STATISTICAL ANALYSIS PLAN

Final Version 2.0 - Addendum Version 8.0

MorphoSys AG

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GERMANY

A Phase II, Single-Arm, Open-Label, Multicentre Study to Evaluate the Safety and Efficacy of Lenalidomide Combined with MOR00208 in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R-R DLBCL)

Protocol No: MOR208C203

IND Number:	114,856
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Sponsor:	MorphoSys AG
Author:	[redacted]
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	Version 2.0 – Addendum Version 1.0, 09 August, 2019
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	Version 2.0 – Addendum Version 5.0, 02 December, 2020
	Version 2.0 – Addendum Version 6.0, 21 December, 2020
	Version 2.0 – Addendum Version 7.0, 31 March, 2021
	Version 2.0 – Addendum Version 8.0, 10 February, 2023

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SIGNATURE PAGE

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[redacted]

Addendum 8.0 – Changes to Addendum 7.0

SAP Section	Changes	Rationale
SAP ADDENDUM 8.0	• Definition of the distinction between combined therapy phase and monotherapy phase for observing Adverse Events per exposure time to treatment described in specific details (Section 20.11.3)	• Modifying the algorithm for incorporating counts of treatment emergent Adverse Events when doses are skipped at the start of monotherapy phase or events beyond end of treatment for classification to the monotherapy period (Section 23.1.1)
	• Forest Plots will be updated to the 48-month landmark instead of the 30 month landmark (Section 20.8.2)	• This is due to the longer follow up time in the study (23.1.2)

Addendum 7.0 – Changes to Addendum 6.0

SAP Section	Changes	Rationale
SAP ADDENDUM 7.0	• Addition of analyses to address the impact of the Corona pandemic on trial conduct.	• Regulatory requirement and sponsor responsibility to monitor the influence of the pandemic on trial conduct

Addendum 6.0 – Changes to Addendum 5.0

SAP Section	Changes	Rationale
SAP ADDENDUM 6.0	• Addition of a sensitivity analysis	• Sensitivity analysis of scientific interest
	• Extension of search terms and phrases used to classify death	• Modification of the search algorithm to account for new data entries in the data base
	• Extension of search terms used to identify patients who discontinued LEN as planned after 12 Cycles as per protocol	• Modification of the search algorithm to account for new data entries in the data base

Addendum 5.0 – Changes to Addendum 4.0

SAP Section	Changes	Rationale
SAP ADDENDUM 5.0	• Addition of multiple sensitivity analyses using the SAF instead of the FAS • Addition of multiple subgroup and supportive analyses • Addition of multiple safety-related tabulations	• Analyses applying the Intent-to-treat principle • Additional subgroup and supportive analyses to address relevant scientific questions • Additional safety-related analyses to evaluate the safety of the treatment

Addendum 4.0 - Changes to Addendum 3.0

SAP Section	Changes	Rationale
SAP ADDENDUM 4.0	Additional subgroup analyses on centrally confirmed DLBCL patients.	To account for updated central pathology information.

Addendum 3.0 - Changes to Addendum 2.0

SAP Section	Changes	Rationale
SAP ADDENDUM 3.0	Update on the signature page: new “Head of Drug Safety & Pharmacovigilance”	Department head has changed
SAP ADDENDUM 3.0	Forest plots for 24 month rates of PFS, DoR and OS in non-biomarker subgroups	A graphical illustration facilitating data interpretation

Addendum 2.0 - Changes to Addendum 1.0

SAP Section	Changes	Rationale
SAP ADDENDUM 2.0	Efficacy assessment in subgroups of different BCL-2 expression levels	Relevant analysis from the medical and scientific point
SAP ADDENDUM 2.0	Efficacy in different age subgroups	Relevant analysis from the medical and scientific point
SAP ADDENDUM 2.0	Identification of patients with a history of indolent lymphoma	Improved detection algorithm covering a broader range of search terms
SAP ADDENDUM 2.0	Swimmers plot for patients with history of indolent lymphoma	A graphical illustration facilitating data interpretation
SAP ADDENDUM 2.0	Deaths	Improved algorithm to cover a broader range of terms
SAP ADDENDUM 2.0	Lenalidomide dose intensity	Relevant information for interpreting both efficacy and safety data
SAP ADDENDUM 2.0	Categorization of the NHL reference diagnosis as determined by central pathology	Mapping of the central pathology assessment with the terms used for reporting
SAP ADDENDUM 2.0	Efficacy endpoints are reported for selected NHL subtypes as determined by central pathology. Swimmer plots are generated by NHL subtypes	Relevant for the interpretation of efficacy data

Addendum 1.0 - Changes to SAP Version 2.0

SAP Section	Changes	Rationale
8.2 Enrolled patients	Some categories for study drug discontinuation were added.	The updated patient disposition shows the patient flow more granular.
All Sections	All Listings specified for the FAS are produced for the SAF.	One patient who is not in the FAS should also be represented in the Listings.
SAP ADDENDUM	A visualization for the distribution of compliance by Cycle was added.	A graphical illustration is useful for interpretation.
SAP ADDENDUM	An analysis for the relative dose change was added.	The information is relevant for interpretation of efficacy outcome variables.
SAP ADDENDUM	Additional analyses on drug safety were added: • TEAE by search category • Time to first TEAE • Tabulation of most frequent TEAEs with 10% cut-off • Reasons for temporary MOR00208 and LEN interruptions	Helpful information to interpret drug safety.
SAP ADDENDUM	Additional efficacy analyses: • Time to PR • Time to best response • Event-free survival	Helpful information to interpret the efficacy of the drug combination.
SAP ADDENDUM	Subgroup analyses: • Safety and efficacy in patients who discontinued LEN • Safety in patients who are treated with a reduced dose of LEN (incidence of TEAEs, duration of TEAEs) • Patients treated with different CMC batches (efficacy and safety are evaluated) • Efficacy by age category • OS by best response • Forest plots for various efficacy variables and	Various subgroup analyses were added to obtain a clearer picture on the efficacy and safety of the drug combination in different subgroups.

	different subgroups • Efficacy in patients ineligible for stem cell transplantation: definition of additional subgroups • Patients with high and low NK cell numbers at baseline: additional subgroup definition • Swimmers plot for responders	
APPENDIX	APPENDIX: LIST OF MEDDRA QUERIES	MedDRA queries necessary to perform some of the safety-relevant analyses specified in the SAP Addendum.

Changes to the Previous Version

SAP Section	Changes	Rationale
High Level Summary of changes	The SAP has been re-written with 1. Additional sections (Eg: 6. Definition and general Methodology), 2. Additional definitions. (Eg: Reference start date and Study day) 3. Additional details (Eg: censoring rules for PFS endpoint),	In the previous SAP some of the details were missing. Additional Sections are added for the sake of completeness and providing added clarification on Statistical programming to be performed. Additional definitions are provided because they were not provided in the previous SAP and they are needed for the sake of completeness and clear guidance on Statistical programming. Additional Details are added for the sake of completeness and providing added clarification on Statistical programming to be performed.
Signature Page	[redacted]	1. – 6. Organizational changes

2 List of abbreviations and definition of terms	Addition of 1. ABC: Activated B-cell 2. GCB: Germinal center B-cell 3. GEP: Gene expression profiling 4. HDC/HDT: High-dose chemotherapy 5. IHC: Immuno-histochemistry 6. INV: Investigator 7. IV: Intravenous Removed 8. ANC: Absolute neutrophil count 9. CPH: Cox proportional hazards 10. CS: Clinically significant 11. DoBOR: Duration of best overall response 12. ROC: Receiver operating characteristic	1.-7. Abbreviations are now included due to addition of new details 8.-12. Definitions and abbreviations are not used in this SAP version
3 Introduction	1. Section “1. Purpose and scope of the document” from the previous SAP version renamed to “3. Introduction” 2. Section “2. Introduction” from the previous SAP version removed	1. Details from section remained unchanged 2. Information from this section are already documented in the protocol and are not necessary for the SAP
4 Study Objectives and Endpoints	1. Section “3. Study Objectives” and “4. Study endpoints” from the previous SAP version combined to one section 2. Removed “Patients MUST have been treated with at least one dose of both study medications in order to qualify for the primary endpoint” in ORR endpoint definition 3. Definition of secondary endpoints DCR, DoR, PFS, OS, TTNT removed 4. Secondary endpoint definition for safety expanded to “Incidence , frequency and severity of treatment-emergent AEs” 5. Addition of anti-MOR00208 antibody response classification in secondary endpoint of immunogenicity 6. Endpoint definition for item 10: evaluation of efficacy parameters in cohorts with different International Prognostic Index classifications added 7. Endpoint definition for study objective 11: evaluation of TTP added 8. Endpoint “Immune Response” from previous SAP version removed 9. Endpoint “Biomarkers” from previous SAP version removed 10. Definition for study endpoint 12 includes new biomarker subgroups, e.g. Cell-of-origin	1. The new table with combined information on study objectives and endpoints provides direct link between objectives and endpoints 2. Restriction for the primary endpoint not needed for the calculation of ORR 3. A reference to the corresponding sections is presented for each endpoint with detailed description of the endpoints 4. Detail added for the definition 5. New definition added 6. Endpoint definition added 7. Endpoint definition added 8. No corresponding study objective was defined in the SAP 9. These endpoints are not considered in the new SAP version 10. New biomarker subgroups of interest included according to L-MIND protocol
5 Study Design	1. Section “5. Study Design” from the	1. Information from the previous

	previous SAP version renamed to "5.1 General study design" and definition of "primary refractory disease" and "Relapsed/recurrent disease" removed 2. Section "6. Schedule of assessments" from the previous SAP version renamed to "5.2 Schedule of assessments" with a change of reference. Instead of the appendix, the new reference is to the protocol 3. Section "Determination of Sample Size" renamed to "5.3 Determination of sample size" 4. Section "5.4 Timing of analyses" added 5. Section "9.7 Safety-Run-In" from the previous SAP version renamed to "5.4.1 Safety run-in analysis" with changes in the wording 6. Section "5.4.2 Primary Analysis" added 7. Section "7.1 Final Analysis" from the previous SAP version renamed to "5.4.3 Final analysis" with addition information regarding the timing of the final analysis. With regards to further exploratory analyses, the phrase is changed to "MorphoSys may perform further exploratory analyses…"	SAP version remained unchanged. Definitions were removed, since they don't belong to the study design 2. Since the schedule of assessments is not essential for the SAP a reference to the protocol is sufficient and need not to be in the appendix of the SAP 3. Since sample size considerations belong to the study design, it is moved to this section. Information from the previous SAP version remained unchanged 4. Section added. Different subsections regarding the timing of analyses were presented in different sections and are now presented under one section for a better overview 5. Information from the previous SAP remained similar with wording corrections 6. Section with details added 7. Information from previous SAP version remained unchanged with a minor word correction. Details on the timing of the final analysis added
6 Definition and general Methodology	Addition of new sections with details: 6.1 Enrolment date 6.2 Study drug and study treatment 6.3 Study drug administration 6.3.1 Date of first administration of study drug 6.3.2 Date of last administration of study drug 6.3.3 Date of first administration of study treatment 6.3.4 Date of last administration of study treatment 6.4 Reference start date and Study day 6.5 Screening failure 6.6 Time unit 6.7 Baseline	All sections with information and definitions added

	6.8 On treatment assessment/event 6.9 Start and end date for time to event variables 6.10 Date of last contact 6.11 Analysis Windows 6.12 Selection of data in the event of multiple records in a window	
6.13 Analysis populations	1. Addition of section "6.13.1 Screened patients" and "6.13.2 Enrolled patients" 2. Information from section "8 Analysis populations" from the previous SAP version is incorporated in each subsection for each analysis set 3. In section "6.13.3 Full analysis set (FAS)" restriction of "Patients in FAS have to have at least one post-baseline efficacy assessment" is replaced by "A listing showing the patients who have been excluded from the efficacy analysis will be provided" 4. Section "6.13.4 Per protocol set (PPS)" includes definition of PPS with regards to protocol deviations and definition of protocol grouped into new categories 5. Section "6.13.5 Safety set (SAF)" includes a more detailed description of SAF 6. Section "6.13.8 Planned analyses for the different populations" added 7. Section "6.13.9 Withdrawal of informed consent" added	1. Definition added 2. For a better overview, each analysis set is described in a separate subsection 3. Exclusion from efficacy analysis also covers the case of patients without post-baseline assessment 4. Details for the definition of PPS added 5. More details are added to SAF definition 6. Section added and provides more details 7. Section added and provides more details
6.14 Cheson criteria	Section with its subsections 6.14.1 Response criteria 6.14.2 Disease progression 6.14.3 Change in imaging modality added	Section with its subsections and information added to provide more details
7.1 General principles of statistical programming	Information based on section "9.1.1 Statistical Methods" from the previous SAP version. Statistical programming with SAS changed to version 9.4 or above	Newer version of SAS software available
7.2 Variable types and descriptive statistics	Section "9.1.1 Statistical Methods" from the previous SAP version renamed to "7.2 Variable types and descriptive statistics" with addition of definition of reference number of subjects and more detailed description of continuous and categorical variables. Addition of definition of "Time variables" and "Time to Event Variables". Removed descriptions on significance levels	Information on variable types and analysis methods added. Time to event variables and time variables added. Since descriptive analyses are performed without statistical tests, no significance level needs to be specified. With the change of CRO, no [redacted] SOPs are applicable, but [redacted] SOPs

	and reference to [redacted] SOPs and changed to [redacted] SOPs	
7.3 Convention on missing data	Section "9.1.2.1.2 Missing Data" from the previous SAP version renamed to "7.3 Convention on missing data" with reference to each section for the handling of missing data	For a better overview each method for handling missing data is presented in the respective section for the respective data
7.4 Data included in the analysis and cut-off date	Section added	Section added and provides more details
7.5 Specifications and Analysis Database	Section added	Section added and provides more details
8 Patient disposition, background and baseline characteristics	1. Description of patient disposition summaries added with extension on details given in section "9.2.1 Subject Disposition" from the previous SAP version 2. Addition of section "8.1 Screened patients" "8.2 Enrolled patients" "8.3 Follow-up period" 3. Section "9.2.2 Protocol Noncompliance" from previous SAP version renamed to "8.4 Protocol deviations" with a change in the structure of protocol deviations. Groups of protocol deviations are reduced to four categories 4. Section "9.2.3 Background and Demographic Characteristics" from the previous SAP version renamed to "8.5 Baseline and demographic characteristics" with an extension on variables to be summarized 5. Addition of section "8.6.1 Coding and definitions" "8.6.2 DLBCL-specific medical history and diagnosis" 6. Section "8.6.2.1 Handling of incomplete dates regarding DLBCL-specific medical history" added with information from section "8.2.7 medical Histories" from the previous SAP version 7. Section "9.2.4 International Prognostic Index" from the previous SAP version renamed to "8.6.2.2 Calculation of the International Prognostic Index (IPI)" with deletion of sentences referring to analysis of IPI for DLBCL patients only 8. Section "8.6.3 Reason for ASCT ineligibility" added 9. Section "9.2.8 Pre-Medication for MOR infusion" from the previous SAP version renamed to "8.8 Pre-medication for	1. Details added 2. Sections added to provide more details 3. The protocol deviations are categorized into four groups and provide a better overview 4. Some variables for demographic characteristics added 5. Sections added to provide more details 6. Information remained unchanged, but is added as a separate section 7. Information from the previous SAP version remained unchanged. Removal of restriction on DLBCL patients only, restriction results in an analysis set, which is not defined in 6.13 8. Section added to provide more details 9. Information from the previous SAP version remained unchanged.

	MOR00208 infusion"	
8.7 Prior and concomitant medications and non-drug treatments/procedures	1. Section "8.7.1 Coding" contains information from section "9.2.6 Prior and Concomitant medications and therapies" from the previous SAP version regarding the coding of prior/concomitant medications. Additional information on coding of surgical and medical procedures 2. Section "8.7.2 Definitions" added with information from section "9.2.6 Prior and Concomitant medications and therapies" from the previous SAP version with additional details on each definition. Addition of time variables 3. Section "8.7.3 Data presentation" added with information concomitant medications summary from the previous SAP version. Additional list of variables to be summarized provided 4. Section "8.7.4 DLBCL-specific prior therapies" added with subsections regarding variables to be summarized, handling of missing dates, definitions of refractoriness, definitions of early/late relapse after first line treatment, imputation of missing values 5. Section "8.7.5 Non-Study anti-cancer treatment" added	1. Information from the previous SAP version remained unchanged. Information for surgical and medical procedures added 2. Details added to the definitions. Additional details and variables provided 3. Variables for summary tables added to provide more details 4. Section with subsections and details added for more details 5. Additional details and definitions are provided
8.9 Study treatment	1. Addition of section "8.9.1 Treatment cycles" 2. Addition of section "8.9.2 Exposure" with information from previous SAP version and additional details for the definition of last date of exposure and exposure analysis 3. Addition of sections "8.9.3 Dose reduction" "8.9.4 Dose interruption" "8.9.5 Permanent discontinuations" 4. Section "8.9.6.1 MOR00208" for compliance includes information from the previous SAP version 5. Section "8.9.6.2 LEN" added with extension on information from the previous SAP version	1. Section added for more details 2. Information added 3. Sections added for more details 4. Information from the previous SAP version remained unchanged with minor wording and editorial changes 5. Information added for more details. Additional details and calculation descriptions are provided
9 Primary Objective	1. Section "9.3.1 Primary Efficacy Analysis" from the previous SAP version renamed to "9 Primary Objective" with addition of separate subsections 2. Addition of subsections "9.1 Endpoint: Best objective response rate" "9.2 Main analysis" "9.3 Sensitivity Analysis"	1. New structure provides a better overview of the primary endpoint 2. The information from the previous SAP version remained mainly unchanged, but essential additional details added, such as formal details for the main analysis and the statement. Details regarding

	"9.4 Concordance between IRC and investigator (INV) assessment" with information from previous SAP and addition of more details and analyses	the concordance between IRC and INV assessment added
10.1 Secondary objective 1	1. Section "9.3.2.1 Disease control Rate (DCR)" from the previous SAP version renamed to "10.1 Secondary objective 1" with addition of separate subsections 2. Addition of subsections "10.1.1 Objective" "10.1.2 Endpoint: Disease control rate" "10.1.3 Main analysis" "10.1.4 Sensitivity analyses" with information from previous SAP version and addition of more details and analyses	1. New structure provides a better overview of the endpoint 2. The information from the previous SAP version remained mainly unchanged, but essential details are added similar to ORR
10.2 Secondary objective 2	1. Section "9.3.2.4 Progression-Free Survival (PFS)" from the previous SAP version renamed to "10.2 Secondary objective 2" with addition of separate subsections 2. Addition of subsections "10.2.1 Objective" "10.2.2 Endpoint: Progression-free survival" "10.2.3 Disease assessments" "10.2.4 Censoring rules" "10.2.5 Main analysis" "10.2.6 Sensitivity analyses" with information from previous SAP version with addition of more details and analyses 3. Censoring rule table added	1. New structure provides a better overview of the endpoint 2. The information from the previous SAP version remained mainly unchanged, but essential details and sections now provided 3. Rules for censoring expanded
10.3 Secondary objective 3	1. Information is based on section "9.3.2.2 Duration of Response (DoR), Duration of Best Overall Response (DoBOR), and Time to Next Treatment (TNNT)" with addition of separate subsections 2. Addition of subsections "10.3.1 Objective" "10.3.2 Endpoint: Duration of response" "10.3.3 Censoring rules" "10.3.4 Main analysis" "10.3.5 Sensitivity analyses" with minor information from the previous SAP and addition of more details and analyses 3. Detailed description for censoring and handling of missing response assessments 4. Details regarding Duration of Best overall response are removed	1. New structure provides a better overview of the endpoint 2. Minor information from the previous SAP version remained unchanged. Essential details are provided now 3. Details on censoring added. Details on missing response assessments added 4. Replaced by details for duration of CR as sensitivity analysis
10.4 Secondary objective 4	1. Section "9.3.2.5 Overall Survival (OS)" from the previous SAP version renamed to "10.4 Secondary objective 4" with addition of separate subsections	1. New structure provides a better overview of the endpoint 2. Information from the previous

	2. Addition of subsections "10.4.1 Objective" "10.4.2 Endpoint: Overall survival" "10.4.3 Censoring rules and imputation" "10.4.4 Main analysis" "10.4.5 Sensitivity analysis" with information from the previous SAP version and additional details and analyses 3. Addition of handling of missing dates	SAP version remained mainly unchanged with minor wording corrections. Additional details are provided for each subsection 3. Information added to provide more details
10.5 Secondary objective 5 and secondary objective 11	1. Section "9.3.2.3 time to Progression (TTP)" from the previous SAP version renamed to "10.5 Secondary objective 5 and secondary objective 11" with addition of separate subsections 2. Addition of subsections "10.5.1 Objectives" "10.5.2 Endpoint: Time to progression" "10.5.3 Main analyses" "10.5.4 Sensitivity analyses for Objective 5" with information from the previous SAP version and additional details and analyses 3. Information regarding most recent therapy added	1. New structure provides a better overview of the endpoint 2. Information from the previous SAP version remained mainly unchanged with minor wording corrections. Definition for TTP expanded. Additional details are provides for each subsection 3. Information added for more details
10.6 Secondary objective 6	1. Information is based on section "9.3.2.2 Duration of Response (DoR), Duration of Best Response (DoBOR), and Time to Next Treatment (TTNT)" with addition of separate subsections 2. Addition of subsections "10.6.1 Objective" "10.6.2 Endpoint: Time to next treatment" "10.6.3 Main analysis" "10.6.4 Sensitivity and subgroup analyses" with information from the previous SAP version and additional details and analyses 3. Definition of TTNT expanded and includes the case of death as an event 4. Analyses stratified by IPI groups removed	1. New structure provides a better overview of the endpoint 2. Additional details are provided. 3. Information added for more details 4. TTNT stratified by IPI is not essential for this endpoint
10.7 Secondary objective 7	1. Section "9.5 Safety Analysis" from the previous SAP version renamed to "10.7 Secondary objective 7" with addition of separate subsections 2. Addition of subsections "10.7.1 Objective" "10.7.2 Endpoint: Incidence, frequency and severity of treatment-emergent adverse events (AEs)" "10.7.3 Main analysis" 3. Section "10.7.3.1 Overview" contains	1. New structure provides a better overview of the endpoint 2. Information from the previous SAP version remained unchanged 3. In the previous SAP version different safety assessments were mentioned in different subsections, but are merged into one section for a better

	categories for safety assessments given in the previous SAP version in different subsections 4. Section "10.7.3.2 Adverse events" added with definition of an AE and rules for reporting AEs 5. Section "10.7.3.3 Treatment-emergent adverse events" added with information from the previous SAP version and additional details 6. Addition of subsections "10.7.3.4 Adverse events of special interest" "10.7.3.5 Relationship to study drug" "10.7.3.6 coding of adverse events" "10.7.3.7 Grading of adverse events" "10.7.3.8 Deaths" "10.7.3.9 General rule for reporting" 7. Section "10.7.3.10 AE summaries" contains variables to be summarized from the previous SAP version with additional variables to be summarized	overview 4. Section added for more details 5. Information on TEAE expanded. Additional details are provided 6. Subsections added 7. List of variables to be summarized expanded. Additional variables are provided with additional details
10.8 Secondary objective 8	1. Section "9.4.2 Immunogenictiy analysis" from the previous SAP version renamed to "10.8 Secondary objective 8" with addition of subsections 2. Addition of the categorization of anti-MOR00208 antibody response 3. Addition of the subsections "10.8.1 Objective" "10.8.2 Endpoint: Percentage of patients who develop anti-MOR00208 antibodies as determined by a positive anti-MOR00208 antibody titre" "10.8.3 Main analysis"	1. New structure provides a better overview of the endpoint 2. The categorization added 3. Information and details from the previous SAP version remained unchanged
10.9 Secondary objective 9	1. Section "9.4.1 Pharmacokinetic Analysis" from the previous SAP version renamed to "10.9 Secondary objective 9" with addition of subsections 2. Addition of information on population PK analysis in subsection "10.9.3.3 Population PK analysis"	1. New structure provides a better overview of the endpoint. Information in the previous SAP remained unchanged with minor wording corrections 2. Section added for more details
10.10 Secondary objective 10	Section with corresponding subsections and details added	Section added for more details
10.11 Secondary objective 11	Section added with reference to section 10.5.3.2	Section added for more details
10.12 Secondary objective 12	1. Section "9.4.3 Exploratory Biomarker Analysis" from the previous SAP version renamed to "10.11 Secondary objective 11" with addition of subsections 2. Addition of subsections "10.12.1 Objective"	1. New structure provides a better overview of the endpoint. 2. Information on the subgroups expanded. Additional details are provided

	"10.12.2 Endpoint" "10.12.3 Main analysis" "10.12.4 Sensitivity analyses" with detailed description of subgroups, including new subgroups	
11 Exploratory efficacy analyses	Section added with minor information on "time to response" from the previous SAP version	Section added for more details
12 Descriptive biomarker analyses	Section added	Section added for more details
13 Additional Safety analyses	1. Section "9.5.3 Vital Signs; body Weight and Height" from the previous SAP version renamed to "13.2.1 Vital signs variables" with minor changes in wording and additional variables 2. Addition of subsection "13.2.2 Vital signs analysis" with details 3. Section "9.5.2 Physical examination" from the previous SAP version renamed to "13.3 Physical examination" with some wording and editorial changes 4. Section "9.5.4 Electrocardiograms (12-lead ECG)" from previous SAP renamed to "13.4 Electrocardiogram (ECG)" 5. Section "13.4.1 ECG Variables" added 6. Section "13.4.2 ECG Analysis" added with information on normal ranges for ECG variables from section "9.5.4 Electrocardiograms (12-lead ECG)" from previous SAP version and additional details on analyses with detailed table on clinically notable ECG values 7. Section "9.5.5 Clinical Laboratory Evaluations" from previous SAP version renamed to "13.5 Laboratory data" 8. Section "13.5.1 Laboratory Variables" added with less laboratory parameters 9. Section "13.5.2 Grading of Laboratory data" added 10. Section "13.5.3 Laboratory Analysis" added 11. Section "13.6 ECOG scores analyses" added 12. Section "13.7 B-symptoms" added	1. Some variables added 2. Information added 3. Information from the previous SAP version remained unchanged with minor wording changes 4. New structure and numbering of section provides a better overview 5. Section added for more details 6. Information from previous SAP remains unchanged. Additional details provided, including table on clinically notable ECG values 7. New structure and numbering of section provides a better overview 8. Not all laboratory variables need to be analysed 9. Section added for more details 10. Section added for more details 11. Information on ECOG expanded, additional information is provided 12. Section added for more details
14 General Guidance on reporting	Section added	To provide a consistent reporting
15 Reference	Standard Operating Procedure from [redacted] removed	Not needed due to change of CRO

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABC	Activated B-cell
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-dependent cell-mediated phagocytosis
ASCT	Autologous stem-cell transplantation
AE	Adverse event
ANOVA	Analysis of variance
ATC	Anatomical therapeutic chemical
BCL-2/-6	B-cell CLL/lymphoma 2/6
BLQ	Below the limit of quantification
BMI	Body mass index
CD16/19/20	Cluster of differentiation 16/19/20
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CLL	Chronic lymphocytic leukaemia
CR	Complete response
CRF	Case report form
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computed tomography
CTC(AE)	Common Terminology Criteria (for Adverse Events)
CV	Coefficient of variation
DCR	Disease control rate
DLBCL	Diffuse large B-cell lymphoma
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European medicines agency

EOT	End of treatment
FAS	Full analysis set
FDA	Food and Drug Administration
FU	Follow up
GCB	Germinal center B -cell
GEP	Gene expression profiling
HDC/HDT	High-dose chemotherapy
HR	Heart rate
IAS	Immunogenicity analysis set
ICF	Informed consent form
ICH	International Conference on Harmonization
IHC	Immuno-histochemistry
IND	Investigational new drug
INV	Investigator
IPI	International prognostic index
IRR	Infusion-related reaction
IRC	Independent Radiology/Clinical Review Committee
IV	Intravenous
IWG	International Working Group
LEN	Lenalidomide
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
ms	Millisecond
NCI	National Cancer Institute
NCS	Not clinically significant
NHL	Non-Hodgkin lymphoma
NK	Natural killer

ORR	Objective response rate (complete response + partial response)
OS	Overall survival
PD	Progressive disease
PE	Physical examination
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PKAS	PK analysis set
PPS	Per-protocol set
PR	Partial response
PR (ECG)	PR interval
PT	Preferred term
QC/QA	Quality control/quality assurance
QRS	QRS interval
QT	QT interval
QTc	QT interval corrected
QTcB	QT interval, Bazett's correction
QTcF	QT interval, Fridericia's correction
R-CHOP	**R**ituximab plus **c**yclophosphamide, **h**ydroxydaunorubicin (also referred to as doxorubicin or adriamycin), and **o**ncovin (vincristine) plus **p**rednisone or **p**rednisolone
RR (ECG)	Relative rate
R-R DLBCL	Relapsed or refractory diffuse large B-cell lymphoma
R-R NHL	Relapsed or refractory non-Hodgkin lymphoma
R-R CLL/SLL	Relapsed or refractory chronic lymphocytic leukaemia/ small lymphocytic lymphoma
RTX	Rituximab
SAE	Serious adverse event
SAF	Safety analysis set

SAP	Statistical analysis plan
SD	Stable disease
SI	System international
SLL	Small lymphocytic lymphoma
SmPC	Summary of product characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SPM	Second primary malignancy
StD	Standard deviation
TEAE	Treatment-emergent adverse event
TFR	Tumour flare
TLS	Tumour lysis syndrome
TTNT	Time to next treatment
TTP	Time to progression
US	United States
WHO-DDE	World Health Organization–Drug Dictionary Enhanced

3. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting of data collected from MorphoSys protocol MOR208C203, Amendment 3.0, Version 6.0, dated 23-Oct-2017. Any amendments to the protocol which do not affect the statistical aspects of the trial will not necessitate an SAP update.

This study is a single-arm, multicentre, open-label, phase IIa study of lenalidomide (LEN) combined with MOR00208 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (R-R DLBCL). The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials. All work planned and reported from this SAP will follow internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society, for statistical practice.

The planned analyses identified in this SAP may be included in clinical study report (CSRs) and/or in relevant summary report documents (e.g. regulatory submissions, or future manuscripts). Also, *post-hoc* exploratory analyses not necessarily identified in this SAP may be performed to further examine study data and will not require updating the final SAP. Any post-hoc, or unplanned, exploratory analysis performed will be clearly identified as such and described in the final CSR.

The following documents were reviewed in preparation of this SAP:

- Clinical Research Protocol MOR208C203, Amendment 3; Version 6.0, dated 23-Oct-2017
- Annotated electronic Case report forms (eCRFs), Version 6.0, dated 03-May-2018
- ICH Guidance on Statistical Principles for Clinical Trials (E9)

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

4. STUDY OBJECTIVES AND ENDPOINTS

An overview of the study objectives and endpoints is depicted in Table 1.

