CLINICAL TRIAL PROTOCOL

Brief description of Clinical Trial	**A Phase Ib, open-label, randomized study to assess safety and preliminary efficacy of Tafasitamab in addition to R-CHOP or Tafasitamab plus Lenalidomide in addition to R-CHOP in patients with newly diagnosed Diffuse Large B-Cell Lymphoma (DLBCL) – First-MIND**
Clinical Trial Phase:	Phase Ib
Product Name:	Tafasitamab
Sponsor:	MorphoSys AG
Sponsor's Address:	Semmelweisstrasse 7 D-82152 Planegg GERMANY
Clinical Trial Protocol Number:	MOR208C107
EudraCT No.:	2019-001268-31
IND No.:	145,009
Effective Date:	05-FEB-2020
Applicable countries:	International (North America and Europe)
Version of the Clinical Trial Protocol:	Version 6.0

VERSION 2.0, SUMMARY OF CHANGES

Section	Change
[redacted]	[redacted]
[redacted]	[redacted].
[redacted]	[redacted]

VERSION 3.0, SUMMARY OF CHANGES

Section	Change and Rationale
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VERSION 4.0, SUMMARY OF CHANGES

Section	Change and rationale
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VERSION 5.0, SUMMARY OF CHANGES

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VERSION 6.0, SUMMARY OF CHANGES

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SIGNATURES

SPONSOR'S SIGNATURES

Clinical Trial Protocol Approved/Authorised by:

Signature: _____ **Date:** _____

[redacted]

Signature: _____ **Date:** _____

[redacted]

COORDINATING INVESTIGATOR'S SIGNATURE

I have read and understood all pages of this clinical trial protocol. I confirm that this protocol contains all the information required to conduct this clinical trial. I agree that I am responsible for the overall clinical trial conduct.

Country Coordinating Investigator:

Signature: ---------- **Date:** ----------
*(*DD-MMM-YYYY*)*

Printed Name: ----------

Address: ----------

PRINCIPAL INVESTIGATOR'S SIGNATURE

I have read and understood all pages of this clinical trial protocol. I agree that this protocol contains all the information required to conduct this clinical trial. I agree to conduct the clinical trial as outlined in the clinical trial protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the clinical trial in accordance with ICH GCP guidelines and the provisions of the Declaration of Helsinki, copies of both documents have been given to me by the sponsor, I will also ensure that co-investigator(s) and other relevant members of the my staff have access to copies of this protocol, the ICH GCP guidelines and the Declaration of Helsinki to enable them to work in accordance with the provisions of these documents.

Signature: ---------- **Date:** ----------
(DD-MMM-YYYY)

Printed Name: ----------

Address: ----------

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1 SYNOPSIS

Title of Clinical Trial	**A Phase Ib, open-label, randomized study to assess safety and preliminary efficacy of Tafasitamab in addition to R-CHOP or Tafasitamab plus Lenalidomide in addition to R-CHOP in patients with newly diagnosed Diffuse Large B-Cell Lymphoma – First-MIND**
Investigational Medicinal Products	Tafasitamab Lenalidomide
Clinical Trial Protocol Number	MOR208C107
IND Number	145,009
EudraCT Number	2019-001268-31
Sponsor	**Sponsor:** Semmelweisstrasse 7 D-82152 Planegg GERMANY
Clinical Trial Phase	Phase Ib
Background / Rationale	Diffuse large B-cell lymphoma (DLBCL) represent approximately 40% of all non-Hodgkin lymphomas (NHLs). Median age at diagnosis is 64 years and the majority of patients present with advanced disease. DLBCL is increasingly recognized as a heterogeneous disorder and the existence of biologically defined subgroups with different cell of origin (COO) can be shown (Flowers, 2010; Lenz, 2008; Vaidya, 2014). The immune-chemotherapy regimen consisting of the anti-CD20 monoclonal antibody (mAb) rituximab plus the standard CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) (R-CHOP) is the current standard of care (SoC) for the treatment of newly diagnosed DLBCL. Rituximab improved the outcome compared with CHOP alone in untreated patients with DLBCL, but still 30–40% of patients relapse (Habermann, 2006; Coiffier, 2010). Thus, the development of a more effective initial therapy is essential to improve long-term outcomes. Literature data suggests that at least a part of the untreated DLBCL patients exhibits low CD20 expression (16-42%; Johnson, 2009; Tokunaga, 2014; Choi, 2016; Boltezar, 2018). Low CD20 expression was reported to be associated with inferior survival (5-year event-free survival [EFS] 39.4% in CD20-low compared to 66.5% in CD20-high group) (Choi, 2016). Particularly for those

	patients targeting of an additional, independent antigen might be of value. The B-lymphocyte lineage specific surface antigen CD19 is the earliest and most broadly expressed of the selective B-cell markers and is highly expressed on tumor cells of most patients with B-NHL. Due to its lineage-specific expression pattern, targeting CD19 has clinical utility as a therapeutic approach to NHL treatment (Hammer, 2012). Tafasitamab is an Fc-enhanced, humanised, mAb with significantly enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP) and direct cytotoxic effects (apoptosis). The Fc-enhancement led to increased binding affinity for Fc receptors on effector cells, particularly on NK cells, thereby increasing NK-cell mediated effector functions (ADCC) on tumor cell lines *in vitro*. In preclinical studies, anti-tumor activity was increased versus respective monotherapy treatments when tafasitamab was combined with Rituximab, different chemotherapeutic and non-chemotherapeutic drugs including lenalidomide. These data suggest a rationale and a potential benefit of the tafasitamab add-on strategy to R-CHOP independent of CD20 expression status. Monotherapy with tafasitamab has shown preliminary signs of clinical efficacy and acceptable toxicity in a phase I study in R/R chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (NCT01161511) and a phase IIa study in R/R NHL (NCT01685008). In patients with relapsed-refractory (R/R) DLBCL, treatment with tafasitamab until progression showed single agent activity with 26% ORR, with some responses ongoing for several years (Jurczak, 2018). Lenalidomide belongs to a class of immunomodulating agents (immunomodulatory drugs [IMiDs]), which have demonstrated direct tumoricidal and immunomodulatory actions. Lenalidomide has both anti-proliferative and antiangiogenic activities, modulating the tumor cell microenvironment and stimulating the activity of effector cells such as cytotoxic T-cells and natural killer (NK) cells. Lenalidomide demonstrated manageable toxicity when administered as monotherapy and in combination, as well as a synergistic effect with rituximab, administered alone or as a part of an immune-chemotherapeutic regimen (see below). Preclinical data suggest that the combination of tafasitamab with lenalidomide may act synergistically by increasing NK cell-mediated ADCC, making this a combination of interest for further study in patients with B-cell lymphoma. In the phase II L-MIND

	study (NCT02399085) in patients with R/R DLBCL, the combination of tafasitamab with lenalidomide achieved a high ORR of 58%, a CR rate of 33% and a median PFS of 16 months (Salles, 2018) and this combination has recently received breakthrough therapy designation by the FDA. Tafasitamab as single agent is well tolerated and its primary side effects consist of those induced by B-cell depletion (Jurczak, 2018). In combination with lenalidomide, tafasitamab had little additive toxicity to lenalidomide. The most common treatment-emergent adverse events grade ≥3 (percentage of patients with AE) were neutropenia (36%), thrombocytopenia (12%), febrile neutropenia (7%), anemia (6%), pneumonia and lung infection (7%) and rashes (7%) (Salles, 2018). The safety and tolerability of tafasitamab or tafasitamab plus lenalidomide in addition to R-CHOP has not yet been tested in humans. This open label, prospective phase Ib study is designed to confirm the safety and preliminary efficacy of tafasitamab or tafasitamab plus lenalidomide in addition to R-CHOP in patients with newly diagnosed DLBCL.
Treatment Arms	Arm A: Tafasitamab in addition to R-CHOP Arm B: Tafasitamab plus lenalidomide in addition to R-CHOP
Clinical Trial Objectives	**Primary Objective** To assess safety and tolerability of tafasitamab in addition to R-CHOP and tafasitamab plus lenalidomide in addition to R-CHOP **Key Secondary Objective** To assess efficacy of tafasitamab in addition to R-CHOP and tafasitamab plus lenalidomide in addition to R-CHOP **Secondary Objectives** 1. To assess long-term safety and tolerability of tafasitamab in addition to R-CHOP and tafasitamab plus lenalidomide in addition to R-CHOP

	2. To assess long-term efficacy of tafasitamab in addition to R-CHOP and tafasitamab plus lenalidomide in addition to R-CHOP 3. To assess the pharmacokinetic profile of tafasitamab in each treatment arm 4. To assess the potential immunogenicity of tafasitamab in each treatment arm **Exploratory Objectives** 1. To evaluate residual disease burden by serial ctDNA assessment 2. To perform longitudinal analysis of NKCC in peripheral blood 3. To assess the relationship between potential molecular or cellular markers and efficacy of tafasitamab in addition to R-CHOP or tafasitamab and lenalidomide in addition to R-CHOP
Clinical Trial Endpoints	**Primary Endpoint** Incidence and severity of treatment-emergent adverse events (TEAEs)
	Key Secondary Endpoints 1. Objective Response Rate (ORR) at the end of treatment 2. Metabolic, PET-negative complete response (CR) rate at the end of treatment **Secondary Endpoints** 1. Incidence and severity of AEs in the follow-up period. 2. i. Best Objective Response Rate (ORR) until the end of study ii. Metabolic, PET-negative complete response (CR) rate until the end of study iii. Progression-free survival (PFS) at 12 and 24 months iv. Event-free survival (EFS) at 12 and 24 months v. Time to next anti-lymphoma treatment (TTNT) vi. Overall survival at 12 and 24 months 3. Tafasitamab serum concentrations (Ctrough levels and Cmax levels on Day 1 of each cycle)

	4. Number and percentage of patients developing anti-tafasitamab antibodies, and semi-quantitative titer assessments
	Exploratory Endpoints 1. Descriptive statistics of ctDNA by visit 2. Descriptive statistics of NKCC in peripheral blood by visit 3. The relationship of the following endpoints may be assessed for the following markers: **Endpoints:** i. ORR ii. PFS **Markers:** For the following molecular and/or cellular markers, e.g.: i. Cell of origin ii. NK-cell count in the tumor tissue iii. NK-cell gene expression signature in the tumor tissue iv. Macrophage count in the tumor tissue v. Macrophage gene expression signature in the tumor tissue vi. Quantitative and semi-quantitative CD19 expression on tumor cells (in diagnostic biopsies and at progression/relapse if available) vii. Quantitative and semi-quantitative CD20 expression on tumor cells (in diagnostic biopsies and at progression/relapse if available)
Design, Sample Size and Methodology	This is a Phase Ib, open-label, randomized study of tafasitamab given in addition to R-CHOP or tafasitamab plus lenalidomide given in addition to R-CHOP in patients with newly diagnosed Diffuse Large B-Cell Lymphoma. Each of the two arms will enroll approximately 30 patients (for a total of approximately 60 patients). If a patient discontinues the trial for any reason other than treatment related toxicity or progression/relapse of disease or death, this patient may be replaced. Safety monitoring will be performed continuously throughout the study. For further detail see section 6.1 and 6.3. Safety Committee meetings will be held to evaluate safety data and to monitor if stopping rules have been met. In case stopping rules were met, enrolment in the concerned arm will pause until the Safety Committee will meet. The committee will advice the

	Sponsor on whether treatment with study drugs of ongoing patients and enrolment in the concerned arm should be stopped. In addition, an independent Data and Safety Monitoring Board (iDSMB) will review safety data at defined timepoints and give advice to the sponsor in regards to the safety of the study treatment. The Study consists of two phases: **1. Safety Run-in Phase:** Initially, 12 patients will be enrolled in each arm. In order to evaluate the safety in accordance with the stopping rules (section 6.3), enrolment may be paused when 12 patients in each arm have been recruited and have been followed for 21 days after C1D1. **2. Main Phase:** If no unexpected safety signals (except for those being causally related to R-CHOP) are observed in either arm, enrolment will continue as planned to enrol additional approximately 18 patients in each arm in the main phase. Stopping rules for the Safety Run-in Phase and the Main Phase of the study are described in the section 6.3. As this is a Phase Ib study to primarily explore safety objectives, no formal statistical hypothesis will be considered for the sample size calculation of this study.
Indication	Newly diagnosed DLBCL
Population	Adult patients with newly diagnosed, previously untreated DLBCL
Inclusion Criteria	1. Age ≥18 years 2. Written informed consent 3. Previously untreated, newly diagnosed DLBCL, not otherwise specified (NOS) 4. Tumor tissue for retrospective central pathology review and correlative studies must be provided as an adjunct to participation in this study. 5. Patients must have at least one measurable disease site. The lesion must have a greatest transverse diameter of ≥1.5 cm and greatest perpendicular diameter of ≥1.0 cm at screening. The lesion must be confirmed to be PET-positive at the latest at the time of randomization. 6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

	7. International Prognostic Index (IPI) status of 2 to 5 8. Appropriate candidate for R-CHOP 9. Left ventricular ejection fraction (LVEF) of ≥50%, assessed by echocardiography or cardiac multi-gated acquisition (MUGA) scan 10. Patient must have the following laboratory criteria at screening: a. Absolute neutrophil count (ANC) ≥ 1.5 x 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 x 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 ≤ 1.5 × upper limit of normal (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 d. Alanine transaminase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) ≤3 × ULN, or <5 × ULN in cases of documented liver involvement e. Serum creatinine clearance **(all countries except US:)** must be ≥50 mL/minute either measured or calculated using a standard Cockcroft and Gault formula (Cockroft, 1976) **(US only:)** must be ≥60 mL/minute either measured or calculated using a standard Cockcroft and Gault formula (Cockroft, 1976) 11. **Females of childbearing potential (FCBP) must:** **Applicable in all countries except 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 oocyte during the course of study and for 3 months after the last dose of study drug or, for R-CHOP, according to the local guidelines, whichever is longer. c. agree to ongoing pregnancy testing during the course of the study, and after study therapy has

	ended. This applies even if the patient applies 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 R-CHOP, according to the local guidelines, whichever is longer. Please refer also to section 7.3.1 **Applicable in US:** a. 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). b. refrain from breast feeding and donating oocytes during the course of study and for 3 months after the last dose of study drug or, for R-CHOP, according to the US guidelines, whichever takes longer. c. agree to ongoing pregnancy testing during the course of the study (every 3 weeks in women with regular menstrual cycle and every 2 weeks in women with irregular menstrual cycle), and after study therapy has ended (even if true abstinence is the chosen method of birth control). d. not get pregnant while taking the study drug and for at least 3 months after stopping the study drug by using at the same time 2 effective methods of contraception (at least one highly effective method and one additional effective method, see Appendix G each time engaging in sexual activity with a male, starting at least 4 weeks before taking the study drug, while taking the study drug, during breaks (dose interruptions) and for at least 3 months after stopping the study drug, or, for R-CHOP; according to the US guidelines, whichever is longer. True abstinence (see Appendix G) from heterosexual sexual intercourse is also an acceptable method of contraception. The use of emergency contraception is also permitted.

	12. Male participants must: **Applicable in all countries except US:** Use an effective barrier method of contraception without interruption if the patient is sexually active with female of childbearing potential (FCBP). Male participants should refrain from donating sperm during the study participation and for 3 months after the last dose of study drug, or, for R-CHOP, according to the local guidelines, whichever is longer **Applicable in US**: Use latex or synthetic condom each time they have sex with a woman of childbearing potential. True abstinence (see Appendix G) from heterosexual sexual intercourse is also an acceptable method of contraception. The use of emergency contraception is also permitted. Male participants should refrain from donating sperm during the study participation and for 3 months after the last dose of study drug or, for R-CHOP, according to the US guidelines, whichever is longer. 13. In the opinion of investigator, the patient must: a. be able and willing to receive adequate prophylaxis and/or therapy for thromboembolic events, e.g. aspirin 70-325 mg daily or low molecular weight heparin. This is due to increased risk of thrombosis in patients treated with lenalidomide without prophylaxis. Patients unable or unwilling to take any prophylaxis are not eligible b. be able to understand, give written informed consent, and comply with all study-related procedures, medication use, and evaluations c. not have a history of noncompliance in relation to medical regimens or be considered potentially unreliable and/or uncooperative d. be able to understand the reason for complying with the special conditions of the pregnancy prevention risk management plan and give written acknowledgement of this. e.
Exclusion Criteria	Patient who have: 1. Any other histological type of lymphoma according to WHO2016 classification of lymphoid neoplasms, e.g. primary mediastinal (thymic) large B-cell lymphoma

	(PMBL), known double- or triple-hit lymphoma or Burkitt's lymphoma. 2. Transformed NHL and evidence for composite lymphoma 3. History of radiation therapy to ≥25% of the bone marrow for other diseases or history of anthracycline therapy 4. History of prior non-hematologic malignancy except for the following: a. Malignancy treated with curative intent and with no evidence of active disease present for more than 2 years before screening b. Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer. c. Adequately treated carcinoma in situ without current evidence of disease 5. History of myocardial infarction ≤6 months, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening arrhythmias 6. Patients with: a. Known positive test result for hepatitis C (hepatitis C virus [HCV] antibody serology testing) and a positive test for HCV RNA. Patients with positive serology must have been tested locally for HCV RNA and are eligible, in case of negative HCV RNA test results. b. Known positive test results for chronic HBV infection (defined by HBsAg positivity). Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA was undetectable (local test result), provided that they are willing to undergo ongoing DNA testing. Antiviral prophylaxis may be administered as per institutional guidelines. Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible. c. Known seropositive for or history of active viral infection with human immunodeficiency virus (HIV) d. Known active bacterial, viral, fungal, mycobacterial, or other infection at screening e. Known CNS lymphoma involvement f. History or evidence of clinically significant cardiovascular, CNS and/or other systemic disease that would in the investigator opinion preclude

	participation in the study or compromise the patient's ability to give informed consent g. History or evidence of rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption h. Vaccination with live vaccine within 21 days prior to study randomization i. Major surgery (excluding lymph node biopsy) within up to 21 days prior to signing the informed consent form, unless the patient is recovered at the time of signing the informed consent form j. Any anti-cancer and/or investigational therapy within 21 days prior to the start of Cycle 1. Note: Steroid pre-phase is permitted k. Pregnancy or lactation l. History of hypersensitivity to any component of R-CHOP, to lenalidomide, to compounds of similar biological or chemical composition as tafasitamab, IMiDs® and/or the excipients contained in the study drug formulations or R-CHOP m. Any contraindication concerning any individual components of R-CHOP
Sample Size, Planned total number of Clinical Trial Sites and Locations	A total of approximately 60 patients will be enrolled in the study. Initially, 12 patients in each arm will be enrolled in the safety run-in phase. Once safety will be confirmed, additional approximately 18 patients in each arm will be enrolled in the main phase. If a patient discontinues the trial for any reason other than treatment related toxicity or progression/relapse of disease or death, this patient may be replaced. Approximately 30-40 centers in the North America and Europe will be participating in this trial.
Anticipated Screening Failure and Drop-Out Rate	Screening Failure Rate: 25% Drop-Out Rate: Patients who drop out before 2 years after randomization: 15%, thereof patients who drop-out before end of treatment (EOT): 10%
Duration of the Study	• Screening: The screening period will last for a maximum of 21 days from date of signature of ICF to date of randomization. • Planned treatment: 6 cycles of 21 days. • Follow-up: Starts on the day of End of Treatment Visit and will last up to 18 months after End of Treatment Visit. Clinical evaluation will be performed approximately every 3 months until final completion of trial, CTs approximately every 6 months until final completion of trial.

