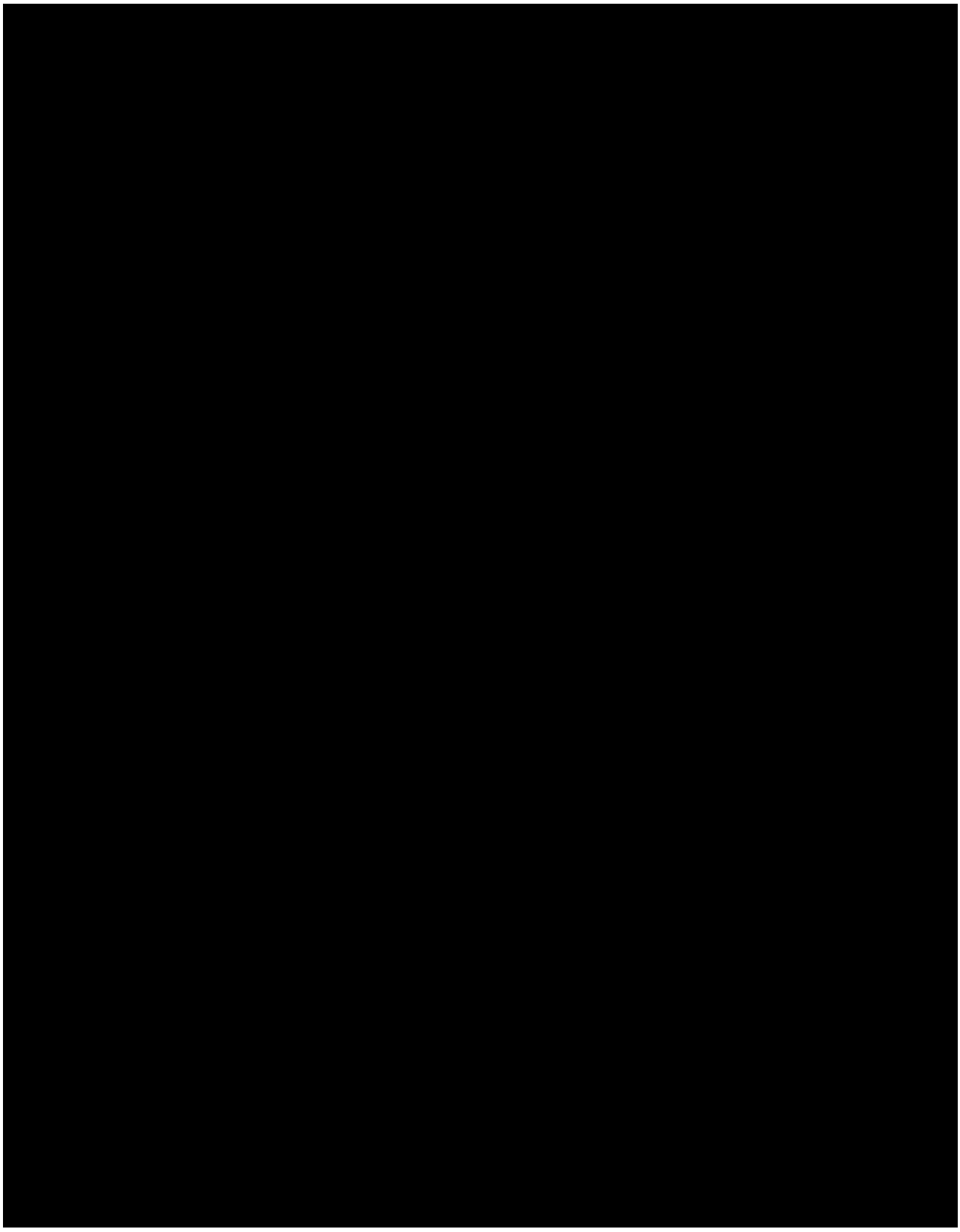
To evaluate [redacted]

- [redacted]
- The tafasitamab administration [redacted]

[redacted] to limit potential AEs occurring shortly after treatment initiation (e.g. IRRs or tumor lysis syndrome [TLS]).

[redacted]





3.5 Benefit/Risk Assessment

The risk assessment of tafasitamab and LEN is based on the data from nonclinical studies as well as on clinical experience from completed and ongoing clinical trials. Tafasitamab monotherapy was well tolerated in R/R B-cell lymphomas (BCLs) (Jurczak *et al.*, 2018). Similarly, tafasitamab plus LEN showed a manageable safety profile in the L-MIND trial in R/R DLBCL (Salles *et al.,* 2020) and received FDA approval in the US on 31 JUL 2020.

Furthermore, tafasitamab (Minjuvi®) was granted conditional approval in R/R DLBCL in Europe on 26 AUG 2021, and thereafter in other countries.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of tafasitamab is available in the current version of the IB.

3.5.1 Risk Assessment

As per Monjuvi® (2021) USPI, tafasitamab is approved for use at a dose of 12 mg/kg. [redacted]. Based on the clinical experience of tafasitamab in combination with LEN from L-MIND, the most common side effects (≥ 20%) of tafasitamab plus LEN were neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite. Serious adverse events (SAEs) were reported in ≥ 6% of patients, and included infections including pneumonia and febrile neutropenia. Management of AEs due to the tafasitamab plus LEN combination is detailed in Section 7.3.

3.5.2 Benefit Assessment

[redacted]

The combination of tafasitamab plus LEN provides clinical benefit for patients with R/R DLBCL as demonstrated in the L-MIND trial. Based on the clinical efficacy data as of data cut-off of 30 OCT 2020, for patients who had their DLBCL diagnosis confirmed by central pathology, combining tafasitamab plus LEN, showed an ORR of 53.5% (95% CI: 41.3; 65.5) with a CR rate of 35.2% (95% CI: 24.2; 47.5) and a median DoR of 43.9 months (95% CI: 15.0; no response [NR]). Compared with monotherapy of tafasitamab and LEN, an ORR of > 50% is considered highly clinically meaningful in the relapse-refractory setting of DLBCL not eligible to high dose chemotherapy and ASCT. Furthermore, the safety data from the L-MIND trial indicates that the addition of tafasitamab to LEN adds little additional toxicity, based on the characterized safety profile of LEN administered as monotherapy.

3.5.3 Overall Benefit Risk Conclusion

[redacted]

4 OBJECTIVES, ENDPOINTS AND ESTIMANDS

4.1 Objectives and Endpoints

The following study objectives and corresponding endpoints are listed in Table 8 below.

Table 8: Objectives and Corresponding Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of tafasitamab administered [redacted] in combination with lenalidomide in R/R DLBCL patients • To determine a recommended dose for tafasitamab [redacted] in combination with lenalidomide in R/R DLBCL patients	Incidence and severity of TEAEs
Secondary	
To evaluate the pharmacokinetic profile of tafasitamab after [redacted] in combination with lenalidomide	Tafasitamab serum concentrations after 3 (C_{trough} and C_{max}) and 12 (C_{trough}) treatment cycles
To assess anti-tumor activity of tafasitamab after [redacted] in combination with lenalidomide	• Best Objective Response Rate (ORR) by investigator assessment up to treatment Cycle 12 based on Cheson *et al*. (2007) • Duration of Response (DoR) by investigator assessment based on Cheson *et al*. (2007) • Progression-Free Survival by investigator assessment based on Cheson *et al*. (2007)
To assess the incidence of anti-drug antibodies to tafasitamab	Number and percentage of patients developing anti-tafasitamab antibodies up to treatment Cycle 12
[redacted]	

Abbreviations: C_{max}=maximum concentration; [redacted]; C_{trough}=minimum concentration; DLBCL=diffuse large B-cell lymphoma; LEN=lenalidomide; [redacted]; NA=not applicable; [redacted]; ORR=objective response rate; PK=pharmacokinetic; [redacted] R/R=relapsed/refractory; TEAEs=treatment-emergent adverse events.

4.1.1 Primary Estimand

Rationale for estimand: The primary objective of the study is to evaluate the safety and tolerability [redacted] of tafasitamab in combination with LEN. [redacted]

The estimand is described by the following attributes:

Population: All R/R DLBCL patients who receive at least [redacted]

Endpoint: Incidence and severity of TEAEs.

TEAEs are defined as all AEs which start or worsen after the first dose of study treatment until 90 days after the last dose of the study treatment.

Treatment condition: Treatment consisting of tafasitamab and LEN combination will be administered until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first. LEN can be given for up to 12 cycles in total, after which patients can continue with tafasitamab as monotherapy until progression or unacceptable toxicity.

Intercurrent events:

- TEAE data will be collected regardless of dose modifications, study treatment interruptions or non-adherence to study treatment, and included in the analysis (treatment policy strategy).
- TEAE data will be collected, regardless of whether patients take permitted concomitant medications or not and included in the analysis (treatment policy strategy).
- No further TEAE data past the start date of prohibited concomitant medication will be analyzed (while on treatment strategy). For a list of prohibited concomitant medication, refer to Section 7.9.
- No further TEAE data past withdrawal of consent will be collected (while on treatment strategy).
- In case of discontinuation from study treatment due to unacceptable toxicity, disease progression or any other reason, TEAE data will be collected until 90 days after the last dose of the study treatment and included in the analysis (while on treatment strategy).

Population-level summary: cumulative incidence and severity of TEAEs in the population as defined in the estimand attribute above until the last patient on study completes the 90-day safety follow-up visit.

4.1.2 Supplemental Estimand

Rationale for estimand: For safety signal detection, all collected TEAE data are relevant [redacted]. The estimand is described by the following attributes:

Population: All R/R DLBCL patients who receive at least one dose of any component of the study treatment (tafasitamab or LEN or tafasitamab plus LEN).

Endpoint: Same as primary estimand.

Treatment condition: Same as primary estimand.

Intercurrent events: Same as primary estimand.

Population-level summary: Same as primary estimand.

5 STUDY DESIGN

5.1 Overall Design

MOR208C115 (MINDway) is an open-label, multi-center, phase 1b/2 study of tafasitamab combined with LEN to evaluate the safety and PK [redacted] in adult patients with R/R DLBCL.

Patients will receive LEN in combination with tafasitamab in 28-day cycles. [redacted]
Tafasitamab will be administered as intravenous infusion according to the following dosing schedule:

- [redacted]

LEN (25 mg) will be administered for a maximum of 12 cycles or until disease progression, unacceptable toxicity, withdrawal, death or lost to follow up, whichever comes first. After cycle 12 or LEN discontinuation, patients will continue with tafasitamab monotherapy [redacted] until disease progression, unacceptable toxicity, withdrawal, death or lost to follow up, whichever comes first.

[redacted]. If a patient discontinues the study for reasons other than safety before the completion of the predefined safety observation window (5 weeks) as per Section 8.4, the patient may be replaced.

[redacted]

A patient is considered to have started the study and entered the screening period when they have signed the informed consent form.

[redacted]. This safety window will also be maintained [redacted]

Patient is considered enrolled in the study if they received at least one dose of any study treatment (tafasitamab or LEN).

The end of the study is reached for an individual patient if any of the following applies: withdrawal, lost to follow up, death or completion of the end of study (EOS)/90-Day Safety Follow-up visit after treatment discontinuation. Regardless of the reason for treatment discontinuation on study (with the exception of withdrawal of consent, death or lost to follow up) all patients must complete a Safety Follow-up visit 90 days after the last dose of study treatment, see Section 2.

The end of the study is reached when all patients still on study treatment have been followed for at least 3 years, or when the final patient on study has completed their last visit, whichever comes first.

Patients who are receiving ongoing treatment at the end of study may continue treatment with either of the options below upon assessment of a clinical benefit of continued treatment by the investigator and in accordance with the local regulatory guidance:

- commercially available tafasitamab for the approved dose regimen locally; or
- participation in the tafasitamab extension study if above option is not available

Upon study closure, Incyte will notify the applicable regulatory agencies in accordance with local requirements.

No overall survival follow-up after EOT will be performed in the study.

5.2 Data and Safety Monitoring Committee

A data and safety monitoring committee (DSMC), consisting of Sponsor representatives and investigators, will continuously monitor the study and can recommend to stop enrollment at any time based on emerging safety data and pre-defined stopping rules. In addition, pre-defined DSMC meetings will take place when 6 patients have completed the 5-week safety observation period (35 days from C1D1 onwards) [redacted] respectively.

Details of specific responsibilities, composition, meeting formats and frequency of the DSMC are outlined in the Data Safety Monitoring Committee Charter.

A recommendation [redacted]

The DSMC recommendations will be guided by pre-defined safety criteria that apply to the safety observation window of 35 days (from Cycle 1 Day 1 to Cycle 2 Day 7).

Pre-defined safety criteria (stopping rules):

- [redacted]
- [redacted]
- [redacted]

The pre-defined safety events are the following according to CTCAE version 5:

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

Events that are clearly attributed to the underlying disease or LEN alone will be discussed at the DSMC and a decision will be made whether these events should be considered as a pre-defined safety event.

If the safety results [redacted] in approximately 45 patients in total.

6 STUDY POPULATION

The study will enroll approximately 51 patients with histologically confirmed diagnosis of R/R DLBCL based on the local pathology report.

All patients must meet below listed eligibility criteria to be enrolled in the study. Prospective approvals of deviations to eligibility criteria, also known as protocol waivers or exemptions, are not permitted.

6.1 Inclusion Criteria

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

1. Capable of giving signed informed consent as described in Appendix 2: Regulatory, Ethical, and Trial Oversight Considerations which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. Patient must be at least 18 years of age and of legal age (whichever is higher) in the jurisdiction in which the study is taking place at the time of signing the informed consent.
3. One of the following histologically confirmed diagnoses:
    - DLBCL not otherwise specified (NOS)
    - T cell/histiocyte-rich large B-cell lymphoma (THRLBCL)
    - Epstein-Barr virus (EBV) positive DLBCL of the elderly (EBV-positive DLBCL)
    - Grade 3b follicular lymphoma
    - Composite lymphoma with a DLBCL component with a subsequent DLBCL relapse, according to the Revised European American Lymphoma/World Health Organization (REAL/WHO) classification

    Additionally, patients with the evidence of histological transformation to DLBCL from an earlier diagnosis of low-grade lymphoma (i.e., an indolent pathology such as follicular lymphoma, marginal zone lymphoma, chronic lymphocytic leukemia) into DLBCL with a subsequent DLBCL relapse are also eligible.
4. Tumor tissue for retrospective central pathology review must be provided as an adjunct to participation in this study. If archival formalin fixed paraffin embedded tumor tissue acquired ≤3 years prior to screening is not available, a fresh tumor tissue sample from the patient should be obtained. Archival formalin fixed paraffin embedded tumor tissue acquired >3 years prior to screening is acceptable only in cases where a fresh tumor biopsy cannot be collected due to a safety risk e.g. due to co-morbidity, or inaccessible tumor site.

