REDACTED PROTOCOL

CLINICAL STUDY PROTOCOL

Protocol Number: MOR208C205

Protocol Title: A Phase II, Two-Cohort, Open-Label, Multicenter Study to Evaluate the Safety and Preliminary Efficacy of MOR00208 Combined with Idelalisib or Venetoclax in Patients with Relapsed or Refractory CLL/SLL Previously Treated with Bruton's Tyrosine Kinase (BTK) Inhibitor

IND Number:	114,856
EudraCT Number:	2015-002915-14
Phase of Development:	II
Sponsor:	MorphoSys AG
Sponsor's Address:	Semmelweisstr. 7 D-82152 Planegg GERMANY
Date of Protocol:	10 January 2019
ClinicalTrials.gov Identifier:	NCT02639910

SIGNATURES

CTP Amendment No. 7, Version 11.0, dated 10 January 2019

Approved/Authorized By:

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

[redacted]
MorphoSys AG

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

[redacted]
MorphoSys AG

Country Coordinating Investigator's Signature (in countries where required)

I have read the entire clinical study protocol. I agree that this protocol version contains all the information required to conduct this study.

Investigator:

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

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

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

Signature of Principal Investigator

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

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

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

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Medical Monitor (24/7 Medical Coverage)	**Globally*:** Telephone: +[redacted] * This is a chargeable telephone number allowing a global reach from both landlines and mobile phones) [redacted] On this internet page a list of country-specific toll-free telephone numbers is provided. Note that not all countries globally have access to toll-free numbers as indicated on the "24/7 Medical Help desk" index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.

1 TABLE OF CONTENTS

1.1 Overall of Contents

1.2 List of Tables

(Excluding those in the appendix)

1.3 List of Figures

2 PROTOCOL SYNOPSIS

Title of Study	A Phase II, Two-Cohort, Open-Label, Multicenter Study to Evaluate the Safety and Preliminary Efficacy of MOR00208 Combined with Idelalisib or Venetoclax in Patients with Relapsed or Refractory CLL/SLL Previously Treated with Bruton's Tyrosine Kinase (BTK) Inhibitor
Investigational Drugs	MOR00208 is an Fc-enhanced, humanized, monoclonal antibody targeting the B cell surface antigen (CD19) Idelalisib (Zydelig®) is a small molecule inhibitor of phosphoinositide-3-kinase (PI3K) delta, which is hyperactive in B cell malignancies Venetoclax (Venclexta® in the US and Venclyxto® in the EU) is a small molecule inhibitor of the B-cell lymphoma 2 (BCL-2) protein, which is over-expressed in B cell malignancies
Protocol Number	MOR208C205
IND Number	114,856
EudraCT Number	2015-002915-14
Sponsor and CRO	**Sponsor:** MorphoSys AG Semmelweisstr. 7 82152 Planegg Germany **Clinical Research Organization (CRO):** [redacted]
Study Phase	Phase II
Investigators/Study Sites	Approx. 22 sites
Planned Sample Size	Approx. 12 patients per cohort
Background/Study Purpose and Rationale	Chronic lymphocytic leukemia (CLL) is the most common hematological malignancy. The median age at diagnosis is 72 years (Eichhorst et al., 2011). Treatment is tailored to the disease and patient characteristics, taking comorbidities, age and prognostic factors into considerations which results in substantial variability of progression-free survival (PFS) and overall survival ranging from several months to >10 years. Several combination regimens such as FCR (fludarabine, cyclophosphamide, rituximab) are currently available for the first-line treatment of CLL/small lymphocytic lymphoma (SLL) patients. Following their approval in recent years, novel agents (ibrutinib, idelalisib, obinutuzumab and venetoclax) provide further effective therapeutic options for CLL/SLL patients. Owing to its efficacy and

	safety profile, the BTK inhibitor ibrutinib has developed into an important treatment option for treatment naïve and relapsed/refractory patients. Despite the prolonged median PFS under treatment with ibrutinib it is expected that the majority of CLL patients will relapse. Patients with relapsed and refractory CLL (R/R CLL) who received ibrutinib and had to discontinue treatment due to progression or intolerance have a particularly dismal prognosis. According to Jain et al. (2015), the median survival for all the patients was 3.1 months after discontinuing ibrutinib and did not differ significantly between transformed and untransformed patients with CLL. In a recent publication, Maddocks et al. (2015) report a median survival following CLL progression of 17.6 months and show that the disease tends to progress quickly in patients, especially when the drug therapy is stopped. Most recently published very limited retrospective data showed that alternate kinase inhibitor (KI) choice, including idelalisib treatment after ibrutinib discontinuation, achieved an overall response rate (ORR) of 50% without any complete responses (CR) (Mato et al., 2015). More accurate data on ORR are available with venetoclax monotherapy from prospective study in CLL patients relapsed or refractory to ibrutinib therapy showing an ORR of 60.5% (Jones et al., 2015). Importantly, patients in whom ibrutinib (or other BTK inhibitor) failed had frequently been pretreated with anti-CD20 antibodies in previous lines of therapy and are considered largely refractory to available anti-CD20 treatment approach. Overall, the lack of effective treatment for this patient population constitutes an urgent unmet medical need. MOR00208 is an Fc-optimized, humanized monoclonal antibody targeting the B cell antigen CD19 and has been shown to significantly enhance *in vitro* antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cell mediated phagocytosis (ADCP) and direct cytotoxic effects (apoptosis) on the tumor cells (Horton et al., 2008). MOR00208 has significant single-agent activity in preclinical model and displays synergy with idelalisib (a small molecule inhibitor of PI3K delta) and with venetoclax (a small molecule inhibitor of BCL-2) which are approved for CLL treatment (MorphoSys data on file). A phase I trial demonstrated safety and preliminary efficacy of MOR00208 in patients with relapsed or refractory CLL/SLL (Woyach et al., 2014a). In all 27 patients enrolled into this trial, the drug was generally well tolerated, infusion reactions of grade 1 and 2 being the most common toxicities; the maximum tolerated dose (MTD) was not reached. Efficacy in that phase I trial was encouraging, with approximately 67% of patients achieving a partial response (PR) by clinical criteria and 30% according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria.

	MOR00208 has demonstrated clinically significant single-agent efficacy in clinical studies in a variety of B cell non-Hodgkin's lymphomas (NHLs) with durable overall response rates (ORR) of up to 27% (Jurczak et al., 2015). Idelalisib and MOR00208 have a safety profile which allows for the treatment of frail and elderly patients who constitute the main population of R/R CLL patients. Based on the current clinical and preclinical data the combination of MOR00208 with idelalisib or venetoclax are therefore investigated in R/R CLL or R/R SLL patients pretreated with a BTK inhibitor (e.g., ibrutinib).
Study Objectives (Key Primary and Secondary)	**PRIMARY OBJECTIVE**: To determine the safety of MOR00208 combined with idelalisib or venetoclax **SECONDARY OBJECTIVES:** 1. To determine the quality of the response 2. To assess the potential immunogenicity of MOR00208 3. To assess the pharmacokinetic (PK) profile of MOR00208 **EXPLORATORY OBJECTIVES:** • To assess minimal residual disease (MRD) in patients achieving a complete or partial response • To explore putative predictive biomarkers • To determine and correlate prognostic factors with efficacy parameters
Study Endpoints (Key Primary and Secondary)	**PRIMARY ENDPOINT:** Incidence and severity of adverse events (AEs) **SECONDARY ENDPOINTS:** 1. Overall response rate (ORR): defined for Cohort A as percentage of patients achieving a complete response (CR), a partial response (PR) or a partial response with lymphocytosis (PRL), and for Cohort B as percentage of patients achieving a CR or a PR 2. Anti-MOR00208 antibody formation 3. Pharmacokinetic analysis for MOR00208 **EXPLORATORY ENDPOINTS:** • Proportion of patients with MRD-negativity • Absolute and percentage change from baseline in measurements for B-, T- and NK cell populations • Analysis of exploratory and diagnostic biomarkers from blood (e.g., CD19 expression, BTK and phospholipase C (PLC)γ2 mutational status, CD16 expression on NK cells, antibody dependent cell mediated cytotoxicity (ADCC) capacity, cytogenetics and mutational analysis).

Design and Methodology/Patient Population	This is a two-cohort, multicenter, open-label study of MOR00208 combined with idelalisib or venetoclax in adult patients with R/R CLL or R/R SLL pretreated with a BTK inhibitor (e.g., ibrutinib) as single agent or as part of combination therapy. Patients will be treated in this trial in either Cohort A (MOR00208 and idelalisib) or Cohort B (MOR00208 and venetoclax) for up to 24 cycles at maximum or until progression of disease, withdrawal of consent, unacceptable toxicity, death or patient being lost to follow-up, whichever occurs first. The study will include a safety run-in phase for each cohort enrolling 10- approximately 12 patients per combination treatment. The safety run-in phase will be concluded with an evaluation of the safety data of all treated patients once 10 patients completed at least one cycle of treatment in Cohort A or at least 5 weeks of combination treatment in Cohort B. This evaluation will be done by an Independent Data Monitoring Committee (IDMC). In Cohort A there will be an additional safety evaluation of the safety data from the first 3 patients, who completed at least one cycle of treatment. The first 3 patients in Cohort A will be dosed sequentially, at least 48 hours apart. The next 7-9 patients may be dosed in parallel after the safety evaluation and a positive recommendation from the IDMC. In Cohort B all 10-12 patients will be dosed sequentially, at least one week apart. Patients completing the main study will be invited to participate in an optional biological marker sub-study as described in detail in Section 15.13 Appendix M.
Key Inclusion/Exclusion Criteria	**INCLUSION CRITERIA:** **Diagnosis/Trial Population** 1. Age ≥18 years 2. Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL): a) history of diagnosis of CLL or SLL that meets IWCLL diagnostic criteria (Hallek et al., 2008) b) histologically confirmed diagnosis of SLL by lymph node biopsy and documented within medical records c) indication for treatment as defined by the IWCLL guidelines (Hallek et al., 2008) 3. Patients must have both of the following: a) relapsed or refractory disease as defined in the protocol while receiving a BTK inhibitor (e.g., ibrutinib) therapy or intolerance of such therapy b) single-agent or combination therapy with a BTK inhibitor for at least one month must be the patient's most recent prior anticancer therapy 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 5. Patients with a past medical history of autologous or allogeneic stem cell transplantation must exhibit full hematological recovery without any evidence or ongoing

	treatment of active graft versus host disease before enrolment into the study. **Laboratory Values** 6. Patients must meet the following laboratory criteria at screening: • Adequate bone marrow function as follows: a) absolute neutrophil count (ANC) ≥1.0 × 10^9/L b) platelet count ≥30 × 10^9/L in the absence of clinically significant evidence of bleeding c) **Cohort B only:** hemoglobin ≥ 8.0 g/dL • Adequate hepatic and renal function as follows: d) total serum bilirubin ≤1.5 × upper limit of normal (ULN) or ≤3 × ULN in cases of documented liver involvement by CLL. (For patients with Gilbert's disease, serum bilirubin up to ≤3 x ULN is allowed provided normal direct bilirubin.) e) alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN or <3 × ULN in cases of documented liver involvement by CLL f) serum creatinine clearance calculated using a standard Cockcroft-Gault formula (Cockroft & Gault, 1976) must be: • **Cohort A only:** ≥30 mL/min • **Cohort B only:** ≥50 mL/min **Other Inclusion Criteria** 7. Females of childbearing potential (FCBP, as defined in the protocol) must: a) not be pregnant as confirmed by a negative serum pregnancy test at screening and a urine pregnancy test prior to starting study therapy b) refrain from breastfeeding and donating blood or oocytes during the course of the study and for 3 months after the last dose of study medication (Note: All females are prohibited to donate blood within the before mentioned time frame) c) agree to ongoing pregnancy testing during the course of the study, and until 3 months after study therapy has ended. This applies even if the patient practices complete and continued sexual abstinence d) commit to continued abstinence from heterosexual intercourse if it is in accordance with her lifestyle or agree to use and be able to comply with the use of highly effective contraception without interruption during the study and for 3 months after the last dose of study medication e) FCBP using hormonal contraceptives should add a barrier method as a second form of contraception since it is

currently unknown whether idelalisib or venetoclax may affect the effectiveness of hormonal contraceptives

8. Males must use a highly effective method of contraception without interruption, if the patient is sexually active with a FCBP, and refrain from donating blood or sperm during the study participation and for 3 months after the last dose of study medication
9. In the opinion of the Investigator the patients must:
   a) be able to understand, give written informed consent to, and comply with all study-related procedures, medication use, and evaluations
   b) not have a history of noncompliance in relation to medical regimens or be considered potentially unreliable and/or uncooperative

EXCLUSION CRITERIA:

Diagnosis

1. Patients who have:
   a) non-Hodgkin's lymphomas other than CLL/SLL
   b) transformed CLL/SLL or Richter's syndrome as defined by the IWCLL guidelines (Hallek et al., 2008)
   c) active and uncontrolled autoimmune cytopenia

Previous and Current Treatment

2. Patients who have received treatment with a BTK inhibitor (e.g., ibrutinib) within 5 days prior to Day 1 dosing.
3. Patients who have, within 14 days prior to Day 1 dosing:
   a) not discontinued CD20-targeted therapy, chemotherapy, radiotherapy, investigational anticancer therapy or other lymphoma-specific therapy
   b) systemic corticosteroids in doses greater than prednisone equivalent to 20 mg/day (Exception: Patients with signs of rapidly progressing disease per discussion between the Investigator and sponsor's medical monitor)
   c) received live vaccines. (Note: Vaccinations against influenza with inactivated virus or vaccination for pneumococcal diseases are allowed.)
4. Patients who:
   a) have, in the opinion of the Investigator, not recovered sufficiently from the adverse toxic effects of prior therapies
   b) have a history of previous severe allergic reactions to prior monoclonal antibody therapy, and/or hypersensitivity to the active substances or to any of the inactive ingredients / excipients contained in the study drug formulations (for details see FDA Prescribing Information or EMA SmPC of Zydelig®(**Cohort A only**) or Venclexta® & Venclyxto® (**Cohort B only**))
   c) concurrently use other anticancer or experimental treatments

	d) were previously treated with • CD19-targeted therapy (applicable for Cohort A and B) • **Cohort A only:** a PI3K inhibitor treatment (e.g., idelalisib, duvelisib) • **Cohort B only:** a BCL-2 inhibitor treatment (e.g., venetoclax) e) **Cohort B only:** has a known allergy to both xanthine oxidase inhibitors and rasburicase f) **Cohort B only:** has received strong or moderate CYP3A inhibitors or inducers within 7 days, or has consumed grapefruit, grapefruit products, Seville oranges or star fruit within 3 days prior to the first dose of venetoclax (see for details in the protocol) **Patient's Medical History** 5. Prior history of malignancies other than CLL, unless the patient has been free of the disease for ≥5 years prior to screening. Exceptions to the ≥5 year time limit include a history of the following: a) basal cell carcinoma of the skin b) squamous cell carcinoma of the skin c) carcinoma *in situ* of the cervix d) carcinoma *in situ* of the breast e) carcinoma *in situ* of the bladder f) incidental histological finding of prostate cancer (Tumor/Nodes/Metastasis [TNM] stage of T1a or T1b) 6. Patients with myelodysplastic syndrome 7. Patients with systemic diseases (e.g., cardiovascular, renal, hepatic) that would in the Investigator's opinion preclude participation in the study or compromise the patient's ability to give informed consent 8. Patients with diagnosis of myocardial infarction within 6 months prior to enrolment, New York Heart Association (NYHA) class II or higher congestive heart failure, uncontrolled angina pectoris, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemia or significant conduction system abnormalities, in the opinion of the Investigator. (Note: Patients with stable, asymptomatic atrial fibrillation are allowed in the study provided they do not meet the other cardiac exclusion criteria) 9. Patients who: a) suffered significant traumatic injury or underwent major surgery within 14 days prior to treatment start b) have not recovered from sequelae of traumatic injury or surgical operations until Day 1 dosing 10. Patients with central nervous system (CNS) involvement or impairment:

	a) CNS primary or secondary malignancy in present or past medical history (unless patient has been free of the disease for ≥ 5 years prior to screening)[1] b) CNS, meningeal or epidural malignancies (e.g., brain metastases, known leukemic meningeosis)[1] [1] Note: Screening for cerebrospinal fluid (CSF)/CNS involvement is not required but may be performed at the discretion of the Investigator. c) CNS lesions/cerebrovascular event(s) with clinically significant sequelae d) history or evidence of clinically significant cerebrovascular CNS that would in the Investigator's opinion preclude participation in the study or compromise the patient's ability to give informed consent. 11. Patients with: a) chronic diarrhoea and malabsorption syndrome b) any evidence of ongoing systemic viral, bacterial, or fungal infection (including Pneumocystis jirovecii pneumonia and Cytomegalovirus infection) c) history of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis d) **Cohort A only:** ongoing inflammatory bowel disease as ulcerative colitis or Crohn's disease e) **Cohort A only:** severe chronic obstructive pulmonary disease (COPD), pulmonary emphysema or drug-induced pneumonitis diagnosed in previous medical history 12. Patients with known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV) (Additional information: no safety data on the use of CD19 antibodies in HIV positive patients are currently available) 13. Patients with known positive hepatitis B and/or C serology (as defined in the protocol).
Dose, Route of Administration, Treatment Regimen	Patients will be treated with **MOR00208** and **idelalisib** or **venetoclax** for up to 24 cycles at maximum or until progression of disease, withdrawal of consent, unacceptable toxicity, death or patient is lost to follow-up, whichever occurs first. **MOR00208 dose:** 12 mg/kg For the first 3 months of the study, each 28-day cycle will consist of a MOR00208 intravenous infusion of the dose of 12 mg/kg 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 biweekly basis (every 14 days) with infusions on Days 1 and 15 of each cycle from Cycle 4 to 6, and on a monthly basis on Day 1 of each cycle from Cycle 7. **Idelalisib dose**:

	Patients will self-administer the dose of 150 mg twice daily orally continuously during the study duration. **Venetoclax dose**: To mitigate the risk for tumor lysis syndrome (TLS), treatment of patients with venetoclax will be initiated at 20 mg up daily dose from Cycle 1 Day 8 (C1D8) for 7 days, followed by a weekly ramp-up dosing schedule (50 mg, 100 mg, 200 mg daily dose) to the recommended daily dose of 400 mg, starting from C2D8. Patients will self-administer venetoclax throughout the study duration except during hospitalization.
Study Participation Duration	Treatment with MOR00208 and idelalisib or venetoclax will continue until disease progression. If a compound specific adverse reaction occurs that requires the discontinuation of MOR00208, idelalisib or venetoclax the other therapy will be continued until progression of disease, withdrawal of consent, unacceptable toxicity, death or patient being lost to follow-up, whichever occurs first. The duration of the main study is limited to a maximum of 5 years in total. Patients who have not progressed at the end of the treatment period (after 24 treatment cycles) or at the end of the total study duration may continue with MOR00208 treatment upon Investigator's discretion.
Supply, Preparation and Administration	**MOR00208 DP** is a lyophilisate supplied in single-use 20 mL glass vials. Each vial contains 200 mg of MOR00208 for reconstitution with 5 mL of water for injection. Reconstitution yields 40 mg/mL MOR00208 in 25 mM sodium citrate, 200 mM trehalose and 0.02% (w/v) polysorbate 20 at pH 6.0. Each product vial is intended to deliver 200 mg of MOR00208 in 5 mL of reconstituted solution. MOR00208 will be diluted into a 250 mL infusion bag containing 0.9% (w/v) sodium chloride for injection. **Idelalisib** 100 and 150 mg film-coated tablets in bottles of 60 tablets, as commercially available. **Venetoclax** 10 mg, 50 mg and 100 mg film-coated tablets as commercially available for oral administration.
Safety Assessments	The safety and tolerability of study drug treatments will be evaluated based on AEs (incidence and severity), performance status, physical examinations, 12-lead resting electrocardiograms (ECGs), and laboratory safety evaluations. Laboratory and AE toxicities will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 or higher. The safety run-in phase will be evaluated by an IDMC.
Efficacy Assessments	Criteria of the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) for CLL subjects (Hallek et al., 2008) will be

	used to determine rates of response and progression for patients with CLL, with the modification that treatment-related lymphocytosis (Note: PRL is applicable in Cohort A only) in the absence of other signs or symptoms of disease progression will not be considered as progressive disease (Cheson et al., 2012; Hallek et al., 2012; NCCN NHL 2015 Guidelines). For patients with SLL, assessments will be performed using the Lugano Classification criteria for SLL subjects (Cheson et al., 2014). Patients who develop a partial response will be assessed using MRD testing from peripherial blood (PB) and from bone marrow if PB MRD negativity is reached. Furthermore, patients who develop a complete response as per standard criteria will be assessed using MRD testing and bone marrow aspiration/biopsy as described in IWCLL (Hallek et al., 2008).
Pharmacokinetics	The PK profile of MOR00208 will be investigated during the course of the study.
Immunogenicity	Immunogenicity of MOR00208 (anti-MOR00208 antibody analysis) will be investigated during the course of the study.
Biomarker Assessments	Blood for the analysis of exploratory biomarkers will be collected throughout the study and will be analyzed for markers which are important in the mechanism of action of, or could predict response to, the study drugs. Exploratory biomarkers (e.g., absolute and percentage change from baseline in measurements for B-, T-, NK cell populations, CD19 expression on B cells, CD16 expression on NK cells, ADCC capacity and optional FcγR genotyping) are planned to be investigated in the course of the study.
Disease Risk Assessment	Critical prognostic information, in particular the cytogenetic risk factors, serum marker of β_2-microglobulin, expression of CD38 and ZAP-70, optional mutational analysis (e.g., IGHV, TP53, NOTCH1, BTK and PLCγ2) are determined at baseline and will be used to evaluate patient subpopulation in regards to the parameters investigated.
Statistical Methods and Planned Analyses	The primary objective of the main study is to evaluate the safety of MOR00208 combined with idelalisib or venetoclax. The trial is designed as a two-cohort study (Cohort A: MOR00208 and idelalisib; Cohort B: MOR00208 and venetoclax). The primary and secondary endpoints will be analyzed descriptively for each cohort using appropriate statistics (counts/ percentages for discrete variables, mean, median, standard deviation, minimum, maximum, number of valid observations for continuous variables). For specific variables, P values and 95% confidence limits will be presented. Kaplan-Meier estimates will be used where applicable. No formal statistical hypothesis testing is planned.

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABC	Antibodies bound per cell
ADCC	Antibody dependent cell mediated cytotoxicity
ADCP	Antibody dependent cell mediated phagocytosis
AE	Adverse event
AESI	Adverse event of special interest
AIHA	Autoimmune hemolytic anemia
Akt	Protein kinase B (PKB)
ALC	Absolute lymphocyte count
ALL	Acute lymphoblastic leukemia
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine transaminase (serum glutamic pyruvic transaminase)
ANC	Absolute neutrophil count
Anti-HBc	Hepatitis B core antibody
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
ASCT	Autologous stem cell transplantation
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration time curve
BCL-2	B-Cell Lymphoma 2
BCRP	Breast cancer resistance protein
BEN	Bendamustine
BID	*bis in diem*, twice daily
bpm	Beats per minute
BR	Bendamustine/rituximab combination therapy
brpm	Breaths per minute
BTK	Bruton's tyrosine kinase
C1D1	Cycle 1 Day 1
CD	Cluster of differentiation
CDC	Complement-dependent cytotoxicity
CFR	Code of Federal Regulations
CI	Confidence interval
CIRS	Cumulative Illness Rating Scale
CrCl	Creatinine clearance
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CMV	Cytomegalovirus

CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CO_2	Carbon dioxide
CR	Complete response/remission
CRi	Complete response with incomplete marrow recovery
CRO	Contract research organization
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CxD1	Day 1 of any cycle
CxD15	Day 15 of any cycle
DLBCL	Diffuse large B cell lymphoma
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DP	Drug product
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full analysis set
FCBP	Females of childbearing potential
FCR	Fludarabine/cyclophosphamide/rituximab combination therapy
FcγR	Fc (fragment crystallizable) gamma receptors
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
FISH	Flourescence in-situ hybridization
FL	Follicular lymphoma; follicular B cell non-Hodgkin's lymphoma
FSH	Follicle stimulating hormone
FU	Follow-up

GCB	Germinal center B-cell like
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma-glutamyl transpeptidase
Gi/L	Giga per liter = 1 x 10^9/L
GLP	Good Laboratory Practice
HCG	Human chorionic gonadotropin
HCL	Hairy cell leukemia
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hct	Hematocrit
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IGHV	Immunoglobulin heavy-chain variable
IHC	Immunohistochemistry
IND	Investigational New Drug application
INN	International Nonproprietary Name
INR	International Normalized Ratio
IRB	Institutional Review Board
ITK	Interleukin-2 inducible tyrosine kinase
IV	Intravenous(ly)
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
KI	Kinase inhibitor
LD	Longest diameter
LDi	Longest traverse diameter of a lesion
LDH	Lactate dehydrogenase
LDT	Lymphocyte doubling time
LEN	Lenalidomide
LPD	Longest perpendicular diameter
LVD	Longest vertical dimension

mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal residual disease
MTD	Maximum tolerated dose
mTOR	Mechanistic target of rapamycin (formerly: mammalian target of rapamycin)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NK	Natural killer (cells)
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OATP	Organic anion-transporting polypeptide
ORR	Overall response rate
OS	Overall survival
PB	Peripheral blood
PCR	Polymerase chain reaction
PD	1. Pharmacodynamic(s), 2. Progressive disease
PE	Physical examination
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Principal Investigator
PIS	Patient Information Sheet
PI3K	Phosphoinositide-3-kinase
PJP	Pneumocystis jirovecii pneumonia
PK	Pharmacokinetic(s)
PKAS	PK analysis set
PLC	Phospholipase C
PO	*per os*, oral(ly)
PPD	Cross product of the LDi and perpendicular diameter
PPS	Per-protocol set
PR	Partial response/remission
PRL	Partial response with lymphocytosis
PT	Preferred Term
RBC	Red blood cell
RNA	Ribonucleic acid
R/R CLL	Relapsed or refractory chronic lymphocytic leukemia
R/R SLL	Relapsed or refractory small lymphocytic lymphoma

RTX	Rituximab
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SCID	Severe combined immunodeficiency
SD	Stable disease
SDi	Shortest axis perpendicular to the LDi
SLL	Small lymphocytic lymphoma
smIG	Surface immunoglobulins
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPD	Sum of the products of the perpendicular diameters for multiple lesions
TEAE	Treatment emergent adverse event
TEN	Toxic epidermal necrolysis
TLS	Tumor lysis syndrome
TNM	Tumor/Nodes/Metastasis staging
TP53	Tumor protein p53
UGT	UDP-glucuronosyltransferase (uridine 5'-diphospho-glucuronosyltransferase)
ULN	Upper limit of normal
US	United States of America
WBC	White blood cell
WFI	Water for injection
WHO	World Health Organization
WHO DDE	World Health Organization Drug Dictionary Enhanced
ZAP-70	Zeta-chain-associated protein kinase 70

4 BACKGROUND

4.1 Overview of Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL) is the most common leukemia and one of the most common B cell chronic lymphoproliferative disorders in the Western world with an incidence rate (provided as number of newly diagnosed patients per year per 100,000 population) in the US of 6.75 (men) and 3.65 (women), with a similar incidence rate in Europe, notably 5.87 (men) and 4.01 (women) (Sant et al., 2010; Yamamoto and Goodman, 2008). The median age at diagnosis is 72 years (Eichhorst et al., 2011).

CLL is characterized by the progressive accumulation of functionally incompetent lymphocytes, which are usually of monoclonal origin. The diagnosis of CLL is based on the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines requiring an absolute B lymphocyte count in the peripheral blood >5000/microliter (µl) with a majority of morphologically mature-appearing small lymphocytes and demonstration of clonality of circulating B lymphocytes by flow-cytometry of the peripheral blood (Hallek et al., 2008). A majority of the lymphocyte population should express the following markers: expression of either kappa or lambda light chains, expression of B cell associated markers (CD19, CD20 (usually weak), CD23, expression of the T-cell marker CD5, low levels of surface immunoglobulins (smIG).

Patients with CLL are frequently clinically asymptomatic at initial diagnosis. Upon further development of the disease, a spectrum of CLL specific clinical features might develop such as B-symptoms, lymphadenopathy, hepatosplenomegaly, and organ infiltration. Laboratory features frequently observed in CLL patients that often become clinically significant are: immunoglobulin abnormalities and a status of immunodeficiency that contributes to increased likelihood of infections, autoimmune hemolytic anemia, thrombocytopenia, and pancytopenia.

Small lymphocytic lymphoma (SLL) is considered a CLL variant that lacks the clonal lymphocytosis required for the CLL diagnosis, but otherwise shares pathological and immunophenotypic features (Campo et al., 2011). The definition of SLL requires the presence of lymphadenopathy and/or splenomegaly. Moreover, the number of B lymphocytes in the peripheral blood should not exceed 5 x 10^9/L. In SLL, the diagnosis should be confirmed by histopathologic evaluation of a lymph node biopsy whenever possible (Hallek et al., 2008). The incidence of SLL is approximately 25% of CLL in the US (Dores et al., 2007).

The natural history of CLL is very variable with survival times ranging from several months to >10 years after diagnosis. Several prognostic scores have been developed over time. The clinical staging systems according to Binet and Rai have found a wide range of application; see Appendix A for Binet classification (Binet et al., 1981). Since then a multitude of prognostic parameters have been identified. Prognostic markers in widespread clinical use are lymphocyte doubling time, β2-mircroglobulin and cytogenetic markers (Shanafelt et al., 2006).

4.2 Treatment of Chronic Lymphocytic Leukemia

In general practice, newly diagnosed patients with asymptomatic early-stage disease (Rai 0, Binet A) should be monitored without therapy unless they have evidence of disease

progression. Whereas patients at intermediate (stages I and II) and high risk (stages III and IV) according to the modified Rai classification or at Binet stage B or C usually benefit from the initiation of treatment (Hallek et al., 2008). Prognostic markers such as patient age and comorbidities are the key aspects for treatment selection in symptomatic CLL requiring systemic treatment. There are several options in first-line treatment, which include combination therapy with purine analogs (e.g., fludarabine/cyclophosphamide/rituximab [FCR] regimen), alkylating agents (e.g., chlorambucil) and/or monoclonal antibodies (mAb) to the CD20-antigen (e.g., rituximab, ofatumumab, obinutuzumab). Special considerations apply to elderly and comorbid patients and patients with the adverse prognostic cytogenetic marker del(17p). For the group of patients with del(17p), one of the following treatment strategies is generally considered: ibrutinib, FCR, alemtuzumab in combination with corticosteroids or possibly allogeneic stem cell transplantation.

Patients with R/R CLL frequently become refractory to chemotherapy and anti-CD20 therapies. Several treatment options can be considered, including re-treatment with the patients' previous regimen.

Ibrutinib and the combination of idelalisib/rituximab have been approved by EMA and FDA. In addition, venetoclax has been recently approved. For patients with R/R CLL, ibrutinib is a commonly used therapeutic option which is also often feasible in elderly and comorbid patients. Ibrutinib has demonstrated significant efficacy in relapsed CLL with durable remissions, including in patients with del(17p)13.1, with moderate toxicity. Recent data demonstrate even more impressive efficacy in previously untreated patients with CLL. Therefore, ibrutinib has been approved by FDA and EMA in 2016 as a first-line treatment for patients with CLL. The approval is based on data from the randomized, multi-center, open-label Phase 3 RESONATE-2 trial, which evaluated the use of ibrutinib versus chlorambucil in 269 treatment-naive patients with CLL or SLL aged 65 years or older. Ibrutinib significantly prolonged progression-free survival (median PFS was not reached for ibrutinib vs. 18.9 months for chlorambucil) reducing the risk of progression or death by 84% versus chlorambucil. Ibrutinib was also associated with a significantly higher overall response rate versus chlorambucil (ORR of 86% vs. 35%, respectively) (Burger et al., 2015). In several combination trials, ibrutinib has been administered with therapeutic monoclonal antibodies (e.g., rituximab and ofatumumab), chemotherapy (e.g., FCR and BR), and select targeted immune therapies (e.g., lenalidomide). Combination approaches have generally yielded improved overall response rates (ORRs) in part through earlier resolution of persistent lymphocytosis (Byrd et al., 2014b). Most recent results from a large randomized phase III study showed that the combination of ibrutinib and bendamustine/rituximab (BR) decreases the risk of progression and death remarkably (Chanan-Khan et al., 2015).