Investigational Product(s) and Control Drug(s)	The investigational products tafasitamab or tafasitamab plus lenalidomide will be given in addition to standard of care i.e. R-CHOP treatment in this study. *Note: **R-CHOP** is considered the current standard of care for first-line treatment of newly diagnosed DLBCL and serves as a backbone in this study. R-CHOP is considered a non-IMP and is not provided by the sponsor.* *Note: **Rituximab** or equivalent approved biosimilar anti-CD20 will be used as per investigator's choice. Subcutaneous formulation of Rituximab will not be allowed in this Phase Ib trial.*
Dose, Route of Administration, Treatment Regimen	**Tafasitamab in addition to R-CHOP in patients with newly diagnosed DLBCL** Treatment consists of tafasitamab in addition to R-CHOP for six 21-day cycles **Tafasitamab dose:** 12 mg/kg body weight Each 21-day cycle (Cycles 1-6) will consist of a tafasitamab intravenous (IV) infusion on Day 1, Day 8 and Day 15 **R-CHOP:** Rituximab or equivalent approved biosimilar 375mg/m^2, IV Day 1 of every 21-day cycle Cyclophosphamide 750 mg/m^2, IV Day 1 of 21-day cycle Doxorubicin 50mg/m^2, IV Day 1 of 21-day cycle Vincristine 1.4 mg/m^2 (max 2 mg) IV Day 1 of 21-day cycle Prednisone/Prednisolone 100 mg, per oral, Day 1-5 of every 21-day cycle **Tafasitamab plus lenalidomide in addition to R-CHOP in patients with newly diagnosed DLBCL** Treatment consists of tafasitamab plus lenalidomide in addition to R-CHOP for six 21-day cycles **Tafasitamab dose:** 12 mg/kg body weight Each 21-day cycle (cycles 1-6) will consist of a tafasitamab IV infusion on Day 1, Day 8 and Day 15

	Lenalidomide: Patients will self-administer a starting dose of 25 mg lenalidomide orally daily on **Days 1–10 of each 21-day cycle**. Dose modification in response to toxicity is allowed in 5 mg steps to a minimum dose of 10 mg and will be specified in the toxicity management section of the protocol. **R-CHOP:** Rituximab or approved biosimilar 375mg/m^2, IV Day 1 of every 21-day cycle Cyclophosphamide 750 mg/m^2, IV Day 1 of 21-day cycle Doxorubicin 50mg/m^2, IV Day 1 of 21-day cycle Vincristine 1.4 mg/m^2 (max 2 mg) IV. Day 1 of 21-day cycle Prednisone/Prednisolone 100 mg, per oral, Day 1-5 of every 21-day cycle.
Co-Medication	6 cycles of R-CHOP: Patients will be treated with R-CHOP according to the institutional guidelines. R-CHOP serves as a backbone treatment. Steroid pre-phase: In patients with urgent need for a steroid pre-phase before initiation of therapy, the use of oral prednisone 25-100 mg/d or equivalent over 7 days is allowed after tumor investigations (imaging, blood samples) for screening have been performed. Under exceptional circumstances and at the discretion of the investigator, the steroid pre-phase can be started prior to acquisition of PET. Any pre-phase steroid use must be adequately documented and justified in the patient's source data. IRR prophylaxis for tafasitamab infusions should be administered in accordance with the protocol and consist of oral acetaminophen (e.g., 650−1000 mg), an antihistamine such as diphenhydramine hydrochloride (50−100 mg) and glucocorticosteroids (e.g. 100 mg IV prednisone or prednisolone or equivalent) 30−60 minutes prior to the start of the infusion (unless contraindicated). Note: the Day 1 steroid dose being part of CHOP (100 mg prednisone or prednisolone or equivalent, IV or PO) can be used as further component of premedication prior to Tafasitamab infusion.

	Prophylaxis of venous thromboembolism (VTE) for patients receiving lenalidomide: Patients in the tafasitamab plus lenalidomide in addition to R-CHOP arm must receive e.g. aspirin 70-325mg daily or low molecular weight heparin. This is due to increased risk of thrombosis in patients treated with lenalidomide without prophylaxis. CNS prophylaxis: Central nervous system (CNS) prophylaxis with intrathecal chemotherapy may be given according to institutional practice. CNS prophylaxis with intravenous methotrexate is allowed only if it was pre-planned and it may be administered only after the last treatment cycle and after the End of Treatment tumor assessment by PET/CT or PET/MRI. Pre-planned radiotherapy: Pre-planned local radiotherapy may be administered to initial sites of bulky or extranodal disease according to institutional guidelines. Pre-planned radiotherapy may be administered only after the last treatment cycle and after the End of Treatment tumor assessment by PET/CT or PET/MRI. Use of growth factors: The use of granulocyte colony stimulating factor (G-CSF) or pegylated G-CSF is mandatory for the prophylaxis of neutropenia and should be administered as per institutional guidelines. Prophylaxis of tumor lysis syndrome (TLS): In patients with high risk of tumor lysis syndrome (e.g. patients with large tumor burden, elevated lactate dehydrogenase (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.
Supply and Preparation	**Tafasitamab DP** is a lyophilisate 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% (w/v) polysorbate 20 at ph 6.0. Each product vial is intended to deliver 200 mg of tafasitamab in 5 ml of reconstituted solution. Tafasitamab will be diluted into a 250 ml infusion bag containing 0.9% (w/v) sodium chloride for injection. **Lenalidomide** will be provided by the sponsor. R-CHOP is not an IMP. It will be not provided by the sponsor.

	Note: Rituximab or an equivalent approved biosimilar will be used as per investigator´s choice.
Visit Schedule and Assessments	Please refer to the Schedule of Assessments (SoA)
Efficacy Assessments	Disease response assessments will be made according to the revised response criteria for malignant lymphoma based on the guidelines of the Lugano Classification (as reported by Cheson, 2014) and will be based on investigator assessment. Efficacy will be evaluated in terms of ORR, DoR, PFS, EFS, OS, TTP and TTNT.
Safety Assessments	The safety and tolerability of study treatment (tafasitamab in addition to R-CHOP or tafasitamab and lenalidomide in addition to R-CHOP) will be evaluated by means of AE reports (nature, severity, frequency, causality), performance status, physical examinations, ECG and laboratory safety evaluations. Laboratory and AE reports will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for adverse events (CTCAE), version 5.0.
Pharmacokinetics of Tafasitamab	The pharmacokinetic profile of tafasitamab will be investigated during the course of the study. Tafasitamab PK samples will be collected as outlined in the Schedule of Assessments.
Immunogenicity Assessments (anti-tafasitamab antibodies)	The potential immunogenicity of tafasitamab will be investigated during the course of the study. Anti-tafasitamab antibody samples will be collected as outlined in the Schedule of Assessments.
Other Assessments	Blood and tumor specimens for the analysis of exploratory biomarkers will be collected throughout the study. • Tumor biopsies at screening and if available at progression/relapse • Peripheral blood samples will be collected as outlined in the Schedule of Assessments.
Biomarker Assessment(s)	Blood and tumor specimens for the analysis of exploratory biomarkers will be collected throughout the study. A range of exploratory biomarkers are planned to be investigated during the course of the study including tumor CD19 and CD20 expression, B-, T- and NK and other cell counts in peripheral blood or tumor tissue. To facilitate the investigational research blood samples will be stored for the analysis of peripheral blood mononuclear cell populations (e.g. monocytes or CD4+ T-cells).

	To assess the pharmacodynamic effect of tafasitamab, circulating tumor DNA (ctDNA) will be quantified serially in the peripheral blood as an early indicator of treatment response and to detect minimal residual disease (MRD). Gene expression profiling of diagnostic tumor biopsies will be used to determine the cell of origin (COO) subtype and to assess tumor infiltrating immune cells via their gene expression signature. Together, with the quantification of tumor-associated macrophages and tumor infiltrating NK cells by immunohistochemistry this will provide a deeper understanding of the mode of action of tafasitamab.
Statistical Methods and Data Analysis	As this is a Phase 1b study, Primary, Secondary and Exploratory endpoints will be analyzed using descriptive statistics. No formal statistical tests will be performed. Primary completion analyses are planned to be performed after all randomized patients completed their treatment phase or discontinued earlier. Final Analyses will be performed at the end of Follow-up period. Details will be provided in the Statistical Analysis Plan (SAP).
Stopping Rules	If any of the situations listed below occur, the Sponsor will pause enrolment in the relevant study arm. The Safety Committee and the iDSMB will convene ad-hoc meetings and make recommendations on e.g. whether to stop further enrolment and stop treatment of ongoing patients. The Sponsor will make the final decisions, taking account of these recommendations. 1) The situations are as follows. During Safety Run-in Phase: if any of the events listed below (*A*-*C*)* occur in ≥4 of the first 12 patients in either of the two arms who have received at least one dose of study drug. 2) During Main Phase: if any of the events listed below (*A*-*C*)* occur in more than 33% of the currently randomized patients in either of the two arms who received at least one dose of study drug. ***A)*** *a grade 4 or higher non-hematologic adverse event (in either of the two arms)* ***B)*** *a grade 3 or higher thrombosis/embolism suspected to be related to treatment with lenalidomide (only for the tafasitamab-lenalidomide-R-CHOP arm)*

	C) a dose reduction or delay of over 7 days of R-CHOP (for the total across both treatment arms). *Any combination of events (A-C) occurring in ≥ 4 patients during the Safety Run-in Phase or in more than 33% of the currently randomized patients during the Main Phase will lead to a Safety Data Review.

2 TABLES OF CONTENT

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3 LIST OF ABBREVIATIONS

ABC	Activated B-cell
ADCC	Antibody-dependent cytotoxicity
ADCP	Antibody-dependent Cell-mediated Phagocytosis
ADR	Adverse Drug Reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
AGES	Österreichische Agentur für Gesundheit und Ernährungs-sicherheit GmbH, (Austrian regulatory agency)
ALL	Acute Lymphoblastic Leukemia
ALP	Alkaline phosphatase
ALT	Alanine amino Transferase
ANC	Absolute Neutrophil Count
ANSM	Agence nationale de sécurité du médicament et des produits de santé (French regulatory agency)
aPTT	Activated Partial Thromboplastin Time
ASCT	Autologous Stem Cell Transplantation
AST	Aspartate amino Transferase
ATC	Anatomical Therapeutic Chemical
AUC28	Area under the time-concentration curve from 0-28 days
BEN	Bendamustine
β-HCG	β-human chorionic gonadotropin
CDC	Complement-dependent Cytotoxicity
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CI	Confidence Interval
Cmax	Concentration max.
CML	Chronic Myeloid Leukemia
CNS	Central Nervous System
CLL/SLL	Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
COO	Cell of Origin
CR	Complete Response
CRS	Cytokine Release Snndrome
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
Ctrough	Concentration trough
DLBCL	Diffuse Large B-cell Lymphoma
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
DP	Drug Product
DSUR	Development Safety Update Report
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
EDV	End-diastolic volume
eCRF	Electronic Case Report Form
EFS	Event Free Survival
EMA	European Medicines Agency
EOT	End of Treatment
ESV	End-systolicv volume
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAMPH	Federal Agency for Medicines and Health Products (Belgian regulatory agency)
FAS	Full Analysis Set
Fc	Fragment Crystallizable
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FISH	Fluorescent In Situ Hybridization
FU	Follow-up
GCB	Germinal Centre B-cell
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GI	Gastrointenstinal
GLP	Good Laboratory Practice
HBV	Hepatitis B Virus
HBcAb	Hepatitis Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HCL	Hairy Cell Leukemia
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IAS	Immunogenicity Analysis Set
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iDSMB	Independent Data and Safety Monitoring Board
IHC	Immunohistochemistry
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMiD	Immunomodulatory Drug
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INFARMED	National Authority of Medicines and Health Products, I.P. (Portuguese regulatory agency)
INR	International Normalized Ratio
IPI	International Prognostic Index
IRB	Institutional Review Board

IRR	Infusion-related reaction
IRT	Interactive Response Technology
IU	International Units
IUD	Intrauterine device
IV	Intravenous
LDH	Lactate Dehydrogenase
LDi	Longest Diameter
LEN	Lenalidomide
LVEF	Left Ventricular Ejection Fraction
Lugano 2014	Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J Clin Oncol.* 2014;32(27):3059-3068.
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multigated Acquisition
mg	Milligram
mL	Millilitre
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
ng	Nanogram
NHL	Non-Hodgkin lymphoma
NK	Natural Killer
NKCC	Natural Killer Cell Count
NOS	Not Otherwise Specified
NSAID	Non-Steroidal Anti-Inflammatories
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PE	Physical Examination
PEI	Paul-Ehrlich Institute (German regulatory agency)
Peg-G-CSF	Pegylated granulocyte colony-stimulating factor
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PMBL	Primary Mediastinal Large B-cell Lymphoma
PML	Progressive Multifocal Leukoencephalopathy
PO	Per Os
PPD	Perpendicular Diameters
PPS	Per Protocol Set
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time

RBC	Red Blood Cell
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
RNA	Ribonucleic Acid
R/R	Relapsed/Refractory
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SAF	Safety Set
SD	Standard Deviation
SDi	Smallest Diameter
SCID	Severe Combined Immuno Deficiency
SmPC	Summary of Product Characteristics
SoA	Schedule of Assessments
SoC	Standard of Care
SOP	Standard Operating Procedure
SPD	Sum of the Product of the Perpendicular Diameters
SUKL	Státní Ústav pro Kontrolu Léčiv (Czech regulatory agency)
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV	Stroke Volume
TEAE	Treatment Emergent Adverse Event
TLS	Tumor Lysis Syndrome
TTNT	Time to Next Anti-lymphoma Treatment
TTP	Time to Progression
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
VTE	Venous Thromboembolism
WBC	White Blood Cell
WHO	World Health Organisation
WFI	Water for Injection

4 BACKGROUND INFORMATION

4.1 Overview of Diffuse Large B-Cell Lymphoma

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy in adults. The majority of NHLs are of B-cell origin, with multiple different histologic subtypes (according to the WHO 2016 classification) that confer different clinical outcomes. Generally, NHL can be divided into aggressive and indolent lymphomas.

Diffuse large B-cell lymphoma (DLBCL) is the most common NHL, representing approximately 40% of all NHLs, and its rate of incidence continues to increase with 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 with distinct cell of origin subtypes, each arising from different stage of normal B-cell development. Several studies have shown that the distinct COO subtypes, Germinal Centre B-cell type (GCB) and activated B-cell type (ABC) have unique mutational profile and also different prognostic outcomes (Lenz, 2008; Flowers, 2010; Vaidya, 2014; Schmitz, 2018).

4.2 Current Treatment of DLBCL and Unmet Medical Need

The immune-chemotherapy regimen consisting of the anti-CD20 monoclonal antibody (mAb) rituximab (R) plus the CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy (R-CHOP) is the current standard of care (SoC) for the treatment of newly diagnosed DLBCL patients. Based on recent data published at ASH2018, there is no added benefit of 8 vs. 6 cycles of R-CHOP in previously untreated DLBCL. Thus, rituximab with 6 cycles of CHOP-21 should be considered SoC (Sehn, 2018). Although the addition of rituximab to CHOP dramatically improved outcomes compared with CHOP alone, still 30–40% DLBCL patients are primary refractory or relapse (Habermann, 2006; Coiffier, 2010). Although some patients with relapsed/refractory DLBCL can be salvaged with second line chemotherapy followed by consolidation with high dose chemotherapy and autologous stem cell transplantation (ASCT), the majority will succumb to the disease. Thus, the development of a more effective initial therapy is essential to improve long-term outcomes.

Various alternative regimens have been explored in an attempt to improve the efficacy of R-CHOP e.g. by increasing the intensity of the chemotherapy, increasing the dose of rituximab, adding maintenance therapy, adding targeted agents to R-CHOP or by using consolidation with high dose therapy and ASCT in the initial management of DLBCL. However, these approaches have largely been unsuccessful, including attempt at maximising dose density with R-CHOP 14 (Pfreundschuh, 2008; Cunningham, 2013; Delarue, 2013). Recent large, randomized, phase III DLBCL trials including BO21005/GOYA, comparing the efficacy and safety of Obinutuzumab plus CHOP (G-CHOP) with R-CHOP (Vitolo, 2017), DA-EPOCH-R (Wilson, 2016), and REMARC, comparing lenalidomide maintenance with placebo (Thieblemont, 2016) did not demonstrate clinically meaningful benefit for the experimental therapies being tested, reflecting a continued need to improve upon SoC therapies.

4.3 Lenalidomide in Hematological Malignancies

Lenalidomide belongs to a class of immunomodulating agents (immunomodulatory drugs [IMiDs]), which have demonstrated direct tumoricidal and immunomodulatory actions. Lenalidomide has both anti-proliferative and antiangiogenic activities, modulating the tumor cell microenvironment and stimulating the activity of effector cells such as cytotoxic T-cells and natural killer (NK) cells. Lenalidomide is FDA- and EMA-approved in multiple myeloma, mantle-cell lymphoma and in $5q^-$ myelodysplastic syndromes.

Lenalidomide monotherapy was investigated in patients with relapsed/refractory (R/R) DLBCL patients and shown to result in poor outcomes (Witzig, 2011; Czuczman, 2017). Lenalidomide demonstrated manageable toxicity as single agent or in combination with rituximab in R/R DLBCL or in combination with R-CHOP in the so called R^2-CHOP regimen in untreated DLBCL (see below). It is currently unknown whether the cell of origin (COO) has an impact on lenalidomide efficacy in frontline DLBCL therapy.

A dose finding phase Ib trial of lenalidomide (dose levels 15, 20 and 25mg given days 1-10) in combination with R-CHOP given every 21 days was conducted in newly diagnosed DLBCL patients and showed that lenalidomide did not affect dose intensity and schedule of R-CHOP, was safe and associated with high (100% ORR, 77% CR) response rates (Nowakowski, 2011). Based on this study and another single arm phase II study with a different lenalidomide dosing regimen (15 mg, days 1-14 q21 days) (Vitolo, 2014), it was concluded that lenalidomide can be safely combined with R-CHOP in the initial treatment of patients with DLBCL. The phase III ROBUST trial of oral lenalidomide (15 mg, days 1-14) plus R-CHOP versus placebo plus R-CHOP in patients with previously untreated ABC-type DLBCL did not meet its primary endpoint for PFS, although a positive trend favoring lenalidomide plus R-CHOP has been observed in advanced-stage and higher-risk patients (NCT 02285062). The most common grade 3/4 adverse events reported were neutropenia (60% in the lenalidomide/R-CHOP arm vs 48% in the placebo/R-CHOP arm), anemia (22% vs 14%), thrombocytopenia (17% vs 11%), leukopenia (14% vs 15%), febrile neutropenia (14% vs 9%), and lymphopenia (11% vs 8%). The safety profile of lenalidomide plus R-CHOP was consistent with those of the individual medicines, and no new safety signals were identified with the combination (Vitolo, 2019).

In contrast, the results of the recent ECOG-ACRIN1412 trial, a randomized phase II trial of R-CHOP in combination with Lenalidomide (25 mg/day on day 1-10 of each 21-day cycle) have shown promising efficacy in newly diagnosed DLBCL with 34% reduction in risk of progression or death in R^2-CHOP arm compared to R-CHOP arm. Lenalidomide in addition to R-CHOP was well tolerated despite a higher frequency of haematological toxicity and febrile neutropenia compared to R-CHOP. Importantly, there was no increase in treatment-related mortality in the R^2-CHOP arm (1%) compared to R-CHOP arm (4%) (Nowakowski, 2019).

4.4 Overview of Tafasitamab

Tafasitamab (synonyms: MOR00208; XmAb®5574) is an Fc-engineered mAb that binds to the human B-cell surface antigen CD19. Tafasitamab possesses significantly increased tumor cytotoxicity when compared to the tafasitamab version with a non-engineered Fc region. The increased binding of tafasitamab to Fc gamma receptors (FcγR), due to the engineered mutations, significantly enhances *in vitro* 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. Tafasitamab has not been shown to mediate complement-dependent cytotoxicity (CDC).

More specifically, in preclinical studies, tafasitamab has been shown to significantly enhance *in vitro* ADCC, ADCP, and direct cytotoxic effects (apoptosis) on CD19+ tumor cell lines spanning a broad range of human lymphomas and leukemias (Burkitt lymphoma, CLL, hairy cell leukemia [HCL], CD19+ chronic myeloid leukemia [CML], DLBCL and acute lymphoblastic leukemia [ALL]), expressing levels of CD19 antigen ranging from 15,000 to 105,000 molecules/cell. Similar effects were also noted in relation to freshly isolated patient CLL or ALL cells and are also expected to translate to primary NHL cells since the expression range reported for ALL and CLL B-cells covers the range observed for NHL B-cells (Ginaldi, 1998; Olejniczak, 2006). Tafasitamab has also shown superior efficacy to its non-engineered version in relation to its ability to induce a marked reduction in tumor growth, inhibit tumor growth rate and increase survival *in vivo* in xenograft models of human lymphoma in severe combined immunodeficiency (SCID) mice (Investigator's Brochure [IB]).