5. Patients must have:
    a. Relapsed and/or refractory disease as defined in Appendix 3: Study Specific Definitions
    b. At least one bidimensionally measurable disease site. The lesion must have a greatest transverse diameter of ≥ 1.5 cm and greatest perpendicular diameter of ≥ 1.0 cm at baseline. The lesion must be positive on positron emission tomography (PET) scan for definition (see Juweid *et al.,* 2007)
    c. Received at least one, but no more than three previous systemic regimens for the treatment of DLBCL and one therapy line must have included a cluster of differentiation-20 (CD20)-targeted therapy (e.g., rituximab [RTX])
    d. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
6. Patients that are not eligible to undergo intensive salvage therapy including autologous stem cell transplantation (ASCT). The reason for a patient's ineligibility must meet one of the criteria described below and documented in the patient's source data:
    a. Inadequate performance status (Karnofsky performance status ≤ 80%; see Appendix 5: Karnofsky Performance Status Scale)
    b. Disease not responsive to salvage chemotherapy. Responsiveness is defined as a tumor demonstrating either complete response (CR) or partial response (PR) to salvage chemotherapy
    c. Inadequate major organ function (any of the below):
        i. symptomatic congestive heart failure
        ii. lung function-forced vital capacity (FVC), forced expiratory volume in 1 second (FEV-1), and corrected diffusion capacity of the lung for carbon monoxide (DLCO) ≤ 60%
        iii. liver function-total serum bilirubin and transaminases > 2 x upper limit of normal (ULN)
    d. History or evidence of significant co-morbid medical or psychiatric illness which would significantly compromise the patient's clinical care and chances of survival
    e. Inability to collect adequate stem cell graft (e.g. < 1-2 x 10^6 CD34+ cells free of tumor contamination/kg recipient body weight)
7. Patients must meet the following laboratory criteria at screening:
    a. Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by recent bone marrow aspiration and bone marrow biopsy)
    b. Platelet count ≥ 75 × 10^9/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by recent bone marrow aspiration and bone marrow biopsy)
    c. Total serum bilirubin ≤ 2.5 × ULN unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma. Patients with Gilbert's syndrome or documented liver involvement by lymphoma may be included if their total bilirubin is ≤ 5 × ULN (see exclusion criterion 6g)

d. Alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) ≤ 3 × ULN or < 5 × ULN in cases of documented liver involvement
e. Serum creatinine CL must be ≥ 60 mL/minute either measured or calculated using a standard Cockcroft and Gault formula (see Appendix 6: Cockcroft-Gault Formula)

8. Patients who received previous CD19 targeted therapy (other than tafasitamab) must have CD19 positive lymphoma confirmed on a biopsy taken since completing the prior CD19 targeted therapy
9. Patients with primary refractory disease (see Appendix 3: Study Specific Definitions) who received at least one, but no more than three previous systemic regimens (including a CD20 targeted therapy) for the treatment of DLBCL are eligible

6.2 Exclusion Criteria

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

1. General provisions:
   a. Patients who are legally institutionalized, or patients under judicial protection
   b. Concurrent enrollment in another interventional clinical study
2. Patients who have:
   a. Any other histological type of lymphoma including primary mediastinal (thymic) large B-cell (PMBL) or Burkitt lymphoma
   b. Known "double/triple hit" genetics (high grade B-cell lymphoma) characterized by simultaneous detection of *MYC* with *BCL2* and/or *BCL6* translocation(s) defined by fluorescence *in situ* hybridization. *MYC*, *BCL2*, *BCL6* testing prior to study enrollment is not required
3. Patients who have:
   a. Not discontinued (within 14 days prior to Day 1 dosing): CD20 targeted therapy, chemotherapy, radiotherapy, investigational anticancer therapy or other lymphoma-specific therapy
   b. Undergone major surgery (within 4 weeks prior to Day 1 dosing) or suffered from significant traumatic injury
   c. Received live vaccines (within 4 weeks prior to Day 1 dosing) (see Appendix 7: COVID-19: Infection Prophylaxis and Vaccines)
   d. Required parenteral antimicrobial therapy for active, intercurrent infections (within 14 days prior to Day 1 dosing).
4. Patients who:
   a. Have, in the opinion of the investigator, not recovered sufficiently from the adverse toxic effects of prior therapies
   b. Were previously treated with tafasitamab or IMiDs® (e.g., thalidomide, LEN)
   c. Have a history of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, IMiDs® and/or the excipients contained in the study treatment formulations

d. Have undergone ASCT within the period ≤ 3 months prior to signing the ICF. Patients who have a more distant history of ASCT must exhibit full hematological recovery before enrollment into the study
e. Have undergone previous allogenic stem cell transplantation
f. Have a history of deep venous thrombosis/embolism, threatening thromboembolism or known thrombophilia or are at high risk for a thromboembolic event in the opinion of the investigator and who are not willing/able to take venous thromboembolism (VTE) prophylaxis during the entire treatment period
g. Concurrently use other anticancer or experimental treatments

5. History of other malignancy that could affect compliance with the protocol or interpretation of results. Exceptions:

a. Patients with any malignancy appropriately treated with curative intent and the malignancy has been in remission without treatment for >2 years prior to enrollment are eligible
b. Patients with low-grade, early-stage prostate cancer (Gleason score 6 or below, Stage 1 or 2) with no requirement for therapy at any time prior to study are eligible

6. Patients with:

a. Positive hepatitis B and/or C serology (see Appendix 8: Hepatitis Virus Serology for details)
b. Known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV)
c. Central nervous system (CNS) lymphoma involvement – present or past medical history
d. 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 patient's ability to give informed consent
e. History or evidence of rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
f. Gastrointestinal (GI) abnormalities (issue with absorption) including the inability to take oral medication
g. History or evidence of severe hepatic impairment (total serum bilirubin > 3mg/dL), jaundice unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma (see inclusion criterion 7c)
h. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical class
i. Any other medical condition which, in the investigator's opinion, makes the patient unsuitable for the study

7. Contraception provisions:

Females: Due to the teratogenic potential of LEN, FCBP must follow the rules listed below (otherwise excluded):

Applicable in all countries except the US:

a. Not be pregnant as confirmed by a negative serum pregnancy test at screening and a medically supervised urine pregnancy test prior to starting study therapy
b. Refrain from breast feeding and donating oocytes during the study and for 3 months after the last dose of study drug or according to local guidelines for LEN, whichever is longer
c. Agree to ongoing pregnancy testing during the course of the study, and after study treatment has ended. This includes pregnancy testing and counseling if a patient misses her period or if there is any abnormality in her menstrual bleeding and applies even if the patient practices complete sexual abstinence
d. Commit to continued abstinence from heterosexual intercourse if it is in accordance with her lifestyle (which must be reviewed on a monthly basis) or agree to use and be able to comply with the use of highly effective contraception without interruption at least 4 weeks prior to start of study drugs, during the study treatment and for 3 months after the last dose of study drug, or, for LEN, according to the local guidelines, whichever is longer

Applicable in the US:

e. Not be pregnant as confirmed by pregnancy tests performed before treatment initiation, within 10–14 days and again within 24 hours of initiating treatment (even if true abstinence is the chosen method of birth control)
f. Refrain from breast feeding and donating oocytes during the study and for 3 months after the last dose of study drug, or according to US guidelines for LEN, whichever is longer
g. Agree to ongoing pregnancy testing during the study (every 4 weeks in women with regular menstrual cycle and every two weeks in women with irregular menstrual cycle), and after study therapy has ended (even if true abstinence is the chosen method of birth control). This includes pregnancy testing and counseling if a patient misses her period or if there is any abnormality in her menstrual bleeding
h. Not get pregnant while taking the study treatment and for at least 3 months after the last dose of study treatments by using at the same time 2 effective methods of contraception, at least one highly effective method and one additional effective method (see Appendix 13: Contraceptive Guidance and Collection of Pregnancy Information), each time engaging in sexual activity with a male, starting at least 4 weeks before taking the study treatment, while taking the study treatment, during breaks (dose interruptions) and for at least 3 months after stopping the study treatment, or for LEN, according to the US guidelines, whichever is longer. True abstinence from heterosexual sexual intercourse is also an acceptable method of contraception. The use of emergency contraception is also permitted

8. Due to teratogenic potential of lenalidomide, male participants must follow the rules listed below (otherwise excluded):

Applicable in all countries except the US:

a. Use an effective barrier method of contraception without interruption if the patient is sexually active with a FCBP. Male patients should refrain from donating sperm during the study participation and for 3 months after the last dose of study treatment, or according to the local guidelines for LEN, whichever is longer

Applicable in the US:

b. Use a latex or synthetic condom each time they have sex with a FCBP. True abstinence from heterosexual sexual intercourse is also an acceptable method of contraception. The use of emergency contraception is also permitted. Male patients should refrain from donating sperm during the study participation and for 3 months after the last dose of study drug, or according to the US guidelines for LEN, whichever is longer

6.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered into the treatment period. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients. This includes:

- Informed consent
- Inclusion/exclusion criteria
- Reason for screen failure (e.g., withdrawal of informed consent, death, etc.)
- Demography
- AEs (only if the patient experienced an SAE between signing the ICF and date of screen failure)

Patients can be re-screened at the discretion of the investigator under certain circumstances. Re-screening is restricted to one attempt per patient and can only be performed if one of the following criteria is met:

- The patient has already consented and met all of the inclusion and none of the exclusion criteria and his or her enrollment was delayed due to an unexpected event
- The patient previously failed to be eligible due to any event (e.g., planned surgery, laboratory test result) that has been resolved
- The patient previously failed screening but has become eligible for the study based on a change in the inclusion and exclusion criteria as the result of a protocol amendment
- The patient failed screening due to non-progressed / non-relapsed disease at the time of screening and is later clinically diagnosed as having progressed/relapsed
- A patient should only be rescreened if there is a clear indication that the patient may be eligible according to the currently valid study protocol

The following procedures should be performed for re-screened patients:

- The patient must sign and date a new ICF as part of the re-screening procedure
- The eligible patient will receive a new unique identification number
- A new electronic case report form (eCRF) should be completed
- The patient will be documented as rescreened in the source documents and eCRF

A rescreened patient can be enrolled, if all of the current inclusion criteria are met and none of the exclusion criteria are met.

7 STUDY TREATMENT(S)

7.1 Investigational Medicinal Products Administered

Tafasitamab must be handled and/or prepared as described in the Drug Handling Manual, the IB for tafasitamab, and other safety-relevant documents (e.g., Summary of Product Characteristics (SmPC) for the European Medicines Agency (EMA) or the Prescribing Information (PI, US FDA) for LEN). Tafasitamab will be administered in combination with LEN 25 mg [redacted] as shown in Figure 2, Figure 3, and Table 9.

Table 9: Overview of IMPs in MINDway

IMP Name	Tafasitamab	LEN
Formulation	Vial	Capsule
Unit Dose Strength(s)/Dosage Level(s)	200 mg	25 mg 10 mg 5 mg
Route of Administration	i.v.	Oral

Abbreviations: i.v.=intravenous; LEN=lenalidomide.

On days when both study drugs are given together, LEN should be administered prior to tafasitamab.

7.1.1 Tafasitamab (IMP)

Tafasitamab will be centrally supplied. Tafasitamab must be stored under 2° C to 8° C in its original package in an appropriate storage facility accessible only to the pharmacist(s), the investigator, or a duly designated person.

Tafasitamab is a lyophilizate supplied in single-use 20 mL glass vials. Each vial contains 200 mg of tafasitamab for reconstitution with 5 mL of water for injection (WFI). Reconstitution yields 40 mg/mL tafasitamab in 25 mM sodium citrate, 200 mM trehalose and 0.02% weight by volume (w/v) polysorbate 20 at pH 6.0. Reconstituted tafasitamab will be diluted into an infusion bag of 0.9% w/v sodium chloride solution for injection according to the description given in the Drug Handling Manual. The solution after reconstitution is colorless to slightly yellow and essentially free of foreign particles; it may contain a few white to whitish product-related particles.

The individual tafasitamab infusion will be prepared under aseptic conditions and administered at the study site, according to the directions of the sponsor, which will be provided in a Drug Handling Manual. In general, a vial of tafasitamab must be used as soon as possible after

reconstitution with WFI. After dilution for infusion, administration of tafasitamab should take place as soon as possible. Maximum allowed storage times and conditions will be detailed in the Drug Handling Manual.

Tafasitamab will be administered i.v. as per schedule of assessment and dosing scheme, respectively (see Section 2 and Table 5).

Tafasitamab should **NOT** be administered as an i.v. push or bolus but as an i.v. infusion.

In the first 28-day cycle (Cycle 1) tafasitamab is given on Day 1, Day 4 and Day 8 at a dose of 12 mg/kg to mitigate the risk of IRRs and TLS.

Body weight will be measured on Day 1 of each cycle. This baseline–weight can be used to calculate the tafasitamab dose during the given cycle provided the weight does not deviate more than ±10% from baseline during the course of this cycle. Using actual body weight measured prior to the particular tafasitamab infusion on visits other than Day 1 of the cycle is also allowed for dose calculation, if this is preferred by investigators.

In cases where the patient's body weight changes more than ± 10% from weight measured on Day 1 of the cycle, the current weight, measured 24 hours prior to the particular tafasitamab infusion must be used to calculate the tafasitamab dose.

Guidance on the infusion duration for each visit is summarized [redacted] Further details on the infusion rates are provided in the drug handling manual. If required, the investigator should use clinical judgement to optimize patient safety by administering the infusion more slowly.

[redacted]

Additionally, further guidance on infusion rate modifications for subsequent administrations in case of IRRs Grade ≥3 is summarized in Table 11 below.

Please note that general management of IRRs is described in Section 7.3.1.

Table 11: Infusion Rate Modifications for Tafasitamab Infusion ([redacted]) in Case of IRR's, Cytokine Release Syndrome (CRS)

Infusion related reaction, Cytokine release syndrome	Infusion Rate
IRR Grade 3 and/or Grade 2 CRS during Cycle 1	If IRR Grade 3 and/or Grade 2 CRS in Cycle 1 has resolved and no further IRR Grade ≥3 events are observed in cycle 2 and 3, the patient may receive tafasitamab with shorter infusion time from Cycle 4 Day 1 onward at the discretion of the investigator
IRR Grade 3 and/or Grade 2 CRS during any other Cycle	If IRR Grade 3 and/or Grade 2 CRS has resolved, tafasitamab administrations must be given at regular infusion rate i.e. approximately 4 hours in the current and subsequent Cycle. If the patient experiences no further IRR Grade ≥3, they may receive the tafasitamab administration with short infusion time from the next but one cycle onward at the discretion of the investigator.
IRR Grade 4 and/or Grade 3 CRS, Grade 4 CRS	Tafasitamab administration should be permanently discontinued.