Table 1: Study objectives and endpoints

Study objective	Endpoint	Analysis
Primary objective:	**Primary endpoint:**	
To determine the activity of a combination of LEN with MOR00208 in terms of objective response rate (ORR = complete response (CR) + partial response (PR)) in adult patients with R-R DLBCL	Best Objective Response Rate (ORR), defined as the proportion of responders whose *best* response at any time throughout treatment or follow-up is complete or partial (ORR=CR+PR)	See section 9
Secondary objectives:	**Secondary endpoints:**	
1. To determine the disease control rate (DCR = CR + PR + stable disease (SD) as best response)	Disease Control Rate (DCR = CR+PR+SD as best response)	See section 10.1
2. To determine progression-free survival (PFS)	Progression-free Survival (PFS)	See section
3. To determine the duration of response (DoR)	Duration of Response (DoR)	See section 10.3
4. To determine the overall survival (OS)	Overall Survival (OS)	See section 10.4
5. To determine time to progression (TTP)	TTP	See section 10.5

6. To determine the time to next treatment (TTNT)	To determine the time to next treatment (TTNT)	See section 10.6
7. To determine the safety of LEN combined with MOR00208 assessed according to the frequency and severity of adverse events (AEs)	Incidence, frequency and severity of treatment-emergent AEs	See section 10.7
8. To assess the potential immunogenicity of MOR00208 (anti-MOR00208 antibodies)	Anti-MOR00208 antibody formation (ADA): number and percentage of patients who develop anti-MOR00208 antibodies; Titer determination; Characterization of ADA-positive samples (neutralizing vs non-neutralizing)	See section 10.8
9. To assess the pharmacokinetics (PK) of MOR00208	Summary statistics for PK: plasma concentration-time profiles of MOR00208 and appropriate individual PK parameters (e.g. accumulation ratios).	See section 10.9
10. To make a preliminary evaluation of ORR, DCR, DoR, PFS, OS, TTP and TTNT in patients treated with a combination of LEN plus MOR00208 in cohorts with a "low risk", "low-intermediate risk", "high-intermediate risk" and "high risk" according to the International Prognostic Index (IPI)	ORR, DCR, DoR, PFS, OS, TTP, and TTNT stratified by: • four risk categories: "low risk", "low-intermediate risk", "high-intermediate risk" and "high risk" • 2 risk categories: patients with "low risk" and "low-intermediate risk" vs. patients with "high-intermediate risk" and "high" risk	See section 10.10
11. To compare each patient's TTP on LEN plus MOR00208 with the TTP of their most recent prior therapy	TTP in patients treated with LEN plus MOR00208, and TTP in each individual´s most recent prior treatment therapy.	See section 10.11
12. To correlate efficacy parameters with certain	Stratification of efficacy parameter according	See section

biomarkers (e.g. baseline tumour CD19 expression level, peripheral Natural Killer (NK) cell count, constitutional FcγRIIIa and FcγRIIa polymorphism status)	to the following subgroups: • FcγRIIIa affinity (high affinity: FCGR3A-158V homozygosity vs. low affinity: FCGR3A-158F homozygosity, or FCGR3A-158F/V heterozygosity) • FcγRIIa affinity (high affinity: FCGR2A-131H homozygosity vs. low affinity: FCGR2A-131R homozygosity, or FCGR2A-131H/R heterozygosity) • Cell-of-origin (determined by immuno-histochemistry/central pathology: Germinal center B-cell (GCB) vs. non- GCB) • Peripheral NK cell numbers at baseline (< median of NK cell numbers/µl vs. ≥ median of NK cell numbers/µl)	10.12

5. STUDY DESIGN

5.1 General study design

This is a single-arm, multicentre, open-label phase II, study of LEN combined with MOR00208 in adult patients with DLBCL who have relapsed after or are refractory to at least one, but no more than three previous systemic regimens administered for the treatment of their DLBCL and who are not candidates for high-dose chemotherapy (HDC) and subsequent autologous stem cell transplantation (ASCT) and are thus considered to have exhausted their therapeutic options for demonstrable clinical benefit. One prior therapy line must include an anti-CD20 targeted therapy (e.g. rituximab (RTX)).

Patients with primary refractory DLBCL, patients with known "double/triple hit" DLBCL genetics or those who have undergone previous allogenic stem cell transplantation are not eligible for study participation. Additionally, patients with a history of ASCT ≤3 months prior to the requirement to provide signed informed consent cannot be included in the study.

This study will consist of two parts, which will be performed sequentially. During the course of the first part, six patients will be enrolled in the study and will complete the first cycle of study treatment. Once the sixth patient in the cohort has completed Cycle 1 Day 22 visit, a Safety Review Panel which consists of the sponsor, a representative of the participating investigators and two independent expert clinical haematologists will perform a clinical safety review based on the number and type of AEs occurring during the first cycle and on laboratory values (biochemistry and haematology). A LEN dose will be considered tolerated

or in need of reduction after discussion of these data between the sponsor's Clinical Program Leader (or designee), the sponsor's Drug Safety Officer (or designee), a representative of the participating investigators and two expert clinical haematologists who are not participating in the study. The second part of the study will only be opened for enrolment by the sponsor following the outcome of this discussion.

Treatment consisting of **LEN** and **MOR00208 combination** will be administered up to twelve 28-day cycles (Figure 1) at specified dose levels.

MOR00208 dose: 12 mg/kg

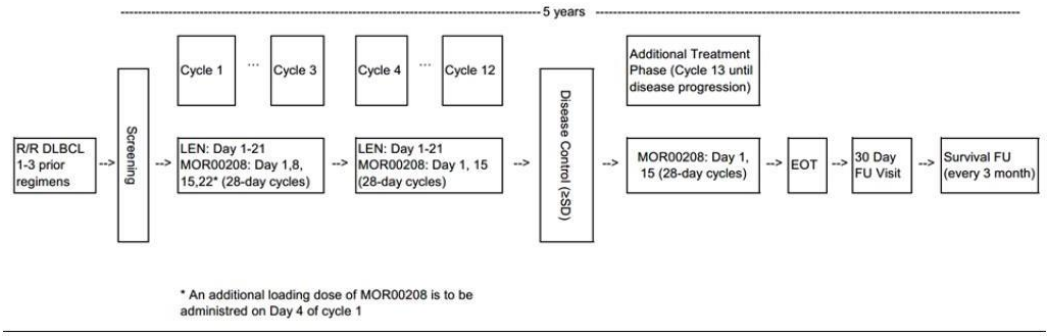
For the first three cycles (Cycles 1-3) of the study each cycle will consist of a MOR00208 infusion on Day 1, Day 8, Day 15 and Day 22 of the cycle. Additionally, a loading dose will be administered on Day 4 of Cycle 1. Thereafter MOR00208 will be administered on a bi-weekly (every 14 days) basis with infusions on Day 1 and Day 15 of each 28-day cycle.

MOR00208 can be administered until disease progression, or unacceptable toxicity, or discontinuation for any other reason, whichever comes first. It is up to the investigator to decide according to the individual risk/benefit ratio if the patient should continue further treatment with MOR00208 in spite of disease progression.

LEN:

Patients will self-administer a starting dose of 25 mg oral LEN daily on Days 1–21 of each cycle. Treatment with LEN may be modified in a de-escalating fashion or discontinued based upon clinical and laboratory findings. Detailed dose modification guidelines to manage haematologic and/or other toxicities are provided in the respective sections of the protocol. LEN can be given for up to 12 cycles in total. Treatment with LEN will have to be stopped in the case of disease progression, or unacceptable toxicity, or discontinuation for any other reason, whichever comes first.

Figure 1: Study design



Abbreviations: EOT=end of treatment; FU=follow-up; LEN=lenalidomide; R-R DLBCL=relapsed or refractory diffuse large B-cell lymphoma.

Objective disease response assessments will be made according to the revised response criteria based on the guidelines of the International Working Group (IWG) reported by Cheson et al. (2007). The data used for the primary statistical analyses will be derived from a central independent review of the radiological + clinical disease assessments. A charter outlining the central imaging plus clinical assessment will be prepared.

Approximately 80 patients with R-R DLBCL who meet the inclusion criteria and have none of the exclusion criteria will be enrolled in the study. This study will be conducted under a United States (US) Food and Drug Administration (FDA) Investigational New Drug (IND) application.

5.2 Schedule of assessments

For a detailed schedule of assessments, please refer to the Protocol Section 7.

5.3 Determination of sample size

Approximately 80 patients with R-R DLBCL who meet all of the inclusion criteria and have none of the exclusion criteria will be enrolled into the study. The study will be performed with an interim stop for the evaluation of the safety of the LEN dosage. No adjustment of sample size or adaptation of efficacy evaluations will be made at this point. As the primary purpose of this study is to evaluate the clinical efficacy of 25 mg daily oral LEN combined with 12 mg/kg MOR00208 administered by IV infusion in patients with R-R DLBCL, no formal statistical hypothesis testing will be performed.

For the determination of a suitable sample size, it is assumed that the combination treatment could improve the ORR of LEN from a value of 20% (under monotherapy) to 35% (under combination therapy). Applying an exact binomial test with a two-sided significance level of 5% and a power of 85% the estimated sample size is 73 patients (calculation performed by nQuery Advisor® 7.0). According to this scenario an observed ORR of 32% would lead to the conclusion that the outcome is statistically superior to outcomes observed previously for the monotherapy. Assuming a drop-out rate of 10%, a total sample size of about 80 patients is estimated.

The sample size determination has been conducted using various possible monotherapy and combination effect ORR rates and various power assumptions. Literature evaluation of study results concerning the ORR rates of LEN or comparable products (as mono- or combination therapy) as well as study results for MOR00208 ongoing studies were used to justify assumptions on response rates (Witzig et al., 2011; Wang et al., 2013).

5.4 Timing of analyses

5.4.1 Safety run-in analysis

A Safety Review Panel consisting of the sponsor, a representative of the participating investigators and two independent expert clinical haematologists will perform a clinical safety review after the first six patients have been accrued based on the number and type of AEs occurring during the first cycle and on laboratory values (biochemistry and haematology). A total of six patients will be evaluated. A LEN dose will be considered tolerated or in need of reduction after discussion of these data between the sponsor's Clinical Program Leader (or designee), the sponsor's Drug Safety Officer (or designee), a representative of the participating investigators and two expert clinical haematologists who are not participating in the study. The second part of the study will only be opened for enrolment by the sponsor following the outcome of this discussion.

5.4.2 Primary analysis

The primary analysis will be conducted earliest after all patients have undergone at least one post-baseline response assessment (for those patients who did not discontinue before due to reasons such as death, adverse event, informed consent withdrawal etc.). The sponsor will decide when to perform the primary analysis (approximately 12 months after the last patient has been enrolled). All results of the primary analysis will be made available to MorphoSys AG prior to completion of the final CSR.

5.4.3 Final analysis

The final analysis will be performed when all patients have performed their End of Treatment visit. The analyses will be conducted after database lock. All study results will be made available to MorphoSys AG prior to completion of the final CSR.

MorphoSys may perform further exploratory analyses to investigate correlations between different biomarker and response variables. Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR, but will not necessitate an update of the final SAP. Any results from these unplanned analyses (post-hoc) will also be clearly identified in the text of the CSR.

6. DEFINITIONS AND GENERAL METHODOLOGY

6.1 Enrolment date

The first date of administration of any study drug (i.e., MOR00208 or LEN).

6.2 Study drug and study treatment

Study treatment refers to MOR00208 in combination with LEN. Study drug refers to the individual drugs: MOR00208 or LEN.

6.3 Study drug administration

6.3.1 Date of first administration of study drug

The date of first administration of study drug is the first date when a non-zero dose of study drug is administered and is referred as “start date of study drug”. Start date of study drug is defined for each drug which is part of study treatment.

6.3.2 Date of last administration of study drug

The date of last administration of study drug (“last date of study drug”) is the last date when a non-zero dose of study drug is administered.

Last date of study drug is defined for each drug which is part of study treatment.

6.3.3 Date of first administration of study treatment

The date of first administration of study treatment ("start date of study treatment") is the first date when a non-zero dose of any component of study treatment is administered.

For example: if the 1st dose of MOR00208 is taken on 03JAN2017, and 1st dose of LEN is taken on 05JAN2018, then the "Start date of study treatment" is 03JAN2017.

6.3.4 Date of last administration of study treatment

The date of last administration of study treatment ("last date of study treatment") is the last date when a non-zero dose of any component of study treatment is administered.

For example: if the last dose of MOR00208 is taken on 13APR2017, and last dose of LEN is taken on 20APR2018, then the "Last date of study treatment" is 20APR2018.

6.4 Reference start date and study day

The reference start date **for all safety assessments** (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) will be the start date of study treatment.

The reference start date **for all efficacy assessments** (e.g. tumour assessment, death, ECOG performance status) will be the start date of study treatment.

For **any non-safety screening assessments** or events such as baseline disease characteristics or medical history (e.g., time since diagnosis of disease) that occurred prior to start date of study treatment the reference start date will be the start date of study treatment.

The study day describes the day of the event or assessment date, relative to the reference start date (i.e., the study treatment).

The reference start date is designated as Study Day 1. Study Day –1 is the day that precedes Study Day 1. Study Day 0 is not defined.

The study day will be calculated as:

- The date of the event (visit date, onset date of an event, assessment date etc.) minus reference start date + 1 if the event is on or after the reference start date.
- The date of the event (visit date, onset date of an event, assessment date etc.) minus reference start date if the event precedes the reference start date.

The study day will be displayed in the data listings. It will not be used for numerical computations for example calculating exposure.

6.5 Screening failure

These patients are not treated. Screening failures are patients who have signed informed consent and failed screening criteria in a study. Patients who signed informed consent and fulfilled screening criteria, but have never received treatment are not considered as screening failures.

6.6 Time unit

A month-length is 30.4375 days (365.25 / 12). If duration is to be reported in months, duration in days is divided by 30.4375. If duration is to be reported in years, duration in days will be divided by 365.25.

6.7 Baseline

Baseline is the result of an investigation describing the "true" uninfluenced state of the patient, defined as the period from the date of signing any informed consent document to the start date of study treatment. Assessments, specified to be collected post-dose on the first date of treatment are not considered as baseline values.

For **efficacy evaluations**, the last non-missing assessment, including unscheduled assessments on or before the start date of study treatment will be used as "baseline" value or "baseline" assessment. In the context of baseline definition, the efficacy evaluations also include the ECOG performance status.

For **safety evaluations**, unless otherwise stated, the last available assessment, including unscheduled assessments on or before the start date of study treatment will be used as "baseline" value or ''baseline" assessment.

If patients have no value as defined above, the baseline result will be missing.

6.8 On treatment assessment/event

An **on-treatment assessment/event** is defined as any assessment/event happening after the start date of study treatment, i.e. assessments/events happening in the following time interval (including the lower and upper limits): start date of study treatment + 1; last date of study treatment + 30 days.

Assessments collected post-dose on the start date of study treatment are on-treatment assessments. Data listings will include all assessments/events, flagging those which are not on-treatment assessments/events.

A **post-treatment assessment/event** is defined as any assessment/event happening after the completion of on-treatment phase, that is assessments/events happening in the

following time interval (including the lower and upper limits): date of last administration of study treatment + 30 days + 1; Date of Study Discontinuation.

6.9 Start and end date for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall response at that assessment is CR/PR/SD/UNK/NE.

Otherwise - if overall response is progression – the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates

For all "time to event" variables, other than duration of response, the start date of study treatment will be used as the start date.

For the calculation of duration of response the following start date should be used:

Date of first documented response is the assessment date of the first overall response of CR or PR.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall response was recorded as progressive disease.
- When there is no documentation of radiologic evidence of progression, and the patient discontinued for 'Disease progression' due to documented clinical deterioration of disease, the date of discontinuation is used as date of progression.
- If no post-baseline assessments are available (before an event or a censoring reason occurred) the start date of study treatment is used as the end date.

Calculation of 'time to event' variables

Time to event = End Date - Start date + 1 (in days).

When no post-baseline tumor assessments are available, the start date of study treatment will be used as end date (duration = 1 day).

6.10 Date of last contact

The date of last contact is derived for patients not known to have died at the analysis cut-off date (see section 7.4) based on the latest date among the following:

- Actual assessment dates (Labs, vital signs, performance status, tumour imaging, EOT completion, PK sample collection dates).
- Antineoplastic therapies administered after study drug discontinuation.
- Adverse events dates.
- "Date of contact" or "Last known date patient alive" collected on the "Survival Follow-up" eCRF page (if applicable).
- Date of study completion or discontinuation from the "End of Survival Follow-up" eCRF page.
- Study treatment start/end date.

The date of last contact is defined as the latest date from the above list or the cut-off date whichever comes first. In case that a date is only partially complete the following rules will be applied. If month and year are present and only the day is missing the first day of the month will be used to impute the missing date. If day and month or year is missing the date will not be imputed. The date of last contact is used for censoring of patients in the analysis of overall survival and time to next treatment.

6.11 Analysis windows

For parameters that will be summarized by visit, the nominal visit as recorded in the eCRF will be used. There will be no additional analysis windowing done based on the assessment date.

In order to summarize over time, parameters recorded at each visit (i.e. performance status, PK, vital signs), assessments (including unscheduled ones) will be time-slotted if indicated.

6.12 Selection of data in the event of multiple records in a window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value per visit, whereas a time-to-event analysis would not require one value per analysis window but rather one value for the study.

Unless otherwise noted throughout the rest of this document, when a single value is needed, the following rule(s) will be used:

- If more than one assessment occurs during the same nominal visit time window of the planned visit, select the record closest to the nominal day for that particular visit day.
- If there are two assessments that are equidistant from the nominal planned visit day, the data of the assessment after the scheduled study day will be used.
- The last measurement will be used if multiple measurements are all taken on the same day.

6.13 Analysis populations

The following analysis populations will be defined:

6.13.1 All patients screened

The All patients screened population consists of all patients who signed informed consent and completed the *Informed Consent* eCRF page.

6.13.2 Enrolled patients

The Enrolled patients population consists of all patients who received at least one dose of any study drug (MOR00208 or LEN).

6.13.3 Full analysis set (FAS)

The FAS includes all patients who received at least one dose of MOR00208 and one dose of LEN. This means that both study drugs must have been administered at least once. The FAS will be the primary population for the analysis of efficacy and baseline characteristics.

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

6.13.4 Per protocol set (PPS)

The PPS includes all patients in the FAS who do not have any major protocol deviations that could confound the interpretation of the primary analyses conducted on the FAS. The PPS includes all patients in the FAS who have received at least one dose of MOR00208 and LEN, and underwent at least one post-baseline response assessment.

Those protocol deviations leading to exclusion from the PPS will be listed including the patient number

6.13.5 Safety set (SAF)

The SAF includes all patients who received at least one dose of MOR00208 or LEN and had at least one post-baseline safety assessment.

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

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

6.13.6 PK analysis set (PKAS)

The PKAS will include all patients who received at least one dose of MOR00208 and have at least one quantifiable serum MOR00208 concentration (PK parameters will be calculated as data permits).

6.13.7 Immunogenicity analysis set (IAS)

The IAS includes all patients who have at least one anti-MOR00208 antibody assessment.

6.13.8 Planned analyses for the different populations

The number of patients in each analysis set will be summarized.

Table 2 gives an overview of the assessments performed on the different analysis sets.

Table 2: Overview of the analyses performed on the different analysis populations

Analysis	All patients screened	FAS	PPS	SAF	PKAS	IAS
Patient disposition	x					
Summary of baseline characteristics		x		x		
Overall response rate, disease control rate (central and local evaluation)		x	x			
PFS (central and local evaluation)		x	x			
Duration of response, duration of best overall response (central and local evaluation)		x	x			
Time to response (central and local evaluation)		x	x			

Time to next treatment		x	x			
Time to progression (central and local evaluation)		x	x			
Overall survival		x	x			
Efficacy subgroup analyses		x	x			
ECOG performance status, B-symptoms		x		x		
Summary of drug exposure and compliance		x		x		
Summary of prior therapies		x		x		
Summary of pre-medication, prior medication, concomitant medication		x		x		
Summary of medical history and current medical condition		x		x		
Summary of vital signs, 12-lead ECG, laboratory safety evaluations, adverse events				x		
Pharmacokinetic analyses					x	
Immunogenicity analyses						x
Descriptive biomarker analyses		x				

6.13.9 Withdrawal of informed consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis data sets. The date on which a patient withdraws full consent is recorded in the eCRF (on the end of treatment eCRF page). Note: Patients who withdraw consent from treatment but consent to post- treatment follow up and/or survival follow up are not considered as having withdrawn full consent and no such withdrawal of consent date is recorded in the eCRF. Such post- treatment assessments will be included in the analysis data sets.

Any data that is entered in the clinical database without the consent of the patient will be excluded from the analysis sets. Only exceptions are the information entered to close a page after the date of withdrawal of consent e.g. End of Treatment, End of post-treatment follow-up.

For OS, death events in some countries can be reported if the death event can be confirmed to be captured from public records. If confirmed, the events will be included in the analysis data sets.

Third party data, e.g. PK, biomarker etc., collected in the clinical database without having obtained consent for collection will not be included in the analysis data sets. Data from such samples if collected prior to the date of consent withdrawal will be included in the analysis unless specific request is made by the patient not to analyze the sample. These data will be excluded by the presence of the appropriate protocol deviation criterion.

6.14 Efficacy Assessments

6.14.1 Response criteria

The efficacy variables / endpoints will be evaluated through central review by an Independent Radiology/Clinical Review Committee (IRC) that will apply the revised response assessment criteria based on the guidelines of the IWG reported by Cheson et al. (2007) (see **Error! Reference source not found.**). The review process will be defined in the IRC Charter.

Local assessment of efficacy response (Cheson criteria) will be required in addition to central review at the beginning of Cycle 3, Cycle 5, Cycle 7, and Cycle 10, at the end of Cycle 12 (for decisions concerning the additional Cycle 13 through Cycle 24 MOR00208 treatment) and at the EOT Visit (to determine whether the disease has progressed). During the treatment phase from Cycle 13 onwards (MOR00208 monotherapy phase) tumour response assessments will be performed as follows: for Cycles 13 - 24 local assessments of response will be done approximately every 3 months ± 2 days from the previous scan. First assessment during this phase can be done directly 3 months after Cycle 12 Day 28 PET/CT assessment. Thus, the first response assessment after Cycle 12 is not needed at Cycle 13 Day 1. Moreover, the first assessment during the MOR00208 monotherapy phase can generally happen later than 3 months after the Cycle 12 Day 28 assessment. From Cycle 25 onwards local assessments of response will be performed approximately once per year ± 2 weeks from the previous scan. Efficacy will be evaluated in terms of (best) ORR (primary endpoint), DCR, DoR, PFS, OS, TTP and TTNT (secondary endpoints) based on both INV and IRC response assessment. For definitions, see Sections 9 (primary endpoint) and 10 (secondary endpoints).

Table 3: Definition of Response Criteria (Cheson et al., 2007)

Response	Definition	Nodal masses	Spleen, liver	Bone marrow
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative b) Variable FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohisto-chemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size on CT a) FDG-avid or PET positive	≥50% decrease in SPD of nodules (for single nodule in greatest	Irrelevant if positive prior to therapy; cell type should be specified

		prior to therapy; one or more PET positive at previously involved site b) Variable FDG-avid or PET negative; regression on CT	transverse diameter); no increase in size of liver or spleen	
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET b) Variable FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	a) Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis b) Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

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

6.14.2 Disease progression

Only objective progressive disease (PD) according to the Cheson criteria as mentioned in Table 3 is considered in all efficacy analyses.

In particular, discontinuation due to PD (from the "End of Treatment Completion" eCRF page), without supporting objective evidence (as defined above), will not be considered as PD in the determination of best overall response rate (ORR) and in the analysis for progression-free survival (PFS).

6.14.3 Change in imaging modality

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

7. STATISTICAL METHODOLOGY

7.1 General principles of statistical programming

The statistical analysis will be performed on the analysis study database with appropriate software, SAS® Software version 9.4 or above (SAS Institute, Cary, N.C.).

7.2 Variable types and descriptive statistics

Descriptive statistics will be calculated using as reference the number of patients in the relevant analysis population (any exception will be specified) according to the nature of the data as follows:

Continuous variables (e.g. age, body weight): number of non-missing observations, arithmetic mean, standard deviation (StD), minimum and maximum values, quartiles (median, Q1 and Q3).

If there are less than 5 observations, only the number of non-missing observations, arithmetic mean, median, minimum and maximum will be presented.

Descriptive statistics of plasma concentrations and PK parameters will include n, arithmetic mean, geometric mean, StD, median, coefficient of variation CV (%), geometric CV (%), minimum and maximum. Geometric mean and the geometric CV (%) will be derived from non-zero values. For plasma concentrations, the number of non-zero values (m) will also be reported.

Categorical variables: (e.g. ECOG, ethnicity) Number of non-missing observations, the number of missing and the relevant percentage on the analysis population, number and relative frequencies. If not defined otherwise, the percentage denominator will be the number of patients with non-missing information.

In case of subcategories, the relative frequencies will be calculated on the basis of the patients in the respective category, in this case a footnote will be added explaining the different denominators.

Time variables (durations): Will be summarized using arithmetic mean, StD, minimum and maximum values, median and quartiles (Q1, Q3) and will be presented in months (unless otherwise stated).

Time to event variables: (PFS, OS, etc.) Unless otherwise stated, Kaplan Meier estimates of Q1, Median, and Q3 along with their 95% Confidence Intervals will be presented.

The majority of data obtained on the eCRF and entered into the database will be provided in separate data listings showing individual patient values. The planning and reporting of statistical analyses will be carried out as described in the [redacted] standard operating procedures (SOPs).

Any patient who withdraws from the study will be analyzed with the data available. Imputation of missing values will not be performed, unless specified in the relevant sections of the SAP.

7.3 Convention on missing data

For the statistical analysis, some particular data handling conventions (handling of missing data, pooling of centers) are planned. The details are present in the respective sections.

7.4 Data included in the analysis and cut-off date

All the analyses mentioned in Sections 8 to 16 will be performed using data collected in the database up to the data cut-off date. A cut-off date will be defined for each of these analyses and will be specified in the outputs.

Of all the termination dates of the patients included in the final analysis, the last termination visit date will be defined as the cut-off date and will be specified in the outputs.

Analyses will be based on the data collected for patients who did not fail screening, and for all patients treated prior to or on the cut-off date.

Any data collected beyond the cut-off date will not be included in the analysis. Only data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. For example, if the cut-off date is 15JUN2017 then an AE starting on 13JUN2017 will be reported, whereas an AE with start date on 17JUN2017 will not be reported.

All events with an event start date either before or on the cut-off date and an event end date after the cut-off date will be reported as “continuing at the cut-off date”. The same rule will be applied to events starting either before or on the cut-off date and not having a documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will appear as missing in listings.

If it is required to impute an end date to be able to perform a specific analysis (e.g. end date after the cut-off date) the cut-off date needs to be imputed as an end date. The imputed date will be displayed and flagged in the listings.

Any data collected beyond a patient's withdrawal of consent will not be included in the analysis; except for SAEs and the date of death provided confirmed by a public registry and patient status entered after the date of withdrawal of consent e.g. end of treatment, end of post-treatment follow-up.

7.5 Specifications and Analysis Database

Based on dataset in SDTM format provided by [redacted]s Clinical Data Services group analysis datasets adhering to CDISC ADaM standard will be generated with SAS ® software, version 9.4 or above, based on the soft lock of data for the main analysis or hard lock study database for the full final statistical analysis (after all the patients discontinue the study) and according to agreed Analysis Dataset Specifications (ADS).

7.6 Pooling of investigative sites

Data will be pooled from all investigative sites for the analyses. The justification for this is based on the following:

- The sites must implement one common protocol.
- The sponsor must provide close monitoring of study procedures and compliance.
- Several sites are expected to recruit a few patients only.
- The study sites must use common data collection procedures.
- For primary endpoint analysis the disease response assessments will be made centrally.

Geographical region, however, may be included as a factor in supportive and/or exploratory analyses, as well as safety analyses.

8. PATIENT DISPOSITION, BACKGROUND AND BASELINE CHARACTERISTICS

The number of patients screened, treated, progressed/relapsed, died, and those included in each analysis population will be summarized. In addition, patients will be listed and summarized who discontinue treatment during the combination phase (cycles 1 to 12), antibody monotherapy treatment phase (> cycle 12), or are being treated despite

progression, along with reasons for discontinuation. The number of patients followed up for overall survival will be summarized.

8.1 Screened patients

The number (%) of patients who were

- Screened
- Screen failure
- Enrolled

will be summarized by country, center, and overall. Percentages will be calculated based on the number of patients screened. In a separate summary the reason for screen failures will be presented.

8.2 Enrolled patients

The following summaries will be provided: % based on the total number of Enrolled patients:

- Number (%) of patients who were treated with study drug (split by MOR00208, LEN, and both study drugs).
- Number (%) of patients who are still on-treatment with study drug split MOR00208, LEN, both drugs, or any drug (all Cycles considered; only for the primary analysis).
- Number (%) of patients who are ongoing with combination treatment (Cycles 1-12).
- Number (%) of patients who discontinued *only* one of the two study drugs (split by LEN only, MOR00208 only), or *both* study drugs during combination treatment (Cycle 1 to 12) including the primary reason for discontinuation. The discontinuation of LEN as per protocol after Cycle 12 will not be considered here. If drugs are sequentially discontinued, the reason for discontinuation of the later drug will be reported as reason for the discontinuation of both drugs.
- Number (%) of patients who discontinued MOR00208 or LEN before completing 12 Cycles. All discontinuations are considered including both the discontinuation of MOR00208/LEN *only* or a sequential discontinuation of both drugs. The reason for discontinuation will also be reported.
- Number (%) of patients who *successfully* completed combination treatment (Cycles 1- 12), i.e., patients who completed 12 Cycles on *both* drugs.
- Number (%) of patients who reached Cycle 13 Day 1 on at least one study drug (split by both drugs, LEN only, MOR00208 only, any study drug).

- Number (%) of patients who are still ongoing with MOR00208 only, LEN only, or both drugs after completion of Cycle 12 (i.e., ongoing from Cycles 13 onwards; only for primary analysis).
- Number (%) of patients who discontinued MOR00208 beyond Cycle 12 regardless of successful or unsuccessful completion of the combination treatment phase, including the reason for discontinuation.
- Number (%) of patients who discontinued MOR00208 after *successful* completion of combination treatment phase (Cycle 1-12) including the reason for discontinuation. Successful completion means that the patient completed 12 Cycles on combination treatment.
- Number (%) of patients who discontinued LEN after completion of the combination treatment (Cycle 1 to 12) including the reason for discontinuation (e.g., completion as per protocol).