The pharmacodynamic (PD) interactions of tafasitamab in combination with two standard-of-care drugs fludarabine and bendamustine (BEN), and one investigational drug, lenalidomide used in the treatment of patients with CLL and NHL, were investigated in a human intravenous (IV) lymphoma model in SCID mice (see IB). In this orthotopic model for disseminated B-cell malignancies, the median survival was superior for all of the groups receiving tafasitamab combination therapy (with fludarabine, BEN or lenalidomide) when compared with the groups receiving tafasitamab monotherapy. The lenalidomide xenograft study showed a clear potentiation of the efficacy benefit of tafasitamab (3 mg/kg) and lenalidomide (100/200 mg/kg) combination therapy compared with the respective monotherapies (1.5x increase in median lifespan).

Tissue cross-reactivity studies have shown that the pattern and distribution of tafasitamab binding to cynomolgus monkey tissues closely parallels those of human tissues. Flow cytometry experiments show tafasitamab binding to human and cynomolgus monkey B-cells, but not to the B-cells of other common laboratory species (such as rat, mouse, rabbit and dog). Therefore, pharmacology studies were restricted to human and cynomolgus monkey cell-based *in vitro* systems, CD19+ human B-cell tumor xenograft models in SCID mice, and cynomolgus monkeys *in vivo*. In *in vivo* studies in cynomolgus monkeys, tafasitamab was shown to induce B-lymphocyte depletion in peripheral blood, bone marrow, spleen and inguinal lymph nodes. Cynomolgus monkeys were also judged to be the only relevant common laboratory species for toxicity studies.

The results of studies evaluating the pharmacokinetics (PK), PD and toxicity of tafasitamab in cynomolgus monkeys, are provided in the IB. The findings in four preclinical studies were limited to the expected pharmacological effects of tafasitamab, with no reports of unanticipated toxicity.

The four studies, all conducted in cynomolgus monkeys included: a 26-week single 10.0 mg/kg dose, PK, PD and toxicity study; a 28-day single IV dose, dose-ranging (0.3, 1.0 and 3.0 mg/kg) PK/PD study; a 29-day, single-dose (3.0 mg/kg) study comparing tafasitamab with two other CD19 antibodies with different Fc regions; and an 8-week toxicity study in which tafasitamab

was administered IV every 2 weeks at a dose of 2.0, 10.0 or 50.0 mg/kg for 8 consecutive weeks with a 90-day recovery period. The aim of the latter Good Laboratory Practice (GLP)-compliant, multiple-dose toxicology study was to support the use of tafasitamab in human clinical studies. Other than the expected dose-related decreases in B-lymphocyte levels and cellularity in spleen tissues, there were no tafasitamab-related changes identified in 'clinical observations', food consumption, body weight, electrocardiography, ophthalmology, urinalysis, coagulation, serum chemistry, and gross anatomic pathology at doses up to 50.0 mg/kg. In addition, GLP-compliant tissue cross-reactivity studies were performed on normal tissue panels from human and cynomolgus monkey donors. No specific staining of structures other than the expected mononuclear leucocytes, lymphocytes and hematopoietic precursor cells was observed.

4.4.1 Clinical Experience with Tafasitamab

The clinical development program of tafasitamab comprises five MorphoSys AG-sponsored clinical trials so far. Monotherapy with tafasitamab has shown preliminary signs of clinical efficacy and acceptable toxicity in a phase I study in R/R chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (NCT01161511) (XmAb®5574-01) and a phase IIa study in R/R NHL (NCT01685008) (MOR208C201). In this study, patients with R/R DLBCL (n=35), treatment with tafasitamab until progression showed single agent activity with 26% ORR, with some responses ongoing for longer than 12 months in 5 out of 9 responding patients (Jurczak, 2018). Additional tafasitamab studies which are currently ongoing evaluate tafasitamab in different combination therapies in patients with R/R DLBCL and R/R CLL.

Preclinical data suggest that the combination of tafasitamab with lenalidomide may act synergistically by increasing NK cell-mediated ADCC, making this a combination of interest for further study in patients with B-cell lymphoma.

In the phase II MOR208C203 L-MIND study (NCT02399085) in patients with R/R DLBCL, the combination of tafasitamab with lenalidomide achieved a high ORR of 58%, a CR rate of 33% and a median PFS of 16 months (Salles, 2018). This combination has recently received breakthrough designation by the FDA. Enrolment is complete with 81 patients and updated results from the ongoing L-MIND study indicate a significant improvement in outcome for these patients who have very limited treatment options (Salles, 2018).

The ongoing Phase II/III study MOR208C204 (B-MIND) (NCT02763319) is a randomized study of tafasitamab combined with bendamustine versus rituximab plus bendamustine in patients with R/R DLBCL who are not candidates for high-dose chemotherapy and ASCT.

The ongoing study MOR208C205 (COSMOS) is a Phase II study of tafasitamab in combination with either idelalisib or venetoclax in R/R CLL/SLL patients (NCT02639910).

4.4.2 Safety of Tafasitamab

To date, a total of 351 patients have been dosed with tafasitamab up to the data lock point of the most recent DSUR report (Version 6, Dec 6th 2018). Tafasitamab was generally well tolerated in clinical studies with no new safety signals being observed compared to other B-cell depleting antibodies.

Tafasitamab has a novel mechanism of action that may have the potential to add to the care of patients with NHL. Based on the available data from the completed clinical study of tafasitamab (Protocol XmAb®5574-01), the data from the ongoing MOR208C201 clinical study, nonclinical studies and experiments, and literature data on CD19, the sponsor believes that the potential benefit of tafasitamab outweighs the potential risks. It is expected that the potential risks will be adequately controlled by the design of this study (e.g., by the inclusion and exclusion criteria) and by frequent monitoring of adverse drug reactions throughout the entire study. As the clinical trials with tafasitamab in combination therapy (MOR208C203, MOR208C204 and MOR208C205) are ongoing, no complete analysis of safety data is available, yet.

Based on the results of the phase I clinical study (XmAb®5574-01) of tafasitamab in patients with CLL/SLL (Woyach, 2014), and the results of the MOR208C201 (Jurczak, 2018) and MOR208C202 (Klisovic, 2017) studies, the anticipated possible risks associated with administration of tafasitamab to patients include the following AEs (incidence ≥ 3%) assessed as expected for tafasitamab treatment:

- Infusion related reactions (IRRs)
- Febrile neutropenia
- Neutropenia
- Thrombocytopenia
- Tumor lysis syndrome
- Upper respiratory tract infections
- Fatigue
- Chills
- Pyrexia
- Nausea
- Diarrhoea
- Headache
- Rash
- Aspartate aminotransferase (AST) and alanine transaminase (ALT) increases.

In clinical trials IRRs were the most frequently reported treatment emergent adverse events (TEAEs) and were all judged as related to tafasitamab. Other frequent adverse drug reactions (ADRs) were hematologic events with neutropenia, febrile neutropenia and thrombocytopenia. Fatigue, chills, pyrexia, nausea, diarrhoea, headache, elevation of liver enzymes, upper respiratory tract infection, rash and tumor lysis syndrome were the most frequent non-hematologic ADRs.

In MOR208C203, a clinical trial in which patients with R/R DLBCL were treated with a combination of tafasitamab and lenalidomide, the first patient was enrolled on 29-Mar-2016. As of 18-Oct-2018 157 patients have been screened, thereof 81 patients have received at least the first dosing.

With data cut-off 05-Jun-2018, the most common treatment-emergent adverse events (any grade/grade ≥3) were neutropenia in 39/35 (48%/43%) patients, thrombocytopenia in 26/14 (32%/17%), anemia in 25/7 (31%/9%), diarrhea in 24/1 (30%/1%), pyrexia in 18/1 (22%/1%) and asthenia in 16/2 (20%/2%) patients. Treatment-related serious adverse events occurred in 16 (19.8%) patients; the majority of the events were infections or neutropenic fever. No infusion related reactions were reported with tafasitamab. 41 (51%) patients required dose reduction with lenalidomide, 58 (72%) patients were able to stay on a daily lenalidomide dose of 20 mg or higher. In 9 (11%) patients lenalidomide was permanently discontinued due to an adverse event.

A detailed tafasitamab exposure-response analysis for safety with results from clinical studies MOR208C201 (tafasitamab monotherapy in R/R NHL (including DLBCL), n=92) and MOR208C203/L-MIND (tafasitamab plus lenalidomide) in R/R DLBCL, n=81) was performed. In both studies, all subjects were treated at the dose level of 12 mg/kg tafasitamab. The tafasitamab exposure metrics AUC28 (ie, area under the time-concentration curve from 0-28 days) and Cmax (overall maximum tafasitamab concentration) were derived by simulation for each subject from a population PK model. The individual exposure metrics were separated into exposure quartiles and analyzed against TEAEs and AESIs. As a conclusion from this analysis, there were no obvious trends for increasing TEAEs or AESIs with increasing exposure. The numbers and percentages of subjects experiencing a TEAE/AESI were equally or randomly distributed across the 4 exposure quartiles (e.g. results for “Any TEAE of Special Interest” in study L-MIND: AUC28 quartile 1: 20 subjects (24.7%); quartile 2: 20 subjects (24.7%), quartile 3: 19 subjects (23.5%); quartile 4: 19 subjects (23.5%)).

The possible risks associated with the administration of tafasitamab are described in detail in the tafasitamab IB.

4.5 Study Rationale

Six cycles of R-CHOP is considered the current SoC therapy in previously untreated DLBCL (Sehn, 2018); however, a substantial number of patients relapse after R-CHOP or are primary refractory to R-CHOP. After a number of phase III studies were unable to demonstrate meaningful benefit of various experimental approaches over R-CHOP, there is a need to evaluate novel approaches in order to improve the activity of R-CHOP in patients with previously untreated DLBCL.

Literature data suggests that at least a part of the untreated DLBCL patients exhibits low CD20 expression (Johnson, 2009; Tokunaga, 2014; Choi, 2016; Boltezar, 2018). Low CD20 expression was reported to be associated with inferior survival (5-year event-free survival [EFS] 39.4% in CD20-low compared to 66.5% in CD20-high group) (Choi, 2016). Particularly for those patients, therapeutic targeting of an additional, independent B-cell antigen might be of value.

The B-lymphocyte lineage specific surface antigen CD19 is the earliest and most broadly expressed of the selective B-cell markers and is highly expressed on tumor cells of most B- NHL.

Due to its lineage-specific expression pattern, targeting CD19 has clinical utility as a therapeutic approach to NHL treatment (Hammer, 2012).

Tafasitamab is an Fc-enhanced, humanised, anti-CD19 mAb with significantly enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP) and direct cytotoxic effects (apoptosis) compared with the parental murine antibody. The Fc-enhancement leads to increased binding affinity for Fc receptors on effector cells, particularly on NK cells, thereby increasing NK-cell mediated effector functions (ADCC) on tumor cell lines *in vitro*.

In preclinical studies, anti-tumor activity was increased versus respective monotherapy treatments when tafasitamab was combined with rituximab, different chemotherapeutic and non-chemotherapeutic drugs including lenalidomide.

A phase I clinical trial investigating tafasitamab in humans has been completed (clinical trial XmAb5574-01, "A Phase I Study of XmAb5574 to Evaluate the Safety, Tolerability and Pharmacokinetics in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia"). Based on data derived from dose levels between 3 and 12 mg/kg, the estimated beta half-life averaged at approximately 13.5 days. The highest tested dose of 12 mg/kg was recommended for phase II (Woyach, 2014).

Lenalidomide belongs to a class of immunomodulating agents (immunomodulatory drugs [IMiDs]), which have demonstrated direct tumoricidal and immunomodulatory actions. Lenalidomide has both anti-proliferative and antiangiogenic activities, modulating the tumor cell microenvironment and stimulating the activity of effector cells such as cytotoxic T-cells and natural killer (NK) cells by various mechanisms. Lenalidomide increases NK cell proliferation and numbers in vivo, modulates expression of co-stimulatory surface receptors on NK cells and stabilizes the immunological synapse between NK cell and target tumor cell. Preclinical data suggest that the combination of tafasitamab with lenalidomide act synergistically by increasing NK cell-mediated ADCC. In the phase II MOR208C203 L-MIND study (NCT02399085) in patients with R/R DLBCL, the combination of tafasitamab with lenalidomide achieved a high ORR of 58%, a CR rate of 33% and a median PFS of 16 months (Salles, 2018).

Taken together, these data suggest a potential benefit of the tafasitamab or tafasitamab plus Lenalidomide add-on strategy to R-CHOP in newly diagnosed DLBCL and thereby provide the rationale for this study.

5 CLINICAL TRIAL PURPOSE AND OBJECTIVES

This open label, prospective, randomized phase Ib study is designed to confirm the safety and preliminary efficacy of tafasitamab in addition to R-CHOP or tafasitamab plus lenalidomide in addition to R-CHOP in patients with newly diagnosed DLBCL.

The **primary and secondary objectives** of the clinical trial are as follows:

	Objective	**Endpoint**
Primary	To assess safety and tolerability of tafasitamab in addition to R-CHOP	Incidence and severity of TEAEs

	Objective	**Endpoint**
	and tafasitamab plus lenalidomide in addition to R-CHOP	
Key Secondary	To assess efficacy (based on Lugano 2014 criteria) of tafasitamab in addition to R-CHOP and tafasitamab plus lenalidomide in addition to R-CHOP	1. Objective Response Rate (ORR) at the end of treatment 2. Metabolic, PET-negative complete response (CR) rate at the end of treatment
Secondary	1. To assess long-term safety and tolerability of tafasitamab in addition to R-CHOP and tafasitamab plus lenalidomide in addition to R-CHOP	Incidence and severity of AEs in the follow-up period.
	2. To assess long term efficacy (based on Lugano 2014 criteria) of tafasitamab in addition to R-CHOP and tafasitamab plus lenalidomide in addition to R-CHOP	i. Best Objective Response Rate (ORR) until the end of study ii. Metabolic, PET-negative complete response (CR) rate until the end of study iii. Progression-free survival (PFS) at 12 and 24 months iv. Event-free survival (EFS) at 12 and 24 months v. Time to next anti-lymphoma treatment (TTNT) vi. Overall survival at 12 and 24 months
	3. To assess the pharmacokinetic (PK) profile of tafasitamab in each treatment arm	Tafasitamab serum concentrations (Ctrough levels and Cmax levels on Day 1 of each cycle)
	4. To assess the potential immunogenicity of	Number and percentage of patients developing anti-tafasitamab antibodies,

	Objective	Endpoint
	tafasitamab in each treatment arm	and semi-quantitative titer assessments.
Exploratory	1. To evaluate residual disease burden by serial ctDNA assessment	Descriptive statistics of ctDNA by visit
	2. To perform longitudinal analysis of NKCC in peripheral blood	Descriptive statistics of NKCC in peripheral blood by visit
	3. To assess the relationship between potential molecular or cellular markers and efficacy of tafasitamab in addition to R-CHOP or tafasitamab and lenalidomide in addition to R-CHOP	The relationship of the following endpoints may be assessed for the following markers: Endpoints: i. ORR ii. PFS Markers, e.g.: i. Cell of origin ii. NK-cell count in the tumor tissue iii. NK-cell gene expression signature in the tumor tissue iv. Macrophage count in the tumor tissue v. Macrophage gene expression signature in the tumor tissue vi. Quantitative and semi-quantitative CD19 expression on tumor cells (in diagnostic biopsies and at progression/relapse if available) vii. Quantitative and semi-quantitative CD20 expression on tumor cells (in diagnostic biopsies and at progression/relapse if available)

6 CLINICAL TRIAL DESIGN

6.1 Overall Clinical Trial Design and Investigational Plan

This is a multicenter, open-label, randomized, Phase Ib trial to assess safety and preliminary efficacy of tafasitamab in addition to R-CHOP or tafasitamab plus lenalidomide in addition to R-CHOP in adult patients with newly diagnosed DLBCL. Approximately 60 patients (30 in each arm) will be randomized in this study. If a patient discontinues the trial for any reason other than treatment related toxicity, progression/relapse of disease or death, this patient may be replaced.

6.1.1 Safety monitoring

Safety monitoring will be performed on a continuous basis as follows:

A. **Sponsor Safety Review Meetings** will be performed every two weeks during the safety run-in phase, and every four weeks during the main study phase. Once all patients are in the follow-up phase, the frequency of these meetings will be decreased to approximately every eight weeks. Overall patient safety data including AEs, laboratory values, ECG outputs as well as physical examination including vital signs of every patient will be part of the review. Safety monitoring will be conducted by representatives of the sponsor with medical and pharmacovigilance expertise and the medical monitors of the CRO. Individual case monitoring by Drug Safety will ensure steady oversight whether stopping rules are likely to be met. In case the stopping rules have been met, an ad-*hoc* meeting of the Safety Committee will be required.

B. **Safety Committee**. The sponsor established a Safety Committee consisting of sponsor representatives with at least two representatives of the participating investigators of this clinical trial. This committee will meet regularly until all patients have completed treatment. During these meetings, safety data including e.g. AEs, laboratory values, ECG outputs as well as physical examination including vital signs of every patient will be reviewed. Details of specific responsibilities, composition, meeting formats and frequency of the Safety Committee are outlined in the *Safety Committee Charter.*

C. In addition, an **independent Data and Safety Monitoring Board (iDSMB)** consisting of independent haematologists will be established. During its meetings, safety data including e.g. AEs, laboratory values, ECG outputs as well as physical examination including vital signs will be reviewed. The iDSMB will provide a recommendation at the end of safety run-in phase when all patients in both arms have finished their first treatment cycle; during the main phase after approximately 40 patients (20 per arm) have finished their first treatment cycle, and at the end of the treatment period (last patient reached C6D21 plus approximately 30 days). Details of specific responsibilities, composition, meeting formats and frequency of the iDSMB will be described separately in the *iDSMB charter* and will follow relevant regulatory requirements for such body.

Furthermore, both committees as described in B. and C. will meet *ad-hoc* in case the stopping rules are met (see Section 6.3). In such situation, both committees will make their recommendation to the Sponsor on whether e.g. treatment with study drugs of ongoing patients and further enrolment in the concerned arm should be stopped.

The trial consists of two phases, see Figure 1.

1. Safety Run-in Phase:

As the addition of tafasitamab to R-CHOP and tafasitamab and lenalidomide plus R-CHOP has not previously been evaluated in a clinical study, a safety run-in phase with 12 patients in each arm will be performed. In order to evaluate the safety in accordance with the stopping rules (Section 6.3), enrolment may be paused when 12 patients in each arm have been recruited and have been followed for 21 days after C1D1.

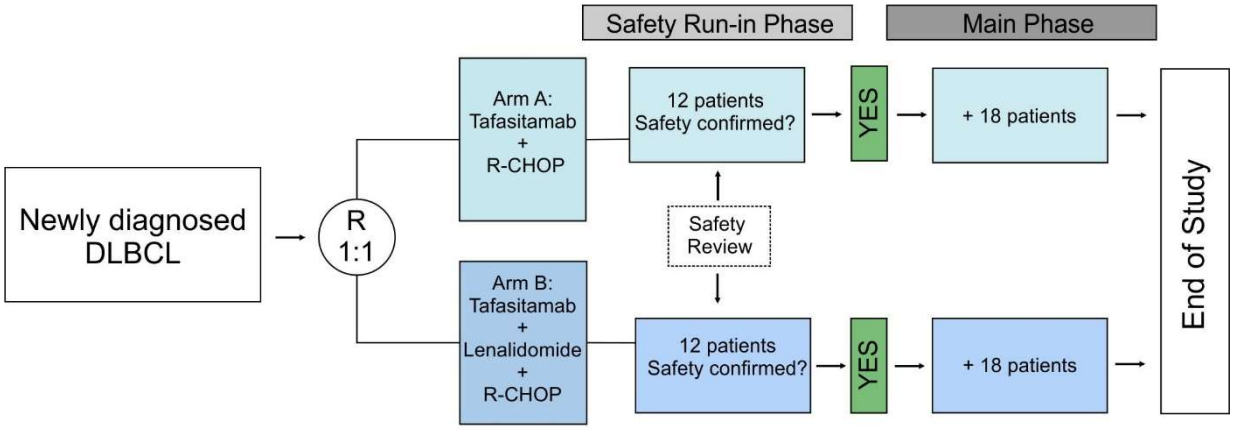
2. Main Phase:

If no unexpected safety signals (except for those being causally related to R-CHOP) are observed in either arm, enrolment will continue as planned to enrol additional approximately 18 patients in each arm in the main phase. Stopping rules are described in Section 6.3.