7.1.2 Lenalidomide (IMP)

LEN (generic) as sourced from commercially available drug suppliers will be provided centrally. Patients will self-administer a starting dose of 25 mg oral daily on Days 1–21 of each cycle until cycle 12 or discontinuation. Treatment with LEN may be modified and/or de-escalated from 25 mg to 5 mg based upon clinical and laboratory findings. Detailed dose modification guidelines to manage hematological and/or other toxicities are provided in the Section 7.3.2.

Patients must be counselled on the reproductive risks associated with LEN, at the timepoints according to SoA (see Section 2).

7.1.3 Pre-Medication for Tafasitamab Infusions

IRRs have been reported for patients with R/R DLBCL treated with tafasitamab and there is a potential increased risk of IRRs with higher dose levels of tafasitamab.

To reduce the risk of IRRs, pre-medication is mandatory for the first 4 infusions (doses) of tafasitamab. Pre-medication for patients who do not experience any IRRs to tafasitamab during the first 4 infusions (doses) will be optional for subsequent infusions at the discretion of the investigator. Otherwise, the pre-medication should be continued for subsequent administrations.

It is suggested that pre-medication is administered between 30 minutes and 2 hours prior to the tafasitamab infusions.

The pre-medication may include the following:

- Antipyretics (e.g., acetaminophen [paracetamol] 1000 mg per dose per by [p.o.] or i.v. or equivalent).
- Histamine H1 receptor blockers (e.g., diphenhydramine 25–50 mg per dose i.v. or equivalent).
- Histamine H2 receptor blockers (e.g., cimetidine 300 mg p.o. (except Austria), ranitidine 150 mg tablet p.o. or equivalent).
- Glucocorticosteroids (methylprednisolone 80–120 mg per dose i.v. or equivalent - please refer to Appendix 9: Equivalent Doses for Corticosteroids.

The investigator may repeat doses of individual agents as required and use other agents, doses and/or formulations in accordance with institutional guidelines. Equivalence for pre-medications includes variations to the stated dose due to the formulations available locally. Any pre-medication given should be reported in the eCRF.

7.1.4 Patient Monitoring During and After Tafasitamab Infusion

Vital signs should be measured as outlined in Section 9.4.1.

All supportive measures consistent with optimal patient care will be provided throughout the study according to institution standards. The observation of patients after the infusion is recommended, however, the duration and potential monitoring of vital signs should be determined by the investigator based on clinical judgement in accordance with local/practice guidelines of the institution. The Sponsor recommends that the investigators consider hospitalization on C1D15 for patients who experienced infusion related events during previous infusions on C1D1, C1D4 and/or C1D8 with 12 mg/kg tafasitamab or if otherwise clinically indicated.

Precautions for anaphylaxis should be observed during tafasitamab administration. Emergency resuscitation equipment and medications should be readily available.

Additional supportive measures should also be available and may include, but are not limited to, epinephrine, antihistamines, corticosteroids, i.v. fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen (paracetamol).

In case of hospitalization of patient as a prophylactic measure in accordance with local/practice guidelines of the institution will not be reported as AE/SAE.

7.2 Standard of Care

Not applicable.

7.3 Dose Modifications, Drug Interruptions and Discontinuation

7.3.1 Tafasitamab Specific Dose Modifications, Drug Interruptions and Discontinuation

Intra-patient dose reductions of tafasitamab are not permitted. Drug interruptions or discontinuation may occur e.g. in case of severe IRRs, Cytokine Release Syndrome (CRS), allergic reactions, infections, febrile neutropenia or severe hematologic toxicity. If a tafasitamab infusion is delayed due to toxicity for more than 2 days during treatment Cycle 1 or for more than 7 days during treatment Cycles 2 and 3, this infusion should be skipped and tafasitamab treatment continued only at the next scheduled timepoint. In case 2 consecutive tafasitamab doses are skipped during the first three treatment Cycles, study drugs will be discontinued, and the EOT visit will be performed. See Table 14 and Table 15 for additional details.

For further details on the management of tafasitamab IRRs and CRS, please see Table 12.

7.3.1.1 Management of Tafasitamab IRRs and Cytokine Release Syndrome (CRS)

IRRs and CRS will be defined according to the NCI-CTCAE, version 5.0 definition of IRR and CRS (see Table 12).

Table 12: Definition of IRR and CRS NCI-CTCAE Version 5.0: IRR and CRS

AE	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 (e.g., antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤ 24 hours	Prolonged (i.e. 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[1]	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2[1]	Life-threatening consequences; urgent intervention indicated

Abbreviations: CRS=cytokine release syndrome; IRR=infusion-related reaction; i.v.=intravenous; NCI-CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs=non-steroidal anti-inflammatories.
Please note: An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies 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 may include: allergic reaction/hypersensitivity (including drug fever), arthralgia (joint pain), bronchospasm, cough, dizziness, dyspnoea, 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.
[1]Applied e.g. via breathing mask.

7.3.1.2 Interventions for Grade 2 IRRs, Grade 1 CRSs

If a patient presents with a grade 2 infusion reaction or grade 1 CRS:

- The infusion should be stopped immediately
- The patient 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 IRR reduced from Grade 2 to Grade 1, according to investigator assessment, the infusion can be continued at an infusion rate of 50% of the speed so far. If, after one hour, the patient'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 patient receives further infusions of tafasitamab, then pre-medication should be given before all subsequent infusions of tafasitamab throughout the study

7.3.1.3 Interventions for Grade 3 IRRs, Grade 2 CRSs

If a patient presents with a grade 3 IRR or grade 2 CRS:

- The infusion should be stopped immediately
- The patient must receive appropriate treatment with an antihistamine and/or acetaminophen (paracetamol) or methylprednisolone (or equivalent) and, if necessary, further medications (i.e. epinephrine, bronchodilator) as clinically indicated
- Only after the complete resolution of all symptoms, and after having received appropriate prophylactic medication(s), the infusion may be resumed at an infusion rate of 25% of the speed so far. If, after 1 hour, the patient's symptoms do not return and vital signs are stable, the infusion rate may be increased to a maximum of 50% of the baseline speed
- If, after the resumption of the infusion, symptoms return (irrespective of grade), the infusion must be stopped immediately and the infusion tubing should be disconnected from the patient
- Based on the investigator's decision the patient may receive further infusions of tafasitamab provided clinically appropriate precautions are undertaken. Pre-medication should be given before all subsequent infusions of tafasitamab throughout the study

If precluded from further tafasitamab administrations, the patient may continue treatment with lenalidomide.

7.3.1.4 Interventions for Grade 4 IRRs, Grade 3 CRSs, Grade 4 CRSs

If a patient presents with a grade 4 infusion reaction or grade 3-4 CRS:

- The infusion should be stopped immediately, and the infusion tubing should be disconnected from the patient
- The patient must receive appropriate treatment with an antihistamine and/or acetaminophen (paracetamol) or methylprednisolone (or equivalent) and, if necessary, further medications (i.e. epinephrine, bronchodilator) as clinically indicated
- The patient must not receive any further tafasitamab infusions but may continue treatment with LEN

7.3.2 LEN Specific Dose Modifications, Drug Interruptions and Discontinuation

LEN may be given only on Days 1 to 21 of each cycle up to 12 cycles in total and must not be administered beyond this period.

In case of LEN-related toxicity (e.g., neutropenia), the dose of LEN may be interrupted temporarily and/or reduced successively level by level from the starting dose of 25 mg daily as described below in Table 13.

Table 13: LEN Dose Modification Guidelines

Starting Dose	25 mg Daily on Days 1–21, Every 28 Days
Dose Level – 1	20 mg daily on Days 1–21, every 28 days
Dose Level – 2	15 mg daily on Days 1–21, every 28 days
Dose Level – 3	10 mg daily on Days 1–21, every 28 days
Dose Level – 4	5 mg daily on Days 1–21, every 28 days

Patients who cannot tolerate Dose Level – 4 are to be discontinued from LEN treatment in the study but should continue therapy with tafasitamab alone.

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

7.3.3 General Dose Modifications, Drug Interruptions and Discontinuation due to Toxicity

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

- ANC is ≥ 1,000/mm^3 (unless neutropenia is due to infiltration of bone marrow)
- Platelets (PLT) ≥ 50,000/mm^3 (unless thrombocytopenia is due to infiltration of bone marrow, patient may have received transfusion) and absence of active bleeding
- No other treatment related toxicities > Grade 2

If, based on medical judgment, the treating physician considers a change in laboratory parameter 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 patient should be dosed. The decision and rationale behind the decision should be documented in the source data.

If any of the above conditions are not met on Day 1 of a new cycle, the patient will be monitored as per institutional guidelines and a new cycle will be initiated when all criteria listed above are met. Specific course of action for a given toxicity occurring in the course of the treatment cycle is described below.

If initiation of the next planned Cycle is delayed by > 28 days for the same persistent study drug-related toxicity, then study drugs will be discontinued, and the EOT visit will be performed.

7.3.3.1 Hematological and Other Toxicities

Patients will be evaluated for AEs at each visit with the NCI CTCAE v5.0 used as a guide for grading severity. The dose and/or administration of study drug(s) for each patient will be interrupted and/or modified following toxicity as described below in Table 14 and Table 15 and Table 13 for LEN dose reduction instructions.

Table 14: Hematological Toxicities

Hematological Toxicity	LEN[1]	Tafasitamab
Neutropenia Grade 4 (ANC < 500/µl) with or without a temperature of ≥ 38.0°C/100.4°F	Interrupt LEN.	Withhold tafasitamab infusion.
	If neutropenia has resolved to ≤ Grade 2 (ANC ≥ 1.000/µl) within 7 days, LEN should be restarted in the next cycle at the same dose. If neutropenia has not resolved to ≤ Grade 2 within 7 days, LEN should be resumed in the next cycle at the next lower dose level (see Table 13 above). Monitor CBC at least QW until neutrophil count is ≥ 1,000/µl.	If neutropenia has resolved to ≤ Grade 2, resume tafasitamab. Monitor CBC at least QW until neutrophil count is ≥ 1,000/µl.
Neutropenia Grade 3 (ANC < 1,000/µl) > 7 days	LEN should be resumed in the next cycle at the next lower dose level (see Table 13 above).	Hold tafasitamab until resolved to ≤ Grade 2 (ANC ≥ 1,000/µl).
Neutropenia Grade 3 (ANC < 1,000/µl) with a temperature of ≥ 38.0°C/100.4°F (Febrile Neutropenia)	Interrupt LEN.	Interrupt tafasitamab.
	If infection is resolving (< 38°C/100.4°F), and neutropenia has resolved to ≤ Grade 2, LEN should be resumed in next cycle at the next lower dose level (see Table 13 above).	If infection is resolving (< 38°C/100.4°F), continue tafasitamab as per protocol.
Neutropenia < Grade 3 associated with infection ≥ Grade 3 or fever (≥ 38.0°C body temperature)	First occurrence interrupt LEN.	Interrupt tafasitamab.
	If infection is resolving (< 38°C/100.4°F), LEN should be restarted in the next cycle at the same dose.	If infection is resolving (< 38°C/100.4°F), continue tafasitamab per protocol.
	Re-occurrence: interrupt LEN. If infection is resolving (< 38°C/100.4°F), LEN should be restarted in the next cycle at the next lower dose level.	
Thrombocytopenia Grade 3-4 (PLT< 50,000/µl) with or without bleeding	Interrupt VTE prophylaxis.	
	Consider platelet transfusion according to institutional guidelines. If thrombocytopenia has resolved to ≤ grade 1, consider change of VTE prophylaxis agent (e.g. 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.	
	Interrupt LEN	Withhold tafasitamab infusion
	Follow CBC at least every 7 days. If thrombocytopenia has resolved to ≤ Grade 2 (PLT ≥ 50,000/µl), LEN should be resumed in the next cycle at the next lower dose level (see Table 13 for LEN dosing).	Follow CBC at least every 7 days. If thrombocytopenia has resolved to ≤ Grade 2 (PLT ≥ 50,000/µl), restart tafasitamab. Monitor as clinically indicated.
Anemia Grade 3-4 (Hemoglobin <8.0 g/dL)	Interrupt LEN Consider transfusion according to institutional guidelines Urgent intervention indicated as per local institutional guidance	Interrupt Tafasitamab Consider transfusion according to institutional guidelines Urgent intervention indicated as per local institutional guidance

Abbreviations: AE=adverse event; ANC=absolute neutrophil count; CBC=complete blood count; VTE=venous thromboembolism; LEN=lenalidomide; PLT=platelets. QW=weekly

[1]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 patient should be dosed. The decision and rationale behind the decision should be documented in the source data.

Table 15: Non-Hematological Toxicities

Non-hematological toxicity	LEN[1]	Tafasitamab
Thromboembolic events ≥ Grade 3	Discontinue LEN permanently.	Continue tafasitamab infusion as per protocol if clinically appropriate.
Allergic reaction or hypersensitivity Grade 2	If related to LEN then interrupt/skip the dose.	If related to tafasitamab then interrupt/skip the dose.
	Note: if the causality cannot be determined, and the AE may be related to LEN and/or tafasitamab, both drugs should be held.	
	If toxicity resolves to ≤ Grade 1, restart LEN at the next lower dose level (see Table 13 above).	If toxicity resolves to ≤ Grade 1, tafasitamab may be resumed.
Allergic reaction or hypersensitivity ≥ Grade 3	If related to LEN then discontinue permanently.	If related to tafasitamab then discontinue permanently.
	Note: If the causality cannot be determined and the AE may be related to LEN and/or tafasitamab, discontinue both drugs permanently.	
Rash Grade 2 or 3 non-desquamating (blistering)	If related to LEN then interrupt the dose. If the AE resolves to ≤ Grade 1, restart LEN at the same level (see Table 13 above).	If related to tafasitamab then interrupt the dose. If toxicity resolves to ≤ Grade 1, tafasitamab may be resumed.
	Note: if the causality cannot be determined, and the AE may be related to LEN and/or tafasitamab, interrupt both drugs.	
Rash Desquamating (blistering) ≥ Grade 3 OR Non-desquamating Grade 4	If related to LEN then discontinue permanently.	If related to tafasitamab then discontinue permanently.
	Note: If the causality cannot be determined and the AE may be related to LEN and/or tafasitamab, discontinue both drugs permanently.	
TFR Grade 3–4[2]	Interrupt LEN. If the AE resolves to grade ≤ 1, restart LEN and maintain the same dose level (see Table 13 above).	Continue tafasitamab infusion as per protocol if clinically appropriate.
TFR Grade 1–2[2]	Continue LEN.	Continue tafasitamab infusion as per protocol.
Constipation ≥ Grade 3	Interrupt LEN. If the AE resolves to ≤ Grade 2, restart at same dose level.	Continue tafasitamab infusion as per protocol if clinically appropriate.
Other non-hematologic AEs ≥ Grade 3	Interrupt LEN. If the AE resolves to ≤ Grade 2, restart at the same or next lower dose level per the investigator's discretion.	Continue tafasitamab infusion as per protocol if clinically appropriate.
Other LEN related AEs in patients with moderate renal impairment (creatinine CL 59-30 mL/min)	If the AE resolves to ≤ grade 2, restart at the same or next lower dose level per the investigator's discretion (see Table 13 above).	Continue tafasitamab infusion as per protocol if clinically appropriate.
Creatinine CL decreases to < 30 mL/min	Interrupt LEN during the current cycle. If creatinine CL ≥ 30 mL/min in the next cycle, restart at the next lower dose level.	Continue tafasitamab/ infusion as per protocol if clinically appropriate.