The emerging resistance to and off-target side effects of ibrutinib have led to active development of second-generation and more specific BTK inhibitors, such as acalabrutinib (ACP-196), ONO/GS-4059, and BGB-3111. Acalabrutinib, which is more potent and selective than ibrutinib with reduced off-target side effects, has recently demonstrated clinical efficacy in relapsed CLL patients and showed encouriging preliminary results offering a favorable safety profile and high response rates that appear durable also in treatment-naive patients in Phase 1/2 studies. (Byrd et al., 2016a; Byrd et al., 2016b; Wierda et al., 2016). Currently, a

Phase 3 study (NCT02477696) directly comparing ACP-196 with ibrutinib in high-risk patients with relapsed CLL has commenced.

Response rates for ibrutinib are high compared with other treatments for CLL; however, some patients develop progressive CLL or transform when receiving ibrutinib. CLL patients who progress early on ibrutinib are difficult to treat and have poor outcomes. The clinical experience is that R/R CLL patients pretreated with ibrutinib experience a very aggressive course of disease with a median overall survival of only 3.1 months (Jain et al., 2015). Many of the patients enrolled on clinical trials with ibrutinib had relapsed CLL with poor prognostic features. In a recent publication, Maddocks et al. (2015) report a median survival following CLL progression of 17.6 months and show that the disease tends to progress quickly in patients, especially when the drug therapy is stopped.

It was demonstrated in a recent retrospective analysis of CLL patients at 10 large US cancer centres that the majority of patients who discontinue a kinase inhibitor (KI) therapy (e.g. idelalisib after ibrutinib discontinuation) due to toxicity or progression respond to subsequent alternate KI therapy with the following outcome: median PFS=11. 9 months for all patients (n=40); median PFS=7 months for CLL progressors. These very limited data showed that alternate KI choice, including idelalisib treatment after ibrutinib discontinuation, achieved an overall response rate (ORR) of 50% (95% CI, 33.4%-66.6%; n=38) without any complete responses (CR) (Mato et al., 2015). Moreover, further limited data were recently published on salvageability after ibrutinib discontinuation from the UK without specifying ORR but describing that 50% of patients with ≥3 prior treatment lines (total n=12) remained alive where 4 patients out of those 12 patients received idelalisib therapy following ibrutinib discontinuation (Hillmen et al., 2016).

More accurate data on ORR are available with venetoclax monotherapy from prospective study in CLL patients relapsed or refractory to ibrutinib therapy (ClinicalTrials.gov Identifier: NCT02141282) showing an overall response rate of 60.5% with a 95% confidence interval of 43.4-76.0% (Jones et al., 2015).

Importantly, according to a recent multivariable analysis an anti-CD20 antibody of rituximab in combination with venetoclax therapy significantly increases CR rates (51%, n=49 vs. 20%, n=116, respectively) and the durability of remissions over venetoclax monotherapy for patients with R/R CLL without prior BTK inhibitor therapy (Roberts et al., 2016). These encouriging data suggest that adding an antibody to a small molecule can further deepen the response and increase clinical benefits for the patients which might translate into improved survival.

The presence of del(17p)/tumor protein p53 (TP53) mutation and complex karyotype may also contribute to the genomic instability in CLL cells, and prior therapies can promote subclonal mutations and refractory disease in patients with CLL. BTK mutations and clonal evolution may occur and produce ibrutinib resistance. There are recent data reported on acquired ibrutinib resistance and BTK mutation (C481S and phospholipase Cγ2-mutation) in patients with CLL who progressed on ibrutinib therapy (Woyach et al., 2014b). However, it is still unclear whether BTK mutations contribute to clonal evolution and promote transformations of CLL on ibrutinib therapy.

Patients with increased genomic instability may be at risk for relapse; combination therapies designed to avoid the development of resistance appear to be the most rational choice for such patient population.

Patients with progressive CLL need additional therapy quickly after ibrutinib discontinuation for effective salvage (Woyach et al., 2014c), even though the therapeutic options after ibrutinib treatment are very limited. In this respect, the population of ibrutinib-pretreated R/R CLL patients and those with intolerance to ibrutinib are in urgent need of novel therapeutic options.

4.3 Idelalisib in Hematological Malignancies

Idelalisib inhibits the phosphotidylinositol 3-kinase-delta (p110δ) (PI3Kδ), which is hyperactive in B cell malignancies including CLL. PI3Kδ is central to multiple signaling pathways that drive proliferation, survival, homing and retention of malignant cells in lymphoid tissue and bone marrow. Idelalisib is an oral phenylquinazolin derivative that selectively inhibits the adenosine triphosphate (ATP)-binding at the PI3K p110-d catalytic domain. This prevents phosphorylation and subsequent activation of protein kinase B (Akt) and mechanistic target of rapamycin (mTOR), which results in lymphoma cell death.

Idelalisib is approved by the FDA for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities. Furthermore, as monotherapy for the treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies. EMA has approved idelalisib in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. Furthermore, as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.

In clinical studies, idelalisib has proven to show clinically meaningful anti-lymphoma effects in a range of hematological malignancies in addition to the approved indications FL and CLL including mantle cell lymphoma and a mix of indolent lymphoma indications (Hewett et al., 2015).

Idelalisib was investigated as single agent in 125 patients with indolent lymphomas (follicular lymphoma, SLL, marginal-zone lymphoma, lymphoplasmocytic lymphoma) after failure of prior pretreatment (Gopal et al., 2014). The ORR across all lymphoma entities in this study was 57%. The response rate in the SLL population of this study was 61%.

A pivotal phase III study investigated idelalisib at a dose of 150 mg twice daily in combination with RTX versus RTX single agent treatment in R/R CLL patients deemed ineligible for further cytotoxic chemotherapy because of significant myelosuppression related to previous chemotherapy, creatinine clearance (CrCl) < 60 mL/min, or a Cumulative Illness Rating Scale (CIRS) value > 6 (Furman et al., 2014).

Compared with single agent RTX, combination therapy resulted in a significantly higher rate of PFS at 24 weeks (93% vs. 46%) and a significantly higher 12-month overall survival rate

(92% vs. 80%). The ORR among patients receiving combination therapy was impressive (81% vs. 13% for RTX only); see Table 1.

Table 1: Efficacy of Idealisib in Relapsed CLL in Phase III Trial of Idelalisib plus Rituximab Versus Placebo plus Rituximab (Furman et al., 2014)

	Idelalisib plus Rituximab (N=110)	**Placebo plus Rituximab (N=110)**	
Median PFS (primary endpoint)	Not reached[1]	5.5 months	
Rate of PFS at 24 weeks	93%	46%	HR = 0.15, P < 0.001
Rate of OS at 12 months	92%	80%	HR = 0.28, P = 0.02
Overall response rate	81%	13%	OR = 29.92, P < 0.001

[1] Disease progression occurred in only 12 patients.
Abbreviations: PFS=progression-free survival; OS=overall survival; HR=hazard ratio; OR=odds ratio.

The most common adverse events (AEs) in the idelalisib/RTX group (≥15%) were: pyrexia, fatigue, nausea, chills, diarrhea, infusion-related reaction (IRR), and cough. The majority of the AEs were Grade 1 or 2. Most common (≥5%) serious adverse events (SAEs) were pneumonia, pyrexia, and febrile neutropenia. The AE profile observed for the combination therapy was not significantly different from that observed for the single agent idelalisib studies in particular the study described above on 125 patients with indolent B-NHL entities (Gopal et al., 2014).

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee has most recently carried out a safety review started after a higher rate of serious adverse events related to infections, such as pneumonia, occurred. These were seen in three clinical trials among patients, who received idelalisib in addition to other cancer medicines. In its conclusion, Committee for Medicinal Products for Human Use had confirmed, that the medicine's benefits outweigh its risks in the treatment of CLL.

4.4 Venetoclax in Hematological Malignancies

Venetoclax is a selective and orally bioavailable small-molecule inhibitor of B-cell lymphoma 2 (BCL-2), an antiapoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL cells where it mediates tumor cell survival and has been associated with resistance to chemotherapeutics. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilization and the activation of caspases. In nonclinical studies, venetoclax has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2.

Venetoclax is the first FDA-approved treatment that targets the BCL-2 protein, which supports cancer cell growth and is overexpressed in many patients with CLL. The FDA approved venetoclax (Venclexta) under accelerated approval based on overall response rate for the treatment of patients with CLL with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy. The EMA recently approved venetoclax (Venclyxto®) as monotherapy for the treatment of CLL in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or for the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

The efficacy of venetoclax was established in an open-label, single-arm, multicenter clinical trial with relapsed or refractory CLL with 17p deletion who had received at least one prior therapy (Stilgenbauer et al., 2016). Results of this trial show that venetoclax monotherapy is active and well tolerated in patients, providing a new therapeutic option for this very poor prognosis population. 107 patients were enrolled into the study. An overall response by independent review was achieved in 85 of 107 patients including 7.5% CR+CRi. The median time to first response was 0.8 months (range: 0.1 to 8.1 months). Responses with venetoclax seem durable, with median duration of overall response and progression-free survival not yet reached after a median follow-up of 12 months. Minimal residual disease (MRD) was evaluated in peripheral blood and bone marrow for patients who achieved CR or CRi, following treatment with venetoclax. Three percent (3/106) were MRD negative in the peripheral blood and bone marrow (less than one CLL cell per 10^4 leukocytes). The most common grade 3/4 adverse events were neutropenia (40%), infection (20%], anaemia (18%), and thrombocytopenia (15%). 11 patients died in the study within 30 days of the last dose of venetoclax; seven due to disease progression and four from an adverse event (none assessed as treatment related).

Further studies of venetoclax are ongoing in CLL in sequence or in combination with other agents (e.g. obinutuzumab, rituximab, ibrutinib, bendamustine). Moreover, there is a recently initiatied Phase 3 study in patients with multiple myeloma (NCT02755597).

4.5 Overview of MOR00208

MOR00208 (also referred to as XmAb®5574) is an Fc-enhanced mAb that binds to the human B cell surface antigen CD19. MOR00208 possesses significantly increased tumor cytotoxicity when compared with the parental, non-enhanceed, murine 4G7 CD19 antibody. The increased binding of MOR00208 to Fc gamma receptors (FcγR), due to the engineered mutations, significantly enhances *in vitro* antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cell mediated phagocytosis (ADCP), and its direct cytotoxic effects (apoptosis) on the tumor cells when compared with the non-enhanced parental murine antibody (Horton et al., 2008). MOR00208 has not been shown to mediate complement-dependent cytotoxicity (CDC).

4.5.1 Nonclinical Studies

More specifically, in preclinical studies, MOR00208 has been shown to significantly enhance *in vitro* ADCC, ADCP, and direct cytotoxic effects (apoptosis) on $CD19^+$ tumor cell lines

spanning a broad range of human lymphomas and leukemias (Burkitt's lymphoma, CLL, hairy cell leukemia (HCL), $CD19^+$ chronic myeloid leukemia (CML), diffuse large B cell lymphoma (DLBCL) and acute lymphoblastic leukemia (ALL), expressing levels of CD19 antigen ranging from 15,000 to 105,000 molecules/cell. Similar effects have also been observed in relation to freshly isolated patient CLL or ALL cells and are also expected to translate to primary non-Hodgkin's lymphoma (NHL) cells since the expression range reported for ALL and CLL B cells covers the range observed for NHL B cells (Ginaldi et al., 1998; Olejniczak et al., 2006). MOR00208 has also shown superior efficacy to its non-enhanced parental antibody regarding its ability to induce a marked reduction in tumor growth, inhibit tumor growth rate and increase survival *in vivo* in xenograft models of human lymphoma in severe combined immunodeficiency (SCID) mice (Investigator's Brochure [IB]).

The pharmacodynamic (PD) interactions of MOR00208 in combination with two standard-of-care drugs fludarabine and bendamustine (BEN), and one investigational drug, lenalidomide (LEN) used in the treatment of patients with CLL and NHL, were investigated in a human IV lymphoma model in SCID mice (IB). In this orthotopic model for disseminated B cell malignancies, the median survival was superior for all groups receiving MOR00208 combination therapy (with fludarabine, BEN or LEN) when compared with the groups receiving MOR00208 monotherapy. The LEN xenograft study showed a clear potentiation of the efficacy benefit of MOR00208 (3 mg/kg) and LEN (100/200 mg/kg) combination therapy compared with the respective monotherapies (1.5 x increase in median lifespan).

Tissue cross-reactivity studies have shown that the pattern and distribution of MOR00208 binding to cynomolgus monkey tissues closely parallels those of human tissues. Flow cytometry experiments show MOR00208 binding to human and cynomolgus monkey B cells, but not to the B cells of other common laboratory species (such as rat, mouse, rabbit and dog). Therefore, pharmacology studies were restricted to human and cynomolgus monkey cell-based *in vitro* systems, CD19+ human B cell tumor xenograft models in SCID mice, and cynomolgus monkeys *in vivo*. In *in vivo* studies in cynomolgus monkeys, MOR00208 was shown to induce B lymphocyte depletion in peripheral blood, bone marrow, spleen and inguinal lymph nodes. Cynomolgus monkeys were also judged to be the only relevant common laboratory species for toxicity studies.

The results of studies evaluating the pharmacokinetics (PK), PD and toxicity of MOR00208 in cynomolgus monkeys, are provided in the IB. The findings in 5 preclinical studies were limited to the expected pharmacological effects of MOR00208, with no reports of unanticipated toxicity.

The four studies, all conducted in cynomolgus monkeys included: a 26-week single 10.0 mg/kg dose, PK, PD and toxicity study; a 28-day single IV dose, dose-ranging (0.3, 1.0 and 3.0 mg/kg) PK/PD study; a 29-day, single-dose (3.0 mg/kg) study comparing MOR00208 with two other CD19 antibodies with different Fc regions; an 8-week toxicity study in which MOR00208 was administered IV every 2 weeks at a dose of 2, 10 or 50 mg/kg for 8 consecutive weeks with a 90-day recovery period; and a 13-week toxicity study in which MOR00208 was administered IV weekly to sexually mature cynomolgus monkeys at doses of 10, 30 or 100 mg/kg for 13 consecutive weeks with a 132-day recovery period. The aim of the latter Good Laboratory Practice (GLP)-compliant, multiple-dose toxicology studies was to support the use of MOR00208 in human clinical studies. As expected pharmacological effect, a reversible lack

of germinal centers in lymphoid organs and markedly reduced peripheral CD20+ B cell counts were observed, which were consistent with lowered IgG levels in serum as well as a reversible reduction in the T-cell dependent antibody response. There were no MOR00208-related effects on body weight, clinical signs, food consumption, blood pressure, electrocardiography, respiratory rate, ophthalmology, neurobehavioural observations, hematology, coagulation, urine or cytokine analysis. MOR00208 had no effects on menstrual cycle length in females and no histopathology/microscopic changes to male and female reproductive organs. Overall, MOR00208 administration to the cynomolgus monkey was very well tolerated at doses up to 100 mg/kg. In addition, GLP-compliant tissue cross-reactivity studies were performed on normal tissue panels from human and cynomolgus monkey donors. No specific staining of structures other than the expected mononuclear leukocytes, lymphocytes and hematopoietic precursor cells was observed.

4.5.2 Clinical Experience with MOR00208 in CLL

Protocol XmAb5574-01:
A Phase 1 Study of XmAb®5574 to Evaluate the Safety, Tolerability, and Pharmacokinetics in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia

The first study in humans was a phase I trial exploring the use of MOR00208 (also known as XmAb®5574 or MOR208) in adult patients diagnosed according to International Workshop on CLL guidelines (Hallek et al., 2008) with active, treatment-requiring R/R CLL/SLL. Results of the study were reported by Woyach et al. (2014a).

Twenty-seven patients were enrolled to 6 escalating dose levels, with expansion at the highest dose level of 12 mg/kg. Nine doses of MOR00208 were infused over 8 weeks. The maximum tolerated dose (MTD) was not reached; the drug was generally well tolerated, IRRs of grade 1 or 2 being the most common toxicities. Treatment-related grade 3 or 4 AEs occurred in 5 patients and included neutropenia, thrombocytopenia, increased aspartate aminotransferase (AST), febrile neutropenia, and tumor lysis syndrome (TLS). MOR00208 showed preliminary efficacy, with 18 patients (66.7%) responding by physical examination criteria and laboratory studies, and 8 patients (29.6%) responding by computed tomography (CT) criteria. MOR00208 showed a terminal elimination half-life of approximately 14 days. A dose of 12 mg/kg was recommended for use in subsequent studies.

4.5.3 Safety of MOR00208

MOR00208 has a novel mechanism of action that may have the potential to add to the care of patients with NHL, particularly CLL and SLL. Based on the available data from the completed clinical study of MOR00208 (Protocol XmAb®5574-01), the preliminary data from the ongoing MOR208C201 and MOR208C202 clinical studies, nonclinical studies and experiments, and literature data on CD19, the sponsor is of the opinion that the potential benefit of MOR00208 outweighs the potential risks. It is expected that the potential risks will be adequately controlled by the design of this trial (e.g., by the inclusion and exclusion criteria) and by frequent monitoring of potential adverse drug reactions throughout the entire study. The anticipated possible risks associated with administration of MOR00208 to patients include the following AEs with a suspected relationship to MOR00208 treatment:

- IRRs (mostly Grade 1/2)
- Febrile neutropenia
- Neutropenia
- Thrombocytopenia
- Tumour lysis syndrome
- Upper respiratory tract infections
- Fatigue
- Chills
- Pyrexia
- Nausea
- Diarrhoea
- Headache
- Rash
- Aspartate- (AST) and alanine transaminase (ALT) increases.

Since a major pharmacological effect of MOR00208 is B cell depletion, the risks associated with the use of approved B cell depleting therapeutics based on the labelling of other agents with similar effects should be considered. The anticipated possible risks include: B cell depletion, absolute lymphocyte count (ALC) reduction, IRRs, TLS, neutropenia/ thrombocytopenia, hepatitis B reactivation, progressive multifocal leukoencephalopathy, mucocutaneous reactions, and infections.

The incidence of toxicities observed in the first in human phase I trial of MOR00208 in CLL is shown in Table 2. The MTD was not reached in this trial, and the drug was generally well tolerated.

The possible risks associated with the administration of MOR00208 are described in detail in the MOR00208 IB.

Table 2: Adverse Events at Least Possibly Attributable to MOR00208 in Phase I Study of MOR00208 in R/R CLL (Woyach et al., 2014a)

Toxicity	0.3 mg/kg (N=1)	1 mg/kg (N=1)	3 mg/kg (N=3)	6 mg/kg (N=3)	9 mg/kg (N=3)	12 mg/kg (N=16)	Total (%)
Any Event	**1**	**1**	**3**	**3**	**2**	**14**	**24 (88.9)**
Dose Limiting Toxicities							
Grade 4 neutropenia lasting ≥ 7 days with febrile neutropenia						1	**1 (3.7)**
Other Grade3/4 Toxicities							
Neutropenia		1				1	**2 (7.4)**
Thrombocytopenia						2	**2 (7.4)**
Tumor lysis syndrome						1	**1 (3.7)**
Increased AST						1	**1 (3.7)**
Grade 1/2 Toxicities Occurring in >1 Patient							
Infusion reaction	1	1	1	2	2	11	**18 (66.7)**
Increased AST	1		2	1			**4 (14.8)**
Increased ALT			2	1		2	**5 (18.5)**
Neutropenia	1					1	**2 (7.4)**
Thrombocytopenia					1	2	**3 (11.1)**
Fever	1		1		1	1	**4 (14.8)**
Chills	1		1	1			**3 (11.1)**
Peripheral sensory neuropathy				1		2	**3 (11.1)**
Diarrhea				1		1	**2 (7.4)**
Flushing	1					1	**2 (7.4)**
Hyperuricemia			1			1	**2 (7.4)**
Hypocalcemia			1			1	**2 (7.4)**
Increased lipase			1			1	**2 (7.4)**

5 STUDY PURPOSE/RATIONALE

5.1 Disease Background and Rationale

CLL is a lymphoproliferative disorder characterized by progressive accumulation of morphologically mature but functionally incompetent lymphocytes in the blood, bone marrow, and lymphoid tissues. The disease affects mainly the elderly. Its clinical course of ranges from indolent disease (Rai 0, Binet A) with long-term survival over 12 years to aggressive disease (Rai III/IV, Binet C) (Binet, 1981; Rai, 1987) with median survival of 2 years (Montserrat, 1995).

SLL and CLL are generally considered a different manifestation of the same disease. Whereas CLL is found in the blood and bone marrow, SLL primarily presents in the lymph nodes. The median age at diagnosis of CLL is 72 years (Eichhorst et al., 2011). The natural history of SLL is generally indolent or slowly progressive; SLL, however, is considered incurable.

Traditional therapy of R/R CLL consisted in the administration of chemotherapeutic agents which could be combined with anti-CD20 targeted treatments. Over time patients with R/R CLL became increasingly refractory to chemotherapy and anti-CD20 treatment, or were not eligible for intensive chemotherapy regimen due to advanced age or comorbidities.

Therefore, the approval of novel small molecules like ibrutinib, venetoclax and idelalisib combined with RTX for CLL has been an important milestone. In particular, the treatment with single agent ibrutinib has become a cornerstone of the treatment of R/R CLL. Despite the prolonged median PFS under treatment with ibrutinib, it is expected that most CLL patients will relapse. R/R CLL patients who relapse after or during ibrutinib treatment have a dismal prognosis insofar as most therapeutic options have been exploited to this point and CLL takes an increasingly aggressive course. So far, limited survival data are available on patients discontinuing ibrutinib. According to Jain et al. (2015), the median survival for all the patients was 3.1 months after discontinuing ibrutinib and did not differ significantly between transformed and untransformed (those who progressed and those who discontinued for other reasons) patients with CLL. In a recent publication, Maddocks et al. (2015) report a median survival following CLL progression of 17.6 months and show that disease tends to progress quickly in patients, especially when the drug therapy is stopped. Available limited ORR data in this particular patient population with ibrutinib discontinuation are summarized in Section 4.2.

Despite recently approved therapeutic agents and combination therapies, CLL remains an incurable disease and most patients eventually relapse and/or die. There still remains an unmet medical need for improved and novel combination treatments for subjects with CLL requiring treatment, especially for ibrutinib-pretreated patients with R/R CLL.

5.2 Rationale for the Use of Idelalisib in CLL/SLL

Phosphoinositide-3-kinases (PI3Ks) play an essential role in cellular growth, differentiation, migration, and metabolism. Impaired PI3K signaling leads to deficiencies within the immune system, whereas uncontrolled PI3K signaling can lead to autoproliferation and the development of leukemias. The hematopoietic-selective isoform PI3K-δ specifically helps to regulate the activation, proliferation, migration and survival of B lymphocytes.

Idelalisib is a first-in-class, orally administered, potent reversible small-molecule inhibitor of PI3K-γ and δ, approved in combination with rituximab for the treatment of R/R CLL and as monotherapy for relapsed FL and SLL.

In a pivotal phase III trial in patients with relapsed CLL who were not able to receive cytotoxic agents, recipients of idelalisib plus RTX had significantly improved PFS, overall survival, overall response and lymph node response, compared with recipients of placebo plus RTX. In a pivotal phase II trial, idelalisib monotherapy was effective in patients with relapsed indolent NHL who were refractory to RTX and an alkylating agent, including in the subgroups of patients with follicular lymphoma or SLL. Idelalisib had a generally manageable AE profile.

Furthermore, recently published *in vitro* results suggest that idelalisib may serve as an alternative therapy in the setting of ibrutinib resistance at clinically achievable doses since BTK-mutated CLL cells may still be sensitive to other agents that target the B-cell receptor signaling pathway including idelalisib (Cheng et al., 2015).

5.3 Rationale for the Use of MOR00208 in CLL/SLL

The effects of MOR00208 appear to involve ADCC, ADCP, and direct cytotoxic activity (apoptosis). MOR00208 demonstrated single-agent activity in R/R CLL/SLL, R/R DLBCL, follicular lymphoma and other indolent NHLs (Jurczak et al., 2015; Woyach et al., 2014a). MOR00208 elicits only mild hematological AEs and has a manageable toxicity profile. The predominant AEs are IRRs, a class effect of many therapeutic antibodies, which typically occur during the first to third application.

As RTX-based regimens have become standard first-line treatment in CLL, the efficacy of RTX combined with chemotherapy in the second-line setting has decreased and there is a need for new therapies in patients progressing or relapsing after first- or second-line RTX-based treatment. The CD19 antigen is an attractive target in CLL as CD19 is typically expressed and has a signalling function that contributes to the malignant phenotype and is not down-regulated in patients pretreated with CD20-targeted agents. Thus, it might be possible to overcome the absolute or relative RTX resistance in R/R CLL by using MOR00208 instead of RTX and thereby to improve the clinical outcome in the R/R CLL patient population. In addition, there are accumulated data that CLL cells become CD20 negative after ibrutinib therapy but remain CD19 positive (unpublished data by Woyach).

In summary, further clinical investigation of MOR00208 is warranted in subjects with CLL/SLL.

5.4 Rationale for the Use of Venetoclax in CLL/SLL

The balance between pro-apoptotic and anti-apoptotic proteins is often dysregulated in hematologic malignancies, and particularly lymphoid cancers, and thus contributes to the survival of malignant B-cells (Anderson et al., 2016). Permeabilization of the mitochondrial outer membrane and thus triggering of apoptosis is determined by the balance of activity between 3 subfamilies of the BCL2 family of proteins: the mediators (BAX and BAK), which disrupt the mitochondrial membrane; the antiapoptotic proteins (BCL2, BCLxL, BCLw,MCL-1, and A1), which act to constrain BAX and BAK; and the BH3-only proteins (BIM, BID, PUMA, NOXA, HRK, and BAD), which are activated under conditions of cellular stress and function to inhibit the antiapoptotic proteins or to activate BAX and BAK (Anderson et al., 2016; Czabotar et al., 2014; Llambi et al., 2011).

The BCL-2 protein inhibits apoptosis and was found to be over-expressed in CLL (Anderson et al., 2016). Venetoclax is a selective and potent inhibitor of BCL-2 (Souers et al. 2013). Preclinical studies confirmed that venetoclax selectively inhibits BCL-2 and thus induces apoptosis of lymphoid cells while avoiding the BCLxL mediated platelet toxicity (Souers et al. 2013; Vogler et al., 2013).

Venetoclax is the first FDA-approved treatment that targets the BCL-2 protein, which supports cancer cell growth and is overexpressed in many patients with CLL. The FDA approved venetoclax (Venclexta) under accelerated approval based on overall response rate for the treatment of patients with CLL with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy. The EMA recently approved venetoclax (Venclyxto®) as monotherapy for the treatment of CLL in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or for the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

5.5 Rationale for the Combination of MOR00208 and Idelalisib in CLL/SLL

The rationale for idelalisib and MOR00208 is described in detail in Sections 5.2 and 5.4.

The AE profiles of MOR00208 and idelalisib are largely non-overlapping. The administration of MOR00208 is mainly associated with mild to moderate IRRs, which occur especially at the beginning of treatment. Apart from that, mild hematological AEs have been observed, whereas idelalisib was associated mainly with pyrexia, fatigue, nausea, cough, pneumonia, chills, rash, abdominal pain, and diarrhea. In addition, hematological AEs such as neutropenia and laboratory abnormalities such as hypertriglyceridemia, hyperglycemia, ALT and AST elevations or even fatal and/or serious hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation have been found associated with the use of idelalisib. According to clinical experience with CLL patients treated with idelalisib combined with RTX or ofatumumab, current clinical trials have not shown a clinically significant increase in the number of observed AEs, particularly not in hematological AEs. Therefore, MOR00208 is considered to be a reasonable candidate for combination therapy with idelalisib from safety perspective.

Anti-CD20 RTX is commonly used in all treatment lines in CLL/SLL and it is assumed that the majority of patients who are eligible for the trial will have had prior RTX exposure with ultimate experience of progression or relapse after such treatment. Thus, it is assumed that MOR00208 in combination with idelalisib conveys benefit to this patient population that would otherwise not be achieved by continuing RTX-based regimen. Beyond that both compounds have a confirmed clinical activity in R/R CLL, MOR00208 demonstrated a synergistic activity with idelalisib in a series of *in vitro* experiments (MorphoSys data on file) and idelalisib showed promising *in vitro* results in the setting of ibrutinib resistance (Cheng et al., 2015). Therefore, one can expect that the combination of anti-CD19 MOR00208 and idelalisib in a clinical setting may be more beneficial compared with single agent treatment and might be possible to overcome the ibrutinib resistance in this particular patient population.

Furthermore, idelalisib monotherapy is an accepted treatment for R/R CLL patients since idelalisib with or without RTX is included as preferred option for patients with R/R CLL disease regardless of their age and comorbidities according to Version 2.2015 of the NCCN Guidelines for Non-Hodgkin's Lymphomas (updates in Version 1.2015 of the NCCN Guidelines for Non-Hodgkin's Lymphomas from Version 5.2014 include that from idelalisib+RTX was changed to idelalisib±RTX in various R/R CLL patient populations). Therefore, it is the opinion of the sponsor that MOR00208 in combination with idelalisib but without RTX is a reasonable investigational treatment opportunity in this clinical trial.

Consequently, MorphoSys has developed the present protocol of an open-label study to evaluate the safety and preliminary efficacy of a combined treatment of MOR00208 with idelalisib in adult patients with R/R CLL previously treated with a BTK inhibitor (e.g., ibrutinib) in Cohort A. The main objective of this study is to offer a novel treatment option to patients whose disease relapsed or became refractory during or after therapy with a BTK inhibitor such as ibrutinib or who did not tolerate such therapy, taking into consideration that these patients have particularly dismal prognosis.

As the combination therapy of MOR00208 and idealisib will be evaluated for the first time in a clinical setting, a safety run-in phase was introduced in the study design. The study will include a safety run-in phase, which will be started with an evaluation of the safety data of 3 patients who completed at least one cycle of treatment. This evaluation will be done by an Independent Data Monitoring Committee (IDMC). After the evaluation of the safety data from the first 3 patients for Cycle 1 of treatment and a positive recommendation from the IDMC the next 7-9 patients may be dosed in parallel. An additional IDMC review will take place after 10 patients have completed at least 1 cycle of treatment. The IDMC will evaluate the number and type of AEs occurring during the first cycle, as well as the laboratory parameters (e.g., clinical biochemistry and hematology) and other relevant safety data as necessary, with the prospect of providing a recommendation on the study, going forward.

5.6 Rationale for the Combination of MOR00208 and Venetoclax in CLL/SLL

The rationale for venetoclax and MOR00208 is described in detail in Sections 5.3 and 5.4.

