PROTOCOL

A PHASE 3, RANDOMIZED, OPEN-LABEL, CONTROLLED, MULTICENTER STUDY OF ZANDELISIB (ME-401) IN COMBINATION WITH RITUXIMAB VERSUS STANDARD IMMUNOCHEMOTHERAPY IN PATIENTS WITH RELAPSED INDOLENT NON-HODGKIN'S LYMPHOMA (INHL) – THE COASTAL STUDY

ZANDELISIB (ME-401)

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CLINICAL STUDY PROTOCOL

Protocol Number: ME-401-004

A Phase 3, Randomized, Open-Label, Controlled, Multicenter Study of Zandelisib (ME-401) in Combination with Rituximab Versus Standard Immunochemotherapy in Patients with Relapsed Indolent Non-Hodgkin's Lymphoma (iNHL) – The COASTAL Study

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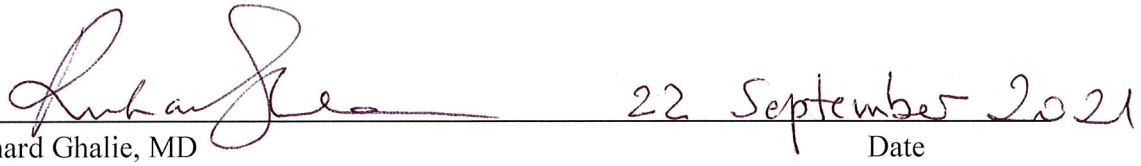
SPONSOR'S PROTOCOL SIGNATURE PAGE

By signing below, the Sponsor declares that this study will be conducted in accordance with current United States (US) Food and Drug Administration Code of Federal Regulations, Good Clinical Practice (GCP) standards, the Declaration of Helsinki (Brazil 2013), and local ethical and legal requirements.



22 September 2021

Richard Ghalie, MD
Chief Medical Officer

Date

INVESTIGATOR'S SIGNATURE PAGE AND COMPLIANCE STATEMENT

By signing below, the Investigator agrees to adhere to the protocol as written and agrees that any deviations from or changes to the protocol must be approved MEI Pharma, Inc., before seeking documented approval from the Institutional Review Board (IRB)/Ethics Committee (EC), except when necessary to eliminate any immediate hazard(s) to the study participants.

The Investigator further agrees to conduct the study in accordance with the current International Council on Harmonization (ICH) Guidelines, the Guidelines for Good Clinical Practice (GCP), and local ethical and regulatory requirements. The Investigator agrees to ensure all staff members involved in the conduct of this study have the necessary training and are informed about their obligations to meet protocol, regulatory, and ethical commitments.

The information contained in this protocol is proprietary and provided to me in confidence, and may not be disclosed to any other party, in any form, without prior authorization from MEI Pharma, Inc., except to the extent necessary for the conduct of the study at this study site.

Principal Investigator:

_____

Signature Date

_____

Printed name

_____

Institution

PROTOCOL SYNOPSIS

Title:	A Phase 3, Randomized, Open-Label, Controlled, Multicenter Study of Zandelisib (ME-401) in Combination with Rituximab Versus Standard Immunochemotherapy in Patients with Relapsed Indolent Non-Hodgkin's Lymphoma (iNHL) – The COASTAL Study
Rationale:	Indolent B-cell lymphomas (NHLs), which include follicular lymphoma (FL) and marginal zona lymphoma (MZL), generally have a good prognosis and median survival rates longer than 10 years, but are not curable with current available therapeutic options, especially for those with advanced stages at diagnosis. While FL and MZL respond initially to therapy, their natural history is characterized by remissions and relapses. Although most relapses can be generally treated with success, the quality and duration of remissions decreases over time. Finally, these lymphomas evolve into refractory disease or undergo transformation into an aggressive histologic type with poor prognosis. Therapeutic options for previously untreated FL and MZL include single agent anti-CD20 immunotherapy (most commonly with rituximab (Rituxan®, MabThera®, or biosimilar, [R]); in this protocol, henceforth, R refers to rituximab, i.e., Rituxan, MabThera, or biosimilar); to anti-CD20-based immunochemotherapy (most commonly the combination of R with cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone (CHOP) designated as R-CHOP or the alkylating agent bendamustine (B) designated as R-B. Other chemotherapy regimens are also acceptable in combination with an anti-CD20 antibody as well as the combination of R and lenalidomide (Revlimid® [L]) (R-L). For patients with relapsed disease, a similar immunochemotherapy approach, utilizing a chemotherapy regimen not previously administered, can be used. The combinations of R-B showed high rates of objective response of ≥90%, and median progression-free survival (PFS) of 23-24 months. Combination of R and chemotherapy for relapsed disease is associated with a PFS of about 18 months. Response outcome varies based on duration of prior response, disease-and patient-related factors. However, the disease will inevitably relapse. Therefore, active agents with different mechanisms of action than cytotoxic chemotherapy are needed for patients with relapsed disease. Furthermore, since the median age of patients with FL and MZL at relapse is >60 years, new treatment options must be well-tolerated and avoid the toxicities typically reported with chemotherapy. Phosphoinositide 3 kinase (PI3K) inhibitors, a novel class of drugs for B-cell malignancies, have proven to be active in patients with FL and MZL, but the benefit of therapy is often limited by class-associated toxicities potentially related to immune dysfunction, including effects on regulatory T-cells. These toxicities are often delayed and cumulative in nature, and include diarrhea and colitis, stomatitis, hepatitis (elevation of transaminases), infectious and non-infectious pneumonitis. Zandelisib (code name ME-401), is an orally bioavailable PI3Kδ inhibitor with optimal pharmacologic properties and high potency, with a plasma half-life ($t_{½}$) of approximately 28 hours supporting once-daily dosing. In an ongoing Phase 1b study (ME-401-002), zandelisib has been evaluated in a continuous daily dosing schedule (CS) and an intermittent schedule (IS), with zandelisib given daily for 2 initial cycles followed by 1 week on, 3 weeks off therapy in every subsequent 28-day cycle. Preliminary data indicate that both treatment schedules were associated with a high and comparable response rate in subjects with indolent B-cell malignancies, while the IS led to a significant reduction in Grade (Gr) 3 class-related adverse events (AE) compared to CS. The incidence of these AEs with the IS and the CS, respectively, were: colitis/diarrhea (5% and 23%), rash/skin reaction (0% and 8%), stomatitis (0% and 3%), AST/ALT elevation (2% and 8%), pneumonia/infectious pneumonitis (2% and 10.0%). With IS dosing, these Gr 3 AEs were not reported beyond Cycle 3,

	when zandelisib is administered for 1 week per cycle, whereas there is a continued increase in the cumulative risk of Gr 3 AEs in the CS group. In 36 subjects with FL in the IS group, the overall response rate (ORR) was 83% (76% in monotherapy group, 89% in zandelisib in combination with rituximab), and the median duration of response (DOR) was not reached with a median follow-up of 13.2 months (15.4 months for monotherapy and 12.8 months in combination with rituximab). The ORR in 9 subjects with CLL/SLL was 89% (100% monotherapy and 83% combination therapy with rituximab) and 100% in 4 subjects with MZL (all enrolled in the rituximab combination group). Therapy on IS proved to be well tolerated, with few subjects experiencing Gr 3 class-related AEs. Those who had treatment interruptions were successfully re-challenged with zandelisib therapy. To date, approximately 300 subjects have been treated with zandelisib as a single agent or in combination with other agents. Zandelisib monotherapy is being evaluated in a global Phase 2 study in subjects with FL who have received 2 prior lines of therapy. IS dosing is being evaluated in all clinical studies with zandelisib. Please, refer to the current Investigator's Brochure for detailed information. This study aims to test the hypothesis that zandelisib in combination with rituximab has better clinical activity and risk/benefit profile compared to standard 2nd line immunochemotherapy (R-CHOP/R-B) in subjects with relapsed FL or MZL.
Target Population:	Subjects with relapsed or refractory FL or MZL who received ≥1 line of prior systemic therapy.
Number of Subjects:	534 randomized subjects
Duration of Treatment:	Standard immunochemotherapy (R-B and R-CHOP): 6 cycles (approximately 4 to 6 months) Zandelisib plus rituximab: • R, 6 cycles (approximately 6 months) • Zandelisib, 26 cycles of therapy (approximately 24 months)
Indication:	Relapsed or refractory FL or MZL
Investigational Product(s):	Zandelisib (in combination with R)
Control Treatment:	Immunochemotherapy: R-B or R-CHOP for Cycles 1-6. For administration, see Administration section.
Dose(s)/Route(s)/ Schedule(s) of Administration:	**Study Treatments** Zandelisib: Administered in a 28-day cycle. Zandelisib capsule should be taken once a day on dosing days at approximately the same time in the morning on an empty stomach on the following schedule: 60 mg daily for the first two cycles of therapy (56 days) followed by: 60 mg for the first 7 days followed by 21 days off treatment in every subsequent 28-day cycle, defined as the IS. Rituximab: R is administered by intravenous infusion according to institutional standards • R 375 mg/m^2 body surface on Day (D)1, D8, D15, and D22 of Cycle (C)1 and then on D1 of C3, C4, C5, and C6 for a total of 8 doses in 6 cycles

	Dosing of immunochemotherapy (C1-C6): R-B will be administered in a 28-day cycle as follows: • R intravenously (IV) 375 mg/m2 body surface on D1 • B IV 90 mg/m2 body surface on D1 and D2 R-CHOP will be administered in a 21-day cycle as follows: • R IV 375 mg/m2 body surface on D1 • Cyclophosphamide IV 750 mg/m2 body surface on D1 • Doxorubicin IV 50 mg/m2 body surface on D1 • Vincristine IV 1.4 mg/m2 body surface (maximum dose 2 mg) on D1 • Prednisone 100 mg daily orally (PO) from D1 to D5 The chemotherapy regimen administered in the study must be different from the one used as prior line of therapy. • Subjects who received B with anti-CD20 antibody (R or obinutuzumab [O]) as a prior line of therapy will be allocated to R-CHOP if randomized to the R-chemotherapy treatment group • Subjects who received CHOP or another chemotherapy regimen, (e.g., cyclophosphamide, vincristine, prednisone (CVP), fludarabine, + mitoxantrone + dexamethasone, [FND]), with anti-CD 20 antibody (R or O) or R-L previously, will be allocated to R-B if randomized to the R-chemotherapy group.
Objectives:	**Primary Objective** • To demonstrate that zandelisib in combination with R is superior to standard immunochemotherapy in prolonging PFS as determined by the Independent Response Review Committee (IRRC) in previously treated subjects with follicular and marginal zone lymphoma **Secondary objectives** • To compare zandelisib + R to standard immunochemotherapy by ORR and complete response rate (CRR) as determined by the IRRC • To compare zandelisib + R to standard immunochemotherapy by overall survival (OS) • Time to next anti-lymphoma treatment (TTNT) • PFS on next anti-lymphoma treatment (PFS2) • To evaluate Patient Reported Outcome (PRO) assessment with o FlymSI-18 o PRO with EuroQol 5 Dimension 3 Level (EQ-5D-3L) • To evaluate the safety and tolerability of zandelisib in combination with R **Exploratory objectives** **To evaluate** • Efficacy: o PFS, ORR and CRR, as determined by the Investigator o ORR at week 24 by the Investigator and by the IRRC

	o DOR by the Investigator and by the IRRC o Time to progression (TTP) by the Investigator and by the IRRC • To characterize the relationship between zandelisib exposure in plasma with efficacy and safety
Study Design:	This is an open label, randomized, two-arm Phase 3 study in subjects with relapsed or refractory FL and MZL to evaluate efficacy and safety of zandelisib in combination with rituximab in comparison to standard immunochemotherapy (R-B or R-CHOP). Subjects must have relapsed after at least one previous line of systemic immunochemotherapy. Previous treatments must have included an anti-CD20 monoclonal antibody (mAb) with chemotherapy such as B, CHOP, CVP, FND, or similar regimens, or an anti-CD20 mAb with L. Subjects who meet the eligibility criteria will be randomly assigned in a 1:1 ratio to one of the treatment arms: • Arm 1: R plus zandelisib • Arm 2: R plus chemotherapy (CHOP or B) Subjects will be stratified based on following criteria: • Prior treatment regimen: anti-CD20 mAb in combination with non-bendamustine chemotherapy regimen or R-L vs. anti-CD20 mAb in combination with B • Number of prior therapies: 1 vs. >1 • NHL histology: FL vs. MZL • Duration of treatment-free interval from the last lymphoma-directed therapy: ≤24 months vs. >24 months Study treatments will be administered as detailed above. Treatment will be discontinued at any time in case of disease progression or unacceptable toxicity. Before treatment discontinuation due to any reason, including disease progression, it is recommended that the Investigator review the reasons with the Sponsor's medical monitor or designee. Primary analysis will be based on assessment of efficacy by an IRRC. Subject management will be based on disease response assessment according to investigators. During the study, continuing review of safety data by the sponsor and an independent Data Monitoring Committee (DMC) will be performed. An independent DMC will regularly review safety and efficacy data from all subjects to assess benefit/risk profile of zandelisib-rituximab therapy. Details of this review will be outlined in a separate DMC charter document. The DMC will meet at least once every 3 months, with the first data review meeting occurring when approximately 60 subjects (~30 in each arm) have completed at least 1 cycle of treatment or 6 months after the first subject is dosed, whichever occurs first. The study is composed of the following periods: • Screening • Treatment • Follow-up (efficacy follow-up until disease progression, safety follow-up, and survival follow-up)