Abbreviations: AE(s)=adverse event(s); LEN=lenalidomide; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; TFR=tumor flare reaction.

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

[2]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 (TFR is the only AE that will be graded using NCI-CTCAE version 3.0).

Grade 1: Mild pain not interfering with function; Grade 2: Moderate pain; pain or analgesics interfering with function but not with activities of daily living.; Grade 3: Severe pain; pain or analgesics interfering with function and interfering with activities of daily living; Grade 4: Disabling.; Grade 5: Death.

7.3.3.2 Additional Information

The most up-to-date information regarding constitution, dosing, interaction with other medicinal products and most frequent AEs related to the administration of LEN and tafasitamab are contained in the SmPC (EMA), PI (US FDA) and the current tafasitamab IB, respectively, and supplied to the study sites.

7.3.3.3 Tumor Flare With LEN

Patients in this study should be monitored for tumor flare (TFR). TFR is defined as a sudden and tender increase in the size of the disease bearing sites, including the lymph nodes, spleen and/or the liver, often accompanied by low-grade fever, non-pruritic diffuse rash and in some cases, an increase in the peripheral blood lymphocyte counts. TFR is an expected toxicity with LEN, especially in patients with a high tumor burden and may mimic disease progression. Therefore, careful monitoring and evaluation is important prior to discontinuing a study patient for PD in the initial cycles of LEN therapy. There are currently no laboratory or radiological tests to help distinguish TFR from PD. The distinction should be made on clinical grounds, incorporating observations such as associated physical findings, laboratory findings, and pace of disease before and after the initiation of treatment. TFR should be recorded as an AE of special interest (graded using the NCI-CTCAE 3.0 criteria) and not as PD.

Treatment of TFR is at the discretion of the investigator and dependent on the severity, clinical situation and institutional standards.

7.3.3.4 Tumor Lysis Syndrome (TLS)

TLS results from the rapid breakdown of tumor cells and the release of their intracellular content into the bloodstream. The release of large amounts of potassium, phosphorus, and nucleic acids overwhelms normal homeostatic mechanisms, resulting in hyperkalemia, hyperphosphatemia, hyperuricemia, and secondary hypocalcemia. Elevated lactate dehydrogenase (LDH) and elevated AST are potential indicators for TLS. The onset of TLS is rapid, usually within 24-48 hours of receipt of the first dose of anticancer medication, but can also occur after the first week of treatment. Left untreated, TLS can lead to acute renal failure, cardiac dysrhythmia, neurologic complications, and seizures.

Bulky disease, moderate renal insufficiency, a high number of circulating lymphoma cells and high uric acid levels (>8 mg/dL) prior to therapy, increase the likelihood of TLS.

In patients with high risk of tumor lysis syndrome (e.g. patients with large tumor burden, elevated LDH, or high proliferation rate of tumor cells), TLS prophylaxis should be considered. All approaches to mitigate the risk of developing TLS, such as adequate hydration or hypouricemic agents (e.g. allopurinol or rasburicase), may be used in high risk patients as per institutional guidelines. Patients should be monitored closely for TLS during treatment with tafasitamab. These measures are described in the IB.

7.3.3.5 Thromboembolism

LEN increases the risk of thrombotic events in patients who are at high risk of thrombosis. High risk is defined, for example, as a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk of a thromboembolic event and/or a known hypercoagulable state, regardless of thromboembolic history. It is recommended that patients

receive adequate anticoagulation therapy according to the institutional standards and investigator's discretion. It should be tailored to the patient's individual risk/benefit profile by taking into account the individual thrombotic and bleeding risk, and the quality of compliance with VTE prophylaxis. Anticoagulants may include acetylsalicylic acid (e.g., aspirin) prophylaxis, low molecular weight heparin, warfarin or new oral anticoagulants (NOACs, e.g., dabigatran, rivaroxaban).

7.4 Overdose

For this study, any dose of tafasitamab greater than 120% of the assigned dosage per single infusion as per protocol (see Section 7.7) will be considered an overdose.

For LEN, the overdose is defined as any dose greater than the planned dose (i.e., above 100%) for a particular patient as per protocol (see Section 7.7).

The sponsor does not recommend specific treatment for an overdose. Symptomatic treatment including but not limited to blood product transfusions, growth factors, antibiotics, antiemetics and analgesics may be administered per investigator's discretion.

In the event of an overdose, the investigator/treating physician should:

- Evaluate the patient carefully with regards to an immediate measure for the patients safety
- Contact the medical monitor immediately.
- Determine, in consultation with the medical monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely follow the patient for AEs and laboratory abnormalities and report any observed symptoms as AE and SAE as applicable.
- Obtain a sample for PK analysis if requested by the medical monitor (determined on a case-by-case basis)
- Document the overdose and actions taken in the source documentation (see Section 9.4.9).

7.5 Measures to Minimize Bias: Randomization and Blinding

Not applicable.

7.6 Preparation/Handling/Storage/Accountability

Each investigator is responsible for ensuring that deliveries of IMPs 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 and related plans and guidance. Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment.

Authorized site staff must confirm appropriate temperature conditions have been maintained for all IMP received. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with information provided on the labels of IMP with access limited to the investigator and authorized site staff.

7.7 Treatment Compliance

Dosing modifications due to toxicity are described in Section 7.3.

Patients will receive tafasitamab under the direct supervision of study personnel. Each administration volume or dose will be checked and the vial/outer package code and volume or dose per administration will be recorded in each patient's eCRF as well as in the source data.

A patient will be considered compliant with the protocol if the tafasitamab dose administered is ≥ 80% to ≤ 120% of the assigned dosage per single infusion.

LEN is to be dispensed in 28-day cycles. Patients should return all unused or empty LEN bottles/blister packs to the site throughout the treatment period of the study, as instructed by the investigator. A patient will be considered compliant with the protocol if the LEN dose administered is ≥ 80% to ≤ 120% of the assigned dosage during a particular cycle.

Drug accountability will be checked by the field monitor during site visits and at the completion of the study.

7.8 Prior and Concomitant Therapy

Prior therapy must be recorded in the eCRF as follows:

- All prior immunosuppressive medications administered/taken within the past 5 years prior to signing the ICF
- Corticosteroids for symptom control administered/taken within the three weeks prior to signing the ICF
- All other medications and therapies (including non-drug procedures) taken by/administered to the patient within 30 days prior to signing the ICF

Any concomitant therapy up to 4 weeks (medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) and non-drug procedures) that the patient is receiving at the time of signing the ICF or receives during the study must be recorded in the eCRF.

eCRF records of prior and concomitant medication include at least the dose, regimen, route of administration, indication, and dates of use (start, end).

Patients may receive concomitant medications that are medically indicated as standard care for the treatment of symptoms, AEs, and intercurrent illnesses. Medications to treat concomitant diseases like diabetes, hypertension, bronchial asthma, chronic obstructive pulmonary disease (COPD) etc., are allowed. Patients will also receive therapy to mitigate side effects of the study medication as clinically indicated, as well as best supportive care (BSC) as per institutional guidelines. This may include, but is not limited to, antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics, and other medications intended to treat symptoms.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.8.1 Recording of Prior Lines of Anti-Lymphoma Therapy

Information should be provided on any previous DLBCL specific- therapies since the time point of the first diagnosis of DLBCL. The generic or the trade name of a medication may be recorded.

To become eligible for the MOR208C115 study the patients must have received at least one, but no more than three previous systemic therapy lines for the treatment of DLBCL, and at least one therapy line must have included a CD20 targeted therapy (e.g., RTX).

Planned consolidation of responding patients, i.e. by radiotherapy or second line regimens with or without ASCT, is regarded as one therapy line. Changing to a different chemotherapy regimen is regarded as a separate line of therapy, **unless** the change was caused by toxicity of the employed regimen.

Radiotherapy of the involved site (limited field radiotherapy) or radiation pre-planned to occur at the conclusion of systemic cytotoxic therapy will not be considered a separate prior line of therapy.

The administration of a mAb alone with a curative/therapeutic intent (e.g., RTX monotherapy) counts as a separate line of therapy. On the other hand, the addition of a mAb to chemotherapy or mAb maintenance treatment subsequent to chemotherapy/chemoimmunotherapy regimen is considered one treatment therapy line, provided that the mAb was part of the initial treatment plan.

As for the ASCT, the induction, consolidation, stem cell collection, preparative regimen including transplantation, and maintenance will be considered a single line of therapy.

7.8.2 Growth Factors

Growth factors may be prescribed during the treatment and follow-up periods at the investigator's discretion, according to institutional standards. Growth factors or platelet, transfusions should not be administered during the screening period solely for the purpose of improving a patient's blood values in order to meet eligibility criteria.

7.8.3 Anticancer Therapies

Patients should not have received a CD20 targeted therapy, chemotherapy, radiotherapy, investigational anticancer therapy or other lymphoma specific- therapy within 14 days prior to Cycle 1 day 1 of the study. In addition, no radiotherapy (including limited field radiotherapy) is permitted after the baseline PET/computed tomography (CT) scan for initial disease assessment has been performed. Other than the study drugs, patients should not receive any other DLBCL specific- therapy during the study treatment period. The patient should not receive any investigational agent other than tafasitamab and LEN during the treatment period of the study.

After disease progression has been recorded, additional antineoplastic therapies are permitted at the discretion of the investigator and in accordance with the local guidelines and should be recorded in the eCRF.

7.8.4 Systemic Glucocorticosteroids

The use of systemic glucocorticosteroids is generally discouraged unless as part of pre-medication as described in Section 7.1.3 because their potential anti-lymphoma activity in patients with DLBCL may confound interpretation of antitumor effects mediated by study treatment (tafasitamab and LEN).

Additionally, systemic corticosteroids is allowed in doses up to 20 mg/day prednisone or equivalent (i.e. equipotent corticosteroid) are permitted, provided the dosing is stable (not increased within the last month), but only for the treatment of non-neoplastic comorbid indications (e.g., rheumatoid arthritis).

7.8.4.1 Screening

Patients may potentially receive systemic glucocorticosteroids in doses above 20 mg/day (prednisone or equivalent) to manage severe DLBCL manifestations (e.g., compressive disease, rapidly progressing symptomatic adenopathy) during Screening as per institutional standards. For these patients the glucocorticosteroids treatment needs to be tapered to a total daily dosage of 20 mg or less of prednisone or its equivalent prior to study treatment(s) administration on Cycle 1, Day 1.

7.8.4.2 Cycle 1 Through EOT Visit

Systemic glucocorticosteroids in doses above 20 mg/day (prednisone or equivalent) are not allowed during **Cycle 1 through EOT visit**, with the exceptions of pre-medication, CRS treatment at any time. Additionally, systemic doses above 20 mg/day (prednisone or equivalent; please refer to Appendix 9: Equivalent Doses for Corticosteroids) will be allowed for antiemetic prophylaxis for up to 24 hours.

In the event a patient experiences an exacerbation of a chronic non-neoplastic condition such as COPD, bronchial asthma or rheumatoid arthritis, peak doses above 20 mg/day (prednisone or equivalent) may be allowed for a limited period of time; the glucocorticosteroid dosage and the allowable treatment period will be determined by the investigator on a case-by-case basis following agreement with the medical monitor of the study. The specified systemic glucocorticosteroid use at a daily dose above 20 mg, if short in duration, is not likely to confound the treatment effect and efficacy analysis.

Similarly, patients who develop severe or life-threatening conditions that may be alleviated by systemic glucocorticosteroid therapy (e.g., adrenal insufficiency) are permitted to receive such drugs and are not required to discontinue study participation.

The investigator should aim to discuss the systemic usage of glucocorticosteroids in doses above 20 mg/day (prednisone or equivalent) with the medical monitor of the study prior to the implementation.

7.8.4.3 Other Provisions on Glucocorticosteroids

Single dose, topical, intranasal, inhaled eye drops or local injections (e.g., intra-articular) containing corticosteroids are permitted during study participation.

Immunosuppressive therapies other than systemic glucocorticosteroids as described are not permitted.

7.8.5 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 careful benefit-risk assessment in patients receiving LEN.

7.9 Prohibited Medication/Therapy

No 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.

The patient may not receive any investigational agent other than tafasitamab and LEN during the treatment period of the study.

After disease progression/relapse has been observed, additional anti-lymphoma therapies are permitted at the discretion of the investigator and in accordance with the local treatment guidelines. These therapies should be recorded in the eCRF as next anti-lymphoma treatments.

Live vaccines must not be administered to patients during the treatment and up-to 90 days after the last dose of the study drug in this study. Killed, inactivated vaccines, such as an injectable annual influenza vaccine, are permitted. Investigators should follow institutional guidelines concerning infection chemoprophylaxis for patients regarded to be at high risk for infection. See Appendix 7: COVID-19: Infection Prophylaxis and Vaccines.

7.10 Rescue Medication

Not applicable.

7.11 Restrictions

Note: LEN is structurally related to thalidomide. Thalidomide is a known human teratogenic substance that causes severe life-threatening birth defects. If LEN is taken during pregnancy, a teratogenic effect can be expected. Therefore, LEN is contraindicated during pregnancy. In FCBP LEN is contraindicated unless the conditions for pregnancy prevention are complied with Appendix 13: Contraceptive Guidance and Collection of Pregnancy Information.

Patients should refrain from donating blood during the course of study and for 3 months after the last dose of study treatment.