The toxicity profile of venetoclax and MOR208 is potentially overlapping, however with significantly lower incidences of reported toxicities for MOR208. Non-hematologic ADRs

including diarrhea, nausea, vomiting, headache, fatigue, upper respiratory tract infections, and pyrexia frequently occur with administration of venetoclax in patients with CLL (incidence > 15%). These ADRs were also observed with treatment of MOR208, however with a lower incidence (≤ 8%). TLS is the major risk of treatment with venetoclax. TLS and relevant laboratory abnormalities were reported in 6% of CLL patients with recommended risk stratification, dosing regimen and prophylaxis. Also under treatment with MOR208 four patients (3%) developed TLS so far. Two in the ALL indication (9%), one in NHL (1%) and one in CLL (4%). To prevent an increase of this risk by concomitant use of both drugs in trial MOR208C205, treatment with MOR208 will start one week before the start of the ramp-up treatment with venetoclax at the lowest dose of 20 mg. Neutropenia is a frequent adverse drug reaction of venetoclax: Grade 3 or 4 events were experienced in 41% of patients, 6% of the patients had serious AE of neutropenia. Under MOR208 treatment > Grade 3 neutropenia was reported for 9 % of patients overall (7% in NHL, 18% in ALL, and 11% in CLL). None of them were serious. To reduce the risk for neutropenia preventive treatment with G-CSF may be considered if clinically indicated. Therefore, MOR00208 is considered to be a reasonable candidate for combination therapy with venetoclax from safety perspective.

Importantly, MOR00208 demonstrated a synergistic activity with venetoclax *in vitro* experiments (MorphoSys data on file). A preclinical in vitro combination study was performed in order to investigate the potential of venetoclax to enhance the cytotoxic potential of MOR00208 against CD19-positive target cells. The general concept of this study was based on the fact that cytotoxic agents such as venetoclax are very potent in reducing initial tumor load. This is thought to increase the benefit of immune therapies which are known to be positively affected by low tumor mass, e.g. via more favorable effector-to-target (E:T) ratios. In a FACS-based ADCC assay the combination resulted in a synergistic enhancement of the cytotoxic activity compared to either drug alone. Combination of MOR00208 with venetoclax showed enhanced maximal cytotoxicity compared to MOR00208 alone and provide a promising rationale for the combination of MOR00208 and venetoclax in clinical trials.

Moreover, both compounds have a confirmed clinical activity as single agent in R/R CLL as previously detailed in the protocol and further data described in Section 4.2 suggest that adding an antibody to a small molecule like venetoclax can further deepen the response and increase clinical benefits for the patients which might translate into improved survival. Therefore, one can expect that the combination of anti-CD19 MOR00208 and venetoclax in a clinical setting may be more beneficial compared with single agent treatment.

Consequently, MorphoSys has developed the present protocol of an open-label study to evaluate the safety and preliminary efficacy of a combined treatment of MOR00208 with venetoclax in adult patients with R/R CLL previously treated with a BTK inhibitor (e.g., ibrutinib) in Cohort B. The main objective of this study is to offer a novel treatment option to patients whose disease relapsed or became refractory during or after therapy with a BTK inhibitor such as ibrutinib or who did not tolerate such therapy, taking into consideration that these patients have particularly dismal prognosis. As the combination therapy of MOR00208 and venetoclax will be evaluated for the first time in a clinical setting, a safety run-in phase was introduced in the study design as described in Section 7.1 and 10.4.

5.7 Rationale for Dose and Schedule of MOR00208 Administration

Based on the data from the following 3 clinical studies:

- XmAb5574-01, phase I trial in R/R CLL/SLL patients – completed
- MOR208C201, phase IIa trial in R/R NHL – ongoing
- MOR208C202, phase IIa trial in R/R ALL – terminated

where MOR00208 was administered as monotherapy, an integrated analysis was performed on safety, efficacy and PK data. As a result, no relationship between MOR00208 dose or MOR00208 exposure and toxicity-related events could be observed. This analysis also included R/R NHL patients from study MOR208C201, which were dosed at 12 mg/kg on a weekly basis for 3 months. Sixteen of these patients entered further maintenance treatment (biweekly or monthly MOR00208 administrations), and several of these 16 patients have been treated with MOR00208 for more than 1 year; treatment is still ongoing with no increase in incidences of toxicity-related events for MOR00208. For this reason, MOR00208 given at a dose of 12 mg/kg is considered to be safe and well tolerated, if applied on a weekly schedule for more than 2 months.

Furthermore, it could be shown in R/R CLL and R/R DLBCL patients that clinical efficacy clearly correlated with drug exposure over the first 2 cycles and that 12 mg/kg administered weekly for 2 cycles was the regimen which led most reliably to such beneficial drug levels. It could also be shown that several patients who continued treatment after more than 2 months and therefore kept high drug levels over time further improved in their clinical response.

Taken together, MOR00208 administered at 12 mg/kg was found to be safe and well tolerated in R/R CLL/SLL, NHL and ALL patients. Thus, 3 cycles of weekly dosing at 12 mg/kg (plus a loading dose on Day 4 of Cycle 1) followed by further treatment of biweekly dosing at the same dose level, followed by monthly treatment from Cycle 7 Day 1, is the regimen of choice for study MOR208C205.

5.8 Rationale for Washout Period of Previous Treatment

The disease may progress quickly, especially when ibrutinib therapy is stopped, which points to a need for clinical trials to allow shorter washout periods for these patients (Maddocks et al., 2015). Therefore, it is the opinion of the sponsor that a rather short washout period serves the best interest of the patients. Patients should resume anticancer treatment after the discontinuation of previous ibrutinib (or other BTK inhibitor) therapy as soon as possible due to the high unmet medical need for this patient population.

5.8.1 Therapeutic Antibodies from Previous Combination Treatment with Ibrutinib

Patients may have received combination treatment of ibrutinib with a therapeutic antibody prior to be enrolled into study MOR208C205. Although therapeutic antibodies typically show half-lives in the range of 2 to 3 weeks (e.g., RTX: median half-life 22 days in NHL patients, 32 days in CLL patients according to the FDA Prescribing Information), the washout phase for such patients is set to only 14 days. Therefore, a certain amount of the therapeutic antibody from previous treatment is still expected to be present after 14 days.

5.8.2 Previous Treatment with Ibrutinib and Other BTK Inhibitors

The terminal elimination half-life of ibrutinib is 4 to 6 hours according to FDA Prescribing Information (Appendix B) and 4 to 13 hours according to the European Summary of Product Characteristics (SmPC; Appendix B). Other BTK inhibitors are currently in phase I-III clinical development e.g., acalabrutinib (ACP-196; Acerta Pharma/AstraZeneca), CC-292 (AVL-292; Celgene), ONO-4059 (Ono/Gilead Sciences) and BGB-3111 (BeiGene). Acalabrutinib has a short mean half-life of 1 hour (Byrd et al., 2016b). The PK-PD relationship of CC-292 was assessed in healthy donors. After single oral dose of 2 mg/kg plasma concentration peaked within 30-120 minutes and declined to near or below the lower limit of detection within 24 hours post dose (Westlin et al., 2012; Evans et al., 2013). Based on results from a phase I study in patients with non-germinal center B-cell like diffuse large B cell lymphoma (non-GCB DLBCL) (ONO-4059POE001), ONO-4059 has a half-life of approximately 5-7 hours (Dyer et al., 2014). It can thus be assumed that the proposed 5-day washout period will suffice to largely clear ibrutinib and other BTK inhibitors from systemic circulation and also from peripheral compartments.

The half-life of BTK, i.e., the target protein of ibrutinib and other BTK inhibitors, is estimated up to 20 hours (Saffran et al., 1994; Yu et al., 2006; Evans et al., 2013). It can thus be assumed that the pharmacological effect of ibrutinib and other BTK inhibitors, i.e., the inhibition of BTK, will have already ceased after the proposed 5-day washout phase. This is also supported by the finding that free BTK protein levels recovered toward 75% of predose values within approximately 4 days after treatment with CC-292 (Evans et al., 2013).

Given the homology between BTK and interleukin-2 inducible tyrosine kinase (ITK), it was confirmed using molecular and phenotypic analysis that ibrutinib irreversibly inhibits ITK (Dubovsky et al., 2013). This also may be the case for the other above mentioned BTK inhibitors. ITK expression in FcγR-stimulated NK cells leads to increased calcium mobilization, granule release, and cytotoxicity (Khurana et al., 2007). As FcγR stimulation is requisite for antibody-dependent NK-cell mediated cytotoxicity (ADCC), it could be shown that ibrutinib abrogates RTX anti-tumor efficacy as a result of inhibition of FcγR-stimulated NK cell function *in vitro* and *in vivo* (Kohrt et al., 2014).

However, human NK cells have a turnover time in blood of about 2 weeks (Zhang et al., 2007), and thus it can be assumed that after a 5-day washout period of ibrutinib, before MOR00208 administration, NK cell activity will start to recover and will have fully recovered after the second dose of MOR00208 (C1D4).

Taken together, the proposed 5 day washout period is (i) sufficient to largely clear BTK inhibitors from the circulation based on available PK parameters, (ii) sufficient to largely revert the pharmacodynamic effect of BTK inhibitors based on the available data on the stability of the BTK protein and (iii) sufficiently allows clinical activity of MOR00208 as NK cell activity can be assumed.

5.9 Rationale for Biomarker Assessment

Several prognostic markers have been described that can be used as stratification factors for CLL/SLL therapies. These include del(17p), del(11q), del(13q14), trisomy 12, immunoglobulin heavy-chain variable (IGHV), NOTCH1 and TP53 mutations as well as serum parameters (thymidine kinase, β2 microglobulin) or CLL cell markers (CD38, ZAP-70). There is increasing evidence from prospective clinical trials that detection of certain chromosomal deletions has prognostic significance in CLL. For example, patients with leukemia cells that have del(17p) and/or TP53 mutations have an inferior prognosis and appear to be resistant to standard chemotherapy regimens (Hallek et al., 2008, Stilgenbauer et al., 2014). The presence of del(17p)/TP53 mutation and complex karyotype may also contribute to the genomic instability in CLL cells, and prior therapies can promote subclonal mutations and refractory disease in patients with CLL.

BTK mutations and clonal evolution may occur and produce ibrutinib resistance. There are recent data reported on acquired ibrutinib resistance and BTK mutation (C481S) and phospholipase Cγ2 mutation in patients with CLL who progressed on ibrutinib therapy (Woyach et al., 2014b). Further, expression levels of BCL2/BH3 protein family members have been analyzed and certain ratios might correlate with response to BCL2 inhibitors (Roberts et al., 2012).

Therefore, detection of these and other cytogenetic abnormalities could have prognostic value and may guide therapeutic decisions.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

To determine the safety of MOR00208 combined with idelalisib or venetoclax

6.1.2 Secondary Objectives

1. To determine the quality of the response
2. To assess the potential immunogenicity of MOR00208
3. To assess the pharmacokinetic (PK) profile of MOR00208

6.1.3 Exploratory Objectives

- To assess minimal residual disease (MRD) in patients achieving a complete or partial response
- To explore putative predictive biomarkers
- To determine and correlate prognostic factors with efficacy parameters

6.2 Study Endpoints

6.2.1 Primary Endpoint

Incidence and severity of adverse events (AEs)

6.2.2 Secondary Endpoints

1. Overall response rate (ORR): defined for Cohort A as percentage of patients achieving a complete response (CR), a partial response (PR) or a partial response with lymphocytosis (PRL), and for Cohort B as percentage of patients achieving a CR or a PR
2. Anti-MOR00208 antibody formation
3. Pharmacokinetic analysis for MOR00208

6.2.3 Exploratory Endpoints

- Proportion of patients with MRD-negativity
- Absolute and percentage change from baseline in measurements for B-, T- and NK cell populations
- Analysis of exploratory and diagnostic biomarkers from blood (e.g., CD19 expression, BTK and PLCγ2 mutational status, CD16 expression on NK cells, antibody dependent cell mediated cytotoxicity (ADCC) capacity, cytogenetics and mutational analysis).

7 INVESTIGATIONAL PLAN

7.1 Description of Study Design

This is a multicenter, two-cohort, open-label phase II study of MOR00208 combined with idelalisib (Cohort A) or venetoclax (Cohort B) for the treatment of adult patients with R/R CLL or R/R SLL pretreated with a BTK inhibitor as a single agent or as part of a combination therapy. Recruitment of a patient into Cohort A or B is at the discretion of the Investigator. A total of approximately 12 patients are planned to be enrolled in each cohort in Europe and the US. Figure 1 illustrates the design of the main study.

The main study will include a safety run-in phase for each cohort enrolling 10- approximately 12 patients per combination treatment. MOR00208 will be administered at a dose of 12.0 mg/kg as intravenous (IV) infusion, idelalisib in Cohort A as 150 mg oral tablets twice daily and venetoclax in Cohort B as 400 mg oral tablets daily dose. To mitigate the risk for TLS treatment of patients with venetoclax will be initiated after an initial treatment with MOR00208 at 20 mg up from C1D8 for 7 days, followed by a weekly ramp-up dosing schedule to the recommended daily dose of 400 mg. The safety run-in phase will be concluded with an evaluation of the safety data of all treated patients once 10 patients completed at least one treatment cycle in Cohort A or at least 5 weeks of combination treatment in Cohort B. The first 3 patients in Cohort A will be dosed sequentially at least 48 hours apart. In Cohort B all 10-approximately 12 patients will be dosed sequentially, at least one week apart.

In Cohort A there will be two safety evaluations. After completion of the first cycle the safety data of the first three patients will be evaluated. This evaluation will be done by an IDMC composed of experts in the field of oncology and clinical biostatistics who have no other role in the study and do not have an affiliation with the Investigators or the sponsor. After the evaluation of the safety data from the first 3 patients for Cycle 1 of treatment and a positive recommendation from the IDMC the next 7- approximately 9 patients may be dosed in parallel. An additional IDMC review will take place after 10 patients completed at least 1 cycle of treatment.

In Cohort B the safety evaluation will be performed by an IDMC after the first 10 patients completed at least 5 weeks of combination treatment. The evaluation will be done by the IDMC as already described. Importantly, all patients in Cohort B, who participate in the safety run-in phase, will be hospitalized on the day of the first two dose escalations of venetoclax (C1D8 and C1D15).

The criteria for the evaluation of safety of the combination therapy will be defined by the IDMC and laid down in the IDMC Charter of the trial.

If safety evaluation results in a recommended dose reduction of idelalisib or venetoclax, the sponsor will reconsider dosing and amend the protocol accordingly.

During the study, MOR00208 will be administered as infusions 12.0 mg/kg in 28-day cycles. From Cycle 1 to 3, each cycle will consist of weekly infusions (on Day 1, Day 8, Day 15 and Day 22). In Cycle 1, an additional loading dose will be administered on Day 4. From Cycle 4 to 6, MOR00208 will be administered on a biweekly basis with infusions on Day 1 and Day 15

of each cycle. Thereafter, MOR00208 will be administered on Day 1 of each cycle starting with Cycle 7 Day 1.

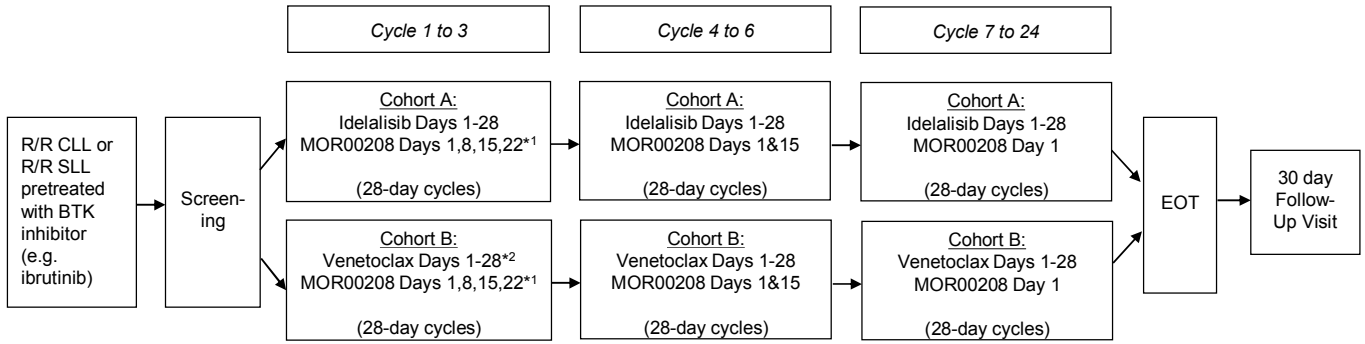
Idealisib will be self-administered twice daily starting on Day 1 of each cycle. Venetoclax will be self-administered (except during hospitalization) starting from Cycle1 Day8 and on Day1 of each cycle onwards. Treatment with idelalisib or venetoclax may be modified in a de-escalating fashion or discontinued based upon clinical and laboratory findings. In case idealisib or venetoclax treatment was stopped due to side effects suspected to be related to idealisib or venetoclax, the patient may continue MOR00208 treatment.

Progressive disease will require discontinuation of study medication.

Patients who benefit from treatment are allowed to continue MOR00208 treatment beyond Cycle 24 at Investigator's discretion. The total duration of the main study will be limited to a maximum of 5 years from first patient first visit or up to the timepoint of approximately 30 days after last patient received his last treatment, whichever comes first.

Patients completing the main study will be invited to participate in an optional biological marker sub-study as described in detail in Section 15.13 Appendix M.

Figure 1: Study Design



*1 Additional loading dose of MOR00208 on Cycle 1 Day 4

*2 Weekly ramp up of Venetoclax starting on Cycle 1 Day 8 (C1D8: 20mg, C1D15: 50mg, C1D22:100mg, C2D1: 200mg). Venetoclax dosis 400mg up from Cycle 2 Day 8

Abbreviations: EOT=end of treatment; BTK=Bruton's tyrosine kinase; R/R CLL=relapsed or refractory chronic lymphocytic leukemia; R/R SLL=relapsed or refractory small lymphocytic lymphoma.

7.2 Patient Selection Criteria

All patients must sign informed consent and meet the following selection criteria at screening and baseline to participate in the study.

7.2.1 Inclusion Criteria

Diagnosis/Trial Population

1. Age ≥18 years
2. Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL):
   a) history of diagnosis of CLL or SLL that meets IWCLL diagnostic criteria (Appendix C)
   b) histologically confirmed diagnosis of SLL by lymph node biopsy and documented within medical records
   c) indication for treatment as defined by the IWCLL guidelines (Appendix D)
3. Patients must have both of the following:
   a) relapsed[1] or refractory[2] disease while receiving a BTK inhibitor (e.g., ibrutinib) or intolerance of such therapy
   b) single-agent or combination therapy with a BTK inhibitor for at least one month must be the patient's most recent prior anticancer therapy

   [1] relapsed disease is defined as progressive disease in subjects who have previously achieved a PR or CR to most recent BTK inhibitor therapy
   [2] refractory disease is defined as progressive disease in subjects who have previously not achieved a PR or CR to most recent BTK inhibitor therapy, or stable disease as best response after 12 months of receiving the most recent BTK inhibitor therapy
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
5. Patients with a past medical history of autologous or allogeneic stem cell transplantation must exhibit full hematological recovery without any evidence or ongoing treatment of active graft versus host disease before enrolment into the study.

Laboratory Values

6. Patients must meet the following laboratory criteria at screening:
   - Adequate bone marrow function as follows:
   a) absolute neutrophil count (ANC) ≥ 1.0×10^9/L
   b) platelet count ≥ 30×10^9/L in the absence of clinically significant evidence of bleeding
   c) **Cohort B only:** hemoglobin ≥ 8.0 g/dL
   - Adequate hepatic and renal function as follows:
   d) total serum bilirubin ≤ 1.5 × ULN or ≤ 3 × ULN in cases of documented liver involvement by CLL (For patients with Gilbert's disease, serum bilirubin up to 3 × ULN is allowed provided normal direct bilirubin.)
   e) ALT and AST ≤ 2.5 × ULN or <3 ×ULN in cases of documented liver involvement by CLL

f) serum creatinine clearance calculated using a standard Cockcroft-Gault formula (Cockroft & Gault, 1976; see Appendix E) must be:
   - **Cohort A only:** ≥ 30 mL/min
   - **Cohort B only:** ≥ 50 mL/min

Other Inclusion Criteria

7. Females of childbearing potential (FCBP; see Appendix F) must:
   a) not be pregnant as confirmed by a negative serum pregnancy test at screening and a urine pregnancy test prior to starting study therapy
   b) refrain from breastfeeding and donating blood or oocytes during the course of the study and for 3 months after the last dose of study medication (Note: All female patients are prohibited to donate blood within the before mentioned time frame)
   c) agree to ongoing pregnancy testing during the course of the study, and until 3 months after study therapy has ended. This applies even if the patient practices complete and continued sexual abstinence
   d) commit to continued abstinence from heterosexual intercourse if it is in accordance with her lifestyle or agree to use and be able to comply with the use of highly effective contraception (see Appendix F) without interruption during the study and for 3 months after the last dose of study medication
   e) FCBP using hormonal contraceptives should add a barrier method as a second form of contraception since it is currently unknown whether idelalisib or venetoclax may affect the effectiveness of hormonal contraceptives
8. Males must use a highly effective method of contraception (see Appendix F) without interruption, if the patient is sexually active with a FCBP, refrain from donating blood or sperm during the study participation and for 3 months after the last dose of study medication
9. In the opinion of the Investigator the patients must:
   a) be able to understand, give written informed consent to, and comply with all study-related procedures, medication use, and evaluations
   b) not have a history of noncompliance in relation to medical regimens or be considered potentially unreliable and/or uncooperative

7.2.2 Exclusion Criteria

Diagnosis

1. Patients who have:
   a) non-Hodgkin's lymphomas other than CLL/SLL
   b) transformed CLL/SLL or Richter's syndrome as defined by the IWCLL (Hallek et al., 2008)
   c) active and uncontrolled autoimmune cytopenia

Previous and Current Treatment

2. Patients who have received treatment with a BTK inhibitor within 5 days prior to Day 1 dosing.
3. Patients who have, within 14 days prior to Day 1 dosing:
   a) not discontinued CD20-targeted therapy, chemotherapy, radiotherapy, investigational anticancer therapy or other lymphoma-specific therapy
   b) systemic corticosteroids in doses greater than prednisone equivalent to 20 mg/day (Exception: Patients with signs of rapidly progressing disease per discussion between the Investigator and sponsor's medical monitor)
   c) received live vaccines. (Note: Vaccinations against influenza with inactivated virus or vaccination for pneumococcal diseases are allowed.)
4. Patients who:
   a) have, in the opinion of the Investigator, not recovered sufficiently from the adverse toxic effects of prior therapies
   b) have a history of previous severe allergic reactions to prior monoclonal antibody therapy, and/or hypersensitivity to the active substances or to any of the inactive ingredients / excipients contained in the study drug formulations (for details see FDA Prescribing Information or EMA SmPC of Zydelig® (**Cohort A only**) or Venclexta® & Venclyxto® (**Cohort B only**))
   c) concurrently use other anticancer or experimental treatments
   d) were previously treated with:
      - CD19-targeted therapy (applicable for Cohort A and B)
      - **Cohort A only:** a PI3K inhibitor treatment (e.g., idelalisib, duvelisib)
      - **Cohort B only:** a BCL-2 inhibitor treatment (e.g., venetoclax)
   e) **Cohort B only:** has a known allergy to both xanthine oxidase inhibitors and rasburicase
   f) **Cohort B only:** has received strong or moderate CYP3A inhibitors or inducers within 7 days, or has consumed grapefruit, grapefruit products, Seville oranges or star fruit within 3 days prior to the first dose of venetoclax (see for details in the protocol)

Patient's Medical History

5. Prior history of malignancies other than CLL, unless the patient has been free of the disease for ≥5 years prior to screening. Exceptions to the ≥5 year time limit include a history of the following:
   a) basal cell carcinoma of the skin
   b) squamous cell carcinoma of the skin

c) carcinoma *in situ* of the cervix
d) carcinoma *in situ* of the breast
e) carcinoma *in situ* of the bladder
f) incidental histological finding of prostate cancer (Tumor/Nodes/Metastasis [TNM] stage of T1a or T1b)

6. Patients with myelodysplastic syndrome
7. Patients with systemic diseases (e.g., cardiovascular, renal, hepatic) that would in the Investigator's opinion preclude participation in the study or compromise the patient's ability to give informed consent
8. Patients with diagnosis of myocardial infarction within 6 months prior to enrolment, New York Heart Association (NYHA; see Appendix G) class II or higher congestive heart failure, uncontrolled angina pectoris, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemia or significant conduction system abnormalities, in the opinion of the Investigator. (Note: Patients with stable, asymptomatic atrial fibrillation are allowed in the study provided they do not meet the other cardiac exclusion criteria)
9. Patients who:
   a) suffered significant traumatic injury or underwent major surgery within 14 days prior to treatment start
   b) have not recovered from sequelae of traumatic injury or surgical operations until Day 1 dosing
10. Patients with central nervous system (CNS) involvement or impairment:
    a) CNS primary or secondary malignancy in present or past medical history (unless patient has been free of the disease for ≥ 5 years prior to screening)[1]
    b) CNS, meningeal or epidural malignancies (e.g., brain metastases, known leukemic meningeosis)[1]
    c) CNS lesions/cerebrovascular event(s) with clinically significant sequelae
    d) history or evidence of clinically significant cerebrovascular CNS that would in the Investigator's opinion preclude participation in the study or compromise the patient's ability to give informed consent.

[1] Note: Screening for cerebrospinal fluid (CSF)/CNS involvement is not required but may be performed at the discretion of the Investigator

11. Patients with:
    a) chronic diarrhoea and malabsorption syndrome
    b) any evidence of ongoing systemic viral, bacterial, or fungal infection (including Pneumocystis jirovecii pneumonia and Cytomegalovirus infection)
    c) history of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis
    d) **Cohort A only:** ongoing inflammatory bowel disease as ulcerative colitis or Crohn's disease
    e) **Cohort A only:** severe chronic obstructive pulmonary disease (COPD), or pulmonary emphysema or drug-induced pneumonitis diagnosed in previous medical history

12. Patients with known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV). (Additional information: no safety data on the use of CD19 antibodies in HIV positive patients are currently available)
13. Patients with known positive hepatitis B and/or C serology
    a) hepatitis B virus (HBV): patients with positive serology for HBV, defined as positivity for hepatitis B surface antigen (HBsAg) or total hepatitis B core antibody (anti-HBc). (Note: Patients positive for anti-HBc may be included if HBV DNA is not detectable, but have to be monitored in 2-month intervals via HBV DNA testing)
    b) hepatitis C virus (HCV): patients with positive HCV serology (defined as positive for HCV antibody [anti-HCV]) unless confirmed negative for HCV-ribonucleic acid (RNA)

7.2.3 Withdrawal Criteria

Patients may withdraw voluntarily from participation in the study or from study treatment at any time and for any reason. A patient's participation in the study may terminate at his/her request or on the basis of the Investigator's clinical judgment. The reason for patient withdrawal will be documented in the source data and noted on the electronic case report form (eCRF).

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations at the 30-Day Safety Follow-up visit.

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

It should be clearly documented in the source data whether patients withdrew their consent and will not enter the follow-up phase, or if patients withdrew their consent for study drug treatment but will continue further participation in the study.

Among the reasons for premature withdrawal are:

- Intercurrent illness (a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the patient's termination from the study)
- General or specific changes in the patient's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria
- Important protocol deviation (the patient's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements, e.g., drug noncompliance, failure to return for defined number of visits)

7.2.4 Study Treatment Discontinuation

Besides withdrawal of consent, there are further reasons for premature study treatment discontinuation of a patient, which may include but are not limited to:

- Death

- Adverse events
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Pregnancy
- Progression of disease
- Loss to follow-up
- Withdrawal of a patient at the specific request of the sponsor.

Please note:

- Patients who are withdrawn for any reason may not re-enter this clinical study at any time.
- For patients who are lost to follow-up, at least three attempts of contact should be made by the site and documented in the source data.

7.3 Investigator Study or Site Termination

The Investigator and the sponsor both reserve the right to terminate the study at any time at a given clinical study center. The sponsor also reserves the right to terminate the entire study, a specific cohort or temporarily interrupt enrolment in a specific cohort and/or dosing of already enrolled patients for further evaluation, for example, if during the ongoing evaluation of the risk/benefit ratio, the sponsor decides that the risks outweigh the benefits of MOR00208 and/or the combination partner idelalisib or venetoclax.

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

7.4 End of Study and Subsequent Treatment

The end of the main study is reached for an individual patient, if any of the following applies:

- Patient has withdrawn consent (see Section 7.2.3)
- Patient has completed 30-Day Safety Follow-up visit
- Study treatment was permanently discontinued (see Section 7.2.4)

The individual end of the main study is defined by the above criteria, whichever occurs first.

The end of the main study is defined as 5 years after the first patient was enrolled (C1D1) or approximately 30 days after last patient received his last treatment, whichever comes first. The whole study will end after the completion of both the main and sub-study (see for details in Section 12.11 and 15.13.5). At the end of the study, access to MOR00208 treatment can be made available to those patients who continue to derive benefit from MOR00208 treatment.

8 TREATMENTS

8.1 Study Treatments

In this open-label study the treatment consisting of MOR00208 and idelalisib or venetoclax will be as scheduled, until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first.

Each Investigator is responsible for ensuring that deliveries of study drugs and other study materials from the sponsor and other drugs from the appropriate suppliers are correctly received, recorded, handled and stored safely and properly in accordance with all applicable regulatory guidelines, and used in accordance with this protocol. The Investigator can delegate these tasks to another person (according to the local laws and regulations). Drug accountability forms will be kept by each site participating in the study and will be checked during monitoring visits. All dosages prescribed to the patient and all dose changes during the study must be recorded in the eCRF.

Study drug must be handled and/or prepared as described in the Study Drug Preparation Manual, the Investigator Brochure (IB) for MOR00208, and other safety-relevant documents (e.g., the Prescribing Information by US FDA and the European SmPC for idelalisib or the Prescribing Information by US FDA for venetoclax).

MOR00208 and idelalisib or venetoclax will be centrally supplied. Other medications will be provided by the investigative site and not by the sponsor.

8.1.1 MOR00208

MOR00208 drug product (DP) must be stored under refrigeration at 2 to 8°C in its original package in an appropriate storage facility accessible only to the pharmacist(s), the Investigator, or a duly designated person.

MOR00208 DP is a yellowish lyophilisate supplied in single-use 20 mL glass vials. Each vial contains 200 mg of MOR00208 for reconstitution with 5 mL water for injection (WFI).

Reconstitution yields 40 mg/mL MOR00208 in 25 mM sodium citrate, 200 mM trehalose and 0.02% (w/v) polysorbate 20 at pH 6.0. Each product vial is intended to deliver 200 mg of MOR00208 in 5 mL of reconstituted solution. The solution after reconstitution is colorless to slightly yellow and essentially free of foreign particles; it may contain a few white to whitish product-related particles.

For administration, MOR00208 will be diluted into a commercially available 250 mL infusion container with 0.9% (w/v) sodium chloride for injection.

MOR00208 will be administered IV at a dose of 12.0 mg/kg**.** For the first 3 months (3 cycles) of the study, each cycle will consist of a MOR00208 infusion on Day 1, Day 8, Day 15 and Day 22 of the cycle. In addition, a loading dose will be administered on Day 4 of Cycle 1. Thereafter, MOR00208 will be administered on a biweekly basis (every 14 days) with infusions on Day 1 and Day 15 of each cycle from Cycle 4 to 6, and on a monthly basis on Day 1 of each cycle from Cycle 7 Day 1.

The individual MOR00208 infusion will be prepared under aseptic conditions and administered at the study site, according to the directions of the sponsor, which will be provided in a Study Drug Preparation Manual. In general, a vial of MOR00208 must be used as soon as possible after reconstitution with WFI. Any solution remaining in the vial has to be discarded. After dilution for infusion, administration of MOR00208 should take place as soon as possible. Maximum allowed storage times and conditions will be detailed in the Study Drug Preparation Manual.

For the first infusion, the intravenous (IV) infusion rate should be 70 mL/h for the first 30 minutes and subsequently increased to a rate of 125 mL/h; the total infusion duration should ideally not exceed 2.5 hours. All subsequent MOR00208 infusions will be administered IV at a constant rate of 125 mL/h over an approximately 2-hour period. MOR00208 should not be administered as an IV push or bolus.