Duration of Study:	The study will end when all subjects have completed follow-up for OS, or if the Sponsor terminates the study, whichever occurs first. Approximate duration of the study for a patient will be at least 5 years.
Primary Endpoint:	• PFS as determined by the IRRC
Secondary Endpoints:	• Efficacy: ORR and CRR as determined by the IRRC • OS • TTNT • PFS2 • PRO – time to deterioration in the 9-item DRS-P subset of FlymSI-18 • PRO – time to improvement in the 9-item DRS-P subset of FlymSI-18 • PRO – functional and well-being (FWB) score and change from baseline in the DRS-P and FWB subscales and total score of FlymSI-18 at specified study visits • PRO – change from baseline in EQ-5D-3L total score and VAS score at specified study visits • Treatment-emergent AEs, serious AEs, and laboratory abnormalities
Exploratory Endpoints:	• Efficacy: o PFS, CRR, and ORR as determined by the Investigator o ORR at 24 weeks by the Investigator and by the IRRC o DOR by the Investigator and by the IRRC o TTP, by the Investigator and by the IRRC • Estimates of zandelisib exposure by population pharmacokinetic method and association with efficacy and safety variables
Main Criteria for Inclusion/Exclusion:	**Criteria for inclusion:** 1. Male or female subjects ≥18 years of age, ≥19 years in Korea, or ≥20 years for subjects in Japan and Taiwan, at time of signing informed consent 2. Histologically confirmed diagnosis of CD20 positive iNHL with histological subtype limited to: a. FL Gr 1, Gr 2, or Gr 3a b. MZL (splenic, nodal, or extra-nodal) [Histopathological report confirming diagnosis must be available during screening procedures] 3. Subjects with relapsed or refractory disease who received ≥1 prior lines of therapy that must have included an anti-CD20 antibody in combination with cytotoxic chemotherapy or L, with or without subsequent maintenance therapy. [A line of therapy is defined as following: a minimum of 2 consecutive cycles of immunochemotherapy or R-L, at least 4 doses of anti-CD20 mAb (R) single agent therapy, a minimum of 2 consecutive cycles of therapy with an investigational agent. Maintenance therapy given after an induction treatment (e.g., R maintenance) is considered as the same line of therapy]. [Please see Exclusion Criteria #2 for further clarification]. Relapsed or refractory disease defined as: • Relapsed disease: disease progression after a response (complete response [CR] or partial response [PR]) lasting ≥6 months

	• Refractory disease: no response to therapy (no CR or PR) or response lasting <6 months 4. Subjects must have at least one bi-dimensionally measurable nodal lesion with the longest diameter >1.5 cm and/or an extranodal lesion >1.0 cm in the longest diameter (that has not been previously irradiated) according to the Lugano Classification 5. Adequate hematologic parameters at screening unless abnormal values are due to disease per Investigator assessment: • Absolute neutrophil count (ANC) ≥1.0 × 10^9/L (≥1,000/mm^3) • Platelet count ≥75.0 × 10^9/L (≥75,000/mm^3) • Hemoglobin ≥9 g/dL 6. Adequate renal and hepatic function per local laboratory reference range at screening as follows: • Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤1.5 × upper limit of normal (ULN) • Total bilirubin ≤2.0 × ULN or ≤3 × ULN for subjects with Gilbert-Meulengracht syndrome • Estimated glomerular filtration rate (eGFR) >50 mL/min using the Cockcroft-Gault equation (Appendix 2) 7. QT-interval corrected according to Fridericia's formula (QTcF) ≤450 msec; subjects with QTc >450 msec but <480 msec may be enrolled provided the QTc prolongation is due to a right bundle branch block (RBBB), left bundle branch block (LBBB), or pacemaker and is confirmed stable by a cardiologist. 8. Left ventricular ejection fraction (LVEF) ≥45% as measured by echocardiogram (ECHO) or multi-gated acquisition scan. [If LVEF <45% by ECHO, a repeat measurement can be conducted within the screening period.] 9. Subjects must have completed any prior systemic anti-cancer treatment ≥4 weeks (or ≥5 times the half-life [t½] of used therapeutics [including investigational therapy], whichever is longer) or radiation therapy ≥2 weeks before study D1, and ≥3 months before study D1 for high dose therapy with stem cell transplantation, radioimmunotherapy, and CAR T-cell therapy. 10. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 11. Life expectancy of at least 3 months 12. All AEs and laboratory toxicities related to prior therapy must resolve to Gr ≤1 prior to the start of the study therapy (unless otherwise specified in eligibility criteria) 13. For females of childbearing potential, a negative serum human chorionic gonadotropin (hCG) pregnancy test within 28 days of study D1 and negative result (urine or serum) on study D1 14. Subjects must agree to use appropriate contraception methods during the clinical study (Appendix 3) 15. Subject is willing and able to comply with all scheduled visits, treatment plans, laboratory tests, and other study procedures. **Criteria for exclusion:** 1. Histologically confirmed diagnosis of FL Gr 3b or transformed disease • For subjects with clinical signs of rapid disease progression (e.g., marked B-symptoms), and laboratory or radiographic indication (e.g., high lactate dehydrogenase level or standardized uptake value by PET), a fresh tumor biopsy is recommended to rule out transformed disease 2. Subjects who received both R/O-B and R/O-CHOP (or other anthracycline-containing regimen) as previous lines of therapy, and those who received only single agent anti-CD20 mAb therapy as prior line of treatment 3. Prior therapy with PI3K inhibitors 4. Ongoing or history of drug-induced pneumonitis

	5. Known lymphomatous involvement of the central nervous system 6. Seropositive for or active viral infection with hepatitis B virus: • HBsAg positive • HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA by PCR [Note: Subjects who are HBsAg negative and viral DNA PCR negative are eligible. These subjects should receive prophylactic therapy for hepatitis as per institutional standards.] 7. Known seropositive for, or active infection with hepatitis C virus. • Subjects with positive hepatitis C virus (HCV) antibodies are eligible with negative PCR test for HCV 8. Known seropositive for, or active and uncontrolled infection with human immunodeficiency virus (HIV), or with acquired immunodeficiency syndrome (AIDS), or currently taking medications for HIV that are contraindicated for concomitant use in this study 9. Known seropositive for, or active infection with human T-cell leukemia virus type 1 10. Any uncontrolled clinically significant illness including, but not limited to, active infections requiring systemic antimicrobial therapy, hypertension, angina, arrhythmias or other uncontrolled cardiovascular condition, pulmonary disease, autoimmune dysfunction, and urinary infection or flow obstruction. 11. Hypersensitivity or other clinically significant reaction to the study drug or its inactive ingredients or other therapy used in the study 12. Major surgical procedure within 4 weeks prior to study D1 (minor surgical procedures, e.g., lymph node biopsy, performed within 1 day or with an overnight stay are allowed) 13. Previous or concurrent cancer that is distinct in primary site or histology from indolent B cell NHL within 3 years before start of study treatment **except for** curatively treated cervical cancer in situ, non-melanoma skin cancer, and superficial bladder tumors (Ta [non-invasive tumor], Tis [carcinoma in situ], and T1 [tumor invades lamina propria]), and asymptomatic localized prostate cancer with no requirement for systemic therapy or requiring only hormonal therapy and with normal prostate-specific antigen values within ≥12 months prior to randomization 14. History of clinically significant cardiovascular abnormalities such as congestive heart failure (New York Heart Association (NYHA) classification ≥ II [NYHA 1994]), myocardial infarction within 6 months of study entry. 15. History of clinically significant gastrointestinal (GI) conditions, particularly: • Known GI condition that would interfere with swallowing or the oral absorption or tolerance of study drug • Pre-existing malabsorption syndrome or other clinical situation that would affect oral absorption 16. Females who are pregnant; females who plan to breastfeed during study treatment through 90 days after ending treatment 17. Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results. 18. Any illness or medical conditions that are unstable or could jeopardize the safety of the subjects and their compliance in the study. Inability to understand and sign informed consent form. 19. Received a live virus vaccination within 28 days of first dose of study drug, (e.g., yellow fever vaccination)
Methodology:	Efficacy will be assessed based on radiological tumor evaluations of neck, chest, abdomen and pelvis by using contrast-enhanced computed tomography (CT) scan (or magnetic resonance imaging (MRI) if CT scan is not tolerated) and/or PET-CT imaging modality. PET-CT imaging is the recommended method of assessment per

	Lugano Classification (Cheson 2014) for 18F-fluorodeoxy glucose (FDG)-avid disease and will be performed at baseline, after initial 24 weeks (±1 week) on study (after completion of treatment in control arm and initial 6 cycles of therapy in study arm), and for confirmation of CR (if initially assessed by CT scan only for FDG-avid disease). Contrast-enhanced CT scan or MRI scan to be done at screening and all other timepoints. Confirmation of PD can be done using CT or PET-CT scan. The Investigator should discuss assessment of PD with the Sponsor's medical monitor or designee. For subjects who have variable FDG-avid tumors, CT and/or MRI imaging can be used if PET-CT imaging is not optimal for assessment of disease status and response. During the treatment phase as well as during the efficacy follow-up period, radiological tumor assessment by CT scan will be performed every 12 weeks for the first 3 scans (weeks 12, 24 and 36 [±1 week]), followed by 3 scans every 16 weeks (weeks 52, 68 and 84 [±1 week]), a scan at week 104 (±1 week), and every 24 weeks (±2 weeks) thereafter. CT scans will be evaluated locally at the study site and assessed by central review. The response assessment will be based on the modified Lugano Classification (Cheson 2014). Bone marrow biopsy/aspirate will be mandatory at Screening if PET scan is not performed or is not evaluable. If the baseline biopsy is positive for lymphoma infiltration and PET scan is not utilized for response assessment, it will be mandatory to perform it again to confirm the first CR. For subjects with MZL, if gastric involvement is suspected, an endoscopy shall be performed at baseline. At CR, endoscopy is required if not observed radiographically and the endoscopy was positive at baseline. All subjects will be followed after treatment discontinuation for OS, TTNT, and PFS2, if applicable, at 3-month intervals during the follow-up period (up to 5 years after the last subject's randomization), except for subjects who withdraw consent. Subjects or their healthcare providers will be contacted either in person, by telephone, or e-mail. Safety evaluations will be conducted at screening, and continuously during the treatment period, and at the safety follow-up visit. During the follow-up period, AEs and SAEs will be reported for up to 30 days after the last dose of study drug. After 30 days post last dose, only SAEs deemed related to study drug will be reported. Sparse blood samples will be collected from all subjects randomized to the zandelisib + R group to measure zandelisib plasma concentrations to evaluate the exposure-efficacy and exposure-safety profile of zandelisib.
Time Point/Frame of Measurement for Primary Variable(s):	The study duration for primary completion of PFS is approximately 64 months with 36 months enrollment period and 28 months follow-up (after last subject enrolled).
Statistical Analyses:	The primary objective is to demonstrate that zandelisib in combination with R is superior to standard immunochemotherapy in prolonging PFS as determined by the IRRC in previously treated subjects with FL and MZL. A group-sequential design including 1 interim and 1 final analysis is planned for this study. At each analysis, the superiority hypothesis for the primary endpoint IRRC assessed PFS will be tested using a 1-sided stratified log-rank test with an overall family-wise error rate one-sided alpha of 0.025 controlled to adjust for multiplicity, utilizing Lan-DeMets O'Brien-Fleming approximation spending function. The interim analysis is planned to take place after approximately 248 (75% of the 330 planned) IRRC assessed PFS events have occurred. If the statistical significance for PFS is not achieved at the interim analysis, the primary PFS analysis will be performed after 330 IRRC assessed PFS events have been observed. The alpha-spending for the interim and final analyses will be 0.0096 and 0.0221, respectively. If statistical significance is successfully met at the interim analysis or the primary analysis, the study will be declared positive based on the primary endpoint of IRRC assessed PFS, and the testing of selected secondary endpoints (ORR by IRRC

	assessment, CRR by IRRC assessment, FlymSI-18 disease related symptoms subscale-physical ([DRSP] and OS) will proceed, by utilizing a hierarchical testing procedure (detailed in the Statistical Analysis Plan). Assuming a hazard ratio (HR) of 0.70, approximately 330 IRRC assessed PFS events at primary analysis are required to yield 87.5% power to detect superiority of zandelisib in combination with rituximab over standard immunochemotherapy. A planned sample size of approximately 534 is based on the following assumptions: • median time to PFS for the control group of 24 months • accrual duration of 36 months • annual dropout rate of 3% • 28 months minimal follow-up time (after the last subject is randomized) Efficacy analyses will be performed in the intent-to-treat (ITT) population, which is defined as all subjects who are randomized. All safety summaries and analyses will be based on the Safety Population, defined as all randomized subjects receiving at least 1 dose of any study drug. Safety analyses will be performed by actual treatment group.