7.11.1 Restrictions Applicable in All Countries Except US

- All men and all women of childbearing potential should undergo counselling on the need to avoid pregnancy.
- Patients should be capable of complying with the requirements of safe use of LEN
- Patients must be provided with appropriate patient educational brochure and patient card

The following restrictions apply while the patient is receiving study treatments and for the specified times before and after:

- FCBP should use reliable methods of contraception at least 4 weeks prior to start of study treatments until 3 months after discontinuing study treatments. Acceptable methods of contraception include true abstinence, implant, tubal ligation, levonorgestrel releasing intrauterine system, medroxyprogesterone acetate depot, ovulation inhibitory progesterone-only pills (i.e., desogestrel) and vasectomized partner (vasectomy must have been confirmed by two negative semen analyses). All these methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse

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

- True abstinence is part of the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to the investigational product, and withdrawal are not acceptable methods of contraception. If FCBP wish to become pregnant they should be advised to arrange for the freezing of oocytes prior to the start of study treatment
- Male patients should avoid unprotected sex with a FCBP during treatment with the study treatments and for a washout period of 3 months. Patients should refrain from donating sperm from the start of dosing until 3 months after discontinuing study treatments. If male patients wish to father children, they should be advised to arrange for freezing of sperm samples prior to the start of study treatment

7.11.2 Restrictions Applicable in US

- All men, and all women of childbearing potential should undergo pregnancy and risk interview and counselling on the need to avoid pregnancy, including contraception requirements (females), barrier contraception requirements (males), true abstinence and emergency contraception
- Patients should be capable of complying with the requirements of safe use of LEN
- Patients must be provided with an appropriate patient educational brochure and a patient card. The following restrictions apply while the patient is receiving study treatments, and for the specified times before and after:
    - FCBP should use at the same time 2 effective methods of contraception (at least one highly effective method and one effective method, (see below for definition) each time when engaging in sexual activity with a male, starting at least 4 weeks before taking the study treatment, while taking the study treatment, during breaks (dose interruptions), and for at least 3 months after stopping the study treatment. True abstinence (see below for definition) from heterosexual sexual intercourse is also an acceptable method of contraception. The use of emergency contraception is also permitted. If females of child-bearing potential wish to become pregnant they should be advised to arrange for freezing oocytes prior to the start of study treatment

- Male patients should use latex or synthetic condom each time they have sex with an FCBP while taking the study treatment, during breaks (dose interruptions), and for at least three months after stopping the study treatment. True abstinence (see definition below) from heterosexual sexual intercourse is also an acceptable method of contraception. The use of emergency contraception is permitted

Highly effective birth control methods: Intrauterine device, hormonal methods (birth control pills, hormonal patches, injections, vaginal rings, or implants), tubal ligation, partner's vasectomy.

True abstinence: true abstinence is part of the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to the investigational product, and withdrawal are not acceptable methods of contraception.

Additional effective birth control methods: male latex or synthetic condom, diaphragm, cervical cap.

Unacceptable methods of birth control: progesterone-only "mini-pills", intrauterine device Progesterone T, female condoms, natural family planning (rhythm method) or breastfeeding, fertility awareness, withdrawal, and cervical shield (A cervical shield should not be confused with a cervical cap, which is an effective method of contraception).

7.12 Treatment After the End of the Study

If the study is terminated early by the Sponsor for reasons other than safety, alternative methods of drug supply may be considered for patients that are benefitting from treatment, in accordance with local regulatory guidance.

The Sponsor does not have any plans to provide study treatment to patients after the end of the study.

End of Study: The end of the study is reached when all patients still on study treatment have been followed for at least 3 years, or when the final patient on study has completed their last visit, whichever comes first.

Patients who are receiving ongoing treatment at the end of study may continue treatment with either of the options below upon assessment of a clinical benefit of continued treatment by the investigator and in accordance with the local regulatory guidance:

- commercially available tafasitamab for the approved dose regimen locally; or
- participation in the tafasitamab extension study if above option is not available

End of study visit for a patient: An end of study visit for a patient is defined as the visit taking place when the patient has completed 90-day safety follow up after the last tafasitamab dose given.

8 PATIENT DISCONTINUATION

8.1 Discontinuation From the Study

A patient may withdraw from participation in the study at any time at his/her own request or may be removed at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. If such premature discontinuation occurs, the investigator should determine the primary reason for a patient´s premature discontinuation from the study and record the information in the eCRF. If the reason for premature discontinuation is an adverse event, monitoring should continue until the outcome is evident, unless the patient has withdrawn his/her consent to study participation.

If the patient withdraws consent, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

See SoA (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2 Discontinuation of Study Treatment

Study treatment must be discontinued for a patient under the following circumstances:

- Pregnancy or expressed intend to become pregnant
- Disease progression
- Withdrawal of consent
- Use of prohibited treatment, including participation in another interventional study and/or initiation of new anti-cancer treatment (see Section 7.9 for details)
- Unacceptable toxicity or TEAE, as determined by the investigator
- Protocol Deviation that may impact the benefit/risk assessment for the individual patient following discussion with the Medical Monitor
- Occurrence of new diseases that could influence the treatment efficacy, for which the study medications are contraindicated or that are treated with a medication that is not permitted as a concomitant medication
- Any other medical condition that may jeopardize the patient's safety if he or she continues on study treatment

The investigator is encouraged to keep a patient experiencing clinical benefit on study treatment per investigator discretion unless significant toxicity puts the patient at risk or repeated cases of routine noncompliance put the study outcomes at risk.

An End of Treatment visit must be performed within 14 days after decision on treatment discontinuation. See the SoA (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

Patients who are withdrawn for any reason may not re-enter this clinical study at any time.

8.3 Lost to Follow-Up

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

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

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (at least 3 attempts should be made). These contact attempts should be documented in the patient's medical record
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up, which will be recorded in the eCRF

8.4 Replacement of Patient

If a patient discontinues the study for reasons other than safety before the completion of the predefined safety observation window (35 days from C1D1), this patient may be replaced.

9 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Section 2.

Adherence to the study design requirements, including those specified in the SoA (see Section 2), is essential and required for study conduct.

Protocol waivers or exemptions are not allowed, except where necessary to eliminate an immediate hazard to study patients.

9.1 Demographic and Baseline Characteristics

Demographic variables to be recorded include year of birth/ age, gender, and race/ ethnicity.

Relevant medical history and current medical conditions data includes data until signature of the ICF. The assessment of the lymphoma should include disease staging. In order to reflect the patient's status at the time of screening, the standard Ann Arbor staging system used for DLBCL 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 10: International Prognostic Index and Ann Arbor Staging Classification). Additionally, the disease risk assessment as per International Prognostic Index (IPI) (see Appendix 10: International Prognostic Index and Ann Arbor Staging Classification) and patient status as per ECOG performance status criteria (see Appendix 11: ECOG Performance Status Scale) will be recorded.

9.2 Physical Examinations

Physical examination will be performed by the investigator or a qualified designee according to the SoA (see Section 2).

Full PE must be performed according to the best standards of local medical practice but should include at least vital signs and palpable tumor assessments, general appearance, skin, head, eyes, ears, nose, throat including Waldeyer lymphatic structures, lungs, breasts and axillae, cardiovascular system, back and spine, abdomen (if applicable including spleen size below the costal margin), extremities, infusion site, lymph nodes, and neurological examination. Limited physical examination will be guided by the individual patient's status and will include body systems associated with symptoms and/or the underlying DLBCL disease (lymph node status, liver, spleen). Limited physical examinations may be focused on tumor response assessment (e.g., lymph node status, liver, spleen) and AEs per investigator discretion.

9.3 Efficacy Assessments

Efficacy will be evaluated in terms of ORR, DoR and PFS. The ORR is defined as the proportion of patients with a best overall response of CR or PR (ORR = CR + PR) based on local radiological + clinical evaluations up until disease progression or end of treatment, whichever is earlier.

Disease response assessments will be made according to the revised response criteria based on the guidelines of the IWG reported by Cheson *et al.* (2007) (see Appendix 4: International Working Group Resource Criteria for Malignant Lymphoma. All response assessments made by the local radiology + clinical review will be considered for the efficacy analysis.

9.3.1 Radiographic Imaging Assessment

Initial disease and disease response assessments will be made by positron emission tomography PET CT (CT should be done with IV contrast) or PET-MRI at the time points indicated in the SoA (see Section 2). Additional radiographic assessments may be performed by the investigator during the course of the study, if deemed necessary.

If progression/relapse is suspected on the basis of clinical symptoms, PET-CT or PET-MRI should be performed to confirm disease progression.

Tumor measurements and disease assessment (local) will be performed as indicated in Section 2 by CT. The CT portion of PET/CT will be acceptable in place of CT for tumor measurement and disease assessment, *only* when the CT portion is of adequate diagnostic-quality, and using adequate intravenous contrast.

Magnetic resonance imaging (MRI) may be used in lieu of CT, and PET-MRI in lieu of PET-CT for patients with contraindications to the administration of contrast agents, or due to other medical reasons, at the same time points as CT, or in addition to CT, at the discretion of the investigator (in this case, MRI may be performed as/when appropriate). The method used at baseline should be used throughout the study unless otherwise medically indicated.

If available and of acceptable quality, previously performed PET-CT or PET-MRI examinations, in accordance with the standard of care, that were done up to four weeks prior to the date of informed consent may be used for a patient's baseline radiology assessment. Additional PET-CT

or PET-MRI or CT or MRI examinations may be performed by the investigator in the course of the study, if deemed necessary (e.g., to confirm the occurrence of a CR or to make important treatment-related decisions). Whenever feasible, in such cases the investigator should seek prior approval of the sponsor for the additional imaging.

If the patient discontinues from treatment, a PET-CT or PET -MRI scan is only required at the EOT Visit if it was not performed in the cycle prior to the end of treatment or if disease progression was not already radiologically confirmed. CT may be performed in lieu of PET-CT if the patient discontinues from treatment within Cycle 1

The same scan modality should be used for all assessments, and all patients are required to have scans of the neck/chest/abdomen/pelvis.

If it is impossible for the patient to have their PET examination in fasted state, adequate procedures should be in place to measure and control blood glucose level.

9.3.2 Bone Marrow Assessment

Histological examination of the bone marrow should be performed locally at the protocol specified time-points as indicated in the SoA (see Section 2).

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

The achievement of CR in the course of study must be confirmed locally, by clinical and radiologic evaluation along with bone marrow confirmation. The latter applies only in case the bone marrow was involved by lymphoma before study entry. If bone marrow was not involved by lymphoma before commencing the study treatment, then bone marrow confirmation biopsy is not required. The repeated bone marrow examination is also not required for patients in whom bone marrow has already been cleared of the infiltrate at previous evaluation, i.e. their previous response was CR.

9.4 Safety Assessments

9.4.1 Vital Signs

Vital signs will be measured at the time points described in the SoA (see Section 2).

They will include temperature, systolic and diastolic blood pressure, pulse and respiratory rate.

Vital signs are to be obtained pre-tafasitamab infusion, and then at least 3 times during the infusion, and as clinically indicated.

Vital signs will be measured immediately prior to infusion, 15 ± 5, 30 ± 10, and then every 60 ± 15 minutes during infusion and at end of infusion (± 20 min). The actual time of vital sign measurements should be accurately documented. If the infusion is interrupted and/or subsequently restarted, vital signs should be assessed every 60 ± 15 minutes after the first hour. The frequency or the length of the monitoring period may be adapted if clinically indicated, for example if in the opinion of the investigator the vital sign results, at the time of event onset, are clinically significant. In such a case the patient's vital sign measurements should continue to be recorded until they have returned to normal or pre-infusion levels and an AE recorded.

All supportive measures consistent with optimal patient care will be provided throughout the study according to institutional standards. The observation of patients after the infusion is recommended, however, the duration and potential monitoring of vital signs should be determined by the investigator based on clinical judgement in accordance with local/practice guidelines of the institution. The Sponsor recommends that the investigators consider hospitalization on C1D15 for patients who experienced infusion related events during previous infusions on C1D1, C1D4 and/or C1D8 with 12 mg/kg tafasitamab or if otherwise clinically indicated.

In case of hospitalization of patient as a prophylactic measure in accordance with local/practice guidelines of the institution will not be reported as AE/SAE.

If possible, before vital signs are measured, the patient should be resting for at least 5 minutes. The same position should be used each time vital signs are measured for a given patient, and blood pressure should be measured from the arm contralateral to the site of study drug administration.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g., television, cell phones).

Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF

Body temperature should be measured according to normal hospital practice.

Any clinically significant changes occurring during the study should be recorded in the AE section of the eCRF.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

9.4.2 Electrocardiograms (ECGs)

Standard local 12-lead resting ECGs will be obtained at the various time points described in the SoA (see Section 2). Ideally, ECGs will be recorded after the patient has rested in a supine position for at least 5 minutes. Heart rate, PR, QRS, RR and QT intervals will be recorded.

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

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

9.4.3 Pregnancy

Details of all pregnancies in female patients and female partners of male patients will be collected after the start of study treatment and until 3 months after the last dose of study treatment.

If a pregnancy is reported/ detected, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 13: Contraceptive Guidance and Collection of Pregnancy Information. Every infant has to be followed up for up to 3 months after delivery.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.4.3.1 Pregnancy Testing

A pregnancy test will be performed for FCBP at various time points (in accordance with lenalidomide SmPC/USPI), either by urine pregnancy test or beta-human chorionic gonadotropin (β-HCG) test of a serum sample as specified in the SoA (see Section 2). The pregnancy test assay should have a minimum sensitivity of 25 IU/mL.

Applicable in all countries except US: FCBP must have two negative pregnancy tests prior to starting the study treatment, even if true abstinence is the chosen method of birth control. The first pregnancy test must be performed during screening and the second pregnancy test must be performed within the 24 hours prior to the start of study treatment. The patient must not receive study treatment until the investigator or designee has verified that the results of these pregnancy tests are negative. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. Lenalidomide treatment must be discontinued during this evaluation.

Applicable in US: FCBP must have two negative pregnancy tests prior to starting study treatment, even if true abstinence is the chosen method of birth control. The first pregnancy test must be performed within 10-14 days before study treatment initiation, the second pregnancy test must be performed within 24 hours prior to the start of study treatment. The patient must not receive study treatment until the investigator or designee has verified that the results of these pregnancy tests are negative. See Appendix 13: Contraceptive Guidance and Collection of Pregnancy Information for more information. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. Lenalidomide treatment must be discontinued during this evaluation.

9.4.4 Viral Serology

Patients will be examined locally according to the schedule in Section 2 for viral hepatitis B and hepatitis C.

Hepatitis B biomarkers include hepatitis B surface antigen (HBsAg), total anti-hepatitis B core antibody (HBcAb) and anti-hepatitis B surface antibody (anti-HBsAb). Patients with a positive test for anti-HBc can only be included if hepatitis B virus (HBV) deoxyribonucleic acid (DNA) is not detected. **In these patients only**, HBV DNA should be assessed at various subsequent visits as outlined in Section 2.

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

- HBsAg positive
- HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable HBV DNA

Note: Patients who are HBsAg negative, anti-HBc positive and HBV DNA negative are eligible.

Note: Patients who exhibit the classical vaccination profile of anti-HBs positive, anti-HBc negative, and HBsAg negative are eligible.

If HBV DNA becomes detectable during treatment, patients should be prophylactically treated and followed-up for potential hepatitis B reactivation. If the HBV-DNA assay is positive, then patients 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.

Hepatitis C serology is to be done at screening only. Hepatitis C biomarkers include anti-hepatitis C virus (HCV) antibody. For patients who are positive for anti-HCV antibody, HCV-ribonucleic acid (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.