As this is a Phase Ib study to primarily explore safety objectives, no formal statistical hypothesis will be considered for the sample size calculation of this trial.

It is expected that approximately 10% of the patients will prematurely withdraw from the trial prior to end of treatment. An additional approximately 5% are expected to prematurely withdraw between end of treatment and end of 24 months after randomization.

Figure 1: Trial design



All patients are expected to receive 6 cycles of study treatment (each cycle consisting of 21 days) and to be followed up for 24 months (or 731 days) from the date of randomization. For more details see Section 6.4.

3. End of Study

The end of study is defined as the timepoint when data collection will stop and the final analysis of the study will occur. The end of study will happen after all patients have completed their End of Study/Early Follow-up Termination Visit.

6.2 Early Study Termination

The study can be terminated at any time for any reason by the sponsor. Should this be necessary, the patient will be contacted by the investigator or his/her designee. The patient should be seen as soon as possible for an Early Study Treatment Discontinuation Visit or Early Follow-up Termination Visit as applicable, and the assessments outlined in the Schedule of Assessments (Section 10) should be performed. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6.3 Stopping Rules

If any of the situations listed below occur, the Sponsor will pause enrolment in the relevant study arm. The Safety Committee and the iDSMB will convene ad-hoc meetings and make recommendations on e.g. whether to stop further enrolment and stop treatment of ongoing patients. The Sponsor will make the final decisions, taking account of these recommendations.

The situations are as follows:

1) During Safety Run-in Phase: if any of the events listed below (*A-C*)* occur in ≥4 of the first 12 patients in either of the two arms who have received at least one dose of study drug.

2) During Main Phase: if any of the events listed below (*A-C*)* occur in more than 33% of the currently randomized patients in either of the two arms who received at least one dose of study drug.

A) *a grade 4 or higher non-hematologic adverse event (in either of the two treatment arms)*
B) *a grade 3 or higher thrombosis/embolism suspected to be related to treatment with lenalidomide (only for the tafasitamab-lenalidomide-R-CHOP arm)*
C) *a dose reduction or delay of over 7 days of R-CHOP (for the total across both treatment arms)*

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

* Any combination of events (A-C) occurring in ≥ 4 patients during the Safety Run-in Phase or in more than 33% of the currently randomized patients during the Main Phase will lead to a Safety Data Review.

6.4 Clinical Trial Duration

From the time of providing informed consent, each patient is expected to be included in the study for a duration of approximately 25 months. Three periods are defined for each patient in the study.

6.4.1 Screening period

The screening period of a maximum of 21 days is the interval between the date of signing of informed consent and the date of randomization.

The ICF must be signed prior to beginning any study related assessments. Standard of care assessments done on the day of consent (but prior to signing the ICF) do not need to be repeated solely for the purpose of screening and may be used as study data, if they meet the protocol requirements.

During screening, each patient who signs the ICF will be allocated a unique identification number. All patients who fulfil all inclusion criteria and who are not barred by any of the exclusion criteria will be randomly assigned to treatment comprising tafasitamab in addition to R-CHOP or tafasitamab plus lenalidomide in addition to R-CHOP in a 1:1 ratio.
Study treatment should start within 24 hours after randomization.

6.4.2 Treatment period

The treatment period starts with the first administration of study drug (C1D1) and consists of 6 cycles, each 21 days. The End of Treatment Visit or Early Study Treatment Discontinuation Visit will be performed 6±2 weeks after End of Treatment. End of Treatment is defined as day 21 of the last treatment cycle the patient started. Patients who discontinue early because of progression/relapse of disease may have the Early Study Treatment Discontinuation Visit earlier at the discretion of the investigator.

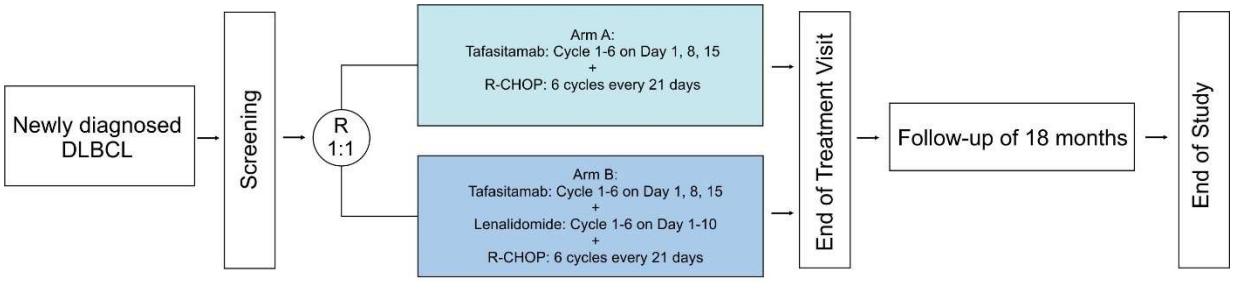
All assessments specified in Section 10 should be performed within the acceptable visit windows (+/- 2 days) on Day 1, Day 8 and Day 15 of each cycle (Note: C1D1 visit window: +1 day).

6.4.3 Follow-up period

The Follow-up period starts at the End of Treatment or Early Study Treatment Discontinuation Visit; the 30-day safety follow-up visit will be included in this visit. Clinical evaluation will be performed every 3 months. CT scans will be performed every 6 months until final completion of study or until disease progression/relapse. All patients are expected to be followed up for a total of 18 months after the End of Treatment Visit or Early Study Treatment Discontinuation Visit. The End of Study Visit or Early Follow-up Termination Visit marks the completion of the study for an individual patient.

The assessments outlined in the Section 10 should be performed within the acceptable visit windows during the follow-up period once patient has completed 6 cycles of tafasitamab in addition to R-CHOP (Arm A) and tafasitamab and lenalidomide in addition to R-CHOP (Arm B). A visit window of +/- 2 weeks is allowed throughout the follow-up.

Figure 2: Clinical trial periods: Screening, Treatment and Follow-up



6.5 Risks and Benefits to Patients

All eligible patients will be treated with standard of care for six cycles of R-CHOP as a potentially curative treatment approach. In addition, patients will receive either tafasitamab (Arm A) or tafasitamab plus lenalidomide (Arm B) as an add-on to R-CHOP to potentially improve the CR rate and hence to possibly reduce the treatment failure rate. Based on the safety profile of tafasitamab single agent and the well manageable safety profile of the tafasitamab plus lenalidomide combination (as demonstrated in the L-MIND study in R/R DLBCL), it is expected that the overall risk-benefit is favorable without additional toxicities compared to the treatment with R-CHOP only.

The predictable risks and most common side effects of tafasitamab +/- lenalidomide are infusion-related reactions, transient neutropenia, thrombocytopenia, anemia, diarrhea, pyrexia and asthenia. Treatment-related serious AEs consist mainly of infections or neutropenic fever.

Together, the potential risks identified with tafasitamab +/- lenalidomide alongside with the measures in place to minimize risk to patients participating in this trial are justified by the anticipated benefits that may be achieved by the add-on treatment in patients with newly diagnosed DLBCL, which constitutes a life-threatening condition.

7 SELECTION AND WITHDRAWAL OF PATIENTS

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are enrolled in the study.

The patients are not allowed to participate in additional parallel investigational drug or device studies.
The sponsor is not providing waivers to the clinical trial protocol as deviations might have a negative impact on patient safety or the scientific integrity and regulatory acceptability of the clinical trial.

7.1 Inclusion Criteria

Patients considered for participation in the clinical trial must meet all of the following criteria:

1. Age ≥18 years
2. Written informed consent
3. Previously untreated, newly diagnosed and histologically confirmed DLBCL, NOS
4. Tumor tissue for retrospective central pathology review and correlative studies must be provided as an adjunct to participation in this study.
5. Patients must have at least one measurable disease site. The lesion must have a greatest transverse diameter of ≥1.5 cm and greatest perpendicular diameter of ≥1.0 cm at screening. The lesion must be confirmed to be PET-positive at the latest at the time of randomization.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
7. International Prognostic Index (IPI) status of 2 to 5
8. Appropriate candidate for R-CHOP.
9. Left ventricular ejection fraction (LVEF) of ≥50%, assessed by echocardiography or cardiac multi-gated acquisition (MUGA) scan
10. Patient must have the following laboratory criteria at screening:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 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 x 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 ≤ 1.5 × upper limit of normal (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
    d. Alanine transaminase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) ≤3 × ULN, or <5 × ULN in cases of documented liver involvement
    e. Serum creatinine clearance
       (all countries except US:) must be ≥ 50 mL/minute either measured or calculated using a standard Cockcroft and Gault formula (Cockroft, 1976)
       (US only:) must be ≥ 60 mL/minute either measured or calculated using a standard Cockcroft and Gault formula (Cockroft, 1976)

11. Females of childbearing potential (FCBP) must:

Applicable in all countries except 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 oocyte during the course of study and for 3 months after the last dose of study drug or, for R-CHOP, according to the local guidelines, whichever is longer.
c. agree to ongoing pregnancy testing during the course of the study, and after study therapy has ended. This applies even if the patient applies 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 R-CHOP, according to the local guidelines, whichever is longer. Please refer to section 7.3.1

Applicable in US:

a. 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).
b. refrain from breast feeding and donating oocytes during the course of study and for 3 months after the last dose of study drug or, for R-CHOP, according to the US guidelines, whichever is longer.
c. agree to ongoing pregnancy testing during the course of the study (every 3 weeks in women with regular menstrual cycle and every 2 weeks in women with irregular menstrual cycle), and after study therapy has ended (even if true abstinence is the chosen method of birth control).
d. not get pregnant while taking the study drug and for at least 3 months after stopping the study drug by using at the same time 2 effective methods of contraception (at least one highly effective method and one additional effective method, see Appendix G) each time engaging in sexual activity with a male, starting at least 4 weeks before taking the study drug, while taking the study drug, during breaks (dose interruptions) and for at least 3 months after stopping the study drug or, for R-CHOP, according to the US guidelines, whichever is longer. True abstinence (see Appendix G) from heterosexual sexual intercourse is also an acceptable method of contraception. The use of emergency contraception is also permitted.

12. Male participants must:

Applicable in all countries except US:

Use an effective barrier method of contraception without interruption if the patient is sexually active with female of childbearing potential (FCBP) . Male participants should refrain from donating sperm during the study participation and for 3 months after the last dose of study drug, or, for R-CHOP, according to the local guidelines, whichever is longer.

Applicable in US:
Use latex or synthetic condom each time they have sex with a woman of childbearing potential. True abstinence (see Appendix G) from heterosexual sexual intercourse is also an acceptable method of contraception. The use of emergency contraception is also permitted. Male participants should refrain from donating sperm during the study participation and for 3 months after the last dose of study drug, or, for R-CHOP, according to the US guidelines, whichever is longer.

13. In the opinion of investigator, the patient must:
    a. be able and willing to receive adequate prophylaxis and/or therapy for thromboembolic events, e.g. aspirin 70-325 mg daily or low molecular weight heparin. This is due to increased risk of thrombosis in patients treated with lenalidomide without prophylaxis. Patients unable or unwilling to take any prophylaxis are not eligible
    b. be able to understand, give written informed consent, and comply with all study-related procedures, medication use, and evaluations
    c. not have a history of noncompliance in relation to medical regimens or be considered potentially unreliable and/or uncooperative
    d. be able to understand the reason for complying with the special conditions of the pregnancy prevention risk management plan and give written acknowledgement of this.

7.2 Exclusion Criteria

Patients must be excluded from participating in this clinical trial if they meet any of the following criteria:

1. Any other histological type of lymphoma according to WHO2016 classification of lymphoid neoplasms, e.g. primary mediastinal (thymic) large B-cell (PMBL), known double- or triple-hit lymphoma or Burkitt's lymphoma.
2. Transformed NHL and/or evidence of composite lymphoma
3. History of radiation therapy to ≥25% of the bone marrow for other diseases or history of anthracycline therapy
4. History of prior non-hematologic malignancy except for the following:
    a. Malignancy treated with curative intent and with no evidence of active disease present for more than 2 years before screening
    b. Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer.
    c. Adequately treated carcinoma in situ without current evidence of disease.
5. History of myocardial infarction ≤6 months, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening arrhythmias.
6. Patients with:
    a. Known positive test result for hepatitis C (hepatitis C virus [HCV] antibody serology testing) and a positive test for HCV RNA. Patients with positive serology must have been tested locally for HCV RNA and are eligible, in case of negative HCV RNA test results.
    b. Known positive test results for chronic HBV infection (defined by HBsAg positivity). Patients with occult or prior HBV infection (defined as negative

HBsAg and positive total HBcAb) may be included if HBV DNA was undetectable (local test result), provided that they are willing to undergo ongoing DNA testing. Antiviral prophylaxis may be administered as per institutional guidelines. Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible.

c. Known seropositive for or history of active viral infection with human immunodeficiency virus (HIV)
d. Known active bacterial, viral, fungal, mycobacterial, or other infection at screening.
e. Known CNS lymphoma involvement
f. History or evidence of clinically significant cardiovascular, CNS and/or other systemic disease that would in the investigator opinion preclude participation in the study or compromise the patient's ability to give informed consent
g. History or evidence of rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption
h. Vaccination with live vaccine within 21 days prior to study randomization
i. Major surgery (excluding lymph node biopsy) within up to 21 days prior to signing the informed consent form, unless the patient is recovered at the time of signing the informed consent form
j. Any anti-cancer and/or investigational therapy within 21 days prior to the start of Cycle 1. Note: Steroid pre-phase is permitted
k. Pregnancy or lactation
l. History of hypersensitivity to any component of R-CHOP, to lenalidomide, to compounds of similar biological or chemical composition as tafasitamab, IMiDs® and/or the excipients contained in the study drug formulations or R-CHOP
m. Any contraindication concerning any individual component of R-CHOP

7.3 Restrictions

Note: Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic substance that causes severe life-threatening birth defects. If lenalidomide is taken during pregnancy, a teratogenic effect can be expected. Therefore, lenalidomide is contraindicated during pregnancy. In women of child bearing potential lenalidomide is contraindicated unless the conditions for pregnancy prevention are complied with. See Appendix H to decide whether a female is of childbearing potential.

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

7.3.1 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 lenalidomide.
- Patients must be provided with appropriate patient educational brochure and patient card.

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

1. Women of child-bearing potential should use reliable methods of contraception at least 4 weeks prior to start of study drugs until 3 months after discontinuing study drugs, or, for R-CHOP, according to the local guidelines, whichever is longer. 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 vasectomised partner (vasectomy must have been confirmed by two negative semen analysis). 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 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.

2. Male patients should avoid unprotected sex with a female of child- bearing potential during treatment with the study drugs and for a washout period of 3 months after last dose of study drug, or, for R-CHOP, according to the local guidelines, whichever is longer. Patients should refrain from donating sperm from the start of dosing until 3 months after discontinuing study drugs or, for R-CHOP, according to the local guidelines, whichever is longer. 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.

7.3.2 Restrictions applicable in US

- All men, and all women of childbearing potential should undergo 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 lenalidomide.
- Patients must be provided with an appropriate patient educational brochure and a patient card.

The following restrictions apply while the patient is receiving study drugs, and for the

specified times before and after:

1. Females of childbearing potential should use at the same time 2 effective methods of contraception (at least one highly effective method and one effective method, see Appendix G) each time when engaging in sexual activity with a male, starting at least 4 weeks before taking the study drug, while taking the study drug, during breaks (dose interruptions), and for at least 3 months after stopping the study drug or, for R-CHOP, according to the US guidelines, whichever is longer. True abstinence (see Appendix G) 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.

2. Male patients should use latex or synthetic condom each time they have sex with a female of childbearing potential while taking the study drug, during breaks (dose interruptions), and for at least three months after stopping the study drug or, for R-CHOP, according to the US guidelines, whichever is longer. True abstinence (see Appendix G) from heterosexual sexual intercourse is also an acceptable method of contraception. The use of emergency contraception is permitted.

7.4 Withdrawal and Termination Criteria

7.4.1 Patient Withdrawal

For patients withdrawing for any reason from the clinical trial the Early Study Treatment Discontinuation or Early Follow-up Termination Visit, as applicable and as outlined in the Section 10 should be performed.

An explanation should be given of why the patient is withdrawing or being withdrawn from the clinical trial.

The reason for withdrawal must be noted in the Case Report Form (CRF). If the reason for withdrawal is a clinical AE, monitoring will continue until the outcome is evident. The specific event or test result(s) must be recorded in the CRF.

For patients who show clinical signs of progression/relapse of disease, an unscheduled radiological confirmation of disease progression/relapse should be performed.

In case of radiologically confirmed disease progression/relapse, patients should undergo the Early Study Treatment Discontinuation Visit and continue with the follow-up period of the trial and may receive other anti-cancer treatments (see Section 8.7.2.1) unless they must be withdrawn per patient or investigator decision.

Patient Decision

In accordance with the Declaration of Helsinki, each patient is free to withdraw from the study at any time.

Investigator Decision

Investigator(s) also have the right to withdraw patients from the study or from study treatment in the event of illness, adverse events (AEs), or other reasons concerning the health or well-being of the patient, or in the case of lack of co-operation.

The investigators are encouraged to keep a patient experiencing clinical benefit in the study unless significant toxicity puts the patient at risk or repeated cases of routine noncompliance puts the study outcomes at risk.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations.

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient´s premature withdrawal from the study and record the information on the eCRF. If the reason for withdrawal is an AE, monitoring should continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF.

Patients who are withdrawn for any reason shall not re-enter the study at any time.

Patient Replacement

Patients dropping out during screening may be replaced. If a patient discontinues the trial for any reason other than treatment related toxicity or progression/relapse of disease or death, this patient may be replaced.

7.4.2 Clinical Trial or Clinical Trial Site Termination

The investigator and the sponsor both reserve the right to terminate the study at any time at a given clinical study center. The sponsor also reserves the right to terminate the entire study or temporarily interrupt enrolment and/or dosing of already enrolled patients for further evaluation, for example, if during the ongoing evaluation of the risk/benefit ratio the sponsor decides that the study risks outweigh its benefits.

Should a termination of a given clinical study center or the whole study become necessary, then the procedures will be arranged with all involved parties. In terminating a study center, or the entire study, the sponsor and the investigators will ensure that adequate consideration is given to the protection of the patients' interests. Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and competent authorities will be notified of premature termination in accordance with applicable regulatory requirements.

8 STUDY TREATMENT

For the purpose of this protocol the following definitions apply:

Study drug shall be used synonymously with Investigational Medicinal Product (Section 8.2). Study drugs are tafasitamab and lenalidomide.

Study treatment is defined as tafasitamab in addition to R-CHOP (Arm A) or tafasitamab plus lenalidomide in addition to R-CHOP (Arm B).

Study treatment consists of tafasitamab in addition to six cycles of R-CHOP (Arm A) or tafasitamab and lenalidomide in addition to six cycles of R-CHOP (Arm B) and will be administered for up to six 21-day cycles (see Figure 2). See section 8.7 for mandatory, recommended and prohibited concomitant therapy.

8.1 Definition of Treatment Cycle

A complete treatment cycle is defined as 21 calendar days during which tafasitamab in addition to R-CHOP (Arm A) or tafasitamab and lenalidomide in addition to R-CHOP (Arm B) will be administered according to the following plan.

Arm A: Tafasitamab in addition to R-CHOP

Study treatment consisting of tafasitamab and R-CHOP will be in 21-day cycles for 6 cycles.

Drug	**Dose**	**Dosing days (21-day cycle)**
Tafasitamab	12 mg/kg IV	1, 8, 15
Rituximab	375 mg/m^2 IV	1
Cyclophosphamide	750 mg/ m^2 IV	1
Doxorubicin	50 mg/m^2 IV	1

Vincristine	1,4 mg/m^2 (max 2.0 mg total) IV	1
Prednisone/Prednisolone	100 mg/day p.o.	1-5

Arm B: Tafasitamab plus lenalidomide in addition to R-CHOP

Study treatment consisting of tafasitamab plus lenalidomide in addition to R-CHOP will be administered in 21-day cycles for 6 cycles.