8.1.2 Idelalisib

Idelalisib is supplied as film coated tablets of 150 mg or 100 mg. They are to be stored at 20 to 30°C (US only). Tablets should be dispensed from the original bottle.

The recommended starting dose is 150 mg orally, twice daily (BID). It may be taken with or without food approximately at the same time of the day. Ideally, doses should be taken at ~12-hour intervals (e.g., at ~8 AM and at ~8 PM) on a BID schedule beginning ~30 minutes prior to the initial MOR00208 infusion.

Treatment may be continued as scheduled until progression of disease, withdrawal of consent, unacceptable toxicity, death or patient is lost to follow-up, whichever occurs first.

If the patient misses a dose of idelalisib within 6 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal dosing schedule. If a patient misses a dose by more than 6 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

Idelalisib (Zydelig®) contains the azo coloring agent sunset yellow FCF (E110), which may cause allergic reactions.

8.1.3 Venetoclax

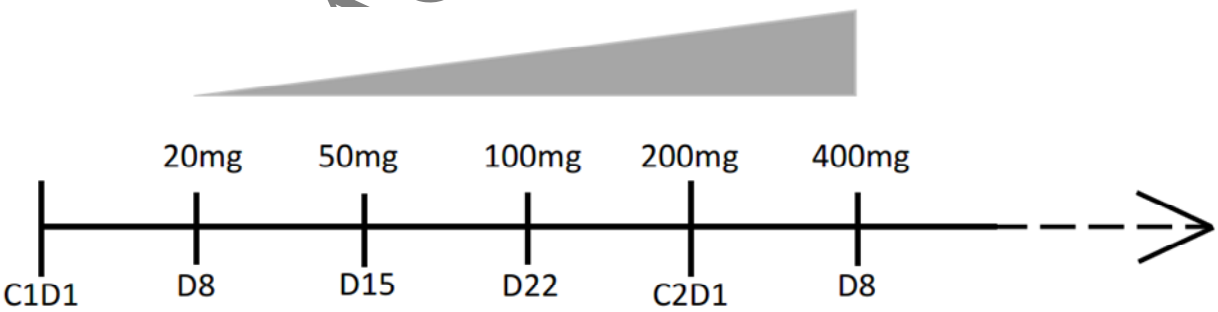
Venetoclax 10 mg, 50 mg and 100 mg tablets as commercially available for oral administration. They are to be stored at or below 30°C (86°F; US only).

Venetoclax dose should be administered according to a weekly ramp-up schedule over 5 weeks to the recommended daily dose of 400 mg. Figure 2 illustrates this initial ramp-up. Dosing schedule for ramp-up phase as follows, daily dose of venetoclax: 20 mg 1st week of combination treatment, 50 mg 2nd week, 100 mg 3rd week, 200 mg 4th week and 400 mg 5th week and thereafter. The 5-week ramp-up dosing schedule, starting on C1D8, is designed to gradually reduce tumor burden (debulk) and decrease the risk of tumor lysis syndrome (TLS). Assessment of patient-specific factors for level of risk of TLS and prophylaxis for TLS should be performed prior to first dose of venetoclax (see Section 8.10.1).

The first 4 weeks of venetoclax treatment will be supplied with respective venetoclax tablets, according to the ramp-up schedule. Once the ramp-up phase is completed, the 400 mg dose is achieved using 100 mg tablets supplied as monthly package of 120 tablets.

Venetoclax should be taken as scheduled orally once daily until disease progression or unacceptable toxicity is observed. Venetoclax tablets should be taken with a meal and water at approximately the same time each day. Tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing. If the patient misses a dose within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal daily dosing schedule. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the next day. If the patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time.

Figure 2: Ramp-up Dosing Schedule for Venetoclax



8.2 Pre-Medication for MOR00208 Infusions

IRRs have commonly been reported for patients with CLL or NHL treated with MOR00208.

Therefore, pre-medication including:

- Antipyretics (e.g., acetaminophen [paracetamol] 500-1000 mg per dose orally [PO] or IV or equivalent),
- Histamine H_1 receptor blockers (e.g., diphenhydramine 25–50 mg per dose IV or equivalent) and
- Glucocorticosteroids (methylprednisolone 80–120 mg per dose IV or equivalent (see Appendix H)

should be given for the first 3 infusions. In medically justified cases, the Investigator may repeat doses of individual agents as required and use other agents, doses and/or formulations in accordance with institutional guidelines. Any pre-medication given should be reported in the eCRF.

Pre-medication for patients who do not experience any IRRs to MOR00208 during the first 3 infusions (doses) will be optional for subsequent infusions at the discretion of the Investigator. Otherwise, the pre-medication should be continued for subsequent administrations of MOR00208.

8.3 Patient Monitoring During MOR00208 Infusion

Vital signs should be measured as outlined in Section 9.3.2.2. All supportive measures consistent with optimal patient care will be provided throughout the study according to institution standards.

Precautions for anaphylaxis should be observed during MOR00208 administration. Emergency resuscitation equipment and medications should be readily available. Additional supportive measures should also be available and may include, but are not limited to, epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen (paracetamol).

8.4 Management of MOR00208 Infusion-Related Reactions

Infusion-related reactions (IRRs) will be defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03 (see Table 3) or higher.

Table 3: **Definition of Infusion-Related Reactions and Cytokine Release Syndrome**

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
IRR	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (i.e., not rapidly responsive to symptomatic medication, brief interruption of infusion, or both); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; consequences; pressor or ventilatory support indicated

Abbreviations: IRR=infusion-related reaction; IV=intravenous; NSAIDs=non-steroidal anti-inflammatory drugs.

Note: An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnoea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritis/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); vomiting.

Management of Grade 2 IRRs

If a patient presents with a Grade 2 infusion reaction:

- The infusion should be stopped immediately.
- The patient should receive appropriate further treatment with an antihistamine and/or acetaminophen (paracetamol) or methylprednisolone (or equivalent) if clinically indicated.
- Once the symptoms have been resolved or reduced to ≤Grade 1 according to Investigator assessment, the infusion can be continued at an infusion rate of 50%. If, after one hour, the patient's symptoms do not return and vital signs are stable, the infusion rate may be increased every 30 minutes, as tolerated, to the baseline rate.

If a patient who developed a Grade 1 or 2 IRR receives further infusions, then pre-medication should be given before all subsequent infusions of MOR00208.

Management of Grade 3 IRRs

If a patient presents with a grade 3 IRR:

- The infusion should be stopped immediately.
- The patient must receive appropriate treatment with an antihistamine and/or acetaminophen (paracetamol) or methylprednisolone (or equivalent) and, if necessary, further medications (i.e., epinephrine, bronchodilator).
- Once the symptoms have been resolved or reduced to ≤Grade 1, and after having received appropriate prophylactic medication(s) as described above, the infusion may be resumed at an infusion rate of 25%. If, after 1 hour, the patient's symptoms do not return and vital signs are stable, the infusion rate may be increased to a maximum of 50%.
- If, after the resumption of infusion, symptoms return (irrespective of grade), the infusion must be stopped immediately and the infusion tubing should be disconnected from the patient. Based on the Investigator's decision the patient may receive further study drug(s), provided clinically appropriate precautions are undertaken. Infusion of MOR00208 should be discontinued permanently upon the third Grade 3 infusion reaction.

Management of Grade 4 IRRs

If a patient presents with a Grade 4 IRR:

- The infusion should be stopped immediately and the infusion tubing should be disconnected from the patient.
- The patient should receive appropriate treatment with an antihistamine and/or acetaminophen (paracetamol) or methylprednisolone (or equivalent) and, if necessary, further medications (i.e., epinephrine, bronchodilator).

The patient must not receive further infusions of MOR00208 that is judged by the Investigator to be the cause of the IRR, but should continue treatment with the other study drug as per protocol.

8.5 Definition for Tumor Lysis Syndrome and Prophylaxis in Cohort B

8.5.1 Definition of Tumor Lysis Syndrome

The tumor lysis syndrome occurs when tumor cells release their contents into the bloodstream, either spontaneously or in response to therapy, leading to the characteristic findings of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. These electrolyte and metabolic disturbances can progress to clinical toxic effects, including renal insufficiency, cardiac arrhythmias, seizures, and death due to multiorgan failure (Howard et al., 2011). Clinical manifestations may include nausea, vomiting, lethargy, oedema, fluid overload, congestive heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope and possibly sudden death. The clinical manifestations may have their onset prior to initiation of cytotoxic therapy but more commonly present within 12–72 h after administration of cytotoxic therapy (Cairo et Bishop, 2004).

In the current classification system the tumor lysis syndrome can be classified as laboratory or clinical as described in Table 4. In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death (Howard et al., 2011).

Table 4: Definitions of Laboratory and Clinical Tumor Lysis Syndrome

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid >8.0 mg/dL (475.8 µmol/L) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus >4.5 mg/dL (1.5 mmol/L) in adults or >6.5 mg/dL (2.1 mmol/L) in children	
Hyperkalemia	Potassium >6.0 mmol/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dL (1.75 mmol/L) or ionized calcium <1.12 (0.3 mmol/L) *	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia

Acute kidney injury **	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) (or a single value >1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hr for 6 hr

* The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4 − albumin in grams per deciliter).

** Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome (Levin et al., 2007)

8.5.2 Prophylaxis for Tumor Lysis Syndrome in Cohort B

Patients enrolling in Cohort B will be assessed for TLS risk and categorized in a risk category at screening Prior to the initiation of the first doses of MOR00208 medical prophylaxis for TLS should be initiated according to the institutional standard of care.

Administration of venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 5-week ramp-up phase with venetoclax. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose and at each dose increase. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Therefore, tumor burden assessments, including radiographic evaluation (e.g., CT scan), blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) should be performed in all patients and the pre-existing abnormalities should be corrected prior to initiation of treatment with venetoclax. Reduced renal function (creatinine clearance [CrCl] <80 mL/min) further increases the risk. The risk may decrease as tumor burden decreases. Table 5 describes the recommended TLS prophylaxis and monitoring during treatment with venetoclax based on tumor burden determination from clinical trial data. Importantly, all patients in Cohort B, who participate in the safety run-in phase, will be hospitalized on the day of the first two dose escalations of venetoclax (C1D8 and C1D15).

Table 5: Recommended TLS Prophylaxis Based on Tumor Burden From Clinical Trial Data of Venetoclax

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring[c,d]
		Hydration[a]	Antihyperuricemics	Setting and Frequency of Assessments
Low	All LN <5 cm AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol[b]	Outpatient • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses • Consider hospitalization for patients with CrCl <80mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Oral (1.5-2 L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital at first dose of 20 mg and 50 mg • Pre-dose, 4, 8,12 and 24 hours Outpatient at subsequent ramp-up doses • Pre-dose, 6 to 8 hours, 24 hours

Note: Consider all patient comorbidities before final determination of prophylaxis and monitoring schedule.
[a]Administer intravenous hydration for any patient who cannot tolerate oral hydration.
[b]Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.
[c]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[d]For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose

8.6 Dose Modifications of MOR00208

In a phase I study of MOR00208 in CLL, the MTD was not reached and the drug was generally well tolerated, IRRs of grade 1 or 2 being the most common toxicities. Treatment-related grade 3 or 4 AEs occurred in 5 out of 27 patients and included neutropenia, thrombocytopenia, increased AST, febrile neutropenia, and TLS. There was one CLL patient with dose-limiting toxicity (DLT) of grade 4 neutropenia lasting ≥ 7 days with febrile neutropenia

Dose reductions of MOR00208 are not allowed during the course of the study due to the relatively mild AE profiles of MOR00208.

In the case of clinically significant grade ≥3 toxicities that are not described in Table 8 & Table 9 and Sections 8.9 & 8.10:

- MOR00208 doses should be omitted until the toxicity grading diminishes in severity to grade ≤1 or returns to a baseline grade, provided the condition was pre-existing at baseline
- Missed doses of MOR00208 should not be made up for. If the patient misses a subsequent MOR00208 dose, the second missed dose should be administered immediately after the toxicity resolves.
- During monthly treatment with MOR00208, every missed dose should be administered immediately after the toxicity resolves.

If the Investigator considers a clinical finding and/or laboratory parameter change to represent natural fluctuation or progression of the underlying disease, then it will be at the Investigator's discretion (and depend on the assessment of the individual risk/benefit ratio) to determine whether the patient should be dosed. The decision and rationale behind the decision should be documented in the source data.

For MOR00208 dose modification instructions for specific toxicities, see Table 8 & Table 9 and Sections 8.9 & 8.10.

8.7 Dose Modifications of Idelalisib

In the event of severe or life-threatening toxicities related to idelalisib, the drug must be withheld until the toxicity is resolved. If resuming idelalisib after interruption, reduce the dose to 100 mg twice daily. Re-escalation to 150 mg twice daily is allowed at the Investigator's discretion.

Recurrence of severe or life-threatening idelalisib-related toxicity upon rechallenge should result in permanent discontinuation of idelalisib.

For dose modification instructions for specific toxicities related to idelalisib, see Section 8.9 and Table 8.

8.8 Dose Modifications of Venetoclax

8.8.1 General Rules

Dose should be interrupted or reduced for toxicities. For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than

2 weeks when at the daily dose of 400 mg, reassess for risk of TLS to determine if reinitiation with a reduced dose is necessary (e.g., all or some levels of the dose ramp-up schedule).

For dose modification instructions for specific (hematologic and other) toxicities related to venetoclax see Table 6 below and Table 9 in Section 8.10.

Table 6: Dose Modification for Toxicity During Venetoclax Treatment

Dose at Interruption, mg	Restart Dose, mg[a]
400	300
300	200
200	100
100[b]	50
50[b]	20
20[b]	10

[a]During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose.
[b]Dose reductions below 100 mg are not allowed after the ramp-up phase.

8.8.2 Dose Modifications During the Ramp-up Phase

Dose should be interrupted or reduced for toxicities according to Table 6 and Table 9.

Ramp-up phase of venetoclax will be performed at regular scheduled visits. In cases when dose modification of venetoclax needs to be performed at an unscheduled visit (e.g., due to dosing interruption or reduction of venetoclax which leads to changed treatment schedule of venetoclax), relevant evaluations and safety measures should be performed (see Section 9.2.8).

In exceptional cases duly justified due to other reasons, during the safety run-in phase patients might discontinue venetoclax treatment permanently per discussion between the Investigator and sponsor's medical monitor to ensure patient safety.

8.8.3 Dose Modifications After the Ramp-up Phase

Dose should be interrupted or reduced for toxicities according to Table 6 and Table 9.

Note: Dose modifications below 100 mg daily dose are not allowed, once the individual highest dose of venetoclax is reached. Patients who need dose reductions below 100 mg daily dose should discontinue venetoclax treatment permanently and may proceed with MOR00208 treatment only, per discussion between the Investigator and sponsor's medical monitor.

8.8.4 Dose Modifications of Venetoclax for Use with CYP3A, P-gp, BCRP and OATP Inhibitors

Concomitant use of venetoclax with *strong or moderate* CYP3A inhibitors (e.g., strong: ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole and voriconazole; moderate: erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil) or inducers (e.g., strong: carbamazepine, phenytoin, rifampin, St. John's wort; moderate: bosentan, efavirenz, etravirine, modafinil, nafcillin) during ramp-up phase is

contraindicated. Co-administration of CYP3A4 inducers may lead to decreased venetoclax exposure and consequently a risk for lack of efficacy. Concomitant use of venetoclax with strong CYP3A inhibitors increases venetoclax exposure (i.e., C_{max} and AUC) and may increase the risk for TLS during ramp-up phase. For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 50% when moderate CYP3A inhibitors and 75% when *strong* CYP3A inhibitors must be used concomitantly, but not below 100 mg. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor.

Venetoclax is a P-gp, breast cancer resistance protein (BCRP) and organic anion-transporting polypeptide (OATP) inhibitor in vitro. Therefore, avoid concomitant use of venetoclax with P-gp and BCRP inhibitors and substrates (BCRP substrates: e.g., digoxin, dabigatran, everolimus, sirolimus; P-gp substrates: e.g., digoxin, everolimus, and sirolimus) and consider alternative treatments. If a statin (OATP substrate) is used concomitantly with venetoclax, close monitoring of statin-related toxicity is recommended. In vitro data suggest venetoclax has inhibition potential on P-gp substrates at therapeutic dose levels in the gut. Co-administration of a single dose of rifampin, a P-gp inhibitor, increased venetoclax C_{max} by 106% and $AUC_{\infty}$by 78%. Therefore, if a narrow therapeutic index P-gp inhibitor must be used, then it should be taken at least 6 hours before venetoclax and reduce the venetoclax dose by at least 50%, but not below 100 mg after the ramp-up phase. Monitor these patients more closely for signs of toxicities. Resume the venetoclax dose that was used prior to initiating the P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.

The recommendations for managing drug-drug interactions are summarized in Table 7.

Table 7: Management of Potential Venetoclax Interactions with CYP3A Inhibitors or Inducers, BCRP and P-gp Inhibitors and Substrates

Inhibitors	Ramp-Up Phase	Steady Daily Dose (After Ramp-Up Phase)
Strong and moderate CYP3A inhibitors and inducers	Contraindicated	Avoid inhibitor use or reduce venetoclax dose by at least 75% when strong and 50% when moderate CYP3A inhibitors, but not below 100 mg
P-gp and BCRP inhibitors and substrates	P-gp and BCRP inhibitors, or narrow therapeutic index P-gp substrates; furthermore, grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with venetoclax. If a P-gp inhibitor must be used, reduce venetoclax dose by at least 50%, but not below 100 mg after the ramp-up phase. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.	

8.9 Guidance for Managing Specific Adverse Events for the Combination of MOR00208 and Idelalisib

Recommendations for managing specific adverse events (based on the FDA Prescribing Information and the European SmPC) are summarized in Table 8.

Table 8: Guidance for Study Drug (Idelalisib/MOR00208) Dose Modifications Based on Type and Severity of Treatment-Emergent Adverse Events or Laboratory Abnormalities

NCI CTCAE Grade	Recommendation	
	Idelalisib	MOR00208
HEMATOLOGICAL ADVERSE EVENTS		
Neutropenia		
Grade 2 (<1.5-1.0 x 10^9/L)	Maintain current dose level and schedule.	Maintain dosing as per protocol.
Grade 3 (<1.0-0.5 x 10^9/L)	Maintain current idelalisib dose level and schedule. Monitor ANC at least weekly. Consider growth factor support.	Maintain dosing as per protocol. Monitor ANC at least weekly. Consider growth factor support.
Grade 4 (<0.5 x 10^9/L) or occurrence of neutropenic fever or infection	Withhold idelalisib and monitor ANC at least weekly until ANC ≥0.5x10^9/L and/or neutropenic fever or infection is resolved. Thereafter may resume idelalisib at lower (100 mg BID) dose at Investigator's discretion. Consider growth factor support.	Withhold MOR00208 and monitor ANC at least weekly until ANC ≥0.5x10^9/L and/or neutropenic fever or infection is resolved. Thereafter, may resume as per protocol. Consider growth factor support.
Thrombocytopenia		
Grade 2 (<75-50 x 10^9/L)	Maintain current dose level and schedule.	Maintain dosing as per protocol.
Grade 3 (<50-25 x 10^9/L)	Maintain current dose level and schedule. Monitor platelets at least weekly.	Maintain dosing as per protocol. Monitor platelets at least weekly.
Grade 4 (<25 x 10^9/L)	Withhold idelalisib until platelet count reach ≥25x10^9/L. Consider transfusion support. Monitor platelets at least weekly. May resume idelalisib at lower (100 mg BID) dose level when platelet counts have returned to ≥25x10^9/L.	Withhold MOR00208 until platelet count reach ≥25x10^9/L. Consider transfusion support. Monitor platelets at least weekly. Thereafter, may resume dosing as per protocol.
Anemia		
Grade ≥3 (Grade 3 defined as: Hemoglobin <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated)	Maintain dosing as per protocol. Consider transfusion and growth factor support in accordance with institutional guidelines.	Maintain dosing as per protocol. Consider transfusion and growth factor support in accordance with institutional guidelines.
Grade 4 (Life-threatening consequences; urgent intervention indicated)	Withhold idelalisib until Grade 3 and monitor at least weekly. Thereafter, maintain dosing as per protocol.	Withhold MOR00208 until Grade 3 and monitor at least weekly. Thereafter, maintain dosing as per protocol.

NCI CTCAE Grade	Recommendation	
	Idelalisib	MOR00208
NON-HEMATOLOGICAL ADVERSE EVENTS		
Dermatological Events		
Grade ≤2	Maintain current dose and schedule. Monitor patients for the development of severe cutaneous reactions.	Maintain dosing as per protocol. Monitor patients for the development of severe cutaneous reactions.
Grade 3 or 4	Withhold idelalisib until Grade ≤1 is reached. May resume at lower dose (100 mg BID) at Investigator's discretion. Discontinue idelalisib permanently if rechallenge results in recurrence of Grade 3-4 toxicity.	Withhold MOR00208 until Grade ≤2 is reached and thereafter may resume dosing as per protocol.
CAVE: Stevens-Johnson syndrome/ Toxic epidermal necrolysis	If Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, treatment with idelalisib should be immediately and permanently discontinued and the patient treated accordingly.	If Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, treatment with MOR00208 should be immediately and permanently discontinued and the patient treated accordingly.
Gastrointestinal Events (Diarrhea/Colitis)		
All Grades	Obtain patient history, perform physical examination and diagnostic work-up to rule out infectious etiology. Provide adequate symptomatic support including oral hydration/i.v. fluid supplementation, dietary modification and antimotility agents as warranted. Supportive care should provided until diarrhea Grade≤1. If the infection can be ruled-out follow below mentioned diarrhea-management recommendations. For patients who develop severe abdominal pain, particularly if early during therapy, the possibility of a bowel obstruction or perforation should be considered. Appropriate clinical and radiographic examination should be performed, and supportive care and surgical intervention should be considered. Idelalisib treatment should be discontinued permanently in patients who experience intestinal perforation (see details in Section 8.9.2).	
Grade 2 (increase of 4-6 stools per day over baseline – moderate diarrhea)	Maintain dosing as per protocol. Monitor at least weekly until resolved.	Maintain dosing as per protocol. Monitor at least weekly until resolved.
Grade 3 (increase of ≥ 7 stools per day over baseline, fecal incontinence – severe diarrhea)	Withhold idelalisib until Grade ≤1. Monitor at least weekly until resolved, then may resume at lower dose (100 mg BID).	Maintain dosing as per protocol. In case diarrhea/colitis does not respond to antimotilty agents or patient's general condition deteriorates, withhold MOR00208 until Grade ≤2 is reached and thereafter may resume dosing as per protocol.
Grade 4 (life-threatening)	Discontinue idelalisib permanently.	Withhold MOR00208 until Grade ≤2 is reached and thereafter may resume dosing as per protocol.

NCI CTCAE Grade	Recommendation	
	Idelalisib	MOR00208
Hepatic Events (Elevations in ALT, AST, or bilirubin)		
Grade 2 (ALT/AST>3-5xULN) (Bilirubin>1.5-3xULN)	Maintain current dose level and schedule. Monitor ALT, AST and bilirubin at least weekly.	Maintain dosing as per protocol. Monitor ALT, AST and bilirubin at least weekly.
Grade 3 (ALT/AST>5-20xULN) (Bilirubin>3-10xULN)	Withhold idelalisib. Monitor for liver toxicity at least weekly until all abnormalities are Grade ≤1 or to baseline values.Then may resume at lower dose (100 mg BID).	Withhold MOR00208. Monitor for liver toxicity at least weekly until all abnormalities are Grade ≤1 or to baseline values. Thereafter, may resume dosing as per protocol.
Grade 4 (ALT/AST>20xULN) (Bilirubin>10xULN)	Discontinue idelalisib permanently.	Withhold MOR00208. Monitor for liver toxicity at least weekly until all abnormalities are Grade ≤1 or to baseline values. Thereafter, may resume dosing as per protocol.
Pulmonary Events (Pneumonitis or Organizing pneumonia)		
Grade 1	Maintain current dose and schedule if patient is asymptomatic. CAVE: If pneumonitis or organizing pneumonia is suspected with any severity of symptoms, interrupt idelalisib treatment until the etiology of the pulmonary symptoms has been determined. Patients with pneumonitis or organizing pneumonia thought to be caused by idelalisib should be treated with discontinuation of idelalisib and administration of corticosteroids. Monitor patient until resolved.	Maintain dosing as per protocol. Monitor patient until resolved or symptoms subside.
Grade 2	Discontinue idelalisib permanently.	Maintain dosing as per protocol. Monitor patient until resolved.
Grade ≥3	Discontinue idelalisib permanently.	Withhold MOR00208 until toxicity diminishes in severity to Grade ≤2. Thereafter, may resume dosing as per protocol.
Serious infections		
Pneumocystis jirovecii pneumonia (PJP)		
Prophylaxis for PJP during and after idelalisib treatment	**Prophylaxis for PJP should be administered to all patients throughout idelalisib treatment, and for a period of 2 to 6 months after discontinuation**. The duration of post-treatment prophylaxis should be based on clinical judgment and may take into account a patient's risk factors such as concomitant corticosteroid treatment and prolonged neutropenia.	
Any Grade	Idelalisib treatment should be interrupted in patients with suspected PJP infection of any grade and permanently discontinued if PJP infection is confirmed. Appropriate	MOR00208 administration should be withheld for patients with suspected PJP infection of any grade and permanently discontinued if PJP infection is confirmed. Appropriate

NCI CTCAE Grade	Recommendation	
	Idelalisib	MOR00208
	medical therapy or other interventions should be instituted.	medical therapy or other interventions should be instituted.
Cytomegalovirus (CMV)		
CMV monitoring	A central CMV laboratory test (serology and polymerase chain reaction [PCR]) will be performed for all patients at screening. Patient with negative serology should be monitored locally in accordance with institutional guidelines. Patient with positive serology or with other evidence of a history of CMV infection should be carefully monitored with a PCR based methodology: • monthly, if the initial PCR result was negative without associated clinical signs of CMV infection • weekly, if significant CMV viremia is detected.	
Any Grade	For patients with evidence of CMV viremia and clinical signs of CMV infection, idelalisib should be immediately interrupted until the infection has resolved per discussion between the Investigator and sponsor's medical monitor. If the benefits of resuming idelalisib are judged to outweigh the risks, consideration should be given to administering pre-emptive CMV therapy in accordance with institution al guidelines.	For patients with evidence of CMV viremia and clinical signs of CMV infection, MOR00208 should be immediately interrupted until the infection has resolved per discussion between the Investigator and sponsor's medical monitor. If the benefits of resuming MOR00208 are judged to outweigh the risks, consideration should be given to administering pre-emptive CMV therapy in accordance with institutional guidelines.

8.9.1 Management of Hepatic Events

Hepatotoxicity (Elevations in ALT, AST or bilirubin)

Background: Fatal and/or serious hepatotoxicity occurred in 14% of idelalisib treated patients. Elevations in ALT and AST of Grade 3 and 4 (>5xULN) have been observed in clinical studies of idelalisib. In general, these laboratory findings occurred within the first 12 weeks of treatment; they were generally asymptomatic and were reversible with dose interruption. Most patients resumed treatment at a lower dose without recurrence. After resumption of treatment at a lower dose, 26% of patients had recurrence of ALT and AST elevations. The anticipated possible risks associated with the administration of MOR00208 to patients include ALT and AST increases; however, there was only one non-serious Grade 3 AE reported related to MOR00208 in a phase I trial of R/R CLL.

Management: In the event of **Grade 3** hepatic adverse events of elevations in ALT, AST or bilirubin, idelalisib treatment should be withheld. Liver enzymes and bilirubin should be monitored at least weekly until all abnormalities reached Grade ≤1 or returned to baseline values, then idelalisib treatment may be resumed at lower dose (100 mg BID). Idelalisib treatment must be discontinued permanently in the event of **Grade 4** hepatic adverse events of elevations in ALT, AST or bilirubin.

In the event of **Grade 3 or 4** hepatic adverse events of elevations in ALT, AST or bilirubin, MOR00208 administration should be withheld and liver enzymes and bilirubin should be monitored at least weekly until all abnormalities reached Grade ≤1. Thereafter, dosing of MOR00208 may be resumed as per protocol.

8.9.2 Management of Gastrointestinal Events

Diarrhea/colitis

Background: Fatal and/or serious and severe diarrhea or colitis occurred in 14% of idelalisib treated patients across clinical trials. Diarrhea due to idelalisib can occur at any time and responds poorly to antimotility agents. Median time to resolution across trials ranged between 1 week and 1 month following interruption of idelalisib therapy and, in some instances, use of corticosteroids. Cases of severe drug-related colitis occurred relatively late (months) after start of idelalisib therapy, sometimes with rapid aggravation, but resolved within a few weeks with dose interruption and additional symptomatic treatment (e.g., anti-inflammatory agents such as enteric budesonide). There is very limited experience from the idelalisib treatment of patients with a history of inflammatory bowel disease.

Only mild and moderate (Grade ≤2) non-serious gastrointestinal AEs including diarrhea, constipation and abdominal pain occurred among CLL patients treated with MOR00208.

Management: Providing an antidiarrheal (e.g., loperamide) may lessen symptoms. Consideration should be given to intervene with enteric steroidal (e.g., budesonide) or non-steroidal (e.g., sulfasalazine) anti-inflammatory agents.

In the event of **Grade 3** diarrhea/colitis, treatment with idelalisib must be withheld until Grade ≤1. Patient should be monitored at least weekly until diarrhea/colitis has resolved, thereafter, treatment with idelalisib may be resumed at lower dose (100 mg BID).

In the event of **Grade 3** diarrhea/colitis, MOR00208 treatment should be maintained as per protocol. In case diarrhea/colitis does not respond to antimotilty agents or patient's general condition deteriorates, MOR00208 must be withheld until Grade ≤2 is reached and thereafter dosing of MOR00208 may be resumed as per protocol.

In the event of **Grade 4** diarrhea/colitis treatment with idelalisib must be discontinued permanently and MOR00208 administration should be withheld until Grade ≤2 is reached and thereafter dosing of MOR00208 may be resumed as per protocol .

Intestinal perforation

Background: Fatal and serious intestinal perforation occurred in idelalisib treated patients. At the time of perforation, some patients had moderate to severe diarrhea. Advise patients to promptly report any new or worsening abdominal pain, chills, fever, nausea, or vomiting.

Management: In patients who develop severe abdominal pain, particularly if early during therapy, the possibility of a bowel obstruction or perforation should be considered. Appropriate clinical and radiographic examination should be performed and supportive care and surgical intervention should be considered. Idelalisib treatment should be discontinued permanently in patients who experience intestinal perforation. MOR00208 administration should be withheld until the event resolved and thereafter, dosing of MOR00208 may be resumed as per protocol at the Investigator's discretion.

8.9.3 Management of Pulmonary Events

Pneumonitis

Background: Fatal and serious pneumonitis occurred in patients treated with idelalisib. Clinical manifestations included interstitial infiltrates and organizing pneumonia. Patients taking idelalisib who present with pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation, and patients presenting with serious lung events that do not respond to conventional antimicrobial therapy should be evaluated for pneumonitis. Pneumonitis did not occur in patients treated with MOR00208.

Management: Idelalisib and MOR00208 treatment should be maintained if patient is asymptomatic. If pneumonitis or organizing pneumonia is suspected with any severity of symptoms, idelalisib treatment should be interrupted until the etiology of the pulmonary symptoms has been determined. Patients with pneumonitis or organizing pneumonia thought to be caused by idelalisib should be treated with discontinuation of idelalisib and administration of corticosteroids. Patient should be monitored until pneumonitis or organizing pneumonia is resolved.

In the event of **Grade ≥2** pneumonitis idelalisib treatment must be discontinued permanently.

In the event of **Grade ≥3** pneumonitis MOR00208 treatment must be withheld until toxicity diminishes in severity to Grade ≤2. Thereafter, dosing of MOR00208 may be resumed as per protocol at Investigator's discretion.