9.4.5 Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments, as defined in Table 16 must be conducted in accordance with the SoA (see Section 2).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Laboratory results are required for determining patient eligibility for study enrollment and as a prerequisite prior to study drug administration. Samples will be collected and evaluated in the local laboratory (can be done on the day before study drug administration). The investigator or designee must review laboratory results before dosing so that the administration of the IMP may be adjusted or paused if necessary.

The investigator must document this review and record any clinically significant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All abnormal laboratory test values considered clinically significant during participation in the study (until 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.

During screening, it is permitted to repeat the local laboratory assessment of serum chemistry and hematology parameters due to the variability of the parameters and their dependence on multitude of factors (e.g., hydration, muscle mass). This is, 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 (e.g., dehydration, imaging procedure with a contrast, pre-phase treatment). This procedure and the rationale behind it must be explicitly documented in source data. Such repeated assessment of the concerned parameters will not be counted as "re- screening" for that patient.

The laboratory results including sampling time/date will be kept in the patient's source documentation and reported in the eCRF. All blood samples will be processed and handled according to standard laboratory procedures.

Table 16: Local Laboratory Assessments

Laboratory Test	Parameter
Urinalysis	Appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, urobilinogen. Microscopy will only be performed if clinically indicated
Pregnancy tests in FCBP	Refer to Section 9.4.3.1
Hematology	WBC with differential count (lymphocytes, monocytes, neutrophils, band neutrophils*, eosinophils, basophils), hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, platelet count, RBC count, erythrocyte sedimentation rate *Band neutrophils may be performed optionally.
Serum chemistry	ALT, total albumin, ALP, amylase, AST, bicarbonate, bilirubin (total), urea or blood urea nitrogen, total calcium, chloride, creatinine, creatine kinase, GGT, glucose, LDH, lipase, phosphate, potassium, protein (total), sodium, uric acid, magnesium, β2-microglobulin, C-reactive protein, HbA1c in patients with diabetes mellitus II, TSH
Coagulation	aPTT or PTT, PT and /or INR (In accordance with the local institutional practice. Ideally both PT and INR should be provided).
Hepatitis serology/virology	Refer to Section 9.4.4

Abbreviations: ALT=alanine aminotransferase; ALP=alanine phosphatase; AST=aspartate aminotransferase; FCBP=female of childbearing potential; GGT=gamma-glutamyl transferase; HbA1c=glycated hemoglobin; LDH= lactate dehydrogenase; RBC=red blood cell; WBC=white blood cells, TSH=Thyroid stimulating hormone

9.4.6 Diagnostic Lymphoma Biopsy and Central Pathology Review

For each participating patient suitable and sufficient archival tumor tissue material must be provided (see Section 6.1 on inclusion criteria). 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.

If archival formalin fixed paraffin embedded tumor tissue acquired ≤ 3 years prior to screening is not available, a fresh tumor tissue sample from the patient should be obtained. If a fresh tumor biopsy poses any risk to patient safety e.g. due to co-morbidity, age, or inaccessible tumor site, an earlier tumor tissue may be acceptable upon consultation with the medical monitor.

The local pathology report indicating DLBCL diagnosis will determine a patient's eligibility for study enrollment.

Central pathology review is mandatory, but retrospective in nature and not intended to determine a patient's eligibility. Tissue samples (or archival paraffin blocks, as stated above) should be submitted within 30 days of patient enrollment in the study. Patients can be enrolled prior to submission of tissue sample(s).

If the DLBCL diagnosis of the local pathologist cannot be confirmed by the central pathologist, and a patient's treatment has already commenced, they may remain in the study at the discretion of the treating physician.

Patients who received previous CD19 targeted therapy (other than tafasitamab) must have CD19 positive lymphoma confirmed on a biopsy (as per local institutional guidelines), taken since completing the prior CD19 targeted therapy.

The local pathology report indicating DLBCL diagnosis and CD19 positivity will determine a patient's eligibility for study enrollment. In this patient group, a sample of this most recent biopsy should be provided for central pathology confirmation of both DLBCL diagnosis and CD19 expression. Only the most recent biopsy needs to be provided, it is not necessary to provide tissue taken at different stages of disease.

9.4.7 AEs, SAEs and AESI

The definitions of an AE or SAE can be found in Appendix 12: AEs: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

AEs of Special Interest (AESIs) are defined in Section 9.4.7.4.

The patient (or, when appropriate, a caregiver, surrogate) informs the investigator about any AEs.

The investigator is responsible for detecting, documenting, recording, and following up on events that meet the definition of an AE, AESI or SAE.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE and AESI reports are provided in Appendix 12: AEs: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

9.4.7.1 Time Period and Frequency for Collecting AE, SAE and AESIs Information

All AEs, SAEs and AESIs will be collected and recorded in eCRF from the signing of the ICF until the end of study visit.

If the investigator learns of any SAE/AESI, including a death, at any time after a patient has completed the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

Medical occurrences that begin before obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

All SAEs and AESIs will be reported to the sponsor or designee within 24 hours, as indicated in Appendix 12: AEs: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting. The investigator will submit any updated SAE and AESI data to the sponsor within 24 hours of it being available.

9.4.7.2 Follow-Up of AEs, SAEs and AESIs

After the initial AE/SAE report, the investigator is required to proactively follow up on each event at subsequent patient visits/contacts. During patient's participation in the study all events will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 8.3). After End of Study visit only SAEs and AESIs will be followed. Further information on follow-up procedures is given in Appendix 12: AEs: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

9.4.7.3 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met
- The sponsor will comply with regulatory requirements relating to safety reporting to the regulatory authorities, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators
- The sponsor must prepare safety reports for suspected unexpected serious adverse reactions (SUSARs) according to applicable regulatory requirements and sponsor policy, and will provide to investigators, as applicable
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., 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 and unless such reporting to IRB/IEC is performed by the sponsor

9.4.7.4 AESIs

AESIs for this study are:

- TLS
- IRRs and allergic reactions to study treatment ≥ Grade 3
- CRS
- Second primary malignancies
- Hepatitis B reactivation
- Progressive multifocal leukoencephalopathy (PML)
- TFR

9.4.8 B-Symptoms, ECOG Performance Status

B-symptoms and ECOG performance status will be assessed at the time points indicated in the SoA (see Section 2). Refer to Appendix 10: International Prognostic Index and Ann Arbor Staging Classification and Appendix 11: ECOG Performance Status Scale for details.

9.4.9 Reporting of Treatment Errors, Misuse or Abuse

Study treatment errors and uses outside of what is foreseen in the protocol, including misuse or abuse, will be recorded in the dose administration eCRF.

The investigator should report symptoms associated with overdose as AE, and within 24 hours of awareness if symptoms meet the definition of an SAE (for definition of overdose refer to Section 7.4, definition of SAE refer to Appendix 12: AEs: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting).

The investigator should inform the sponsor within 24 hours of awareness of misuse and abuse and should follow the procedures for reporting of SAEs/AESIs as outlined in Appendix 12: AEs: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient**.** Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information. Abuse refers to persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

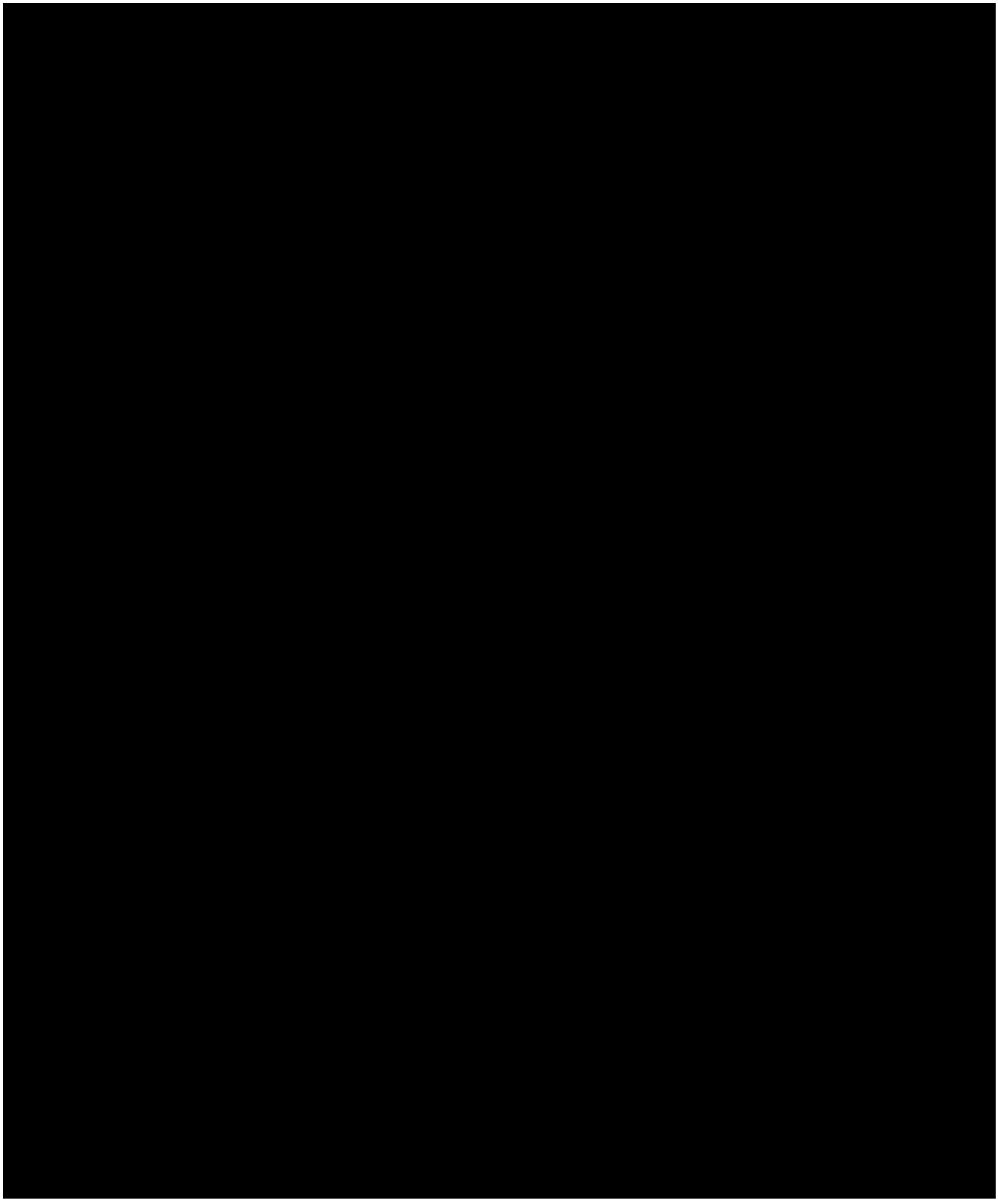
Study medication errors and uses outside as directed in the protocol, including misuse or abuse, will be recorded as protocol deviations. Any symptoms or signs associated with medication error, misuse or abuse should be reported as AEs in accordance with Section 9.4.7.

9.5 Pharmacokinetics and Immunogenicity

Blood samples for PK and Immunogenicity (tafasitamab ADAs) will be collected on the visits and time-points specified in the SoA (see Section 2).

The details of blood sample handling and shipment instructions will be provided in a separate laboratory manual.

Actual dates and times of PK and ADA blood sampling will be recorded in the eCRF.



10 STATISTICAL CONSIDERATIONS

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software version 9.3 or higher.

Continuous, quantitative variable summaries will include the number of patients (N) (with non-missing values/valid cases), mean, standard deviation, minimum, 25th quartile, median, 75th quartile and maximum, except for PK metrics, where additional statistics may be used.

Categorical, qualitative variable summaries will include the frequency and percentage of patients/entries in the particular category.

Definition of baseline value: the last pre-administration observation will be used as the baseline value for calculating post-administration changes from baseline.

All data obtained via the eCRF and entered into the database will be provided in separate data listings showing individual patient's values. A SAP detailing the statistical analyses will be finalized prior to first patient first visit.

The planning and reporting of statistical analysis will be carried out as described in the sponsor's SOPs governing clinical study.

The sponsor and/or designated contract research organization (CRO) will analyze the data. Any data analysis carried out independently by the investigator should be submitted to the sponsor before publication or presentation. It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis.

10.1 Sample Size Determination

As this is a Phase 1b/2 study, Primary, Secondary [redacted] endpoints will be analyzed using descriptive statistics. No formal statistical tests will be performed.

[redacted]

Primary completion analysis and final analysis are planned to be performed. Details will be provided in the SAP.

10.2 Populations for Analyses

Patients who were screened but never started study treatment will be listed. Screening failures will not be included in any of the summary tables (except of the patient disposition table).

10.2.1 Analysis Set for the Primary Estimand (PAS)

The PAS includes all patients who receive at least one [redacted], and had at least one post-baseline safety assessment.

A valid safety assessment includes death. A "no AE" record is also considered as a valid safety assessment.

10.2.2 Enrolled Patients

The Enrolled patient population consists of all patients who received at least one dose of any study treatment (tafasitamab or LEN).

10.2.3 Full Analysis Set (FAS)

The FAS includes all patients who received at least one dose of tafasitamab and one dose of LEN. This means that both study drugs must have been administered at least once. The FAS will be the primary population for the analysis of efficacy and baseline characteristics.

A listing showing the patients who have been excluded from the efficacy analysis will be provided.

10.2.4 Safety Set (SAF)

The SAF includes all patients who received at least one dose of tafasitamab or LEN and had at least one post-baseline safety assessment.

A valid safety assessment includes death. A "no AE" record is also considered as a valid safety assessment.

Analyses using the SAF will be based on the treatment study drug actually received.

10.2.5 PK Analysis Set (PKAS)

The PKAS will include all patients who received at least one dose of tafasitamab and have at least one quantifiable serum tafasitamab concentration.

10.2.6 Immunogenicity Analysis Set (IAS)

The IAS includes all patients who have at least one valid anti-tafasitamab antibody assessment.

10.2.7 Per Protocol Set (PPS)

Patients included in FAS without any important protocol deviation that would influence efficacy endpoints.

All protocol deviations or conditions leading to exclusion from the PPS will be detailed in the data handling plan and SAP. Sensitivity analyses for efficacy endpoints may be performed using PPS.

PAS is used to estimate the PAS and SAF is used to estimate the supplemental estimand for the primary objective.

10.3 Statistical Analyses

A SAP detailing the statistical analyses will be finalized prior to first patient first visit. Details of the analyses to be performed on data from this study will be provided in a separate SAP. All analyses will be presented [redacted]) and whenever applicable, overall.

Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the clinical study report.

Missing values will not be substituted by estimated values, but treated as missing in the statistical evaluation. All data from all patients dosed in the clinical study will be included in all listings, plots, summary tables, and statistical analyses where appropriate.