Drug	**Dose**	**Dosing days (21-day cycle)**
Tafasitamab	12 mg/kg IV	1, 8, 15
Lenalidomide*	25 mg/day p.o.	1 - 10
Rituximab	375 mg/m^2 IV	1
Cyclophosphamide	750 mg/ m^2 IV	1
Doxorubicin	50 mg/m^2 IV	1
Vincristine	1,4 mg/m^2 (max 2.0 mg total) IV	1
Prednisone/Prednisolone	100 mg/day p.o.	1-5

IV= intravenous, p.o.= per os

***Lenalidomide:** Patients will self-administer a starting dose of 25 mg oral lenalidomide daily on **Days 1–10 of each 21-day cycle**. Dose modification due to toxicity is allowed in 5 mg steps. The minimum dose of lenalidomide is 10 mg on Days 1-10. Please refer to section 8.5 for the lenalidomide dose reduction guidelines.

8.2 Investigational Medicinal Product(s)

8.2.1 Tafasitamab

8.2.1.1 Tafasitamab Supplies

The sponsor will supply the Investigational Medicinal Product tafasitamab for this study.

8.2.1.2 Tafasitamab Dosage form, Packaging, Storage and Preparation

Study sites must store tafasitamab vials under refrigeration at 2° C to 8° C in its original package in an appropriate storage facility accessible only to the study site personnel.

Tafasitamab drug product (DP) is a yellowish lyophilisate supplied in single-use 20 mL glass vials. Each vial contains 200 mg of tafasitamab for reconstitution with 5 mL water for injection (WFI). Reconstitution yields 40 mg/mL tafasitamab in 25 mM sodium citrate, 200 mM trehalose and 0.02% (w/v) polysorbate 20 at pH 6.0. Each product vial is intended to deliver 200 mg of tafasitamab in 5 ml of reconstituted solution. The solution after reconstitution is colorless to slightly yellow and essentially free of foreign particles; it may contain a few white to whitish product-related particles.

For administration, tafasitamab will be diluted into a commercially available 250 mL infusion container with 0.9% (w/v) sodium chloride for injection.

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; any solution remaining in the vial has to be discarded. 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.

8.2.1.3 Tafasitamab Administration

Tafasitamab will be administered IV at a dose of 12mg/kg body weight for 6 cycles. Each 21-day cycle will consist of tafasitamab infusions on Day 1, Day 8 and Day 15, i.e. each patient will be treated with a maximum of 18 infusions of tafasitamab over the 6 cycles.

Please refer to section 8.7 of the protocol for pre-medication for tafasitamab infusions.

For the first infusion, the IV infusion rate should be 70 mL/h for the first 30 minutes and subsequently increased to a rate of 125 mL/h; the total infusion duration will be approximately 2.5 hours.

All subsequent tafasitamab infusions will be administered IV at a constant rate of approximately 125 mL/h over an approximately 2-hour period. Tafasitamab should NOT be administered as an IV push or bolus.

The infusion rate escalation schedules in this protocol and the Drug Handling Manual are recommendations. If required, the investigator should use clinical judgement to optimise patient safety by administering the infusion more slowly.

8.2.1.4 Patient Monitoring During Tafasitamab Infusion

Vital signs should be measured as outlined in Section 9.8. All supportive measures consistent with optimal patient care will be provided throughout the study according to institution standards.

Precautions for anaphylaxis should be observed during tafasitamab administration. Emergency resuscitation equipment and medications must be readily available. Additional supportive measures should also be available and may include, but are not limited to, epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen (paracetamol).

8.2.2 Lenalidomide

8.2.2.1 Lenalidomide Supplies

The Sponsor will supply the Investigational Medicinal Product lenalidomide from a commercial source as capsules in various dose strengths for oral administration as outlined in the Drug Handling Manual.

8.2.2.2 Lenalidomide Administration

Patients will self-administer a starting dose of 25 mg oral lenalidomide daily on **Days 1–10 of each 21-day cycle**. Lenalidomide dose may be reduced according to the guidelines described in section 8.5.3.

8.3 R-CHOP

R-CHOP is the standard of care and will be given according to institutional guidelines. R-CHOP is not an IMP and will not be supplied by the Sponsor.

8.3.1 R-CHOP administration

Rituximab is advised to be given approximately 30 minutes after the tafasitamab infusion, followed by the CHOP chemotherapy which will be given approximately 30 minutes after the end of the rituximab infusion.

Note: The Day 1 steroid dose being part of CHOP (100 mg prednisone or prednisolone or equivalent, IV or PO) can be used as further component of premedication prior to Tafasitamab infusion.

8.4 Treatment Compliance and Product Accountability

Patients will receive tafasitamab under the direct supervision of study site 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.

The dosing of tafasitamab will be considered appropriate if the tafasitamab dose administered is ≥80% to ≤120% of the assigned dosage per single infusion. Overdose treatment is described in Section 8.6.

Lenalidomide is to be dispensed at the initiation of each new treatment cycle for treatment from D1-10. Patients should return all unused or empty lenalidomide blister packs to the site throughout the treatment period of the study, as instructed by the investigator and keep record of lenalidomide intake at home, which will be reviewed by site personnel on an ongoing basis. A patient will be considered compliant with the protocol if the planned lenalidomide dose administered is ≥80% to 100% of the assigned dosage. Overdose treatment is described in Section 8.6.

R-CHOP therapy (non IMP) must be documented in the eCRF.

8.5 Recommended Dose Modifications, Drug Interruptions and Discontinuation Guidelines

8.5.1 Tafasitamab Dose Modifications, Drug Interruptions and Discontinuation

Dose reductions of tafasitamab are not permitted. Drug interruptions or discontinuation may occur in case of e.g. severe infusion-related reactions, allergic reactions, infections, febrile neutropenia or severe hematologic toxicity. Delaying the tafasitamab dosing is permitted for no more than 2 days (example: If dosing was planned on Day 8 delaying that dose is allowed up to day 10). Alternatively, a tafasitamab infusion may be skipped completely (e.g. on Day 8 or Day 15) and the next scheduled dose will be administered.

8.5.2 Management of Tafasitamab Infusion-Related Reactions (IRRs) and Cytokine Release Syndrome (CRS)

IRRs will be defined according to the NCI-CTCAE, Version 5.0 definition of IRR and cytokine release syndrome (Table 1).

Table 1 Definition of Infusion-Related Reaction and Cytokine Release Syndrome

NCI-CTCAE Version 5.0: Infusion-Related Reaction and Cytokine Release Syndrome

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
IRR	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV 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
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to < 40% O2*	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2*	Life-threatening consequences; urgent intervention indicated

Abbreviations: IRR=infusion-related reaction; IV=intravenous; 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); Vomiting

* Applied e.g. via breathing mask

8.5.3 Interventions for IRRs and CRSs

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 reduced to Grade 1 according to investigator assessment, the infusion can be continued at an infusion rate of 50% of the speed so far. If, after

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

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)

• only after the complete resolution of all symptoms, and after having received appropriate prophylactic medication(s) as described above, the infusion may be resumed at an infusion rate of 25% of the speed so far. If, after 1 hour, the 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 tafasitamab provided clinically appropriate precautions were undertaken. If a patient who developed a grade 3 IRR or grade 2 CRS receives further infusions, then premedication should be given before all subsequent infusions of tafasitamab throughout the study.

If precluded from further tafasitamab administrations, the patient may continue treatment with R-CHOP or lenalidomide in addition to R-CHOP.

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)

The patient must not receive any further tafasitamab infusions, but may continue treatment with R-CHOP or lenalidomide in addition to R-CHOP as per protocol.

8.5.4 Lenalidomide Dose Modifications, Drug Interruptions and Discontinuation

Lenalidomide may be given only on Day 1 to 10 of each cycle and must not be administered beyond this period.

The dose of lenalidomide may be reduced successively level by level from the starting dose of 25mg daily. This is described in below Table 2.

Table 2 Lenalidomide Dose Modification Guidelines

Starting dose	25 mg daily on Days 1-10 of each 21-day cycle
Dose Level -1	20 mg daily on Days 1-10 of each 21-day cycle
Dose Level -2	15 mg daily on Days 1-10 of each 21-day cycle
Dose Level -3	10 mg daily on Days 1-10 of each 21-day cycle

Guidelines for lenalidomide dose interruptions or discontinuations are described in Table 3 and Table 4.

Lenalidomide may be interrupted (up to 3 days) within the 10-day dosing period and may be restarted within this period at the same dose or at dose level -1, but may not be extended beyond day 10 of this cycle. If lenalidomide 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 next cycle. There will be no more than one dose reduction from one cycle to the next. Once a patient's lenalidomide dose has been reduced, no dose re-escalation is permitted.

Patients who cannot tolerate Dose Level -3 are to be discontinued from lenalidomide treatment in arm B but should continue therapy with tafasitamab plus R-CHOP for the total duration of six cycles, if possible.

Additional information

The most up-to-date information regarding constitution, dosing and most frequent AEs related to the administration of lenalidomide are contained in the summary of product characteristics (SmPC) which will be distributed to the participating sites.

8.5.5 Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone/Prednisolone Dose Modifications and Drug Interruptions and Discontinuation

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

8.5.6 Criteria to Start Next Treatment Cycle (day 1 of cycle 2-6)

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

- ANC ≥ 1,000/mm3 (unless neutropenia is due to infiltration of bone marrow)
- Platelets ≥ 75 000/mm3 (unless thrombocytopenia is due to infiltration of bone marrow)
- All other toxicities have resolved to ≤ Grade 2

In case of overlapping toxicities it should be ensured that study drugs (lenalidomide, tafasitamab) are reduced or interrupted or discontinued (see below) before any dose reductions of R-CHOP.

If the above mentioned criteria are not met on Day 1 of the planned new cycle, the next cycle should not be commenced. The patient will be evaluated again within 7 days. If the above mentioned criteria are met at any time within 7 days, the next treatment cycle may be initiated.

If the above mentioned criteria are still not met after 7 days delay, the next cycle should not commence. The patient will be evaluated again after another 7 days (or earlier). If the above mentioned criteria are met at any time within 7 days, the next treatment cycle may be initiated.

For Patients in Arm B, lenalidomide should be decreased to the next lower dose level (Table 3). If lenalidomide was already at the lowest dose level, lenalidomide treatment should be permanently discontinued.

If the above mentioned criteria are still not met after 14 days delay, the next cycle should not commence. The complete blood count should be repeated at a frequency deemed appropriate by the investigator. If the above mentioned criteria are met in Arm B, lenalidomide should be permanently discontinued and tafasitamab should be interrupted in this treatment cycle while R-CHOP treatment may be resumed. In Arm A tafasitamab should be interrupted, while R-CHOP treatment may be resumed.

If the above mentioned criteria are fulfilled, but the patient developed **non-hematological toxicity** as described in Table 4 due to lenalidomide, tafasitamab plus R-CHOP should continue even if lenalidomide is interrupted. Lenalidomide may be resumed at the next cycle if the criteria are met. Skipped doses of lenalidomide will not be made up for.

If the above mentioned criteria are fulfilled, but the patient developed **non-hematological toxicity** due to tafasitamab (for example Grade 4 IRR), lenalidomide plus R-CHOP or R-CHOP should continue even if tafasitamab was discontinued. Note that visits on Day 8 and Day 15 should still take place in such case as outlined in Section 10.

Any individual component of R-CHOP may be omitted (or reduced in dose) due to specific toxicities related to Rituximab, Vincristin, Doxorubicin, Cyclophosphamide or Prednisone in accordance with institutional guidelines.

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

8.5.6.1 Dose Modifications, Drug Interruptions and Discontinuation in Case of Hematological Toxicity (day 2-21 of each cycle)

Patients will be evaluated for AEs at each visit with the NCI CTCAE v5.0 used as a guide for grading severity. The dose of lenalidomide for each patient will be checked, interrupted and/or modified following toxicity as described below. Refer to Table 3 and Table 4 for instructions on dosing interruptions/modifications and for lenalidomide dose reduction instructions.

The toxicity management of R-CHOP will be performed according to institutional guidelines.

Guidance on managing specific toxicities is summarised in Table 3 and Table 4. Note that even if tafasitamab is interrupted or discontinued due to toxicities, visits on Day 8 and Day 15 should still take place as outlined in Section 10.

Table 3 Dose modifications and drug interruptions and discontinuation in case of specific hematological toxicities*

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

Hematological toxicity	Lenalidomide**	Tafasitamab
Trombocytopenia with bleeding***	Interrupt VTE prophylaxis Consider platelet transfusion If bleeding has been controlled and thrombocytopenia 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.	
Thrombocytopenia Grade 4	Interrupt VTE prophylaxis*** Consider platelet transfusion 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 lenalidomide	Continue tafasitamab infusion as per protocol (unless thrombocytopenia is severe, see below).
	If thrombocytopenia has resolved to ≤ Grade 2 within 7 days, lenalidomide should be restarted in the subsequent cycle at the same dose. If thrombocytopenia has not resolved to ≤ Grade 2 within 7 days, lenalidomide should be resumed in	Interrupt tafasitamab in case of very pronounced Grade 4 thrombocytopenia (platelets < 10,000/μL) unless platelet transfusion is administered If a tafasitamab infusion is delayed for three or more days, then this infusion should be skipped and tafasitamab treatment continued only at the next scheduled timepoint.

Hematological toxicity	Lenalidomide**	Tafasitamab
	the next cycle at the next lower dose level (Table 2).	

Abbreviations: ANC=absolute neutrophil count

*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.

** Lenalidomide may be given only on Day 1 to 10 of each cycle and must not be administered beyond this period

*** Patients in arm B and arm A (if applicable)

8.5.7 Dose Modifications, Drug Interruptions and Discontinuation in Case of Non-Hematological Toxicity

Table 4 Dose modifications, drug interruptions and discontinuation in case of specific non-hematological toxicity*

Non-hematological toxicity	Lenalidomide**	Tafasitamab
Thromboembolic events Grade 3-4	Discontinue permanently lenalidomide	Continue tafasitamab infusion as per protocol if clinically appropriate
Allergic reaction or hypersensitivity grade 2	If related to lenalidomide then interrupt the dose	If related to tafasitamab then interrupt the dose
	If toxicity resolves to ≤ Grade 1, restart lenalidomide at the next lower dose level (Table 2)	If toxicity resolves to ≤ Grade 1, tafasitamab may be resumed If a tafasitamab infusion is delayed for three or more days, then this infusion should be skipped and tafasitamab treatment continued only at the next scheduled timepoint.
Allergic reaction or hypersensitivity ≥ Grade 3	If related to lenalidomide then discontinue permanently	If related to tafasitamab then discontinue permanently
	Note: If the causality can not be determined and the AE may be related to lenalidomide and/or tafasitamab, discontinue both drugs permanently.	
Rash Grade 2 or 3 non-desquamating (blistering)	If related to lenalidomide then interrupt the dose	If related to tafasitamab then interrupt the dose

Non-hematological toxicity	Lenalidomide**	Tafasitamab
	If the AE resolves to ≤ Grade 1, restart lenalidomide at the same level (Table 2)	If toxicity resolves to ≤ Grade 1, tafasitamab may be resumed If a tafasitamab infusion is delayed for three or more days, then this infusion should be skipped and tafasitamab treatment continued only at the next scheduled timepoint.
Rash Desquamating (blistering) ≥ Grade 3	If related to lenalidomide then discontinue permanently	If related to tafasitamab then discontinue permanently
OR Non-desquamating Grade 4	Note: If the causality can not be determined and the AE may be related to lenalidomide and/or tafasitamab, discontinue both drugs permanently.	
Tumor flare reaction Grade 3-4***	Interrupt lenalidomide If the AE resolves to grade ≤1, restart lenalidomide and maintain the same dose level (Table 2)	Continue tafasitamab infusion as per protocol if clinically appropriate
Tumor flare reaction Grade 1-2***	Continue lenalidomide	Continue tafasitamab infusion as per protocol
Obstipation ≥ Grade 3	Interrupt lenalidomide If the AE resolves to ≤ Grade 2, restart at same dose level	Continue tafasitamab infusion as per protocol if clinically appropriate
Other lenalidomide related nonhematologic AEs ≥ Grade 3	Interrupt lenalidomide 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

*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.

** Lenalidomide may be given only on Day 1 to 10 of each cycle and must not be administered beyond this period

*** 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. (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

8.6 Tafasitamab and Lenalidomide Overdose Treatment

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

For purposes of this trial, overdose of tafasitamab is defined as any tafasitamab dose above 120% of the assigned dosage per single infusion as per protocol (see section 8.4).
For lenalidomide the overdose is defined as any dose greater than the planned dose for a particular patient as per protocol (see section 8.4).

"Overdose" should be entered in the eCRF. If accompanied by symptoms, the overdose should be reported as adverse event in the adverse event page of the eCRF together with the observed symptoms.

8.7 Concomitant and Prohibited Medication

For possible drug-drug interactions and contraindications of Lenalidomide or R-CHOP or any concomitant medication please refer to the respective SmPCs (section 4.5) or to the respective Prescribing Information (section Drug Interactions, section Contraindications).

8.7.1 Prior and Concomitant Medication

Corticosteroids administered/taken within three weeks before ICF signature will be recorded in the eCRF. Patients may continue the medications they were receiving at screening. Patients may receive concomitant medications that are medically indicated as standard of care for the treatment of symptoms and intercurrent illnesses such as diabetes, hypertension, bronchial asthma, or chronic obstructive pulmonary disease. Patients may also receive therapy to mitigate side effects of the study treatment as clinically indicated, as well as best supportive care as per institutional guidelines. All concomitant medications should be recorded in the eCRF.

8.7.1.1 Pre-Medication for Tafasitamab Infusions

Tafasitamab infusions should be administered to patients after pre-medication with oral acetaminophen (e.g., 650−1000 mg), an antihistamine such as diphenhydramine hydrochloride (50−100 mg) and glucocorticosteroids (e.g. 100 mg IV prednisone or prednisolone or equivalent) 30−60 minutes prior to starting each infusion (unless contraindicated). Note: the Day 1 steroid dose being part of CHOP (100 mg prednisone or prednisolone or equivalent, IV or PO) can be used as further component of premedication prior to Tafasitamab infusion. Premedication is mandatory for the first cycle. For patients who do not experience ≥ Grade 2 IRRs / ≥ Grade 1 CRSs to tafasitamab during the first cycle, premedication will be optional for subsequent antibody infusions at the discretion of the investigator. Otherwise, the premedication should be continued for subsequent administrations.

8.7.1.2 Steroid Pre-Phase

In patients with urgent need for a steroid pre-phase before initiation of therapy, the use of oral prednisone 25-100 mg/d or equivalent over 7 days is allowed after screening tumor investigations (imaging, blood samples) have been completed.

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

Any pre-phase steroid use must be recorded in the eCRF and adequately documented and justified in the patient's source data.

8.7.1.3 CNS Prophylaxis

Central nervous system (CNS) prophylaxis with intrathecal chemotherapy may be given according to institutional practice. CNS prophylaxis with intravenous methotrexate is allowed only if it was pre-planned before randomization and it may be administered only after the last treatment cycle and after the End of Treatment tumor assessment by PET/CT or PET/MRI.

8.7.1.4 G-CSF

As per the National Comprehensive Cancer Network guidelines, CHOP belongs to chemotherapy regimens with an intermediate risk for febrile neutropenia. There is the potential for increased neutropenia risk with the addition of monoclonal antibodies such as Rituximab or tafasitamab, as well as lenalidomide. To mitigate the risk of febrile neutropenia, primary neutropenia prophylaxis with G-CSF or Peg-G-CSF is mandatory in this study. The dose and schedule of the selected drug will be done according to local practice and institutional guidelines.

8.7.1.5 Pre-planned radiotherapy

Pre-planned local radiotherapy may be administered to initial sites of bulky or extranodal disease according to institutional guidelines. Pre-planned radiotherapy may be administered only after the last treatment cycle and after the End of Treatment tumor assessment by PET/CT or PET/MRI. However, the decision to administer radiotherapy as well as the location to be treated must be determined before randomization. In this case, the radiotherapy will not count as a next anti-lymphoma treatment. All unplanned radiotherapy administered to patients or a decision to switch radiotherapy to a different lesion will be considered as a next anti-lymphoma treatment.

8.7.1.6 Prophylaxis of Venous Thromboembolism (VTE) for Patients Receiving Lenalidomide

Prophylaxis of VTE is mandatory in patients receiving lenalidomide (Arm B) due to increased risk of thrombosis in patients treated with lenalidomide without prophylaxis. Patients must receive e.g. aspirin 70-325mg p.o. daily or low molecular weight heparin. Patients with a history of VTE or thrombophilia may participate if they are willing to be on full anticoagulation during the treatment if randomized to Arm B. The choice of VTE prophylaxis agent is at investigator´s discretion and should be tailored to the patient's individual risk/benefit profile by taking into account the individual thrombotic risk, bleeding risk, and the quality of compliance with the VTE prophylaxis.