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
B	bendamustine
BCRP	breast cancer resistance protein transporter
BP	blood pressure
BUN	blood urea nitrogen
C	cycle
CBC	complete blood count
CHOP	combination of cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma concentration
CMH	Cochran–Mantel–Haenszel
CMV	cytomegalovirus
CONMED	concomitant medication
COVID-19	coronavirus disease 2019
CR	complete response
CRO	Contract Research Organization
CRR	complete response rate
CRF	Case Report Form
CT	computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVP	combination of cyclophosphamide, vincristine, prednisone
C1D1	Cycle 1 Day 1
D	day
DLBCL	diffuse large B-cell lymphoma

Abbreviation	Definition
DMC	Data Monitoring Committee
DOR	duration of response
DRS-E	disease-related symptoms subscale – emotional
DRS-P	disease-related symptoms subscale – physical
FWB	functional and well-being
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	efficacy evaluable
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ePRO	electronic patient reported outcome
EQ-5D-3L	EuroQoL-5 Dimension 3 Level
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FDG	^{18}F-fluorodeoxy glucose
FL	follicular lymphoma
FlymSI-18	Follicular Lymphoma Symptom lndex-18
FND	combination of fludarabine, mitoxantrone, dexamethasone
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
Gr	grade
HBc	hepatitis B core protein
HBs Ag	hepatitis B surface antigen
hCG	human chorionic gonadotropin
Hct	hematocrit
HCV	hepatitis C virus
HR	hazard ratio
HrRt	heart rate

Abbreviation	Definition
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IP	investigational product
IRB	Institutional Review Board
IRRC	Independent Response Review Committee
IS	intermittent schedule
IUD	intrauterine device
IV	intravenous(ly)
L	lenalidomide
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MCR	metabolic complete response
MDP	metabolic disease progression
MRI	magnetic resonance imaging
MUGA	multi-gated acquisition scan
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
(i)NHL	(indolent) non-Hodgkin lymphoma
NIP	non-infectious pneumonitis
NYHA	New York Heart Association
O	obinutuzumab
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography

Abbreviation	Definition
PFS	progression-free survival
PFS2	PFS on next anti-lymphoma treatment
P-gp	P-glycoprotein
PI	prescribing information
PI3K	phosphoinositide 3-kinase
PI3Kδ	phosphoinositide 3-kinase delta isoform
PI3Ki	phosphoinositide 3-kinase inhibitor
PK	pharmacokinetic(s)
PO	per os, by mouth, orally
PP	per protocol
PT	prothrombin time
PJP	*Pneumocystis jiroveci* pneumonitis
PR	partial response
PRO	patient reported outcome
QD	once daily
QoL	Quality of Life
QTc	QT corrected (corrected QT-interval)
QTcF	QT-interval corrected according to Fridericia's formula
R	rituximab
R-B	rituximab plus bendamustine
R-CHOP	combination of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R-L	lenalidomide plus rituximab combination therapy
R-CVP	combination of rituximab, cyclophosphamide, vincristine, prednisone
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SIV	site initiation visit
SLL	small lymphocytic leukemia
SOC	standard of care
SRC	Safety Review Committee
TEAE	treatment-emergent adverse event
TENS	toxic epidermal necrolysis syndrome

Abbreviation	Definition
TREG	T-regulatory cell
TSE	treatment side effects
TTNT	time to next anti-lymphoma treatment
TTP	time to progression
ULN	upper limit of normal
US(A)	United States (of America)
VAS	visual analogue scale
WBC	white blood cell

1. INTRODUCTION AND RATIONALE

1.1. Background

Non-Hodgkin's lymphoma (NHL) is one of the most common cancers in the world ranking as the 5th to 9th among cancer in most countries; almost 510,000 new cases were estimated in 2018 (Miranda-Filho 2019, Bray 2018). It is estimated that in 2020 approximately 77,000 people will be diagnosed with NHL and approximately 20,000 will die from this cancer in the United States (US) (Cancer Facts and Figures, American Cancer Society 2020).

NHL comprises more than 30 types; classification is based on the type of lymphocyte involved, B-cells or T-cell. NHL is further classified by other factors, including whether it is aggressive (fast-growing) or indolent (slow-growing) (Swerdlow 2016).

1.1.1. Follicular Lymphoma

Follicular lymphoma (FL) is typically an indolent form of B-cell NHL (iNHL). This lymphoma subtype accounts for 20 to 30 percent of all NHL cases (Provencio 2017). Of the approximately 72,240 cases of NHL diagnosed in 2017 in the US, (National Cancer Institute 2017) approximately 20% were likely to be follicular lymphomas (National Cancer Institute 2017). About 18,000 and 25,000 new cases of FL were expected in the US and the EU, respectively, in 2015 (Howlader 2020, Dreyling 2021). No sex preponderance is seen for follicular lymphomas, but the incidence increases with age, and varies across racial groups and geographic regions. In the US, the incidence is 2 to 3 times higher in white individuals than in those of African descent (Nabhan 2012).

The overall survival (OS) rate of treated patients with FL is 77 to 86% at 5 years with a median survival of approximately 20 years for all patients and is better -in younger patients and those with better performance status, and significantly lower for patients with transformed disease (Provencio 2017, Mozas 2020).

Several systemic therapeutic options are available for patients with FL, ranging from single agent anti-CD20 immunotherapy (most commonly with rituximab (Rituxan®, [R]; MabThera®) (McLaughlin 1998, Hainsworth 2005); to anti-CD20-based immunochemotherapy (most commonly the combination of R with cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisone (CHOP) designated as R-CHOP (Czuczman 1999) or the alkylating agent bendamustine (B) designated as R-B (Rummel 2005, Robinson 2008). Other chemotherapy regimens are also acceptable in combination with an anti-CD20 antibody. Immunochemotherapy is typically preferred in younger and fit patients, and achieves an objective response rate >90%, with a substantial proportion of complete responses (CRs), and a progression-free survival (PFS) of 65.5% at 5 years of follow-up (Flinn 2019).

Rituximab (R)-lenalidomide (L) (R-L) combination has been evaluated in randomized studies in patients with relapsed and/or refractory (R/R) iNHL (Leonard 2019) and for treatment of previously untreated patients with FL (Morschhauser 2018). It has been reported that efficacy in patients treated with R-L as front-line therapy are comparable with results in patients treated with chemoimmunotherapy, where the overall response rate (ORR) was 61% in R-L arm and 65% in R-chemotherapy arm, with PFS at three years of follow-up being 77% and 78% for R-L and R-chemotherapy, respectively (Leonard 2019).

This information justifies the patient population for this study as those who received prior therapy that included anti-CD20 antibody in combination with a chemotherapeutic regimen or L.

For patients with relapsed disease, a similar immunochemotherapy approach, utilizing a chemotherapy regimen not previously administered, can be used. The combinations of R-B showed high rates of objective response of ≥90%, and median PFS of 23 to 24 months for R-B (Robinson 2008, Rummel 2005). Combination of R and chemotherapy may be employed for relapsed disease, but it is associated with a shorter median PFS of about 18 months (Link 2019). Although the current treatments for iNHL are initially effective in inducing responses in most patients, they are not curative and show decreasing efficacy and development of resistance to therapy with repeated administrations.

However, the disease will inevitably relapse; therefore, active agents with different mechanisms of action than cytotoxic chemotherapy are needed for this patient population, with the goal of extending the duration of disease control at relapse from initial therapy. Furthermore, since the median age of patients with FL and marginal zone lymphoma (MZL) at relapse is >60 years, new treatment options must be well-tolerated and avoid the toxicities typically reported with chemotherapy.

1.1.2. Marginal Zone Lymphoma

MZL represents approximately 5-15% of all non-Hodgkin lymphomas (Zucca 2020) and is the third most common type among iNHLs (Al-Hamadani 2015); however, it remains largely understudied. Frontline therapy for MZL differs greatly based upon the subtype (extranodal, nodal, mucosal) (Swerdlow 2016), and the underlying etiology; hence, defining a standard treatment regimen for MZL has been difficult (Noy 2017). Treatments include anti-CD20 antibody (rituximab) based regimens either as monotherapy or in combination with systemic chemotherapy. Targeted therapy with ibrutinib (a Bruton tyrosine kinase [BTK] inhibitor) is also now used in relapsed/refractory cases across MZL subtypes (Denlinger 2018) for patients who have received at least one prior anti-CD20 based therapy (Imbruvica® US prescribing information); ORR with ibrutinib was 48% and median PFS was 14.2 months (Noy 2017). Outcomes were also analyzed by MZL subtypes, the median PFS was 13.8 months for extranodal MZL, 19.4 months for splenic MZL, and 8.3 months for nodal MZL. The estimated 18-month OS rate was 81%.

No single standard of care is available for patients who relapse after initial treatment and depending on disease characteristics and previously used therapies various regimens combining R and chemotherapy-containing regimens have classically been the treatment of choice in the second line of treatment, resulting in ORR of 85%–93% and complete response (CR) rate of 54%-78% (Zucca 2017, Brown 2009, Cervetti 2010, Orciuolo 2010, Laribi 2016). Treatment-related toxicities with these therapies such as Grade (Gr) 3 and 4 myelosuppression frequently limit treatment participation in many patients (Noy 2017). Autologous and allogeneic hematopoietic progenitor cell transplantation has been performed in selected patients with relapsed/refractory MZL, achieving durable remissions and frequently cures, albeit at cost of significant morbidity (Shimoni 2017).

In the current landscape of MZL, standardized treatment algorithms still lack sufficient evidence-based guidelines required to guide optimal therapy. Combination therapies that include BTK inhibition as well as other agents, such as PI3Ks, are ongoing.

1.1.3. Therapeutic Options

For patients with advanced-stage FL and MZL requiring systemic lymphoma-directed treatment, initial therapy typically consists of an anti-CD20 antibody given alone or in combination with chemotherapy. Bendamustine and CHOP are the most frequently used chemotherapy regimens, with CVP (cyclophosphamide, vincristine, prednisone), chlorambucil, or a pyrimidine-based regimen used less commonly (Zucca 2020, NCCN 2020, Denlinger 2018). Front-line therapy with single-agent rituximab in FL is typically reserved for patients unfit to receive chemotherapy-based regimens due to age and/or co-morbidities, for patients with low tumor burden for whom the risk/benefit assessment of chemotherapy is considered unfavorable, or for patients who refuse chemotherapy. Therefore, patients treated with single-agent rituximab as first-line therapy are a heterogeneous group with respect to baseline characteristics and treatment outcome. Because immunochemotherapy is more commonly used as initial therapy in FL and in patients with MZL whose disease had progressed after initial rituximab therapy, this Phase 3 study will require failure of prior immunochemotherapy as a pre-requisite for eligibility.

For patients with FL and MZL whose disease does not respond to or who relapse after treatment with an anti-CD20 antibody and chemotherapy, the most common treatment approach is the combination of R with either CHOP (R-CHOP) or B (R-B) administered for a total of 6 cycles of therapy, and using a chemotherapy regimen not administered in a prior line of therapy (Zucca 2020, NCCN 2020, Robinson 2008, Gribben 2007, Rummel 2005). These two immunochemotherapy regimens are the most commonly used in both front-line treatment and for patients with relapsed disease (NCCN 2020, Dreyling 2021). R as a single agent or in combination with chemotherapy has been used in 70% of patients who have received second-line therapy (Link 2019).

1.1.4. Phosphoinositide 3-kinase δ (PI3Kδ)

Signaling through the BCR provides a strong proliferative and survival stimulus to the cell; interfering with such signaling is therefore a rational approach to the treatment of B-cell malignancies. In leukocytes, BCR signaling is mediated partly by the activation of PI3Kδ. The activation of PI3Kδ ultimately leads to cell survival, proliferation, and immune regulation (Herman 2012).

PI3Kδ is frequently active in B-cell malignancies and is central to multiple signaling pathways that drive proliferation, survival, homing, and retention of malignant B-cells in lymphoid tissue and bone marrow. Because PI3Kδ is the main PI3K isoform expressed in lymphoid cells, but is expressed at low or undetectable levels in most other tissue, inhibitors of PI3Kδ should be selective for the immune system and relatively non-toxic in other organs (Brown 2014).

1.1.5. Investigational Drug Zandelisib (Code Name ME-401)

1.1.6. Pharmacokinetic and Pharmacodynamic Profile

Zandelisib, is an orally bioavailable PI3Kδ inhibitor with optimal pharmacologic properties, including high potency with half-maximal inhibitory concentration (IC_{50}) for PI3Kδ of 0.6 nM in a cellular assay, plasma half-life ($t_{½}$) of approximately 28 hours supporting once-daily dosing, and high volume of distribution indicating wide access to tissues, high specificity to the δ isoform at clinically relevant concentrations, and prolonged residence time on the target.

Maximum plasma concentration (C_{max}) and area under the concentration versus time curve from time zero to the last timepoint ($AUC_{(0–last)}$) demonstrated linear increases over the dose range of 10 mg to 150 mg with a t_{max} of 5-6 h.

1.1.7. Dose Selection and Justification

Robust responses have been achieved in the ongoing Phase Ib study at various dose levels: 60 mg, 120 mg, 180 mg.