  NOTES:

  - The following reasons for 'End of Treatment' as entered on the 'End of Treatment' eCRF page will be summarized under the term as "As per protocol":
    - "CYCLE COMPLETED - LAST DOSE OF LENALIDOMIDE ON AUG, 20TH 2017"
    - "AS PER PROTOCOL"
    - "PER PROTOCOL"
    - "TREATMENT COMPLETED PER PROTOCOL"
    - „ACCORDING TO PROTOCOL"
    - "IT WAS STOPPED AFTER 12 CYCLES PER PROTOCOL"
    - "PATIENT COMPLETED 12 CYCLES TREATMENT"
    - "COMPLETED"
    - "LEN TREATMENT COMPLETED"
  - Patients are only treated with LEN for 12 Cycles as per protocol. However, patients who reached Cycle 13, and who are still on treatment with MOR00208 are not depicted on the 'End of Treatment' page as only patients who have undergone an 'End of Treatment Visit' will be represented on this page. To also consider LEN discontinuations 'as per protocol' for patients who are still ongoing with MOR00208 treatment the following strategy will be applied:

    Patients who reached Cycle 13 and who are not already represented on the 'End of Treatment' page will also be reported as having discontinued LEN. The reason for discontinuation will be reported as "As per protocol" if there is no evidence from

the recoded adverse events that a patient has discontinued LEN due to an adverse event, i.e. action taken with LEN for the respective event is recorded as 'Study drug permanently discontinued due to this AE. In the latter case the reason for discontinuation will be reported as "Adverse Event".

- Number (%) of patients who discontinued LEN at any time during the study including the reason for discontinuation.
- Number (%) of patients who discontinued MOR00208 at any time during the study including the reason for discontinuation.
- Number (%) of patients who discontinued LEN at any time during the study without discontinuation of MOR00208 at the same time including the reason for discontinuation.
- Number (%) of patients who discontinued MOR00208 at any time during the study without discontinuation of MOR00208 at the same time including the reason for discontinuation.

Listings showing the reason for being eligible based on inclusion and exclusion criteria will be shown. Another listing depicting information on patient disposition will be prepared.

8.3 Survival follow-up period and survival follow-up

8.3.1 Summary statistics

The following summaries will be provided (based on the total number of SAF patients):

- Number (%) of patients who have entered the survival follow-up following the 30-day safety follow-up visit.
- Number (%) of patients who have discontinued from the survival follow-up.
- Reasons for discontinuation from the survival follow-up.

8.3.2 Duration of overall survival follow-up

- A summary table showing the duration of follow-up will be presented for the FAS population. Summary information regarding the follow-up of patients is displayed in order to describe the maturity of data and quality of follow-up.
- Follow-up of the study will be summarized using the following metric to provide a comprehensive assessment of follow-up for patients: Follow-up time elapsed from study start reference date = (Date of event or censoring – study start reference date +

1)/30.4375 (months) regardless of censoring. Date of event or censoring is the same as the one defined in the section for overall survival analysis.

8.4 Protocol deviations

Key protocol deviation will be identified based on reviews of the data prior to database lock. Protocol deviations will be summarized overall and by center, and tabulated according to the following categories:

- Prohibited concomitant medication
- Informed consent form
- Eligibility criteria
- Laboratory assessments
- Procedure or test
- Study drug and treatment
- Visit schedule
- Other

Only protocol deviations directly affecting the patient will be reported. Protocol deviations pertaining to the study centers will not be considered. The number (%) of patients in the SAF with at least one of the above protocol deviations will be tabulated.

8.5 Baseline and demographic characteristics

Descriptive statistics will be presented for continuous variables. The number and percentage (%) of patients in each category will be presented for categorical variables. All summaries will be presented for the FAS and the SAF. For categorical variables, the number and percentage of patients with missing data will be provided. Listings for demographic data will be produced for the SAF.

The following continuous variables will summarized:

- Age (as continuous variable [years])
- Height [cm]
- Weight [kg]
- Number of prior systemic treatment lines (DLBCL medications) as categorical variable
- Number of patients with 1 vs. ≥ 2 prior anti-DLBCL medications

- BMI (calculated as weight[kg] / height[m]^2 using weight at baseline)
- Time since first DLBCL diagnosis [months]
- Time since discontinuation of last prior anti-DLBCL medication or ASCT [months]

The following categorical variables will be summarized:

- Age as categorical variable:
  - with subgroups < 65 vs. ≥ 65 years of age
  - with subgroups < 60 vs. ≥ 60 years of age
  - with subgroups < 70 vs. ≥ 70 years of age
- LDH levels at baseline (within reference range vs. beyond reference range)
- Prior ASCT (yes vs. no)
- Cell of origin (GCB vs. non-GCB based on immuno-histochemistry/central pathology)
- Cell of origin (GCB vs. ABC based on gene expression profiling)
- Rituximab refractoriness (yes vs. no)
- Refractoriness to last prior therapy (yes vs. no)
- Primary refractoriness (yes vs. no)
- ECOG
- Ann Arbor Disease Stage dichotomized (I and II vs. III and IV)
- Sex
- Race (Black or African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, White, Other)
- IPI score dichotomized (score 0-2 vs. 3-5, i.e., “low risk” and “low-intermediate risk” vs. “intermediate-high risk” and “high risk”)
- FcγRIIIa affinity (high affinity: FCGR3A-158V homozygosity vs. low affinity: FCGR3A-158F homozygosity, or FCGR3A-158F/V heterozygosity)
- FcγRIIa affinity (high affinity: FCGR2A-131H homozygosity vs. low affinity: FCGR2A-131R homozygosity, or FCGR2A-131H/R heterozygosity)

Note: the calculation of derived variables is described in the respective sections below.

8.6 Medical history and current medical conditions

8.6.1 Coding and definitions

Medical history and current medical conditions will be summarized by body system, preferred term and by toxicity grade. Coding will be performed using the current version of the Medical Dictionary for Regulatory Activities (MedDRA Version 21.0 or higher). Listings will also be provided for the SAF.

Notes:

- Toxicity grade will be coded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V4.03 or higher.
- Medical history is defined as records in the "Medical History and Current Medical Conditions"- eCRF form which are not ongoing at Cycle 1 Day 1.
- Current medical conditions are defined as records in the "Medical History and Current Medical Conditions"- eCRF form which are ongoing at Cycle 1 Day 1.

8.6.2 DLBCL-specific medical history and diagnosis

Data on the diagnosis of DLBCL will be presented in a summary table and in listings (SAF). The table will include a summary of the following:

- Stage at screening and initial diagnosis.
- Ann Arbor Disease Stage dichotomized (I and II vs. III and IV).
- Disease risk (IPI) at screening by category (0, 1, 2, 3, 4, 5).
- Disease risk (IPI) at screening (dichotomized: low risk and low-intermediate risk vs. intermediate-high risk and high risk).
- Time since initial diagnosis of DLBCL.
- Bulky disease (present vs. absent) at screening (defined as having a longest lesion diameter of ≥ 7.5 cm as assessed by central radiological assessment).
- Time since first progression/relapse.
- Time since last progression/relapse.
- NHL subtype as per central pathology (DLBCL, Follicular Lymphoma, Mantle Cell Lymphoma etc.).
- Lactate dehydrogenase (LDH) levels at baseline (elevated vs. not elevated).
- Time since discontinuation of last prior anti-DLBCL medication or ASCT [months].

- Relapse after initial diagnosis (relapse ≤12 months after initial DLBCL diagnosis vs. relapse >12 months after initial DLBCL diagnosis)

The results of the central pathology have been reviewed by Morphosys and been classified for the tabulation into NHL subtypes. For the subgroup analysis based on dichotomized NHL pathology results the patients with the following diagnoses have been classified further as non-DLBCL patients:

- MARGINAL ZONE LYMPHOMA
- FOLLICULAR LYMPHOMA, GRADE 2
- MANTLE CELL LYMPHOMA, CLASSIC TYPE
- FOLLICULAR LYMPHOMA (GRADE 2 + 3A)

The event times (in months) are defined as (for example):

[(reference start date) – (date of initial diagnosis of DLBCL)]/30.4375

A listing of the recorded diagnostic lymph node biopsy will also be presented depicting the information on the Diagnostic Lymph Node Biopsy eCRF page. Another listing will show information on NHL subtype as determined by central pathology (the pathological description of the sample as well as the NHL entity used for tabulation).

Data on bone marrow aspiration and biopsies as recorded throughout the study will be summarized in a table and also listed. The data table will summarize the following information on:

- Potential complete response.
- Type of examination.
- Percentage of lymphocytes.
- Type of infiltration.
- Identification of indolent lymphoma in the bone marrow.
- Degree of lymphoma involvement.

Disease involvement assessment of the spleen/liver may occur as part of the full or limited physical examinations throughout the study and recorded data will be presented in a listing.

1.1.1 Handling of incomplete dates regarding DLBCL-specific medical history

If the 'Date of initial diagnosis of DLBCL' is only partially completed, the 'Time since first DLBCL diagnosis' will be calculated based on the following imputation rules:

Table 4: Imputation rules for the 'Date of initial diagnosis of DLBCL'

Component of the Date			Variable
DD	**MMM**	**YYYY**	**Date of initial diagnosis of DLBCL**
✓	✓	✓	No imputation
x	✓	✓	Day 15 of the month
x	x	✓	No imputation
x	x	x	

If the 'Date of initial diagnosis of DLBCL' cannot be imputed, the 'Time since first DLBCL diagnosis' will be considered as 'Unknown'.

If the 'Date of progression/relapse' is missing, the 'Time since first/last progression/relapse' will be calculated based on the following imputation rules:

Table 5: Imputation rules for the 'Date of progression/relapse'

Component of the Date			Variable
DD	**MMM**	**YYYY**	**Date of progression/relapse**
✓	✓	✓	No imputation
x	✓	✓	First day of the month
x	x	✓	No imputation
x	x	x	

If the 'Date of progression/relapse' cannot be imputed, the 'time since first/last progression/relapse' will be considered as 'Unknown'.

2.1.1 Calculation of the International Prognostic Index (IPI):

The IPI is being calculated from the following items based on the information collected on the eCRF page '*Ann Arbor Disease Staging and Disease Risk Assessment'*:

- Age older than 60 years.
- Lactate dehydrogenase level higher than upper limit of normal.
- ECOG performance status score of 2 or greater.
- Stage III or IV disease.
- More than one involved extranodal disease site.

The IPI gives one point for each of the above characteristics, for a total score ranging from zero to five correlating with the following risk groups:

- Low risk: 0–1 point.
- Low-intermediate risk: 2 points.
- High-intermediate risk: 3 points.
- High risk: 4–5 points.

The categories above will also be collapsed into *low risk* (0–2 points) and *high risk* (3–5 points).

8.6.3 Reason for ASCT ineligibility

The reason for ASCT ineligibility as collected in the eCRF will be listed using the SAF. Additionally, the following three categories will be defined for a table summarizing the number of patients who are ASCT ineligible due to the following reasons (see also Table 6):

- **Chemorefractory:**
    - Chemorefractory patients as indicated on the eCRF page 'ASCT Ineligibility Criteria' ('Failure to achieve PR or CR with salvage therapy').
    - Patients who underwent a stem cell transplantation before as indicated on the eCRF page 'Prior Cancer Therapies for DLBCL – Autologous Stem Cell Transplants'.
    - The presence or absence of any other reason such as comorbidities or high age will be ignored.
- **High age (in presence of absence of comorbidities):**

- All patients who are ineligible due to high age as indicated on the eCRF page 'ASCT Ineligibility Criteria' ('Age > 70 years').
- Only those patients will be considered who are not already in the 'Chemorefractory' group.
- Presence or absence of other reasons such as comorbidities will be ignored.

- **Other reasons**
  - All other patients who are not in the categories above will be considered as ASCT ineligible due to other reasons.

Table 6: Reasons for ASCT Ineligibility

Priority	High level category	Reason from eCRF
1	Chemo-refractory	Failure to achieve PR or CR with salvage therapy
		Prior ASCT as indicated in eCRF page 'Prior Cancer Therapies for DLBCL – Autologous Stem Cell Transplants'
2	Age or Comorbidity	Age >70 years
		Diffusion lung capacity for carbon monoxide <50% by pulmonary function test
		Left ventricular ejection fraction <50% by multiple gated acquisition echocardiogram
		Other organ dysfunction or comorbidities precluding the use of HDT/ASCT on the basis of unacceptable risk of treatment
3	Patient refusal or Other	Patient refusal of HDT/ASCT
		Other Reason

8.6.4 History of indolent lymphoma

A listing depicting patients with a history of indolent lymphoma will be generated for the SAF. Entries for 'Condition' on the eCRF page 'Medical History and Current Medical Conditions' will be searched for the following keywords:

- Indolent lymphoma
- Indolent non-hodgkin lymphoma
- Indolent NHL
- Other indolent lymphoma
- Follicular lymphoma
- Follicular non hodgkin's lymphoma
- Marginal zone lymphoma
- Splenic marginal zone lymphoma
- Extranodal marginal zone lymphoma
- MALT
- Mucosa associated lymphoid tissue lymphoma
- Chronic lymphocytic leukemia
- Small lymphocytic lymphoma
- Waldenström macroglobulinemia

The listing will show the verbatim term as entered in the eCRF, but also the MedDRA-coded NHL subtype.

8.7 Prior and concomitant medications and non-drug treatments/procedures

8.7.1 Coding

Prior, concomitant and pre-medications will be recorded and coded using the current WHO Drug Dictionary Enhanced (WHO-DDE) and grouped by Anatomical Therapeutic Chemical (ATC) Level 2 and preferred name classes. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term.

8.7.2 Definitions

- **Pre-medication**: Medication given prior to MOR00208 infusion to mitigate potential infusion-related reactions. Pre-medication encompasses antipyretics, histamine receptor blockers, glucocorticosteroids, meperidine.
- **Prior medication/non-drug treatment:** If the treatment start and stop dates are both before the start date of study treatment, the medication will be classified as prior medication. Patients will only be counted once for multiple drug use (by preferred drug name).
- **Concomitant medication/non-drug treatment:** If the treatment start date is after start of study treatment the medication will be considered as concomitant medication. Patients will only be counted once for multiple drug use (by preferred drug name). If the medication stop date is incomplete, the following algorithm will apply to exclude the medication from the category *concomitant medication*:
  - If stop day is missing but month is complete, medication will only be excluded from concomitant medication if stop month is before month of treatment start.
  - If stop day and month are missing but year is complete, medication will only be excluded from concomitant medication if stop year is before year of treatment start.
  - If stop date is completely missing, medication will not be excluded.

- **Prior and concomitant medication/non-drug treatment:** Medications with start date before start date of study treatment but ongoing or with stop date after the start of study treatment will be considered both as prior and as concomitant medications. Patients will only be counted once for multiple drug use (by preferred drug name).
- **Duration of response (DoR) to prior anti-DLBCL medication or ASCT (in months)**:

  (date of assessment of tumour progression – date of assessment of first documented response + 1) / 30.4375.
- **Time since last anti-DLBCL medication/radiation therapy/surgery (in months)**:

  (first date of study treatment – end of treatment date for last prior anti-DLBCL medication/radiation therapy/surgery) / 30.4375.
- **Time since last ASCT (in months):**

  (first date of study treatment – date of procedure) / 30.4375.

8.7.3 Data presentation

Summary tables will be presented for:

- Prior medications.
- Concomitant medications which started before start of study treatment.
- Concomitant medications which started after start of study treatment.
- Prior non-drug treatments and procedures.
- Concomitant Non-Drug Treatments and Procedures Which Started Before Start of Study Treatment.
- Concomitant Non-Drug Treatments and Procedures Which Started After Start of Study Treatment.

All summaries will be conducted on both the FAS and SAF. Listings will be shown for pre-medication, prior medication, and concomitant medication, and listings for prior and concomitant non-drug treatments/procedures (for the SAF).

8.7.4 DLBCL-specific prior therapies

3.1.1 Prior therapy procedures

Prior anti-neoplastic therapies will be summarized:

- Prior anti-DLBCL medications:
  - Patients with at least one prior anti-DLBCL medication.
  - Number of therapy lines (as categorical variable).
  - Time since last prior anti-DLBCL medication.
  - Number of patients with 1 vs. ≥ 2 prior anti-DLBCL medications
- Prior radiation therapy:
  - Patients with at least one prior anti-cancer radiotherapy.
- Prior surgery:
  - Patients with at least one prior anti-cancer Surgery.
- Prior autologous stem cell transplantation (ASCT):
  - Patients with prior autologous stem cell transplantation.
  - Duration of response.
- Duration of response to last prior systemic anti-DLBCL medication or ASCT:

  - The duration of response to the patients´ last prior anti-DLBCL medication (in case the last prior therapy was a medication) or ASCT (in case the last prior treatment was an ASCT) will be summarized.

Separate listings will be presented on prior anti-DLBCL medications, radiation therapies, surgeries, and ASCT. Listings on individual DLBCL-specific procedures will include information on:

- The type and date of the initial response.
- The type and date of the best overall response.
- Date of progression.
- Reason for therapy discontinuation.
- Therapy start date.
- Therapy end date.
- The number of cycles.
- Therapy type.
- Medication name.
- Number of the particular therapy line.
- Duration of response (only for anti-DLBCL medication, and prior ASCT).

4.1.1 Handling of incomplete dates regarding prior therapies

Handling of missing values for 'Duration of Response (DoR)' to prior therapies

In case the date of initial response or progression is only partially completed the DoR as entered on the eCRF pages for 'Prior Cancer Therapies for DLBCL-Autologous Stem Cell Transplants' and 'Prior Cancer Therapies for DLBCL Medications' will be used. If the entry for DoR to previous therapy line is missing and the date of initial response or progression is only partially completed the following imputation rules will apply:

Table 7: Imputation rules for the 'Date of initial response' and 'Date of progression/relapse'

Component of the Date			Variable	
DD	**MMM**	**YYYY**	**Date of initial response**	**Date of progression/relapse**
✓	✓	✓	No imputation	No imputation
x	✓	✓	First day of the month	Last day of the month

x	x	✓	No imputation	No imputation
x	x	x		

The 'Duration of Response' to a particular prior therapy will be considered as 'Unknown' if the dates required for derivation cannot be imputed.

Handling of missing values for the derived variables 'Time since the last prior anti-DLBCL medication/radiation/surgery/ASCT'

A partial completion date for the completion of the last prior therapy will be imputed using the following algorithm for the last regimen:

Table 8: Imputation rules for 'End Date' of last prior anti-DLBCL medication, the 'Date of procedure' (for surgery, radiation, ASCT)

Component of the Date			Variable	
DD	**MMM**	**YYYY**	**'End Date' of last prior anti-DLBCL medication**	**Date of procedure (surgery, radiation, ASCT)**
✓	✓	✓	No imputation	No imputation
x	✓	✓	Day 15 of the month	Day 15 of the month
x	x	✓	No imputation	No imputation
x	x	x		

The 'Time since last prior anti-DLBCL medication/radiation/surgery/ASCT' will be considered as 'Unknown' if the dates required for derivation cannot be imputed.

5.1.1 Refractoriness to prior therapies

Three subgroups for treatment refractoriness in prior therapy lines will be defined using information on prior anti-DLBCL medications collected in the eCRF.

- Primary refractoriness
- Refractoriness to the last prior treatment line
- Rituximab refractoriness

The number (%) of patients in each of these subgroups will be presented. The information will also be provided in listings (for the SAF). The refractoriness to prior therapies will be derived for the FAS only.

8.7.4.1.1 Primary refractoriness

Primary refractoriness is defined as disease progression in the course of the first line treatment, or showing a response of less than PR (i.e., PD or SD) as best response to the first line treatment, or disease progression within ≤ 6 months from the completion of first-line therapy (i.e., the 'End Date' for the first therapy line as entered on the eCRF page 'Prior Cancer Therapies for DLBCL Medications').

- Only systemic anti-DLBCL medications as entered on the 'Prior Cancer Therapies for DLBCL Medications' eCRF page will considered as first line treatment
- If the status for 'Primary refractoriness' cannot be determined the patient will be considered as having an "Unknown" status.

8.7.4.1.2 Refractoriness to the last prior treatment line

Refractoriness to the last prior treatment is defined as having less than a PR (i.e., SD or PD) as best overall response to the most recent therapy, progression during the course of treatment, or progression within ≤ 6 months from the completion of the most recent therapy line (i.e., the 'End Date' for the most recent therapy line as entered on the eCRF page 'Prior Cancer Therapies for DLBCL Medications').

- Only systemic anti-DLBCL medications as entered on the 'Prior Cancer Therapies for DLBCL Medications' eCRF page will considered as last prior treatment.
- If the status for 'Refractoriness to the last prior treatment line' cannot be determined the patient will be considered as having an "Unknown" status.

8.7.4.1.3 Rituximab refractoriness

Rituximab refractoriness is defined as having reached less than a partial response to any rituximab-containing treatment regimen, progression during the course of treatment, or progression within ≤ 6 months from the completion of any rituximab-containing (i.e., the 'End Date' for any rituximab-containing therapy line as entered on the eCRF page 'Prior Cancer Therapies for DLBCL Medications'). If the status for 'Rituximab refractoriness' cannot be determined the patient will be considered as having and "Unknown" status.

8.7.4.1.4 Imputation of missing values required for defining refractoriness subgroups

The '**End Date'** for the first treatment line, or the last prior treatment line or any Rituximab-containing treatment line, will be imputed as follows:

- In case day is missing but month and year are complete, the first day of the month or the starting date of the next treatment, whichever is later will be used.
- In case day and month are missing but year is complete, the date will be considered as missing.
- In case day, month and year are missing, the date will be considered as missing.

The **'Date of progression/relapse'** for a particular therapy line will be imputed as follows:

- In case day is missing but month and year are complete, the last day of the month will be used.
- In case day and month are missing but year is complete, the date will be considered as missing.
- In case day, month and year are missing, the date will be considered as missing.
- If the **'Date of progression/relapse'** is completely missing or cannot be replaced by imputation, the following strategy will be used:
    - If the 'Start Date' of the subsequent therapy line is present, the 'Start Date' will be used as a surrogate for the 'Date of progression/relapse' for the previous line of treatment. If the day for the Start Date missing, the day will be imputed using the last day of the month.
    - If the 'Start Date' of the subsequent therapy line is missing, but the 'End Date' of the subsequent therapy line is present the 'End Date' will be used as a surrogate for the 'Date of progression/relapse' for the treatment line of interest (the patient will be considered as 'refractory'). If the day for the 'End Date' missing, the day will be imputed using the last day of the month.

      NOTE: The 'End Date' of the subsequent therapy will only be used as a surrogate if the time interval between the 'End Date' of the subsequent line and the 'End Date' of the previous line is ≤ 6 months (the patient will be considered 'refractory'). Otherwise the refractory status will be considered as 'Unknown'.
    - If L-MIND constitutes the immediate treatment line after the line of interest the 'Informed Consent' date as entered on the 'Informed Consent' eCRF page will be used.

Table 9: Overview of imputation rules for 'End Date' and 'Date of progression/relapse' for the therapy line of interest

Component of the Date			Variable	
DD	**MMM**	**YYYY**	**'End Date' for the treatment line of interest**	**'Date of progression/relapse' for the treatment line of interest**
✓	✓	✓	No imputation	No imputation
x	✓	✓	1st day of the month	Last day of the month
x	x	✓	No imputation	1. **'Start Date' of the subsequent treatment** (a partially completed date can be imputed as outlined in Table **10**) 2. **'Stop Date' of the subsequent treatment** if the 'Stop Date' is ≤ 6 months after the 'End Date' of the therapy line of interest (a partially completed date can be imputed as outlined in Table **10**) 3. 'Informed Consent' date for L-MIND study participation if the subsequent treatment is L-MIND
x	x	x		

Table 10: Overview of imputation rules for a partially completed 'Start Date' or 'End Date' for the therapy line <u>subsequent</u> to the therapy line of interest (if the 'Date of progression/relapse' for the therapy line of interest has to be imputed)

Component of the Date			Variable	
DD	**MMM**	**YYYY**	**'Start Date'**	**'End Date'**
✓	✓	✓	No imputation	No imputation
x	✓	✓	Last day of the month	Last day of the month

x	x	✓	No imputation	No imputation
x	x	X		

8.7.5 Early vs. late relapse after DLBCL diagnosis

Patients having an 'early relapse' or 'late relapse' after their initial DLBCL diagnosis will be summarized. The following definitions will apply:

- Early relapse after initial DLBCL diagnosis: relapse ≤12 months after initial DLBCL diagnosis.
- Late relapse after initial DLBCL diagnosis: relapse >12 months after initial DLBCL diagnosis.

The 'Date of initial diagnosis of DLBCL' and the 'Date of first progression/relapse' can be found on the 'Diagnosis of DLBCL' eCRF page.

The following imputation rules will be applied in the situation of partially completed dates:

Table 11: Imputation rules for the 'Date of initial diagnosis of DLBCL' and the 'Date of first progression/relapse'

Component of the Date			**Variable**	
DD	**MMM**	**YYYY**	**Date of initial diagnosis of DLBCL**	**Date of first progression/relapse**
✓	✓	✓	No imputation	No Imputation
x	✓	✓	1st day of the month	Last day of the month
x	x	✓	No imputation	No imputation
x	x	x		

- If day and month are missing, but only the year is present for one or both variables required the patient will be assigned to the category 'Late relapse after initial DLBCL diagnosis' if the difference between the year for the 'Date of initial diagnosis of DLBCL' and the year for the 'Date of first progression/relapse' is two years or higher. In case the difference for the years is only one year the relapse category after initial DLBCL diagnosis will be considered as 'Unknown'. In case the year is the same for both variables the patient will be assigned to the category 'Early relapse after initial DLBCL diagnosis'
- If the relapse category cannot be determined, the patient will be considered as 'Unknown'.

8.7.6 Non-study anti-DLBCL treatment

Data on non-study anti-DLBCL treatments will be provided for patients who are still on any study drug, and for patients who have already discontinued the treatment (based on the '*Other Anti-Neoplastic Therapies after end of Study Drug Treatment*' and "*Concurrent Anti-Neoplastic Therapies Medications"* eCRF pages). The following summaries will be presented for both the FAS and the SAF:

- The number (%) of patients who received non-study cancer treatment prior to study treatment discontinuation.
- The number (%) of patients who received non-study cancer treatment after study treatment discontinuation.
- The number (%) of patients who received non-study cancer treatment without a documented radiological progression as per CHESON Criteria.
- The type of anti-cancer treatment received by ATC level 2 class and preferred name.
- Time to start of non-study anti-cancer treatment.
- Therapy line of non-study anti-cancer treatment.
- Reason for stopping non-study anti-cancer treatment.

Time to start of anti-cancer therapy is defined as (start date of anti-cancer treatment – date of last dose of study treatment + 1). In case the anti-cancer therapy started before the last dose of study treatment the time will be set to zero. If the start date of anti-cancer treatment is missing, then the time to start of anti-cancer treatment for that patient will be missing. Listings on other non-study cancer treatments will be presented for the SAF.

8.8 Pre-Medication for MOR00208 infusion

Due to the occurrence of infusion related reactions (IRRs), patients may receive pre-medications administered prior to MOR00208 infusions. These may include antipyretics, histamines, glucocorticosteroids, and meperidine. Pre-medications and their doses will be listed for all patients who received either LEN or MOR00208 (SAF population).

8.9 Study treatment

8.9.1 Treatment cycles

The patients will be administered study treatment according to cycles. Each Treatment cycle will consist of 28 days. The duration of exposure for each study treatment drug is defined according to regimen as outlined below.

MOR00208:

The planned administration of MOR00208 is as follows:

- Cycle 1: Day 1, Day 4 (loading dose), Day 8, Day 15, Day 22.
- Cycle 2: Day 1, Day 8, Day 15, Day 22.
- Cycle 3: Day 1, Day 8, Day 15, Day 22.
- Cycle 4 onwards: Day 1 and Day 15.

MOR00208 will be administered at a dose of 12.0 mg/kg IV. Dose reductions of MOR00208 are not allowed during the course of the study. Unless contraindicated the MOR00208 treatment should continue, even if the patient discontinues LEN treatment.

LEN:

The planned administration of LEN is as follows:

- Cycle 1 to Cycle 12: 25 mg oral LEN daily on days 1-21 of the respective cycle.
- Reduced LEN doses after reduction of the total daily dose (see Section 8.9.3) will also be administered on days 1-21 until Cycle 12.

8.9.2 Exposure

6.1.1 Duration of exposure to study drug

Exposure to study treatment and each study drug will be summarized for the FAS and the SAF.

Duration of exposure (days) = (last date of exposure to study drug) – (date of first administration of study drug) + 1.

Taking into account the period of rest between infusions, the **last date of exposure** is defined as follows:

- For MOR00208: When the study drug is administered over several regular doses with regular time intervals, the last date of exposure is identified according to the planned dose schedule of the cycle. If no rest period is included in the cycle then the last date of exposure is: (last date of administration of the study drug) + (length of time interval-1). **Length of time interval**: 7 days in Cycle 1-3 and 14 days from Cycle 4 onwards. In case a patient dies before the end of the time interval the date of death will be used to truncate the time interval, i.e., in this case the last date of exposure will be set as the date of death.
- For LEN, the last date of exposure will be defined as the last date of administration. Thus, planned dose interruptions between days 22 to 28 of each cycle, as per protocol, will not be considered. That is, only day 1 to 21 will be considered as being exposed to LEN.

7.1.1 Duration of exposure to study treatment

Duration of exposure (days) = (last date of exposure of all the study drugs) – (date of first administration of study treatment) + 1.

The definition of exposure is specified in the section *duration of exposure to study drug*.

8.1.1 The duration of exposure to study treatment / drug will be calculated in months.

9.1.1 Exposure analysis

- The number of patients completing each cycle will be summarized. A patient is considered to have completed a cycle for MOR00208 if he/she was compliant for all MOR00208 infusions during the cycle. A patient is considered to have completed a cycle for LEN if he/she was compliant (see Section 8.9.6) for LEN administration during the cycle.
- Summary statistics will be displayed. The duration of exposure will also be summarized according to the following categories: Month 1-2, 3-4, 5-6, 7-8, etc.
- Number of infusions with MOR00208 will be summarized as follows:
  - The total number of MOR00208 infusions will be summarized
  - The number (%) of patients belonging to the following categories will be derived:

    0-2 infusions, 3-4 infusions, 5-6 infusions, 7-8 infusions, etc.

8.9.3 Dose reduction

Dose reductions are only possible for LEN, but not for MOR00208. The number (%) of patients with any dose reduction will be summarized for LEN. The number (%) of patients with a reduction to a minimum of 20 mg, 15 mg, 10 mg, or 5 mg without having completely discontinued treatment will be shown. Moreover, the number (%) of patients who had no reduction at all or only a reduction to 20 mg (but not lower) will be summarized.

8.9.4 Dose interruption

The number (%) of patients with temporary interruptions and the associated reasons will be summarized for both study drugs.