8.7.1.7 Prophylaxis of Hepatitis B Reactivation

Patients in countries where prophylactic anti-viral medications for hepatitis B reactivation

are the standard of care may be treated prophylactically. Patients with occult HBV infection, defined as negative HBsAg and positive total HBcAb and negative HBV DNA, are eligible and must undergo ongoing DNA testing (irrespective of prophylactic treatment) as described in the Schedule of Assessments (Section 10).

8.7.1.8 Anti-Infectious Prophylaxis

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

8.7.1.9 Prophylaxis of tumor lysis syndrome

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 with high risk of TLS should be followed closely and appropriate laboratory monitoring should be performed as per institutional guidelines.

8.7.2 Prohibited Medication

8.7.2.1 Anticancer Therapies

No radiotherapy (including limited field radiotherapy) is permitted after the screening PET/CT scan for initial disease assessment has been performed, except for the pre-planned radiotherapy described in Section 8.7.1.5. Other than the study drugs, R-CHOP and permitted concomitant medication, 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 lenalidomide during the treatment period of the study.

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

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

8.7.2.2 Live vaccines

Because of the immunosuppressive effects of the study treatment, administration of any live vaccine is not recommended during the treatment period and at least 6 months after the end of treatment.
Thereafter the decision to administer live vaccine is at the investigator's discretion and should follow local guidelines for R-CHOP (the haematological status of individual patient, including B-cell depletion, should be considered).

8.8 End of Clinical Trial Treatment

It is the responsibility of the investigator to provide follow-up medical care for all patients, who have completed study treatment (or discontinued study treatment early), or should refer them for appropriate ongoing care.

9 CLINICAL TRIAL PROCEDURES

All study-required procedures should occur as outlined in Section 10. Excursions from the timing of assessments will be considered protocol deviations and should be recorded in the documents along with the reasons for excursion.

9.1 Patient Numbering

Each patient is identified in the study by a 7-digit Patient Number (Patient No.) that is assigned by the Interactive Response Technology (IRT) system when the patient is screened (i.e. signs the ICF), and is retained as the primary identifier for the patient throughout his/her entire participation in the trial.

- The Patient No. consists of the 5-digit Center Number (assigned to the study site) and a sequential 2-digit patient number suffixed to it, so that each patient is numbered uniquely across the entire study
- The investigator or designated study personnel will contact the IRT system and provide the requested identifying information for the patient to register them into the IRT system and assign a Patient No.
- Once assigned, the Patient No. must not be reused for any other patient.

9.2 Assigning Patients to Treatment Groups

All patients who fulfil all inclusion criteria and who are not barred by any of the exclusion criteria will be treated with R-CHOP and randomly assigned to study drugs comprising tafasitamab or tafasitamab plus lenalidomide in a 1:1 ratio.

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

9.3 Re-Screening

A patient 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:

1. The patient has already consented and met all of the inclusion and none of the exclusion criteria and his or her randomization was delayed due to an unexpected change in the patient's personal situation (e.g. family issues).

2. The patient previously failed to be eligible due to any event (e.g., planned surgery, laboratory test result) that has been resolved.

Note: A patient should only be re-screened if there is a clear indication that the patient may be eligible according to the currently valid study protocol.

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

1. The eligible patient will receive a new Patient number via the IRT

2. A new electronic case report form (eCRF) will be completed

3. The patient will be documented as re-screened in the source documents.

A re-screened patient can be randomized, if all of the inclusion criteria are met and none of the exclusion criteria are met.

9.4 Demographic Data/Relevant Medical History and Current Medical Conditions/Baseline Stage and Prognostic Classification

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

At the time of signing of the ICF, relevant medical history and current medical conditions should be recorded. The medical history of DLBCL should be documented in detail, including all symptoms at screening. Also, examinations leading to the diagnosis of DLBCL should be documented in the patient's source documents. This may include, for example, results of laboratory examinations, imaging results, or clinical symptoms related to DLBCL. 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 (Appendix C). Additionally, the disease risk assessment as per IPI (Appendix D) and patient status as per Eastern Cooperative Oncology Group (ECOG) performance status criteria (see Appendix B), will be recorded.

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

9.5 Diagnostic Lymphoma Biopsy and Central Pathology Review

For each participating patient suitable and sufficient archival tumor tissue material must be provided. A central pathologist will provide confirmation of the histological diagnosis of DLBCL. 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.

The local pathology report indicating DLBCL diagnosis is acceptable for determining a patient's eligibility for receiving the first trial treatment. Central pathology review is mandatory, but retrospective in nature. Tissue samples or archival tumor tissue material, as stated above should be submitted within 30 days of patient randomization. Archival paraffin blocks are preferred. In exceptional cases where no such blocks can be provided, unstained slides are also acceptable. In such case, tissue curls will be required in addition.

In case of discrepancies between the assessments of the local and the central pathologists, the assessment of the central pathologist prevails. If the DLBCL diagnosis of the local pathologist cannot be confirmed by the central pathologist, and a patient's treatment has already commenced, the patient may remain in the study.

9.6 Bone marrow assessment

As per the Lugano criteria (Cheson, 2014), a bone marrow aspiration and biopsy is not mandated in patients who undergo PET/CT or PET/MRI. However, bone marrow assessments may be

performed according to investigator´s discretion. The data of such examination will be collected in the eCRF.

9.7 Radiographic Imaging Assessment

Radiographic assessments will be performed at the timepoints indicated in the Schedule of Assessments (Section 10). Additional radiographic assessments may be performed by the investigator during the course of the study, if deemed necessary.

A CT scan (with contrast unless contraindicated) covering at least the neck, chest, abdomen, pelvis, and any other disease sites as well as PET scans are required for the pre-treatment tumor assessment. The use of historical PET/CT or PET/MRI scans within a maximum of 21 days before signature of ICF is permitted as long as they are of acceptable quality and cover the aforementioned anatomical areas. Information on extranodal involvement (e.g. gastric or skin involvement) will be recorded in the source documents.

During the course of the study, response assessments will be performed covering the aforementioned anatomical areas as for screening unless additional regions are deemed required to be covered.

A mid-treatment CT/MRI should be performed at Cycle 3 D18 +/- 3 days, i.e. prior to the end of cycle 3; a mid-treatment PET/CT (or PET/MRI) is optional and should be triggered by local guidelines.

An end of treatment PET/CT or PET/MRI should be performed 4-8 weeks after the last study treatment.

During the follow-up period CT scans should be performed roughly every 6 months.

If disease progression/relapse is diagnosed purely on the basis of clinical symptoms, a CT scan with IV contrast (or MRI if IV contrast is contraindicated) or PET/CT (or PET/MRI) is required within 4 weeks of diagnosing disease progression/relapse based on symptoms. If such imaging was performed, it does not need to be repeated at the Early Treatment Discontinuation visit.

NOTE: PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality.

If using a hybrid machine to acquire both PET and CT, the PET must be performed prior to the CT with IV contrast as to not compromise PET results.

If independent CT and PET scanners are used, and the patient is receiving both scans on the same day, the PET must be performed prior to the CT with IV contrast. Assessment of PET results is based on Lugano classification (Cheson, 2014; see Appendix E)

Lesion measurements and other parameters relevant for the response assessment based on Lugano classification (Cheson, 2014; see Appendix E) will be collected in the eCRF.

9.8 Vital Signs

Vital signs include blood pressure, heart rate, body temperature.

Vital signs will be measured at the time points described in the Schedule of Assessments (Section 10). Vital signs are to be obtained pre-tafasitamab infusion, and then at least 3 times during the infusion, and as clinically indicated.

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 corresponding AEs to be recorded.

If possible, before vital signs are measured, the patient should be resting for at least 5 minutes. Ideally/Optimally, 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. Body temperature should be measured according to normal hospital practice.

9.9 Electrocardiograms, Echocardiograms or Cardiac MUGA scans

Standard 12-lead resting ECGs will be obtained at the various time points described in the Schedule of Assessments (Section 10). Ideally, ECGs will be recorded after the patient has rested in a supine position for at least 5 minutes. ECG will first be interpreted locally.

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.

The sponsor will further organize a central review of ECG tracings. In case of discrepancies between the outcome of the local and the central assessment, the assessment of the central reviewer will prevail.

Echocardiogram or cardiac MUGA scan will be obtained at screening and at End of Treatment Visit or Early Study Treatment Discontinuation Visit to evaluate cardiac function, including assessment of LVEF (data will be collected in the eCRF).

LVEF is the central measure of left ventricular systolic function. LVEF is the fraction of chamber volume ejected in systole (stroke volume) in relation to the volume of the blood in the ventricle at the end of diastole (end-diastolic volume). SV is calculated as the difference between EDV and end systolic volume (ESV). LVEF is calculated from:

LVEF: [SV/EDV] x 100

9.10 Physical Examination (PE)

Physical examination will be performed according to Schedule of Assessments (Section 10).

A full PE will be performed by the investigator or a qualified designee during the screening and at the End of Treatment Visit or Early Study Treatment Discontinuation Visit.

Full physical examination should include at least: cardiovascular, respiratory, abdominal, and neurologic assessment. The tumor assessment includes the evaluation of presence and degree of enlarged lymph nodes, liver and spleen assessments.

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 PEs may be focused on tumor response assessment (e.g., lymph nodes, liver, spleen) and AEs per investigator discretion.

9.11 Body Weight Measurement

Body weight will be measured as indicated in the Schedule of Assessments (Section 10).

The body weight measured on Day 1 of a cycle will be used to calculate the tafasitamab dose to be used throughout this cycle.

9.12 B-symptoms, ECOG performance status

B-symptoms and ECOG performance status will be assessed at the timepoints indicated in the Schedule of Assessments (Section 10).

9.13 Hepatitis Virus Serology

Patients will be examined according to the schedule in Section 10 for viral hepatitis B and C. Hepatitis B biomarkers include hepatitis B surface antigen (HBsAg), total anti-hepatitis B core antibody (anti-HBc) and anti-hepatitis B surface antibody (anti-HBs). Patients with a positive test for anti-HBc can only be included if hepatitis B viral DNA (HBV DNA) is not detected. **In these patients only**, HBV DNA should be assessed at various subsequent visits as outlined in Section 10.

In the context of exclusion criteria, seropositive for or active viral infection with hepatitis B virus (HBV) means:

a) HBsAg positive
b) 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 antibody (anti-HCV). 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 Hepatitis C Virus (HCV) antibodies **and** a positive test for HCV RNA.

9.14 Pregnancy Testing

A pregnancy test will be performed for females of childbearing potential (FCBP) at various time points either by urine pregnancy test or beta-human chorionic gonadotropin (β-HCG) test of a serum sample (see Section 10). 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 drug, 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 drug. The patient must not receive study drug until the Investigator or Designee has verified that the results of these pregnancy tests are negative.

Applicable in US: FCBP must have two negative pregnancy tests prior to starting study drug, even if true abstinence is the chosen method of birth control. The first pregnancy test must be performed within 10-14 days before study drug initiation, the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient must not receive study drug until the Investigator or Designee has verified that the results of these pregnancy tests are negative.

9.15 Local Laboratory Testing

Local laboratory tests will be performed according to Section 10.

Laboratory results are required for determining patient eligibility for study enrolment and will be used for the primary statistical analysis of the study results.

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, vomiting, imaging procedure with a contrast). This procedure and the rationale behind it must be explicitly documented in source data. Such repeated assessment (once only) of the concerned parameters will not be counted as “re- screening” for that patient.

Local laboratory samples may be taken up to 24 hours before study drug administration. Local laboratory results will be used for taking treatment or clinically related decisions, or for the immediate safety management of a study patient. The investigator or designee should review,

laboratory results before dosing so that the administration of the investigational medicinal product (IMP) may be adjusted or interrupted if necessary.

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

9.16 Immunogenicity (anti-tafasitamab antibodies)

Serum samples for anti-tafasitamab antibody analysis will be collected according to the Schedule of Assessments (Section 10).

Serum samples for anti-tafasitamab antibody analysis will be handled and stored as specified in the laboratory manual at the study site until shipment on dry ice to an external analytical laboratory. At each sampling time point, the obtained serum sample should be split into 2 aliquots (a primary and a back-up sample).

9.17 Tafasitamab Pharmacokinetic Assessments

Serum samples for tafasitamab PK analysis will be collected according to the Schedule of Assessments (Section 10).

Serum samples for PK analysis of tafasitamab will be handled and stored as specified in the laboratory manual at the study site until shipment on dry ice to an external analytical laboratory. At each sampling time point, the obtained serum sample should be split into 2 aliquots (a primary and a back-up sample).

9.18 Other Laboratory Evaluations

Blood and tumor specimens for the analysis of exploratory biomarkers will be collected throughout the study according to the Schedule of Assessments (Section 10) and will be characterized for markers, which are important in the mechanism of action of tafasitamab, or could predict response to the study drugs.

Samples for exploratory biomarker analysis will be handled and stored as specified in the laboratory manual.

10 SCHEDULE OF ASSESSMENTS

Clinical Trial Schedule of Assessments

Screening and Treatment Periods, and Early Study Treatment Discontinuation Visit or End of Treatment Visit

	SCR Baseline	Cycle 1 (21d)			Cycle 2 (21d)			Cycle 3 (21d)				Cycle 4 (21d)			Cycle 5 (21d)			Cycle 6 (21d)			Early Study Treatment Discontinuation/ End of Treatment Visit [a]
		D1	D8	D15	D1	D8	D15	D1	D8	D15	D18	D1	D8	D15	D1	D8	D15	D1	D8	D15	
Day*	**- 21– 0**	1	8	15	1	8	15	1	8	15	18	1	8	15	1	8	15	1	8	15	**6 weeks ± 2 weeks from End of Treatment**
Starting Evaluations and Eligibility																					
Informed consent	X																				
Inclusion/exclusion criteria	X	X1																			
Demography and Medical History[b]	X																				
Disease staging/Ann Arbor	X																				
Disease risk assessment (IPI)	X																				
Pre-planned radiotherapy	X																				
Pre-planned CNS prophylaxis with IV Methotrexate	X																				
Throughout Evaluations																					
Prior and concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (F- Full / L-Limited)[c]	F	L			L			L				L			L			L			F
ECOG performance status	X	X			X			X				X			X			X			X
Body weight	X	X			X			X				X			X			X			X
B-symptoms	X	X			X			X				X			X			X			X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
12-lead resting ECG	X											X									X
Adverse events (AEs, SAEs and AESIs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
New anti-lymphoma treatment																					X
Laboratory																					
All countries: Serum Pregnancy test (FCBP)[e] (local)	X																				X
EU countries: Urine pregnancy test (FCBP)[e] (local)		X1			X1			X1				X1			X1			X1			
US only: Urine pregnancy test (FCBP) (local)[m]		X1		(X1)	X1		(X1)	X1		(X1)		X1		(X1)	X1		(X1)	X1		(X1)	X
Pregnancy and Risk Counselling[e]	X	X			X			X				X			X			X			X
US only: Pregnancy and Risk Interview guideline	X	X			X			X				X			X			X			X
Hematology[f] and Serum chemistry[g] (local)	X	X1	X1	X1	X1	X1	X1	X1	X1	X1		X1	X1	X1	X1	X1	X1	X1	X1	X1	X
Coagulation (aPTT or PTT, PT, INR) (local)	X											X									
Serology Hepatitis B, Hepatitis C (local)	X																				X
Hep. B DNA by PCR (if indicated; local)[h]	X				X			X				X			X			X			X
Hep. C RNA by PCR (if indicated; local)[h]	X																				
Serum IgG, IgA and IgM (local)	X											X									X
Thyroid Stimulating Hormone (TSH; local)	X											X									X

	SCR Baseline	Cycle 1 (21d)			Cycle 2 (21d)			Cycle 3 (21d)				Cycle 4 (21d)			Cycle 5 (21d)			Cycle 6 (21d)			Early Study Treatment Discontinuation/ End of Treatment Visit [a]
		D1	D8	D15	D1	D8	D15	D1	D8	D15	D18	D1	D8	D15	D1	D8	D15	D1	D8	D15	
B-, T- and NK cell flow cytometry (central)		X1	X1	X1	X1							X1									X
Blood cell count and NKCC at baseline (central)		X1																			
ctDNA in peripheral blood (central)		X1			X1							X1									X
Immunophenotyping and functional assays PBMC (central)		X1			X1																X
Anti-tafasitamab antibodies (central)		X1						X1							X1						X
PK tafasitamab (central)		X2			X2			X2				X2			X2			X2			X
Imaging and Tumor evaluation																					
PET/CT or PET/MRI [i]	X																				X
CT or MRI [i]											X[l]										
Echocardiogram or cardiac MUGA scan	X																				X
Tumor evaluation[i]	X										X[l]										X
Biopsy /Tissue																					
Bone marrow aspiration and biopsy[j] (local)	X																				X
Tissue block	X																				
Fresh tumor tissue (only for participants of substudy)	X																				X[l]
Drug Administration[k]																					
Mandatory pre-infusion medication[k]		X1	X1	X1																	
Tafasitamab infusion[k]		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
If randomized to Tafasitamab + Lenalidomide arm																					
Lenalidomide tablets allocation (incl. patient home intake record)		X			X			X				X			X			X			

X1: pre-dose; X2: pre-dose and 1 hour (± 15 min) after end of tafasitamab infusion

Footnotes:

* A visit window of ± 2 days is allowed for all visits starting from C1D8 until C6D15. For C1D1 a visit window of +1 day applies. Study treatment should start within 24 hours of randomization.

a End of treatment Visit is defined as 6 ± 2 weeks after End of Treatment. End of Treatment is defined as day 21 of the last treatment cycle the patient started. Patients who discontinue early because of toxicity or withdraw consent at any time during the study should return for an Early Study Treatment Discontinuation Visit 6 +/-2 weeks after day 21 of the last treatment cycle the patient started. Patients who discontinue early because of progression/relapse of disease may have this visit earlier at the discretion of the investigator.

b At screening, age, sex, race/ethnic origin and relevant medical history will be recorded. This includes history of prior non-hematologic cancers, e.g. prostate cancer, melanoma.

c Full physical examination should include at least: cardiovascular, respiratory, abdominal, and neurologic assessment. The tumor assessment includes the evaluation of presence and degree of enlarged lymph nodes, liver and spleen assessments. Limited physical examination will be guided by the individual patient's status and will include body systems associated with symptoms (e.g. respiratory, heart, skin) and/or the underlying DLBCL disease (lymph node status, liver, spleen).

d Vital signs include blood pressure, heart rate, body temperature. Vital signs are to be obtained pre-tafasitamab infusion, and then at least 3 times during the infusion, and as clinically indicated.

e Note: Risk counselling is mandatory for all participants, incl. males at screening. After randomization, risk counselling will only continue at the indicated frequency for patients that are randomized to Arm B. A serum/urine pregnancy test is mandatory only for females of childbearing potential (FCBP). For US only: the serum pregnancy test for FCBP at screening needs to be done within 10-14 days prior to treatment initiation.

f Hematology lab includes hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count, percent and absolute white count differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils).

g At screening and during treatment, serum chemistry includes Na, K, Ca, phosphate, chloride, creatinine, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, LDH, AP, uric acid, calculated creatinine clearance and C-reactive protein, glucose.

h HCV RNA by PCR only if the patient is anti-HCV antibody positive. In anti-HBc-positive patients, the HBV DNA titer needs to be determined using real-time PCR at Day 1 of each cycle and until at least 1 year after the last treatment cycle.

i Tumor measurements by PET/CT or PET/MRI of the neck, chest, abdomen and pelvis to be performed according to the Lugano criteria for malignant lymphoma (Cheson, 2014; see Appendix E) at screening and 6 ±2 weeks after day 21 of the last treatment cycle the patient started. Note: A mid-treatment CT or MRI scan and tumor evaluation is required at Cycle 3 D18 ± 3 days prior to the end of cycle 3; a mid-treatment PET/CT is optional. Every effort should be made to use the same scan modality (CT or MRI) for all assessments. If progression/relapse is diagnosed purely on the basis of clinical symptoms, a CT-scan or PET/CT is required within 4 weeks of clinical diagnosis. In such case the imaging does not need to be repeated at the early treatment termination visit. MRI scans may be used instead of CT-scans in patients for whom CT-scans are contraindicated. Screening visit PET/CT or PET/MRI: A PET/CT or PET/MRI of suitable quality that has been taken less than 21 days prior to signing the ICF may be used.

j As per the Lugano criteria (Cheson, 2014), a bone marrow aspiration and biopsy is not mandated in patients who undergo PET/CT or PET/MRI. However, bone marrow assessments may be performed according to local guidelines. The data of such examination will be collected in the eCRF.

k Tafasitamab infusions should be given after pre-medication with oral acetaminophen (650 – 1000 mg), an antihistamine such as diphenhydramine hydrochloride (50-100 mg), and glucocorticosteroids (e.g. 100 mg IV prednisone or prednisolone or equivalent) 30-60 minutes prior to starting each infusion in cycle 1. The Day 1 steroid dose being part of CHOP (100 mg prednisone or prednisolone or equivalent, IV or PO) can be used as part of the premedication prior to Tafasitamab infusion. After cycle 1, for patients who do not experience any grade 2 or higher infusion-related reactions (IRRs) with their previous infusion, pre-mediation at subsequent treatments may be omitted according to institutional treatment guidelines. **NOTE:** The R-CHOP treatment is considered to be standard of care (SoC) and will be given according to institutional guidelines. Rituximab is advised to be given approximately 30 minutes after the end of tafasitamab infusion, followed by the CHOP chemotherapy which will be given approximately 30 minutes after the end of the rituximab infusion.

l In selected centres, if the patient progresses and agrees on an additional biopsy, fresh material shall be provided

m **Applicable in US**: For FCBP who have regular menstrual cycles, urine pregnancy test should be performed on day 1 of each cycle and at the End of Tretment visit. For FCBP with irregular menstrual cycle,s urine pregnancy tests should be done on day 1 and on day 15 of each cycle, and at End of Treatment Visit.