After continuous once daily administration of 60 mg of zandelisib, Day 28 steady-state plasma trough concentrations were greater than 5 ng/mL, the EC_{90} value for inhibition of basophil activation, in 18 out of 19 subjects or approximately 95% of subjects. Therefore, 60 mg once daily was designated as the minimum biologically effective dose of zandelisib. This concept of designating a minimum biologically effective dose (also referred to as an optimal biologically active dose) based on the extent of inhibition of the intended target enzyme/pathway, in the current context inhibition of PI3Kδ, has been recommended for dose selection of molecularly targeted agents such as zandelisib.

In subjects enrolled at 120 mg and 180 mg dose levels, zandelisib trough concentrations were consistently greater than 5 ng/mL in all subjects and nearly dose proportionally higher when compared to trough concentrations observed values at the 60 mg dose level.

Overall, based on pharmacokinetic (PK)-pharmacodynamic (PD) relationship identified at dose levels ranging from 10 mg to 150 mg and safety and efficacy in cancer patients at dose levels ranging from 60 mg to 180 mg once daily, the recommended phase 2 dose of zandelisib was established to be 60 mg administered once daily.

1.1.8. Safety, Efficacy, and Dosing Schedule

Study ME-401-002 is an ongoing study of zandelisib monotherapy and zandelisib in combination with rituximab or in combination with zanubrutinib in subjects with relapsed/refractory B-cell malignancies. The study consists of a dose escalation phase followed by a dose expansion phase evaluating zandelisib as a single agent, in combination with rituximab, and in combination with a novel BTK inhibitor zanubrutinib.

In the dose escalation phase of the study, dose levels of 60, 120, and 180 mg, administered daily continuously in 28-day cycles, were evaluated with 6-12 subjects enrolled at each dose level. High response rates were obtained at all dose levels tested and no dose-limiting toxicities were observed. Based on these results, dose escalation did not proceed beyond 180 mg solely to define the MTD.

There are certain adverse events (AEs) consistently associated with the use of PI3Kδ inhibitors. These ‘class specific’ toxicities include diarrhea/colitis, rash, stomatitis, hepatitis (elevation in transaminases), and pneumonitis (both infectious and non-infectious). When zandelisib was given initially on a daily continuous schedule (CS) these AEs, primarily involving diarrhea/colitis and skin rash, occurred at Gr 3 severity in approximately 1/3rd of subjects. These class specific toxicities were selected as AEs of special interest (AESI) that were followed in initial clinical studies with zandelisib.

Emerging evidence suggests that these class specific AEs are a consequence of immune dysregulation, primarily involving T-regulatory cells (TREGs). In the majority of cases, these

class specific toxicities are delayed in nature and tend to accumulate over time. To mitigate these potential toxicities, a novel, rationally designed schedule was subsequently evaluated in the Phase 1b study (ME-401-002). This consists of 2 cycles of continuous daily dosing followed by subsequent cycles of 1 week of continuous daily dosing followed by 3 weeks off (intermittent schedule [IS]). Preliminary data indicates that the majority of subjects developed response to treatment after the first two cycles of daily dosing with zandelisib. Therefore, this schedule enables an early and constant inhibition of the target with daily dosing, followed by regular treatment breaks to minimize the potential effect on TREGs and development of AESI.

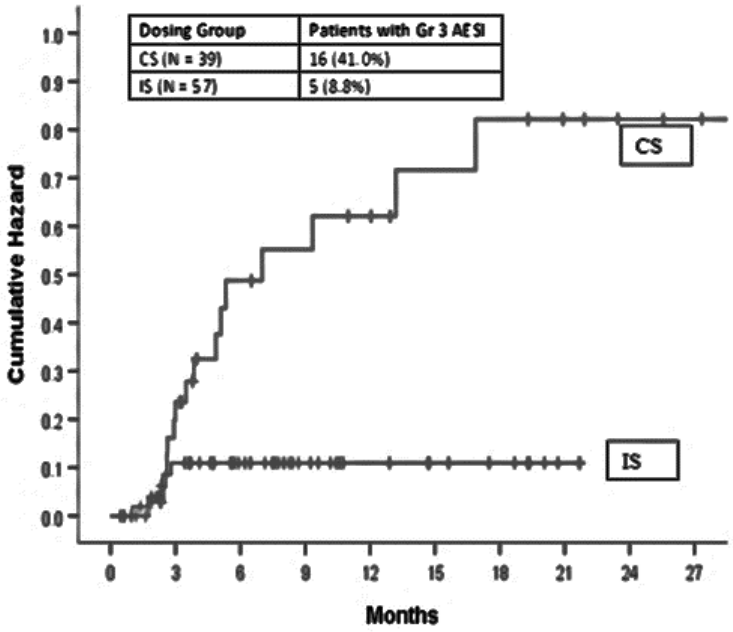
Initial comparison of CS and IS shows a substantially lower number of Gr 3 drug-related AESIs in subjects treated on IS (Table 1). As shown in Figure 1, subjects on IS had a significantly lower number of related Gr 3 AESIs compared to those on CS. At the same time, the ORRs were similar in subjects who received CS and those who received IS. In 29 efficacy evaluable subjects with FL the ORR was 79% with IS dosing and in 26 evaluable subjects the ORR was 70% with CS dosing. For 8 evaluable subjects with CLL/SLL, the ORR was 75% with IS dosing, and in 10 evaluable subjects with CLL/SLL the ORR was 100% with CS dosing. Also, there was no overall difference in ORR between subjects who received zandelisib alone or in combination with rituximab (Zelenetz 2019).

Table 1: Grade 3 Drug-Related Adverse Events of Special Interest (N = 96)

	CS Total Group (N = 39)	**IS Total Group (N = 57)**
Colitis/diarrhea	9 (23%)	3 (5.0%)
Rash/skin reactions	3 (8%)	0
Stomatitis	1 (3%)	0
AST/ALT elevation	3 (8%)	1 (2%)
Pneumonia/pneumonitis	4 (10%)	1 (2%)

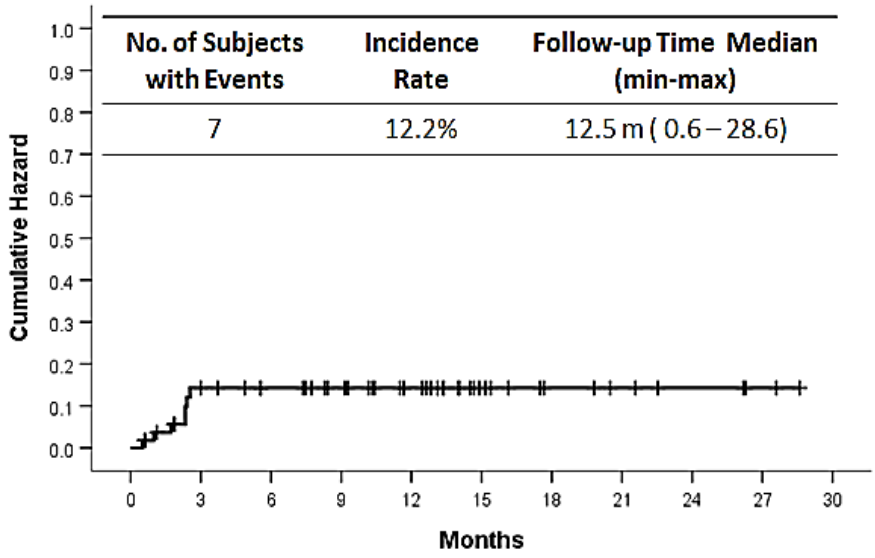
Data cut off 16 September 2019
Abbreviations: CS = continuous daily dosing; IS = intermittent schedule, i.e.,1 week on and 3 weeks off therapy in a 4-week cycle

Figure 1: Number of Subjects and Time to Grade 3 Drug-Related AESI by Schedule (N = 96)



The updated analysis (Zelenetz 2020) for the safety in 57 subjects on IS only, indicate a low incidence of Gr 3 AESI : diarrhea (3.5%), colitis (3.5%), ALT/AST elevation (1.8%), rash (1.8%), non-infectious pneumonitis (1.8%); there were no Gr 4 or 5 AESIs reported. No Grade 3 AESI was reported beyond Cycle 3 (Figure 2). It is important to note that all 5 subjects who had treatment interruption due to AESI and were re-challenged, tolerated continuing therapy well.

Figure 2: Time to First Grade ≥3 AESI (N = 57)



Myelosuppression is uncommon with the following Gr 3 hematologic laboratory abnormalities observed: neutropenia in 11 subjects (19.3%); thrombocytopenia in 2 subjects (3.5%), and ALT elevation in two subjects (3.5%). In all, 4 subjects (7%) discontinued due to AEs (Zelenetz 2020).

There were no notable differences in the incidence of Gr ≥3 AESI between subjects who received only 1 prior systemic therapy and those who received 2 or more prior therapies.

The incidence of Gr 3 AESIs for those receiving 60 mg of zandelisib IS regimen with 1 prior therapy (26 subjects) were: colitis/diarrhea 2 (7.7%), rash/skin reaction 0; ALT/AST elevation 1 (3.8%); and pneumonia/pneumonitis 0. Of note, of the 26 subjects treated on IS after only 1 prior systemic therapy, 16 were in combination with rituximab.

For subjects receiving 60 mg of zandelisib IS regimen with >1 prior therapy (30 subjects), the incidence of Gr 3 AESIs were: colitis/diarrhea 1 (3.3%); rash/skin reaction 1 (3.3%); ALT/AST elevation 1 (3.3%); pneumonia1 (3.3%); and non-infectious pneumonitis 1 (3.3%).

Continuing evaluation of zandelisib efficacy indicates strong activity in the 57 subjects dosed on the IS, with ORR for FL of 83% (76% in monotherapy group, 89% in combination group (R plus zandelisib). Median duration of response (DOR) was not reached for monotherapy and zandelisib in combination with rituximab. The ORR for CLL/SLL was 89% (100% monotherapy and 83% combination therapy), and 100% (4/4) in MZL (in combination group only).

The efficacy and safety of zandelisib administered as a single agent using the IS is being evaluated in an ongoing Phase 2 study (ME-401-003, TIDAL) in subjects with relapsed or refractory FL whose disease failed at least two prior lines of systemic therapy (NCT03768505).

To date, approximately 300 subjects have been dosed with zandelisib from the ongoing Phase 1b (ME-401-002) and Phase 2 (ME-401-003) studies. The therapy with zandelisib as single agent or in combination with R, given on IS dosing, has been associated with high ORR and is well tolerated with few discontinuations due to toxicity.

Please refer to the current IB for full details of preclinical and clinical studies with zandelisib.

1.2. Study Rationale

For patients with relapsed FL and MZL, R in combination with chemotherapy or B (typically a chemotherapy regimen not used in front-line therapy) can be used. The combination of R-B showed satisfactory rates of objective response of ≥90%, with median PFS of 23 to 24 months (Robinson 2008, Rummel 2005). Combination of R and chemotherapy may be employed for relapsed disease, but it is associated with a shorter median PFS of about 18 months (Link 2019). However, repeated courses of chemotherapy is associated with cumulative toxicity, including myelosuppression, neuropathy, cardiac toxicity, and secondary cancers (Lunning 2012). Since the median age of patients with FL and MZL at relapse is ≥60 years (Robinson 2008, Denlinger 2018, Kahl 2010), new treatment options for relapsed disease must be well-tolerated and avoid the toxicities typically reported with chemotherapy, necessitating the exploration of new chemotherapy-free options.

The high frequency of PI3Kδ pathway alterations in NHL led to the development of PI3Kδ inhibitors in this disease. Three drugs with PI3Kδ inhibitory activity, Zydelig® (idelalisib), Aliqopa™ (copanlisib), and Copiktra® (duvelisib) (Furman 2014, Krause 2018, Flinn 2018) have

been approved for clinical use in patients with multiple relapsed/refractory FL, based on single arm studies, in the US and other countries.

Recently presented data about treatment patterns of patients with relapsed or refractory FL treated in community practice with the first-approved PI3Kδ inhibitor idelalisib indicates that many patients cannot tolerate long term therapy, with 46.9–91.7% discontinuing therapy due to toxicities, and median duration of therapy of 5.5 months (Andorsky 2019). Better tolerated options with strong activity are needed.

Despite ongoing efforts in recent years to provide new therapies for patients with relapsed FL and MZL, the high clinical unmet need remains as patients need active and well-tolerated therapy to delay time to the next disease progression. As the majority of patients are >65 years old, finding well-tolerated therapies becomes a very important task.

Zandelisib is a highly selective inhibitor of PI3Kδ and shows promising clinical activity alone and in combination with rituximab in the treatment of iNHLs. Zandelisib preliminary data indicate high level of activity in patients with relapsed/refractory FL and MZL, and that therapy can be well tolerated given on an IS. In the Phase 1b study, ORR for FL is 83% and 100% for MZL. With the utilization of IS, Gr 3 AESIs decreased significantly.

This Phase 3 trial addresses the need for patients who have relapsed or progressed after receiving chemotherapy in combination with an anti-CD20 antibody (R) or with R and L, using a potentially less toxic therapeutic regimen of a PI3Kδ inhibitor in combination with rituximab compared to traditional immunochemotherapies (R-CHOP and R-B). Zandelisib is continuing to be evaluated in an ongoing Phase 1b and a Phase 2 study as a single agent or in combination with other therapies. It has been demonstrated that zandelisib alone or in combination with rituximab induces strong efficacy and is well tolerated, and that supports further evaluation in a Phase 3 trial to introduce a chemotherapy-free option for patients with relapsed indolent NHL.