If a patient discontinues the study for reasons other than safety before the completion of the predefined safety observation window, this patient may be replaced.

In the event of a significant volume of missing data, sensitivity analyses for the efficacy [redacted] endpoints may be performed using the principle of multiple imputation.

This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

10.3.1 Analysis Time Points

The following analyses are pre-planned: An internal DSMC, consisting of Sponsor representatives and investigators, will continuously monitor the study and can recommend to stop enrollment at any time based on emerging safety data. In addition, pre-defined DSMC meetings will take place when [redacted]

Patient profiles and Listings of AEs will be provided in case a DSMC Safety Data Review is performed.

10.3.1.1 Primary Analysis

Primary analysis will be performed when all patients have either reached C3D28 or discontinued the study prior to C3D28.

Primary and Secondary Objectives will be analyzed at the time of primary analysis completion. Details will be provided in the SAP.

10.3.1.2 Final Analysis

The final analysis of the study will occur approximately 3 years after the last patient was enrolled.

At the time of Final Analysis, analyses performed during Primary Analysis will be repeated using updated data in addition to the performance of Secondary [redacted] objectives.

Additional analyses for safety or efficacy endpoints may be performed if needed or if requested by authorities.

10.3.2 Efficacy Analyses

Disease response assessments will be made according to the revised response criteria based on the guidelines of the IWG reported by Cheson *et al.* (2007) (see Appendix 4: International Working *Group* Resource Criteria for Malignant Lymphoma).

10.3.2.1 Best ORR Until EOS by Investigator Assessment (Secondary Endpoint)

The best ORR by investigator assessment is defined as the proportion of patients with CR or PR based on the best response achieved until the end of study. The best ORR along with 95% exact CI (using Clopper-Pearson exact method) will be presented. The number and percentage of patients with CR or PR will be presented.

10.3.2.2 Duration of Response (DoR) by Investigator Assessment (Secondary Endpoint)

DoR is defined as the time interval between the initial time point of tumor response (CR or PR whichever status is recorded first) and the first date that recurrence of progressive disease is documented. Response duration by the local assessment (investigator) will be tabulated with descriptive statistics.

Disease progression is defined as the first occurrence of progressive disease according to the revised response criteria (Cheson *et al.,* 2007) as assessed by the investigator.

10.3.2.3 Progression-Free Survival by Investigator Assessment (Secondary Endpoint)

PFS is defined as the time from the date of randomization to the date of the first radiologically documented disease progression or death due to any cause. If a patient has not progressed or died at the analysis cut-off date or when he/she receives further anti-neoplastic therapy, PFS will be censored on the date of the last adequate tumor evaluation before the earlier of the cut-off date or start of the further antineoplastic therapy date.

Kaplan Meier plots will be used to estimate the distribution of PFS. The PFS probabilities and the associate 95% CI will be summarized.

10.3.3 Safety Analyses (Primary Endpoint)

The primary objective of this study is to evaluate the safety and tolerability of [redacted] tafasitamab i.v. [redacted] combined with LEN in patients with R/R DLBCL.

As this is a Phase 1b/2 study, no formal hypothesis testing will be performed.

To assess safety and tolerability, the incidence and severity of hematological and non-hematological AEs including clinically significant laboratory abnormalities will be determined. AEs will be categorized with regards to seriousness, intensity, toxicity, study treatment relationship, outcome and action taken. AE reports will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE), version 5.0.

All Safety Analyses will be presented by [redacted].

10.3.4 Patient Disposition

An overview table will be provided for all patients and will include the number of patients enrolled, the number of patients in each analysis population set, the number of completers and the number of withdrawals and the reasons for withdrawal. Compliance parameters for drug administration will be tabulated.

Demographic information will be summarized using descriptive statistics or counts and percentages.

General medical histories and DLBCL-specific medical histories will be summarized by counts and percentages using appropriate classification codes. Concomitant medications will be recorded and tabulated with counts/percentages showing the number of medications/percentages used in each medication class.

10.3.5 Additional Secondary Endpoint Analyses

10.3.5.1 Pharmacokinetic Analysis

Tafasitamab serum concentrations will be summarized using descriptive statistics. Mean concentrations (on original and on log-linear scale) will be visualized in figures.

In addition, tafasitamab PK data will be used for population PK analysis. Details of the intended population PK analysis will be described in a separate analysis plan and results of the analysis will be described in a separate population PK report.

10.3.5.2 Immunogenicity Analysis

The absolute number and percentage of patients, who develop anti-tafasitamab antibodies, and the results of anti-tafasitamab antibody titer determinations of confirmed positive samples will be tabulated.

10.3.7 Additional Safety Analysis

10.3.7.1 AEs

All AEs which start or worsen on or after the first dose of study treatment until 90 days after the last dose of the study treatment, i.e. of end of the study, will be considered as a TEAE. AEs that start during the study (and did not worsen after the first dose of study treatment) but before the time of the first dose of study treatment (e.g. screening period) will be classified as a non-TEAE and will be included in AEs listings, but will not be summarized.

TEAEs will be coded according to MedDRA System Organ Class (SOC) and preferred terms classifications. Incidence and frequency of all AEs will be summarized by SOC, preferred term, relationship to treatment, severity and seriousness.

An AE summary table will be presented showing the number of events, number of patients and the percentage of patients in each arm and overall having:

- All TEAEs
- TEAEs by maximum severity
- SAEs
- Drug-related TEAEs
- Drug-related TEAEs in each severity/toxicity grading
- TEAEs that led to treatment discontinuation
- IRRs by grade

AEs of Special Interests in this study are defined in Section 9.4.7.4.

The sponsor will describe AESIs, in addition to those reported as SAEs. AESI tabulations will be analogous to the tabulation of TEAEs.

The sponsor will describe other significant AEs as appropriate, e.g., laboratory abnormalities that qualify as AEs (other than those meeting the definition for serious) and any events that led to an intervention (including premature discontinuation of IMP, increase of dose interval, or significant additional concomitant therapy), in addition to those reported as SAEs.

In addition to the investigator's evaluation of normal or abnormal, the sponsor will internally evaluate each clinical laboratory result, vital sign result, and ECG result for whether it reflects a *new abnormality*, and for numeric data, whether it reflects a *significant worsening* from baseline or an *outlying result* or *extreme value*. These terms are defined for clinical laboratory results, vital sign results, and ECG results as follows:

- A new abnormality will be any abnormal post baseline result for a patient whose baseline was within normal limits
- A significant worsening will be any numeric clinical laboratory result, vital sign result, or ECG interval measurement that represents a change from baseline by ≥ 25% of the baseline value, in the direction away from normal (i.e., in the direction that is clinically significant)
- An outlying result for any numeric laboratory result, vital sign result, or ECG interval measurement will be any post-administration change from baseline that meets either of the following criteria:

  <25th Percentile - 1.5 * (interquartile range) OR
  >75th Percentile + 1.5 * (interquartile range)

- An extreme value for any numeric laboratory result, vital sign result, or ECG interval measurement will be any post-administration change from baseline that meets either of the following criteria:

  <25th Percentile - 3 * (interquartile range) OR
  >75th Percentile + 3 * (interquartile range)

Patients who demonstrate new abnormal results will be noted in data listings. All results showing a significant worsening will be noted in data listings. Outlying results or extreme values will be identified and reviewed in the context of the patient's other abnormal results.

10.3.7.2 Clinical Laboratory Evaluation

The analysis of local laboratory parameters for each treatment arm will be presented, separated into blood parameters (e.g., hematology, serum chemistry, coagulation, serology for hepatitis B and C) urine parameters (e.g., urinalysis) and serum pregnancy test.

All data collected in the course of the study will be listed.

The following analyses will be performed, where appropriate, for measurements of hematology and blood chemistry tests:

- Standard descriptive statistics for values measured at baseline and post-baseline visits including changes from baseline
- For selected laboratory parameter, shifts in assessments from baseline to worst-post baseline value
- Number (and percentage) of patients with clinically significant changes for selected tests

Each abnormal value measured in the local laboratory will be flagged to show whether it is a value below or above the reference range for the given local laboratory. For the assessment of laboratory variables, the investigator will need to judge their clinical significance.

The assessment of the clinical significance of central laboratory variables will be tabulated by time point for each clinical laboratory value using frequency tabulations.

Clinical laboratory values with available NCI-CTCAE grades may be presented with additional frequency and shift tables based on these grades.

Laboratory values that are outside the reference range will also be flagged in the data listings, along with the corresponding reference ranges.

The analyses will be performed on PAS and SAF. Further details will be specified in the SAP.

10.3.7.3 Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for vital signs. These summaries will be presented for the SAF at all time points. Each abnormal value will be flagged to show whether it is a value below or above the normal limit.

10.3.7.4 ECGs

Summary ECG assessment (categories: 'normal'; 'abnormal, clinically significant'; 'abnormal, not clinically significant') will be tabulated by time point using frequency tabulations.

Each result of the 12-lead ECG (PR, QRS, RR and QT interval values) will be flagged to show whether it is a value below or above the normal limit.

Summary statistics for all time points will be displayed for QT and both QTc correction methods. The Bazett's correction method for QTc will be applied as follows:

QT interval corrected for heart rate according to Bazett: (QTcB) = QT/ $\sqrt{RR}$
QT interval corrected for heart rate according to Fridericia: (QTcF) = QT/ $\sqrt[3]{RR}$

Where relative rate (RR) = 60/heart rate.

Also, the number and percentage of patients with QTc values above the normal limit (> 450 ms, > 480 ms, > 500 ms) and the number and percentage of patients who experienced a change ≥ 30 ms or a change ≥ 60 ms will be presented by time point.

10.3.8 Estimands

Table 17: The Estimand Summary

Objective	Analysis Population Set	Variable/ Endpoint	Treatment Condition of Interest	Handling of IEs	Population-Level Summary	Estimation
Primary objective: evaluate the safety and tolerability of [redacted] of tafasitamab in combination with LEN	PAS	Incidence and severity of TEAEs	Treatment consisting of tafasitamab and LEN combination will be administered until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first. LEN can be given for up to 12 cycles in total, after which patients can continue with tafasitamab as monotherapy until progression or unacceptable toxicity	1. Dose modifications, study treatment interruptions or non-adherence to study treatment: treatment policy strategy 2. Permitted concomitant medications: treatment policy strategy 3. Prohibited concomitant medication: while on treatment strategy 4. Withdrawal of consent: while on treatment strategy 5. Study discontinuation: while on treatment strategy	Cumulative incidence and severity of TEAEs in the population at risk until the last patient on study completes the 90-day safety follow-up visit	Categorical variable summaries including the frequency and percentage of patients/entries in the particular category

Abbreviations: IE=intercurrent events; LEN=lenalidomide; PAS=primary estimand; TEAEs=treatment-emergent adverse events.

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12 APPENDICES

12.1 Appendix 1: List of Abbreviations and Definitions of Terms

5PS	5-point scale
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-dependent cell-mediated phagocytosis
AE	Adverse event
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukemia
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
Anti-HBc	Hepatitis B core antibody
Anti-HCV	Anti-hepatitis C virus
aPTT	activated Partial thromboplastin time
ASCT	Autologous stem cell transplantation
AST	Aspartate transaminase
AUC	Area under the curve
β-HCG	Beta-human chorionic gonadotropin
BCL	B-cell lymphoma
BSC	Best supportive care
C1D1	Cycle 1 Day 1
CBC	Complete blood count
CD	Cluster of differentiation
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum concentration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COVID-19	Disease caused by SARS-CoV-2 (coronavirus)
CR	Complete response
CRO	Contract research organization
CRS	Cytokine release syndrome
CT	Computed tomography

[redacted]	[redacted]
C_{trough}	Minimum concentration
CSR	Clinical study report
dL	Deciliter
DLBCL	Diffuse large B-cell lymphoma
DLCO	Diffusing capacity of the lungs for carbon monoxide
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSMC	Data and Safety Monitoring Committee
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
EU	European Union
EU CTR	EU clinical trial regulation
FAS	Full analysis set
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FEV-1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
µg/mL	Micrograms per milliliter
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HbA1c	Glycated hemoglobin
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

HRT	Hormonal replacement therapy
IAS	Immunogenicity analysis set
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgA	Immunoglobulin A
IHC	Immunohistochemistry
IMP	Investigational medicinal product
INR	International normalized ratio
IPI	International prognostic index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion related reaction
i.v.	Intravenous(ly)
KG	Kilogram
µl	Microliter
LDH	Lactate dehydrogenase
Ldi	Longest transverse diameter
LEN	Lenalidomide
mAb	Monoclonal antibody
mg	Milligram
mL	Milliliter
mL/h	Milliliter per hour
mm	Millimeter
[redacted]	[redacted]
MRI	Magnetic resonance imaging
NCI-CTCAE 5.0	National Cancer Institute-Common Terminology Criteria for Adverse Events, version 5.0
NHL	Non-Hodgkin lymphoma
[redacted]	[redacted]
NOACs	New oral anticoagulants
NOAEL	No observed adverse effect level
NR	No response
ORR	Objective response rate
PAS	Primary estimand
PD	Progressive disease

[redacted]	[redacted]
PET	Positron emission tomography
PI	Prescribing information
PK	Pharmacokinetics
PKAS	Pharmacokinetic analysis set
PLM	Progressive multifocal leukoencephalopathy
PLT	Platelets
PMBL	Primary mediastinal large B-cell lymphoma
p.o.	By mouth
POP-PK	Population-PK
PPD	Cross product of the Ldi and perpendicular diameter
PPS	Per protocol set
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QTcB	QT interval corrected for heart rate according to Bazett
QTcF	QT interval corrected for heart rate according to Fridericia
QTLs	Quality tolerance limits
RBCs	Red blood cells
REAL	Revised European American Lymphoma (Classification)
RNA	Ribonucleic acid
R/R	Relapsed or refractory
RTX	Rituximab
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical analysis plan
SD	Stable disease
SDi	Shortest axis perpendicular to the LDi
SLL	Small lymphocytic lymphoma
SmPC	Summary of product characteristics
SoA	Schedule of assessments
SOC	System organ class
SPD	Sum of the product of the perpendicular diameters for multiple lesions
SUSAR	Suspected unexpected serious adverse reactions
TB	Tuberculosis
TFR	Tumor flare reaction
THRLBCL	T cell/histiocyte-rich large B-cell lymphoma

TLS	Tumor lysis syndrome
ULN	Upper limit of normal
US	United States
USPI	United States prescribing information
VTE	Venous thromboembolism
[redacted]	[redacted]
[redacted]	[redacted]
QW	Weekly
TEAE(s)	Treatment emergent adverse event(s)
V_{ss}	Volume of distribution at steady state
WFI	Water for injection
WHO	World Health Organization
w/v	Weight by volume

12.2 Appendix 2: Regulatory, Ethical, and Trial Oversight Considerations

12.2.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC and reviewed and approved by the Health Authority and IRB/IEC before the study is initiated.