8.9.4 Management of Serious Infections (PJP, CMV, PML)

Background: Adverse drug reactions of any grade reported in clinical studies such as infections including opportunistic infections as well as bacterial and viral infections such as pneumonia, bronchitis, and sepsis (including PJP and CMV) were very common in patients with hematologic malignancies receiving idelalisib. Moreover, serious and fatal infections have occurred in patients treated with idelalisib, including opportunistic infections such as PJP and CMV.

In clinical studies with idelalisib higher frequencies of infections including Grade 3 and 4 infections were observed in idelalisib arms compared to control arms without idelalisib treatment. Most frequently observed were infections in the respiratory system and septic events. In many instances, the pathogen was not identified; however, both conventional and opportunistic pathogens including PJP and CMV were identified. Nearly all PJP infections, including fatal cases, occurred in the absence of PJP prophylaxis. There have been cases of PJP after stopping idelalisib treatment.

Cases of progressive multifocal leukoencephalopathy (PML) have been reported following the use of idelalisib within the context of prior- or concomitant immunosuppressive therapies that have been associated with PML. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms.

Management of PJP: Please note: **Prophylaxis for PJP should be administered to all patients throughout idelalisib treatment and for a period of 2 to 6 months after discontinuation.** The duration of post-treatment prophylaxis should be based on clinical judgment and may take into account a patient's risk factors such as concomitant corticosteroid treatment and prolonged

neutropenia. Prophylaxis shall be administered in accordance with institutional guidelines (e.g., with trimethoprim+sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone).

Idelalisib and MOR00208 treatment should be interrupted in patients with suspected PJP infection of any grade and permanently discontinued if PJP infection is confirmed. Appropriate medical therapy or other interventions should be instituted.

Management of CMV: A central CMV laboratory test (serology and polymerase chain reaction [PCR]) will be performed for all patients at screening. Patients with negative serology should be monitored locally in accordance with institutional guidelines. Patients with positive serology or with other evidence of a history of CMV infection should be carefully monitored with a PCR based methodology:

- monthly, if the initial PCR result was negative without associated clinical signs of CMV infection
- weekly, if significant CMV viremia is detected.

For patients with evidence of CMV viremia and clinical signs of CMV infection, idelalisib and MOR00208 should be immediately interrupted until the infection has resolved per discussion between the Investigator and sponsor's medical monitor. If the benefits of resuming idelalisib and/or MOR00208 are judged to outweigh the risks, consideration should be given to administering pre-emptive CMV therapy in accordance with institutional guidelines.

Note: All patients should be monitored for respiratory signs and symptoms throughout the trial and should be advised to report new respiratory symptoms promptly to their Investigator.

Management of PML: If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for John Cunningham viral DNA and repeat neurological assessments should be considered.

8.9.5 Management of Dermatological Events

Severe cutaneous reactions / rash

Background: Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred when idelalisib was administered concomitantly with other medicinal products associated with these syndromes (BEN, RTX, allopurinol, and amoxicillin). Stevens-Johnson syndrome and toxic epidermal necrolysis occurred within one month of combination treatment, resulting in several deaths. Other severe or life-threatening (Grade ≥3) cutaneous reactions, including dermatitis exfoliative, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, exfoliative rash, and skin disorder, have been reported in idelalisib-treated patients.

Management: Patients should be monitored for the development of severe cutaneous reactions.

In the event of **Grade 3 or 4** severe cutaneous reactions treatment with idelalisib must be withheld until Grade ≤1 is reached. Thereafter, idelalisib treatment may be resumed at lower dose (100 mg BID) at the Investigator's discretion. Idelalisib treatment must be discontinued permanently if rechallenge with idelalisib results in recurrence of Grade 3-4 toxicity.

In the event of **Grade 3 or 4** severe cutaneous reactions MOR00208 administration should be withheld until Grade ≤2 is reached and thereafter MOR00208 treatment may be resumed as per protocol.

CAVE: If Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, treatment with idelalisib and MOR00208 should be immediately and permanently discontinued and the patient treated accordingly.

8.9.6 Management of Hematological and Immunological Events

Neutropenia

Background: Treatment-emergent Grade 3 or 4 neutropenia occurred in 31% of idelalisib-treated patients across clinical trials and in 7% of MOR00208-treated patients in a phase I clinical trial in R/R CLL. There was one CLL patient treated with MOR00208 who experienced DLT of Grade 4 neutropenia lasting ≥7 days with febrile neutropenia in a phase I clinical trial of R/R CLL.

Management: Blood counts including absolute neutrophil count (ANC) should be monitored at least every 2 weeks during the first 6 months of therapy with idelalisib, and at least weekly in patients while neutrophil counts are less than $1.0x10^9$/L.

In the event of a **Grade 4** neutropenia (<$0.5x10^9$/L) idelalisib treatment and MOR00208 administration must be withheld. ANC should be monitored at least weekly until ANC ≥$0.5x10^9$/L and/or neutropenic fever or infection is resolved. Thereafter, idelalisib treatment may be resumed at lower dose (100 mg BID) at the Investigator's discretion and MOR00208 treatment may be resumed as per protocol. Growth factors support can be considered.

Thrombocytopenia

Background: Treatment-emergent Grade ≥3 thrombocytopenia occurred in idelalisib-treated patients across clinical trials and in 7% of MOR00208-treated patients in a phase I clinical trial in R/R CLL.

Management: Platelet count should be monitored at least weekly if platelet counts are <$50x10^9$/L. In the event of a **Grade 3** thrombocytopenia (<50-$25x10^9$/L) idelalisib dose and MOR00208 administration should be maintained. In the event of a **Grade 4** thrombocytopenia (<$25x10^9$/L) idelalisib treatment and MOR00208 administration must be withheld until platelet counts reach ≥$25x10^9$/L. Transfusion support can be considered. When platelet counts have returned to ≥$25x10^9$/L, idelalisib treatment may be resumed at lower dose (100 mg BID) and MOR00208 treatment may be resumed as per protocol.

Anemia

Background: There was no serious AE related to MOR00208 treatment reported in CLL patients.

Management: In patients with Grade ≤3 anemia dosing of idelalisib and MOR00208 should be maintained as per protocol. Transfusion and growth factor support can be considered in accordance with institutional guidelines. In patients with **Grade 4** idelalisib and MOR00208 should be withheld until Grade 3 and hemoglobin should be monitored at least weekly. Thereafter, dosing may be maintained as per protocol.

Anaphylaxis

Background: Serious allergic reactions, including anaphylaxis, have been reported in patients on idelalisib.

Management: In patients who develop serious allergic reactions, idelalisib and MOR00208 administration must be discontinued permanently and appropriate supportive measures should be instituted.

8.9.7 Management of Tumor Lysis Syndrome

Background: Based on the results of the phase I clinical study of MOR00208 in patients with CLL/SLL and the preliminary results of the MOR208C201 and MOR208C202 studies, the anticipated possible risks associated with administration of MOR00208 to patients include TLS with a suspected relationship to MOR00208 treatment. In the phase I trial of MOR00208 in patients with CLL/SLL one patient did develop TLS which required rasburicase and intravenous fluids, however, subsequent infusions were tolerated without incident. It is notable that this patient had received no prior chemotherapy and had been treated only with single agent CD20 antibody therapy prior to receipt of MOR00208. Patients with TLS may experience hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatemia, cardiac dysrhythmias, and acute renal failure. Definition of TLS is described in Section 8.5.1.

Management: Subjects with TLS should receive rapid reversal of hyperkalemia, intravenous hydration, antihyperuricemic agents, and appropriate cardiac and renal support, including dialysis as indicated. Medical prophylaxis and management should be initiated according to the institutional standard of care. Withholding of treatment with MOR00208 and idelalisib can be considered at the Investigator's discretion. Upon recovery to baseline functioning, such patients should continue study treatment to maintain tumor control.

8.9.8 Teratogenicity

Embryo-fetal toxicity, pregnancy and lactation

Based on findings in animals, idelalisib may cause fetal harm when administered to a pregnant woman. Therefore, fertile males and females of childbearing potential should abstain from sexual intercourse or use highly effective contraception (see Appendix F) while taking idelalisib and for 3 months after stopping treatment. If a female patient becomes pregnant or decides to breastfeed during the course of the study, all study therapy must be discontinued.

8.10 Guidance for Managing Specific Adverse Events for the combination of MOR00208 and Venetoclax

Recommendations for managing specific adverse events (based on the FDA Prescribing Information) are summarized in Table 9.

Table 9: Recommended Dose Modifications for Toxicities

NCI CTCAE Grade[a]	Occurrence	Action	
		Venetoclax	MOR00208
Tumor Lysis Syndrome			
All Grades (Blood chemistry changes or symptoms suggestive of TLS)	Any	Withhold the next day's dose of venetoclax. If resolved within 24 to 48 hours of last dose, resume venetoclax at the same dose.	Maintain MOR00208 dosing as per protocol.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume venetoclax at a reduced dose.	
		For any events of clinical TLS, [b] resume venetoclax at a reduced dose following resolution.	Withhold MOR000208 for any events of clinical TLS[b]. After resolution MOR00208 therapy may be resumed at the discretion of the physician.
Non-Hematologic Toxicities			
Grade 3 or 4 non- hematologic toxicities	1st occurrence	Interrupt venetoclax. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.	Interrupt MOR00208. Once the toxicity has resolved to Grade 1 or baseline level, MOR00208 therapy may be resumed.

NCI CTCAE Grade[a]	Occurrence	Action	
		Venetoclax	MOR00208
	2nd and subsequent occurrences	Interrupt venetoclax. Follow dose reduction guidelines in Table 6 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician, but not below 100 mg daily dose after the ramp-up phase.	Interrupt MOR00208. After resolution MOR00208 therapy may be resumed at the discretion of the physician.
Hematologic Toxicities			
Grade 3 or 4 neutropenia with infection or fever or Grade 4 hematologic toxicities (except lymphopenia)	1st occurrence	Interrupt venetoclax. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose.	Interrupt MOR00208. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with MOR00208 if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, MOR00208 therapy may be resumed.

NCI CTCAE Grade[a]	Occurrence	Action	
		Venetoclax	MOR00208
	2nd and subsequent occurrences	Interrupt venetoclax. Consider transfusion and growth factor support as clinically indicated in accordance with institutional guidelines. Follow dose reduction guidelines in Table 6 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician, but not below 100 mg daily dose after the ramp-up phase.	Interrupt MOR00208. Consider transfusion and growth factor support as clinically indicated in accordance with institutional guidelines. MOR00208 therapy may be resumed after resolution as follows: Neutropenia: Withhold MOR00208 and monitor ANC at least weekly until ANC $\geq 0.5 \times 10^9$/L and/or neutropenic fever or infection is resolved. Thereafter, may resume as per protocol. Thrombocytopenia: withhold MOR00208 until platelet count reach $\geq 25 \times 10^9$/L and monitor at least weekly. Thereafter, may resume as per protocol. Anemia: Withhold MOR00208 until Grade 3 and monitor at least weekly. Thereafter, may resume as per protocol.

Consider discontinuing venetoclax for patients who require dose reductions to less than 100 mg for more than 2 weeks during the ramp-up phase. Dose modifications below 100 mg are not allowed after the ramp-up phase and patient should discontinue venetoclax treatment.

[a] Adverse reactions were graded using NCI CTCAE version 4.03.

[b] Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures.

8.10.1 Management of Tumor Lysis Syndrome

Background: Tumor lysis syndrome is an important identified risk when initiating venetoclax. In the initial Phase 1 dose-finding trials, which had shorter (2-3 week) ramp-up phase and higher starting dose, the incidence of TLS was 12% (9/77; 4 laboratory TLS, 5 clinical TLS), including 2 fatal events and 3 events of acute renal failure, 1 requiring dialysis. The risk of TLS was reduced after revision of the dosing regimen and modification to prophylaxis and monitoring measures. In venetoclax clinical trials, patients with any measurable lymph node ≥10 cm or those with both an ALC ≥25 x 10^9/L and any measurable lymph node ≥5 cm were hospitalized to enable more intensive hydration and monitoring for the first day of dosing at 20 mg and 50 mg during the ramp-up phase. In 66 patients with CLL starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg, the rate of TLS was 6%. All events either met laboratory TLS criteria (laboratory abnormalities that met ≥2 of the following within 24 hours of each other: potassium >6 mmol/L, uric acid >476 µmol/L, calcium <1.75 mmol/L, or phosphorus >1.5 mmol/L); or were reported as TLS events. The events occurred in patients who had a lymph node(s) ≥5 cm or ALC ≥25 x 10^9/L. No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias or sudden death and/or seizures was observed in these patients. All patients had CrCl ≥50 mL/min.

Based on the results of the phase I clinical study of MOR00208 in patients with CLL/SLL and the preliminary results of the MOR208C201 and MOR208C202 studies, the anticipated possible risks associated with administration of MOR00208 to patients include TLS with a suspected relationship to MOR00208 treatment. In the phase I trial of MOR00208 in patients with CLL/SLL one patient did develop TLS which required rasburicase and intravenous fluids, however, subsequent infusions were tolerated without incident. It is notable that this patient had received no prior chemotherapy and had been treated only with single agent CD20 antibody therapy prior to receipt of MOR00208.

Management: Patients enrolling in Cohort B will be assessed for TLS risk and should receive appropriate prophylaxis for TLS as described in detail in Section 8.5 and 9.3.3.6. Importantly, all patients in Cohort B, who participate in the safety run-in phase, will be hospitalized on the day of the first two dose escalations of venetoclax (C1D8 and C1D15). Nephrology or acute dialysis service should be consulted or contacted on admission per institutional standards to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS.

MOR000208 should be withheld for any events of clinical TLS (clinical TLS is defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures). After resolution MOR00208 therapy may be resumed at the discretion of the physician.

During the ramp-up phase with venetoclax blood chemistries should be monitored and abnormalities should be managed promptly. Dosing should be interrupted if needed. More intensive measures should be employed (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases. For any events of clinical TLS, resume venetoclax at a reduced dose following resolution. Concomitant use of venetoclax with strong or moderate CYP3A inhibitors or inducers within 7 days prior to the first dose of venetoclax and during ramp-up phase of venetoclax is contraindicated. P-gp and BCRP inhibitors increases venetoclax exposure may increase the risk of TLS; therefore, concomitant use of venetoclax with P-gp and

BCRP inhibitors at initiation and during ramp-up phase should be avoided and requires venetoclax dose adjustment.

Patients should be advised of the potential risk of TLS to immediately report any signs and symptoms associated with this event (fever, chills, nausea, vomiting, confusion, shortness of breath, seizure, irregular heartbeat, dark or cloudy urine, unusual tiredness, muscle pain, and/or joint discomfort) to their doctor for evaluation, and to be adequately hydrated every day when taking venetoclax to reduce the risk of TLS.

8.10.2 Management of Hematologic Toxicities

Background: Grade 3 or 4 neutropenia and febrile neutropenia occurred in 41% (98/240) and 5% of patients treated with venetoclax, respectively. Dosage adjustments of venetoclax due to adverse reactions occurred in 9.6% of patients. The most frequent adverse reactions leading to dose adjustments of venetoclax were neutropenia, febrile neutropenia, and thrombocytopenia. Most hematological toxicities AEs were first reported in the initial months of treatment of venetoclax, with highest incidence and prevalence of AEs in the first month and decreasing with time on study (Davids et al., 2016). Moreover, autoimmune hemolytic anemia (AIHA) and anemia were reported among the most frequent serious adverse reactions (≥2%). The most frequent adverse reactions leading to drug discontinuation were thrombocytopenia and AIHA.

Serious infections including events of sepsis with fatal outcome have been reported in patients treated with venetoclax.

Treatment-emergent Grade 3 or 4 neutropenia occurred in 7% of MOR00208-treated patients in a phase I clinical trial in R/R CLL. There was one CLL patient treated with MOR00208 who experienced DLT of Grade 4 neutropenia lasting ≥7 days with febrile neutropenia in a phase I clinical trial of R/R CLL.

Management: Interrupt venetoclax and MOR00208 at 1st occurrence of Grade 3/4 neutropenia with infection or fever, or Grade 4 hematologic toxicities (except lymphopenia). Once the toxicity has resolved to Grade 1 or baseline level, venetoclax and MOR00208 therapy may be resumed at the same dose of venetoclax.

At 2nd and subsequent occurrences interrupt venetoclax and MOR00208. Consider transfusion and growth factor support as clinically indicated in accordance with institutional guidelines. Follow dose reduction guidelines in Table 6 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician, but not below 100 mg daily dose after the ramp-up phase.

At 2nd and subsequent occurrences withhold MOR00208 and may resume as follows:

- Neutropenia: monitor ANC at least weekly until ANC $\geq 0.5 \times 10^9$/L and/or neutropenic fever or infection is resolved
- Thrombocytopenia: monitor platelet count at least weekly until platelet count reach $\geq 25 \times 10^9$/L
- Anemia: monitor at least weekly until Grade 3

Thereafter, may resume as per protocol.

Patients should be advised to contact their doctor immediately if they develop a fever or any signs of infection.

Testing for AIHA (e.g. direct Coombs test, reticulocyte count) should be performed in patients receiving venetoclax treatment in accordance with institutional guidelines if AIHA is suspected of any grade.

Measures including antimicrobial therapy for any signs of infection including sepsis should be considered.

8.10.3 Management of Teratogenicity

Embryo-fetal Toxicity, Pregnancy and Lactation

Based on its mechanism of action and findings in animals, venetoclax may cause embryofetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of venetoclax to pregnant animals at exposures equivalent to that observed in patients at the recommended dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight. There are no adequate and well-controlled studies in pregnant woman using venetoclax. Advise females of reproductive potential to avoid pregnancy during treatment. If venetoclax is used during pregnancy or if the patient becomes pregnant while taking venetoclax, the patient should be apprised of the potential hazard to the fetus.

Pregnancy - Risk Summary

There are no available human data on the use of venetoclax in pregnant women. Based on toxicity observed in mice, venetoclax may cause fetal harm when administered to pregnant women. In mice, venetoclax was fetotoxic at exposures 1.2 times the human clinical exposure based on AUC at the recommended human dose of 400 mg daily. If venetoclax is used during pregnancy or if the patient becomes pregnant while taking venetoclax, the patient should be apprised of the potential risk to a fetus. The background risk in the general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Animal data. In embryo-fetal development studies, venetoclax was administered to pregnant mice and rabbits during the period of organogenesis. In mice, venetoclax was associated with increased postimplantation loss and decreased fetal body weight at 150 mg/kg/day (maternal exposures approximately 1.2 times the human AUC exposure at the recommended dose of 400 mg daily). No teratogenicity was observed in either the mouse or the rabbit.

Lactation - Risk Summary

There are no data on the presence of venetoclax in human milk, the effects of venetoclax on the breastfed child, or the effects of venetoclax on milk production. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in breastfed infants from venetoclax is unknown, advise nursing women to discontinue breastfeeding during treatment with venetoclax.

Females and Males of Reproductive Potential

Venetoclax may cause fetal harm. Females of reproductive potential should undergo pregnancy testing before initiation of venetoclax. Advise females of reproductive potential to use effective contraception during treatment with venetoclax and for at least 30 days after the last dose. Based on findings in animals, male fertility may be compromised by treatment with venetoclax.

8.11 Rules for Permanent Stop of Study Medication Intake

If treatment needs to be interrupted for ≤ 28 days for drug-related toxicity of the same study drug (idelalisib or venetoclax or MOR00208), treatment should continue at the next protocol scheduled visit whenever possible. Missing visits or doses of either drug should not be made up for, with exception for the make up of a missed MOR00208 dose during the monthly MOR00208 treatment, as described in Section 8.12.

If treatment with one study drug needs to be interrupted for >28 days for the same, persistent, drug-related toxicity, the patient should continue to be dosed with the other study drug, as per protocol.

If treatment with both study drugs needs to be interrupted for >28 days for the same persistent study drug-related toxicity, judged by the Investigator to be related to both study drugs (idelalisib/venetoclax and MOR00208), then the End of Treatment (EOT) visit will be performed and the patient will enter the follow-up period.

8.12 Treatment Accountability and Compliance

The pharmacist or other designated individual will maintain records of study treatment delivered to the study site; the inventory at the site; the distribution to and use by each patient; and the return of materials to the sponsor or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the product and study patients.

Patients will receive MOR00208 under the direct supervision of study personnel. Each administration volume or dose will be checked and the vial/outer package code and volume or dose per administration will be recorded in each patient's eCRF as well as in the source data.

At each visit after initiation of treatment, site staff will record compliance of patients with their assigned regimen. Patients will be instructed to bring unused/partially used/empty medication containers of idelalisib or venetoclax back for inspection on Day 1 of each cycle, starting with Cycle 2, or on the EOT visit as compliance will be assessed by tablet counts.

Patients are to be reminded of the importance of compliance with their assigned regimen, with an emphasis on taking their study drug on schedule, and maintaining the prescribed interval between doses.

Investigators will maintain records that document adequately that the patients were provided with the correct study treatment kits and will reconcile the products received from the drug dispensing center. Drug accountability will be checked by the field monitor during site visits and at the completion of the trial.

Noncompliance in general is defined as taking ≤80% or >120% of one MOR00208 dose and/or ≤80% or >120% of the idelalisib or venetoclax intake per cycle during any outpatient evaluation period.

Moreover, one MOR00208 dose can be missed between Cycles 1 and 3, between Cycles 4 and

12 and one dose between Cycles 13 and 24 without the patient being non-compliant. Note that MOR00208 dose omissions due to toxicity are covered in Sections 8.6 and 8.9.

Discontinuation for noncompliance is at the Investigator's discretion and is to be noted on the eCRF.

8.13 Prior and Concomitant Therapy

Patients are allowed to continue the medications that they are taking at baseline. Patients may also receive concomitant medications that are medically indicated as standard care for the treatment of symptoms and intercurrent illnesses. Medications to treat concomitant diseases, e.g., diabetes, hypertension, bronchial asthma and COPD are allowed. Patients may also receive therapy to mitigate side effects of the study medication as clinically indicated, as well as best supportive care as per institutional guidelines. This may include, e.g., antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics, and other medications intended to treat symptoms. The Investigator should instruct the patient not to take any additional medications (including over-the-counter products) during the study without prior consultation.

Investigators should document all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) taken within 30 days prior to signature of ICF.

The following prior and concomitant therapy will be recorded in the eCRF:

- Medication and other therapy (including non-drug procedure) taken by/administered to the patient within 30 days prior to signature of ICF
- Medication and other therapy (including non-drug procedure) taken by/administered to the patient during the course of the study
- All prior medications/non-drug procedures, if deemed relevant by the Investigator, shall be entered into the eCRF.

The entry must include the dose, regimen, route of administration, indication, and dates of use (start, end).

After the baseline visit, medication to treat minor treatment-emergent illness(es) is generally permitted; however, the therapies listed below are expressly prohibited throughout the study.

The following medications are prohibited:

- Treatment with a BTK inhibitor within 5 days prior to Day 1 dosing
- CD20-targeted therapy, chemotherapy, radiotherapy, investigational anticancer therapy or other lymphoma specific therapy within 14 days prior to Day 1.
- Systemic corticosteroids in doses greater than prednisone equivalent to 20 mg/day within 14 days prior to Day 1 dosing (Exception: Patients with signs of rapidly progressing disease per discussion between the Investigator and sponsor's medical monitor)
- Live vaccines within 14 days prior to Cycle 1 Day 1 and during the treatment period.

Note:

- Vaccinations against influenza with inactivated virus or vaccination for pneumococcal diseases are allowed.
- **Cohort B only:** Do not administer live attenuated vaccines after treatment with venetoclax until B-cell recovery occurs.

- Other than study drugs anti-cancer therapies
- **Cohort B only:**
  - Within 7 days prior to the first dose of venetoclax: Strong or moderate CYP3A inhibitors (e.g., strong: ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole and voriconazole; moderate: erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil), strong or moderate CYP3A inducers (e.g., strong: carbamazepine, phenytoin, rifampin, St. John's wort; moderate: bosentan, efavirenz, etravirine, modafinil, nafcillin)
  - Within 3 days prior to the first dose of venetoclax: Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit
  - During ramp-up phase of venetoclax: Strong or moderate CYP3A inhibitors or inducers

Growth Factors

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

Anticoagulants

Warfarin therapy is allowed with caution during the study treatment with idelalisib or venetoclax. The international normalized ratio (INR) should be monitored closely in patients receiving warfarin upon co-administration and following ceasing treatment with idelalisib in Cohort A and with venetoclax in Cohort B. Discussion with the sponsor's medical monitor is highly recommended about the use of other anticoagulation therapies, such as systemic or low-molecular weight heparin.

Infection Prophylaxis

Investigators should follow institutional guidelines on infection chemoprophylaxis for patients regarded to be at high risk for infection.

Corticosteroids

After first dosing with study drug, patients are allowed to receive topical, enteric, inhaled, or systemic corticosteroids for therapy of CLL manifestations, comorbid conditions, autoimmune anemia and/or thrombocytopenia or for pretreatment of MOR00208 infusions. Patients who develop conditions that may be alleviated by systemic corticosteroid therapy are permitted to receive such drugs and are not required to discontinue study participation.

Anticancer Therapies

The use of concurrent antineoplastic therapies other than study drugs, including, but not limited to, chemotherapies, hormonal therapy, immunotherapy, biological response modifiers, mAbs with or without conjugation, radio-isotopic therapies, and targeted small molecules are not permitted during the entire treatment period of this study. Allogeneic stem-cell transplantation is considered to be a protocol prohibited anticancer therapy.

Cohort A only: The following medications should be avoided (as per SmPC of idealisib):

Effects of other medicinal products on idelalisib:

- Co-administration of idelalisib with moderate or strong CYP3A inducers such as rifampicin, phenytoin, St. John's wort (*Hypericum perforatum*), or carbamazepine should be avoided. Idelalisib exposure and thus efficacy may be reduced when coadministered with CYP3A inducers.
- No initial dose adjustment of idelalisib is considered necessary when administered with CYP3A/ P-glycoprotein (P-gp) inhibitors (e.g., ketoconazole), but an intensified monitoring of adverse reactions is recommended.

Effects of idelalisib on other medicinal products:

- The primary metabolite of idelalisib, GS-563117, is a strong CYP3A4 inhibitor. Thus, idelalisib has the potential to interact with medicinal products that are metabolized by CYP3A, which may lead to increased serum concentrations of the other product (see Appendix I). When idelalisib is co-administered with other medicinal products, the label information for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors. Concomitant treatment of idelalisib with CYP3A substrates with serious and/or life-threatening adverse reactions (e.g., alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam) should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible.
- CYP2C8 substrates: *In vitro*, idelalisib both inhibited and induced CYP2C8, but it is not known whether this translates to an in vivo effect on CYP2C8 substrates. Caution is advised if idelalisib is used together with narrow therapeutic index drugs that are substrates of CYP2C8 (e.g., paclitaxel).
- Substrates of inducible enzymes (e.g., CYP2C9, CYP2C19, CYP2B6 and UGT): *In vitro*, idelalisib was an inducer of several enzymes, and a risk for decreased exposure and thereby decreased efficacy of substrates of inducible enzymes such as CYP2C9, CYP2C19, CYP2B6 and UGT cannot be excluded. Caution is advised if idelalisib is used together with narrow therapeutic index drugs that are substrates of these enzymes (e.g., warfarin, phenytoin, S-mephenytoin).
- Breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP)1B1, OATP1B3 and P-gp substrates: Co-administration of multiple doses of idelalisib 150 mg twice daily to healthy subjects resulted in comparable exposures for

rosuvastatin (AUC 90% CI: 87, 121) and digoxin (AUC 90%; CI: 98, 111 [sic, SmPC]), suggesting no clinically relevant inhibition of BCRP, OATP1B1/1B3 or systemic P-gp by idelalisib. A risk for P-gp inhibition in the gastrointestinal tract, that could result in increased exposure of sensitive substrates for intestinal P-gp such as dabigatran etexilate, cannot be excluded.

Cohort B only: The following medications should be avoided:

Avoid concomitant use of venetoclax with strong or moderate CYP3A inhibitors or inducers after the ramp-up phase of venetoclax. P-gp and BCRP inhibitors, or narrow therapeutic index P-gp substrates; furthermore, grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with venetoclax. Consider alternative treatments.

The recommendations for managing drug-drug interactions and dose modifications of venetoclax are summarized in Table 7 and detailed in Section 8.8.4.

9 STUDY PROCEDURES

9.1 Schedule of Procedures and Assessments

The Schedule of Procedures and Assessments is presented on the following pages (Table 10). All examinations/assessments that need to be performed at a specific visit are indicated with an "X" and the respective date, obtained from these assessments need to be documented in the source data. Each cycle consists of 28 days.

Note: Missed visits should not be made up.

- In case a visit (C4D1, C7D1, C13D1, etc.), where a radiological examination needs to be performed, is missed, the radiological examination needs to be performed as soon as possible after the missed visit, preferably within the scheduled timeframe of the respective visit (of ±7 days for the assessments on Cycle 4 and Cycle 7 and ± 14 days window for the following examinations).
- In case a CxD1 visit is missed and therefore no idelalisib or venetoclax is given out to the patient, idelalisib or venetoclax should be provided to the patient at the next possible timepoint, either during an unscheduled visit or at CxD15. If missed visit was due to toxicity please follow the guidance for toxicity management.