8.9.5 Permanent discontinuations

A summary of patients who discontinued permanently will be provided for both study drugs. The reasons for permanent discontinuation from the study drug will be summarized for each study drug.

8.9.6 Compliance

10.1.1 MOR00208

Compliance for MOR00208 will be calculated by taking the actual MOR00208 infusion dose divided with the planned MOR00208 infusion dose. Compliance will be summarized per single infusion and per cycle:

- MOR00208 compliance per **single infusion**: if the MOR00208 dose administered is ≥80% and ≤120% of the planned dosage.
- MOR00208 compliance **per cycle**: if this quantity is ≥80% and ≤120% of the planned dosage for the cycle, then the patient will be considered compliant for that cycle.

11.1.1 LEN

LEN is taken for the first 21 days of each cycle. Patients experiencing a transient treatment interruption, e.g., due to toxicities, or patients undergoing treatment discontinuation may take LEN for less than 21 days, which would not be considered as non-compliance. Similarly, a planned reduction of the *Total Daily Dose* will not be considered as non-compliance.

For some patients and Cycles the *Total Daily Dose* will be reached by combining tablets of two different *Dose Strengths*. Compliance will be calculated as follows:

If (total used dose)/(total planned dose) is between 80% and 120%, both inclusive, of the assigned dosage during a particular cycle, then the patient is considered compliant for LEN during that particular cycle. The *Total Planned Dose* and the *Total Used Dose* will be derived as follows:

For patients who did <u>not</u> experience a dose change or treatment interruption (as indicated on the eCRF page *'Lenalidomide Dosing Record'*):

- The ***Total Planned Dose*** will be calculated as follows:

  21 x *Total Daily Dose* (as entered on the eCRF page *'Lenalidomide Dosing Record'*).

- The ***Total Used Dose*** will be calculated as follows:
  - For patients and cycles in which the Total Daily Dose is reached by taking one capsule only:

Total Used Dose = (Number of Capsules Dispensed - Number of Capsules Returned) x Dose Strength.

For patients and cycles in which the Total Daily Dose is reached by combining two or more capsules of different Dose Strengths (e.g., Dose Strength 1 and Dose Strength 2):

Total Used Dose = [(Number of Capsules of Dose Strength 1 Dispensed -Number of Capsules of Dose Strength 1 Returned) x Dose Strength 1] + [(Number of Capsules of Dose Strength 2 Dispensed - Number of Capsules of Dose Strength 2 Returned) x Dose Strength 2].

For patients who experienced a dose change, treatment interruption or treatment discontinuation (as indicated on the eCRF page '*Lenalidomide Dosing Record*'):

- The ***Total Planned Dose*** will be calculated as follows:
  - Patients who required a dose change or interruption and did not start LEN treatment (with same or changed dose) before completion of that particular Cycle the dose change/interruption happened:

    Min[21, (*Dosing Stop Date* – *Dosing Start Date* + 1)] x *Total Daily Dose* (as entered on the eCRF page *'Lenalidomide Dosing Record'*).

    Note: Separate log lines on the eCRF page *'Lenalidomide Dosing Record'* may exist for patients who reach the *Total Daily Dose* by combining capsules of different dose strengths. In this case, *Total Daily Dose*, *Dosing Start Date* and *Dosing Stop Date* are identical across the different eCRF log lines and only information from one log line will be used. In rare cases it may happen that actually Dosing Stop Date – Dosing Start Date + 1 is > 21, in this case the planned dose is calculated with 21 days only.
  - Patients who required a dose change / treatment interruption, and started the new *Total Daily Dose* / re-initiated treatment (in case of interruption) before completion of that particular Cycle the dose change/interruption happened:

    E.g., for one dose reduction, or one interruption:

    [(*Dosing Stop Date* for *Total Daily Dose* 1 – *Dosing Start Date* for *Total Daily Dose* 1 + 1 Day) x *Total Daily Dose 1*] + [(*Dosing Stop Date* for *Total Daily Dose* 2 – *Dosing Start Date* for *Total Daily Dose* 2 + 1 Day) x *Total Daily Dose 2*].

    Notes:

- Separate log lines on the eCRF page *'Lenalidomide Dosing Record'* will show the *Total Daily Dose* before and after dose change, or before and after treatment interruption, respectively.

- In case of treatment interruption *Total Daily Dose 1* and *Total Daily Dose 2* (in case of only one interruption) will be identical.

- Separate log lines may exist showing the identical information on *Dosing Start Date*, *Dosing Stop Date*, and *Total Daily Dose* in case the *Total Daily Dose* is reached by combining different *Dose Strengths*. In this situation, only the information from one eCRF log line will be used.

- The ***Total Used Dose*** will be calculated as follows:
  - Patients who required a dose change or treatment interruption, and did not start LEN treatment (with same or changed dose) before completion of that particular Cycle the dose change/interruption happened:
    - For patients and Cycles in which the *Total Daily Dose* (as entered in the eCRF page 'Lenalidomide Dosing Record') is reached by taking one capsule only: *Total Used Dose* = (*Number of Capsules Dispensed - Number of Capsules Returned*) x *Dose Strength*.
      Note: Only one log line on the eCRF page *'Lenalidomide Dosing Record'* will exist for this situation.
    - For patients and cycles in which the *Total Daily Dose* (as entered in the eCRF page *'Lenalidomide Dosing Record'*) is reached by combining capsules of different *Dose Strengths:*

      E.g., Dose Strength 1 and Dose Strength 2:

      Total Used Dose = [(Number of Capsules of **Dose Strength 1** Dispensed - Number of Capsules of **Dose Strength 1** Returned) x **Dose Strength 1**] **+** [(Number of Capsules of **Dose Strength 2** Dispensed - Number of Capsules of **Dose Strength 2** Returned) x **Dose Strength 2**]**.**

      Note: Several log lines with the same *Dosing Start Date* on the eCRF page *'Lenalidomide Dosing Record'* exist for this situation (representing the different dose strengths).
  - Patients who required a dose change / treatment interruption, and started the new *Total Daily Dose* / re-initiated treatment (in case of interruption) before completion of that particular Cycle the dose change/interruption happened:
    - Change of the *Total Daily Dose* within a particular Cycle:

Capsules of only one dose strength or a combination of several dose strengths might be used before or after dose change to reach the targeted *Total Daily Dose*. The *Total Used Dose* will be calculated as follows:

E.g., for capsules of two different dose strengths before and after dose change:

Total Used Dose = [(Number of Capsules of **Dose Strength 1** Dispensed before dose change - Number of Capsules of **Dose Strength 1** Returned before dose change) x **Dose Strength 1**] + [(Number of Capsules of **Dose Strength 2** Dispensed before dose change - Number of Capsules of **Dose Strength 2** Returned before dose change) x **Dose Strength 2**] **+** [(Number of Capsules of **Dose Strength 1** Dispensed after dose change - Number of Capsules of **Dose Strength 1** Returned after dose change) x **Dose Strength 1**] + [(Number of Capsules of **Dose Strength 2** Dispensed after dose change - Number of Capsules of **Dose Strength 2** Returned after dose change) x **Dose Strength 2**].

Note: In case only one dose strength is being used before or after changing the *Total Daily Dose,* one of the summands (e.g., the terms for Dose Strength 2) will become 0.

- Interruption and re-initiation of treatment within a particular Cycle: Capsules of only one dose strength or a combination of several dose strengths might be used to reach the targeted Total Daily Dose. The Total Used Dose will be calculated as follows (e.g., for capsules of two different dose strengths):

  Total Used Dose = [Number of Capsules of **Dose Strength 1** Dispensed before dose change x **Dose Strength 1**] + [Number of Capsules of **Dose Strength 2** Dispensed before dose change x **Dose Strength 2**] **+** [Number of Capsules of **Dose Strength 1** Returned after dose change x **Dose Strength 1**] + [Number of Capsules of **Dose Strength 2** Returned after dose change x **Dose Strength 2**].

  Notes: The *Total Daily Dose* before and after interruption in a particular Cycle is represented in separate log lines on the eCRF page *'Lenalidomide Dosing Record'.*

- The following applies if the ***Total Planned Dose*** is 0 for an entire Cycle:

- If the ***Total Used Dose*** is 0 for the Cycle, the patient will be considered as compliant for that particular Cycle.
- If the ***Total Used Dose*** is not 0, the patient will be considered as non-compliant for that particular Cycle.

Listings showing eCRF entries on LEN dosing records, MOR00208 dosing administration, and MOR00208 infusion details will be produced (for the SAF). A listing will be generated showing the compliance per cycle for each individual for both LEN and MOR00208 (for the SAF).

9. PRIMARY OBJECTIVE

The primary objective is to determine the activity of a combination of LEN with MOR00208 in terms of best objective response rate (ORR = rate of patients with complete response [CR] or partial response [PR]) in adult patients with R-R DLBCL.

9.1 Endpoint: Best objective response rate

The best ORR is defined as the proportion of patients with CR or PR as best response achieved at any time during the study. The denominator will be the total number of patients included in the analysis population.

9.2 Main analysis

The number and percentage of patients classified as having best overall response of CR or PR as well as 95% confidence limits (using the Clopper-Pearson exact method) will be presented. The number and percentage of patients with CR, and the number and percentage of patients with PR as best response will be shown. The main analysis will be conducted on the FAS for both the IRC response assessment, and the local, i.e., investigator (INV) response assessment.

For the main analysis of best ORR:

- The tumour assessments will be derived according to the IWG treatment response criteria for malignant lymphoma (Cheson et al., 2007; see Section 6.14), by an Independent Radiology/Clinical Review Committee (IRC). The review process will be defined in the IRC Charter.
- Patients with no post-baseline assessment of response will be included as non-responders.

- Patients with a best response of "Not Evaluable" will be summarized by reason for having unknown status. The following reasons will be used:
    - No valid post-baseline assessment available.
    - All post-baseline assessments have overall response "Unknown" or "Not evaluable" or "Indeterminate".
    - New anti-cancer therapy started before first post-baseline assessment.
- No formal hypothesis testing will be conducted.

The main analysis will be performed using the FAS.

9.3 Sensitivity analyses

- The main analysis as described in Section 9.2 will be conducted based on the INV assessment.
- The main analysis as described in Section 9.2 will be conducted using the PPS (based on INV and IRC assessment).
- The analysis as described in Section 9.2 will be performed excluding the patients with no post-baseline assessment of response or with all post-baseline assessments categorized as "Unknown". The analysis will be performed using the FAS based in both IRC and INV assessment.
- The number (%) of patients will be descriptively tabulated by categories of individual best outcome in tumor response assessments (CR, PR, SD, PD, Not Evaluable). Listings will be generated for both central and local response assessments (for the SAF).

9.4 Concordance between IRC and investigator (INV) assessment

The concordance rate in terms of response assessment represents the agreement in the best overall outcome (CR, PR, SD, PD, Not Evaluable, and Not Available) in tumour response assessments between the IRC and INV assessment. The concordance rate is the number of patients that are concordant over the total number of patients assessed, and will be calculated across all response categories. A contingency table will be generated. The concordance rate is calculated by adding the diagonal counts and dividing by the total number of patients assessed. Moreover, the agreement (%) of the INV assessment by the IRC in terms of best ORR will be calculated (i.e., the proportion of patients with a best response of CR or PR by investigator assessment that have a confirmed best response of CR or PR by the IRC assessment).

Patients who have been evaluated by investigator assessment, but not by central review assessment will be excluded from the concordance analysis.

The proportion (%) of patients who had at least one central review among the total number of patients who underwent at least one INV assessment will be calculated. Moreover, the proportion (%) of the total number of central reviews among the total number of INV assessments will be derived (i.e., the total number of central reviews across all visits and all patients divided with the total number of investigator response assessments across all visits and all patients multiplied by 100). The analysis will be conducted using the FAS.

10. SECONDARY OBJECTIVES

10.1 Secondary objective 1

10.1.1 Objective

To determine the activity of a combination of LEN with MOR00208 in terms of disease control rate (DCR = complete response (CR) + partial response (PR) + stable disease (SD) as best objective response) in adult patients with R-R DLBCL.

10.1.2 Endpoint: Disease control rate

DCR is defined as the proportion of patients having CR, PR or SD based on the best objective response achieved at any time during the study. The denominator will be the total number of patients included in the analysis population.

10.1.3 Main analysis

The number and percentage of patients classified as having best overall response of CR or PR or SD as well as 95% confidence limits (using Clopper-Pearson exact method) will be presented. The number and percentage of patients with CR, the number and percentage of patients with PR and the number and percentage of patients with SD as best response will be presented. The main analysis will be conducted on the FAS for the both IRC and INV response assessments.

For the main analysis of DCR:

- The tumour assessments will be derived according to the IWG treatment response criteria for malignant lymphoma (Cheson et al., 2007; see Appendix), by an Independent Radiology/Clinical Review Committee (IRC). The review process will be defined in the IRC Charter.
- Patients with no post-baseline assessment of response will be included as non-responders.
- Patients with a DCR of “unknown” will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment.
- All post-baseline assessments have overall response “Unknown” or “Not evaluable”.
- New anti-cancer therapy started before first post-baseline assessment.

- No formal hypothesis testing will be conducted.

10.1.4 Sensitivity analyses

- The main analysis as described in Section 10.1.3 will be conducted based on the INV assessment.
- The analysis mentioned in Section 10.1.3 will be performed excluding the patients with no post-baseline assessment of response or with all post-baseline assessments categorized as “Unknown”. The analysis will be performed using the FAS based in both IRC and INV assessment.

10.2 Secondary objective 2

10.2.1 Objective

To determine the activity of a combination of LEN with MOR00208 in terms of progression-free survival (PFS).

10.2.2 Endpoint: Progression-free survival

PFS will be defined as the time (in months) from the date of the first administration of any study drug to the date of tumour progression or death from any cause (see Independent Review Charter version 4.3, 10-JUL-2018). The date of progression will be the first date for which progressive disease was assessed as the objective response. The tumour assessments will be derived according to the IWG treatment response criteria for malignant lymphoma (Cheson et al., 2007; see section 6.14), by an Independent Radiology/Clinical Review Committee (IRC). The review process will be defined in the IRC Charter.

10.2.3 Disease assessments

Disease assessments will be performed with either PET/CT scans or CT/MRI scans as per the schedule in Table 12.

Table 12: Schedule of Tumour Assessments

Evaluation	Screen-ing	C3 D1	C5 D1	C7 D1	C10 D1	C12 D28	C13 D1	Every 3 months	From C25 D1 on-ward once per year	EOT visit
Disease response assessment (PET/CT or PET/MRI)	X					X			X[$]	X
CT or MRI scan for tumour measurement and disease response assessment		X	X	X	X		X*	X	X	

*Can be done approx. 3 months after C12D28 PET/CT or PET/MRI assessment.

[$]Only if deemed necessary and not more frequently than once per year. A window of ± 2 weeks is allowed by the protocol for these assessments. Tumour assessments will continue until disease progression, death or study discontinuation (whichever occurs first).

10.2.4 Censoring rules

12.1.1 Censoring situations

If a patient is alive and progression-free at the date of the analysis (i.e., cut-off date), the patient will be censored, and the reason for censoring will be provided as per Table 13.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of start date of treatment is used.

Table 13: Censoring Rules

Situation	Date of Progression or Censoring	Outcome	Censoring reason
Ongoing and No event until data cut-off	Date of last adequate tumour assessment	Censored	Ongoing
Discontinued the study with no event	Date of last adequate tumour assessment	Censored	Discontinued without event
No baseline tumour assessment	Date of C1D1	Censored	No baseline tumour assessment
Lost to follow-up	Date of last IRC tumour assessment (or C1D1 in case of study discontinuation w/o progression before any post-baseline assessment)	Censored	Lost to follow-up
Patient received non-study anti-DLBCL treatment before disease progression	Date of last adequate tumour assessment before start of non-study cancer treatment	Censored	New anti-cancer therapy started
Clinical Progression*	Date of last adequate tumour assessment	Censored for Analysis based on Investigator assessment only	Clinical Progression not validated by Cheson Criteria
PD by modality not including PET Scan is not confirmed by modality including PET Scan**.	Date of last adequate tumour assessment	Censored for Analysis based on Investigator assessment only	Non-PET PD not confirmed by PET.
Death before any date of PD assessment	Date of death	Progressed	
Death between adequate assessments	Date of death	Progressed	
Death or progression after two or more	Date of last adequate	Censored	Event documented

Situation	Date of Progression or Censoring	Outcome	Censoring reason
missed visits	tumour assessment		after two or more missing tumor assessments
EOT after two or more missed assessments without disease progression	Date of Last adequate Tumour Assessment	Censored	Adequate assessment no longer available

Abbreviations: EOT = End of Treatment; IRC = Independent Review Committee; PD = progressive disease; CT = Computed tomography; PET = Positron emission tomography. *Progression as per Investigator's assessment and without meeting PD criteria according to Response Criteria for Malignant Lymphoma (Cheson et al., 2007). **The rule only applies in case a PET-including modality is performed after a non-PET including modality.

13.1.1 Identification of two or more missing tumour assessments

If death or progression happens after two or more missed Tumour Assessments (TA), then the event is censored.

- An event occurring after two or more missing assessments or non-adequate tumour assessments will be censored on the date of last adequate tumour assessment.
- In one of the sensitivity analyses for PFS, an event occurring after two or more missing assessments is back-dated to the date of next scheduled assessment. The date of next scheduled assessment is the date of the last adequate tumour assessment plus the protocol specified time interval for assessments.
- If the patient has an EOT after two missed assessments without an event, then the patient will be censored for PFS at the last assessment and the censoring reason will be 'Adequate assessment no longer available'.
- Table 14 shows the maximum time [days] that can elapse between two response assessments without resulting in censoring.

Table 14: Time windows for missing response assessments

Missed tumor assessments	No tumor assessment between	Censored at
C3D1, C5D1	C1D1, C1D1 + 114 days (4 x 28 + 2)	C1D1
C5D1, C7D1	C3D1, C3D1 + 115 days (4 x	C3D1

	28 + 1 + 2)	
C7D1, C10D1	C5D1, C5D1 + 144 days (5 x 28 + 2 + 2)	C5D1
C10D1, C12D28	C7D1, C7D1 + 173 days (6 x 28 + 2 + 4 - 1)	C7D1
C12D28, C15D1/C16D1	C10D1, C10D1 + 186 days (6 x 28 + 2 + 2 + 14)	C10D1
C15D1/C16D1, C18D1/C19D1	C12D28, C12D28 + 184 days (6 x 28 + 14 + 2)	C12D28
C18D1/C19D1, C21D1/C22D1	C15D1/C16D1 + 172 days (6 x 28 + 4)	C15D1/C16D1
C21D1/C22D1, C24D1/C25D1	C18D1/C19D1 + 172 days (6 x 28 + 4)	C18D1/C19D1
C24D1/C25D1	C21D1/C22D1 + 451 days (3 x 28 + 2 + 365)	C21D1/C22D1
Tumor assessments in Year 3 and Year 4 after treatment initiation*	C24D1/C25D1 + 730 days (2 x 365)	C24D1/C25D1

*Apply this interval also for assessments after C24D1/C25D1

10.2.5 Main analysis

- The tumour assessments will be derived according to the IWG treatment response criteria for malignant lymphoma (Cheson et al., 2007), by an Independent Radiology/Clinical Review Committee (IRC). The review process will be defined in the IRC Charter.
- The distribution of PFS will be estimated using the Kaplan-Meier (K-M) method. The median PFS time along with 95% confidence intervals will be presented (Brookmeyer and Crowley 1982). 25th and 75th percentiles will be considered as well.
- The PFS probabilities at specific time points (1 month, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months), and the associated 95% CIs (Greenwood formula) will be summarized.
- PFS events will be described according to the type of event (death, documented tumour progression).
- The reason for censoring will be tabulated.
- A plot of the Kaplan-Meier curve for PFS will be provided.
- The median follow-up time for PFS including a 95% confidence interval (Brookmeyer and Crowley 1982) will be calculated using the reverse Kaplan-Meier method.
- No formal hypothesis testing will be conducted.
- The main analysis will be conducted on the FAS for both the IRC and INV response assessment.

10.2.6 Sensitivity analyses

- The main analysis as described in Section 10.2.5 will be conducted on the PPS.
- The main analysis as described in Section 10.2.5 will be conducted based on the INV response assessment as entered on the 'Lymphoma Tumour Assessment' eCRF page. The same censoring rules will apply as for the analysis based on the IRC assessment. If the response assessment is not based on radiological examination the date when the diagnosis of relapse or progression was made by the investigator is considered as the date of progression. The analysis will be conducted using both the FAS and the PPS.
- Patients having more than one missed visit, but having an available death date, will be included in the time-to-event analysis and considered as having a PFS event. The analysis will be performed on the FAS for both IRC and INV response assessment.

10.2.7 Concordance between IRC and INV assessment of PFS events

The concordance rate in terms of PFS events represents the agreement (PFS event, No PFS event) regarding the definition of these events based on the IRC and INV tumour response assessment, respectively. A contingency table will be generated and the concordance rate is calculated by adding the diagonal counts and dividing by the total number of patients. This concordance analysis will be performed on the FAS.

10.3 Secondary objective 3

10.3.1 Objective

To determine the duration of response (DoR).

10.3.2 Endpoint: Duration of response

DoR is defined as the elapsed time between the date of first documented response (CR or PR) and the following date of event defined as the first documented progression or death:

DoR [days] = date of assessment of tumour progression or death – date of assessment of first documented response of (CR or PR) + 1.

The DoR will be reported in months.

10.3.3 Censoring rules

14.1.1 Censoring situations

If a patient is alive and progression-free at the date of the analysis (i.e., at the cut-off date), the patient will be censored, and the reason for censoring will be provided as per Table 13.

15.1.1 Identification of two or more missing response assessments

If death or progression happens after two or more missed Tumour Assessments (TA), then the event is censored.

- An event occurring after two or more missing assessments or non-adequate tumour assessments will be censored on the date of last adequate tumour assessment.
- In one of the sensitivity analyses for PFS, an event occurring after two or more missing assessments is back-dated to the date of next scheduled assessment. The date of next scheduled assessment is the date of the last adequate tumour assessment plus the protocol specified time interval for assessments.
- If the patient has an EOT after two missed assessments without an event, then the patient will be censored for PFS at the last assessment and the censoring reason will be 'Adequate assessment no longer available'.

The maximum time [days] that can elapse between two response assessments without resulting in censoring is the same as for PFS and is shown in Table 14.

10.3.4 Main analysis

- The tumour assessments will be derived according to the IWG treatment response criteria for malignant lymphoma (Cheson et al., 2007), by an Independent Radiology/Clinical Review Committee (IRC). The review process will be defined in the IRC Charter.
- The distribution of DoR will be estimated using the Kaplan-Meier (K-M) method. The median DoR along with 95% confidence interval will be presented. 25th and 75th percentiles will also be shown.
- A plot of the Kaplan-Meier curve for DoR will be provided.
- The DoR probabilities at specific time points (1 month, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months), and the associated 95% CIs (Greenwood formula) will be summarized.
- No formal hypothesis testing will be conducted.
- The main analysis will be conducted on the FAS based on the IRC response assessment.

10.3.5 Sensitivity analyses

- The main analysis as described in Section 10.3.4 will be conducted based on the INV response assessment as entered on the 'Lymphoma Tumour Assessment' eCRF page. The same censoring rules will apply as for the analysis based on the IRC assessment. The analysis will be conducted using the FAS.
- DoR stratified by best overall response: The DoR will be stratified by patients who reached PR as best overall response, and patients who reached CR as best overall response:
  - The stratified DoR will be tabulated according to both INV and IRC response assessment (for the FAS):
    - Kaplan-Meier methods will be used to derive median, Q1, Q3, and 95% confidence intervals (for the FAS).
    - Kaplan-Meier curves will be presented. The graph will include the following strata: DoR for patients with PR as best response, CR as best response, and one group representing the DoR for all responders (for the FAS).
- Duration of CR:

The duration of CR (in days) is defined as follows: (date of assessment of tumour progression or death – date of assessment of tumour response [CR] + 1). The duration of CR will be reported in months and tabulated according to both local and IRC radiological assessments. The duration of CR will be analysed using Kaplan-Meier methods (median, Q1, Q3, 95% confidence intervals). A Kaplan-Meier curve will be shown. The analysis will be performed on the FAS for both IRC and INV response assessment.

10.4 Secondary objective 4

10.4.1 Objective

To determine the overall survival (OS).

10.4.2 Endpoint: Overall survival

Overall survival (OS) is defined as the time from the date of the first administration of any study drug until death from any cause (documented by the date of death).

10.4.3 Censoring rules and imputation

Patients who are alive or who drop out early for any reason will be censored at date of last contact.

If for a patient's death month and year are provided but the day is missing, the day will set to the first day of the month, unless other qualifying study data support survival until a later date during the same month. If day and month or year is missing, no imputation will be done and the date of death will be censored at the date of last contact. A listing showing the information on eCRF pages for survival follow-up and end of survival follow-up will be presented (for the SAF).

10.4.4 Main analysis

- The distribution of OS will be estimated using the Kaplan-Meier (K-M) method. The median OS time along with 95% confidence intervals will be presented (Brookmeyer and Crowley 1982). 25th and 75th percentiles will be considered as well.
- The OS probabilities at specific time points (1 month, 3 months, 6 months, 12 months, 18 months, 24 months, 36 months, 48 months), and the associate 95% CIs (Greenwood formula) will be summarized.
- A plot of the Kaplan-Meier curve for OS will be provided.
- The median follow-up for OS will be calculated using the reverse Kaplan-Meier method.
- No formal hypothesis testing will be conducted.
- The main analysis will be conducted on the FAS.

10.4.5 Sensitivity analyses

- The main analysis as described in Section 10.4.4 will be conducted on the PPS.

10.5 Secondary objective 5 and secondary objective 11

10.5.1 Objectives

- Objective 5: To determine the time to progression (TTP).
- Objective 11: To compare each patient's TTP on LEN plus MOR00208 with the TTP of their most recent prior therapy.

10.5.2 Endpoint: Time to progression

TTP is defined as the time from the first administration of any study drug until documented DLBCL progression or death as a result of lymphoma. Death from other causes than lymphoma will not be considered in relation to the TTP evaluation.

If a patient does not have an event, TTP will be censored on the date of the last tumour assessment before the data analysis cut-off date or the anti-neoplastic therapy start date if the patient started any new anti-neoplastic therapy or the date of death for death from other causes than lymphoma.

10.5.3 Main analyses

16.1.1 Main analysis for Objective 5

- The tumour assessments will be derived according to the IWG treatment response criteria for malignant lymphoma (Cheson et al., 2007), by an Independent Radiology/Clinical Review Committee (IRC). The review process will be defined in the IRC Charter.
- The distribution of TTP will be estimated using the Kaplan-Meier (K-M) method. The median TTP along with 95% confidence intervals will be presented (Brookmeyer and Crowley 1982). 25th and 75th percentiles will be considered as well.
- The TTP probabilities at specific time points (1 month, 3 months, 6 months, 12 months, 18 months, 24 months), and the associate 95% CIs (Greenwood formula) will be summarized.
- TTP events will be described according to the type of events (death due to lymphoma, documented tumour progression).
- A plot of the Kaplan-Meier curve for TTP will be provided.
- No formal hypothesis testing will be conducted.

17.1.1 Analysis for Objective 11

TTP will be compared with TTP of each patient's most recent therapy via tabulating descriptive statistics for TTP of patient's most recent therapy. A graph showing the Kaplan- Meier curve for patients´ last prior treatment will be generated for the FAS.

The following therapies will be considered as most recent therapy:

- Last prior systemic anti-DLBCL medication (taken from the eCRF page: Prior Cancer Therapies for DLBCL-Medications)
- ASCT in case the last prior treatment was ASCT (taken from the eCRF page: Prior Cancer Therapies for DLBCL-Autologous Stem Cell Transplants)

10.5.4 Sensitivity analyses

18.1.1 Sensitivity analyses for Objective 5

- The analyses will be conducted based on the INV response assessment as entered on the 'Lymphoma Tumour Assessment' eCRF page. The same censoring rules will apply as for the analysis based on IRC assessments.
- Patients lost to follow-up or having an event after more than one missed visit, but having an available death date, will be included in the time-to-event analysis and considered as having a TTP event.

19.1.1 Sensitivity analyses for Objective 11

No sensitivity analyses will be conducted.

10.6 Secondary objective 6

10.6.1 Objective

To determine the time to next treatment (TTNT).

10.6.2 Endpoint: Time to next treatment

Time to next treatment (TTNT) is defined as the time from the first administration of any study drug to the institution of next anti-neoplastic therapy (for any reason including disease progression, treatment toxicity and patient preference) or death due to any cause, whatever comes first.

Patients without documented institution of a new anti-neoplastic therapy will be censored at the date of last contact.

10.6.3 Analysis

- The distribution of TTNT will be estimated using the Kaplan-Meier (K-M) method. The median TTNT along with 95% confidence intervals will be presented (Brookmeyer and Crowley 1982). 25th and 75th percentiles will be considered as well.
- The TTNT probabilities at specific time points (1 month, 3 months, 6 months, 12 months, 18 months, 24 months), and the associate 95% CIs (Greenwood formula) will be summarized.
- A plot of the Kaplan-Meier curves for TTNT will be provided.
- No formal hypothesis testing will be conducted.
- The main analysis will be conducted on the FAS.

10.7 Secondary objective 7

10.7.1 Objective

To determine the safety of LEN combined with MOR00208 assessed according to the frequency and severity of adverse events (AEs).

10.7.2 Endpoint: Incidence, frequency and severity of treatment-emergent adverse events (AEs)

10.7.3 Analysis

With the exception of the Listing on pre-treatment AEs emerging in patients who have never been exposed to any drug, all safety analyses including the analysis on AEs will be conducted using the Safety Set (SAF). The pre-treatment AEs emerging in patients who have never been exposed to any drug will be reported on the population of "All screened patients".

20.1.1 Overview

The analysis of safety assessments in this trial will include summaries of the following categories of safety and tolerability:

1. Adverse Events (AEs, number and severity)
   - Treatment-emergent AEs (TEAEs)
   - Treatment-emergent Serious AEs (SAEs)
   - TEAEs by maximum toxicity grade
   - TEAEs by intensity
   - TEAE suspected to be related to a study drug
   - TEAEs leading to study discontinuation and AEs leading to death
   - AEs of special interest (AESI)
2. Vital signs: systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate
3. Physical Examination
4. 12-lead ECG parameters: PR, QRS, RR and QT interval values
5. Laboratory safety evaluations (blood chemistry, haematology, coagulation, urinalysis, anti-MOR00208 antibodies)
6. ECOG Performance Status
7. B-Symptoms

21.1.1 Adverse events

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

An AE can therefore be any unfavourable 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 informed consent form (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.

In addition, overdoses exceeding the planned infusion dose by 20% should be recorded as AEs.