As noted above, patients with relapsed FL and MZL have fewer choices of efficacious and well-tolerated treatment. After failure of initial treatment patients are treated with various immunochemotherapy regimens. Finding effective and well tolerated therapeutic options for patients who failed initial treatment remains high clinical unmet need in this patient population.

1.2.1. Selection of Primary Efficacy Endpoint

Progression-free survival (PFS) is selected as the primary efficacy endpoint. It is an established surrogate for OS and has been used as primary endpoint in Phase 3 registrational trials in NHL (Cheson 2007).

1.2.2. Study Comparators

- R in combination with B (R-B).
- R in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

The comparator treatments used in this study namely R-B and R-CHOP are recommended standards of care for B-cell malignancies per the National Comprehensive Cancer Network (NCCN Guidelines, v1 2020) and the European Society for Medical Oncology (ESMO) (Dreyling 2021, Zucca 2020) guidelines for diagnosis and treatment of B-cell lymphomas, and

remain the first choice of therapy for patients in front line therapy. Although, other regimens and agents can be used for treatment of patients with relapsed or refractory disease, these two regimens were selected for control arm as two most commonly used options and to minimize potential imbalance associated with introduction of multiple options.

2. STUDY OBJECTIVES

2.1. Primary Objectives

- To demonstrate that zandelisib in combination with R is superior to standard immunochemotherapy in prolonging PFS as determined by the Independent Response Review Committee (IRRC) in previously treated subjects with follicular and marginal zone lymphoma

2.2. Secondary Objectives

- To compare zandelisib + R to standard immunochemotherapy by ORR and complete response rate (CRR) as determined by the IRRC
- To compare zandelisib + R to standard immunochemotherapy by overall survival (OS)
- Time to next anti-lymphoma treatment (TTNT)
- Progression-free survival on next anti-lymphoma treatment (PFS2)
- To Evaluate Patient Reported Outcomes (PRO) with
    - FlymSI-18
    - EuroQoL 5 Dimension 3-Level (EQ-5D-3L)
- To evaluate the safety and tolerability of zandelisib in combination with R

2.3. Exploratory Objectives

To evaluate:

- Efficacy:
    - PFS, ORR and CRR, as determined by the Investigator
    - ORR at week 24 by the Investigator and by the IRRC
    - DOR by the Investigator and by the IRRC
    - Time to progression (TTP), by the Investigator and by the IRRC
- To characterize the relationship between zandelisib exposure in plasma with efficacy and safety

3. STUDY ENDPOINTS

3.1. Primary Endpoint

- PFS as determined by the IRRC

3.2. Secondary Endpoints

- Efficacy: ORR and CRR as determined by the IRRC
- OS
- TTNT
- PFS2
- PRO – time to deterioration in the 9-item disease-related symptoms subscale-physical (DRS-P) subset of FlymSI-18
- PRO – time to improvement in the 9-item DRS-P subset of FlymSI-18
- PRO – functional and well-being (FWB) score and change from baseline in the DRS-P and FWB subscales and total score of FlymSI-18 at specified study visits
- PRO – change from baseline in EQ-5D-3L total score and VAS score at specified study visits
- TEAEs, serious AEs (SAEs), and laboratory abnormalities

3.3. Exploratory Endpoints

- Efficacy:
  - PFS, CRR, and ORR as determined by the Investigator
  - ORR at 24 weeks by the Investigator and by the IRRC
  - DOR by the Investigator and by the IRRC
  - TTP by the Investigator and by the IRRC
- Estimates of zandelisib exposure by population PK method and association with efficacy and safety variables

4. STUDY DESIGN

This is an open label, two-arm Phase 3 study in subjects with relapsed or refractory FL or MZL to evaluate efficacy and safety of zandelisib in combination with rituximab compared with standard immunochemotherapy (R-B [rituximab + bendamustine], or R-CHOP [combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone]). The subjects must have relapsed after ≥1 previous line of therapy; prior therapy must have included anti-CD20 monoclonal antibody treatment (e.g., R, obinutuzumab [O]) in combination with a chemotherapeutic regimen containing an alkylating agent (B or CVP or CHOP or similar), or L.

Subjects will be stratified based on the following criteria:

- Prior treatment regimen: anti-CD20 monoclonal antibody (mAb) in combination with non-bendamustine chemotherapy regimen or R-L vs. anti-CD20 mAb in combination with B
- Number of prior lines of therapy: 1 vs. >1
- NHL histology: FL vs. MZL
- Duration of treatment-free interval from the last lymphoma-directed therapy: ≤24 months vs. >24 months

Subjects who meet the eligibility criteria will be randomly assigned in a 1:1 ratio to one of the treatment arms:

- Arm 1: Rituximab plus zandelisib
- Arm 2: Rituximab plus chemotherapy (CHOP or B)

For Arm 2, selection of therapy regimen will depend on prior therapy, specifically, if a subject had received anti-CD20 mAb in combination with B as a prior therapy, then the subject will receive R-CHOP if randomized to control arm. If a subject received anti-CD20 mAb (e.g., R, O) in combination with chemotherapy regimen (e.g., CHOP or CVP, FND [fludarabine, + mitoxantrone + dexamethasone], or similar regimen) or L, then the subject will receive R-B regimen if randomized to control arm.

During the study, an independent Data Monitoring Committee (DMC) (Section 7.8) will regularly review safety and efficacy data from all subjects as outlined in a separate DMC charter document.

The study is composed of the following periods:

Screening:

After the informed consent procedure has been completed, subjects will be screened during the 28-day period prior to Cycle 1 (C1) Day 1 (D1) to ensure they meet the entry criteria for the study (for details see Section 8.1.2).

Treatment:

Subjects meeting eligibility criteria will be randomized 1:1 to the 2 arms of the study and will start treatment on Cycle 1 Day 1 (C1D1). Treatment will continue for the duration of the protocol prescribed period for each arm of the study. Treatment will be discontinued at any time in case of progression or unacceptable toxicity (see Sections 8.1.4 and 8.1.5). In case of intolerability to R, treatment with R may be discontinued but subjects will continue treatment with other therapies in that arm (zandelisib or chemotherapy).

Disease Assessments:

Efficacy will be assessed based on modified Lugano Criteria wherein radiological tumor evaluations of neck, chest, abdomen and pelvis by using intravenous (IV) (and oral, if indicated, per Imaging Manual) contrast-enhanced computed tomography or magnetic resonance imaging (CT, MRI) and positron emission tomography-computed tomography (PET-CT) imaging modality. PET scans will be done at baseline, after completion of 6 cycles of therapy, and to

confirm CR/metabolic complete response (MCR). CT scans will be done based on the schedule of events (Appendix 1). An independent response assessment will be performed for evaluation of the primary and major secondary efficacy endpoints. Disease management, toxicity, and laboratory assessments will be based on investigator assessments.

Follow-up:

For subjects who discontinue treatment due to reasons other than PD or death, efficacy follow-up will continue until PD, death, withdrawal of consent, or start of new anti-cancer therapy for lymphoma.

All AEs will be reported for up to 30 days after the last dose of study drug (Section 10). AEs leading to discontinuation of study drug will be followed for a minimum of 30 days after the last dose of study drug or until resolution. All SAEs will be reported for 30 days after the last dose of study drug. After 30 days post last dose, only SAEs deemed related to study drug will need to be reported to the Sponsor.

Survival Follow-up:

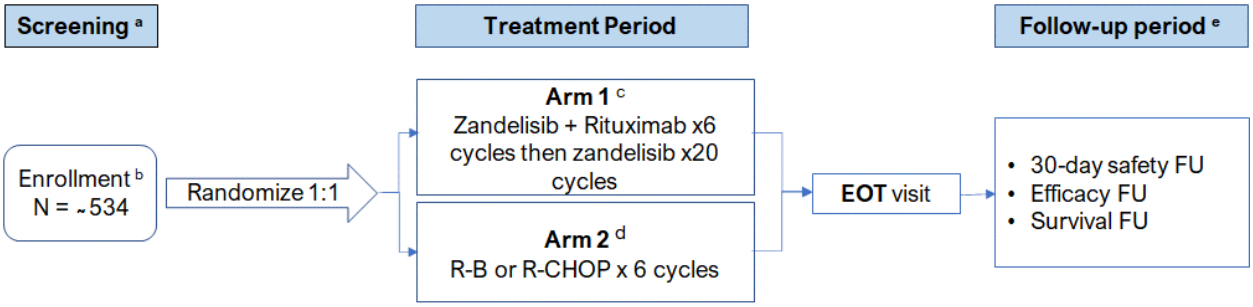
After treatment discontinuation (end of treatment [EOT]), all subjects will be followed for OS every 3 months for 5 years after the last subject's randomization, except for subjects who withdraw consent. Subjects or their healthcare providers will be contacted either in person, by telephone, or e-mail. During OS follow-up TTNT will be recorded.

PFS2 Follow-up:

All subjects will be followed for disease progression as assessed by the investigators that may occur during subsequent treatment following completion of protocol-specified therapy. Follow-up will be approximately every 3 months for collection of date of progression on subsequent therapy (as assessed by the investigators) and start of the next (e.g., third) anti-lymphoma treatment if no PD is reported.

A schematic of the study design is shown in Figure 3.

Figure 3: Study Schematic



a. Screening from Day -28 to -1
b. Subjects should initiate therapy within 3 days of randomization
c. Zandelisib 60 mg QD for 2 cycles followed by IS which consists of 7 days on 21 days off treatment in every 28-day cycle; combination with rituximab is given for 6 cycles, followed by zandelisib for additional 20 cycles of therapy. When administered with zandelisib, R is given on Days 1, 8, 15, and 22 in Cycle 1 then on Day 1 of Cycles 3, 4, 5 and 6
d. R-B or R-CHOP therapy for 6 cycles; R given on Day 1 of each cycle of chemotherapy
e. Follow-up (FU) will include
   - Safety FU at 30 days (± 3 days) from the last dose of study drug. All SAEs will be reported and followed for up to 30 days after the last dose of study drug. After the 30 days only SAEs deemed related to study drug will be reported to the Sponsor
   - Efficacy – for subjects who discontinue treatment for reasons other than PD or death, response FU will continue until PD, death, withdrawal of consent, or start of new anti-cancer therapy for lymphoma
   - Survival FU every 3 months for 5 years until death or withdrawal of consent

Abbreviations: EOT, end of treatment; FU, follow-up; IS, intermittent schedule; PD, progressive disease; R, rituximab; R-B, rituximab + bendamustine; R-CHOP, R + cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisone

4.1. Randomization

After meeting eligibility criteria, subjects will be randomized 1:1 using an Interactive Web (or Voice) Response System process to either zandelisib + rituximab or comparator arm. Subjects randomized to the comparator arm will be allocated to either R-B or R-CHOP according to the treatments they may have received previously. Treatment should begin (C1D1) within 3 days after randomization. Subjects will be stratified based on the following criteria:

- Prior treatment regimen: anti-CD20 mAb in combination with non-bendamustine chemotherapy or R-L vs. anti-CD20 mAb in combination with B
- Number of prior therapies: 1 vs. >1
- NHL histology: FL vs. MZL
- Duration of treatment-free interval from the last dose of the lymphoma-directed therapy: ≤24 months vs. >24 months

4.2. Blinding

This is an open label study. Blinding is not appropriate based on selected therapies for control and investigational arms.

4.3. Duration of Study

The study duration for primary completion of PFS is approximately 64 months with 36 months enrollment period and 28 months follow-up, i.e., 28 months after the last subject is randomized.

4.4. End of Study

The study will end when all subjects have been followed for survival, or lost to follow up, or 5 years from the last subject's randomization, whichever comes first.

4.5. Dosing Schedule for Zandelisib

Zandelisib will be administered 60 mg QD orally for the first 2 cycles of therapy (56 days). Starting with Cycle 3 zandelisib will be administered 60 mg QD for 7 days followed by 21 days off treatment (IS) through Cycle 26.

4.6. Dosing and Schedule for Additional Study Drugs/Comparators

Rituximab will be administered IV 375 mg/m^2 on Days 1, 8, 15 and 22 of C1 and then on D1 of Cycles 3, 4, 5, and 6 for up to a total of 8 doses in 6 cycles.

R-B will be administered every 4 weeks (q4w) as follows: rituximab IV 375 mg/m^2 body surface on D1 and B administered IV 90 mg/m^2 body surface on D1 and D2 of each cycle for 6 cycles.

R-CHOP will be administered once every 3 weeks (q3w) as follows: rituximab IV 375 mg/m^2 body surface on D1; cyclophosphamide IV 750 mg/m^2 body surface on D1; doxorubicin IV 50 mg/m^2 body surface on D1; vincristine IV 1.4 mg/m^2 body surface (maximum dose 2.0 mg) on D1, prednisone 100 mg daily orally (PO) from D1 to D5 of each cycle for 6 cycles.

4.7. Supportive Therapies

Prophylactic or support therapy (e.g., growth factors, blood products) will be managed according to local institutional practices.