Substantial amendments to the protocol will require Health Authority and IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

Depending upon the local regulation the investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC (directly or through the sponsor) in accordance with local regulations and the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC (directly or through the sponsor) 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 the protocol and other procedures specific to the study, requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- Notify the sponsor immediately of an event which might constitute a Serious Breach of the protocol or applicable regulations. A 'Serious Breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial. Contacts for reporting can be found in the Investigator Site File.

12.2.2 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the patient and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, the IRB/IEC, and study center as applicable.

The medical record must include a statement that written informed consent was obtained before conducting any study-specific procedures and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient.

12.2.3 Data Protection

Personal data will be protected in accordance with applicable laws and regulations. The sponsor has implemented appropriate technical and organizational measures to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss. These measures include for example pseudonymization of patient data, access being restricted to authorized persons and controlled using a unique username and a confidential password, encryption of the data during transfers, requirement that premises used for the storage and processing of personal data to be arranged in such a way as to prevent unauthorized access, secure archiving.

Patients will be assigned a unique identifier via the IRT system. The investigator will maintain a confidential patient identification code list in the investigator's study file, on which the investigator documents the names of all patients enrolled in the trial with their unique patient number. The investigator's study file, including the patient identification code list, will be retained at the clinical site according to local regulations; the patient identification code list will be destroyed at the end of the retention period. In order to maintain patient privacy, all eCRFs, study records and communications will identify the patient by the assigned patient number. Any patient records or datasets that are transferred to the sponsor will contain the identifier only , i.e. data is 'pseudonymized'; patient names or any information which would make the patient identifiable will not be transferred.

The use of pseudonymized data and the encryption of the data during transfers limits the risk of personal data security breaches. Should a personal data security breach occur, a process exists in the Data Protection Policy adopted by the sponsor to assess the facts and take mitigation actions as appropriate.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorized personnel appointed by the sponsor, by Quality Assurance auditors, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

12.2.4 Publication Policy

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 study only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated.

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

12.2.5 Dissemination of Clinical Study Data

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov and/or the EU Clinical Trials Register. In addition, upon trial completion and finalization of the trial report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.2.6 Data Quality Assurance

All patient data trial will be recorded on the eCRF by the trained personnel while specifying reasons for missing data (if any) transmitted to the sponsor or designee electronically. The investigator is responsible for verifying that data entries are accurate and correct by signing the CRF. The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact patient safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

The sponsor or designee is responsible for the monitoring and data management of this study including quality checking of the data. Monitoring details describing strategy, methods, responsibilities, and requirements, and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan. Data management details are provided in the Data Management Plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in accordance with local regulations. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.2.7 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. Current medical records must be available. The investigator may need to request previous medical records or transfer records from other institutions outside the clinical study site.

Definition of what constitutes source data can be found in the Investigator Source Data Agreement.

Study monitors will 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 patients 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.

12.2.8 Study and Site Closure

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.

The sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the sponsor. 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 or no recruitment of patients by the investigator

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate therapy and/or follow-up.

12.3 Appendix 3: Study Specific Definitions

For the purposes of this protocol, **primary refractory disease** is defined as a disease progressing in the course of the first line treatment as per International Working Group response criteria (Cheson *et al.,* 2007), and/or, showing a response of less than a PR to first-line treatment or disease recurrence/progression within ≤ 6 months from the completion of first-line therapy.

Disease refractory to last treatment is defined as having had less than a PR to the most recently administered systemic therapy.

Relapsed/progressive/recurrent disease reflects the appearance of any new lesions or increase by ≥50% of previously involved sites from nadir according to the International Working Group response criteria (Cheson *et al.,* 2007), after the most recent systemic therapy.

First act of recruitment (EU): For purposes of EU clinical trial regulation (536/2014) the first act of recruitment of a potential patient is defined as the date of initiation of the first site.

Start of study: A patient is considered to have started the study and entered the screening period when they have signed the informed consent form.

End of Treatment: The end of treatment is defined as the date when the patient has received last tafasitamab dose. An end of treatment visit will be performed within 14 days after decision on treatment discontinuation.

End of Study: The end of the study is reached when all patients still on study treatment have been followed for at least 3 years, or when the final patient on study has completed their last visit, whichever comes first.

Patients who are receiving ongoing treatment at the end of study may continue treatment with either of the options below upon assessment of a clinical benefit of continued treatment by the investigator and in accordance with the local regulatory guidance:

- commercially available tafasitamab for the approved dose regimen locally; or
- participation in the tafasitamab extension study if above option is not available

End of study visit for a patient: An end of study visit for a patient is defined as when the patient has completed 90 day safety follow up after the last tafasitamab dose given.

12.4 Appendix 4: International Working Group Resource Criteria for Malignant Lymphoma

Response Criteria

The response criteria in this study are those defined in the table below. All are based on the International Working Group Response Criteria (Cheson *et al.,* 2007).

Response	Definition	Nodal masses	Spleen, liver	Bone marrow
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative b) Variable FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohisto-chemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size on CT a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site b) Variable FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR but criteria for progressive disease not met	a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET b) Variable FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or progressive disease	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR=complete response; CT=computed tomography; FDG=[^{18}F]fluorodeoxyglucose; PET=positron emission tomography; PR=partial response; SD=stable disease; SPD=sum of the product of the diameters.

12.5 Appendix 5: Karnofsky Performance Status Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Source: Karnofsky and Burchena, 1949.

12.6 Appendix 6: Cockcroft-Gault Formula

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

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

When serum creatinine is measured in µmol/L:

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

Where *Constant* is *1.23* for men and *1.04* for women.

12.7 Appendix 7: COVID-19: Infection Prophylaxis and Vaccines

Live vaccines must not be administered to patients during the treatment and up-to 90 days after the last dose of the study drug in this study. Killed, inactivated vaccines, such as an injectable annual influenza vaccine, are permitted. Investigators should follow institutional guidelines concerning infection chemoprophylaxis for patients regarded to be at high risk for infection.

Whenever possible, relapsed/refractory patients who will be treated with immunosuppressive therapy including tafasitamab-containing regimens should start vaccination against COVID-19 as soon as possible, at least first dose, ideally approximately 2 weeks prior to study treatment start. Based on current safety/benefit considerations and in the absence of data or guidance to the contrary, we recommend that all patients with lymphoma should receive a COVID-19 vaccine (unless explicitly contraindicated), accepting that this might not achieve full protection due to the impaired humoral and/or cellular immunity.

For patients who are already on tafasitamab-[redacted], the advantages and disadvantages of delaying vaccination to allow immune recovery or interrupting therapy requires careful consideration on a case-by-case basis. The recommendation would be to vaccinate these patients despite the fact that may be unable to generate a fully protective immune response to a COVID-19 vaccine.

12.8 Appendix 8: Hepatitis Virus Serology

Patients will be examined according to the **SoA** for viral hepatitis B and C serology. Hepatitis B biomarkers include hepatitis B surface antigen (HBsAg), total anti-hepatitis B core antibody (anti-HBc) and anti-hepatitis B surface antibody (anti-HBsAb). Patients with a positive test for anti-HBc can only be included if HBV DNA is not detected. **In these patients only**, HBV DNA should be assessed at various subsequent visits as outlined in the **SoA**.

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

- HBV surface antigen positive
- HBV surface antigen negative, HBV surface antibody positive and/or HBV core antibody positive and detectable viral DNA. Note: Patients who are HBV surface antigen negative and viral DNA negative are eligible
- Patients who exhibit the classical vaccination profile of HBV surface antibody positive, HBV core antibody negative, and HBV surface antigen negative are eligible

If HBV-DNA becomes detectable during treatment, patients should be prophylactically treated and followed-up for potential hepatitis B reactivation as per local medical practice or institutional guidelines for CD20 antibodies such as RTX. If the HBV-DNA assay is positive, then patients 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.

Hepatitis C serology is to be done at screening only. Hepatitis C biomarkers include anti-HCV antibody. For patients 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.

12.9 Appendix 9: Equivalent Doses for Corticosteroids

Name (INN)	Example	Equivalent doses for 80 – 100 – 120 mg methylprednisolone	Potency
Hydrocortisone	Hydrocortone®	400 – 500 – 600 mg	1
Prednisone	Decortin®	100 – 125 – 150 mg	4
Prednisolone	Decortin® H	100 – 125 – 150 mg	4
Methylprednisolone	Urbason®	80 – 100 – 120 mg	5
Dexamethasone	Fortecortin®	14 – 16 – 20 mg	30

Abbreviations: INN=international nonproprietary name.

12.10 Appendix 10: International Prognostic Index and Ann Arbor Staging Classification

International Prognostic Index Patients > 60 years

Risk Factors	
Ann Arbor Stage III or IV Age > 60 years Elevated LDH ECOG performance status ≥2 Extranodal involvement ≥2	
IPI Risk Group	**Number of IPI Risk Factors**
Low	0 or 1
Low-intermediate	2
High-intermediate	3
High	4 or 5

Abbreviations: ECOG=Eastern Cooperative Oncology Group; IPI=International Prognostic Index; LDH=lactate dehydrogenase.

Age-Adjusted International Prognostic Index Patients ≤ 60 years

Risk Factors	
Ann Arbor Stage III or IV Elevated LDH ECOG performance status ≥ 2	
IPI Risk Group	**Number of aaIPI Risk Factors**
Low	0
Low-intermediate	1
High-intermediate	2
High	3

Abbreviations: aaIPI=age-adjusted International Prognostic Index; ECOG=Eastern Cooperative Oncology Group; IPI=International Prognostic Index; LDH=lactate dehydrogenase.

Ann Arbor Staging Classification for Hodgkin and Non-Hodgkin's Lymphoma

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	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement.

[a]The designation "E" generally refers to **extranodal contiguous extension** (i.e., 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.

All cases are subclassified to indicate the absence (A) or presence (B) of the **systemic ("B") symptoms** of significant unexplained fever (> 38°C; > 100.4°F), night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.

Clinical stage refers to the extent of disease determined by diagnostic tests following a single diagnostic biopsy. If a second biopsy of any kind is obtained, even if negative, the term pathologic stage is used.

Adapted from Carbone *et al.,* 1971 and Lister *et al.,* 1989.

12.11 Appendix 11: ECOG Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., 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

12.12 Appendix 12: AEs: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

12.12.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study treatment, whether or not considered related to the study treatment NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment
Events meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease) • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New conditions detected or diagnosed after informed consent even though these may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient'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 patient's condition • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE • 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

Abbreviations: AE=adverse event; ECG=electrocardiogram.

12.12.2 Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually 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 of a pre-existing condition that did not worsen from baseline cannot be considered an SAE because such an event would not constitute an AE.
d. Results in persistent 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 (e.g., sprained ankle) which may temporarily interfere with or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Abbreviations: AE=adverse event; SAE=serious adverse event.

12.12.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event
- The investigator will then record all relevant AE/SAE information in the eCRF
- It is not acceptable for the investigator to send photocopies of the patient's medical records to the sponsor in lieu of completion of the sponsor/AE/SAE CRF page
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all patient identifiers, except for the patient number, will be redacted on the copies of the medical records before submission to the sponsor
- 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.

Assessment of Intensity

The investigator will assess the intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe

  An event is defined as 'serious' when it meets at least 1 of the predefined criteria as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Severity (toxicity grade)

The toxicity grade of AEs will be graded according to the NCI-CTCAE version 5 of 27 NOV 2017 using the following definitions:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal; local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
- 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 intervention indicated
- Grade 5: Death related to AE

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE • A "reasonable possibility" of a relationship conveys that there are 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 relationship • Alternative causes, such as underlying 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 • The investigator will also consult the IB and/or SmPC/ PI, for marketed products, in his/her assessment • 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 • There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is **very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data** to the sponsor • The investigator may change his/her opinion of causality in light of follow-up information, and update the CRF documentation accordingly. For SAEs, a follow-up report with the updated causality assessment should be sent • The causality assessment is one of the criteria used when determining regulatory reporting requirements
Follow-up of AEs and SAEs
• 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/AESI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals • If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology • New or updated information will be recorded in the originally completed eCRF • The investigator will submit any updated SAE/AESI data to the sponsor within 24 hours of receipt of the information

Abbreviations: AE=adverse event; AESI=adverse event of special interest; ECG=electrocardiogram; eCRF=electronic case report form; IB=Investigator's Brochure NCI-CTCAE; National Cancer Institute-Common Terminology Criteria for Adverse Events; SAE=serious adverse event; SmPC=Summary of Product Characteristics; PI=Product Information.

12.12.4 Reporting of SAEs/AESIs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE/AESI to the sponsor will be the eCRF • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE/AESI data collection tool (see below) • The site will enter the SAE/AESI data into the electronic system as soon as they become available • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE/AESI from a study patient or receives updated data on a previously reported SAE/AESI after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE/ AESI form (see below) • Contacts for SAE/AESI reporting can be found in the Investigator Site File
SAE Reporting to Sponsor via Paper Reporting Form
• The SAE/AESI paper Reporting Form should be transmitted by email or facsimile • Contacts for SAE/AESI reporting can be found in the Investigator Site File

Abbreviations: AESI=adverse event of special interest; SAE=serious adverse event; eCRF=electronic case report form.

12.13 Appendix 13: Contraceptive Guidance and Collection of Pregnancy Information

12.13.1 Definitions

12.13.1.1 Female of Childbearing Potential (FCBP)

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of investigational medicinal product (IMP), additional evaluation should be considered.

12.13.1.2 Female in the Following Categories Are Not Considered FCBP

- Premenopausal with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - 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, a single FSH measurement is insufficient
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal 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 individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity. Genetic abnormality like Turner syndrome), investigator discretion should be applied to determining study entry.

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

12.13.2 Contraception Guidance

12.13.2.1 Male Patients

Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame Section 6.1 on inclusion criteria

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year as described in Table 13-1 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

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 during the time period indicated in Section 6.1 on inclusion criteria

Refrain from donating sperm during the same time period.

12.13.2.2 Female Patients

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the Table 13-1 below. Contraception guidance is to be followed during the time frame in Section 6.1 on inclusion criteria. Refrain from donating eggs during the same time period.

Table 13-1: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the FCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*

Sexual abstinence *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 treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical study. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for 90 days after the last dose of study treatment

Abbreviations: FCBP=female of childbearing potential.

Pregnancy testing will be performed as outlined in the SoA (see Section 2).

12.13.3 Collection of Pregnancy Information

12.13.3.1 Male Patients With Partners Who Become Pregnant

The investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive study treatment.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than the time period described in Section 9.4.3 following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

12.13.3.2 Female Patients Who Become Pregnant

The investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than the time period described in Section 9.4.3 beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor as described in Section 9.4.3. While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

12.14 Appendix 14: [redacted]

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