Please note that in the context of this protocol symptoms that are clearly associated to the progression of underlying malignancy (DLBCL) do not fall under the definition of AEs.

Each AE will be reported to determine the following:

- Relationship to the study drug(s) (suspected/not-suspected)
- Duration (start and end date, or if continuing at end of study)
- NCI-CTCAE Grade (see below)
- 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
- Outcome
- Action taken with study drug(s)
  - no action taken
  - study drug temporarily interrupted
  - study drug permanently discontinued due to this AE
- Other action taken (medication taken; non-drug therapy given; hospitalisation/ prolonged hospitalisation)
- Seriousness: whether it is serious, where an SAE is defined as one that:
  - results in death
  - is life-threatening
  - requires inpatient hospitalisation or prolongation of existing hospitalisation (hospitalisation signifies that the patient was an inpatient for at least one overnight stay) unless hospitalisation is for:
    - Routine treatment or monitoring of the studied indication, not associated with deterioration of symptoms related to DLBCL.

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to DLBCL and has not worsened since signing of the ICF.
- 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.

22.1.1 Treatment-emergent adverse events

An **on-treatment adverse event (or Treatment-emergent Adverse Event – TEAE)** is defined as any adverse event reported in the following time interval (including the lower and upper limits): date of first administration of any study drug; date of last administration of any study drug + 30 days.

If the last date of study drug administration is missing, on-treatment assessments/events include any assessment/event recorded in the database and which occur after the start date of study treatment. Safety summary tables including summaries of on-treatment deaths will be based only on on-treatment assessments/events.

An adverse event present prior to study drug administration but increased in severity after treatment start, will also be included as TEAE.

Events with missing onset dates will be included as TEAE if the end date is not before the start date of treatment.

Adverse events occurring or worsening later than 30 days after the date of last study drug administration or the date of completion/discontinuation of the study are defined as TEAE if these are considered to be related to the study drug.

If the start date and time of an AE are partially or completely missing, the AE will be assumed to be a TEAE if it cannot be definitely shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach). Missing dates and times will not be replaced.

Thus, the following approach will be taken:

- If the start time of an AE is missing but the start date is complete, an AE will only be excluded from TEAE if start day is before day of first treatment or start day is after end day of treatment-emergent period.
- If start time and day are missing but the start month is complete, an AE will only be excluded from TEAE if start month is before month of first treatment or start month is

after end month of treatment-emergent period or if stop date/time is before start of first treatment.

- If start day and months are missing but the start year is complete, an AE will only be excluded from TEAE if start year is before year of first treatment or if start year is after end year of treatment-emergent period or if stop date/time is before start of first treatment.
- If start date is completely missing, an AE will not be excluded from TEAE unless the stop date/time is before start of first treatment.

If the last date of study treatment is missing, on-treatment assessments/events include any assessment/event recorded in the database and which occur after the start date of study treatment.

The incidence of treatment-emergent AEs will be summarized in incidence tables. If a patient experiences more than one occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be counted in the summary tables. All AEs will be listed by patient, along with information regarding onset, duration, relationship to study drug, intensity, toxicity grade, action taken with study drug, treatment of event, and outcomes.

23.1.1 Adverse events of special interest

Adverse events of special interest (AESI) are:

- Tumour flare (TFR)
- Tumour lysis syndrome (TLS),
- Second primary malignancy (SPM)
- Infusion-related reactions (IRRs) ≥ grade 3
- Allergic reactions to study drug ≥ grade 3
- Cytokine release syndrome
- Overdoses

Unlike routine safety assessments, SAEs and AESI are monitored continuously and have special reporting requirements.

24.1.1 Relationship to study drug

The Investigator should determine the causality (relationship to the study drug) based on his/her clinical experience, on Summary of Product Characteristics (SmPC) and Prescribing Information, and on the information given in the Investigator's Brochure (IB) for MOR00208 and the SmPC/prescribing information for LEN. The causal relationship of all AEs to the study drug 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. If no relationship has been provided by the Investigator, the event will be considered as related to the study drug.

25.1.1 Coding of adverse events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be reported by primary system organ class (SOC) and preferred term (PT). The MedDRA version used for reporting the study will be the version used for coding the trial and will be specified in the clinical study report and as a footnote in the related outputs (if possible).

26.1.1 Grading of adverse events

Toxicity grade: determined according to the National Cancer Institute- Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 of June 14, 2010 (or higher), 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; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living
- Grade 4: life-threatening consequences; urgent intervention indicated
- Grade 5: death related to AE

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event although there is not necessarily proportionality among grades (a grade 2 is not twice as bad as a grade 1).

27.1.1 Deaths

All deaths including those that occurred on-treatment and post-treatment, will be listed (SAF), post treatment deaths will be flagged. In addition to the on-treatment deaths and additional summary of all deaths (on-treatment + post-treatment) will be provided.

28.1.1 General rules for reporting

10.7.3.1.1 AE tables

i. All safety analyses will be done using the Safety Set (SAF). The incidence of treatment-emergent AEs will be summarised in incidence tables.
ii. AEs will be summarised by SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 and will be updated to the most current version at the end of the trial. The SOCs and PTs will be used for tabulation.
iii. AE frequency tables will display the number of events (incidence), number of patients experiencing an event and the percentage of patients with the event by System Organ Class (SOC) and Preferred Term (PT).
iv. If a patient experiences more than one occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be counted in the summary tables.
v. If a patient reported more than one AE with the same preferred term, the AE with the maximum toxicity grade will be presented.
vi. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the maximum toxicity grade at the system organ class level, where applicable.
vii. The most common AEs reported (≥10 % for each preferred term) will be presented in descending frequency according to its incidence starting from the most common event.

10.7.3.1.2 AE listings

i. All AEs will be listed by patient, along with information regarding onset, duration, relationship to study drugs, intensity, toxicity grade, action taken with study drug, treatment of event, and outcomes. This listing will be generated for all patients in the SAF.

ii. In the AE listings, AEs that started prior to the administration of any study drug will be flagged as pre-treatment AEs. AEs that start 30 days after the last study treatment and which are not related to one of the study drugs will be flagged as post-treatment AEs.

iii. Special AE listings displaying details of the event(s) captured on the eCRF in a compact format will be provided for:

- Serious Adverse Events.
- TEAEs of toxicity grade 3 or grade 4.
- AEs leading to discontinuation of treatment (split by MOR00208, LEN and overall).
- TEAEs of special interest.
- TEAEs suspected to be related to study drug

- Treatment-emergent SAEs
- TEAEs pertaining to the SOC '*infections and infestations*'
- AEs leading to death.
- Pre-treatment adverse events (i.e., adverse events that happened before administration of any study drug). This listing will be generated for all patients successfully screened but never treated. The pre-treatment AEs will be determined using the analysis population of 'All screened patients'.

29.1.1 AE summaries

10.7.3.1.3 TEAEs (serious and non-serious)

The following summaries will be provided:

i. All TEAEs regardless of study treatment relationship by primary SOC, PT, grade.

ii. All TEAEs regardless of study treatment relationship by primary SOC, PT, intensity.

iii. Most frequent TEAEs *(at least in 10% of the patients),* regardless of study treatment relationship by SOC, PT and grade.

iv. TEAEs regardless of study treatment relationship ≥ grade 3 by primary SOC, PT and grade.

v. TEAEs regardless of study treatment relationship of grade 3 or grade 4 by primary SOC, PT and grade.

vi. TEAEs suspected to be related to the study drug by primary SOC, PT, and grade (according to NCI-CTC toxicity criteria) (split by MOR00208, LEN, both drugs at the same time, and any study drug).

vii. TEAEs suspected to be related to the study drug by primary SOC, PT, and intensity (according to NCI-CTC toxicity criteria) (split by MOR00208, LEN, both drugs at the same time, and any study drug).

viii. TEAEs suspected to be related to the study drug of ≥ grade 3 by primary SOC, PT and grade (split by MOR00208, LEN, both drugs at the same time, and any study drug).

ix. TEAEs suspected to be related to the study drug of grade 3 or grade 4 by primary SOC, PT and grade (split by MOR00208, LEN, both drugs at the same time, and any study drug).

x. Most frequent TEAEs suspected to be related to the study drug *(at least in 10% of the patients)* by primary SOC, PT and grade (split by MOR00208, LEN, both drugs at the same time, and any study drug).

xi. TEAEs leading to any action on MOR00208, on LEN, or either on MOR00208 *or* on LEN regardless of study treatment relationship, by primary SOC, PT and grade.
Note: Any Action = Dose reduction/Dose interruption/Permanent discontinuation.

xii. TEAEs leading to discontinuation of treatment (split by MOR00208, LEN, both drugs at the same time, and overall) regardless of study treatment relationship by primary SOC, PT and grade.
xiii. Most frequent Non-serious TEAEs, regardless of study treatment relationship by primary SOC, PT and grade (at least 5% incidence).

10.7.3.1.4 Treatment-emergent SAEs

The following summaries on treatment-emergent SAEs will be produced:

i. Treatment-emergent SAEs regardless of study treatment relationship, by primary SOC, PT, grade.
ii. Most frequent treatment-emergent SAEs *(at least in 2% of the patients),* regardless of study treatment relationship, PT and grade.
iii. Treatment-emergent SAEs regardless of study treatment relationship ≥ grade 3 by primary SOC, PT, and grade.
iv. Treatment-emergent SAEs of grade 3 or grade 4 regardless of study treatment relationship by primary SOC, PT, and grade.
v. Treatment-emergent SAEs suspected to be related to the study drug by primary SOC, PT, grade (split by MOR00208, LEN, both drugs at the same time, and any study drug).
vi. Treatment-emergent SAEs suspected to be related to study drug ≥ grade 3 by primary SOC, PT, and grade (split by MOR00208, LEN, both drugs at the same time, and any study drug).
vii. Treatment-emergent SAEs suspected to be related to the study drug of grade 3 or grade 4 by primary SOC, PT, and grade (split by MOR00208, LEN, both drugs at the same time, and any study drug).
viii. Most frequent treatment-emergent SAEs suspected to be related to the study drug *(at least in 2% of the patients) by* SOC, PT and grade (split by MOR00208, LEN, both drugs at the same time, and any study drug).
ix. Treatment-emergent SAEs of grade 5 by primary SOC and PT.

10.7.3.1.5 AESIs

AEs of special interest will be presented by primary SOC, PT and grade.

10.7.3.1.6 Deaths

Deaths will be summarized as follows:

- Treatment-emergent deaths (deaths observed within 30 days after last administration of study treatment) in total and grouped by:
  - Deaths *related* to disease progression as indicated on the eCRF pages for '*End of Survival Follow-up' or 'End of Treatment':* all reasons/causes for death containing the phrases:

    - 'PROGRESSIVE DISEASE'
    - 'PROGRESSION DISEASE'
    - 'PROGRESSION OF DISEASE'
    - 'LYMPHOMA'
    - 'MULTIPLE RELAPSING AND REFRACTORY DLBCL'
    - 'DLBCL DISEASE PROGRESSION'
    - 'LYMPHOMA'
    - 'DISEASE PROGRESSION'
    - 'PROGRESSIVE DESEASE'
    - 'PROGRESSION DESEASE'
    - 'RELAPSE'
    - 'IMMEDIATE CAUSE OF DEATH: PARALYTIC ILEUS, DUE TO ABDOMINAL LYMPHOMA PROGRESS'
    - 'PROGRESIVE DISEASE'
    - 'PD'
    - 'RECURRENCE OF LARGE CELL LYMPHOMA'

    will be considered as related to disease progression.

  - Deaths unrelated to disease progression: All on-treatment deaths not considered as related to disease progression will be considered as unrelated to disease progression.

- Post-treatment deaths (deaths observed after 30 days after last administration of study treatment) overall and grouped by:
  - Deaths related to disease progression as indicated on the eCRF page for 'End of Survival Follow-up ': all reasons for death containing the phrases:

    - 'PROGRESSIVE DISEASE'
    - 'PROGRESSION DISEASE'
    - 'PROGRESSION OF DISEASE'
    - 'LYMPHOMA'
    - 'MULTIPLE RELAPSING AND REFRACTORY DLBCL'
    - 'DLBCL DISEASE PROGRESSION'
    - 'DISEASE PROGRESSION'
    - 'PROGRESSIVE DESEASE'

- 'PROGRESSION DESEASE'
- 'RELAPSE'
- 'IMMEDIATE CAUSE OF DEATH: PARALYTIC ILEUS, DUE TO ABDOMINAL LYMPHOMA PROGRESS'
- 'PROGRESIVE DISEASE'
- 'PD'
- 'RECURRENCE OF LARGE CELL LYMPHOMA'

will be considered as related to disease progressio*n*.

- Deaths unrelated to disease progression: all post-treatment deaths not considered as related to disease progression will be considered as unrelated to disease progression.

- Total number of deaths (All deaths (on-treatment + post treatment) are included) overall and grouped by:
  - Deaths related to disease progression as indicated on the eCRF pages for 'End of Survival Follow-up' or 'End of Treatment': all reasons/causes for death containing the phrases:

    - 'PROGRESSIVE DISEASE'
    - 'PROGRESSION DISEASE'
    - 'PROGRESSION OF DISEASE'
    - 'LYMPHOMA'
    - 'MULTIPLE RELAPSING AND REFRACTORY DLBCL'
    - 'DLBCL DISEASE PROGRESSION'
    - 'DISEASE PROGRESSION'
    - 'PROGRESSIVE DESEASE'
    - 'PROGRESSION DESEASE'
    - 'RELAPSE'
    - 'IMMEDIATE CAUSE OF DEATH: PARALYTIC ILEUS, DUE TO ABDOMINAL LYMPHOMA PROGRESS'
    - 'PROGRESIVE DISEASE'
    - 'PD'
    - 'RECURRENCE OF LARGE CELL LYMPHOMA'

  will be considered as related to disease progression.

  - Deaths unrelated to disease progression: All deaths not considered as related to disease progression will be considered as unrelated to disease progression.

A listing on the deaths based on the 'all patients screened' population will be produced indicating if a death is PD-related, and if the death happened on treatment, pre-treatment, or post-treatment.

10.7.3.1.7 Overall Summary of AEs

In addition, an **Overall AE summary table** will be presented showing the incidence and number of patients with at least one of the events:

- At least one TEAE.
- At least one treatment-emergent SAE.
- On-treatment deaths.
- Post-treatment deaths.
- At least one treatment-emergent SAE suspected to be related to the study drug (split by MOR00208, LEN, MOR00208 and LEN, and any study drug).
- At least one TEAE suspected to be related to the study drug (split by MOR00208, LEN, MOR00208 and LEN, and any study drug).
- At least one drug-related TEAE with grade 3 or grade 4 (split by MOR00208, LEN, MOR00208 and LEN, and overall).
- At least one drug-related TEAE by intensity (split by MOR00208, LEN, MOR00208 and LEN, and overall).
- At least one AESI.
- At least one TEAE leading to any action on MOR00208, on LEN, on MOR00208 and LEN, or on any study drug
- TEAEs leading to discontinuation of treatment (split by MOR00208, LEN, MOR00208 and LEN, and overall).
- Treatment-emergent SAEs of grade 5.
- At least one TEAE of PT 'Infusion-related reactions (IRRs) ' ≥ grade 3

Additional safety-related analyses on vital signs, physical examinations, electrocardiogram, and laboratory data are being described in Section 13.

10.8 Secondary objective 8

10.8.1 Objective

To assess the potential immunogenicity of MOR00208 (anti-MOR00208 antibodies).

10.8.2 Endpoint: Percentage of patients who develop anti-MOR00208 antibodies as determined by a positive anti-MOR00208 antibody titre.

10.8.3 Analysis

Assessment of immunogenicity will be performed using the immunogenicity analysis population (IAS).

1. The results of the anti-MOR00208 antibody assessment will be listed for each anti-MOR00208 sample analysed, including a categorization if the anti-MOR00208 antibody response is neutralizing or non-neutralizing.

Note: For 2. and 3. below, "negative" is defined as a sample reported negative in the screening assay OR confirmatory assay. "Positive" is defined as a sample being reported positive in the confirmatory assay.

2. The absolute number and percentage of the following categories will be tabulated by visit:

Patient has positive anti-MOR00208 antibodies (yes/no/missing) by visit:

- Yes, if a titre is available.
- No, if result is reported as negative.
- Missing, if anti-MOR00208 measurement is not available.

3. In addition, the absolute number and percentage of patients who develop anti- MOR00208 antibodies will be tabulated using the following categories:

Patient has developed positive anti-MOR00208 antibodies during study (yes/no/not evaluable/missing):

- Yes, if the patient has at least one positive post-baseline sample containing positive anti-MOR00208 antibodies, baseline sample has to be tested negative.
- No, if baseline as well as all post-baseline results are negative.
- Not evaluable, if the baseline sample of the respective patient was tested positive.
- Missing, if no post-baseline anti-MOR00208 measurement is available.

4. Results (n, mean, median, StD, minimum, maximum) of semi-quantitative anti MOR00208 antibody titre determinations of confirmed positive sample assessments will be tabulated by visit.

10.9 Secondary objective 9

10.9.1 Objective

To assess the pharmacokinetics (PK) of MOR00208.

10.9.2 Endpoint: MOR00208 plasma concentrations at sampling timepoints, accumulation ratios and trough concentrations

10.9.3 Analysis

The main analysis will be conducted on the PKAS. Individual plasma samples for the analysis of MOR00208 PK will be collected on various study days. For evaluation of PK metrics, a patient subsample will be considered consisting of those patients who have at least one quantifiable MOR00208 serum concentration (the PK analysis set, PKAS).

30.1.1 Bioanalytical assessment of pharmacokinetic serum samples

MOR00208 concentration values for each serum sample are to be determined using a validated Ligand Binding Assay. A separate bioanalytical phase plan and report will be generated that provide details on samples handling and processing, methods used for sample analysis, statements on quality control/quality assurance (QC/QA) and results of the each individual sample analyzed for each patient by the bioanalytical labs.

31.1.1 Data analysis

MOR00208 serum concentrations will be summarized based on nominal (scheduled) sampling times. Serum concentrations below the limit of quantification or missing data will be labelled as such in the concentration data listings. Analyte concentrations that are below the limit of quantification (BLQ) will be assigned a value of zero when they precede the first quantifiable sample. All other BLQ samples will be treated as missing data. Summary statistics for MOR00208 serum concentrations will include n, arithmetic mean, StD, geometric mean, coefficient of variation (CV), median, minimum and maximum. The CV will be expressed as a percentage and calculated as follows:

- CV of the arithmetic mean (%) = StD/mean*100.
- CV of the geometric mean (%) = sqrt(exp(variance for log transformed data)–1)*100.

Concentration figures (linear and log y-axis) of mean concentrations +/- StD will be presented. Individual MOR00208 serum concentrations may be excluded from summary statistics and concentration figures (mean) if the actual collection time/date of the sample exceeds allowable windows relative to the scheduled collection time/date.

- For samples collected 1h after the end of MOR00208 infusion, results will be excluded from summary statistics if the deviation of the actual collection time is larger than ± 15 min from the scheduled collection time.
- Results of PK samples collected outside of the allowed window of ± 1 day relative to the scheduled collection day will be excluded from summary statistics. Each 28 day cycle will be considered separately.

Irrespective of exclusion of data points from summary statistics, each obtained MOR00208 serum concentration will be listed and reported.

Accumulation of MOR00208 will be investigated by comparing the average concentration of pre-dose and 1 hour post-dose of Cycle 3 Day 1 (i.e. the 10th dose) with the corresponding mean from the previous visit for which MOR00208 concentration data is available using ANOVA ($\alpha = 0.05$). If no significant difference is found, Cycle 3 Day 1 will be compared to previous visit for which MOR00208 concentration data is available and so forth until two consecutive times a significant difference is found.

32.1.1 Population PK analysis

A population PK analysis of MOR00208 will be conducted. The planned meta-analysis will encompass PK data from study MOR208C203 and other clinical trials with MOR00208. The analysis will provide an understanding of the population PK of MOR00208 and determine the influence of intrinsic and extrinsic factors (such as but not limited to age, gender, race, level of hepatic or renal function and presence of anti-drug antibodies) that may influence PK variability. Details of the intended population PK analysis will be described in a separate population PK protocol and the results will be described in a separate population PK study report.

10.10 Secondary objective 10

To make a preliminary evaluation of ORR, DCR, DoR, PFS, OS, TTP and TTNT in patients treated with a combination of LEN plus MOR00208 in cohorts with a “low risk”, “low- intermediate”, “high-intermediate” and “high” International Prognostic Index (IPI).

10.10.1 Endpoint

ORR, DCR, DoR, PFS, OS, TTP, and TTNT stratified by:

- four risk categories: “low risk”, “low-intermediate risk”, “high-intermediate risk” and “high risk”.
- two risk categories: “low risk” and “low-intermediate risk” vs. “high-intermediate risk” and “high risk”.

10.10.2 Main analysis

- The main analyses are described above in the respective sections addressing ORR, DCR, DoR, PFS, OS, TTP, and TTNT (see Sections 9.2, 10.1.3, 10.3.4, 10.2.5, 10.4.4, 10.5.3, 10.6.3).
- For the analysis comprising two risk categories: An estimate of the hazard ratio and corresponding 95% CI will be calculated for PFS and OS analyses using a Cox proportional hazard model with only one covariate in the model.

10.10.3 Sensitivity analyses

The main analyses as described in Section 10.10.2 will be conducted based on the INV response assessment (see sections 9.3, 10.1.4, 10.3.5, 10.2.6, 10.4.5, and 10.5.4).

10.11 Secondary objective 11

10.11.1 Objective

To compare each patient’s TTP on LEN plus MOR00208 with the TTP of their most recent prior therapy.

10.11.2 End point and main analysis

End point analyses are described in detail above in section 10.5.3.

10.12 Secondary objective 12

10.12.1 Objective

To correlate efficacy parameters with certain biomarkers (e.g. peripheral NK cell count, constitutional FcγRIIIa and FcγRIIa polymorphism status).

10.12.2 Endpoint

PFS, DoR, ORR, OS will be analyzed in the following subgroups:

- FcγRIIIa affinity (high affinity: FCGR3A-158V homozygosity vs. low affinity: FCGR3A-158F homozygosity, or FCGR3A-158F/V heterozygosity).
- FcγRIIa affinity (high affinity: FCGR2A-131H homozygosity vs. low affinity: FCGR2A-131R homozygosity, or FCGR2A-131H/R heterozygosity).
- Peripheral NK cell numbers at baseline (< median of NK cell numbers/µl vs. >= median of NK cell numbers/µl).
- Cell of origin determined by immuno-histochemistry (IHC) (i.e., central pathology) assessment: germinal center B cell (GCB) phenotype vs. non-GCB phenotype.
- Cell of origin determined by gene expression profiling (GEP): GCB phenotype vs. activated B cell (ABC) phenotype vs. unclassified phenotype.

10.12.3 Main analysis

The following analyses will be conducted on the FAS:

- The main analyses pertaining to the biomarker subgroup analyses are being described in the respective sections above addressing ORR, PFS, DoR, and OS (Sections 9.2, 10.1.3, 10.2.5, 10.3.4, and 10.4.4).
- PFS, DoR and OS will be compared between subgroups by a log-rank test.
- For PFS and OS analyses, the estimate of the hazard ratio and corresponding 95% CI will be calculated using a Cox proportional hazards model with only one covariate (i.e., the biomarker in question) in the model.

10.12.4 Sensitivity analyses

The main analysis as described in Section 10.12.3 will be conducted based on the INV response assessment using the FAS.

A comprehensive analysis of all biomarker assessments will be described in a separate biomarker-specific Statistical Analysis Plan, and summarized in a separate report.

11. EXPLORATORY EFFICACY ANALYSES

11.1 Time to response and time to complete response

The time to response will be calculated and tabulated for patients achieving response (PR of CR). The time to response [months] is defined as follows:

((date of assessment of first documented response of (CR or PR)) – (date of first administration of any study drug) + 1) / 30.4375.

Moreover, the time to complete response [months] will be calculated and tabulated for patients achieving complete response. The time to complete response is defined as follows:

((date of assessment of first documented complete response (CR)) – (date of first administration of any study drug) + 1) / 30.4375.

The time to response will be calculated using the FAS for both the INV and IRC assessment.

11.2 PET-Confirmed Complete Responses

Number (%) of patients with a PET-confirmed CR at any point in time will be presented for the IRC response assessment. The device used for imaging for a particular Visit can be found on the 'Lymphoma Tumour Assessment' eCRF page. The following devices will be considered as PET modality:

- PET/CT
- PET/MRI
- PET

A separate listing will show those patients who reached a PET-confirmed CR (SAF).

11.3 Tumor shrinkage over time: Assessment of indicator lesions

Data on lesion size will be presented by descriptive statistics and individual data listings (for the SAF). The sum of the product of the longest perpendicular diameters (SPD) reflecting the lesion area will be used for the analysis (based on the IRC assessment). Data will be presented separately for the two central reviewers.

The area of indicator lesions will be examined as follows:

1. Analysis across all points in time:

- Absolute values and both absolute and the individual relative changes (from baseline) for each patient will be summarized for each visit.

- A graph showing the individual relative changes over time will be generated separately for both central readers. The best overall response of each individual will be indicated by colour coding (CR, PR, SD, PD, NE=not evaluable).

2. Analysis comparing baseline and nadir:

- The area of indicator lesions will be reported at baseline and at the nadir. The absolute value and both the absolute and relative difference between baseline and nadir will be reported.
- A "waterfall plot" indicating the best change (%) for indicator lesions will be generated separately for both central readers.

3. Correlation between radiologists.

The SPD as determined by radiologist 1 at screening and nadir will be correlated with the SPD at screening and nadir as determined by radiologist 2. The Pearson Correlation Coefficient will be derived for both assessments, i.e., at screening and nadir.

Listings showing individual lesion sizes over time will be produced.

11.4 Non-biomarker subgroup analyses

PFS, ORR, DoR, and OS will be reported for the following subgroups. All analyses will be conducted using the FAS based on both IRC and INV response assessment. Kaplan-Meier curves will be provided for PFS, DoR, and OS. For PFS and OS analyses, the estimate of the hazard ratio and corresponding 95% CI will be calculated using a Cox proportional hazards model with only one covariate in the model.

- Gender (Male vs. Female)
- RTX refractoriness (yes vs. no; see section 8.7.4.1.3)
- Refractoriness to last prior treatment line (yes vs. no; see section 8.7.4.1.2)
- Primary refractoriness (yes vs. no; see section 8.7.4.1.1)
- Prior autologous stem cell transplantation (yes vs. no)
- NHL subtype as per central pathology (dichotomized, i.e., DLBCL patients vs. non-DLBCL patients)
- Number of prior treatment lines (1 vs. >= 2)
- Number of prior treatment lines (1 vs. 2 vs. 3 vs. 4)
- Reason for ASCT ineligibility:
    - Chemorefractory

- High age or Comorbidites
- Other

12. DESCRIPTIVE BIOMARKER ANALYSES

Biomarker assessments will be tabulated by descriptive statistics. Summaries will be provided for the following variables:

- CD16 molecules on $CD16^{+}CD56^{+}$ NK cells (continuous variable)
- Percentage specific killing (ADCC assay) (continuous variable)
- FcγRIIIa affinity (categorical variable):
  - 2 subgroups (high affinity: FCGR3A-158V homozygosity vs. low affinity: FCGR3A-158F homozygosity, or FCGR3A-158F/V heterozygosity).
  - 3 subgroups (FCGR3A-158V homozygosity vs. FCGR3A-158F homozygosity vs. FCGR3A-158F/V heterozygosity).
- FcγRIIa affinity (categorical variable):
  - 2 subgroups (high affinity: FCGR2A-131H homozygosity vs. low affinity: FCGR2A-131R homozygosity, or FCGR2A-131H/R heterozygosity).
  - 3 subgroups (FCGR2A-131H homozygosity vs. FCGR2A-131R homozygosity vs. FCGR2A-131H/R heterozygosity).
- NK cell numbers at baseline (continuous and categorical variable):
  - NK cell numbers/µl at baseline (continuous variable).
  - Baseline and demographics characteristics as described in Section 8.5 will be shown for both subgroups defined by NK cell numbers/µl at baseline less than the median and above or equal to the median.
- Longitudinal analyses will be conducted for: Peripheral numbers of NK cells, B cells, and T cells (analysed separately):
  - Summary statistics per visit (a 95% confidence interval for the median will be derived by bootstrapping)
  - Relative change from baseline (a 95% confidence interval for the median will be derived by bootstrapping).
  - Graphical illustration showing individual values for both absolute values and separately relative change from baseline. The median across all patients (without confidence interval) will be shown.

- Graphical illustration showing the median and its 95% confidence interval (via bootstrapping) for both absolute values and relative change per visit across all patients assessed.
- Graphical illustration showing boxplots for both absolute values and relative change per visit across all patients assessed.

- Cell of origin (categorical variable):
  - Cell of origin determined by immuno-histochemistry (IHC) assessment (i.e., central pathology): *germinal center B cell (GCB)* phenotype vs. *non-GCB* phenotype.
  - Cell of origin determined by gene expression profiling (GEP): *GCB* phenotype vs. *activated B cell (ABC)* phenotype vs. *unclassified* phenotype.
- A Listing will provided showing the information on double hit status (genetic lesions in BCL-2 and MYC as assessed by FISH), and triple hit status (genetic lesions in BCL-2, MYC, and BCL-6 as assessed by FISH). Only those patients will be listed who have been assessed.

Concordance between cell-of-origin determination by gene expression profiling and immuno-histochemistry

The concordance rate represents the agreement regarding the cell-of-origin as determined by gene expression profiling (GEP) and immuno-histochemistry (IHC). The concordance rate is the number of patients that are concordant over the total number of patients assessed, and will be calculated across all cell-of-origin categories. The concordance rate will be calculated using the following categories:

Analysis 1: ABC (GEP) and GCB (GEP) vs. Non-GCB (IHC) and GCB (IHC).

Analysis 2: (ABC (GEP) + Unclassified (GEP)) and GCB (GEP) vs. Non-GCB (IHC) and GCB (IHC).

A confusion matrix (i.e., a contingency table with GEP cell-of origin as rows and IHC cell-of-origin as columns) will be generated. The concordance rate will be calculated by adding the diagonal counts and dividing by the total number of patients assessed.

As only a fraction of patients have undergone GEP and IHC analysis, only those patients will be considered for the concordance analysis who have been evaluated by both assessments (i.e., GEP and IHC). Considered for the concordance analysis are only patients from the FAS.

Listings will be provided for all biomarkers (both baseline values and, if applicable, results of subsequent assessments).

All descriptive analysis of biomarkers will be performed using the FAS. Listings will be generated showing individual data on the biomarkers.

13. ADDITIONAL SAFETY ANALYSES

13.1 Adverse events

The analysis of adverse events is comprehensively described in Section 10.7.