5. STUDY POPULATION

All subjects must meet eligibility criteria at screening before randomization.

5.1. Inclusion Criteria

1. Male or female subjects ≥18 years of age, ≥19 years in Korea, or ≥20 years for subjects in Japan and Taiwan, at time of signing informed consent
2. Histologically confirmed diagnosis of CD20 positive iNHL with histological subtype limited to:
    a. FL Gr 1, Gr 2, or Gr 3a
    b. MZL (splenic, nodal, or extra-nodal)

[Histopathological report confirming diagnosis must be available during screening procedures.]

3. Subjects with relapsed disease who received ≥1 prior lines of therapy, that must have included an anti-CD20 antibody in combination with cytotoxic chemotherapy or L, with or without subsequent maintenance therapy. [A line of therapy is defined as following: a minimum of 2 consecutive cycles of immunochemotherapy or R-L, or at least 4 doses of anti-CD20 mAb (R) single agent therapy, a minimum of 2 consecutive cycles of therapy with an investigational agent. Maintenance therapy given after an induction treatment (e.g., R maintenance) is considered as the same line of therapy] [Please see Exclusion Criterion #2 for further clarification]. Relapsed or refractory disease is defined as:
   - Relapsed disease: disease progression after a response (CR or partial response [PR]) lasting ≥6 months
   - Refractory disease: no response to therapy (no CR or PR) or response lasting <6 months
4. Subjects must have at least one bi-dimensionally measurable nodal lesion with the longest diameter >1.5 cm and/or an extranodal lesion >1.0 cm (that has not been previously irradiated) according to the Lugano Classification
5. Adequate hematologic parameters at screening unless abnormal values are due to disease per investigator assessment:
   - Absolute neutrophil count (ANC) ≥1.0 × 10^9/L (≥1,000/mm^3)
   - Platelet count ≥75.0 × 10^9/L (≥75,000/mm^3)
   - Hemoglobin ≥9 g/dL
6. Adequate renal and hepatic function per local laboratory reference range at screening as follows:
   - AST/ALT ≤1.5 × upper limit of normal (ULN)
   - Total bilirubin ≤2.0 × ULN or ≤3 × ULN for subjects with Gilbert-Meulengracht syndrome
   - Estimated glomerular filtration rate (eGFR) >50 mL/min using the Cockcroft-Gault equation (Appendix 2)
7. QT-interval corrected according to Fridericia's formula (QTcF) ≤450 msec; subjects with QTc >450 msec but <480 msec may be enrolled provided the QTc prolongation is due to a right bundle branch block (RBBB), left bundle branch block (LBBB), or pacemaker and is confirmed stable by a cardiologist
8. Left ventricular ejection fraction (LVEF) ≥45% as measured by echocardiogram (ECHO) or multi-gated acquisition scan (MUGA). [If LVEF <45% by ECHO, a repeat measurement can be conducted within the screening period.]
9. Subjects must have completed any prior systemic anti-cancer treatment ≥4 weeks (or ≥5 times the half-life [t½] of used therapeutics [including investigational therapy], whichever is longer) or radiation therapy ≥2 weeks before study Day 1, and ≥3 months

before study Day 1 for high dose therapy with stem cell transplantation, radioimmunotherapy, and CAR T-cell therapy

10. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
11. Life expectancy of at least 3 months
12. All AEs and laboratory toxicities related to prior therapy must resolve to Gr ≤1 prior to the start of the study therapy (unless otherwise specified in eligibility criteria)
13. For females of childbearing potential, a negative serum human chorionic gonadotropin (hCG) pregnancy test within 28 days of study Day 1 and negative result (urine or serum) on study Day 1
14. Subjects must agree to use appropriate contraception methods during the clinical study (Appendix 3)
15. Subject is willing and able to comply with all scheduled visits, treatment plans, laboratory tests, and other study procedures.

5.2. Exclusion Criteria

1. Histologically confirmed diagnosis of FL Gr 3b or transformed disease
   - For subjects with clinical signs of rapid disease progression (e.g., marked B-symptoms), and laboratory or radiographic indication (e.g., high lactate dehydrogenase [LDH] level or standardized uptake value by PET), a fresh tumor biopsy is recommended to rule out transformed disease
2. Subjects who received both R/O-B and R/O-CHOP (or other anthracycline-containing regimen) as previous lines of therapy, or those who received only single agent anti-CD20 mAb therapy as prior line of treatment
3. Prior therapy with PI3K inhibitors
4. Ongoing or history of drug-induced pneumonitis
5. Known lymphomatous involvement of the central nervous system
6. Seropositive for or active viral infection with hepatitis B virus:
   - HBsAg positive
   - HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA by PCR

Note: Subjects who are HBsAg negative and viral DNA PCR negative are eligible. These subjects should receive prophylactic therapy for hepatitis as per institutional standards.

7. Known seropositive for, or active infection with hepatitis C virus
   - Subjects with positive hepatitis C virus (HCV) antibodies are eligible with negative PCR test for HCV
8. Known seropositive for, or active and uncontrolled infection with human immunodeficiency virus (HIV), or with acquired immunodeficiency syndrome (AIDS),

or currently taking medications for HIV that are contraindicated for concomitant use in this study

9. Known seropositive for, or active infection with human T-cell leukemia virus type 1
10. Any uncontrolled clinically significant illness including, but not limited to, active infections requiring systemic antimicrobial therapy, hypertension, angina, arrhythmias, or other uncontrolled cardiovascular conditions, pulmonary disease, or autoimmune dysfunction, and urinary infection or flow obstruction
11. Hypersensitivity or other clinically significant reaction to the study drug or its inactive ingredients or other therapy used in the study
12. Major surgical procedure within 4 weeks prior to study Day 1 (minor surgical procedures, e.g., lymph node biopsy, performed within 1 day or with an overnight stay are allowed)
13. Previous or concurrent cancer that is distinct in primary site or histology from indolent B-cell NHL within 3 years before start of study treatment **except fo**r curatively treated cervical cancer in situ, non-melanoma skin cancer, and superficial bladder tumors (Ta [non-invasive tumor], Tis [carcinoma in situ], and T1 [tumor invades lamina propria]), and asymptomatic localized prostate cancer with no requirement for systemic therapy or requiring only hormonal therapy and with normal prostate-specific antigen values within ≥12 months prior to randomization
14. History of clinically significant cardiovascular abnormalities such as congestive heart failure (New York Heart Association (NYHA) classification ≥ II [NYHA 1994]), myocardial infarction within 6 months of study entry.
15. History of clinically significant gastrointestinal (GI) conditions, particularly:
    - Known GI condition that would interfere with swallowing or the oral absorption or tolerance of study drug
    - Pre-existing malabsorption syndrome or other clinical situation that would affect oral absorption
16. Females who are pregnant; females who plan to breastfeed during study treatment through 90 days after ending treatment
17. Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results
18. Any illness or medical conditions that are unstable or could jeopardize the safety of the subjects and their compliance in the study. Inability to understand and sign informed consent form (ICF)
19. Received a live virus vaccination within 28 days of first dose of study drug, (e.g., yellow fever vaccination).

5.3. Number of Subjects

It is anticipated that approximately 534 subjects will be randomized into the study. For details of sample size calculation see Section 11.2.

6. TREATMENTS

6.1. Preparation and Administration of Investigational Product(s)

6.1.1. Zandelisib

Zandelisib is provided as 60 mg capsules, which require no preparation prior to administration. Subjects should be instructed to swallow the capsules whole and to not chew or crush them.

Zandelisib is dosed on a milligram (mg) basis with no adjustment in dosing based on subject weight. Zandelisib is to be taken orally once a day at approximately the same time each morning in accordance with the IS dosing regimen.

6.1.2. Formulation

Zandelisib drug product is supplied in Size 2 white capsules, with black printing, containing 60 mg of active pharmaceutical ingredient which is blended with microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate.

6.1.3. Storage of Zandelisib

Please refer to the clinical label, which provides storage conditions in accordance with the relevant national/regional pharmacopeial definition of room temperature.

6.1.4. Packaging and Labelling

Zandelisib is supplied as either 28-capsule or 7-capsule blister packets labelled as ME-401 investigational product with storage instructions.

6.1.5. Dispensing of Zandelisib

Zandelisib will be dispensed according to the randomization scheme using the Interactive Web Response System.

6.2. Dose and Administration

Zandelisib 60 mg is taken on dosing days with a glass of liquid to aid in swallowing, on an empty stomach in the morning (i.e., at least 1 hour prior to food intake or 2 hours after food intake). If a subject routinely experiences discomfort with dosing, he or she is permitted to take zandelisib with a light snack. If a dose is missed, it may be taken up to 12 hours after the specified time. After 12 hours, the missed dose should be omitted. If possible, the subject should be advised to separate administration of zandelisib capsules from that of concomitant medications that have a known inhibitory effect on P-glycoprotein (P-gp) and breast cancer resistance protein transporter (BCRP).

On days with PK sampling, subjects should be instructed not to take study drug zandelisib at home. Study drug administration will be done at the clinic in relation to the timing of the PK sample collection. For sampling days see Section 9.5.

6.3. Investigational Product Accountability and Compliance

The Principal Investigator or their representative will account for all investigational product (IP) provided by the Sponsor. All IP will be stored at the site in a secure and locked location. The Principal Investigator shall maintain adequate records of the disposition of IP, including dates, quantity, and use by subjects. Upon completion of the study, all remaining IP will be accounted for and unused material will either be returned to the Sponsor (or designee) by a traceable method (UPS, FedEx, etc.) or destroyed (with documentation of drug destruction provided to the Sponsor), as instructed by the Sponsor.

A compliance assessment and returned study drug accountability will be performed at each visit which includes study drug return (see Section 7.5 for compliance with study drug administration).

6.4. Concomitant Therapy

Data on concomitant medications by prescription and over-the-counter medications will be collected. This data will be recorded from 28 days prior to C1D1 through 30 days after last dose of zandelisib, treatment discontinuation, or until a subsequent anti-cancer therapy is initiated.

Management of concomitant medications for patients taking R will be per the Rituxan USPI and SmPc for MabThera, and other product label applicable to comparators.

6.4.1. Permitted Prophylactic Therapy

Prophylactic therapy for hepatitis and for CMV is allowed. Prophylactic therapy for opportunistic infection, including *Pneumocystis jiroveci* pneumonitis (PJP) is allowed per institutional guidelines or per the investigator's judgement. Prophylaxis for CMV should follow the institutional guidelines or ESMO guidelines (Dreyling 2021).

Prophylactic therapy for hepatitis is recommended per institutional standards.

Administration of all prophylactic and supportive treatments, and dosage must be reported on the concomitant medication page of the eCRF.

6.4.2. Prohibited Concomitant Medications

The following medications/therapies are prohibited while receiving study treatment:

- Other investigational agents
- Systemic corticosteroids in doses >10 mg in prednisone (or equivalent dose of other corticosteroids) are prohibited for one week prior to C1D1 and during the study
- Drugs that are strong inhibitors and inducers of CYP3A4 (Appendix 7)
- Inhibitors and inducers of CYP3A4, CYP2D6, or P-gp are prohibited in subjects receiving doxorubicin. Prophylactic or supportive therapy including weak inhibitors and inducers of CYP3A4, CYP2D6, or P-gp can be used only for AE treatment according to local institutional practices if no other treatment is available.

During the course of study drug treatment, a short course (e.g., <2 weeks) of high-dose corticosteroids (>10 mg/day prednisone) is permitted for premedication to manage

infusion-related reactions or to manage other inflammatory reactions (e.g., asthma). Corticosteroids to treat the underlying FL or MZL are not allowed during the study.

Subjects assigned to receive R-CHOP regimen are allowed to receive higher dose of prednisone based on treatment schedule (100 mg daily for Days 1-5 of each cycle).

6.4.3. Advisory for Concomitant Medications

The following medications/therapies should be used with caution:

- Drugs that are strong/moderate inhibitors and inducers of CYP2C8 (Appendix 6) and moderate inhibitors and inducers of CYP3A4 (Appendix 7)
- Drugs that affect the QT/QTc interval (Appendix 8)
- Orally administered drugs known to inhibit or induce the intestinal transporters BCRP and P-gp.
- Dapsone for PJP prophylaxis (prophylaxis therapy can be used per the investigator's decision)

6.4.4. Advisory on Vaccinations

As per the EU Summary of Product Characteristics (SmPc) for MabThera (R), vaccination with a live vaccine is not recommended while on the study. As per the SmPc for bendamustine, vaccination with a live vaccine for yellow fever is contraindicated.

6.4.4.1. Advisory on COVID-19 Vaccination and Risk Assessment

COVID-19 vaccination, where authorized or approved, is allowed and considered a standard of care for patients who are currently enrolled in this study. The study will follow COVID-19 vaccination guidance and recommendations provided by scientific and medical associations (European Hematology Association, American Society of Hematology, American Society of Clinical Oncology, and NCCN).

The Sponsor completed a risk assessment for the use of COVID-19 vaccination while on study and concluded the benefit of receiving therapy for patients with R/R FL and MZL outweigh the potential risk of delaying treatment due to scheduled COVID-19 vaccination. Any potential risk for patients with NHL that is associated with COVID-19 vaccination, while on therapy for lymphoma, has not been fully established yet. Vaccination for patients participating in this study is permitted. Recommendations regarding COVID-19 vaccination for patients with NHL should adhere to local regulatory and institutional guidance.