Table 10: Schedule of Procedures and Assessments

Evaluation or Procedure	Screening Period	Treatment Period												
	Screening ≤28 Days prior to D1	Cycle 1					Cycle 2				Cycle 3			
Day	Screen	D1	D4	D8 ±1 day	D15 ±1 day	D22 ±1 day	D1 ±1 day	D8 ±1 day	D15 ±1 day	D22 ±1 day	D1 ±1 day	D8 ±1 day	D15 ±1 day	D22 ±1 day
Informed consent	X													
Inclusion/exclusion criteria	X	X[1]												
Demography	X													
Medical history	X													
Disease staging	X													
Disease risk assessment: Cytogenetic testing; β_2-microglobulin (serum); Expression of CD38 and ZAP-70		X[1]												
Optional mutational analysis (e.g., IGHV, TP53, NOTCH1, BTK, PLCγ2, CD19)		X[1]												
Previous/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X													
Limited physical examination		X			X		X		X		X		X	
ECOG performance status	X	X[1]					X				X			
Weight/height [2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B symptoms	X	X					X				X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead resting ECG	X	X[1]			X[3]		X[3]				X[3]			
Urinalysis	X	X					X				X			
HIV testing	X													
Serum pregnancy test (FCBP)[4]	X													
Urine pregnancy test [1,4]		X					X				X			

Evaluation or Procedure	Screening Period	Treatment Period												
	Screening ≤28 Days prior to D1	Cycle 1					Cycle 2				Cycle 3			
Day	Screen	D1	D4	D8 ±1 day	D15 ±1 day	D22 ±1 day	D1 ±1 day	D8 ±1 day	D15 ±1 day	D22 ±1 day	D1 ±1 day	D8 ±1 day	D15 ±1 day	D22 ±1 day
Pregnancy and risks counselling	X													
"Emergency laboratory" [1, 5]		X	X	X	X	X	X	X	X	X	X	X	X	X
Central laboratory (blood) Hematology	X	X[1]			X[1]		X[1]		X[1]		X[1]		X[1]	
Central laboratory (blood) Serum chemistry	X	X[1]			X[1]		X[1]		X[1]		X[1]		X[1]	
Central laboratory (blood) Coagulation	X	X[1]					X[1]				X[1]			
Serology (hepatitis B and C)	X[12]										X[12]			
CMV testing	X[14]						X[14]				X[14]			
B-, T- and NK cell (blood) [1]		X		X			X[17]		X[16]					
CD19 assessment (CD19ABC and % CD19 + cells) (blood) [1]		X		X[16]	X[16]		X[17]							
Anti-MOR00208 antibodies [1]		X					X				X			
Optional FcγR polymorphism (mucosal cheek swab) [1]		X												
CD16 assessment (CD16ABC) (blood) [1]		X												
MRD (blood) [1]		X												
Disease response assessment: CT/MRI of neck, chest, abdomen, pelvis [7]	X													
MOR00208 administration		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispensation of idelalisib/venetoclax tablets		X[17]		X[16]	X[16]	X[16]	X	X[16]			X			
Venetoclax ramp-up [18]				20mg	50mg	100mg	200mg	400mg						
TLS risk assessment [1,16,18]	X			X	X	X	X	X						
(S)AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK MOR00208		X[6]	X[6]		X[6]		X[6]		X[6]		X[6]		X[6]	

Schedule of Procedures and Assessments (continued)

	Additional Treatment Periods				Follow-up Period
Evaluation or Procedure	**Cycle 4 - Cycle 6**		**Cycle 7 - Cycle 24**	**End of Treatment Visit (EOT)**	**30-Day Safety Follow-up Visit**
Day	**D1 ±2 days**	**D15 ±2 days**	**D1 ±2 days**	**Preferably within ≤30 days of last dose of study treatment**	**±2 days**
Concomitant medication	X	X	X	X	X
Complete physical examination				X	
Limited physical examination	X	X	X		X
ECOG performance status	X		X	X	
Weight [2]	X	X	X	X	
Vital signs	X	X	X	X	
B-symptoms	X		X	X	X
12-lead resting ECG	X		X	X	
Urinalysis	X		X	X	
Serum pregnancy test (FCBP) [4]				X	
Urine pregnancy test [1]	X		X		
Emergency Laboratory [1, 5]	X	X	X		
Central laboratory (blood) Hematology)	X[1]		X[1]	X	
Central laboratory (blood) Serum chemistry	X[1]		X[1]	X	
Central laboratory (blood) Coagulation	X[1]		X[1]	X	
Anti-MOR00208 antibodies	X[1, 9]		X[1, 9]	X	
B, T, and NK cell (blood) [1]		X[10]		X	
Disease response assessment: CT/MRI of neck, chest, abdomen, pelvis [7]	X[7]		X[7]	X[7, 8]	

	Additional Treatment Periods				Follow-up Period
Evaluation or Procedure	**Cycle 4 - Cycle 6**		**Cycle 7 - Cycle 24**	**End of Treatment Visit (EOT)**	**30-Day Safety Follow-up Visit**
Day	**D1 ±2 days**	**D15 ±2 days**	**D1 ±2 days**	**Preferably within ≤30 days of last dose of study treatment**	**±2 days**
For CR / PR patients only: bone marrow aspiration & biopsy, MRD assessment	X[11]		X[11]	X[11]	
MOR00208 administration	X	X	X		
Dispensation of idelalisib/venetoclax tablets	X		X		
(S)AE assessment	X	X	X	X	X
CD19 assessment (CD19ABC and % CD19+ cells) (blood)				X	
PK MOR00208	X[1, 9]		X[1, 9]	X	
Antineoplastic therapy after end of study treatment					X
Serology (hepatitis B and C)	X[12]		X[12]		
MRD (blood) [1]	X[13]		X[13]		
CMV testing	X[14]		X[14]		

Abbreviations: ABC=antibodies bound per cell; AE=adverse event; β-HCG=beta-human chorionic gonadotropin; BTK=Bruton's tyrosine kinase; CMV=Cytomegalovirus; CD19=cluster of differentiation 19; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FCBP=female of childbearing potential; HIV=human immunodeficiency virus; IGHV=immunoglobulin heavy-chain variable gene; MRD=minimal residual disease; MRI=magnetic resonance imaging; NK=natural killer; PK=pharmacokinetics; PRO=patient-reported outcomes; SAE=serious adverse event; TLS=tumor lysis syndrome.

Disease risk assessment as per IWCLL guideline: cytogenetic tests: FISH: Minimum required tests are del (17p), del (11q), del (13q), trisomy 12, karyotyping. IGHV information can be obtained from previous CLL history; should otherwise be obtained from baseline investigation, B_2 microglobulin (serum), CD38 (cytometry), ZAP-70 (cytometry).

[1]Before study drug administration.
[2]Body height will be measured at Cycle 1 Day 1 (C1D1) only. Weight and height should be measured while the patient is without shoes but dressed.
[3]12-lead resting ECG performed 1 hour ±10 minutes post-MOR00208 dosing.
[4]Pregnancy tests for FCBP: a serum pregnancy test must be performed at screening within 7 days prior to the start of study drug and a local urine pregnancy test within 24 hours prior to the start of study drug. The results of both tests must be negative in order to receive C1D1 dosing. A β-HCG pregnancy test should also be performed at the EOT visit. At all other indicated timepoints, a urine pregnancy test for FCBP will be performed locally. Pregnancy test must be negative for dosing.
[5]Emergency laboratory sample to be collected and evaluated in the local laboratory as indicated and reviewed by study treating physician before study drug administration.
[6]MOR00208 PK sample will be taken pre-dose and 1 hour ± 10 min after the end of MOR00208 infusion.
[7]Baseline CT/MRI scan has to be performed within 14 days before C1D1. CT scans performed prior to screening as part of the regular clinical work-up of the patient will be allowed up to 6 weeks before C1D1. However, a CT scan must be performed within the 14 day period prior to C1D1 for those patients with signs of rapidly progressing disease at screening. CLL response assessment according to IWCLL guideline (Hallek et al., 2008). SLL response assessment according to the Lugano Classification criteria (Cheson et al., 2014). For CLL and SLL: CTs or MRIs will be performed at C4D1, C7D1, C13D1, C19D1, etc. Time window is ±7 days for visits C4D1 and C7D1 and ±14 days for the following examinations. A CT/MRI scan has to be performed at least 8 weeks after CR was identified by clinical criteria (and before a BM biopsy is obtained for CR confirmation). If a regular CT/MRI scan is scheduled within these 8 weeks according to the schedule of assessment (C4, C7, C13, etc.) this examination should be postponed to meet the confirmation timeline. The following regular CT/MRI scan can be postponed/
skipped, if this examination is within 8 weeks of the CR confirmatory scan.
[8]In case the patient is withdrawn from treatment for reasons other than progression of disease, a CT is only required at the EOT visit if this was not performed within 28 days before EOT.

[9]During Cycles 4 through 24, anti-MOR00208 antibody samples and MOR00208 PK samples (all to be collected pre-dose only) will be collected in odd numbered cycles only (i.e., Cycles 5, 7, 9, 11, etc.)
[10]B/T/NK cell count only in Cycle 4 of additional treatment period.
[11]**For patients with CR:** a MRD assessment from bone marrow aspirate and a local analysis of bone marrow aspiration/biopsy has to be performed for confirmation of CR at least 8 weeks after the CR criteria for tumor response are first met. The result of the CT scan need to be obtained first; if this does not confirm a CR, then a biopsy should not be performed.
For patients with PR and PB MRD negativity: an MRD assessment from bone marrow aspirate/peripheral blood has to be performed at least 8 weeks after the PB MRD negativity was detected.
[12]If positive for hepatitis B serology needs to be followed up locally every 2 months.
[13]Periphal blood sample for MRD assessment has to be taken at C4D1, C7D1, C13D1, C19D1, etc. until BM MRD negativity was confirmed.
For CR patients only: An additional PB sample needs to be obtained at the time when CR is confirmed by CT.
[14]Patients with positive serology or with other evidence of a history of CMV infection at screening should be carefully monitored with PCR
(a) monthly, if initial PCR result has been negative without associated clinical signs of CMV infection or
(b) weekly, if significant CMV viremia has been detected.
[15]During ramp-up of venetoclax patients will receive 20 mg (C1D8), 50 mg (C1D15), 100 mg (C1D22), 200 mg (C2D1) and 400 mg (C2D8), if no contraindications
[16]**Cohort B** –Venetoclax+MOR00208 patients only.
[17]**Cohort A** – Idelalisib+MOR00208 patients only.
[18]In cases when an unscheduled visit needs to be performed during ramp-up phase of venetoclax (e.g., due to dosing interruption or reduction of venetoclax which leads to changed treatment schedule of venetoclax), no risk reassessment for TLS needs to be performed at respective regular visit(s) when MOR00208 is administered.

9.2 Study Periods and Procedures

9.2.1 Patient Information and Informed Consent

The participation of the patients and the investigation of their eligibility are subject to informed consent. Only patients who are able and willing to consent freely to participate after receiving detailed information both verbally and in writing are eligible for enrolment.

Prior to start of any study-related examination, the Investigator or designated staff will inform the patients about the nature, importance, implications, and risks of the trial. The patients will be informed about the study medication, method of administration, blood sampling, imaging techniques, rules of conduct, and any restrictions that might apply. Possible effects (both beneficial and adverse) of the study medication will be discussed. The extent of the examinations to be performed and the invasive and non-invasive investigation methods will be explained. Optional mutational analyses are planned within this trial. (For details please refer to Sections 9.3.6 and 9.3.7.) The examination should be explained to the patients, who are asked to consent voluntarily to this examination on a seperate Pharmacogenomics ICF. The participation in the pharmacogenomics examination is entirely optional and has no influence on the overall study participation.

The patients will be given ample opportunity to ask questions concerning any and all aspects of the study. All patients will be informed that participation is entirely voluntary and that they can cease participation at any time without necessarily giving a reason and without any penalty or loss of benefits to which they were entitled. All patients will have to sign the Informed Consent Form (ICF) as proof of consent and will receive a copy of the Patient Information Sheet (PIS) and ICF.

9.2.2 Screening Period

The Screening Period begins on the date when the ICF is signed; it will last for up to 28 days and is followed by Cycle 1 Day 1 (C1D1). In exceptional cases, the screening period may be extended at the discretion of the investigator for a total of up to 42 days due to any technical/logistic reasons (e.g., extended imaging equipment breakdown and/or servicing, delays in the delivery of central laboratory results). The reason for such extension along with an evaluation by the investigator ensuring that such extension does not pose any health risk for the patient should be documented in the patient's source data.

The assessments to be performed at screening may be grouped as follows:

- Assessment of in/exclusion criteria (see Section 7.2.1 and 7.2.2)
- Pregnancy and risks counselling; pregnancy test for FCBP. Two pregnancy tests must be performed: the first, a serum pregnancy test at screening within 7 days prior to the start of study drug and the second, a local urine pregnancy test within 24 hours prior to the start of study drug. The results of both tests must be negative in order to receive C1D1 dosing (see Section 9.3.2.1).
- Documentation of demography, medical history, previous/concomitant medications, weight/height (see Section 9.3.1)
- Disease assessment of CLL and SLL (CT or MRI scan of neck, chest, abdomen, pelvis) within 14 days before C1D1 (see Sections 9.3.3.1 and 9.3.3.3)
- ECOG performance status (see Section 9.3.8)

- Disease staging (see Appendix A)
- B-symptoms (see Section 9.3.3.5)
- Complete physical examination (see Section 9.3.2.3)
- Vital signs (see Section 9.3.2.2)
- 12-lead resting ECG (see Section 9.3.2.4)
- Blood sampling for hematology, serum chemistry and coagulation (central laboratory) (see Section 9.3.2.5)
- Viral testing: hepatitis B and C, CMV, HIV (see Virus_Serology)
- Urinalysis (see Table 11)
- Recording of (S)AEs (see Section 10.5)

The assessments performed during screening will be used for generating the baseline data.

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

An important procedure to be done at screening is:

- Pregnancy and risks counselling

9.2.3 Documentation of Screening Failures

During screening, patients may prove to be ineligible for participation in the study. The following documents and data should be collected in the eCRF for screening failures:

- Signed ICF
- Demography
- In/exclusion criteria which were not fulfilled by the patient
- Information on AEs (recording or confirmation that none occurred)

No other data will be entered in the eCRF for Screen Failure patients.

9.2.4 Pregnancy and Risks Counselling

In addition, pregnancy and risk counselling will be conducted during the screening period.

9.2.5 Subject Numbering

Each patient is identified in the study by a 7 digit Subject Number, which is assigned when the patient is enrolled for screening and is retained as the primary identifier for the patient throughout study participation. The Subject Number (Subject No.) consists of the country number (two digits), the Center Number (three digits) as assigned by Morphosys to the investigative site with a sequential patient number (two digits) suffixed to it, so that each patient is identified. Upon signing the informed consent form, the patient is assigned to the next sequential Subject Number available to the Investigator.

Once assigned, the Subject No. must not be reused for any other patient.

9.2.6 Re-screening

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

1. The patient has already consented and met all of the inclusion and none of the exclusion criteria and his or her enrolment was delayed due to an unexpected change in the patient's personal situation (e.g., family issues).
2. The patient previously failed to be eligible due to any event (e.g., planned surgery, laboratory test result) or any technical/logistic reason (e.g. screening period elapsed due to unexpected leave or absence of patient) that has been resolved.
3. The patient previously failed screening but has become eligible for the study based on a change in the inclusion and exclusion criteria as the result of a protocol amendment.

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

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

1. The patient must sign and date a new informed consent form (ICF) as part of the re-screening procedure.
2. A new Subject ID will be assigned to the patient.
3. The patient will be documented as re-screened in the source documents.
4. A recording of medical histories, physical examinations, prior treatments for CLL/SLL, AEs, and concurrent medications will be transcribed from the previously used to the new eCRF if the conditions and medications still apply to the current status of the re-screened patient as documented in the source documents. All screening procedures must be completed again.

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

9.2.7 Treatment Period

The treatment period consists of a total of 24 cycles, each cycle lasting 28 days. For the first 3 months (3 cycles) of the study each 28-day cycle will consist of a MOR00208 infusion on Day 1, Day 8, Day 15 and Day 22 of the cycle. In addition, a loading dose will be administered on Day 4 of Cycle 1. Thereafter, MOR00208 will be administered on a biweekly basis (every 14 days) with infusions on Day 1 and Day 15 from Cycle 4 to Cycle 6. MOR00208 will be given on a monthly basis on Day 1 from Cycle 7 to Cycle 24.

One to four visits are foreseen for each treatment cycle. Day 1 is the main visit of each cycle, where the largest number of examinations and assessments will be performed (for detail, see Table 10). Idelalisib or venetoclax tablets will be handed to the patients on Day 1 of each cycle.

Patients who continue to derive benefit from therapy with MOR00208 can stay on MOR00208-treatment even beyond Cycle 24. In this case, the patient should be followed up at further visits (C25D1, C26D1, etc.) as specified for Cycle 7 to Cycle 24 (see the Schedule of Assessments, Table 10). Examinations which are not performed on every cycle, e.g., radiological and PK examinations, should also be followed up according to the specifications made in Table 10.

Patients who achieved a confirmed CR or PR with bone marrow MRD negativity are allowed to stop idelalisib or venetoclax treatment and proceed with monthly MOR00208 treatment per discussion between the Investigator and sponsor's medical monitor.

9.2.8 Unscheduled Visit

The Investigator may at his/her discretion arrange for a patient to have an unscheduled assessment, especially in the case of AEs that require follow-up or an AE considered by the Investigator to be possibly related to the use of study drug. The unscheduled visit page in the CRF must be completed.

Ramp-up phase of venetoclax will be performed at regular scheduled visits. In cases when dose modification of venetoclax needs to be performed at an unscheduled visit (e.g., due to dosing interruption or reduction of venetoclax which leads to changed treatment schedule of venetoclax), the following evaluations and safety measures should be performed at respective unscheduled visit to reinitiate the weekly dosing of venetoclax:

- Risk reassessment and prophylaxis for TLS (see Sections 8.5, 8.10.1 and 9.3.2.6)
    - Evaluation and monitoring of blood chemistry locally (e.g., potassium, uric acid, phosphorus, calcium, and creatinine)
    - Assessment of tumor burden (ALC, physical examination), and comorbidities or symptoms suggestive of TLS
- Hospitalization as prescribed
- Central laboratory of hematology and serum chemistry. Other laboratory parameters (e.g., coagulation parameters, urinalysis) may be determined only if clinically indicated
- Vital signs
- 12-lead resting ECG only if clinically indicated
- Recording of (S)AEs

9.2.9 End of Treatment Visit

Patients will continue on study treatment until documented disease progression, intolerable toxicity, withdrawal of consent to continue study treatment, death, physician decision or early termination of the study. At that time, an End of Treatment (EOT) visit will be performed.

Assessments are to be completed preferably within ≤30 days of last study medication intake. The EOT visit will involve:

- Documentation of concomitant medications
- Blood sampling B-/T-/NK-cell count, CD19 expression assessment (see Section 9.3.6), for anti-MOR00208 antibodies (Section 9.3.5), MOR00208 PK sample (see Section 9.3.4) and a MRD assessment (only in case of CR or PR; see Section 9.3.3.6)

- Disease response assessment of CLL and SLL (CT or MRI scans of neck, chest, abdomen, pelvis)
- Bone marrow aspiration and biopsy (**required** for confirmation of CR)
- B-symptoms (see Section 9.3.3.5)
- Serum pregnancy test for FCBP (see Section 9.3.2.1)
- ECOG performance status (see Section 0)
- Blood sampling for hematology, serum chemistry and coagulation (central laboratory) (see Section 9.3.2.5)
- Urinalysis (see Table 11)
- Complete physical examination (see Section 9.3.2.3)
- Vital signs and weight (see Section 9.3.2.2)
- 12-lead resting ECG (see Section 9.3.2.4)
- Recording of (S)AEs (see Sections 10.2and 10.5)

Assessments can take place within 7 days of the actual EOT visit.

9.2.10 Follow-up Period

9.2.10.1 30-Day Safety Follow-up Visit

Regardless of the reason for study drug discontinuation, patients will have a safety follow-up visit scheduled 30 days after the last dose of the study treatment to follow up for AEs and SAEs that may have occurred after discontinuation from the study treatment.

9.2.10.2 Follow-up for Drug Discontinuation/Patient Withdrawal from Study

If a patient discontinues study treatment and is withdrawn from the study for any reason, the study site should immediately notify the medical monitor. The date and the reason for study discontinuation must be recorded on the eCRF. Patients who discontinue prematurely are to attend an EOT visit, if possible, and complete all assessments.

In the event that a patient discontinues prematurely from the study due to a TEAE or serious TEAE, the TEAE or serious TEAE will be followed until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to be no longer clinically significant.

Once a patient is withdrawn from the study, the patient may not re-enter the study.

9.3 Study Assessments

9.3.1 Demographic Characteristics and Other Baseline Assessments

9.3.1.1 Weight/Height

Body weight (reported in kilogram, kg) and body height should be measured with clothes on but without shoes. Height will be measured at C1D1 only, and weight should be measured at each visit. The values should be entered into the eCRF indicating the actual day of measurement.

For inpatients, body weight can be measured up to 24 hours before study drug administration on Day 1 of each cycle. This baseline weight will be used to calculate the study drug dose during the given cycle provided the weight does not deviate more than ±10% from baseline during the course of this cycle. In case body weight changes more than ±10% from baseline, the current weight will be used to calculate the next and subsequent doses of study drug.

For outpatients, the patient weight must be measured on Day 1 of each cycle. This baseline weight will be used to calculate the study drug dose during the given cycle, provided the patient confirms that their body weight has not changed more than ±10% from baseline. In case body weight changes more than ±10% from baseline, the current weight will be used to calculate the next and subsequent doses of study drug.

For both in- and outpatients, weight measurement will need to be performed at each visit and the values will need to be entered into the eCRF indicating the actual day of measurement. For outpatients, weight measurement may take place pre- or post dose.

9.3.1.2 Demography

Demographic baseline characteristics include age (including date of birth), sex and race.

9.3.1.3 Medical History/Current Medical Conditions

Medical history deserves particular attention because it is paramount for elibigility. Relevant medical history and current medical conditions will be recorded at the time of signing of the ICF. The medical history of CLL/SLL should be documented in detail, including baseline symptoms as well as a detailed history of prior cancer therapies for CLL/SLL, with start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other clinically significant illness. Any previous therapy (e.g., chemotherapy, immunotherapy, or radiation therapy) for CLL/SLL should be recorded in the eCRF.

Findings supporting the diagnosis of the latest progression of CLL/SLL should be recorded in the patient's source documents. Such findings may consist of laboratory examinations, imaging results or clinical symptoms related to CLL/SLL.

9.3.1.4 Disease Staging

Assessments at baseline should also include Binet and modified Rai staging. For details please refer to Appendix A.

9.3.1.5 FcγRII/III Gene Mucosal Cheek Swab

Before study drug administration, mucosal cheek swabs should be done for FcγR genotyping. The assessment is optional (also see Table 13).

9.3.2 Assessment of Safety

9.3.2.1 Pregnancy Testing

For FCBP, two pregnancy tests must be performed; the first, a serum pregnancy test (β-HCG) at screening within 7 days prior to the start of study drug, and the second, a local urine pregnancy test within 24 hours prior to the start of study drug. The results of both tests must be negative in order to receive C1D1 dosing. A β-HCG serum pregnancy test should also be performed at the EOT visit. At all other timepoints indicated in the Schedule of Assessments (Table 10), a urine pregnancy test for FCBP will be performed locally and the result must be negative for dosing.

9.3.2.2 Vital Signs

Vital signs will be measured at the timepoints described in the Schedule of Assessments (Table 10). These assessments include body temperature, systolic and diastolic blood pressure readings (mmHg), heart rate (beats per minute [bpm]), and respiratory rate (breaths per minute [brpm]).

Vital signs will be measured immediately prior to infusion, 15 ± 5 minutes, 30 ± 10 minutes, and then every 60 ±15 minutes during infusion, and at end of infusion (± 20 min). The actual time of vital sign measurements should be accurately documented. If the infusion is interrupted and/or subsequently restarted, vital signs should be assessed every 60 ± 15 minutes after the first hour.

During the safety run-in phase the following measures need to be performed on Cycle 1 Day 1 and Cycle 1 Day 4:

- Patients No. 1-3 (safety run-in phase): vital signs should be measured 1 hour after end of infusion (± 20 min) and 2 hours after end of infusion (± 20 min).
- Patients No. 4- approximately 12 (safety run-in phase): vital signs should be measured 1 hour after end of infusion (± 20 min).

The frequency or the length of the monitoring period may be adapted if clinically indicated, e.g., if in the opinion of the Investigator the vital sign results, at the time of event onset, are clinically significant. In such a case the patient's vital sign measurements should continue to be recorded until they have returned to normal or pre-infusion levels and an AE recorded. If possible, before vital signs are measured, the patient should be resting for at least 5 minutes. The same position should be used each time vital signs are measured for a given patient, and blood pressure should be measured from the arm contralateral to the site of study drug administration. Body temperature should be measured according to normal institutional practice.

9.3.2.3 Physical Examination

A complete physical examination (PE) will be performed by the Investigator or a qualified designee during the screening and at the EOT visit.

Complete PE must be performed according to the best standards of local medical practice, but should include at least palpable tumor assessment, general appearance, skin, head, eyes, ears, nose, throat including Waldeyer lymphatic structures, lungs, breasts and axillae, cardiovascular system, back and spine, abdomen, extremities, infusion site, lymph nodes, and neurological examination.

Limited PEs may be focused on tumor response assessment (lymph nodes, liver, spleen, etc.) and AEs (e.g., attention on respiratory signs and symptoms) at the Investigator's discretion. Such limited PEs will be performed as indicated in the Schedule of Assessments (Table 10). Limited

PE will be performed on Day 1 and 15 of Cycle 1 to 6, on Day 1 of all further visits, and at EOT. Symptom-driven full PEs may be performed as clinically indicated at any study visit.

9.3.2.4 Electrocardiogram

Standard 12-lead resting ECGs should be obtained at the various timepoints described in the Schedule of Assessments (Table 10). ECGs should be recorded after the patient has rested in a supine position for at least 5 minutes. Heart rate, PR, QRS, RR and QT intervals should be determined. All ECGs should be performed and interpreted locally. The Investigator should evaluate the clinical significance of each value outside the reference ranges according to the nature and degree of the observed abnormality. Any new abnormal values considered to be clinically significant should be reported as AEs.

If clinically significant abnormalities are observed or artefacts are present that result in an inability to adequately interpret the results, the ECG should be repeated. An average of all intervals measured in all ECG tracings recorded at a given timepoint may be taken if necessary.

9.3.2.5 Laboratory Assessments

Clinical laboratory tests should be performed according to Table 10 and Table 11. During the course of the study, local ("emergency") and central laboratories will be used.

Central laboratory results are required for determining patient eligibility for study enrolment and will be used in the statistical analysis of the study results. During the course of the study, all scheduled central laboratory results should be reviewed as soon as possible after Day 1 of each cycle.

It is permitted to repeat on a single occasion the central laboratory assessment of serum chemistry and hematology parameters during screening due to the variability of the parameters and their dependence on a multitude of factors (see Section 9.2.2).

Table 11: **Safety Laboratory Evaluations**

Evaluation	Analysis
"Emergency laboratory" (EDTA blood and serum sample)	AST, ALT, bilirubin (total, direct and indirect), direct Coombs test, hemoglobin, platelets, potassium, serum creatinine, sodium, WBCs, including WBC differential (including ANC) [1] Cohort B only: Additional values to be analyzed: calcium, creatinine, inorganic phosphorus (phosphate), potassium and uric acid
Hematology (EDTA blood)	Direct Coombs test, erythrocyte count (RBC count), hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, reticulocytes, WBC with differential count (absolute counts and % of leukocytes: basophils, eosinophils, lymphocytes, monocytes, neutrophils) At screening: should include a peripheral blood smear.
Serum chemistry (serum sample)	ALT, total albumin, ALP, amylase, AST, β_2-microglobulin, bicarbonate, bilirubin (total, direct and indirect), blood urea nitrogen, calcium (total), chloride, cholesterol, creatinine, creatinine kinase, GGT, glucose, LDH, lipase, magnesium, phosphate, potassium, protein (total), serum CrCl calculated using a standard Cockcroft-Gault formula, sodium, triglycerides, uric acid
Coagulation parameters (sodium citrate blood)	Activated partial thromboplastin time, prothrombin time, international normalized ratio
Viral parameters (serum or plasma sample)	Hepatitis B: HBsAg, anti-HBc and HBsAb. HBV DNA if anti-HBc positive, optional Hepatitis C: HCV antibody (HCV RNA quantification if anti-HCV positive) CMV: CMV antibody and CMV copy number per mL (PCR based) HIV-1/-2 Ag and Ab Screening (HIV-1/-2 Ab differentiation if HIV positive)
Pregnancy test (serum sample)	β-HCG serum, females of childbearing potential only
Pregnancy test (urine)	β-HCG urine, females of childbearing potential only
Urinalysis	Clarity (clear, slightly cloudy, cloudy, turbid), bilirubin, color, glucose, hemoglobin, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen. Microscopy will only be performed if clinically indicated.

Abbreviations: ALP= alkaline phosphatase; ALT=alanine transaminase; anti-HBc=hepatitis B core antibody; ANC=absolute neutrophil count; AST=aspartate amino-transferase; β-HCG=beta-human chorionic gonadotropin; CMV=Cytomegalovirus; CrCl=creatinine clearance; DNA=deoxyribonucleic acid; EDTA=ethylenediaminetetra-acetic acid; GGT=gamma-glutamyltransferase; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HIV=human immunodeficiency virus; LDH=lactate dehydrogenase; PCR=polymerase chain reaction; RNA= ribonucleic acid; RBC=red blood cell; WBC=white blood cells.

[1]WBC differential can be automated or manual as per institutional standards. Reticulocytes may be determined only if clinically indicated.

Local ("emergency") laboratory results will be used for treatment or clinically related decisions, or for the immediate safety needs of a study patient. "Emergency laboratory" (local) results should be reviewed as soon as possible after their receipt and before dosing so that the administration of the investigational medicinal product may be adjusted or interrupted if necessary. Emergency laboratory assessments may be performed up to 24 hours before administration of study drugs.

Detailed instructions and amounts of biological samples needed for the respective laboratory measurements will be summarized in the Laboratory Manual. All samples will be collected as non-fasting samples.

Table 11 summarizes laboratory assessments for a safe study conduct and for the evaluation of safety.

Safety and Hematology Laboratory Testing

The laboratory results of the centrally assessed clinical and safety relevant parameters will automatically be entered into the eCRF. The signed and interpreted laboratory results (both local and central) are to be kept in the patient's source documentation. The laboratory results should be reviewed, dated and signed in a timely manner by the Investigators. Any clinically significant discrepancies between local and central laboratory results will be evaluated by the Investigator and medical monitor on a case-by-case basis. All blood samples should be processed and handled according to standard laboratory procedures. The time of blood collection should be documented in the eCRF.

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

Virus Serology

Patients will be examined according to the Schedule of Assessments (Table 10) for viral hepatitis B / C, HIV and Cytomegalovirus (CMV) serology.

Hepatitis B and C

Hepatitis B biomarkers include hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (anti-HBc) and hepatitis B surface antibody (HBsAb). For patients who are positive for anti-HBc, hepatitis B viral DNA (HBV DNA) should be measured.

Seropositive for or active viral infection with HBV:

a) HBsAg positive

b) HBsAg negative, HBsAb positive and/or anti-HBc positive and detectable viral DNA. Note: patients who are HBsAg negative and viral DNA negative are eligible

c) Patients who had HBV but have received an antiviral treatment and show no detectable viral DNA for 6 months prior to the time of signing of the ICF are eligible

d) Patients who exhibit the classical vaccination profile of HBsAb positive, anti-HBc negative, and HBsAg negative are eligible.

If HBV DNA becomes detectable during treatment, patients should be prophylactically treated and followed-up for potential hepatitis B reactivation as per local medical practice or institutional guidelines for CD20 antibodies such as RTX. If the HBV DNA assay is positive, then patients can only stay in the study if they are assessed by a physician experienced in the treatment of hepatitis B and pre-emptive treatment is initiated, if deemed appropriate, and/or according to local practice/guidelines.

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

A positive hepatitis C test is defined as a positive test for anti-HCV and a positive test for HCV RNA.

HIV

Currently, there are no safety data on the use of CD19 antibodies in HIV positive patients available. Patients with known HIV infections will therefore be excluded from the clinical trial. In order to ensure that this patient population (which may also include patients with positive but unknown HIV status) will be adequately identified all patients must undergo HIV testing during screening. HIV testing during screening will be done using standard antibody tests.

Cytomegalovirus

A central CMV laboratory test (serology and PCR) will be performed for all patients at screening. Patient with negative serology should be monitored locally in accordance with institutional guidelines. Patients with positive serology or with other evidence of a history of CMV infection should be carefully monitored with a PCR based methodology:

- monthly, if the initial PCR result was negative without associated clinical signs of CMV infection
- weekly, if significant CMV viremia is detected.

9.3.2.6 Risk Assessment for Tumor Lysis Syndrome for Patients Treated with Venetoclax

Patients enrolling in Cohort B will be assessed for TLS risk and categorized in a risk category at screening as described below:

1. **Low-risk** category: the presence of all measurable lymph nodes with the largest diameter <5 cm by radiologic assessment* baseline AND absolute lymphocyte counts <25 $\times 10^9$/L
2. **Medium-risk** category: the presence of all measurable lymph nodes with the largest diameter ≥5 cm and <10 cm by radiologic assessment* OR absolute lymphocyte count ≥25 $\times 10^9$/L
3. **High-risk** category: the presence of any lymph node with the largest diameter ≥10 cm by radiologic assessment* OR the presence of BOTH an absolute lymphocyte count ≥25 $\times 10^9$/L AND a measurable lymph node with the largest diameter ≥5 cm by radiologic assessment*.

[*] Baseline CT/MRI scan at screening as defined in Footnote_7 to Table 10.

Reassessment of the patient's risk category should be performed before first and each subsequent dose escalation of venetoclax on C1D8, C1D15, C1D22, C2D1 and C2D8 based upon blood chemistry, tumor burden (ALC, physical examination), comorbidities or symptoms suggestive of TLS. In cases when an unscheduled visit needs to be performed during ramp-up phase of venetoclax (e.g., due to dosing interruption or reduction of venetoclax which leads to changed treatment schedule of venetoclax), no risk reassessment for TLS needs to be performed at respective regular visit(s) when MOR00208 is administered. Furthermore, during the safety run-in phase of Cohort B discussion will occur between the Investigator and sponsors's medical monitor regarding the plan for TLS prophylaxis, including hydration, as necessary.