13.2 Vital signs

13.2.1 Vital signs variables

The Vital Signs captured in the eCRF for each patient at each visit are the following:

- Weight (all visits)
- Height (only Screening Visit)
- Systolic Blood Pressure (all visits)
- Diastolic Blood Pressure (all visits)
- Heart Rate (all visits)
- Respiratory Rate (all visits)
- Temperature (all visits)
- Overall interpretation of Vital Signs (all visits)

13.2.2 Vital signs analysis

The following analysis will be performed on these variables:

i. These variables will be summarized by visit by means of descriptive statistics of actual values and change from baseline.
ii. Overall interpretation of Vital Signs will be tabulated to present the corresponding frequency count and percentage at each visit.
iii. The normal ranges for the vital sign variables are:
    - Systolic blood pressure: 70-149 mm Hg
    - Diastolic blood pressure: 60-90 mm Hg
    - Heart rate: 55-110 beats per minute
    - Respiratory rate: 10-24 breaths per minute
    - Body temperature: 36.1-37.8 °C (97.0-100.0 °F)

    Vital Signs will be listed by visit for the SAF and an abnormal value will be flagged to show whether it is a value below or above the normal limit.

The analysis will be performed on the SAF.

13.3 Physical examination

Baseline and End of Treatment full physical examinations will be summarized by body system. New and worsening abnormal physical examination findings during the study will be entered as AEs and analysed within the AE tables. The analysis will be performed on the SAF. Listings on full physical examination will be shown (for the SAF).

13.4 Electrocardiogram (ECG)

13.4.1 ECG variables

The Electrocardiogram variables captured in the eCRF for each patient at each visit are the following:

- QRS Interval
- RR Interval
- PR Interval
- QT Interval
- QTcB: Bazett's correction for QT given by $QTcB = \frac{QT_{max}}{\sqrt{RR}}$, where RR=60/heart rate.
- QTcF: Fridericia's correction for QT given by $QTcF = \frac{QT_{max}}{3\sqrt{RR}}$, where RR=60/heart rate.
- Overall Interpretation of 12 Lead ECG tracing

The variables listed above are not derived by programming, but will be used as entered in the eCRF.

13.4.2 ECG analysis

The following analyses will be performed on these variables:

i. Overall interpretation of 12 Lead ECG tracing will be tabulated to present the corresponding frequency count and percentage at each visit.
ii. ECG variables will be summarized by visit by means of descriptive statistics of actual values and change from baseline.
iii. The normal ranges for the ECG variables are:
    - PR interval: 110-220 ms
    - QRS interval: 60-120 ms
    - RR interval: 600-1200 ms
    - QT interval (also corrected): ≤400 ms
iv. As recommended in the FDA guidance E14 on Clinical Evaluation of QT/QTc interval prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (October 2015), the number and percentage of patients having notable ECG interval values will be as follows in Table 15.

Table 15: Clinically notable ECG values

ECG parameter (unit)	Clinically notable criteria
QTcF (ms)	New > 450 ms New > 480 ms New > 500 ms Increase from Baseline > 30 ms Increase from Baseline > 60 ms
PR duration (ms)	Increase > 25% from Baseline and to PR duration > 200 ms
QRS duration (ms)	Increase > 25% from Baseline and to QRS duration > 110 ms

v. All assessments will be listed and those collected outside of the treatment window will be flagged.

The summaries will include only assessments on treatment. The analysis will be performed on the SAF. Listings on ECG interpretation and ECG intervals will be shown.

13.5 Laboratory data

13.5.1 Laboratory variables

Laboratory parameters measured in the central laboratory can be separated into

- Blood parameters (haematology, serum chemistry, coagulation).
- Urine parameters (urinalysis).

13.5.2 Grading of laboratory data

Laboratory data grades of severity will be derived according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. A severity grade of 0 will be assigned when the value is within normal limits. In the case a local laboratory normal range overlaps into the higher (i.e. non-zero) CTCAE grade, the CTCAE grade will be taken. Lab values having hyper or hypo shifts will be classified as a particular CTCAE grade irrespective of the shift direction (no differentiation between CTCAE grades resulting from increased or decreased lab values). The laboratory values for which CTCAE grades are defined for only one direction of deviation (e.g., platelet count) will be assigned grade 0 in case a laboratory value is outside the reference range, but in a direction for which CTCAE grading is not defined.

Laboratory test results will also be shown by the low/normal/high classifications based on laboratory normal ranges.

For duplicate laboratory measurements taken at the last assessment date on or before the start date of study treatment, the value of lower CTCAE grade will be considered as the baseline value.

For non-gradable labs with duplicate laboratory measurements taken at the last assessment date on or before the start date of study treatment:

- If both within normal range: take average value.
- If one within normal range and the other outside: take the one within normal range.
- If both outside normal range: take the one closest to the normal range.

Laboratory values with missing units or normal range may not be able to be graded or included in laboratory tables.

13.5.3 Laboratory analysis

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed. The limit of quantitation will be used for calculation of descriptive statistics if the data is reported in the form of "≤ x" or "< x" or "≥ x" (x is considered as the limit of quantitation).

The following analysis on laboratory parameters will be performed:

i. Laboratory parameters will be summarized. Descriptive summaries of actual (absolute) values and change-from-baseline values will be presented for haematology and serum chemistry for the SAF by visit. SI units will be used in the generation of these descriptive summaries. The assessment of categorical urinalysis variables will be tabulated by time point for each categorical urine parameter.
ii. Abnormal values will be flagged in the listings (SAF population) to indicate whether the value is below or above the reference range and whether the investigator assessed the abnormal value as clinically significant. A clinically significant result can be commented with "Adverse Event", "Due to primary disease", "Pre-existing condition" or free text.
iii. The assessment of the clinical significance of laboratory variables will be tabulated by time point for each clinical laboratory analyte.
iv. For each laboratory parameter, shifts in assessments from baseline to worst-post baseline will be presented.
v. If NCI-CTCAE grades are available for a clinical laboratory analyte, they will be derived according to NCI CTCAE, Version 4.03, and used to present additional frequency and shift tables based on NCI-CTCAE grades.
   The following summary will be produced for the laboratory data (by laboratory parameter):

- Number (%) of patients with worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed on-treatment
- Shift tables to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters using:
  - CTCAE grades for laboratory parameters where CTCAE grades are defined.
  - The classifications relative to the laboratory reference ranges (low/normal/high) for laboratory parameters where CTCAE grades are not defined.

vi. The following listing will be produced:

- Listing of patients with laboratory values outside the normal ranges with values flagged to show the corresponding CTCAE grade and the classifications relative to the laboratory reference ranges.

The summaries will include only assessments on treatment. The analysis will be performed on the SAF.

13.6 ECOG scores analyses

The analysis of ECOG scores will be performed on FAS and SAF.

The following analyses will be performed on ECOG scores:

- The ECOG performance status will be summarized categorically in a frequency table by visit.
- Shift Tables in ECOG status from baseline to worst post-baseline will be presented.
- The ECOG status will be listed (for the SAF).

13.7 B-symptoms

B-symptoms are defined as any one or more of the following disease-related symptoms or signs:

- Unintentional weight loss of ≥ 10% within the preceding 6 months or less.
- Drenching night sweats without signs of infection.
- Recurrent, unexplained fever with temperatures above 38 °C without signs of infection.

The presence of B-symptoms will be summarized categorically in a frequency table by visit. The analysis will be performed on FAS and SAF. Data listings will be presented (for the SAF).

14. GENERAL GUIDANCE ON REPORTING

14.1 Document headers and footers

The following header will be used for all tables, listings and figures outlined in this document: MOR208C203 – *reporting event* (Cut-off date ddMONyyyy).

The following labels of *reporting event* will be used for all outputs:

- PA for Primary Analysis
- FA for Final Analysis

The following display will be used for outputs:

- footnote 1
- footnote 2
- footnote 3

program source, date and version information.

For example:

MOR208C203- PA (Cut-off date: 06JUN2014)

"/report/pgm_saf/program.sas 07MAY14:15"

In the applicable outputs, the MedDRA version and WHO-DDE version used for reporting the study will be specified as a footnote.

- MedDRA Version <xx.x> has been used for the reporting

- WHO-DDE Version <xx.x> has been used for the reporting

The latest available version of dictionaries at the time of reporting will be used.

14.2 Presentation of output numbering and titles within this document

In practice, the numbering and title for all tables, figures and listings in sections 14 and 16 defined in this document will be formatted as follows, respectively:

Table XX.X-X.X

Title Title Title Title Title Title

Population

Listing XX.X-X.X

Title Title Title Title Title Title

Population

14.3 Presentation of analysis sets

The outputs to be produced based on this document will use 'Screened Patients', 'Enrolled Patients', 'FAS', "PPS', "SAF', "PKAS', 'IAS" in the table/figure/listing titles.

14.4 General rules for presenting frequencies and percentages

If a summary table displays only categorical variables then the convention illustrated in the following example will be used:

Preferred Term	**N=xx** **n (%)**
Total	xx (xx.x)
Fatigue	xx (xx.x)
Nausea	xx (xx.x)
Anemia	xx (xx.x)

However, if a summary table displays both continuous and categorical variables then the convention illustrated in the following example will be used:

	All patients N=xx
Sex, n (%)	
Male	xx (xx.x)
Female	xx (xx.x)
Age (Years)	
n	xx
Mean	xx.x
StD	xx.xx
Median	xx.x
Minimum	xx.x
Maximum	xx.x

14.5 General rule for tables/listings

All other data as documented in the eCRF will be listed and/or tabulated using descriptive statistics or counts/percentages depending on the nature of data. All the data collected and derived in the trial will be presented in patient data listings.

14.6 Format of tables/listings and displays with no data

Where a listing or table has been planned, but no data meet the criteria, then a single line stating 'No data meeting the criteria are present' will be provided in the output. The default tables, listings and figures (TLF) layout will be as follows.

Orientation	Landscape
Paper Size	A4
Margins	Top: 2 cm Bottom: 2 cm Left: 2 cm Right: 2 cm Header: 1.27 cm Footer: 1.27cm
Font	Courier New 8pt
Headers	Protocol number – Type of Analysis (Cut-off date) (Left); Page X of Y (Right) TLF Number and Title
Footers	SAS program name Source Data File name Extract date Date, Time TLF generated

The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity. Also the orientation may be changed to portrait if appropriate.

14.7 Precision rules

For continuous variables, minimum and maximum will be presented to the same precision as the raw data. Mean, median, 25th and 75th percentiles will be presented to one more decimal place and standard deviation to two more decimal places than the raw data. An exception will be made for biomarker representing counts where mean and median will be presented without a decimal place. Geometric mean will be presented to one more decimal place than the raw data. CV of mean and CV of geometric mean will be shown to one decimal place.

For concentrations and PK parameters 3 significant digits apply for mean, geometric mean, median, StD, min and max. Elapsed time and Tmax should have 2 decimal places in the listings.

For categorical variables, the number (n) and percentage (%) of patients per category will be presented. If the count is zero in a cell, then only '0' count will be presented and not '0.0 (0.0)'. The number of missing values will be presented as a "Missing" category. Percentage

values are to be rounded and presented to one decimal place. If percentages are equal to 100, then no decimal places will be presented 'xx (100)'.

The confidence intervals of a percentage will be presented to the same precision as the percentage. The p-values will be presented with three decimals. P-values below 0.001 will be denoted as <0.001. Hazard ratios and respective confidence intervals will be presented to two decimal places.

14.8 General rules for presenting listings

The following general rules for presenting listings should be applied by default for all listings.

For listings, the default sorting order is by patient number and event/assessment date unless otherwise stated.

The first column of the listing will always be "Patient identifier" field.

Where a listing or table has been planned, but no data meet the criteria, then a single line stating 'No data meeting the criteria are present' will be provided in the output.

The study day will always be displayed in the listings if applicable. It will be printed under the label 'Study Day' in all listings. The definition of study day is:

The reference start date ***for all safety assessments*** (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, etc.) will be the start date of study treatment. The following footnote will be added in all safety listings: "Study Day is relative to the first date of study treatment (Day 1)".

The reference start date ***for all efficacy assessments*** (e.g. tumor assessment, death, disease progression, tumor response, performance status) will be the start date of study treatment. The following footnote will be added in all efficacy listings: "Study Day is relative to the first date of study treatment (Day 1)".

For data collected at the visit level: 'Visit' column will be displayed in the listings. Unscheduled visits will appear as "Unsch" (or similar) in all the listings, if any.

For all laboratory parameters, SI units are used as default.

When a variable collected in the eCRF is linked to another variable, one or both variables will be presented in the same column of the listing or in adjacent columns if space permits this.

For example:

- 'Setting'='OTHER' and 'Other, specify'='Lung'
  "OTHER: Lung" will be displayed in the column as 'Setting'.
- 'Dose'='120' and Dose unit ='mg'
  '120 mg' will be displayed in the column as 'dose (unit)'.

- Date = “2012-05-12” and Study day =”5”.
- “12MAY2012 / 5” will be displayed in the column as ‘Date / Study Day’.
- (1) End date = “2012-05-22” and Study day =”15” or
  (2) End date = “ ” and ongoing is ticked:
  (1) “22MAY2012 / 15” will be displayed in the column as ‘End date / Study Day’
  (2) “Ongoing” will be displayed in the column as ‘End date / Study Day’.

14.9 Presentation of Dates

Calendar dates and times (optional) in all the listings will be displayed in the format:

DDMMMYYYY/hh:mm e.g. 2011-01-15/00:20.

Note: If time is not collected, calendar dates will be displayed as: DDMMMYYYY.

15. REFERENCES

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16. ADDENDUM 1.0

16.1 Compliance

The compliance for MOR00208 and LEN as outlined in Section 8.9.6 is summarized by Cycle. Boxplots showing the distribution of compliance within the patient population will be produced. The analyses will be performed for both the FAS.

16.2 Relative dose intensity

The dose intensity of LEN and MOR00208 as defined below will be summarized by Cycle. Boxplots will be generated showing the distribution of the relative dose intensity. The analyses will be conducted using the FAS.

The relative dose intensity for LEN is derived as follows:

- „Planned dose“ for each Cycle: 25 mg x 21 days = 525 mg per Cycle (ignoring dose change, interruptions, discontinuations)
- „Used dose“ for each Cycle: X mg total daily dose x number of pills taken in that Cycle (pills returned – pills dispensed will be used as surrogate for pills taken)
- Relative Dose Intensity by Cycle: „Used dose“ / „Planned dose“ x 100
- A boxplot showing the distribution of the Relative Dose Intensity by Cycle will be generated

The relative dose intensity for MOR00208 is derived as follows:

- „Planned dose“ for a particular Cycle: 250 ml x planned number of infusions for a particular Cycle (varies depending on the Cycle)
- Infusion interruptions and skipped doses will be ignored when determining the „planned dose“
- „Used dose“ for a particular Cycle: sum of actual volume administered across all infusions of a Cycle
- Relative Dose Intensity by Cycle: „Used dose“ / „planned dose“ x 100
- A boxplot showing the distribution of the Relative Dose Intensity by Cycle will be generated

16.3 Additional safety analyses

For all additional safety analyses specified in the SAP Addendum the general approach for reporting the incidence and frequency of adverse events is used as detailed in Section 10.7.

16.3.1 TEAE by 'search category'

The incidence of TEAEs will be summarized by 'search category', PT, and NCI-CTCAE Grade. The following search categories are defined:

1) Search Category: 'Infective pneumonias'

All AEs belonging to Standardised MedDRA Query (SMQ) "Infective pneumonias" will be displayed in a combined fashion. For instance, the following terms will be pooled:

- PT pneumonia
- PT lung infection

2) Search Category: Sepsis

All AEs with PTs including the term "Sepsis" (in MedDRA: 54 terms) will be displayed in a combined fashion. For instance, the following terms will be pooled:

- PT sepsis
- PT neutropenic sepsis
- PT streptococcal sepsis
- PT Klebsiella sepsis

3) Search Category: Urinary tract infections

All AEs with PTs including the term "Urinary tract infection" (in MedDRA: 42 terms) plus all AEs belonging to MedDRA HLT "Urinary tract infections" will be displayed in a combined fashion, for instance, the following terms will be pooled:

- PT urinary tract infection
- PT urinary tract infection bacterial
- PT Escherichia urinary tract infection
- PT urinary tract infection enterococcal

4) Search Category: Rashes

All AEs belonging to MedDRA HLGT "Epidermal and dermal conditions" will be displayed in a combined fashion, for instance, the following terms will be pooled:

- PT rash

- PT rash maculo-papular
- PT rash erythematous
- PT rash pruritic
- PT dermatitis allergic

16.3.2 Time to first TEAE

The time to the first TEAE will be summarized for the following TEAEs:

- Neutropenia ≥ G3 (PT 'neutropenia')
- Thrombocytopenia ≥ G3 (PT 'thrombocytopenia')
- Infections and infestations ≥ G3 (SOC 'infections and infestations')
    - Infective pneumonia ≥ G3 (SMQ code 20000231, narrow scope
- Urinary tract infection ≥ G3 (CMQ as defined in the SAP Appendix)
- Sepsis ≥ G3 (CMQ as defined in the SAP Appendix)
- Febrile neutropenia (PT 'febrile neutropenia')
- Thromboembolic events of all CTCAE Grades (SMQ code 20000081)
- Thromboembolic events ≥ G3 (SMQ code 20000081)

16.3.3 Tabulation of the most frequent TEAEs

Most frequent TEAEs, regardless of study drug relationship, will be tabulated by SOC, PT and NCI-CTCAE Grade. An incidence of 5% will be used as cut-off (i.e., TEAEs that happened in at least 5% of the patients are displayed).

16.3.4 Reasons for temporary MOR00208 and LEN interruptions

The following will be displayed by study drug:

- Number (%) of patients who experienced at least one interruption of dosing.
- The total number of interruptions

Temporary interruptions of MOR00208 include skipped visits and infusion interruptions. Temporary interruptions of LEN include any cases where the full number of 21 capsules was not taken during a cycle due to one or several TEAEs, or if LEN intake stopped within a cycle due to a TEAE, and restarted in the same cycle. This includes cases with or without dose

reduction of LEN. Permanent treatment discontinuations of LEN are not considered in this summary.

Of note, a patient can have more than one reason for a temporary interruption of study drug, and also experience multiple sequential interruptions. Percentages will be based on the number of patients who had at least one temporary interruption of MOR00208 or LEN, respectively.

16.4 Additional efficacy analyses

16.4.1 Time to PR and time to best response

The time to PR and the time to best response will be summarized for the FAS.

16.4.2 Event-free survival

A Kaplan-Meier analysis for event-free survival (EFS) will be performed using the FAS based on the IRC response assessment. The same rules definitions and analysis rules as defined in Section 10.2 will be applied, with the following exception:

The initiation of a new anti-DLBCL therapy (medication, radiation, surgery) will be considered as an EFS event, instead of leading to censoring.

A Kaplan-Meier curve will be produced for illustration.

16.5 Subgroup analyses

16.5.1 Patients who discontinued LEN treatment

Efficacy assessment

A Kaplan-Meier analysis on PFS and OS will be conducted as described in Sections 10.2 and 10.4 for those patients who discontinued LEN treatment at any point in time. That is, regardless whether the discontinuation is due to an adverse event, or as per protocol after Cycle 12. The analysis will start from the moment of LEN discontinuation (zero time elapsed). Both Tables and Kaplan-Meier curves will be produced based on the FAS.

Safety assessment

Incidence and frequency of adverse events will be displayed separately for the periods *before* LEN discontinuation, and *after* LEN discontinuation. All discontinuations of LEN treatment are considered, regardless of the reason for discontinuation (per protocol, or due to AE).

TEAEs are considered for the **pre**-LEN discontinuation period if they are observed in the following interval (including the lower and upper limits): date of first administration of study treatment to date of last administration of LEN + 7 days (or if they are suspected to be related to LEN).

TEAEs are considered for the **post**-LEN discontinuation period if they are observed in the following interval (including the lower and upper limits): date of last administration of LEN + 8 days to date of last administration of MOR00208 + 30 days (if they are not suspected to be related to LEN).

For both periods following will be summarized by SOC, PT, and NCI-CTCAE Grade for the SAF:

- All TEAEs
- TEAEs by ‚Search Category' (see Section 16.3.1)
- SAEs
- AESIs
- G3 vs. G4 TEAEs

Moreover, a Table summarizing fatal TEAEs (i.e., Grade 5 SAEs) will be produced.

A barplot will be produced illustrating the TEAEs that happened with an incidence of ≥10% of patients in the SAF. Each bar will represent a particular PT, and for each bar the fraction of patients with Grade 1, 2, 3, 4, 5 will be indicated by color-coding or shading.

Exposure as described in Section 8.9.2 will be calculated for both the **pre**-LEN discontinuation period (exposure to LEN or the combination LEN/MOR00208), and the **post**- LEN discontinuation period (exposure to MOR00208). The exposure to LEN or the combination for the **pre**-LEN discontinuation period is starting from the first date of LEN dosing. The exposure to MOR00208 only for the **post**-LEN discontinuation period is starting from the first administration of MOR00208 after the discontinuation of LEN.

The Tables displaying the TEAEs and exposure, and the also the barplot will be additionally be produced for an alternative definition of the **pre**- and **post**-LEN discontinuation period.

TEAEs are considered for the **pre**-LEN discontinuation period if they are observed in the following interval (including the lower and upper limits): date of first administration of study treatment to date of last administration of LEN+ 30 days (or if they are suspected to be related to LEN).

TEAEs are considered for the **post**-LEN discontinuation period if they are observed in the following interval (including the lower and upper limits): date of last administration of LEN +

31 days to date of last administration of MOR00208 + 30 days (if they are not suspected to be related to LEN).

16.5.2 Patients who reduced the daily prescribed LEN dose

Incidence and frequency of TEAEs by the degree of LEN dose reduction

TEAEs will be tabulated by SOC, PT, and NCI-CTCAE Grade as described in Section 10.7 for the following subgroups of patients:

- Patients with no reduction of LEN.
- Patients with a minimum LEN dose of 20 mg/day: for this category, all TEAEs that occurred *before* exceeding the threshold of 20 mg/day are considered. The calculation of incidence rates is based on the number of patients in the SAF.
- Patients with a minimum LEN dose of <20 mg/day but ≥5mg/day: for this category, all TEAEs are considered that happened *after* exceeding the threshold of 20 mg/day. The calculation of incidence rates is based on the number of patients who had a reduction to <20 mg/day but ≥5mg/day.

Duration of TEAEs of interest

The duration of various TEAEs of interest will be summarized for the following dose categories:

- Patients who are treated with 25 mg LEN per day
- Patients who are treated with 20 or 15 or 10 or 5 mg LEN per day
- Patients who are treated with 15 or 10 or 5 mg LEN per day

For each category only those TEAEs are considered that happen *during* the period of treatment with the particular dose or dose range defining the categories above (e.g., only those TEAEs are considered that happen during while the patient is on 15 or 10 or 5 mg LEN per day). The duration of a particular TEAE is summarized for the following TEAEs:

- Neutropenia ≥G3 (PT ‘neutropenia‘)
- Thrombocytopenia ≥G3 (PT ‘thrombocytopenia‘)
- Infections and infestations ≥G3 (SOC ‘infections and infestations’)
- Infective pneumonia ≥G3 (SMQ code 20000231, narrow scope)
- Urinary tract infection ≥G3 (CMQ as defined in the SAP Appendix)

- Sepsis ≥G3 (CMQ as defined in the SAP Appendix)
- Febrile neutropenia (PT 'febrile neutropenia')
- Thromboembolic events of all CTCAE Grades (SMQ code 20000081)
- Thromboembolic events ≥G3 (SMQ code 20000081)

16.5.3 Evaluation of the influence of different CMC batches

In L-MIND patients were treated with different production batches of the material patients were treated with (denoted with CMC2 and CMC4 material). A summary will be produced showing the number of patients who were treated with:

- CMC2 only
- CMC4 only
- Both CMC2 and CMC4 material

For those patients who were first treated with CMC2 and later with CMC4 the 'time to switch' will be displayed in a histogram. The time to switch will be summarized.

Evaluation of the influence on safety

Incidence of TEAEs by SOC, PT, Grade **pre**-switch vs. **post**-switch:

- TEAEs
- SAEs
- AESIs
- Fatal TEAEs
- G3 vs. G4 TEAEs

The exposure as defined in Section 8.9.2 will be determined for both the CMC2 and CMC4 material.

Evaluation of the influence on efficacy

Based on the investigator response assessment (INV) the following quantities will be summarized:

- Median time to censoring post-switch due to data cut-off (considering only censored patients; no Kaplan-Meier methodology)

- Median time to PFS event post-switch (considering only patients with PFS event; no Kaplan-Meier methodology)
- Median follow-up time after the switch (applying the reverse Kaplan-Meier method)

Based on the investigator response assessment, a swimmers plot will be produced for the patients who switched from CMC2 to CMC4, indicating:

- The bar length will represent the time to event / censoring
- Point in time when the CMC switch happened
- Point in time when PR or CR were detected first
- Patients without PFS event who are censored due to data cut-off (arrow head on top of bar)
- Patients who experienced a PFS event, or patients who were censored due to other reasons than data cut-off (blunt bar end); patients who are treated despite progression will have a blunt end at the time the PD was detected

16.5.4 Efficacy by age category

Based on the FAS, PFS, OS, ORR, and DoR will be derived for the following subgroups as detailed in the respective SAP sections for both the INV and IRC response assessment. For time-to-event endpoints both Figures and Tables will be produced. The following categories are considered:

- Patients ≤70 years of age
- Patients >70 years of age

16.5.5 Time to event analyses by best response category

OS will be summarized for the following categories based on the FAS:

- Patients having a CR as best response (as determined by IRC)
- Patients having a PR as best response (as determined by IRC)

A Kaplan-Meier curve for the two subgroups will be produced.

16.5.6 Forest plots for biomarker and non-biomarker subgroups

Forest plots for the ORR, the CR rate, and the hazard ratio between the subgroups of a particular subgroup factor (determined from a univariable Cox regression model) will be

produced for the biomarker and non-biomarker subgroups as defined in Sections 10.12, 10.10, and 11.4. The plots will be based on the FAS and generated separately for both the IRC and INV response assessment.

16.5.7 ASCT ineligibility subgroups

Subgroup analyses

In addition to the ASCT ineligibility subgroups as defined in Section 8.6.3, the following four mutually exclusive categories will be defined:

- **Chemorefractory patients:**
  - Chemorefractory patients as indicated on the eCRF page 'ASCT Ineligibility Criteria' ('Failure to achieve PR or CR with salvage therapy').
  - Patients who underwent a stem cell transplantation before as indicated on the eCRF page 'Prior Cancer Therapies for DLBCL – Autologous Stem Cell Transplants'.
  - The presence or absence of any other reason such as comorbidities or high age will be ignored.
- **Co-morbid patients**
  - Only those patients will be considered who are *not* already in the 'Chemorefractory' group.
  - Co-morbid as indicated on the 'ASCT Ineligibility Criteria' page
  - Presence or absence of other reasons such as high age will be ignored.
- **Patients of high age**
  - Only those patients will be considered who are *not* already in the 'Chemorefractory' or 'co-morbid' category.
  - All patients who are ineligible due to high age as indicated on the eCRF page 'ASCT Ineligibility Criteria' ('Age > 70 years'). Other reasons for ASCT ineligibility like 'Refusal' or 'Other reasons' will be ignored.
- **Refusal**
  - Only those patients will be considered who are not already in the 'Chemorefractory', 'Co-morbid', or 'High age' category.
  - All patients who are ineligible due to the patients´ refusal to undergo ASCT as indicated on the eCRF page 'ASCT Ineligibility Criteria'.
- **Other reasons**

- All other patients who are not in the categories above will be considered as ASCT ineligible due to other reasons.

Table 16: Reasons for ASCT Ineligibility

Priority	High level category	Reason from eCRF
1	Chemorefractory	Failure to achieve PR or CR with salvage therapy
		Prior ASCT as indicated in eCRF page 'Prior Cancer Therapies for DLBCL – Autologous Stem Cell Transplants'
2	Comorbidity	Diffusion lung capacity for carbon monoxide <50% by pulmonary function test
		Left ventricular ejection fraction <50% by multiple gated acquisition echocardiogram
		Other organ dysfunction or comorbidities precluding the use of HDT/ASCT on the basis of unacceptable risk of treatment
3	Age	Age >70 years
4	Refusal	Patient refusal of HDT/ASCT
5	Other	Other Reason

The reasons for being ASCT ineligible will be summarized for the FAS. The following subgroup analyses in terms of efficacy will be conducted based on both the INV and IRC response assessment (using the FAS):

- PFS
- OS
- DoR

- ORR

Both Tables and Kaplan-Meier curves for time-to-event analyses will be produced as described in the respective sections that detail the analysis of the listed endpoints. If less than three patients are included in the 'Other' category this subgroup will not be analyzed or displayed in the graphs.

Contingency table for displaying the reasons for ASCT ineligibility

The five reasons for being ASCT ineligible as defined above are presented in a cross-table. The table will show the number of patients who are characterized by a particular combination of two different ASCT ineligibility reasons. For this summary the reasons for ASCT ineligibility are not defined as mutually exclusive, i.e, a patient can have more than one reason for being ASCT ineligible, resulting in the fact that patients can generally be represented multiple times in the table. Percentages are calculated row-wise and are based on the number of patients in FAS with reason for ASCT ineligibility as displayed in the first column.

The contingency table will be produced for:

- The FAS
- The subgroup of patients with only one prior treatment line (on the FAS)
- The subgroup of patients with two prior treatment lines (on the FAS)
- The subgroup of patients with three or four prior treatment lines (on the FAS)

16.5.8 NK cell numbers at baseline

In analogy to the subgroup analysis specified in Section 10.12 the NK cell categories are additionally defined using a cut-off of 100 NK cells/µl (<100 cells/µl vs. ≥100 cells/µl). The following efficacy analyses will be conducted based on the FAS:

- PFS (based on IRC only)
- OS
- ORR (based on IRC only)
- DoR (based on IRC only)

Kaplan-Meier curves will be produced for time-to-event endpoints.

Baseline characteristics in the NK count subgroups defined by the cut-off of 100 NK cells/µl will be tabulated as described in Section 8.5.

16.5.9 Swimmers plot for responders

A swimmers plot will be produced for the responders in the FAS. The bar length will indicate the time on treatment defined as follows: (date end of treatment – date of first dosing with any study drug) + 1. Different landmarks will be indicated in the plot:

- Arrow heads: indicate if a patient is still ongoing on treatment at data cut-off.
- Patients who have discontinued treatment are indicated by a blunt end of the bar.
- Time to partial response and time to complete response is indicated by different symbols.
- A symbol at the start of the bar will indicate if a patient is primary refractory.
- A symbol at the end of the bar will indicate if a patient has already progressed.