6.5. Prohibited Therapies

- Obinutuzumab and ofatumumab
- Other anti-lymphoma therapies not specified in this protocol

6.6. Anticipated Toxicities

As of the 04 January 2020 data cut-off date, the Gr ≥3 AEs noted in the Phase 1b study for the 57 subjects administered zandelisib alone or in combination with rituximab on the IS consisted

of diarrhea/colitis, neutrophil count decreased (7% each), and rash, ALT increased, hyperglycemia, lymphocyte count decreased, blood alkaline phosphatase (ALP) increased, headache, and anemia (1.8% each).

Gr 3 AESIs were: diarrhea and colitis (3.5% each), and ALT/AST elevation, rash, non-infectious pneumonitis (1.8% each); there were no Gr 4 or 5 AESIs reported up to date. There was no Gr 3 pneumonia or stomatitis reported.

Refer to Table 2 for study drug dose interruption or treatment discontinuation in a subject if such toxicity occurs and is not considered related to the underlying disease or other possible etiologies. Subject management will be determined by the treating physician and may include administration of a hematopoietic growth factor for neutropenia, administration of corticosteroids for the treatment of colitis, pneumonitis, and other AEs considered immune mediated (Table 2), and other antimicrobial or anti-viral treatment for prophylactic therapy per institutional standards.

Refer to the current Zandelisib IB for more details.

6.7. Zandelisib Toxicity Management

Subjects who experience toxicities should be managed according to the guidelines provided in Table 2. For subjects who experience a toxicity requiring treatment interruption during Cycle 1, 2 and 3, treatment interruption will be followed by treatment on the IS once the toxicity resolves. For subjects who experience toxicity during Cycles 4-26, toxicities will be managed by interrupting therapy or discontinuation of treatment. Once the toxicity resolves, the therapy should be restarted on the scheduled next cycle of therapy (example: if recovery occurs on day 20 of a cycle, the next treatment cycle will start in 8 days). All treatment interruptions (including any missed doses) and discontinuations and their reasons are to be recorded in the electronic case report form (eCRF). Interrupted treatment is resumed after the toxicity resolves to the grade specified in the table. Subjects who permanently discontinue zandelisib dosing will proceed to the EOT visit and 30-Day Safety Follow-up visit.

Subjects who interrupt study drug dosing for >6 continuous weeks will have zandelisib permanently discontinued unless restarting zandelisib is authorized by the study Medical Monitor.

Table 2: Zandelisib Toxicity Management

Toxicity/Grade	Zandelisib Management		Treatment
	Cycles 1-3	Cycles 4-26	
Non-hematologic Toxicities			
Diarrhea/colitis			
Gr 2	• Hold zandelisib unless diarrhea is confirmed to be due to an infectious agent. For diarrhea of infectious etiology, no dose interruption is required. • Once diarrhea resolves to Gr ≤1 or baseline, resume zandelisib at 60 mg administered on the IS (the first 7 days of each 28-day cycle).		If infectious cause of the diarrhea, including clostridium difficile, is ruled out then proceed with following management steps: • Hold zandelisib and start loperamide or similar anti-diarrheal agent. • If no improvement occurs within 48 hours, start prednisone /prednisolone 0.5-1 mg/kg IV or oral budesonide 9 mg daily or equivalent oral systemic steroids based on local institutional practice. [Note: Based on data from the Phase 1b study, subjects with diarrhea that was preceded by rash in the prior 1-2 weeks often experienced more prolonged and severe diarrhea. Thus, if diarrhea is preceded by rash in the prior weeks, start prednisone/ prednisolone 0.5-1 mg/kg IV or oral budesonide 9 mg daily when subjects experiences rash.]

Table 2: Zandelisib Toxicity Management (Continued)

Toxicity/Grade	Zandelisib Management		Treatment
	Cycles 1-3	Cycles 4-26	
Non-hematologic Toxicities			
Gr 3	• Hold zandelisib until AE resolves to Gr ≤1 or baseline; resume zandelisib at 60 mg administered on the IS. • For recurrence of Gr 3 diarrhea/colitis, discontinue study drug permanently	If the event is considered related to treatment with zandelisib in the opinion of the investigator, permanently discontinue zandelisib.	• Subjects should be hydrated as clinically indicated and administered prednisone/prednisolone 1-2 mg/kg/day IV/oral or equivalent IV/ oral systemic steroids. • If no improvement occurs within 2-3 days, • the corticosteroid dose should be increased to 2 mg/kg/day IV or equivalent oral systemic steroids. • Once improved to Gr ≤1, start tapering the corticosteroid as clinically indicated.
Gr 4	Permanently discontinue zandelisib.		Treat as suggested for Gr 3, or as per institutional standard of care.
Cutaneous Reactions and Mucositis			
Gr 2	Continue zandelisib		• Monitor subjects and determine cause of rash. • Per Investigator's discretion, antihistamines, topical steroids, and systemic steroids may be given.
Gr 3	• Hold zandelisib until AE resolves to Gr ≤1 or baseline; resume zandelisib at 60 mg administered on the IS. • For recurrence of Gr 3, permanently discontinue zandelisib.	If the event is considered related to treatment with zandelisib in the opinion of the investigator, permanently discontinue zandelisib.	• Monitor subjects as clinically indicated until resolution. • Oral antihistamines and systemic corticosteroids such as prednisone/prednisolone 0.5-1 mg/kg/day (or equivalent dose of systemic steroids) should be given until rash resolves to Gr ≤1.

Table 2: Zandelisib Toxicity Management (Continued)

Toxicity/Grade	Zandelisib Management		Treatment
	Cycles 1-3	Cycles 4-26	
Cutaneous Reactions and Mucositis			
Other: Life-threatening toxicity (Gr 4), Stevens-Johnson syndrome of any grade, and TENS of any grade	Permanently discontinue zandelisib.		Treat as per Gr 3 recommendations or per institutional standard of care.
Hepatotoxicity			
Gr 2	For ALT/AST >3–5 × ULN but <5 × ULN, maintain zandelisib treatment dose and schedule.		Monitor once a week until resolved to Gr ≤1 or baseline level.
Gr 3	• For ALT/AST >5-20 × ULN, hold zandelisib. • Resume zandelisib at 60 mg administered on the IS. • For recurrence of Gr 3, permanently discontinue zandelisib. • If Hy's law criteria are met (laboratory parameters, and no other reasonable cause for changes has been identified) then permanently discontinue treatment with zandelisib.	• If the event is considered related to treatment with zandelisib in the opinion of the investigator, permanently discontinue zandelisib. • If Hy's law criteria are met (laboratory parameters, and no other reasonable cause for changes has been identified) then permanently discontinue treatment with zandelisib.	• Monitor once a week until resolved to Gr ≤1 or baseline level. • Treat per institutional standard of care, which may include a course of corticosteroids if clinically indicated. • Assess if Hy's law[a] applies.
Gr 4	For ALT/AST >20 × ULN, permanently discontinue zandelisib.		• Assess if Hy's law applies. • Treat per institutional standard of care, which may include a course of corticosteroids if clinically indicated.

Table 2: Zandelisib Toxicity Management (Continued)

Toxicity/Grade	Zandelisib Management		Treatment
	Cycles 1-3	Cycles 4-26	
Non-infectious pneumonitis (NIP)			
Gr 2	• Hold zandelisib until AE resolves to Gr ≤1 or baseline. • If Gr 2 NIP recurs, discontinue treatment permanently. • Resume zandelisib at 60 mg administered on the IS.	• If the event is considered related to treatment with zandelisib in the opinion of the investigator, permanently discontinue zandelisib.	Rule out infectious etiology of pneumonitis based on institutional guidance, utilizing following methods: chest x-ray, CT scan, pulsometry, nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity. Treat with corticosteroids and per institutional standard of care.
Gr ≥3	Permanently discontinue zandelisib.		Treat per institutional standard of care, including systemic corticosteroids.
Lung Infection/ Pneumonia			
Gr 2	• Continue treatment with zandelisib.		Treat per institutional standard of care.
Gr 3	• Hold zandelisib until AE resolves to Gr ≤1 or baseline. • Resume zandelisib at 60 mg administered on the IS. • For the second occurrence of Gr 3 lung infection within ≥6 months from prior event, retreatment is allowed once patient recovers to Gr ≤1 or baseline. • Discontinue if same event occurs a third time.		Treat per institutional standard of care.
Gr 4	Permanently discontinue zandelisib.		Treat per institutional standard of care.

Table 2: Zandelisib Toxicity Management (Continued)

Toxicity/Grade	Zandelisib Management		Treatment
	Cycles 1-3	Cycles 4-26	
Other non-hematologic toxicities, not listed above, that are <u>considered related to zandelisib</u>			
Gr 2	Continue treatment with zandelisib		Treat per institutional standard of care.
Gr 3	• Hold zandelisib until AE resolves to Gr ≤1 or baseline. • Resume zandelisib at 60 mg administered on the IS. • For recurrence of the same Gr 3, discontinue permanently zandelisib.	If the event is considered related to treatment with zandelisib in the opinion of the investigator, permanently discontinue zandelisib.	Treat per institutional standard of care.
Gr 4	Permanently discontinue zandelisib.		Treat per institutional standard of care.
Cytomegalovirus (CMV) Any grade	• If test is positive (PCR or antigen assessment) based on local laboratory assessments and requires treatment, then hold zandelisib until recovery. • Resume zandelisib on the IS after resolution of asymptomatic CMV reactivation if all the following conditions are met: • CMV reactivation is resolved per the Investigator assessment • CMV reactivation was not associated with end organ disease (e.g., pneumonia, hepatitis, gastroenteritis, retinitis, encephalitis)		• Treat per institutional standard of care. • If all conditions for restarting study drug are met, then secondary CMV prophylaxis must be maintained as per institutional guidelines.
QTc Prolongation assessed as related to treatment	>60 ms increase compared to baseline/screening and >500 ms (both criteria must be met) will require repeated 12-lead ECG test twice and calculate mean level of QTc prolongation based on 3 measurements. If the changes are confirmed, then discuss with the Sponsor's Medical Monitor or designee the risk/benefit assessment of continuing treatment with zandelisib without changes. After review with the Sponsor's Medical Monitor or designee, treatment interruption maybe used until improvement to baseline level or QTc interval <500 ms. If treatment interruption was used, resume treatment with zandelisib on IS. It is very important to assess whether concomitant medications or medical history are more likely reasons for QTc interval prolongation.		

Table 2: Zandelisib Toxicity Management (Continued)

Toxicity/Grade	Zandelisib Management		Treatment
	Cycles 1-3	Cycles 4-26	
Hematologic Toxicities			
Neutropenia			
Gr 3	Zandelisib dosing may continue.		Perform CBC weekly until resolves to Gr ≤2 (unless myelosuppression is due to follicular lymphoma).
Gr 4	• Gr 4 neutropenia or Gr ≥3 febrile neutropenia: hold zandelisib until recovery to Gr ≤2. Resume zandelisib at 60 mg administered on the IS.	• Gr 4 neutropenia or Gr ≥3 febrile neutropenia: hold zandelisib until AE resolves to Gr ≤2. Resume zandelisib at 60 mg administered on the IS. • Recurrence of Gr 4 neutropenia or Gr ≥3 febrile neutropenia: discontinue treatment permanently.	Perform CBC weekly until resolves to Gr <3. Initiate growth factor support if clinically indicated. If subject is receiving filgrastim support or equivalent, CBC should be repeated after 3 days. Weekly CBCs should continue until resolves to Gr <3.
Thrombocytopenia			
Gr 3 without bleeding	Continue therapy with zandelisib.		• Check platelets every 3 days until resolves to <3.
Gr ≥3 with Gr ≥2 bleeding	• Interrupt therapy until resolution to Gr ≤2 thrombocytopenia and no bleeding, resume zandelisib at 60 mg on the IS. • Recurrence of thrombocytopenia Gr ≥3 with Gr ≥2 bleeding: discontinue treatment with zandelisib permanently		• Treat per institutional standards.
Gr 4 without bleeding	• Treatment with zandelisib may continue or may be interrupted based on the Investigator's judgement.		

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CMV = cytomegalovirus; CT = computed tomography; Gr = grade; IS = intermittent schedule; IV = intravenous; NIP = non-infectious pneumonitis; PCR = polymerase chain reaction; TENS = toxic epidermal necrolysis syndrome; ULN = upper limit of normal

* Toxicity graded per CTCAE v5.0.

[a] Hy's law is defined as: cases of drug-related hepatocellular injury are defined as elevated ALT or AST ≥3 × ULN, plus elevated total bilirubin >2 × ULN without findings of cholestasis (defined as serum alkaline phosphatase (ALP) activity <2 × ULN), and no other reason can be found to explain (FDA 2009).