9.3.2.7 Adverse Events

Please refer to Section 10 (Safety Monitoring).

9.3.3 Assessment of Efficacy

9.3.3.1 Tumor Response Assessment

Criteria of the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) for CLL subjects (Hallek et al., 2008) will be used to determine rates of response and progression for patients with CLL, with the modification that treatment-related lymphocytosis (Note: PRL is applicable in Cohort A only) in the absence of other signs or symptoms of disease progression will not be considered as progressive disease (Cheson et al., 2012; Hallek et al., 2012; NCCN NHL 2015 Guidelines). For patients with SLL, assessments will be performed using the Lugano Classification criteria for SLL subjects (Cheson et al., 2014).

The secondary endpoint overall response rate (ORR) will be derived from the local review of radiology and clinical data.

Patients who develop a PR will be assessed using MRD testing from peripherial blood as well as from bone marrow, in case PB MRD negativity status was reached. Furthermore, patients who develop a complete response as per standard criteria will be investigated using MRD testing and bone marrow aspiration/biopsy as described in IWCLL (Hallek et al., 2008).

Overall response assessments include physical exams, recording of symptoms, radiographic and hematological evaluations to evaluate for both AEs and for disease progression per the schedule of assessments. If a patient shows signs of progression, the patient may continue on treatment until progression is confirmed by CT scan. The CT scan should be performed and collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent CT scans. The same scan modality should be used for all assessments, and all patients are required to have scans of the neck/chest/abdomen/pelvis.

Baseline tumor assessments must be performed a maximum of 14 days before C1D1. As response is a secondary endpoint of the trial and that PD will be followed by physical examination, CT scans performed prior to screening as part of the regular clinical work-up of the patient will be allowed up to 6 weeks before C1D1. This is to prevent the re-irradiation of patients who have recently undergone a CT scan. However, a CT scan must be performed within the 14 day period prior to C1D1 for those patients with signs of rapidly progressing disease at screening.

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

Any suspected case of disease progression should be confirmed with a CT scan. Radiological assessment of efficacy response will be required to be reviewed at C4D1, C7D1, C13D1, C19D1, etc., and at the EOT visit (in case the last tumor evaluation was not performed within 28 days). There is a time window of ±7 days for the assessments on Cycle 4 and Cycle 7 and ± 14 days window for the following examinations. Patients should continue to be followed and adhere to study-related procedures until progression has been confirmed.

A CT/MRI scan has to be performed at least 8 weeks after CR was identified by clinical criteria (and before a BM biopsy is obtained for CR confirmation). Clinical criteria should be based on physical examination and/or laboratory values.

In case of this confirmatory CT/MRI scan the following shall apply:

- If a regular CT/MRI scan is scheduled within less than 8 weeks after identification of the CR by clinical criteria, then this examination should be postponed to meet the confirmation timeline of at least 8 weeks.

  and/or

- The following regular CT/MRI scan can be postponed/skipped, if this examination is within 8 weeks of the CR confirmatory scan.

9.3.3.2 Tumor Response Assessment for CLL

Definitions of Tumor Response and Progression

Responses will be categorized locally as CR, PR, PRL, SD, or PD.
(Note: PRL is applicable in Cohort A only.)

The best overall response in the course of the study will be determined. The best overall response is the best response recorded from the start of treatment until disease progression, withdrawal from study or death (taking as a reference for disease progression the smallest measurements recorded since treatment started).

At baseline, up to 6 lymph nodes should be selected as index lesions that will be used to quantitate the status of the disease during study treatment. Ideally, the index lesions should be located in disparate regions of the body. However, it is optimal if mediastinal and retroperitoneal areas of disease are assessed whenever these sites are involved. Any other measurable and abnormal nodal lesions not selected for quantitation as index lesions may be considered non-index lesions. In addition, non-measurable evidence of CLL such as nodal lesions with both diameters <1.0 cm, extranodal lesions, bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, previously irradiated lesions, and lesions with artifacts may be considered as non-index disease. The presence or absence of non-index disease should be recorded at baseline and at the stipulated intervals during treatment. The non-

index disease at baseline will be used as a general reference to further characterize regression or progression of CLL during assessments of the overall tumor response during treatment. Measurements are not required and these lesions should be followed as "present" or "absent".

A table of response definition by the IWCLL 2008 is provided in Appendix J.

Complete Response

To satisfy criteria for a CR, all of the following criteria must be met:

- No evidence of new disease
- ALC in peripheral blood of $< 4 \times 10^9$/L
- Regression of all index nodal masses to normal size ≤ 1.5 cm in the longest diameter (LDi)
- Normal spleen and liver size
- Regression to normal of all nodal non-index disease and disappearance of all detectable non-nodal, non-index disease
- Morphologically negative bone marrow defined as < 30% of nucleated cells being lymphoid cells and no lymphoid nodules in a bone marrow sample that is normocellular for age
- Peripheral blood counts meeting all of the following criteria:
  - ANC $> 1.5 \times 10^9$/L without need for exogenous growth factors (e.g., G-CSF)
  - Platelet count $\geq 100 \times 10^9$/L without need for exogenous growth factors
  - Hemoglobin ≥ 110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogeneous growth factors (e.g., erythropoietin)

Subjects who fulfill all the criteria for a CR (including bone marrow criteria) but who have a persistent anemia, thrombocytopenia, or neutropenia or a hypocellular bone marrow that is related to prior or ongoing drug toxicity (and not to CLL) will be considered as a CR with incomplete marrow recovery (CRi).

Partial Response

To satisfy criteria for a PR, all of the following criteria must be met:

- A decrease in the number of blood lymphocytes by 50% or more from the value before therapy
- Reduction in lymphadenopathy by CT scans as defined by the following:
  - A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s)
  - No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (< 2 cm), an increase of less than 25% is not considered to be significant
- A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan
- The blood count should show one of the following results:
  - Neutrophils more than 1.5 x 10^9/L (1500/µL) without need for exogenous growth factors
  - Platelet counts greater than 100 x 10^9/L (100,000/µL) or 50% improvement over baseline without need for exogenous growth factors
  - Hemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin

Stable Disease

To satisfy criteria for SD, the following criteria must be met:

- No evidence of new disease
- There is neither sufficient evidence of tumor shrinkage to qualify for PR nor sufficient evidence of tumor growth to qualify for definitive PD

Definitive Progressive Disease

The occurrence of any of the following events indicates definitive PD:

- Evidence of any new disease:
  - A new node that measures > 1.5 cm in the longest diameter (LD) and > 1.0 cm in the longest perpendicular diameter (LPD)
  - New or recurrent splenomegaly, with a minimum longest vertical dimension (LVD) of 14 cm
  - New or recurrent hepatomegaly, with a minimum LVD of 20 cm
  - Unequivocal reappearance of an extranodal lesion that had resolved
  - A new unequivocal extranodal lesion of any size
  - New non-index disease (e.g., effusions, ascites, or other organ abnormalities related to CLL)

Isolated new effusions, ascites, or other organ abnormalities are not sufficient evidence alone of a PD unless histologically confirmed. Thus, a declaration of PD should not be made if this is the only manifestation of apparently new disease.

- Evidence of worsening of index lesions, spleen or liver, or non-index disease:
  - Increase by ≥ 50% from the nadir in the sum of the products of the perpendicular diameters (SPD) of index lesions
  - Increase from the nadir by ≥ 50% in the LD of an individual node or extranodal mass that now has an LD of > 1.5 cm and an LPD of > 1.0 cm
  - Splenic progression, defined as an increase in splenic enlargement by ≥ 50% from nadir (with a minimum 2 cm increase and a minimum LVD of 14 cm)
  - Hepatic progression, defined as an increase in hepatic enlargement by ≥ 50% from nadir (with a minimum 2 cm increase and a minimum LVD of 20 cm)
  - Unequivocal increase in the size of non-index disease (e.g., effusions, ascites, or other organ abnormalities related to CLL)
  - Transformation to a more aggressive histology (e.g., Richter's syndrome) as established by biopsy (with the date of the biopsy being considered the date of CLL progression if the subject has no earlier objective documentation of CLL progression).
- Decrease in platelet count or hemoglobin that is attributable to CLL, is not attributable to an autoimmune phenomenon, and is confirmed by bone marrow biopsy showing an infiltrate of clonal CLL cells
  - The current platelet count is < 100 x 10^9/L and there has been a decrease by > 50% from the highest on-study platelet count
  - The current hemoglobin is < 110 g/L (11.0 g/dL) and there has been a decrease by > 20 g/L (2 g/dL) from the highest on-study hemoglobin

If there is uncertainty regarding whether there is true progression, the subject should continue study treatment and remain under close observation. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening CLL will not be considered definitive disease progression; in such subjects, both CLL-related and non-CLL-related causes for the constitutional symptoms should be considered. Worsening of disease during temporary interruption of study treatment (e.g., for intercurrent illness) is not necessarily indicative of resistance to study treatment. In these instances, CT or MRI or other relevant evaluations should be considered in order to document whether definitive disease progression has occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive CLL progression, then the date of progression should be the timepoint at which progression was first objectively documented.

Lymphocytosis During Therapy

Upon initiation of idelalisib treatment, transient increase of absolute lymphocyte count is expected in most patients because idelalisib can mobilize CLL cells from tissues into the peripheral blood. This characteristic pharmacological action can be prominent early in therapy but can persist over time and should not be confused with disease progression in subjects who have persistent control of other CLL-related signs and symptoms. **In the absence of other objective evidence of disease progression, lymphocytosis alone will not preclude subjects from meeting the criteria for PR if other criteria for PR are met and will not be considered evidence of disease progression if occurring in isolation.** Thus, subjects with worsening lymphadenopathy, organomegaly, bone marrow involvement, progressive cytopenias, appearance of new disease, or transformation to a more aggressive lymphoid malignancy histology (e.g., Richter's syndrome) will be considered to have progressed according to IWCLL criteria for progressive disease. Subjects with lymphocytosis without any of these other events will not be considered to have progressed and should be continued on study drug until the occurrence of definitive disease progression (Note: PRL is applicable in Cohort A only).

9.3.3.3 Tumor Response Assessment for SLL

Tumor measurements will be performed by CT as indicated in Table 12. MRI may be used in lieu of CT for patients with contraindications to the administration of contrast agents, or due to other medical reasons, at the same timepoints as CT or, in addition to CT, at the discretion of the Investigator (in this case, MRI may be performed as/when appropriate).

Table 12: Lugano Classification Criteria for SLL (adapted from Cheson et al., 2014)

Response	Site	CT-Based Response
CR		Complete remission requires all of the following:
	Lymph nodes and extralymphatic sites	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
		No extralymphatic sites of disease
	Nonmeasured lesions	Absent
	Organ enlargement	Regress to normal
	New lesions	None
	Bone marrow	Normal by morphology; if indeterminate, IHC negative
PR		Partial remission requires all of the following:
	Lymph nodes and extralymphatic sites	≥ 50% decrease in SPD of up to 6 target nodes and extranodal sites
		When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value
		When no longer visible, 0 x 0 mm
		For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
	Nonmeasured lesions	Absent/normal, regressed, but no increase
	Organ enlargement	Spleen must have regressed by > 50% in length beyond normal (13 cm)
	New lesions	None
	Bone marrow	Normal marrow, persistent infiltration, or no marrow obtained
SD		Stable disease
	Target nodes/nodal masses/ extranodal lesions	< 50% decrease from baseline in SPD of up to 6 target nodes and extranodal sites; no criteria for progressive disease are met
	Nonmeasured lesions	No increase consistent with progression
	Organ enlargement	No increase consistent with progression
	New lesions	None
	Bone marrow	Normal marrow, persistent infiltration, or no marrow obtained
PD		Progressive disease requires at least 1 of the following:
	Individual target nodes/nodal masses	PPD progression

Response	Site	CT-Based Response
PD	Extranodal lesions	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
	Nonmeasured lesions	New or clear progression of preexisting nonmeasured lesions
	New lesions	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent involvement

Abbreviations: CR=complete remission; PR=partial remission; SD=stable disease; PD=progressive disease; CT=computed tomography; LDi=longest transverse diameter of a lesion; IHC=immunohistochemistry; SPD=sum of the product of the perpendicular diameters for multiple lesions; PPD=cross product of the LDi and perpendicular diameter; SDi=shortest axis perpendicular to the LDi.

9.3.3.4 Bone Marrow Aspiration and Biopsy

For patients with CR, a bone marrow aspiration and biopsy has to be performed for confirmation of CR at least 8 weeks after the CR criteria for tumor response were first met. The results of the CT scan need to be obtained first; if this does not confirm a CR, then a BM aspiration/biopsy should not be performed. Histological examination of the bone marrow should be performed locally. Furthermore, patients who achieved a PR and PB MRD negativity need also to perform a bone marrow aspiration/biopsy.

9.3.3.5 B-Symptoms

B-symptoms are defined as any one or more of the disease-related symptoms or signs mentioned in Appendix K. Assessment of the presence or absence of B-symptoms will be performed at screening and on Day 1 of all cycles, as well as the EOT visit, and at the 30-Day Safety Follow-up visit. B-Symptoms will also be assessed in case a patient will be followed up for disease progression after the EOT visit, as described in the Schedule of Assessments (Table 10). B-symptoms should not be reported as AEs. Worsening is generally considered a symptom (but not an objective criterion) of progression.

9.3.3.6 Assessment of MRD Response

New detection technologies such as multicolor flow cytometry and real-time quantitative polymerase chain reaction (PCR) have undergone a critical evaluation and either 4-color flow cytometry (MRD flow) or allele-specific oligonucleotide PCR is reliably sensitive down to a level of approximately one CLL cell in 10,000 leukocytes.

Patients who develop a PR or CR will be assessed using MRD testing from peripherial blood at C1D1, C4D1, C7D1, C13D1, etc. until bone marrow MRD negativity was confirmed. An additional PB sample will be obtained from CR patients at the time when CR is confirmed by CT outside of the scheduled radiological examinations. Additionally, patients with CR or PR will be further assessed for MRD negativity status from bone marrow (aspirate) at least 8 weeks after the PB MRD negativity was detected and only after CR was confirmed by CT/MRI scan. Further details on MRD methodology will be provided separately in the Laboratory Manual.

9.3.4 Assessment of Pharmacokinetics

Concentration-time profiles and PK parameters will be assessed for MOR00208 according to the Schedule of Assessments (Table 10).

Serum samples for PK analysis of MOR00208 will be handled and stored as specified in the Laboratory Manual at the study site until shipment on dry ice to an external analytical laboratory. At each sampling timepoint the obtained serum sample should be split into 2 aliquots (a primary and a back-up sample).

9.3.5 Assessment of Immunogenicity

Serum samples for anti-MOR00208 antibody analysis will be collected according to the Schedule of Assessments (Table 10) and will be handled and stored as specified in the Laboratory Manual at the study site until shipment on dry ice to an external analytical laboratory. At each sampling time point, the obtained serum sample should be split into 2 aliquots (a primary and a back-up sample).

9.3.6 Biomarker Assessment

Explorative biomarkers analyzed at baseline and during the course of the study may include the assements listed in Table 13.

Table 13: **Biomarker Assessment**

ADCC assessment (heparinized blood) (exploratory assay)	ADCC with peripheral blood mononuclear cells
B-/T-/NK cell count (heparinized blood) (exploratory assay)	Absolute cell counts
CD16 expression on peripheral NK cells (heparinized blood) (exploratory assay)	CD16 molecules expressed per cell (CD16 antibodies bound per cell)
CD19 expression on peripheral B cells (heparinized blood) (exploratory assay)	CD19 molecules expressed per cell (CD19 antibodies bound per cell)
Analysis of genetic CD19 alterations (optional) (heparinized blood) (exploratory assay)	CD19 mutational status (DNA isolated from tumor cells)
FcγR genotyping (optional) (mucosal cheek swabs)	FcγR polymorphism (FcγRII/III genes)

Abbreviations: ADCC=antibody dependent cell mediated cytotoxicity; CD=cluster of differentiation; CD16=low affinity Fc receptor; CD19=B lymphocyte antigen CD19; Fc (fragment crystallizable) gamma receptors; NK=natural killer.

The patient is asked for his participation in additional Pharmacogenomic analyses. For this purpose samples will be stored to analyze tumor DNA, RNA (Cohort A and B) and/or protein levels (Cohort B only) of predictive biomarkers. Participation in these optional analyses is completely voluntary and will not affect the participation of the patient in this trial.

Due to the exploratory nature of some assays, the sponsor may decide at any point during the study to terminate these assessments, in which case the sites will be informed accordingly.

9.3.7 Disease Risk Assessment

Disease risk assessment as per IWCLL guideline includes cytogenetics (flourescence in-situ hybridization [FISH] for del(17p), del(11q), del(13q), trisomy 12, del(6q), karyotyping, IGHV mutational status, analysis of serum markers as β2 microglobulin or CLL cell markers as CD38 and ZAP-70 (cytometry).

Additional information on disease risk can be obtained by analysis of TP53, NOTCH1, BTK and PLCγ2 mutational status in CLL cells from peripheral blood (Table 14).

Table 14: **Disease Risk Assessment**

As per IWCLL guideline	Cytogenetic tests for del(17p), del(11q), del(13q), trisomy 12; karyotyping β2 microglobulin (serum); CD38 and ZAP-70 (cytometry); IGHV mutational status (optional)
In addition (optional)	Mutational status of e.g., TP53, NOTCH1, BTK and PLCγ2

Abbreviations: ZAP-70=zeta-chain-associated protein kinase 70; IGHV=immunoglobulin heavy-chain variable; TP53=tumor protein p53; BTK=Bruton's tyrosine kinase; PLC=phospholipase C.

9.3.8 ECOG Performance Status

The Eastern Cooperative Oncology Group (ECOG) performance status scale will be used by the Investigator to assess functional impairment of patients, i.e., how the disease affects their daily living abilities (see Appendix L). Patients will be assessed for ECOG performance status at screening, on Day 1 of each cycle, and at the EOT visit.

10 SAFETY MONITORING

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

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

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

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

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

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

AEs include any clinically significant deterioration of a patient's medical status after the signing of the ICF. Also, an increase in the frequency or intensity of a pre-existing event or conditions and events resulting from protocol mandated procedures (e.g., invasive procedures) fall under the definition of AEs. In addition, overdoses (defined as exceeding the planned MOR00208 dose by >30% and/or more than the daily idelalisib or venetoclax dose according to protocol) 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 (CLL/SLL) do not fall under the definition of AEs.

Each AE should be evaluated to determine the following:

- Relationship to the study drug (suspected/not suspected)
- Duration (start and end date, or if continuing at end of study)
- Intensity: the intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:
  - mild: tolerable
  - moderate: interferes with normal activity
  - severe: incapacitating (causes inability to perform usual activities or work
- Severity, i.e., toxicity grade: determined according to the NCI-CTCAE version 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; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
  - grade 4: life-threatening consequences; urgent intervention indicated
  - grade 5: death related to AE
- Outcome
- Action taken (no action taken; study drug temporarily interrupted; study drug permanently discontinued due to this AE; medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
- Seriousness: whether it is serious, **where an <u>SAE</u> is defined as one that:**
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization signifies that the patient was an inpatient for at least one overnight stay) **unless hospitalization is for**:
    - routine treatment or monitoring of the studied indication, not associated with deterioration of symptoms related to CLL/SLL

- elective or preplanned treatment for a pre-existing condition that is unrelated to CLL/SLL and has not worsened since signing of the informed consent
- social reason and respite care in the absence of any deterioration in the patient's general condition

- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is medically significant, i.e., defined as an event that jeopardises the patient or may require medical intervention to prevent one of the outcomes listed previously.

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

AEs of special interest (AESIs) for MOR00208 are: TLS, IRRs and allergic reactions to study drug ≥ grade 3, cytokine release syndrome and overdoses.

AEs of special interest (AESIs) for idelalisib are: Diarrhea/colitis ≥ grade 3, pneumonitis ≥ grade 3 and elevation of hepatic enzymes ≥ grade 3, Pneumocystis jirovecii pneumonia (PJP), Cytomegalovirus (CMV) infections, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and overdoses.

AEs of special interest (AESIs) for venetoclax are: TLS, neutropenia with infection or fever ≥grade 3, overdoses.

Unlike routine safety assessments, SAEs and AESIs are monitored continuously and have special reporting requirements (see Section 11.2).

The Investigator should determine the causality (relationship to the study drug) based on his/her clinical experience and on the information given in the IB. 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.

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

10.2 Methods and Timing for Capturing and Assessing Safety Parameters

The Investigator is responsible for ensuring that all adverse AEs (for definition, see Section 10.1) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 10.5. For each AE recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness, severity and causality (for the respective definition, see Section 10.1).

10.3 Diagnosis Versus Signs and Symptoms

In general, diagnoses rather than individual symptoms should be reported as the event term. If a diagnosis has been reported as an AE, it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if a myocardial infarction is reported as an AE, there is no need to report elevated creatine phosphokinase and abnormal ECG, or other related signs, symptoms, or laboratory values as separate AEs. However, if such events occur in isolation and myocardial infarction is not diagnosed, then each event should be reported as an AE.

10.4 Safety Review by the Independent Data Monitoring Committee

The safety run-in phase will be concluded with an evaluation of the safety data of all treated patients once 10 patients completed at least one treatment cycle in Cohort A or 5 weeks of combination treatment in Cohort B. The first 3 patients of Cohort A will be dosed sequentially, at least 48 hours apart. In Cohort B all 10-12 patients will be dosed sequentially, at least one week apart.

In Cohort A there will be two safety evaluations. After completion of the first cycle the safety data of the first three patients will be evaluated. This evaluation will be done by the IDMC composed of experts in the field of oncology and clinical biostatistics who have no other role in the study and do not have an affiliation with the Investigators or the sponsor. After the evaluation of the safety data from the first 3 patients for cycle 1 of treatment and a positive recommendation from the IDMC the next 7-9 patients may be dosed in parallel. An additional IDMC review will take place after 10 patients completed at least 1 cycle of treatment.

In Cohort B the safety evaluation will be performed by an IDMC after the first 10 patients completed at least 5 weeks of combination treatment. The evaluation will be done by the IDMC as already described. Importantly, all patients in Cohort B, who participate in the safety run-in phase, will be hospitalized on the day of the first two dose escalations (C1D8 and C1D15).

The criteria for the evaluation of safety of the combination therapy will be defined by the IDMC and laid down in the IDMC Charter of the trial.

The review is based on the number and type of AEs occurring during the first cycle and on laboratory values (biochemistry and hematology) and other relevant safety data as necessary:

- TEAEs sorted by SOC and PT
- TEAEs sorted by frequency
- TEAEs of Grade 3 and 4 according to NCI CTCAE version 4.03 (or higher)
- TEAEs by relationship (by SOC and PT and by frequency)
- Serious adverse events (SAEs)
- TEAEs that requires discontinuation of the study drug
- Laboratory data (hematology and biochemistry)
- Patient deaths
- Concomitant medications

Following each meeting, the IDMC will provide a recommendation to the sponsor whether the study may continue according to the protocol or may suggest changes to the protocol or may recommend stopping the study due to safety reasons.

A primary analysis in order to check for safety and preliminary efficacy will be based on the safety and response assessment data of the enrolled patients up to the time point of 3-18 months after last patient started treatment in Cohort B.

The specific details for decision making are included in the IDMC Charter.

10.5 Adverse Event and Serious Adverse Event Recording and Reporting

All AEs (except non-serious AEs for screening failures) that occur after the provision of informed consent and up to 30 days after last drug administration will be recorded in the eCRF and in the patient's medical records, whether or not they are considered by the Investigator to be related to the study drug. Thereafter, only SAEs/AESIs assessed as related should be recorded. All AEs should be recorded using acceptable diagnoses, if possible. For screening failure patients, non-serious AEs will not be recorded in the eCRF but only in the patient's medical records.

In addition, all SAEs and AESIs will be recorded on the SAE report form. Study centers and Investigators are instructed to report all SAEs and AESIs to the contract research organization (CRO) mentioned below within 24 hours, using the study-specific SAE report form. NOTE: FU SAEs do also have to be reported within 24 hours to the CRO.

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

All non-serious AEs must be followed up for a final outcome. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not yet resolved" is an acceptable final outcome for non-serious AEs at the end of a patient's participation in the study. All SAEs must be followed up for a final outcome until resolution or, if resolution becomes unlikely, until stabilization or death.

Notification of initial or follow-up SAE/AESI information (by using the standard SAE form provided by the sponsor) must be sent by fax to the CRO at one of the following numbers, as appropriate:

Europe:
Fax: +[redacted]
E-mail: [redacted]

United States:
Fax: +[redacted]
E-mail: [redacted]

For any safety-related or protocol related questions, please use the contact numbers below (24/7 coverage):

24/7 Medical Emergency Coverage (out of office hours)	Globally Telephone: +[redacted] In a study related medical emergency situation, when assigned medical monitors for a study cannot be reached by a caller, an on-call physician can be reached 24 hours per day, 7 days per week via [redacted]. (The telephone number above is a chargeable telephone number allowing a global reach from both landlines and mobile phones.) [redacted] On this internet page a list of country-specific toll-free telephone numbers is provided. Note that not all countries globally have access to toll-free numbers as indicated on the "24/7 Medical Help desk" index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.
Medical Emergency Coverage (during Medical Monitor office hours)	**Europe** [redacted] **United States** [redacted]

10.6 Pregnancies

As detailed in the Schedule of Assessments (Table 10) and in Section 9.3.2.1, serum pregnancy testing will be carried out at the Screening, and EOT visits. During the treatment period of the study, urine pregnancy testing will be performed locally and can be repeated if required. Any pregnancy that occurs during study participation should be reported using a Clinical Trial Pregnancy Form. To ensure patient safety, each pregnancy of a study patient or a female partner of a study patient must also be reported within 24 hours of learning of its occurrence by fax to one of the following numbers:

Europe:
Fax: +[redacted]

United States:
Fax: +[redacted]

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

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

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

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

10.7 Deaths

Deaths occurring during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of CLL/SLL should not be reported as SAE. All other on-study deaths, regardless of relationship to study drug, must be immediately reported to the sponsor as SAE (see Section 10.5).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported.

If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. The IDMC will monitor the frequency of deaths from all causes.

11 DATA HANDLING AND ARCHIVING

11.1 Completing and Signing Case Report Forms

An eCRF will be used in this study. The Investigator will be responsible for accurate and timely data entry into the eCRF. Data entry may be delegated to adequately trained site personnel. Any errors should be corrected within the electronic system. In the case of missing data, a reason should be given. The audit trail will record all changes made, the date and time of the correction, and the person correcting the error. The appropriate electronic signature will be provided. The Investigators will receive a copy of their eCRF in a readable format after database lock for archiving.

11.2 Clinical Data Management

The CRO will be responsible for the processing and quality control of the data according to the CRO's standard operating procedures (SOPs). Data management will be carried out by the CRO. The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

Details for data validation and edit checks will be described in appropriate data management documents. Queries will be handled via the eCRF system. Data cleaning will continue until all queries are resolved.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA, Version 18.0 or higher) for AEs and medical history and the WHO Drug Dictionary Enhanced (WHO DDE) for medication.

11.3 Archiving and Filing

All study documentation at the Investigator site and sponsor site will be archived in accordance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance and the clinical trial agreement.

12 STATISTICAL METHODS AND PLANNED ANALYSES

A Statistical Analysis Plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using the Statistical Analysis Software (SAS®) Version 9.3 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. For continuous variables, data will be summarized with the number of subjects (N) (with non-missing values/valid cases), mean, standard deviation, minimum, 25th quartile, median, 75th quartile and maximum, except for pharmacokinetic metrics, where additional statistics may be used. For categorical variables, data will be tabulated with the frequency and percentage of patients/entries for each category.

Missing values will not be imputed. All statistical evaluations will be based on valid cases except for procedures described for calculating response rates or in the case of censoring within the Kaplan-Meier methodology. In the case of incomplete start or stop dates of AEs or concomitant medication appropriate conservative imputation methods will be specified in the SAP.

Baseline values will be defined as the last pre-administration observation used for calculating post-administration changes from baseline.

All data obtained and entered into the database will be provided in separate data listings showing individual patient values. A SAP detailing the statistical analyses and possible deviations from the protocol will be prepared and finalized prior to database lock.

12.1 Determination of Sample Size

The primary endpoint of this study is the incidence and severity of AEs in Cohort A (MOR00208 combined with idelalisib) and Cohort B (MOR00208 combined with venetoclax) and will be analyzed descriptively. In each cohort 12 patients will be enrolled. No formal sample size calculation was performed and no formal statistical hypothesis testing is planned.

12.2 Analysis Sets

The following analysis populations will be used:

Full Analysis Set
The Full analysis set (FAS) will include all subjects who receive at least one dose of MOR00208 and/or one dose of idelalisib in Cohort A and/or one dose of 100 mg daily dose of venetoclax in Cohort B.

Per-Protocol Set
The Per-protocol set (PPS) is the subset of subjects in the FAS without any major protocol deviations. Patients with no post-baseline assessment of response will be excluded from the PPS.

Safety Analysis Set
The Safety analysis set (SAF) will include all subjects who receive at least one dose of MOR00208 and/or one dose of idelalisib or venetoclax.

PK Analysis Set
The PK analysis set (PKAS) will include all patients who have at least one quantifiable serum MOR00208 concentration. PK parameters will be calculated as data permit.

Secondary and supportive efficacy parameters will be evaluated using the FAS and PPS, while safety parameter evaluations will use the SAF, as well as for evaluations on immunogenicity and biomarkers.

The primary analysis of the secondary efficacy endpoint will be based on the FAS, whereas the analysis using the PPS has a supportive function. Decisions about whether a protocol deviation is relevant for the exclusion of a patient from the PPS will be made before database closure.

12.3 Patient Disposition

An overview table will be provided for all patients and will include the number of patients enrolled, the number of patients in each analysis set and the number of withdrawals with reasons for withdrawal.

12.4 Demographic and Baseline Characteristics

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

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

12.5 Safety Analysis

All reported AEs will be coded using MedDRA Version 18.0 or higher. Incidence of all AEs by System Organ Class (SOC), Preferred Term (PT), and relationship to treatment, severity and seriousness will be reported. The incidence of treatment-emergent AEs (TEAEs; events with onset dates on or after the start of the study drug) will be included in incidence tables. Events with missing onset dates will be included as treatment-emergent. If a patient experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. All AEs will be listed by patient, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcomes.

An AE summary table will present the number of events, number of patients and the percentage of patients having TEAEs, SAEs, and TEAEs that led to study discontinuation.

AE frequency tables will display event and patient counts by MedDRA SOC and PT. Such summaries will be displayed for all TEAEs, TEAEs by maximum severity/toxicity, TEAEs by relationship to study drug, SAEs, drug-related TEAEs and TEAEs that led to study discontinuation. Details are described in the SAP.

12.5.1 Clinical Laboratory Evaluations

Clinical laboratory data will be summarized using descriptive statistics including mean values and mean change from baseline values, as well as numbers of patients with values outside limits of the normal range at each timepoint.

12.5.2 Physical Examination, Vital Signs and Electrocardiogram

Physical examination results will be summarized by body system and tabulated as counts and percentages. New and worsening abnormal physical examination findings during the study will be entered as AEs and analyzed within the AE tables in detail. Descriptive summaries of vital sign parameters will be calculated. Summary ECG assessments will be tabulated by timepoint using frequency tabulations. Results of the 12-lead ECG (PR, QRS, RR interval values) will be flagged to show whether a value is below or above the normal limit and summary statistics will be provided for ECG parameters.