17. SAP ADDENDUM 2.0

17.1 Efficacy in subgroups of BCL-2 expression levels determined by IHC

Three complementary subgroups of patients will be defined:

- Patients with high BCL-2 expression: ≥50% BCL-2-positive cells and BCL-2 staining intensity ≥2
- Patients with low BCL-2 expression:
  - <50% BCL-2-positive cells and BCL-2 staining intensity <2
  - <50% BCL-2-positive cells, and BCL-2 staining intensity ≥2 or unknown staining intensity
  - BCL-2 staining intensity <2, and ≥50% BCL-2-positive cells or unknown percentage of positive cells
- Patients with unknown status regarding BCL-2 expression:
  - ≥50% BCL-2-positive cells and unknown BCL-2 staining intensity
  - BCL-2 staining intensity ≥2 and unknown percentage of BCL-2 positive cells
  - Unknown percentage of BCL-2 positive cells, and unknown BCL-2 staining intensity

The following endpoints will be summarized for the BCL-2 subgroups based on the FAS:

- ORR (based on IRC only)
- PFS (based on IRC only)
- DoR (based on IRC only)
- OS

The methodology for summarizing the endpoints are described in Sections 9, 10.2, 10.3, and 10.4. Kaplan-Meier plots will be presented for the time-to-event endpoints.

17.2 Efficacy in alternative age subgroups

In addition to the subgroup analysis specified in Section 16.5.4, selected efficacy endpoints will also be analyzed for the following subgroups:

- Patients of ≤65 years of age
- Patients of >65 years of age

The following endpoints will be summarized for the alternative age subgroups based on the FAS:

- ORR (based on IRC only)
- PFS (based on IRC only)
- DoR (based on IRC only)
- OS

The methodology for summarizing the endpoints are described in Sections 9, 10.2, 10.3, and 10.4. Kaplan-Meier plots will be presented for the time-to-event endpoints.

17.3 Efficacy in different histological subgroups

Selected endpoints will be reported for patients belonging to different pathological subgroups as per central pathology are depicted in Table 17. Pathological subgroups will be identified as outlined in Section 17.8. Moreover, the duration of being progression-free will be visualized in a swimmer plot. Summaries will be generated based on the FAS.

Table 17: Analyses for various NHL subgroups as per central pathology

Histology	Outputs
DLBCL, no further specification	ORR, (CR rate, PR rate) DoR PFS OS Swimmer plot
Composite Lymphoma with DLBCL Component	ORR, (CR rate, PR rate) DoR PFS OS Swimmer plot
Any high grade lymphoma with double or triple hit	ORR, (CR rate, PR rate) Swimmer plot
EBV positive DLBCL + T cell histiocyte-rich large B cell lymphoma	ORR, (CR rate, PR rate) Swimmer plot
Follicular Lymphoma Grade 2 $\pm$ Grade 3A	ORR, (CR rate, PR rate) Swimmer plot
Mantle Cell Lymphoma	ORR, (CR rate, PR rate) Swimmer plot
Marginal Zone Lymphoma	ORR, (CR rate, PR rate) DoR Swimmer plot

Histological transformation to DLBCL from indolent NHL	ORR, (CR rate, PR rate) Swimmers plot
Unknown / missing	ORR, (CR rate, PR rate) Swimmers plot

The methodology for summarizing the endpoints ORR, DoR, PFS, and OS are described in Sections 9, 10.2, 10.3, and 10.4.

The swimmer plot will be designed as follows:

- the length of the bar will indicate the time of being progression free in months.
- a blunt end indicates progression
- an arrow head will indicate that the patient is still progression-free: color-coding for the arrow head will be used to indicate if the patient is still ongoing on PFS-follow- up, or has been censored due to other reasons
- bars will be color-coded to differentiate between patients with PR and CR as best response
- the patient ID will be shown for each bar, together with the number of prior treatment lines
- symbols will be used to indicate the point in time (relative to first dosing with any study drug) when the first PR and first CR was detected
- symbols on the right of the bars will be used to indicate if a patient is primary refractory and/or refractory to his/her last prior treatment lineBest response and progression free survival will be based on the IRC evaluation.

17.4 Identification of transformed lymphoma patients

Section 8.6.4 describes how patients with previous indolent lymphoma (i.e., patients who transformed to high-grade lymphoma) are identified. The algorithm will be modified as follows:

- “Presumed INHL” will be added to the list of search terms.
- Patients who developed a secondary indolent lymphoma after the diagnosis of DLBCL (or other high-grade lymphoma as specified in the protocol) will not be considered.
- Patients who have the reference diagnosis “HISTOLOGICAL TRANSFORMATION TO DLBCL FROM INDOLENT NHL” per central pathology assessment will also be considered.

17.5 Swimmer plot for patients with transformed lymphoma

A swimmer plot for patients with transformed lymphoma will be produced. The strategy to identify patients with previously indolent lymphoma that had transformed to a high-grade lymphoma is outlined in Sections 8.6.4 and 17.4.

The swimmer plot will be produced as described in Section 17.3

17.6 Deaths

Section 10.7.3.1.6 describes how deaths will be summarized according to the following categories: PD-related vs. non-PD-related. The list of terms determining that a death is PD-related will be extended by the terms “Progression”, “Study disease” and “Progression of the disease”. The following terms will lead to a classification into the new “Unknown” category in terms of PD-relatedness:

- “End stage marrow failure”
- “Unkown”

In case that for a patient more than one cause of death is reported in different sections of the eCRF, the patients’s death will be categorized as PD-related if at least one of the causes of death is classified as PD-related.

17.7 Lenalidomide dose intensity

The dose intensity is calculated as average daily dose of treatment.

$$Dose\ Intensity\ (mg/day) = \frac{Cumulative\ dose\ (mg)}{Duration\ of\ exposure\ (days)}$$

While considering treatment duration, discontinuation for any reason (disease progression, AE, Investigator’s decision, etc) will be taken into account.

A total daily dose will be multiplied with the difference between the “dosing stop study day” and the “dosing start study day” + 1 for each cycle. Days where no Lenalidomide capsule is taken are counted as days with a dose of 0 mg. The difference in number of capsules dispensed and returned will not be considered.

Exemplified calculation:

Dosing start day	Dosing end day	Total daily dose (mg)	Total dose (mg)
1	21	25	25 x 21 = 525

30	50	25	25 x 21 = 525
59	79	20	20 x 21 = 420
87	91	10	10 x 5 = 50
Dose intensity = (525 + 525 + 420 + 50) / 91 = 16.7 mg			

Dose intensity of Lenalidomide will be summarized based on the FAS.

17.8 Categorization of reference diagnoses as per central pathology

For reporting, the diagnosis as per central pathology will be coded as follows:

Reference diagnosis as per central pathology	Diagnosis findings as reported by central pathology	Diagnosis for reporting in Tables, Listings, Figures	Non-Hodgkin lymphoma category
DLBCL; NOT OTHERWISE SPECIFIED	• Not available • DLBCL. GCB-TYPE • I AGREE WITH THE DIAGNOSIS OF DLBCL, GCB-TYPE IN BOTH SPECIMENS. ANALYSIS WAS DONE ON 28020/14 • LIKELY DLBCL, VERY LIMITED MATERIAL; IMPORTANT STAINS (E.G. EBV) MISSING	DLBCL	DLBCL
DLBCL; NOT OTHERWISE SPECIFIED	HIGH-GRADE B-CELL LYMPHOMA, WITH MYC AND BCL2 AND BCL6 TRANSLOCATIONS (`TRIPLE HIT LYMPHOMA')	DLBCL (Triple Hit Lymphoma)	DLBCL
DLBCL; NOT	UPDATE WHO: HIGH	DLBCL (Double	DLBCL

OTHERWISE SPECIFIED	GRADE B-CELL LYMPHOMA WITH MYC AND BCL2 TRANSLOCATION ("DOUBLE HIT")	Hit Lymphoma)	
T-CELL HISTIOCYTE RICH LARGE B-CELL LYMPHOMA	• Not available • T-CELL HISTIOCYTE RICH LARGE B-CELL LYMPHOMA	T cell histiocyte rich large B cell lymphoma	DLBCL
DIAGNOSIS NOT CONFIRMED	MARGINAL ZONE LYMPHOMA	Marginal zone lymphoma	Non-DLBCL
COMPOSITE LYMPHOMA WITH A DLBCL COMPONENT	• Not available or • Pathological specifications	Composite lymphoma with a DLBCL component	DLBCL
EPSTEIN-BARR VIRUS (EBV) POSITIVE DLBCL OF THE ELDERLY	Not available	EBV-positive DLBCL	DLBCL
DLBCL; NOT OTHERWISE SPECIFIED	PARTIAL EBV+	EBV-positive DLBCL	DLBCL
DIAGNOSIS NOT CONFIRMED	FOLLICULAR LYMPHOMA GRADE 2	Follicular Lymphoma Grade 2	Non-DLBCL
DIAGNOSIS NOT CONFIRMED	Not available	Unknown	Unknown
DIAGNOSIS NOT CONFIRMED	MANTLE CELL LYMPHOMA, CLASSIC TYPE	Mantle cell lymphoma, classic type	Non-DLBCL
DIAGNOSIS NOT CONFIRMED	FOLLICULAR LYMPHOMA (GRADE 2 + 3A)	Follicular lymphoma (Grade 2 + 3A)	Non-DLBCL
HISTOLOGICAL TRANSFORMATION TO DLBCL FROM INDOLENT NHL	DLBCL, TRANSFORMED FROM MZL	Histological transformation to DLBCL from indolent NHL	DLBCL

18. SAP ADDENDUM 3.0

18.1 Forest plots for 24 month rates of Progression-free Survival, Duration of Response and Overall Survival

Forest plots for the 24 month rates of PFS, DoR and OS will be generated for selected non-biomarker subgroups as defined in Section 11.4. The plots will be based on the FAS and will be generated for the IRC response assessment for PFS and DoR. Estimation of the 24 month rates and the pertaining confidence intervals will be based on the Kaplan-Meier method.

19. SAP ADDENDUM 4.0

For the subgroup of centrally confirmed DLBCL patients (see Section 17.8, Non-Hodgkin lymphoma category of *DLBCL*), the following Table will be created:

- Baseline characteristics: tabulation as described in Section 8.5.

The Table will be created based on both the FAS and the SAF.

20. SAP ADDENDUM 5.0

20.1 Exploratory biomarker analyses

Longitudinal analyses will be conducted for: Peripheral numbers of NK cells and B cells (analysed separately):

Tabulations (for NK cells, B cells; based on FAS):

- Summary statistics per visit (a 95% confidence interval for the median will be derived by bootstrapping) by response status (responders vs. non-responders)
- Absolute change from baseline (a 95% confidence interval for the median will be derived by bootstrapping) by response status (responders vs. non-responders)
- Relative change from baseline (a 95% confidence interval for the median will be derived by bootstrapping) by response status (responders vs. non-responders)

Graphical illustrations (for B cells and NK cells; based on FAS):

- Median and its 95% confidence interval (via bootstrapping) for absolute values, absolute change from baseline and relative change per visit across all patients assessed by response status (responders vs. non-responders). The median over time for responders and non-responders will be depicted in parallel in one graph.
- Spaghetti plots displaying the absolute values, absolute change from baseline, and relative change from baseline by visit (i.e., three individual plots for each cell type). The point in time when the PFS event (based on IRC) happened will be indicated in each plot. Each spaghetti plot will only display the subgroup of patients who
    - have a best response PR or CR (at any point in time) and
    - have experienced a PFS event (based on IRC) within 12 months after treatment start with any study drug
- Spaghetti plots displaying the absolute values, absolute change from baseline, and relative change from baseline by visit (i.e., three individual plots for each cell type). Each spaghetti plot will only display the subgroup of patients who
    - have a best response PR or CR (at any point in time) and
    - have NOT experienced a PFS event (based on IRC) within 12 months after treatment start with any study drug

Listing (for B cells and NK cells; based on the SAF)

A Listing will be provided for patients who:

- have a best response PR or CR (at any point in time) and
- have experienced a PFS event (based on IRC) within 12 months after treatment start with any study drug

The Listing will show the following by Visit:

a) absolute count of B cells and NK cells

b) absolute change from baseline

c) percent change from baseline

d) response category by IRC (if available)

The nominal Visit and the date of the Visit should be indicated for each assessment.

20.2 Time since discontinuation of the last treatment

Based on the FAS, the time since discontinuation of the last anti-DLBCL medication before receiving any study drug in L-MIND will be summarized for the following patient subgroups:

- Patients with one prior treatment line
- Patients with two prior treatment lines
- Patients with three or four prior treatment lines

A Listing (based on the SAF) will be provided indicating the time since discontinuation of the last treatment for each patient including the number of previous treatment lines.

20.3 Time since disease progression in the last prior treatment (systemic anti-DLBCL medication)

Based on the FAS, the time since disease progression in the last anti-DLBCL medication before receiving any study drug in L-MIND will be summarized for the following patient subgroups:

- Patients with one prior treatment line
- Patients with two prior treatment lines
- Patients with three or four prior treatment lines

A Listing (based on the SAF) will be provided indicating the time since disease progression in the last treatment for each patient including the number of previous treatment lines.

20.4 Post-L-MIND anti-DLBCL medications

20.4.1 Summaries

Tabulations of anti-neoplastic therapies after discontinuation of MOR00208+LEN

A Table based on the FAS will be provided summarizing anti-neoplastic therapies after discontinuation of all study drugs. The anti-neoplastic therapies will be displayed for the following categories:

- First line after L-MIND
- Second line after L-MIND
- Third line after L-MIND
- Line 4 or higher after L-MIND

Summary statistics for the number of post-L-MIND anti-neoplastic therapies will be provided.

Summary / analysis of OS

A Kaplan-Meier analysis for OS will be conducted focusing only on the period after the end of treatment of both MOR00208 and LEN. The following four patient subgroups will be defined:

Subgroup	Treatment status	PFS Event / Censoring status (based on IRC)	Post-L-MIND anti-DLBCL medication
1	Both MOR00208 and LEN discontinued	PFS Event (deaths not considered)	Experienced (at least one line)
2	Both MOR00208 and LEN discontinued	PFS Event (deaths not considered)	No post-L-MIND anti-DLBCL medication at all
3	Both MOR00208 and LEN discontinued	Censored for PFS follow-up	Experienced (at least one line)
4	Both MOR00208 and LEN discontinued	Censored for PFS follow-up	No post-L-MIND anti-DLBCL medication at all

Baseline for the OS analysis is the earliest point in time when both requirements are met:

a) Both study drugs discontinued

b) PFS event / censoring happened

A Kaplan-Meier plot will also be generated displaying the four subgroups.

A Table showing the censorings reasons (ongoing at data cut-off, lost to follow-up, ICF withdrawal etc.) for each subgroup will be produced.

A Listing will be provided showing all post-L-MIND anti-DLBCL medications by treatment line, survival status at the data cut-off date, and date of death.

20.4.2 Swimmers plot

Based on the FAS, four swimmers plots will be generated for the four patient subgroups above. The following will be displayed:

- Bar length: [(Date of death or date censoring of OS follow-up) – (Date of PFS event or date of PFS censoring) + 1].
- An arrow head at the end of the bar will indicate if OS follow-up is still ongoing at data cut-off, or the point in time when a patient was censored for OS follow-up. A blunt end will indicate that the patient has died.
- Symbols will be used to indicate the initiation every new treatment line after the treatment with MOR00208 + LEN.

20.5 Relationship between LEN dose intensity and efficacy

20.5.1 DoR and ORR in subgroups of varying relative cumulative LEN exposure

Patients will be categorized according to their relative cumulative LEN dose, which will be derived as follows:

Relative cumulative LEN dose intensity = (cumulative total used dose / reference cumulative dose) x 100.

- The reference cumulative dose represents the cumulative LEN dose a patient is supposed take until he/she progresses per IRC (for summaries of DoR; see below) or until he/she reaches a CR or PR (for summaries of ORR; see below):
    - Example 1 for a summary of DoR: a patient who only progresses later than Cycle 12 experiences the following reference cumulative dose: 12 months x 21 days x 25 mg LEN per day = 6300 mg LEN
    - Example 2 for a summary of DoR: a patient who progresses on Cycle 7, Day 10 experiences the following reference cumulative dose: (6 months x 21 days x 25 mg LEN per day) + (10 days x 25 mg LEN per day) = 3400 mg LEN
    - Example 3 for a summary of ORR: a patient who reaches a CR at Cycle 3 Day 25 experiences the following reference cumulative dose: 3 months x 21 days = 1575 mg LEN
- The cumulative total used dose represents the cumulative LEN dose a patient has actually ingested until he/she progresses per IRC (for summaries of DoR) or until he/she

reaches a CR or PR (for summaries of ORR). The derivation of the total used dose for LEN is described in Section 8.9.6.

Based on the relative cumulative LEN dose intensity, the following patient subgroups will be defined:

- Patients with relative cumulative LEN dose intensity of <50%
- Patients with relative cumulative LEN dose intensity of 50%-80% (inclusive)
- Patients with relative cumulative LEN dose intensity of >80%

The following will be analyzed for the subgroups defined above:

- Summary of DoR including a Kaplan-Meier plot (see Section 10.3)
- Best objective response rate and rates for best response of CR/PR/SD/PD/not evaluable assessment (see Section 9)

20.5.2 Efficacy outcome for patients with defined LEN dose reductions

The following subgroups will be defined:

- Patients with no LEN dose reduction
- Patients with one LEN dose reduction to 20 mg/day
- Patients with two or more LEN dose reductions (i.e., to a maximum reduction to 15, 10, or 5 mg LEN)
- Patients who permanently discontinued LEN (directly, or after having reduced the daily LEN dose before)

Patient subgroups 1-3 are mutually exclusive and the total number of patients in the subgroups should sum up to the total number of patients in the FAS.

Based on the FAS, the following will be summarized / analyzed for each subgroup:

- Baseline characteristics as described in Section 8.5
- Best objective response rate and rates for best response of CR/PR/SD/PD/not evaluable assessment (by IRC) as described in Section 9
- DoR (by IRC) as described in Section 10.3
- PFS (by IRC) as described in Section 10.2

- OS as described in Section 10.4

For the endpoints DoR, PFS, and OS, Kaplan-Meier plots will be presented.

A swimmers plot will be created for all patients with at least one LEN dose reduction at any point in time. The following will apply:

- The bar length will indicate the time on treatment with any study drug (MOR00208 only, LEN only, or both drugs at the same time)
- An arrow head at the top of the bar will indicate whether the patient is still ongoing on any study drug at data cut-off
- Using different symbols and colors/shadings for the symbols, the following will be indicated for each patient:
    - Point in time (relative from baseline) and quality of the initial response (CR or PR)
    - Point in time (relative from baseline) and quality of the best response (CR or PR)
    - Point in time (relative from baseline) of LEN discontinuation
    - Point in time (relative from baseline) of progression by IRC
    - Point in time (relative from baseline) of death
    - Point in time of LEN dose reductions /LEN discontinuations (each reduction will be symbol-/color-coded individually)

20.5.3 Other analyses related to LEN dose reduction

The following will be summarized (FAS):

- Time from baseline until first/second/third/fourth LEN dose reduction or LEN discontinuation
- Number (%) of patients who experienced at least one “deepening of response” (transition from PR to CR or SD to PR or SD to CR by IRC) after having experienced at least one dose reduction

The permanent discontinuation of LEN as per protocol will be ignored (i.e., not be considered in the analysis as dose reduction or discontinuation).

A Listing will be provided for the patients in the SAF who have discontinued both MOR00208 and LEN at the same time (i.e., sequential discontinuations will not be considered). The Listing based on the SAF will display the following:

- Point in time when the TEAE happened that led to the discontinuation of treatment
- The Preferred Term that led to the discontinuation of treatment
- Point in time (relative from baseline) when individual LEN dose reductions / LEN discontinuation happened
- The response status (CR, PR, SD, PD, not evaluable; based on IRC) at the point in time when the discontinuation happened
- The overall outcome (based on the integrated overall clinical assessment) of all central tumor response assessments

20.6 Efficacy analyses for the subgroup of patients confirmed as DLBCL by central pathology based on the FAS

Patients with a Non-Hodgkin Lymphoma category of "DLBCL" by central pathology as defined in Section 17.8 will be considered. All analyse will be based on the FAS.

20.6.1 Efficacy analyses based on all patients centrally confirmed as DLBCL

The following will be summarized / analyzed based on the IRC:

- Disease control rate (see Section 10.1)
- Time to progression including a Kaplan-Meier plot (see Section 10.5)

20.6.2 Efficacy analyses for patient subgroups within the subgroup of patients classified as DLBCL as per central pathology

IPI subgroups (low risk + low-intermediate risk vs. intermediate-high + high risk)

- ORR and rates for best response categories (CR/PR/SD/PD/not evaluable) by IRC (see Section 9)
- PFS by IRC (see Section 10.2)
- OS (see Section 10.4)

For the endpoints PFS and OS, Kaplan-Meier curves will be provided.

Prior treatment lines subgroups (1 prior treatment line vs. ≥2 prior treatment lines)

- ORR and rates for best response categories (CR/PR/SD/PD/not evaluable) by IRC (see Section 9)

Primary refractoriness subgroups (refractory vs. non-refractory)

- PFS by IRC (see Section 10.2)
- OS (see Section 10.4)

Kaplan-Meier plots will be presented.

Last line refractoriness subgroups (refractory vs. non-refractory)

- PFS by IRC (see Section 10.2)
- OS (see Section 10.4)

Kaplan-Meier plots will be presented.

Rituximab refractoriness subgroups (refractory vs. non-refractory)

- PFS by IRC (see Section 10.2)
- OS (see Section 10.4)

Kaplan-Meier plots will be presented.

Age subgroups (≤70 vs. >70 years of age)

- PFS by IRC (see Section 10.2)

A Kaplan-Meier plot will be presented.

Forest plot

Forest plots for various endpoints will be generated, displaying the following biomarker and non-biomarker subgroups in one and the same illustration:

- Non-biomarker subgroups:
    - IPI subgroups dichotomized: low and low-intermediate vs. high-intermediate and high
    - Gender: female vs. male
    - Rituximab refractoriness: yes vs. no

- Refractoriness to last prior treatment line: yes vs. no
- Primary refractoriness: yes vs. no
- Prior autologous stem cell transplantation: yes vs. no
- Number of prior treatment lines dichotomized: 1 vs. ≥2
- Age dichotomized: ≤70 years vs. >70 years of age

- Biomarker subgroups:
  - NK cell numbers at baseline: <100 vs. ≥100 cells/µl
  - Cell of origin by IHC: GCB vs. non-GCB vs. unknown

The following Forest plots displaying an estimate for the expectation together with 95% confidence intervals will be generated:

- Forest plot for ORR (by IRC)
- Forest plot for CR rate (by IRC)
- 24-month PFS rate (by IRC)
- 24-month DoR rate (by IRC)
- 24-month OS rate
- 30-month PFS rate (by IRC)
- 30-month DoR rate (by IRC)
- 30-month OS rate (by IRC)

20.7 Additional subgroup analyses

20.7.1 Efficacy analyses in subgroups of patients enrolled at sites that enrolled ≤3 vs. >3 patients

The following subgroups will be defined:

- Sites recruiting ≤3 patients
- Sites recruiting >3 patients

The following will be summarized / analyzed by subgroup based on the FAS:

- ORR and rates for best response categories (CR/PR/SD/PD/not evaluable) by IRC (see Section 9)

- OS (see Section 10.4)
- Duration of CR (by IRC; Section 10.3.5)

For the endpoints OS and Duration of CR, a Kaplan-Meier plots will be presented.

ORR by site

An analysis on ORR as specified in Section 9 will be also conducted for individual sites that had recruited at least one patient.

20.7.2 Efficacy analyses in subgroups of patients recruited at US sites vs. European sites

The following subgroups will be defined:

- Patients recruited at sites in the USA (US sites)
- Patients recruited at European sites

The following will be analyzed / summarized based on the FAS:

- ORR and rates for best response categories (CR/PR/SD/PD/not evaluable) by IRC (see Section 10.1)
- OS (Section 10.4)
- Duration of CR (by IRC; Section 10.3.5)

For the endpoints OS and duration of CR, Kaplan-Meier plots will be produced.

20.7.3 Efficacy analyses for histological subgroups of NHL

Section 17.3 specifies the analyses of ORR, DoR, OS, and PFS for the NHL subtypes DLBCL- NOS (=DLBCL, not further specified) and Composite Lymphoma as determined by central pathology. The following will be added:

- All analyses will be additionally be produced based on the SAF
- Kaplan-Meier plots will be produced for endpoints DoR, OS, PFS for both FAS and SAF

20.7.4 Listings displaying best response and DoR by NHL subtype

Based on the SAF, a Listing will be produced displaying the following:

- Best response by IRC
- DoR per IRC including the following:
  - Information whether the DoR follow-up has discontinued due to PD
  - Information whether the patient has been censored including the reason for censoring
- Best response by INV
- DoR per INV including the following:
  - Information whether the DoR follow-up has discontinued due to PD
  - Information whether the patient has been censored including the reason for censoring

Based on the SAF, another Listing will be produced displaying the following:

- PFS time and the information if the patient was censored or had a PFS event by IRC
- PFS time and the information if the patient was censored or had a PFS event by INV
- OS time and the information if the patient was censored or had an OS event

20.7.5 Baseline characteristics of various patients subgroups

The baseline characteristics as outlined in Section 8.5 will be summarized for the following subgroups:

- Patients ≤70 years of age: based on the FAS
- Patients >70 years of age: based on the FAS
- Patients confirmed as DLBCL as per central pathology (i.e., patients with a Non-Hodgkin Lymphoma category of "DLBCL" by central pathology as defined in Section 17.8 will be considered): based on the FAS
- Patients confirmed as DLBCL as per central pathology (i.e., patients with a Non-Hodgkin Lymphoma category of "DLBCL" by central pathology as defined in Section 17.8 will be considered): based on the SAF

20.8 Efficacy analyses based on the SAF

20.8.1 Summaries

The following endpoints will be analysed / summarized:

- ORR and rates for best response categories (CR/PR/SD/PD/not evaluable) by IRC (see Section 10.1)
- DoR (by IRC; see Section 10.3)
- DoR (by IRC) by best response (by IRC)
- PFS (by IRC; Section 10.2)
- OS (Section 10.4)

For the endpoints DoR, DoR by best response, PFS, and OS, Kaplan-Meier plots will be generated.

20.8.2 Forest plots

Forest plots for various endpoints will be generated, displaying the following biomarker and non-biomarker subgroups in one and the same illustration:

- Non-biomarker subgroups:
  - IPI subgroups dichotomized: low and low-intermediate vs. high-intermediate and high
  - Gender: female vs. male
  - Rituximab refractoriness: yes vs. no
  - Refractoriness to last prior treatment line: yes vs. no
  - Primary refractoriness: yes vs. no
  - Prior autologous stem cell transplantation: yes vs. no
  - Number of prior treatment lines dichotomized: 1 vs. ≥2
  - Age dichotomized: ≤70 years vs. >70 years of age
- Biomarker subgroups:
  - NK cell numbers at baseline: <100 vs. ≥100 cells/µl
  - Cell of origin by IHC: GCB vs. non-GCB vs. unknown

The following Forest plots displaying an estimate for the expectation together with 95% confidence intervals will be generated:

- Forest plot for ORR (by IRC)
- Forest plot for CR rate (by IRC)
- 24-month PFS rate (by IRC)

- 24-month DoR rate (by IRC)
- 24-month OS rate
- 30-month PFS rate (by IRC)
- 30-month DoR rate (by IRC)
- 30-month OS rate (by IRC)

20.8.3 Analyses for the subgroup of patients confirmed as DLBCL by central pathology based on the SAF

Patients with a Non-Hodgkin Lymphoma category of "DLBCL" by central pathology as defined in Section 17.8 will be considered.

Summaries

The following endpoints will be analysed / summarized:

- ORR and rates for best response categories (CR/PR/SD/PD/not evaluable) by IRC (see Section 9.1)
- DoR (by IRC; Section 10.3)
- DoR (by IRC) by best response (by IRC)
- PFS (by IRC; Section 10.2)
- OS (Section 10.4)

For the endpoints DoR, DoR by best response, PFS, and OS, Kaplan-Meier plots will be generated.

Summaries for the subgroup of primary refractory patients within the subpopulation of DLBCL

- ORR and rates for best response categories (CR/PR/SD/PD/not evaluable) by IRC (see Section 9.1)
- DoR (by IRC; Section 10.3)

For DoR, a Kaplan-Meier graph will be produced.

Forest plots

Forest plots for various endpoints will be generated, displaying the following biomarker and non-biomarker subgroups in one and the same illustration:

- Non-biomarker subgroups:
  - IPI subgroups dichotomized: low and low-intermediate vs. high-intermediate and high
  - Gender: female vs. male
  - Rituximab refractoriness: yes vs. no
  - Refractoriness to last prior treatment line: yes vs. no
  - Primary refractoriness: yes vs. no
  - Prior autologous stem cell transplantation: yes vs. no
  - Number of prior treatment lines dichotomized: 1 vs. ≥2
  - Age dichotomized: ≤70 years vs. >70 years of age
- Biomarker subgroups:
  - NK cell numbers at baseline: <100 vs. ≥100 cells/µl
  - Cell of origin by IHC: GCB vs. non-GCB vs. unknown

The following Forest plots displaying an estimate for the expectation together with 95% confidence intervals will be generated:

- Forest plot for ORR (by IRC)
- Forest plot for CR rate (by IRC)
- 24-month PFS rate (by IRC)
- 24-month DoR rate (by IRC)
- 24-month OS rate

20.9 PFS and DoR analyses applying alternative censoring rules

Analyses for the endpoints PFS and DoR will be performed using alternative censorings rules, i.e., three scenarios that led to censoring as per Table 13 will be considered as a PFS event.

Situation	Outcome as per main analysis (see Table 13)	Censoring date as per main analysis (see Table 13	Outcome as per alternative censoring rules	Date of progression as per alternative censoring rules
Discontinued the	Censored	Date of last	Event	Date of

Situation	Outcome as per main analysis (see Table 13)	Censoring date as per main analysis (see Table 13	Outcome as per alternative censoring rules	Date of progression as per alternative censoring rules
study with no event		adequate tumour assessment		discontinuation of the study drug that was discontinued latest*
Patient received non-study anti-DLBCL treatment before disease progression	Censored	Date of last adequate tumour assessment before start of non-study cancer treatment	Event	Date of initiation of non-study anti-DLBCL treatment
Death or progression after two or more missed visits	Censored	Date of last adequate tumour assessment	Event	Date of the first missed tumour assessment (i.e., the planned date of the assessment that was missed)

*Note: in L-MIND, PFS follow-up stops with treatment discontinuation (a post-treatment PFS follow-up is not conducted in L-MIND).

The censoring strategy for the remaining scenarios described in Table 13 will still apply.

The following analyses applying the alternative censoring rules will be conducted:

20.9.1 Summaries / analyses of PFS

- Based on the FAS and IRC
- Based on the FAS and the investigator tumor response assessment (INV)
- Based on the ITT and IRC

- Based on the ITT and the investigator tumor response assessment (INV)

Kaplan-Meier graphs will be produced for each combination.