Follow Up Period

	FU 1	FU 2	FU 3	FU 4	FU 5	End of study	Early FU term.
Month after Early Study Treatment Discontinuation/ End of Treatment Visit*	**3**	**6**	**9**	**12**	**15**	**18**	**any**
Evaluations							
Survival follow-up[a]	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X
Limited physical examination[b]	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X
B-symptoms	X	X	X	X	X	X	X
Vital signs[c]	X	X	X	X	X	X	X
12-lead resting ECG (only if clinically indicated)						X	X
Adverse events (AEs, SAEs and AESIs)[d]	X	X	X	X	X	X	X
New anti-lymphoma treatment[e]	X	X	X	X	X	X	X
Laboratory							
Serum Pregnancy test (FCBP)[f]	X					X	X
Hematology and Serum chemistry (local)[g]	X	X	X	X	X	X	X
HBV-DNA by PCR (if indicated; local)[h]	X	X	X	X			X
Thyroid Stimulating Hormon (TSH; local)						X	X
B-, T- and NK cell flow cytometry (blood) (central)		X					
Anti-tafasitamab antibodies (central)	X	X					
PK tafasitamab (central)	X	X					
Serum IgG, IgA and IgM (local)	X	X	X	X	X	X	X
ctDNA in peripheral blood (central)		X					
Imaging and Tumor evaluation							
CT or MRI[i]		X		X		X	X
Tumor evaluation[i]	X	X	X	X	X	X	X
Biopsy /Tissue							
Tissue block or slides at time of relapse (optional)[j]							X
Fresh tumor tissue (only for participants of substudy)							X[k]

Footnotes:

* A visit window of ± 2 weeks is allowed throughout the follow-up period

a Should the patient decease at any time, the date of death as well as cause of death should be reported (if available)

b Limited physical examination will be guided by the individual patient's status and will include body systems associated with symptoms (e.g. respiratory, heart, skin) and/or the underlying DLBCL disease (lymph node status, liver, spleen).

c Vital signs include blood pressure, heart rate, body temperature.

d During the FU period AEs (irrespective of the causality) will be reported.

e For patients with disease progression/relapse during the follow-up period or in case end of treatment tumor assessment indicate residual disease (partial metabolic response) or no metabolic response (SD), additional antineoplastic therapies are permitted at the discretion of the investigator. Recording of new anti-lymphoma treatments is requested.

f For females of childbearing potential (FCBP) only

g Hematology lab includes hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count, percent and absolute white count differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils). Serum chemistry includes Na, K, Ca, phosphate, chloride, creatinine, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, LDH, AP, uric acid, calculated creatinine clearance and C-reactive protein, glucose.

h In anti-HBc-positive patients, the HBV DNA titer needs to be determined using real-time PCR at each FU visit until at least 1 year after the last treatment cycle.

i Tumor measurements by CT or MRI of the (neck, if indicated), chest, abdomen and pelvis to be performed according to the Lugano criteria for malignant lymphoma (Cheson, 2014). MRI scans may be used instead of CT-scans in patients for whom CT-scans are contraindicated. In case of early termination, a CT/MRI and tumor evaluation should be performed unless contraindicated. Measurements of tumor response will be performed only until progression/relapse or follow-up completion, whichever comes first.

j Investigators are encouraged to collect an optional tumor biopsy at the time of disease progression/relapse.

k In selected centres, if the patient progresses/relapses and agrees on an additional biopsy, fresh material shall be provided

11 EFFICACY, PHARMACOKINETIC, SAFETY AND OTHER VARIABLES

11.1 Efficacy Assessments

Efficacy assessments will be made according to the revised response criteria for malignant lymphoma based on the guidelines of the Lugano Classification (as reported by Cheson, 2014) and will be based on investigator assessment (Appendix E)

Efficacy will be evaluated in terms of ORR, DoR, PFS, EFS, OS, TTP and TTNT (Please see section 13.12 and section 13.13 for the definition of efficacy endpoints).

Imaging assessment of efficacy/disease response will be recorded at the end of cycle 3 and after the end of treatment (6±2 weeks after day 21 of the last treatment cycle the patient started) as well as approximately every 6 months during the FU period.

11.2 Safety Assessments

11.2.1 Local Safety and Hematology Laboratory Testing

Any abnormal laboratory findings that constitute an AE should be reported as such and should be followed up until the outcome is known. Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the patient's condition (e.g., ordering a white blood cell (WBC) differential count to help characterise a high or low WBC count, or ordering a determination of red blood cell (RBC) indices to help characterise a low hematocrit).

11.2.2 Safety Monitoring

The patients will be closely observed and questioned for any kind of AE during the study procedures and at follow-up appointments throughout the study period with non-leading questioning (e.g., "How do you feel?"). AEs also may be detected when they are volunteered by the patient during or between study visits or through physical examination, laboratory tests, or other assessments.

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

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

11.2.3 Definition of Adverse Events, Serious Adverse Events and Adverse Events of Special Interest

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product, which does not necessarily have a causal relationship to this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not it is considered related to that study drug.

AEs include any clinically significant deterioration of a patient's medical status after the signing of the ICF. Also, an increase in the frequency or intensity of a pre-existing event or conditions and events resulting from protocol mandated procedures (e.g., invasive procedures) fall under the definition of AEs.

Please note that in the context of this protocol symptoms that are clearly associated to disease progression/relapse do not fall under the definition of AEs.

The PI or designee should evaluate each AE to determine the following:

- Relationship to the study drug or R-CHOP (suspected/not suspected)
- Duration (start and end date, or if continuing at end of study)
- Intensity: the intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:
    - mild: tolerable
    - moderate: interferes with normal activity
    - severe: incapacitating (causes inability to perform usual activities or work)
- Severity, i.e., toxicity grade: determined according to the NCI-CTCAE version 5.0, 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 noninvasive 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
- Outcome
    - All non-serious AEs must be followed up for a final outcome. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not yet resolved" is an acceptable final outcome for non-serious AEs at the end of a patient's participation in the study. All SAEs must be followed up for a final

outcome until resolution or, if resolution becomes unlikely, until stabilization or death.

- Action taken (no action taken; study drug or R-CHOP temporarily interrupted; study drug or R-CHOP permanently discontinued due to this AE; medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
- Seriousness: **an SAE is defined as serious if it:**
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization signifies that the patient was an inpatient for at least one overnight stay) **unless hospitalization is for**:
    - routine treatment or monitoring of the studied indication, not associated with deterioration of symptoms related to DLBCL
    - elective or preplanned treatment for a pre-existing condition that is unrelated to DLBCL and has not worsened since signing of the informed consent
    - social reason and respite care in the absence of any deterioration in the patient's general condition
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly or birth defect
  - is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical intervention to prevent one of the outcomes listed previously.

The term "life-threatening" refers to an event in which the patient was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Medical judgment should be exercised in deciding whether an AE is serious in other situations: important AEs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definitions should also be considered as serious.

AEs of special interest (AESIs) for tafasitamab are: TLS, IRRs and allergic reactions to study drug ≥ grade 3, cytokine release syndrome, second primary malignancies, hepatitis B reactivation, progressive multifocal leukoencephalopathy (PML).

AEs of special interest (AESIs) for lenalidomide: Second primary malignancies.

Unlike routine safety assessments, SAEs and AESIs are monitored continuously and have special reporting requirements (see Section 11.2.4 below).

For each AE, the investigator should determine the causality (relationship to the study drug or R-CHOP) based on his/her clinical experience and on the information given in the IB. The causal relationship of all AEs to the study drug or R-CHOP will be judged as either suspected or not suspected. A suspected causal relationship means at least a reasonable possibility that the event is caused by the study drug or R-CHOP. If no relationship has been provided by the investigator, the event will be considered as related to the study drug.

Information about adverse drug reactions already known about the investigational study drugs can be found in the IB or SmPC, or will be communicated in the form of Investigator Notifications. This information will be included in the patient ICF and should be discussed with the patient during the study, as needed.

11.2.4 Reporting of AEs, SAEs and AEs of Special Interest

All AEs that occur after the provision of informed consent until the end of the study will be recorded in the eCRF and in the patient's medical records, whether or not the Investigator considers them to be related to the study drugs (tafasitamab, Lenalidomide) or R-CHOP. All AEs should be recorded in terms of diagnoses, if possible.

For screening failure patients only SAEs will be recorded in the eCRF. Non-serious AEs will only be recorded in the patient's medical records.

In addition, SAEs and AESIs will be recorded on the SAE report form. Study centers and investigators are instructed to report SAEs and AESIs to the contract research organization (CRO) within 24 hours. NOTE: Follow-up SAE reporting has to be sent to the CRO within 24 hours as well. Notification of initial or follow-up SAE/AESI information must be transmitted to the CRO as described in the investigator site file.

The sponsor is responsible for submission of expedited (including 7-day and 15-day SUSAR) reports and periodic reports (including DSURs) to the regulatory authoritiess, IECs/IRBs and investigators as per country specific requirements.

IRRs and allergic reactions to study drugs grade 3 or higher, cytokine release syndrome or TLS, which are AESIs in this study, should be reported as diagnosis along with their respective symptoms in one event term (e.g., "IRR with symptoms of hives, chills and fever" for IRRs; "TLS with symptom of hyperuricemia" for TLSs).

Contact details of the Sponsor's Medical Monitor, the CRO Medical Monitor (24/7 coverage), and for SAE reporting are provided in the Investigator Site File.

11.2.5 Pregnancy

Any pregnancy that occurs during study participation should be reported using a Clinical Trial Pregnancy Form. To ensure patient safety, each pregnancy of a study patient or a female partner of a study patient must also be reported within 24 hours of learning of its occurrence to the CRO as indicated in the investigator site file.

Female study patients who become pregnant must be withdrawn from the study treatment period.

A newly diagnosed pregnancy in a patient or female partner of a study patient who has received any study drug is not considered an SAE unless it meets any criteria of seriousness or it is suspected that the study drug interacted with a contraceptive method and led to pregnancy.

If the pregnancy results in clinical consequences/complications in mother or child, e.g., if the child is born with a birth defect, this should be reported as an SAE of mother or child as applicable.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities or maternal and newborn complications. Every infant has to be followed up for 2 months after delivery.

11.3 Other Variables

11.3.1 Biomarkers

Biomarker assessments will include B-, T- and NK and other cell counts in peripheral blood or tumor tissue, the expression of CD19 and CD20 in tumor tissue, as well as analysis of prognostic and exploratory markers by IHC, FISH (e.g., MYC, BCL2 and BCL6 protein levels and gene rearrangements). Blood samples will be stored to enable the analysis of peripheral blood mononuclear cell populations (e.g. monocytes or CD4+ T-cells), to facilitate the investigational research topics that may arise during the course of the study.

To assess the pharmacodynamic effect of tafasitamab, circulating tumor DNA (ctDNA) will be quantified serially in the peripheral blood as an early indicator of treatment response and to detect minimal residual disease (MRD).

Gene expression profiling of tumor biopsies at screening will be used to determine the cell of origin (COO) subtype and to assess tumor infiltrating immune cells via their gene signature. Together, with the quantification of tumor-associated macrophages and tumor infiltrating NK cells by immunohistochemistry this will provide a deeper understanding of the mode of action of tafasitamab.

Optional analysis of Biomarkers on fresh tumor biopsy samples
In a selected subset of participating centers, and as an optional analysis that a patient needs to consent to individually, fresh biopsy samples will be collected and analysed at a central laboratory. Such analysis will include a quantitative assessment of CD19 and CD20 on malignant B-cells. The selection of centers will be driven by the logistical needs of the planned biomarker analyses.

11.4 Appropriateness of Measurements

All assessments and measurements are appropriate and generally regarded as standard medical practice.

12 DATA HANDLING AND QUALITY ASSURANCE

12.1 Completing and Signing Case Report Forms

For electronic CRFs, trained clinical trial site personnel will enter the data giving reasons for any missing data. Any errors should be corrected within the electronic system. The audit trail will record all changes made, the date and time of the correction, and the person correcting the error. The PI will provide his/her electronic signature on the CRF.

12.2 Clinical Monitoring

MorphoSys or designee will monitor the clinical trial conduct at the clinical trial sites to ensure data quality (accurate and complete data collection), patient's safety and right protection.

12.3 Audit and Inspection

According to ICH E6-GCP, the sponsor or regulatory authorities may audit the investigational site. The sponsor's or CRO's Quality Assurance Unit, independent of the Clinical Research and Development Department, is responsible for auditing the study.

The investigator(s) must accept that regulatory authorities may conduct an inspection to verify compliance of study conduct with regulatory requirements and GCP.

12.4 Clinical Data Management

The sponsor will be responsible for the processing and quality control of the data. The handling of data, including data quality control, will comply with applicable regulatory guidelines. Adverse events and concomitant medications terms will be coded using MedDRA and WHO medication dictionary.

12.5 Archiving

All study documentation at the clinical trial site and sponsor site will be archived in accordance with the applicable regulatory requirements as well as International Council for Harmonization (ICH) E6-Good Clinical Practice (GCP) and the sponsor's quality standards and SOPs.

13 STATISTICAL METHODS AND PLANNED ANALYSIS

13.1 General 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 Statistical Analysis Plan (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 trials.

The sponsor and/or designated 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.

13.2 Timing of Analysis

13.2.1 Safety Run-in Analysis

Patient profiles and Listings of Adverse events will be provided in case a Safety Data Review is performed. For details please see Section 6.3.

13.2.2 Primary Completion Analysis

The primary completion analysis will be performed based on data cut-off 30 days after all patients have performed their End of Treatment Visit (EOT).

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

13.2.3 Final Analysis

After the last patient completed the last visit, a final analysis will be performed.

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

Additional Safety and follow-up analyses may be performed by the sponsor as and when deemed necessary.

13.3 Population for Analysis

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).

13.3.1 Full Analysis Set (FAS)

All patients who are randomized to either study arm will be included in FAS. Efficacy analysis will be performed on FAS. Patients will be analyzed according to the study treatment they were randomized to.

13.3.2 Safety Set (SAF)

All patients who received at least one dose of study drug (tafasitamab or tafasitamab plus lenalidomide). Safety analyses will be performed on SAF.

Patients will be analyzed according to the study treatment they actually received, which is defined as the treatment the patient received on the first day of study treatment.

13.3.3 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 statistical analysis plan. Sensitivity analyses for efficacy endpoints may be performed using PPS.

13.3.4 Pharmacokinetic Analysis Set (PKAS)

All patients who have at least one quantifiable tafasitamab serum concentration.

13.3.5 Immunogenicity Analysis Set (IAS)

All patients with at least one anti-tafasitamab antibody assessment

13.4 Patient Disposition, Demographics and Baseline Characteristics

A table will be provided with the following information:

- Number of patients included in each analysis set.
- Number of patients screened, randomized, received at least one dose of trial treatment, discontinued treatment within first 21 days, discontinued treatment during the 6 cycles of treatment, prematurely discontinued trial and finished complete follow-up and had their scheduled last-visit. Reasons of end of treatment and end of study will be provided.
- Number of patients withdrawn from the trial and the reason for withdrawal.

Demographic information will be summarised using descriptive statistics for the FAS. Gender and race/ethnic origin will be summarised by counts and percentages.

Medical history will be summarised by counts and percentages using MedDRA system organ class (SOC) and preferred term classifications. Concomitant medications will be recorded and coded using the WHO Drug Dictionary Enhanced and grouped by Anatomical Therapeutic Chemical (ATC) classes. Tabulations with counts/percentages will show the number of medications/percentage used in each class.

The following baseline characteristics and medical history related to DLBCL will be summarised displaying the

- duration of disease since initial diagnosis
- IPI
- Ann Arbor staging
- Bulky vs non-bulky disease
- COO (from local lab, if available, and which assay used e.g. gene expression profiling or IHC)
- B symptoms
- Extranodal involvement yes or no
- Number of sites of extranodal involvement
- Bone marrow involvement by PET yes or no
- Bone marrow involvement by biopsy yes, no, not available
- LDH above upper limit of normal yes or no

Details will be provided in the Statistical Analysis Plan.

13.5 Treatments (study treatment, concomitant therapies, compliance)

13.5.1 Study Treatment

Duration of study treatment exposure and cumulative dose will be summarized by treatment arm. The number of patients with dose changes/interruptions will be presented by treatment arm, along with reasons for the dose change/interruption. The safety set will be used for the tables and listings.

13.5.2 Prior and concomitant therapies

Corticosteroids administered/taken within three weeks before ICF signature and concomitant medications and significant non-drug therapies taken concurrently with the study treatment will be listed and summarized by Anatomical Therapeutic Chemical Classification System (ATC) term, preferred term and treatment arm. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

The safety set will be used for all above mentioned concomitant medication tables and listings.

13.5.3 New Anti-lymphoma therapies

New anti-cancer therapies including medications (non-study drugs), surgery and radiotherapy, started after randomization will be listed and summarized by Anatomical Therapeutic Chemical Classification System (ATC) term, preferred term and treatment arm.

The safety set will be used for all above mentioned concomitant medication tables and listings.

13.6 Hypothesis

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

13.7 Sample Size Determination

As this is a Phase Ib study primarily conducted to explore safety endpoints, no formal statistical hypothesis has been established for the sample size calculation of this trial.
With a sample size of 12 patients in each arm, there is a 60% probability to observe 4 or more patients with unacceptable toxicity if the underlying incidence rate of these toxicities is 33%.

With a sample size of 30 patients in each arm, there is a 55% probability to observe 10 or more patients with unacceptable toxicity if the underlying incidence rate of these toxicities is 33%.

13.8 Procedures for Missing, Unused and Spurious Data

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 trial will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

If a patient discontinues the trial for any reason other than treatment related toxicity or progression of disease or death, this patient may be replaced.

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

13.9 Procedures for Reporting Deviations from Original Statistical Plan

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

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

13.10 Primary Objective Analysis

The Primary objective of this trial is to assess the safety and tolerability of tafasitamab in addition to R-CHOP and tafasitamab plus lenalidomide in addition to R-CHOP in patients with newly diagnosed DLBCL. To assess safety and tolerability, the incidence and severity of haematological and non-haematological 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 adverse events (CTCAE), version 5.0. Further details are provided in Section 11.2.

13.11 Key Secondary Objective Analysis

To assess efficacy of tafasitamab in addition to R-CHOP and tafasitamab plus lenalidomide in addition to R-CHOP in terms of ORR and PET-negative CR rate at end of treatment.

13.11.1 Objective response Rate at the end of treatment

The ORR is defined as the proportion of patients with CR or PR based on the response achieved at the end of treatment (tumor scans performed until 56 days after last date of study drug administration).

The ORR along with 95% exact CI (using Clopper-Pearson exact method) will be presented for both treatment arms.

The number and percentage of patients with CR and the number of patients with PR will be presented by treatment arm.