12.6 Efficacy Analysis

12.6.1 Analysis of Secondary Efficacy Endpoint – ORR

The secondary endpoint is overall response (ORR). ORR is defined for Cohort A as percentage of patients achieving a complete response (CR), a partial response (PR) or a partial response with lymphocytosis (PRL), and for Cohort B as percentage of patients achieving a CR or a PR based on local assessment. CR, PR or a PRL is defined according to the criteria of the IWCLL for CLL subjects (Hallek et al., 2008) for patients with CLL, with the modification that treatment-related lymphocytosis in the absence of other signs or symptoms of disease progression will not be considered as progressive disease (Cheson et al., 2012; Hallek et al., 2012; NCCN NHL 2015 Guidelines). For patients with SLL, assessments will be performed using the Lugano Classification criteria for SLL subjects (Cheson et al., 2014).

Local response evaluations (CR, PR, PRL, SD and PD) will be tabulated with counts and percentages for each available visit. Missing response evaluations will be taken into account, with patients with missing responses included in the denominator for calculating rates. The SAP will specify further sensitivity and supportive analyses, as well as possible evaluation of further response parameters (e.g., best response).

12.7 Immunogenicity Analysis

The absolute number and percentage of patients who develop anti-MOR00208 antibodies, and the results of semi-quantitative anti-MOR00208 antibody titre determinations of confirmed positive samples will be tabulated. Further details will be provided in the SAP.

12.8 Pharmacokinetic Analysis

Appropriate PK parameters for MOR00208 will be computed based on non-compartmental data analysis and summarized using descriptive statistics. Mean concentrations (on original and on log-linear scale) will be visualized in figures. Further details of the PK analysis will be specified in the SAP.

12.9 Biomarkers

Blood and protein biomarkers which are important in the mechanism of action of, or could predict response to, the study drugs will be descriptively tabulated, presenting absolute and change to baseline values, if applicable.

For example, flow cytometry results of CD16 expression on NK cells will be descriptively tabulated.

12.10 Primary Analysis

The primary analysis of each cohort of the main study to evaluate safety and preliminary efficacy will be based on the safety data and response assessment of the enrolled patients up to the time point of 3-18 months after last patient started treatment in Cohort B.

12.11 Final Analysis

The final analysis of the main study will be conducted at the end of the main study defined as 5 years after the first patient was enrolled (C1D1) or approximately 30 days after the last patient received his/her last treatment, whichever comes first.

12.12 Independent Data Monitoring Committee

An IDMC will be established by the sponsor to review the safety run-in phase for each cohort. The IDMC will be composed of experts in the field of oncology and clinical biostatistics who have no other role in the study and do not have an affiliation with the Investigators or the sponsor. Based on the safety data, the IDMC recommends in writing to the sponsor whether the study may continue according to the protocol. The IDMC's specific duties as well as statistical monitoring guidelines and procedures will be fully described in an IDMC Charter.

13 STUDY MANAGEMENT

13.1 Regulatory Requirements and Ethical Considerations

Prior to initiation of a study site, MorphoSys will obtain favorable opinion/approval from the appropriate regulatory bodies/local health authorities (in accordance with local regulations) and the IRB/IEC to conduct the study in accordance with ICH GCP and applicable country-specific regulatory requirements.

No substantial changes to the final approved protocol will be initiated without the IRB's/IEC's prior written approval or favorable opinion and approval by the regulatory bodies/local health authorities of a written amendment, except when necessary to eliminate immediate hazards to the patients or when the change involves only logistics or administration. This clinical study was designed and shall be conducted and reported in accordance with the protocol, with ICH E6 GCP guidelines, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki, including, but not limited to:

- IRB/IEC review and favorable opinion/approval of the study protocol and any subsequent amendments

- Patient informed consent
- Investigator reporting requirements

MorphoSys will provide full details of the above procedures, either verbally, in writing, or both.

13.1.1 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IRB/IEC. Approval is required for the study protocol, IB, protocol amendments, ICFs) and PISs.

13.1.2 Informed Consent

The Investigator will obtain freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study that is relevant to the patient's decision to participate prior to any protocol-related activities. As part of this procedure, the Principal Investigator (PI) or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and International Conference on Harmonisation (ICH) guidelines. The PI will provide the sponsor or its representative with a copy of the IRB/IEC-approved ICF template prior to the start of the study. The ICF must be signed, with name and date and time noted by the patient, before the patient is exposed to any study-related procedure, including screening tests for eligibility. The patient should receive a copy of the signed form.

13.2 Data Handling

Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained.

Clinical data will be entered on eCRFs for transmission to the sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the sponsor must carry only coded identifiers such that personally identifying information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by CRO. Access to the EDC system is available to authorized users via the study's Internet web site, where an assigned username and password are required for access.

The eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

13.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

The Investigator and the head of the medical institution (where applicable) agree to allow the monitor direct access to all source data documents.

The Investigator must accept audits by the sponsor's Quality Assurance Unit and/or their authorized representative(s) and ensure direct access to all source data documents.

13.4 Use of Computerized Systems

The following requirements apply to study sites where clinical observations and data are entered directly into the hospital information system or medical office information system, i.e., where paper records are not used on a routine basis: The electronic record will be accepted as a source document, only if the information system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and the date of change.

13.5 Monitoring

The study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

On-site monitoring visits will be made at appropriate times during the study. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs/CRFs for each patient.

The Investigator will make available to the clinical monitor source documents and medical records necessary to complete eCRFs/CRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

13.6 Quality Control and Quality Assurance

The sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the sponsor lies with the Investigator generating the data.

The sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, Standard Operating Procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions.

The Investigator must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP guidelines. If informed that a regulatory inspection will take place, the Investigator must inform the sponsor without delay.

13.7 Protocol Amendment and Protocol Deviation

13.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of patients or the conduct of the study will be classed as administrative amendments and will be submitted to the IRB/IEC and appropriate Regulatory Authorities for information only. The sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IRBs/IECs for approval.

13.7.2 Protocol Deviations

Should a protocol deviation occur, the sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable Regulatory Authority mandates is an Investigator responsibility.

13.8 Investigator Contract and Insurance

Prior to the study commencing, the sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the sponsor (or its designee).

This study is covered under the sponsor's Liability Insurance Policy covering damage to patients according to applicable legal requirements. A copy of the Certificate of Insurance and/or an information leaflet containing essential information about the insurance coverage will be provided to the Investigator as required by Regulatory Authorities, IRBs or IECs.

The Investigator must inform the patients accordingly and must also point out that the patients are allowed to undergo other medical treatment (except in an emergency) only with the Investigator's prior approval or to receive additional medication only with the Investigator's prior approval.

13.9 Publication Policy and Disclosure of Data

Any presentation or publication of data from this study will be intended as a joint publication by the Investigator(s)/appropriate study center personnel and appropriate sponsor personnel. Authorship will follow the International Committee of Medical Journal Editors (ICMJE) *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals* (http://www.icmje.org/recommendations/) and will be defined prior to the first publication.

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

Thus, no Investigator or institution may publish any results of the study conducted at their site, before such a first multicenter publication is made which covers the data from all centers. The

authors have the final responsibility for the decision to submit their manuscript and shall be given full access to the data resulting from the study.

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

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

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

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

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15 APPENDICES

15.1 Appendix A: Binet and Rai Staging System

Binet Staging

Stage	Clinical features
A	Lymphocytosis, does not meet criteria for stages B or C
B	≥ 3 areas of lymphadenopathy*, does not meet criteria for stage C
C	Anemia (Hb < 10 g/dL) or thrombocytopenia (platelets < 100 x10^9/L)

* The four lymphadenopathy areas are: cervical, axillary, inguinal, spleen/liver
Adapted from Binet et al., 1981.

Modified Rai Clinical Stage

Risk category	Clinical features
Low	Lymphocytes > 15 x 10^9/L
Intermediate	As 0 + lymphadenopathy or hepato- or splenomegaly
High	Anemia (Hb ≤ 11 g/dL) or thrombocytopenia (platelets ≤ 100 x10^9/L)

Adapted from Rai et al., 1987.

The Binet clinical staging system and the modified Rai clinical staging system for CLL comprise three stages.

The use of clinical staging systems is recommended in current CLL guidelines, and can guide the initiation of treatment.

15.2 Appendix B: Information on Investigational and Registered Products

The Investigator's Brochure for MOR00208, Summary of Product Characteristics (Europe, EMA) or Prescribing Information (US FDA) for idelalisib or venetoclax approved in the Clinical Trial Application or the updates thereof after they were approved for this study will be supplied to the study sites.

15.3 Appendix C: Diagnostic Criteria for CLL and SLL According to the IWCLL Guidelines 2008

The World Health Organization (WHO) classification of hematopoietic neoplasias describes CLL as leukemic, lymphocytic lymphoma, being only distinguishable from SLL by its leukemic appearance. In the WHO classification, CLL is always a disease of neoplastic B cells, whereas the entity formerly described as T-CLL is now called T-cell prolymphocytic leukemia. It is important to verify that the patient has CLL and not some other lymphoproliferative disease that can masquerade as CLL, such as hairy cell leukemia, or leukemic manifestations of mantle cell lymphoma, marginal zone lymphoma, splenic marginal zone lymphoma with circulating villous lymphocytes, or follicular lymphoma. To achieve this, it is essential to evaluate the blood count, blood smear, and the immune phenotype of the circulating lymphoid cells.

Blood. The diagnosis of CLL requires the presence of at least 5 x 10^9 B lymphocytes/L (5000/μL) in the peripheral blood. The clonality of the circulating B lymphocytes needs to be confirmed by flow cytometry. The leukemia cells found in the blood smear are characteristically small, mature lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli and having partially aggregated chromatin. These cells may be found admixed with larger or atypical cells, cleaved cells, or prolymphocytes, which may comprise up to 55% of the blood lymphocytes. Finding prolymphocytes in excess of this percentage would favor a diagnosis of prolymphocytic leukemia (B-cell PLL). Gumprecht nuclear shadows, or smudge cells, found as cell debris, are other characteristic morphologic features found in CLL.

CLL or SLL might be suspected in otherwise healthy adults who have an absolute increase in the clonal B lymphocytes but who have less than 5 x 10^9/L B lymphocytes in the blood. However, in the absence of lymphadenopathy or organomegaly (as defined by physical examination or CT scans), cytopenias, or disease-related symptoms, the presence of fewer than 5 x 10^9 B lymphocytes per liter of blood is defined as "monoclonal B-lymphocytosis." Monoclonal B-lymphocytosis may progress to frank CLL at a rate of 1% to 2% per year.

The definition of SLL requires the presence of lymphadenopathy and/or splenomegaly. Moreover, the number of B lymphocytes in the peripheral blood should not exceed 5 x 10^9/L. In SLL, the diagnosis should be confirmed by histopathologic evaluation of a lymph node biopsy whenever possible.

Immunophenotype. CLL cells coexpress the T-cell antigen CD5 and B-cell surface antigens CD19, CD20, and CD23. The levels of surface immunoglobulin, CD20, and CD79b are characteristically low compared with those found on normal B cells. Each clone of leukemia cells is restricted to expression of either kappa or lambda immunoglobulin light chains.

Variations of the intensity of expression of these markers may exist and do not prevent inclusion of a patient in clinical trials for CLL. In contrast, B-cell PLL cells do not express CD5 in half of the cases, and typically express high levels of CD20 and surface Ig. In addition, the leukemia cells of mantle cell lymphoma, despite also expressing B-cell surface antigens and CD5, generally do not express CD23.

Marrow examination. A marrow aspirate and biopsy generally are not required for the diagnosis of CLL. In CLL, characteristically more than 30% of the nucleated cells in the aspirate are lymphoid.

From: Hallek et al. Blood. 2008;111(12): 5446-7.

15.4 Appendix D: Indication of Treatment According to the IWCLL Guidelines 2008

Active disease meeting at least 1 of the following IWCLL 2008 criteria for requiring treatment:

1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
2. Massive (ie, at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
3. Massive nodes (i.e., at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
4. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of less than 30 x 10^9/L (30 000/μL), LDT should not be used as a single parameter to define a treatment indication. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (e.g., infections) should be excluded.
5. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
6. Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:
    a) unintentional weight loss of 10% or more within the previous 6 months;
    b) significant fatigue (ie, ECOG PS 2 or worse; inability to work or perform usual activities);
    c) fevers higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection; or
    d) night sweats for more than 1 month without evidence of infection.

From Hallek et al. Blood. 2008;111(12): 5450

15.5 Appendix E: Cockcroft-Gault Formula

Cockcroft-Gault Equation (Cockcroft DW et Gault MH, 1976):

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

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

When serum creatinine is measured in µmol/L:

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

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

15.6 Appendix F: Definitions of Childbearing Potential and Highly Effective Birth Control Methods

Female of Childbearing Potential

A female is considered of childbearing potential (FCBP), i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Fertile Male

A male is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Highly Effective Contraception

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

From: Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 15, 2014

In the course of this study FCBP, using hormonal contraceptives should add a barrier method as a second form of contraception since it is currently unknown whether idelalisib or venetoclax may affect the effectiveness of hormonal contraceptives (see inclusion criterion #7).

15.7 Appendix G: New York Heart Association Functional Classification

Criteria for NYHA Functional Classification

NYHA Class	Criteria
I	No symptoms and no limitation in ordinary physical activity; shortness of breath when walking, stair climbing, etc.
II	Mild symptoms (mild shortness of breath and/or angina pain) and slight limitation during ordinary activity
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity (e.g., walking short distances, approximately >20–100 meters); comfortable only at rest
IV	Severe limitations; patient experiences symptoms even while at rest, mostly bedbound

Abbreviation: NYHA = New York Heart Association.

15.8 Appendix H: Equivalent Doses for Corticosteroids

Equivalent Doses for Corticosteroids

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

15.9 Appendix I: Effect of Idelalisib on Other Medicinal Products that are CYP3A Substrates

Potential interactions between idelalisib and co-administered medicinal products that are CYP3A substrates are listed in the table below (increase is indicated as "↑") (as per Annex I: Summary of Product Characteristics, Section 4.2). This list is not exhaustive and is intended to serve as guidance only. In general, the label information for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors.

Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
ALPHA-1 ADRENORECEPTOR ANTAGONISTS		
Alfuzosin	↑ serum concentrations	Idelalisib should not be co-administered with alfuzosin.
ANALGESICS		
Fentanyl, alfentanil, methadone, buprenorphine/naloxone	↑ serum concentrations	Careful monitoring of adverse reactions (e.g., respiratory depression, sedation) is recommended.
ANTIARRHYTHMICS		
Amiodarone, quinidine	↑ serum concentrations	Idelalisib should not be co-administered with amiodarone or quinidine.
Bepridil, disopyramide, lidocaine	↑ serum concentrations	Clinical monitoring is recommended.
ANTI-CANCER AGENTS		
Tyrosine kinase inhibitors such as dasatinib and nilotinib, also vincristine and vinblastine	↑ serum concentrations	Careful monitoring of the tolerance to these anti-cancer agents is recommended.
ANTICOAGULANTS		
Warfarin	↑ serum concentrations	It is recommended that the international normalised ratio (INR) be monitored upon co-administration and following ceasing treatment with idelalisib.
ANTICONVULSANTS		
Carbamazepine	↑ serum concentrations	Anticonvulsant drug levels should be monitored.
ANTIDEPRESSANTS		
Trazodone	↑ serum concentrations	Careful dose titration of the antidepressant and monitoring for antidepressant response is recommended.

Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
ANTI-GOUT		
Colchicine	↑ serum concentrations	Dose reductions of colchicine may be required. Idelalisib should not be co-administered with colchicine to patients with renal or hepatic impairment.
ANTI-HYPERTENSIVES		
Amlodipine, diltiazem, felodipine, nifedipine, nicardipine	↑ serum concentrations	Clinical monitoring of therapeutic effect and adverse reactions is recommended.
ANTI-INFECTIVES		
Antifungals		
Ketoconazole, itraconazole, posaconazole, voriconazole	↑ serum concentrations	Clinical monitoring is recommended.
Antimycobacterials		
Rifabutin	↑ serum concentrations	Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is recommended.
HCV protease inhibitors		
Boceprevir, telaprevir	↑ serum concentrations	Clinical monitoring is recommended.
Macrolide antibiotics		
Clarithromycin, telithromycin	↑ serum concentrations	No dose adjustment of clarithromycin is required for patients with normal renal function or mild renal impairment (creatinine clearance [CrCl] 60-90 mL/min). Clinical monitoring is recommended for patients with CrCl < 90 mL/min. For patients with CrCl < 60 mL/min, alternative antibacterials should be considered. Clinical monitoring is recommended for telithromycin.
ANTI-PSYCHOTICS/NEUROLEPTICS		
Quetiapine, pimozide	↑ serum concentrations	Idelalisib should not be co-administered with quetiapine or pimozide. Alternative medicinal products, such as olanzapine, may be considered.
ENDOTHELIN RECEPTOR ANTAGONISTS		
Bosentan	↑ serum concentrations	Caution should be exercised and patients closely observed for bosentan-related toxicity.

Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
ERGOT ALKALOIDS		
Ergotamine, dihydroergotamine	↑ serum concentrations	Idelalisib should not be co-administered with ergotamine or dihydroergotamine.
GASTROINTESTINAL MOTILITY AGENTS		
Cisapride	↑ serum concentrations	Idelalisib should not be co-administered with cisapride.
GLUCOCORTICOIDS		
Inhaled/nasal corticosteroids: Budesonide, fluticasone	↑ serum concentrations	Clinical monitoring is recommended.
Oral budesonide	↑ serum concentrations	Clinical monitoring is recommended for increased signs/symptoms of corticosteroid effects.
HMG CO-A REDUCTASE INHIBITORS		
Lovastatin, simvastatin	↑ serum concentrations	Idelalisib should not be co-administered with lovastatin or simvastatin.
Atorvastatin	↑ serum concentrations	Clinical monitoring is recommended and a lower starting dose of atorvastatin may be considered. Alternatively, switching to pravastatin, rosuvastatin, or pitavastatin may be considered.
IMMUNOSUPPRESSANTS		
Ciclosporin, sirolimus, tacrolimus	↑ serum concentrations	Therapeutic monitoring is recommended.

Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
INHALED BETA AGONIST		
Salmeterol	↑ serum concentrations	Concurrent administration of salmeterol and idelalisib is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
PHOSPHODIESTERASE INHIBITORS		
		For pulmonary arterial hypertension:
Sildenafil	↑ serum concentrations	Idelalisib should not be co-administered with sildenafil.
Tadalafil	↑ serum concentrations	Caution should be exercised, including consideration of dose reduction, when co-administering tadalafil with idelalisib.
		For erectile dysfunction:
Sildenafil, tadalafil	↑ serum concentrations	Particular caution must be used and dose reduction may be considered when prescribing sildenafil or tadalafil with idelalisib with increased monitoring for adverse events.
SEDATIVES/HYPNOTICS		
Midazolam (oral), triazolam	↑ serum concentrations	Idelalisib should not be co-administered with midazolam (oral) or triazolam.
Buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ serum concentrations	Concentration monitoring of sedatives/hypnotics is recommended and dose reduction may be considered.

15.10 Appendix J: Response Definition for CLL by the IWCLL Guidelines 2008

Parameter	CR*	PR*	PD*
Group A			
Lymphadenopathy†	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/µL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules Hypocellular marrow defines CRi	50% reduction in marrow infiltrate, or B-lymphoid nodules	--
Group B			
Platelet count	> 100,000/µL	> 100,000/µL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils‡	> 1500/µL	> 1500/µL or > 50% improvement over baseline	--

Group A criteria define the tumor load, group B criteria define the function of the hematopoietic system (or marrow).

*CR (complete remission): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR (partial remission): at least two of the criteria of groupA plus one of the criteria of group B have to be met; SD is absence of progressive disease (PD) and failure to achieve at least a PR;
PD: at least one of the above criteria of group A or group B has to be met.

†Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).

‡These parameters are irrelevant for some response categories.

From: Hallek et al. Blood. 2008;111(12):5446-56.

15.11 Appendix K: Criteria for B-Symptoms

Criteria for B-Symptoms

The presence of:

a) unintentional weight loss of more than 10% within the previous 6 months and/or
b) fevers of greater than 100.5°F or 38.0°C for at least 3 consecutive days without other evidence of infection and/or
c) drenching night sweats without evidence of infection

is denoted by the suffix letter '**B**'.

'**A**' indicates the absence of these symptoms.

15.12 Appendix L: ECOG Performance Status

ECOG Performance Status Scale

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

From: Oken et al. Am J Clin Oncol. 1982;5(6):649-55.

15.13 Appendix M: Optional Sub-Study - Collection of Biological Samples for Evaluation of CD19 Expression after MOR00208 Treatment

15.13.1 Sub-Study Purpose/Rationale

It is of importance and has high clinical value to better understand potential escape mechanisms to MOR00208 treatment and to evaluate whether subsequent CD19-targeting therapeutic options can be offered to patients after MOR00208 treatment. Subsequent CD19-targeting therapy may include novel chimeric antigen receptor (CAR) T-cell therapy, other anti-CD19 targeting antibodies than MOR00208, or potential re-challenging with MOR00208 e.g. after drug holiday as shown for another antibody (Zou Y et al., 2018; Alici E et al., 2016).

It is well described that resistance to targeted antibody treatment could potentially be mediated by alterations in expression of the target antigen as shown in a preclinical Burkitt's lymphoma cell line model where down-modulation of CD20 as well as clonal selection of CD20-negative cells was related to the acquired resistance to rituximab (Smith MR, 2003; Takei K et al., 2006).

For the antigen CD19, emerging data from CD19 targeted CAR T-cell trials in B-cell malignancies demonstrate that a common mechanism of resistance to therapy is the emergence of tumors with loss or downregulation of CD19 antigen via mechanisms like alternative mRNA splicing, CD19 gene deletion and mutation or CD19-negative clonal evolution (Zheng PP et al., 2018; Zhao Z et al., 2018). A recently published Brief Communication paper (Orlando EJ, 2018) underlines that acquired resistance to CD19-targeted CAR T-cell therapy in acute lymphoblastic leukaemia can occure through mutations in the CD19 gene, consequently leading to the loss of CD19 antigen surface expression on tumor cells.

In a Phase I trial (NCT01161511), where relapsed/refractory CLL/SLL patients received MOR00208 treatment, CD19 expression was evaluated, but due to methodological limitations (MOR00208 interference with anti-CD19 detection) the obtained data do not allow proper interpretation of CD19 expression levels during and after the treatment period.

To accurately address CD19 antigen expression during MOR00208 treatment, a validated method for quantitative CD19 assessment was implemented in the COSMOS trial to evaluate samples collected at Cycle 1 Day 1 (baseline value), during treatment at Cycle 2 Day 1 in Cohort A or Cycle 1 Day 8 & 15 in Cohort B, furthermore, at the end of treatment visit (EOT).

Published data on MOR00208 (Horton et al., 2008) or other anti-CD19 antibody clones (Pulczynski et al., 1993; Ghetie, 1997) suggest that CD19 might be downregulated by internalization during MOR00208 treatment to a certain extent. However, so far it is unknown wheter CD19 level will recover after treatment discontinuation in cases where downregulation may occur.

Therefore, post-treatment long term follow up data captured in this sub-study are essential to elucidate changes in CD19 expression level and evaluate the kinetics of CD19 recovery after a potential downregulation. Due to unknown kinetics of a potential CD19 recovery in this disease setting and the expected decline in MOR00208 serum levels, an investigation of CD19 recovery is planned on 4 visits within this sub-study: at the first sub-study visit within approximately 30 days after end of treatment visit (EoT) of the main study, and approximately 1, 3 and 6 months thereafter (see Section 15.13.6).

15.13.2 Sub-Study Objectives and Endpoints

15.13.2.1 Study Objectives

- To assess potential downregulation/loss of CD19 on peripheral B cells (CLL and normal B cells) as escape mechanism to MOR00208 treatment
- To assess the kinetics of CD19 recovery on peripheral B cells (CLL and normal B cells) after MOR00208 treatment discontinuation, if applicable
- To assess MOR00208 serum concentrations as supportive parameter for CD19 expression analysis

15.13.2.2 Exploratory Study Endpoints

- CD19 expression (CD19 ABC (Antibodies bound per cell)
- CD19 mutational status (DNA isolated from tumor cells)
- Detection of alternative CD19 splice variants (RNA isolated from tumor cells)
- MOR00208 serum concentrations

15.13.3 Sub-Study Design

15.13.3.1 Description of Sub-Study design

This is an optional sub-study subsequent to the main study in which biological samples will be collected for investigations on biological markers (e.g., CD19 expression) for CLL disease. Patients who completed the main study will be invited to participate in this optional sub-study. Patients who provided their voluntary consent to participate in the sub-study will have additional blood samples collected as detailed in Section 15.13.6 below. During the participation in the sub-study patients could receive anti-neoplastic therapy for their disease.

15.13.3.2 Study Periods

The sub-study will be implemented to collect blood samples at 4 visits during the sub-study period as described in Section 15.13.6. Patients who already completed the main study before implementation of the sub-study may have less visits than as per regular schedule. No screening, treatment and follow up periods are planned.

15.13.4 Patient Selection Criteria

15.13.4.1 Inclusion Criteria

To be eligible for this sub-study, subjects must have been enrolled in the main study and must have been exposed to study treatment there. Subjects must provide separate written informed consent for this sub-study and should be willing to undergo standard blood collection procedures.

15.13.4.2 Exclusion Criteria

Patients who have been exposed to MOR00208 for less than one cycle in the main study.

15.13.5 End of Sub-Study

The duration of the sub-study will be up to approximately 3.5 years from sub-study introduction until sub-study completion. The end of the sub-study is reached for an individual patient, if patient has completed sub-study visit 4, has withdrawn consent, is lost to follow up or death occurs. The estimated average study duration per individual patient is up to 7 months.

The sub-study will be completed once the last patient in the sub-study completed the last visit, or approximately 7 months after the first visit of the last patient enrolled in the sub-study, whichever comes first.

The sub-study can be terminated at any time for any reason by the sponsor. For general rules applicable for investigator study or site termination please refer to Section 7.3 of the main study protocol. For the entire trial study end please refer to Section 7.4 of main study protocol.

15.13.6 Sub-Study Procedures

15.13.6.1 Schedule of Procedures and Assessments

The Schedule of Procedures and Assessments is presented on the following page (Table 15). All assessments that need to be performed at a specific visit are indicated with an "X".

Note: Any visit performed not in the visit window as described in Table 15 will be not considered as protocol deviation.

Table 15: Sub-Study - Schedule of Procedures and Assessments

Procedure	Sub-Study Period			
	Visit 1 [1,2]	**Visit 2** [2]	**Visit 3** [2]	**Visit 4** [2]
	~30 days after EoT of the Main Study [1]	**~1 month** after Visit 1 ±2 weeks	**~3 months** after Visit 1 ±6 weeks	**~6 months** after Visit 1 −6 weeks/+ ≥6 weeks
Informed consent	X [3]	(X) [3]	(X) [3]	(X) [3]
CD19 assessment (CD19ABC) (blood)	X	X	X	X
Optional analysis of genetic CD19 mutations (blood)	X	X	X	X
Optional analysis of alternative CD19 splice variants (blood)	X	X	X	X
PK MOR00208 (serum)	X	X	X	X
Concommittant anti-tumor therapy	X	X	X	X
SAE (Serious Adverse Event) related to blood sampling	X	X	X	X

[1] Patient should return for Visit 1 of the sub-study within approximately 30 days after end of treatment visit (EoT) of the main study. **Note**: Visit 1 could be on the same day of the 30 day safety follow-up (SFU) visit of main study.

[2] Alternatively, for those patients who already completed the main study before implementation of the sub-study, the visit(s) will be scheduled after ~2 months from EoT of the main study for Visit 2, after ~4 months for Visit 3 and after ~7 months for Visit 4 as applicable. **Note**: These patients may have less visits than as per regular schedule (e.g., only 1 visit if patient completed the main study more than 7 months before enrolment in the sub-study).

[3] Patient must consent to the sub-study before or on first sub-study visit, before blood sample collection of the sub-study. (X) is applicable for those patients who already completed the main study before implementation of the sub-study.

Abbreviations: ABC= Antibodies bound per cell; EoT= End of Treatment visit of the main study

15.13.6.2 Study Assessments

15.13.6.3 CD19 assessment (CD19 ABC)

Blood samples for CD19 assessment will be handled as specified in the Laboratory Manual and shipped at ambient temperature to an external analytical laboratory.

15.13.6.3.1 Analysis of genetic and/or transcriptional CD19 alterations

During the course of the main study the patient will be asked for his participation in additional pharmacogenomic analyses in the sub-study. For this purpose blood samples will be collected, shipped at ambient temperature to an external analytical laboratory and stored to analyze the CD19 mutational status and detection of potential alternative CD19 splice variants. These analyses are optional within the sub-study and participation is completely voluntary.

15.13.6.3.2 Assessment of MOR00208 serum concentrations (PK samples)

Serum samples for PK analysis of MOR00208 will be handled and stored at the sub-study site as specified in the Laboratory Manual until shipment on dry ice to an external analytical laboratory. At each sampling timepoint the serum sample should be split into 2 aliquots (a primary and a back-up sample).

15.13.7 Safety Monitoring

For this sub-study, only serious adverse event (SAE) e.g., related to procedural complications during blood sampling have to be collected. Study centers and Investigators are instructed to report all SAEs to MorphoSys Drug Safety (safety@morphosys.com) within 24 hours, using the sub-study specific SAE report form. Note: Follow up of SAEs also have to be reported within 24 hours.

For definitions please refer to Section 10 of the study protocol.

15.13.8 Study Management and Data Handling

Source documents are considered to be all information within original records and covered on certified copies of original records concerning clinical findings, observations, data or other activities in the clinical sub-study necessary for the reconstruction and evaluation of the sub-study.

The sub-study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

All patients will be informed that participation is entirely voluntary and will have to sign the Informed Consent Form (ICF). Patient must consent to the sub-study before or on first sub-study visit, before blood sample collection of the sub-study. The Investigator will inform any patient participating in the sub-study that this sub-study protocol explicitly allow to undergo any medical treatment including anti-neoplastic therapy for their disease as necessary.

The required data for the sub-study will be collected on the Sub-Study specific Laboratory Requisition Form. These data will not be entered in the eCRF of the main study. Data entered on the Laboratory Requisition Form should be consistent with the source documents, or the discrepancies must be explained.

The primary method of data transmission is via the sub-study specific Laboratory Requisition Form transferred to Central laboratory together with the laboratory samples collected. The data collected on the Laboratory Requisition Form will be transferred to the laboratory database.

The Central laboratory will be responsible for the processing and the quality control of the data collected for the sub-study according to standard operating procedures (SOPs) and sub-study specific procedures.

Queries will be handled via paper based Data Clarification Forms.

All study forms and records transmitted to the Central Laboratory/sponsor must just carry coded identifiers such that personally identifying information is not transmitted.

For further general rules and guidelines applicable regarding study management please refer to Section 13 of the study protocol.

15.13.9 Sub-Study Statistical Methods and Planned Analyses

The analysis will be conducted after completion of the sub-study and reported as an addendum to the Clinical Study Report covering the final analysis of the main study.

Descriptive statistics summarizing CD19 expression levels on peripheral B cells (CLL and normal B cells) will be calculated by visit, respectively. The following will be derived:

- Absolute levels by visit including sub-study visits.
- Relative change from baseline of the main study by sub-study visits.
- Relative change from the "End of Treatment Visit" by sub-study visit.

Descriptive statistics summarizing genetic CD19 mutations and alternative CD19 splice variants in peripheral B cells (CLL and normal B cells) will be calculated by visit, respectively. The following will be derived:

- Proportion of patients with acquired CD19 mutation(s) during the MOR00208 treatment period
- Proportion of patients with detectable alternative CD19 splice variants

CD19 mutational status and alternative CD19 splice variants will be summarized. No formal statistical testing will be conducted. Further details will be specified in the SAP.