20.9.2 Summaries / analyses of DoR

- Based on the FAS and IRC
- Based on the FAS and the investigator tumor response assessment (INV)
- Based on the ITT and IRC
- Based on the ITT and the investigator tumor response assessment (INV)

Kaplan-Meier graphs will be produced for all summary Tables.

20.10 First line treatment category

Summary

The number (%) of patients who received a first-line treatment belonging to the following categories will tabulated:

- Number (%) of patients treated with R-CHOP
- Number (%) of patients treated with R-CHOP equivalent regimens
- Number (%) of patients treated with non-R-CHOP regimens

Based on the 'prior cancer therapies for DLBCL medication' eCRF page, the following strategy will be applied to find out whether a first-line treatment belongs to one of the categories mentioned above. The information on the first line treatment can be reported in the eCRF in several ways:

- One acronym in a single eCRF log line (e.g., "R-CHOP")
- Individual components of a regimen entered in a single eCRF log line (e.g., one log line with entry: "rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone")
- Individual components of a regimen entered across multiple eCRF log lines

The case (small or capital letter) will be ignored during screening. In case a regimen is reported as individual components, the regimen will only be considered as R-CHOP or R-CHOP equivalent if all components belonging to the regimen are present (regardless of any additional drugs that have been co-administered). Multiple search terms for a particular drug will be applied to cover generic and grand names. Both the verbatim terms as entered by the investigator as well as the coded terms will be screened. The following search terms will be used

Treatment category assignment	Search terms used to identify regimens belonging to the treatment category of interest	Search terms used to identify regimen components indicating a particular treatment category (R-CHOP vs. R-CHOP equivalent vs. Other)
R-CHOP	• "R-CHOP" or "RCHOP" or "R CHOP" • "R-mini-CHOP" or "R mini-CHOP" • "R-CHOP14" or "RCHOP14" or "R CHOP14" • "Pola-R-CHP"	("rituximab" or "rtx") and "cyclophos" and "prednis" and "vincris" or "leurocris" or "vcr") **OR:** "CHOP" and ("rituximab" or "rtx") **OR:** "CHP" and ("pola" or "polivy" or "CD79" and ("rtx" or "rituximab") **OR:** "RCHP or R-CHP" and ("pola" or "polivy" or "CD79")
R-CHOP equivalent	• "R-ACVBP" or "RACVBP" or "R ACVBP" • "R-CHOEP" or "RCHOEP" or "R CHOEP" • "R-EPOCH" or "REPOCH" or "R EPOCH" • "R-HyperCVAD" or "R HyperCVAD" • "DA-R-EPOCH" or "R-	("rtx" or "rituximab" or "obinu" or "GA101" or "polivy" or "pola" or "CD79") and "ACVBP" **OR** ("rtx" or "rituximab" or "obinu" or "GA101" or "polivy" or "pola" or "CD79") and (CHOEP or CHOP)

	EPOCH" or "R-DA-EPOCH" or "R DAEPOCH" or "R EPOCH" • "G-CHOP" or "GCHOP" or "G CHOP" • "G-mini-CHOP" or "G mini-CHOP" • "GA101-CHOP" or "GA101 CHOP"	("rtx" or "rituximab" or "obinu" or "GA101" or "polivy" or "pola" or "CD79") and EPOCH

If a patient cannot be classified as having been treated with an R-CHOP or R-CHOP equivalent regimen, the patient will be classified as having received a non-R-CHOP treatment.

Listing

A Listing will be provided showing the first line treatment by the following categories:

- Number (%) of patients treated with R-CHOP
- Number (%) of patients treated with R-CHOP equivalent regimens
- Number (%) of patients treated with non-R-CHOP regimens

The Listing will display the following:

- All components of the first-line regimen as reported verbatim in the eCRF
- The coded terms of the regimen / components
- The start date for all regimen components
- The stop date for all regimen components

20.11 Additional safety-related analyses

20.11.1 Listing of TEAEs summarized in as per Section 16.3.1

Listing for summaries outlined in 16.3.1

20.11.2 Opportunistic infections

TEAEs pertaining to the MedDRA CMQ "Opportunistic Infections" will be summarized by Primary SOC, HLT, PT and NCI-CTCAE Grade regardless of study treatment relationship

(based on the SAF). The PTs used to define the CMQ "Opportunistic Infections" are outlined in the APPENDIX.

A Listing will be provided displaying the TEAEs of the CMQ "Opportunistic infections" (based on the SAF).

20.11.3 TEAEs per patient years of exposure to MOR00208

Summary across both treatment phases:

Based on the SAF, the absolute number of TEAEs (i.e., the actual number of events) by patient years of exposure will be summarized by SOC, PT and NCI-CTCAE Grade. For the summary, patient years of exposure will be defined as follows:

[(end date of the MOR00208) – (start date of MOR00208) + 1] / 365.25.

The TEAEs per patient years of exposure will be reported with three decimal places.

Summary by treatment phase:

Based on the SAF, the number of TEAEs (i.e., the actual number of events) by patient years of exposure to combination treatment vs. MOR00208 monotherapy treatment will be summarized by SOC, PT and NCI-CTCAE Grade. Summaries will be provided separately for the combination treatment (MOR00208 + LEN) and MOR00208 monotherapy phase.

- Exposure to the combination treatment is defined as follows:

  [(Latest date when at least one of either study drug has been discontinued) - (earliest date when the patient is treated with both study drugs) + 1] / 365.25.

  Due to the fact that patients may discontinue LEN before reaching Cycle 12 Day 21 (i.e., the time when LEN is discontinued as per protocol), combination treatment may stop before completing 12 Cycles of LEN.

- Exposure to MOR00208 monotherapy treatment is defined as follows:

  [(Discontinuation date of MOR00208) - (earliest date of MOR00208 infusion after LEN has been permanently discontinued) + 1] / 365.25.

Due to the fact that patients may discontinue LEN before reaching Cycle 12 Day 21 (i.e., the time when LEN is discontinued as per protocol), MOR00208 monotherapy treatment may start before reaching Cycle 13 Day 1.The TEAEs per patient years of exposure will be reported with three decimal places.

20.12 TEAEs leading to study drug modifications

Based on the SAF, TEAEs leading to any Study Drug Modification of MOR00208 or LEN regardless of any study drug relationship by Primary SOC, PT and NCI-CTCAE Grade will be tabulated. TEAEs leading to the following modifications will be reported separately by modification category:

- Any modification (interruption or dose reduction)
- Interruptions
- Dose reductions (only applicable for LEN)

The TEAEs leading to the modifications mentioned above will be reported separately for:

- MOR00208
- LEN
- Any study drug

A Listing will be provided displaying TEAEs leading to study drug modifications (SAF).

20.13 Time to onset of individual TEAEs, duration of individual TEAEs, and cumulative duration of TEAEs per cumulative exposure to tafasitamab

For the categories listed below in this section, the following will be summarized based on the SAF:

- Time to TEAE onset [in days]
- TEAE duration [in days]
- Cumulative duration of TEAEs per cumulative exposure to MOR00208 [in months]
    - The cumulative duration of TEAEs will be reported in months
    - The cumulative exposure to MOR00208 will be calculated in years:
      [(end date of the MOR00208) – (start date of MOR00208) + 1] / 365.25.

The summaries will be provided for the following categories:

- PT Neutropenia (all Grades)
- PT Neutropenia (>= Grade 3)
- PT Thrombocytopenia (all Grades)
- PT Thrombocytopenia (>= Grade 3)

- SOC Infections and infestations (all Grades)
- SOC Infections and infestations (>= Grade 3)
- SMQ "Infective pneumonia" (all Grades)
- SMQ "Infective pneumonia" (>= Grade 3)
- CMQ "Urinary tract infection" (all Grades)
- CMQ "Urinary tract infection" (>= Grade 3)
- CMQ "Sepsis" (all Grades)
- CMQ "Sepsis" (>= Grade 3)
- CMQ "Opportunistic infections" (all Grades)
- CMQ "Opportunistic infections" (>= Grade 3)
- PT Fatigue + PT Asthenia (all Grades)
- All PTs including the verbatim Diarrhoea (all Grades)
- PT Nausea + PT Vomiting (all Grades)
- PT Febrile neutropenia (all Grades)
- SMQ Thromboembolic event (all Grades)
- SMQ Thromboembolic event (>= Grade 3)

21. SAP ADDENDUM 6.0

21.1 Post-L-MIND survival

Summary / analysis of OS

A Kaplan-Meier analysis for OS will be conducted focusing only on the period after the end of treatment of both MOR00208 and LEN. The following four patient subgroups will be defined:

Subgroup	Treatment status	PFS Event / Censoring status (based on INV)	Post-L-MIND anti-DLBCL medication
1	Both MOR00208 and LEN discontinued	PFS Event	Experienced (at least one further treatment)
2	Both MOR00208 and LEN discontinued	PFS Event	No post-L-MIND anti-DLBCL medication at all
3	Both MOR00208 and LEN discontinued	Censored for PFS follow-up	Experienced (at least one further treatment)
4	Both MOR00208 and LEN discontinued	Censored for PFS follow-up	No post-L-MIND anti-DLBCL medication at all

Baseline for the OS analysis is the earliest point in time when both requirements are met:

a) Both study drugs discontinued
b) PFS event / censoring happened

A Kaplan-Meier plot will also be generated displaying the four subgroups.

A Table showing the censorings reasons (ongoing at data cut-off, lost to follow-up, ICF withdrawal etc.) for each subgroup will be produced.

A Listing will be provided showing all post-L-MIND anti-DLBCL medications by treatment line, survival status at the data cut-off date, and date of death.

Swimmers plot

Based on the FAS, four swimmers plots will be generated for the four patient subgroups above. The following will be displayed:

- Bar length: [(Date of death or date censoring of OS follow-up) – (Date of end of treatment) + 1].

- An arrow head at the end of the bar will indicate if OS follow-up is still ongoing at data cut-off, or the point in time when a patient was censored for OS follow-up. A blunt end will indicate that the patient has died.
- Symbols will be used to indicate the initiation every new treatment line after the treatment with MOR00208 + LEN.

21.2 PD-related vs. non-PD-related deaths

The categorization of deaths as outlined in Section 10.7.3.1.6 will be extended. Deaths will be categorized as follows using reasons of death as reported in the eCRF by the investigator:

Reason of death as per investigator	Death category
CONGESTIVE HEART FAILURE	non-PD-related
SUBJECT DEVELOPED SECONDARY MDS/AML AND WAS GETTING TREATMENT. HOWEVER, SUBJECT WAS UNABLE TO GET ASCT. SUBJECT DIED OF COMPLICATIONS OF AML - MULTI SYSTEM ORGAN FAILURE - SECONDARY TO PAST CHEMO.	non-PD-related
AUTOPSY REVEALED CAUSE OF DEATH AS PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY	non-PD-related
INTRACEREBRAL HAEMORRHAGE	non-PD-related
LUNG EDEMA DUE TO CARDIAC DEFICIT	non-PD-related
PNEUMONIA	non-PD-related
RESPIRATORY FAILURE	non-PD-related
STROKE	non-PD-related
SUDDEN DEATH	non-PD-related
END STAGE MARROW FAILURE	non-PD-related
UNKNOWN	Unknown
DIFFUSE LARGE B CELL LYMPHOMA	PD-related
DISEASE PROGRESSION	PD-related
DLBCL DISEASE PROGRESSION	PD-related
IMMEDIATE CAUSE OF DEATH: PARALYTIC ILEUS, DUE TO ABDOMINAL LYMPHOMA PROGRESS	PD-related
LYMPHOMA	PD-related

MULTIPLE RELAPSING AND REFRACTORY DLBCL	PD-related
PROGRESIVE DISEASE	PD-related
PROGRESSION	PD-related
PROGRESSION DESEASE	PD-related
PROGRESSION DISEASE	PD-related
PROGRESSION OF DISEASE	PD-related
PROGRESSION OF THE DISEASE	PD-related
PROGRESSIVE DESEASE	PD-related
PROGRESSIVE DISEASE	PD-related
RELAPSE	PD-related
STUDY DISEASE	PD-related

21.3 Discontinuation of LEN treatment upon completion of Cycle 12

The identification of patients who discontinued LEN as per protocol is described in Section 8.2. The algorithm used to identify patients who completed LEN treatment after 12 Cycles as per protocol will be extended. The following terms/phrases will be used to find patients who discontinued after 12 Cycles:

OTHER: CYCLE COMPLETED - LAST DOSE OF LENALIDOMIDE ON AUG, 20TH 2017

OTHER: AS PER PROTOCOL

OTHER: PER PROTOCOL

OTHER: TREATMENT COMPLETED PER PROTOCOL

OTHER: ACCORDING TO PROTOCOL

OTHER: IT WAS STOPPED AFTER 12 CYCLES PER PROTOCOL

OTHER: COMPLETED

OTHER: LEN TREATMENT COMPLETED

OTHER: LENALIDOMIDE TERMINATED PER PROTOCOLE

OTHER: PATIENT FINISHED THE TREATMENT WITH LENALIDOMIDE BUT IS STILL ONGOING WITH MOR00208

OTHER: PLANNED BY STUDY

OTHER: THIS STUDY DRUG WAS FOR ONLY THE FIRST 12 CYCLES AND WAS COMPLETED IN SEPT 2018

OTHER: TREATMENT COMPLETED

OTHER: TREATMENT COMPLETED AS PER PROTOCOL

OTHER: TREATMENT COMPLETION

OTHER: TREATMENT PHASE (LEN)

22. SAP ADDENDUM 7.0

22.1 COVID-19 related missed visits and assessments

The following will be tabulated for the SAF:

- Number of visits completely missed due to the SARS pandemic
- Number of visits with at least one missed assessment due to the SARS pandemic
- Number of missed assessments (for partially completed visits)
- Number of missed assessments by category

A Listing will be provided showing missed visits or assessments.

23. SAP ADDENDUM 8.0

23.1.1 TEAEs per patient years of exposure to MOR00208 and LEN

Summary across both treatment phases:

Based on the SAF, the absolute number of TEAEs (i.e., the actual number of events) by patient years of exposure will be summarized by SOC, PT and NCI-CTCAE Grade. For the summary, patient years of exposure will be defined as follows:

Exposure to the treatment phase is defined as per section 8.9.2 and all TEAEs are counted.

The TEAEs per patient years of exposure will be reported with two decimal places.

Summary by treatment phase:

Based on the SAF, the number of TEAEs (i.e., the actual number of events) by patient years of exposure to combination treatment vs. MOR00208 monotherapy treatment will be summarized by SOC, PT and NCI-CTCAE Grade. Summaries will be provided separately for the combination treatment (MOR00208 + LEN) and MOR00208 monotherapy phase.

- Exposure to the combination treatment is defined as per section 8.9.2:

  However, for the counts of TEAE the period considered is the earliest date when the patient is treated with both study drugs till the latest date when LEN has been discontinued.

  Because patients may discontinue LEN before reaching Cycle 12 Day 21 (i.e., the time when LEN is discontinued as per protocol), combination treatment may stop before completing 12 Cycles of LEN. The definition of TEAE still applies when AE occurs beyond the discontinuation of LEN for the next 30 day follow up period. For patients who do not continue to monotherapy, any TEAE beyond 30 day follow up and related to either of the drugs will be considered in the combined therapy only. For the others who continue on to monotherapy the TEAEs beyond 30-day period are included in the monotherapy phase.

- Exposure to MOR00208 monotherapy treatment is defined as per section 8.9.2:

  However, for the counts of TEAE the period considered is 1 day after LEN has been permanently discontinued till the discontinuation date of MOR00208.

  Because patients may discontinue LEN before reaching Cycle 12 Day 21 (i.e., the time when LEN is discontinued as per protocol) or they have not received any dose of LEN, MOR00208 monotherapy treatment may start before reaching end of Cycle 12. The definition of TEAE still applies when AE occurs beyond the discontinuation of MOR00208 for the next 30 day follow up period. Any TEAE which still occurs beyond the 30 day follow up period will only be included if the AE is related to MOR00208.

The TEAEs per patient years of exposure will be reported with two decimal places. Additionally, there would be an overlap of the 30 days at the end of combined therapy and monotherapy and hence some of the TEAEs will be included in both treatment phases to not have an underestimation of the TEAE rates. The rates of TEAE by treatment phase is overestimated in this summary outcome compared to the true estimate.

23.1.2 Forest plots

Forest plots for various endpoints will be generated, displaying the following biomarker and non-biomarker subgroups in one and the same illustration:

- Non-biomarker subgroups:
  - IPI subgroups dichotomized: low and low-intermediate vs. high-intermediate and high
  - Gender: female vs. male
  - Rituximab refractoriness: yes vs. no
  - Refractoriness to last prior treatment line: yes vs. no
  - Primary refractoriness: yes vs. no
  - Prior autologous stem cell transplantation: yes vs. no
  - Number of prior treatment lines dichotomized: 1 vs. ≥2
  - Age dichotomized: ≤70 years vs. >70 years of age
- Biomarker subgroups:
  - NK cell numbers at baseline: <100 vs. ≥100 cells/µl
  - Cell of origin by IHC: GCB vs. non-GCB vs. unknown

The following Forest plots displaying an estimate for the expectation together with 95% confidence intervals will be generated:

- Forest plot for ORR (by IRC)
- Forest plot for CR rate (by IRC)
- 48-month PFS rate (by IRC)

- 48-month DoR rate (by IRC)
- 48-month OS rate
- Forest plot for ORR (by IRC for Patients with Centrally Confirmed DLBCL at Baseline)
- Forest plot for CR rate (by IRC for Patients with Centrally Confirmed DLBCL at Baseline)
- 48-month PFS rate (by IRC for Patients with Centrally Confirmed DLBCL at Baseline)
- 48-month DoR rate (by IRC for Patients with Centrally Confirmed DLBCL at Baseline)
- 48-month OS rate (for Patients with Centrally Confirmed DLBCL at Baseline)

APPENDIX: LIST OF CUSTOMIZED MEDDRA QUERIES

Sepsis (CMQ)	PT	PTCD
	Escherichia sepsis	10015296
	Meningococcal sepsis	10027280
	Postpartum sepsis	10036422
	Sepsis	10040047
	Sepsis neonatal	10040049
	Sepsis pasteurella	10040051
	Umbilical sepsis	10045470
	Urosepsis	10048709
	Streptococcal sepsis	10048960
	Neutropenic sepsis	10049151
	Pulmonary sepsis	10051739
	Candida sepsis	10053166
	Group B streptococcus neonatal sepsis	10053588
	Bacterial sepsis	10053840
	Sepsis syndrome	10053879
	Pneumococcal sepsis	10054047
	Stenotrophomonas sepsis	10054137
	Klebsiella sepsis	10054160
	Micrococcal sepsis	10054162
	Brucella sepsis	10054210
	Citrobacter sepsis	10054213
	Enterobacter sepsis	10054219
	Enterococcal sepsis	10054221
	Helicobacter sepsis	10054264

	Staphylococcal sepsis	10056430
	Corynebacterium sepsis	10057767
	Biliary sepsis	10057847
	Abdominal sepsis	10058040
	Wound sepsis	10058041
	Fungal sepsis	10058872
	Anthrax sepsis	10058873
	Haemophilus sepsis	10058875
	Herpes sepsis	10058876
	Pseudomonal sepsis	10058877
	Salmonella sepsis	10058878
	Serratia sepsis	10058879
	Plague sepsis	10058889
	Pseudallescheria sepsis	10058973
	Pelvic sepsis	10059070
	Listeria sepsis	10063085
	Nocardia sepsis	10064952
	Pseudosepsis	10064991
	Post procedural sepsis	10066593
	Burkholderia cepacia complex sepsis	10069684
	Device related sepsis	10069802
	Campylobacter sepsis	10070681
	Viral sepsis	10071362
	Yersinia sepsis	10072902
	Herpes simplex sepsis	10074246
	Shigella sepsis	10074481
	Intestinal sepsis	10075622
	Clostridial sepsis	10078496

	Erysipelothrix sepsis	10080432
	Actinomycotic sepsis	10080434

Urinary Tract Infections (CMQ)	**PT**	**PTCD**
	Urinary tract infection	10046571
	Urinary tract infection enterococcal	10046572
	Urinary tract infection neonatal	10046573
	Urinary tract infection fungal	10049059
	Cytomegalovirus urinary tract infection	10051350
	Escherichia urinary tract infection	10052238
	Urinary tract infection bacterial	10054088
	Genitourinary tract infection	10061182
	Urinary tract infection pseudomonal	10062279
	Urinary tract infection staphylococcal	10062280
	Urinary tract infection viral	10064825
	Prophylaxis urinary tract infection	10066700
	Streptococcal urinary tract infection	10070300
	HLT	**HLTCD**
	Urinary tract infections	10046577

Opportunistic infections (CMQ)	PT	PTCD
	Gastroenteritis salmonella	10017914
	Gastroenteritis shigella	10017915
	Shigella infection	10054178
	Gastroenteritis Escherichia coli	10017903
	Clostridium colitis	10058305
	Clostridium difficile colitis	10009657
	Clostridium difficile infection	10054236
	Bartonellosis	10004145
	Anal candidiasis	10002140
	Balanitis candida	10004074
	Proctitis monilial	10036781
	Candida nappy rash	10007135
	Bladder candidiasis	10058523
	Candida osteomyelitis	10064699
	Endocarditis candida	10014669
	Gastrointestinal candidiasis	10017938
	Genital candidiasis	10018143
	Meningitis candida	10027205
	Mucocutaneous candidiasis	10028080

	Nail candida	10028688
	Neonatal candida infection	10028924
	Oesophageal candidiasis	10030154
	Oral candidiasis	10030963
	Otitis externa candida	10033076
	Respiratory moniliasis	10038705
	Systemic candida	10042938
	Vulvovaginal candidiasis	10047784
	Hepatic candidiasis	10049653
	Nasal candidiasis	10050345
	Oropharyngeal candidiasis	10050346
	Hepatosplenic candidiasis	10051590
	Splenic candidiasis	10051725
	Candida pneumonia	10053158
	Candida sepsis	10053166
	Skin candida	10054152
	Peritoneal candidiasis	10056562
	Stoma site candida	10059052
	Candida endophthalmitis	10059449
	Candidiasis of trachea	10064459
	Candida retinitis	10068612
	Candida cervicitis	10071209
	Candida infection	10074170
	Cerebral candidiasis	10078126
	Denture stomatitis	10080528
	Candida urethritis	10081262
	Urinary tract candidiasis	10083162
	American trypanosomiasis	10001935

	Coccidioidomycosis	10009825
	Disseminated cryptococcosis	10013439
	Neurocryptococcosis	10068368
	Osseous cryptococcosis	10080483
	Cryptosporidiosis infection	10011502
	Congenital cytomegalovirus infection	10010430
	Cytomegalovirus hepatitis	10011830
	Cytomegalovirus infection	10011831
	Cytomegalovirus mononucleosis	10011834
	Encephalitis cytomegalovirus	10014586
	Pneumonia cytomegaloviral	10035676
	Cytomegalovirus chorioretinitis	10048843
	Cytomegalovirus colitis	10048983
	Cytomegalovirus duodenitis	10049014
	Cytomegalovirus enterocolitis	10049015
	Cytomegalovirus gastritis	10049016
	Cytomegalovirus oesophagitis	10049018
	Cytomegalovirus enteritis	10049074
	Disseminated cytomegaloviral infection	10049075
	Cytomegalovirus pancreatitis	10049566
	Cytomegalovirus gastroenteritis	10051349
	Cytomegalovirus urinary tract infection	10051350
	Cytomegalovirus gastrointestinal infection	10052817
	Cytomegalovirus myocarditis	10056261
	Cytomegalovirus syndrome	10056262
	Cytomegalovirus pericarditis	10056721

	Cytomegalovirus viraemia	10058854
	Cytomegalovirus mucocutaneous ulcer	10065036
	Cytomegalovirus myelomeningoradiculitis	10065621
	Cytomegalovirus gastrointestinal ulcer	10075619
	Cytomegalovirus nephritis	10079095
	Congenital hepatitis B infection	10010496
	Hepatitis B	10019731
	Hepatitis B reactivation	10058827
	Acute hepatitis B	10059193
	Asymptomatic viral hepatitis	10063838
	Perinatal HBV infection	10075233
	Gianotti-Crosti syndrome	10053842
	Hepatitis C	10019744
	Hepatitis non-A non-B	10019786
	Congenital varicella infection	10010668
	Eczema herpeticum	10014197
	Exanthema subitum	10015586
	Genital herpes	10018150
	Herpes simplex	10019948
	Congenital herpes simplex infection	10019949
	Herpes simplex encephalitis	10019953
	Herpes simplex meningitis	10019956
	Herpes simplex otitis externa	10019959
	Herpes simplex visceral	10019963
	Herpes virus infection	10019973
	Herpes zoster	10019974

	Human herpesvirus 6 infection	10020431
	Herpes simplex cervicitis	10077449
	Meningitis herpes	10027242
	Meningoencephalitis herpetic	10027285
	Ophthalmic herpes zoster	10030865
	Herpes simplex virus conjunctivitis neonatal	10049458
	Varicella keratitis	10077496
	Pneumonia herpes viral	10035703
	Herpes zoster oticus	10063491
	Varicella	10046980
	Gastritis herpes	10051784
	Herpes simplex gastritis	10074240
	Varicella zoster gastritis	10074241
	Herpes simplex colitis	10074239
	Herpes simplex oesophagitis	10074242
	Varicella zoster oesophagitis	10074243
	Colitis herpes	10051782
	Herpes oesophagitis	10052330
	Meningoencephalitis herpes simplex neonatal	10053586
	Neonatal mucocutaneous herpes simplex	10053587
	Haemorrhagic varicella syndrome	10078873
	Herpes simplex hepatitis	10067389
	Herpes sepsis	10058876
	Herpes zoster infection neurological	10061208
	Herpes ophthalmic	10062004

	Herpes dermatitis	10062639
	Varicella post vaccine	10063522
	Human herpesvirus 7 infection	10063571
	Herpes zoster disseminated	10065038
	Herpes simplex pneumonia	10065046
	Necrotising herpetic retinopathy	10065119
	Human herpesvirus 8 infection	10066435
	Herpes pharyngitis	10066888
	Oral herpes	10067152
	Genital herpes zoster	10072210
	Genital herpes simplex	10073931
	Ophthalmic herpes simplex	10073938
	Herpes simplex pharyngitis	10074244
	Herpes zoster pharyngitis	10074245
	Herpes simplex sepsis	10074246
	Herpes simplex meningoencephalitis	10074247
	Herpes zoster meningoencephalitis	10074248
	Meningomyelitis herpes	10074249
	Herpes simplex meningomyelitis	10074250
	Herpes zoster meningomyelitis	10074251
	Herpes simplex necrotising retinopathy	10074252
	Herpes zoster necrotising retinopathy	10074253
	Varicella zoster pneumonia	10074254
	Herpes zoster meningitis	10074259
	Herpes zoster cutaneous disseminated	10074297

	Nasal herpes	10074936
	Varicella zoster virus infection	10075611
	Disseminated varicella zoster vaccine virus infection	10076667
	Lower respiratory tract herpes infection	10077390
	Herpes zoster meningoradiculitis	10079327
	Herpes simplex viraemia	10080365
	Human herpesvirus 6 encephalitis	10081897
	Proctitis herpes	10036780
	Acute pulmonary histoplasmosis	10001027
	Chronic pulmonary histoplasmosis	10009115
	Endocarditis histoplasma	10014676
	Histoplasmosis	10020141
	Histoplasmosis disseminated	10020144
	Meningitis histoplasma	10027243
	Pericarditis histoplasma	10034489
	Retinitis histoplasma	10038912
	Histoplasmosis cutaneous	10049142
	Presumed ocular histoplasmosis syndrome	10063664
	Anogenital warts	10059313
	Anorectal human papilloma virus infection	10073941
	Laryngeal papilloma	10023849
	Cervicitis human papilloma virus	10051800
	Cervix warts	10063815
	Penile wart	10034325

	Respiratory papilloma	10038707
	Skin papilloma	10040907
	Urethral papilloma	10046462
	Vulvovaginal warts	10047793
	Epidermodysplasia verruciformis	10052339
	Buschke-Lowenstein's tumour	10059427
	Blepharal papilloma	10057885
	Vulvovaginal human papilloma virus infection	10066416
	Papilloma viral infection	10061331
	Oral papilloma	10068322
	Congenital condyloma	10066944
	Tracheal papilloma	10067203
	Sinonasal papilloma	10071665
	Focal epithelial hyperplasia	10076576
	Viral acanthoma	10077282
	Cutaneous leishmaniasis	10011668
	Leishmaniasis	10024198
	Visceral leishmaniasis	10047505
	Mucocutaneous leishmaniasis	10054165
	Congenital malaria	10010538
	Malaria	10025487
	Plasmodium falciparum infection	10035500
	Plasmodium malariae infection	10035501
	Plasmodium ovale infection	10035502
	Plasmodium vivax infection	10035503
	Plasmodium knowlesi infection	10079602
	Cerebral malaria	10063094
	Malarial myocarditis	10054123

	Microsporidia infection	10053982
	Mycobacterium avium complex infection	10058806
	Pneumonia legionella	10035718
	Pneumonia chlamydial	10035673
	Pneumocystis jirovecii pneumonia	10073755
	Pneumonia pseudomonal	10035731
	Pneumonia fungal	10061354
	Progressive multifocal leukoencephalopathy	10036807
	JC virus infection	10023163
	Adenopathy syphilitic	10001242
	Alopecia syphilitic	10001765
	Aortic aneurysm syphilitic	10002887
	Aortitis syphilitic	10002923
	Cardiovascular syphilis	10007658
	Cerebral aneurysm ruptured syphilitic	10008076
	Congenital syphilis	10010641
	Congenital syphilitic encephalitis	10010643
	Congenital syphilitic meningitis	10010644
	Endocarditis syphilitic	10014685
	Eye infection syphilitic	10015938
	Hepatitis syphilitic	10019794
	Myocarditis syphilitic	10028616
	Neurosyphilis	10029339
	Pericarditis syphilitic	10034497
	Peritonitis syphilitic	10034684
	Pinta	10035068

	Pulmonary syphilis	10037434
	Renal syphilis	10038530
	Syphilis anal	10042877
	Syphilis genital	10042880
	Syphilis musculoskeletal	10042881
	Syphilitic endocarditis of heart valve	10042907
	Yaws	10048234
	Yaws of bone	10048235
	Yaws of skin	10048236
	Endemic syphilis	10053025
	Congenital syphilitic osteochondritis	10054002
	Malignant syphilis	10054118
	Tertiary syphilis	10056873
	Secondary syphilis	10056883
	Primary syphilis	10056884
	Spirochaetal infection	10061370
	Syphilis	10062120
	Condyloma latum	10062317
	Latent syphilis	10070738
	Brachyspira infection	10077447
	Penicillium infection	10078580
	Cerebral toxoplasmosis	10057854