13.11.2 The Metabolic, PET-negative complete response rate at the end of treatment

The metabolic PET-negative CR rate is defined as the proportion of patients who achieved metabolic PET-negative CR based on PET/CTs performed 6±2 weeks after End of Treatment.

The metabolic PET-negative CR rate along with 95% exact CI (using Clopper-Pearson exact method) will be presented for both treatment arms.

13.12 Secondary Objectives Analysis

Further details on the subsequent analyses will be specified in SAP.

13.12.1 Long-term Safety Analysis

Incidence and severity of AEs will be presented for patients in the follow-up period, starting from 31st day after End of Treatment to the End of Study Visit.

13.12.2 Efficacy endpoints

To assess efficacy (based on Lugano 2014 criteria) of tafasitamab in addition to R-CHOP and tafasitamab plus lenalidomide in addition to R-CHOP with respect to the following endpoints:

13.12.2.1 Best ORR until End of Study

The best ORR 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 for both treatment arms.

The number and percentage of patients with CR and the number of patients with PR will be presented by treatment arm.

13.12.2.2 Metabolic, PET-negative Complete Response Rate at the End of Study

The metabolic PET-negative CR rate is defined as the proportion of patients who achieved metabolic PET-negative CR based on PET/CTs performed until end of study.

The metabolic PET-negative CR rate along with 95% exact CI (using Clopper-Pearson exact method) will be presented for both treatment arms.

13.12.2.3 Progression Free Survival (PFS) Rate at 12 Months and 24 Months

Tumor assessments will be performed by local radiologists using Lugano 2014 criteria (Cheson, 2014).

PFS is defined as the time from the date of randomization to the date of the first radiologically or histologically/cytologically 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 at 12 and 24 months, and the associate 95% CI will be summarized for each treatment arm.

13.12.2.4 Event-free Survival (EFS) Rate at 12 Months and 24 Months

EFS 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 or start of new anti-lymphoma treatment. If a patient has not progressed or died or started a new anti-lymphoma treatment at the analysis cut-off date, EFS will be censored on the date of last contact.

Kaplan Meier plots will be used to estimate the distribution of EFS. The EFS probabilities at 12 and 24 months, and the associate 95% CI will be summarized for each treatment arm.

13.12.2.5 Time to Next Anti-lymphoma Treatment (TTNT)

Time to next anti-lymphoma treatment (TTNT) is defined as the time from the date of randomization to the date of administration of next anti-lymphoma treatment or death due to any cause. If a patient has not received next anti-lymphoma treatment or did not die until the analysis cut-off date, he/she will be censored on the date of last contact.

Kaplan Meier plots will be used to estimate the distribution of TTNT. The TTNT probabilities at 12 and 24 months, and the associate 95% CI will be summarized for each treatment arm.

13.12.2.6 Overall Survival at 12 Months and 24 Months

Overall survival (OS) is defined as the time from randomization until death from any cause and documented by the date of death.

Kaplan Meier plots will be used to estimate the distribution of OS. The OS probabilities at 12 and 24 months, and the associate 95% CI will be summarized for each treatment arm.

13.12.3 Pharmacokinetic Analysis

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

13.12.4 Immunogenicity Analysis

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

13.12.5 ctDNA Analysis

Descriptive statistics of ctDNA will be performed for both treatment arms and will be presented by means of Min, Max, Mean, Median, Q1, Q3 and 95% CI of mean will be presented by visit.

13.12.6 NKCC Analysis

Descriptive statistics of NKCC will be performed for both treatment arms and will be presented by means of Min, Max, Mean, Median, Q1, Q3 and 95% CI of mean will be presented by visit.

13.13 Exploratory Objective Analysis

The following efficacy endpoints:

a. ORR and

b. PFS

will be assessed in both treatment arms based on the following biomarkers:

i. Cell of origin
ii. NK-cell count in the tumor tissue
iii. NK-cell gene expression signature in the tumor tissue
iv. Macrophage count in the tumor tissue
v. Macrophage gene expression signature in the tumor tissue
vi. Quantitative and semi-quantitative CD19 expression on tumor cells (in diagnostic biopsies and at progression/relapse)
vii. Quantitative and semi-quantitative CD20 expression on tumor cells (in diagnostic biopsies and at progression/relapse)

More details will be provided in the SAP.

13.14 Safety Analysis

The primary and one of the secondary objective of this study is to assess the safety and tolerability of tafasitamab in addition to R-CHOP and tafasitamab plus Lenalidomide in addition to R-CHOP in adult patients with newly diagnosed DLBCL.

All Safety Analysis will be presented by treatment arms and overall.

Primary Endpoint:

Incidence and severity of TEAEs.

Treatment emergent adverse events are all adverse events which start after the first dose of study treatment until 30 days after day 21 of the last treatment cycle the patient started.

Secondary Endpoint:

Incidence and severity of AEs will be presented for patients in the study starting from 31st day after End of Treatment to the End of Study Visit.

Note: At the time of primary completion analysis, all non-treatment emergent AEs collected (AEs prior to first dose of study drug administration and after 30 days of End of Treatment) will be listed.

13.14.1 Adverse Events

All adverse events which start after the first dose of study treatment until 30 days after day 21 of the last treatment cycle the patient startedwill be considered as a treatment emergent adverse event (TEAE). Adverse events that start during the study but before the time of the first dose of study treatment (e.g. screening period) will be classified as a non-treatment emergent adverse event and will be included in adverse events listings, but will not be summarized.

TEAEs will be coded according to MedDRA SOC and preferred terms. Incidence and frequency of all AEs will be summarised by SOC, preferred term, relationship to treatment, severity and seriousness.

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

- All Treatment-emergent adverse events (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.

Adverse Events of Special Interests in this study are:

- Infusion-related reactions ≥ grade 3
- Cytokine release syndrome
- Allergic reactions to tafasitamab ≥ grade 3
- Second primary malignancies
- PML
- Hepatitis B reactivation
- TLS

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

13.14.2 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). 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 subjects with clinically notable 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 relevance of central laboratory variables will be tabulated by time point for each clinical laboratory analyte using frequency tabulations.

Clinical laboratory analytes 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 SAF. Further details will be specified in the SAP.

13.14.3 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.

13.14.4 Electrocardiograms

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:

Bazett's: $QTcB = QT/\sqrt{RR}$
Fridericia's: $QTcF = QT/\sqrt[3]{RR}$

Where relative rate (RR) = 60/heart rate

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

14 SPECIAL REQUIREMENTS AND PROCEDURES

14.1 Regulatory and Ethical Considerations

This trial was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH-GCP), with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki.

Before starting this trial, the clinical trial protocol will be submitted to the IEC/IRB and/or regulatory authorities (in accordance with local regulations) for evaluation. The trial will not start before the IEC/IRB and/or regulatory authorities gives written approval or a favourable opinion as required. Any amendments to the protocol will require IEC/IRB and/or regulatory authority approval as required before implementation, except for changes necessary to eliminate an immediate hazard to patients.

14.2 Investigator's Responsibilities

14.2.1 Overall Responsibilities

Before initiating a trial, the investigator/institution must ensure approval/favorable opinion is obtained from the IEC/IRB for the protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with the protocol, ICH-GCP, applicable local regulations and the ethical principles laid down in the Declaration of Helsinki.

The investigator is responsible to provide oversight of the conduct of the study at their site. Investigators will apply due diligence to avoid protocol deviations. If the investigator feels a protocol amendment is necessary to improve the conduct of the study, such an amendment is required to be agreed upon by the sponsor and approved by the IEC/IRB and/or regulatory authorities as required prior to implementation. Notwithstanding the need for approval of protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this trial, even if this action represents a deviation from the protocol. In such cases, the sponsor must be notified of this action, as well as the IEC/IRB and/or regulatory authorities as required.

14.2.2 Patient Informed Consent

The investigator or his/her representative is responsible to explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study. Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign the informed consent form (ICF) prior to any study-specific procedures being performed. The original ICF must be kept as part of the study records at the site, and a copy must be provided to the patients or their legally authorized representative. Patients must be re-consented to the most current version of the ICF(s) during their participation in the study. The process of obtaining informed consent must be documented in the patient's source documents.

14.2.3 Direct access to Source Data/ Documents

The investigator has to give access to all relevant data and records to monitors, auditors, other designated agents of the sponsor, IEC/IRB, and regulatory authorities as required. Personal medical information will always be treated as confidential. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

14.2.4 Confidentiality Regarding Clinical Trial Patients

Patients will be assigned a unique identifier by the sponsor. The investigator must ensure that any patient´s data that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

14.2.5 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators and sub-investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

14.3 Publication of trial protocol and results

Information on the protocol will be posted in a publicly accessible database such as clinicaltrials.gov and/or the EU Clinical Trials Register. In addition, the results of this trial will

be submitted for publication and/or posted in a publicly accessible database in accordance with local regulations.

14.4 Publication Policy

Any presentation or publication of data from this trial will be intended as a joint publication by the investigator(s)/appropriate trial site personnel and appropriate sponsor personnel. Authorship will follow the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts Submitted to Biomedical Journals and will be defined prior to the first publication.

For multicentre studies, it is mandatory that the first publication be based on data from all centres, and that the data are analysed and submitted as stipulated in the protocol by a statistician assigned by the sponsor.

Thus, no investigator or institution may publish any results of the trial conducted at their site, before such a first multicentre publication is made which covers the data from all sites. The authors have the final responsibility for the decision to submit their manuscript and shall be given full access to the data resulting from the trial.

The coordinating investigator and/or authors shall coordinate any intended publication of trial results with the sponsor, to enable the sponsor to ensure that results are presented in a responsible and coherent manner.

The sponsor reserves the right to review all manuscripts and abstracts at least 60 days before their submission for publication or presentation. This is not intended to restrict or hinder publication or presentation, but is to allow the sponsor to protect the confidentiality of information and to provide comments that may not yet be available to the investigator.

At the sponsor's request, any confidential information (other than trial results) will be deleted and all reasonable comments made by the sponsor will be incorporated prior to the submission for publication or presentation. In the rare event that such publication would affect the patentability of any invention to which the sponsor has rights, the sponsor has the right to request an additional delay to the proposed publication of no more than 90 days so as to allow the sponsor to protect its intellectual property rights.

The results of the trial may be used by the sponsor for the purposes of national and international registration, publication, and information for medical professionals. If necessary, the authorities will be notified of the investigators' names, addresses, qualifications, and extent of involvement.

15 REFERENCES

Boltezar L, Prevodnik VK, Perme MP et al. Comparison of the algorithms classifying the ABC and GCB subtypes in diffuse large B-cell lymphoma. *Oncol Lett.* 2018;15(5):6903–6912.

Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. *Cancer Res.* 1971;31(11):1860-1861.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J Clin Oncol.* 2014;32(27):3059-3068.

Choi CH, Park YH, Lim JH, et al. Prognostic Implication of Semi-quantitative Immunohistochemical Assessment of CD20 Expression in Diffuse Large B-Cell Lymphoma. *J Pathol Transl Med.* 2016;50(2):96-103.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16(1):31-41.

Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood.* 2010;116(12):2040-2045.

Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet.* 2013;381(9880):1817-1826.

Czuczman MS, Trněný M, Davies A, et al. A Phase 2/3 Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Lenalidomide Versus Investigator's Choice in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *Clin Cancer Res.* 2017;23(15):4127-4137.

Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. *Lancet Oncol.* 2013;14(6):525-533.

Flowers CR, Sinha R, Vose JM. Improving outcomes for patients with diffuse large B-cell lymphoma. *CA Cancer J Clin.* 2010;60(6):393-408.

Ginaldi L, De Martinis M, Matutes E, et al. Levels of expression of CD19 and CD20 in chronic B cell leukaemias. *J Clin Pathol.* 1998;51(5):364–369.

Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol.* 2006;24(19):3121-3127.

Hammer O. CD19 as an attractive target for antibody-based therapy. *MAbs*. 2012;4(5):571-577.

Johnson NA, Boyle M, Bashashati A, et al. Diffuse large B-cell lymphoma: reduced CD20 expression is associated with an inferior survival. *Blood.* 2009;113(16):3773-3780.

Jurczak W, Zinzani PL, Gaidano G, et al. Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. *Ann Oncol.* 2018;29(5):1266-1272.

Klisovic R, Winderlich M, Ambarkhane S, et al. Single-agent MOR208 in patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL): a single-arm phase II study. *EHA Library (conference poster).* 2017;180615:E839.

Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large-B-cell lymphomas. *N Engl J Med.* 2008;359(22):2313-2323

Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol.* 1989;7(11):1630-1636.

Nowakowski GS, LaPlant B, Habermann TM, et al. Lenalidomide can be safely combined with R-CHOP (R2CHOP) in the initial chemotherapy for aggressive B-cell lymphomas: phase I study. *Leukemia.* 2011;25(12):1877-1881.

Nowakowski GS, Hong F, Scott DW, et al. Addition of lenalidomide to R-CHOP (R2CHOP) improves outcomes in newly diagnosed diffuse large B-cell lymphoma (DLBCL): First report of ECOG-ACRIN1412 A randomized Phase 2 US Intergroup study of R2CHOP vs R-CHOP. *Hematol Oncol.* 2019;37(S2)37-38.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-55.

Olejniczak SH, Stewart CC, Donohue K, et al. A quantitative exploration of surface antigen expression in common B-cell malignancies using flow cytometry. *Immunol Invest.* 2006;35(1):93-114.

Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol.* 2008;9(2):105-116.

Salles GA, Johannes Duell J, Eva González-Barca E, et al. Single-Arm Phase II Study of MOR208 Combined with Lenalidomide in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma: L-Mind. *Blood*. 2018;132(S1):227.

Schmitz R, Wright GW, Huang DW, et al. Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. *N Engl J Med.* 2018;378(15):1396-1407.

Sehn LH, Congiu AG, Culligan DJ, et al. No Added Benefit of Eight Versus Six Cycles of CHOP When Combined with Rituximab in Previously Untreated Diffuse Large B-Cell Lymphoma Patients: Results from the International Phase III GOYA Study. *Blood*. 2018;132(S1):783-783.

Shipp MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 1993;329(14):987-994.

Thieblemont C, Tilly H, da Silva MG, et al. First Analysis of an International Double-Blind Randomized Phase III Study of Lenalidomide Maintenance in Elderly Patients with DLBCL Treated with R-CHOP in First Line, the Remarc Study from Lysa. *Blood*. 128(22):471-471.

Tokunaga T, Tomita A, Sugimoto K, et al. De novo diffuse large B-cell lymphoma with a CD20 immunohistochemistry-positive and flow cytometry-negative phenotype: molecular mechanisms and correlation with rituximab sensitivity. *Cancer Sci.* 2014;105(1):35-43.

Vaidya R, Witzig TE. Prognostic factors for diffuse large B-cell lymphoma in the R(X)CHOP era. *Ann Oncol*. 2014;25(11):2124-2133.

Vitolo U, Chiappella A, Franceschetti S, et al. Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial. Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial. *Lancet Oncol.* 2014;15(7):730-737.

Vitolo U, Trněný M, Belada D, et al. Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. *J Clin Oncol.* 2017;35(31):3529-3537.

Vitolo U, Witzig TE, Gascoyne RD, et al. ROBUST: First report of phase III randomized study of lenalidomide/R-CHOP (R2-CHOP) vs placebo/R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. *Hematol Oncol.* 2019;37(S2):36-37.

Wilson WH, Sin-Ho J, Pitcher BN, et al. Phase III Randomized Study of R-CHOP Versus DA-EPOCH-R and Molecular Analysis of Untreated Diffuse Large B-Cell Lymphoma: CALGB/Alliance 50303. *Blood*. 2016;128(22):469-469.

Witzig TE, Reeder CB, LaPlant BR, et al. A phase II trial of the oral mTOR inhibitor everolimus in relapsed aggressive lymphoma. *Leukemia*. 2011;25(2):341-347.

Woyach JA, Awan F, Flinn IW, et al. A phase 1 trial of the Fc-engineered CD19 antibody XmAb5574 (MOR00208) demonstrates safety and preliminary efficacy in relapsed CLL. *Blood*. 2014;124(24):3553-3560.

16 APPENDICES

Appendix A

Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

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

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

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

Appendix B

ECOG Performance Status Scale (Oken, 1982)

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

Appendix C

Ann Arbor Staging

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

Note: All cases are subclassified to indicate the absence (A) or presence (B) of the systemic B symptoms of significant unexplained fever (> 38 ^{0}C), night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.

[a] The designation "E" generally refers to extranodal contiguous extension (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.

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

Adapted from:

Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. *Cancer Res*. 1971;31:1860-1861.

Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds Meeting. *J Clin Oncol*. 1989;7:1630-1636.

Appendix D

International Prognostic Index

IPI Risk Factor

Ann Arbor Stage III or IV

Age > 60 years

Serum LDH >1 x ULN

ECOG Performance status ≥ 2

Extranodal involvement ≥ 2[1]

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

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

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

Adapted from:

Shipp MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med.* 1993;329:987-94.

Appendix E

Lugano Response Criteria for Malignant Lymphoma (Cheson, 2014)

Target and Non-Target Lesions

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

All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease as non-target lesions (e.g. cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites, bone, bone marrow).

Split Lesions and Confluent Lesions

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

Response	**Imaging**	**Lymph node and extra lymphatic sites**	**Non target lesions**	**Liver and spleen**	**Bone marrow**	**New lesion**
CR	PET	Score of 1, 2 or 3[a] with our without a residual mass on 5PS[b]	Not applicable	Not applicable	No evidence of FDG-avid disease in marrow	None
	CT	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi. No extra lymphatic site of disease	Absent	Regress to normal	Normal by morphology; if intermediate, IHC negative	None
		Score 4 or 5 [b] with reduced uptake compared with			Residual uptake higher than uptake in normal	

Response	Imaging	Lymph node and extra lymphatic sites	Non target lesions	Liver and spleen	Bone marrow	New lesion
	PET	baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	Not applicable	Not applicable	marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	None
PR	CT	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm x 5 mm, but smaller than normal, use actual	Abnormal/normal, regressed, but no increase	Spleen must have regressed by >50% in length beyond normal	Not applicable	None

Response	Imaging	Lymph node and extra lymphatic sites	Non target lesions	Liver and spleen	Bone marrow	New lesion
		measurement for calculation				
SD	PET	Score 4 or 5 [b] with no significant change in FDG uptake from baseline at interim or end of treatment	Not applicable	Not applicable	No change from baseline	None
	CT	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met	No increase consistent with progression	No increase consistent with progression	Not applicable	None
PD	PET	Score 4 or 5 [b] with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	Not applicable	Not applicable	New or recurrent FDG-avid foci	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation); if uncertain regarding etiology of new lesions, biopsy or interval scan may be considered
		An individual node/lesion must be abnormal with: LDi > 1.5 cm and				Regrowth of previously resolved lesions A new node > 1.5 cm in any axis

Response	Imaging	Lymph node and extra lymphatic sites	Non target lesions	Liver and spleen	Bone marrow	New lesion
	CT	Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly (> 13 cm), the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline.	New or clear progression of preexisting non-target lesions	New or recurrent splenomegaly	New or recurrent involvement	A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma

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

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured;

dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

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

Appendix F

Information on Investigational and Registered Products

The Investigator's Brochure for tafasitamab, Summary of Product Characteristics (approved in EU) for lenalidomide will be supplied to the study sites.

Appendix G (Applicable in US only)

Definition of Highly Effective, Effective and Unacceptable Methods of Birth Control and True Abstinence

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

Unaccaptable methods of birth control are progesterone-only "mini-pills", IUD Progeserone 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 mehtod of contraception)

Appendix H

Females of childbearing potential (FCBP)[1]

Applicable in all countries except US:

Criteria to assess whether a female is not of childbearing potential (at least 1 criterion must be fulfilled):

a) Aged 50+ and naturally occurring amenorrhea of over 1 year (Amenorrhea that occurred as a result of cytostatic therapy or during breastfeeding period does not exclude the possibility that the patient is fertile)

b) Premature ovarian failure that was confirmed by a gynecologist

c) Bilateral salpingo-oophorectomy or hysterectomy as part of medical history

d) XY genotype, Turner syndrome, uterine agenesis

Applicable in US:

Criteria to assess whether a female is not of childbearing potential (any of the following):

a) Females who have been in natural menopause for at least 24 consecutive months

b) Females who have had a hysterectomy and/or bilateral oophorectomy

c) Females who have not started menstruating

[1] This term is used synonymously with „females of reproductive potential“ or „women who can get pregnant“