6.8. Adverse Events of Special Interest for Zandelisib

Certain adverse events require timely review regardless of their severity and reportability. In this study, the following treatment-related events are considered AESIs:

- Diarrhea/colitis ≥Gr 3
- Cutaneous reactions/rash ≥Gr 3
- Mucositis ≥Gr 3
- Transaminases elevation ≥Gr 3
- Non-infectious pneumonitis ≥Gr 2
- Lung infection/pneumonia ≥Gr 3

These AESIs will be reported to the Sponsor if they led to treatment interruption or delays, initiation of concomitant therapy, or treatment discontinuation on zandelisib + R arm in expedited way.

6.9. Additional Study Drugs/Comparators

Other study drugs (R, B, cyclophosphamide, doxorubicin, vincristine, prednisone) are available commercially or may be provided by the Sponsor according to regional regulations and should be administered and managed according to the respective Prescribing Information (PI) and institutional standards. Rituximab biosimilar formulations are allowed for use in this study. Subcutaneous dosing regimen of rituximab is not allowed in this study.

6.9.1. Sourcing of the Standard of Care Products

The standard of care products listed in Section 6.9 (i.e., rituximab, bendamustine, and the components of CHOP) are approved in both the US and the EU to treat patients with various B-cell malignancies. For financial reasons, the Sponsor is sourcing the following standard of care products used in this study from the EU: rituximab (MabThera®, Truxima® or other biosimilar that is approved in both regions), bendamustine, prednisone, cyclophosphamide (Endoxan®), doxorubicin (Adriamycin®), and vincristine (Cellcristin®). All products sourced from the EU to be used in the US must also be approved for use by the US FDA.

6.9.2. Expected Toxicities for Additional Study Drugs/Comparators

Rituximab therapy is known to be associated with the following toxicities per the USPI for Rituxan (in the EU, MabThera Summary of Product Characteristics).

Infusion-related reaction, severe mucocutaneous reactions, hepatitis B virus reactivation, progressive multifocal leukoencephalopathy, tumor lysis syndrome, infections, cardiovascular adverse reactions, renal toxicity, bowel obstruction and perforation, immunization, embryo-fetal toxicity.

Other adverse reactions frequently observed in clinical trial in lymphoid malignancies include fever, chills, asthenia, headache, abdominal pain, pain, and back pain.

For a comprehensive list of toxicities refer to the rituximab PI. Toxicities should be managed per best medical judgement and in accordance with institutional practices.

CHOP

For comprehensive information on toxicities associated with CHOP chemotherapy refer to PI for doxorubicin, cyclophosphamide, vincristine, and prednisone. A summary of toxicities for each drug is provided below. Toxicities resulting from CHOP administration should be managed per best medical judgment and institutional practices.

Doxorubicin has been associated with cardiotoxicity, myelosuppression, hepatotoxicity, and immunosuppression.

Cyclophosphamide has been associated with myelosuppression (e.g., neutropenia), febrile neutropenia, fever, alopecia, nausea, vomiting, diarrhea, urinary tract infection, cardiotoxicity, pulmonary toxicity, among others.

Vincristine has been associated with hypersensitivity, constipation, abdominal cramps, weight loss, nausea, vomiting, oral ulceration, diarrhea, paralytic ileus, intestinal necrosis and/or perforation, anorexia, polyuria, dysuria, and urinary retention, hypertension, hypotension, paresthesia, anemia, leukopenia, and thrombocytopenia, alopecia, and rash.

Prednisone has been associated with fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, weight gain, and increased risk for viral, bacterial, fungal, and protozoan infections.

Bendamustine has been associated with myelosuppression (anemia, thrombocytopenia, neutropenia, lymphopenia, leukopenia), hyperbilirubinemia, pyrexia, nausea, vomiting, anorexia, fatigue, diarrhea, constipation, cough, headache, weight decreased, dyspnea, rash, stomatitis, hepatotoxicity, tumor lysis syndrome, skin reactions, anaphylaxis and infusion reactions and infections, cardiac disorders, and irreversible infertility. For a comprehensive list of toxicities refer to the bendamustine PI. Toxicities should be managed per best medical judgment and institutional practices.

6.10. Dose Modification of Additional Investigational Drugs

For other drugs administered in this study, any toxicity encountered should be managed according to the recommendations described in the US Prescribing Information or the Summary of Product Characteristics for the drug (R, B, cyclophosphamide, doxorubicin, vincristine, and prednisone) and institutional standard of care.

Subjects will be treated for 6 cycles of R with chemotherapy. In case of intolerability to R, treatment with R may be discontinued but subjects will continue treatment with the other therapies in that arm (zandelisib or chemotherapy).

6.11. Safety Run-in for Japanese Subjects in Japan Only

Based on the request of the Japanese Pharmaceutical and Medical Device Agency (PMDA) to evaluate tolerability of zandelisib in combination with R, a tolerability study in Japanese subjects was deemed necessary. To comply with this, a safety run-in study will be conducted in Japan only to establish tolerability of zandelisib + R combination treatment in Japanese subjects. Details of the safety run-in in the Japanese population are described in Appendix 11, and the Japanese Safety Review Committee Charter.

7. STUDY CONDUCT

7.1. General Instructions

See the Schedule of Assessments (Appendix 1) for a detailed list of study procedures and assessments. Instructional details (where applicable) for procedures are contained in Section 8.

7.2. Subject Screening

Subjects will be screened during the 28-day period prior to C1D1 to ensure they meet the entry criteria for the study. The Investigator or an appropriate designee will obtain informed consent from each subject prior to conducting any study-specific procedures. Screening procedures may be completed across multiple days during the screening period and do not need to be completed on consecutive days. During the screening period, the Investigator should carefully review each subject's medical history to ensure eligibility. All inclusion and exclusion criteria should be supported by corresponding documentation in the medical records, including a pathology report confirming the diagnosis of FL or MZL. Screening laboratory tests may be repeated once to confirm eligibility at the discretion of the Investigator (Appendix 1).

7.3. Screen Failures

Subjects who do not meet eligibility criteria will be deemed screen failures. Screen failure subjects may be rescreened one time for study participation if deemed appropriate by the Investigator and the Medical Monitor, and some screening procedures may need to be repeated.

7.4. Deviation from Inclusion/Exclusion Criteria

All subjects must meet the criteria for study entry. No waivers will be provided pertaining to inclusion and exclusion criteria.

7.5. Monitoring Subject Compliance

Subjects will receive paper diaries that they should complete to document the dates and time when they take their zandelisib. Subjects should be instructed to return paper diaries and used investigational product (IP) packages to the site at the next study visit. Site personnel should review the diary and inspect the returned IP packages to ensure the diary appears accurate and study medication was taken in accordance with the protocol. Site personnel should discuss any IP non-compliance with the subject and emphasize the importance of taking the study medication as directed. IP compliance of less than 80% or more than 120% should be documented as a protocol deviation.

7.6. Site Closure

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Non-compliance with International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines
- Inadequate rate of subject recruitment

- Poor protocol adherence
- Inaccurate or incomplete data recording
- No study activity (i.e., all subjects have completed, and all obligations have been fulfilled)

7.7. Follow-up for Response Assessments and Survival

After treatment discontinuation or completion of protocol-specified therapy, all subjects who did not experience disease progression will be followed for response assessments as per protocol-defined schedule until PD, start of new anti-lymphoma therapy, or withdrawal of consent. Survival follow-up will continue until death, withdrawal of consent or subject is lost to follow-up. Survival follow-up will continue for up to 5 years after the last subject's randomization. Subjects or their healthcare providers will be contacted either in person or by telephone.

7.8. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established to review safety and efficacy data collected in the study on a regular basis with the primary purpose of protecting the safety of trial participants, the credibility of the trial, and the validity of trial results. The safety data will include, but will not be limited to, summary of Gr 5 treatment-related TEAEs, and AESIs, events leading to treatment discontinuation. The DMC will review the totality of the safety and efficacy data to assess if any changes to the study conduct or clinical study protocol are required. The DMC will meet at least once every 3 months, with the first data review meeting occurring when approximately 60 subjects (~30 in each arm) have completed at least 1 cycle of treatment or 6 months after the first subject is dosed, whichever occurs first. The frequency of meetings may change based on the DMC decision, which will be reflected in the DMC charter amendment. The DMC will review totality of the data during these meeting to advise the sponsor if any changes to study design are required. Details regarding the DMC are contained in a separate DMC Charter document.

Interim analysis (see Section 11) will be performed by the DMC.

7.8.1. Enrollment Stopping Rules and Additional Safety Considerations

In addition to regular DMC safety and efficacy data review, the DMC will assess whether a pause of enrollment is required for comprehensive data review to evaluate if any potential changes to the study conduct, patient's eligibility criteria or other changes for the clinical study protocol are needed.

7.8.1.1 Stopping Rules Based on Treatment-related Mortality

When 150 subjects (75 in each arm) have been enrolled in the clinical study and completed at least 1 cycle of therapy, the DMC will determine if an enrollment pause is necessary by assessing and comparing the risk/benefit profile of therapies in both arms based on various patients' characteristics (e.g., number of prior lines of treatment). After the initial review, the DMC will continue to assess the data during regularly scheduled meetings every 3 months or as described in the DMC charter based on the DMC decision.

Prior to reaching an enrollment threshold of 150 patients, the DMC will evaluate the totality of safety data, including Gr 5 treatment-related AEs, and apply their clinical judgment to decide if a pause in enrollment is needed.

After reaching an enrollment of 150 patients, the main criteria for review will be Bayesian model-based, recommended by the ASA Safety Workgroup (Fries 2016) and the report by Yao 2013, which incorporates both the observed rates for treatment-related Gr 5 TEAEs and the associated confidence levels around the risks. The thresholds for the observed rates are:

- ≥5% in the zandelisib + R arm; or
- Risk ratio for treatment-related Gr 5 TEAEs in zandelisib + R arm compared with the control arm ≥2.

Historical data show that observed fatal AE rates associated with anti-CD20 immunochemotherapy regimens (both bendamustine and CHOP) in iNHL studies range from 0~3.3% (Fowler 2011, Robinson 2008, Rummel 2008, Sarkozy 2019, Sehn 2016, Van Oers 2006, EMA assessment report on idelalisib 2018). A reasonable estimate of the fatal AE rate to be expected in the control arm would be approximately 2.5%. Therefore, 5% of treatment-related Gr 5 TEAE (doubling the assumed mortality rate in the control arm) is used as one of the thresholds.

7.8.1.2 Additional Safety Considerations

At each meeting, the DMC will review the totality of the safety data, which will include additional evaluation of the frequency of AESI and other AEs to assess risks associated with treatment.

The DMC will review safety data in the investigational treatment arm (zandelisib plus rituximab combination), including a side-by-side comparison of the incidence and severity of AESIs in subjects who were enrolled in the study after failure of one or more than one prior line of therapy.

The following AESI thresholds (% of subjects with an AESI) will be evaluated by the DMC:

- Non-infectious pneumonitis (NIP) ≥Gr 2 in ≥7%
- Diarrhea/colitis ≥Gr 3 in ≥15%
- Skin toxicity ≥Gr 3 in ≥10%
- Hepatic toxicity (AST and/or ALT elevation) ≥Gr 3 in ≥15%
- Infection ≥Gr 3 in ≥25%

These thresholds were selected based on the reported incidence for PI3Kδ inhibitors marketed for the treatment of B-cell malignancies, including ≥Gr 2 pneumonitis reported in up to 5% of patients, ≥Gr 3 diarrhea and colitis in up to 20%, ≥Gr 3 AST/ALT elevation in up to 18%, ≥Gr 3 cutaneous reactions in up to 5%, and ≥Gr 3 infection in up to 31% (Aliqopa USPI, Ukoniq USPI, Copiktra USPI, Zydelig USPI).

The DMC will apply their clinical judgement to overall and relative safety signals within the context of the disease under study. The DMC will assess the totality of the data and make its

recommendation as to whether the study may proceed as per protocol, if enrollment must be held in one or more than one patient subset, or if the study protocol requires modification.

Details for analysis and rationale for selected methods of assessments will be described in the DMC charter and DMC SAP.

7.9. Study Termination

The study will end when all study treatments, study-specific assessments, and study data collection are completed.

This study may be terminated or suspended at any time by the sponsor. If the study is terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and the regulatory authorities. The IRB/EC should be promptly informed and provided the reason(s) for the termination or suspension by the Sponsor and by the Investigator/institution, as specified by the applicable regulatory requirement(s).

8. DESCRIPTION OF STUDY PROCEDURES

A detailed list of study procedures and schedules is presented in Appendix 1.

8.1. General Procedures

8.1.1. Informed Consent

Each subject's signature must be obtained on a written ICF that has been approved by an IRB, EC, or Ethical Review Board prior to any study-specific procedures being performed. The ICF must incorporate a Release of Medical Information that authorizes release of medical records to the trial Investigators, monitors, Sponsor and its designees, the Food and Drug Administration (FDA), or other regulatory authority. The ICF must be in a language fully comprehensible to the prospective subject. The consenting process must be documented in the medical chart and a signed copy of the ICF provided to the subject. The Investigator or an appropriate designee will obtain ICF from each subject prior to conducting any study-specific procedures.

8.1.2. Screening Period

Subjects will be screened during the 28-day period prior to C1D1 to ensure they meet the entry criteria for the study. During the screening period, the Investigator should carefully review each subject's medical history to ensure eligibility. All inclusion and exclusion criteria should be supported by corresponding documentation in the medical records, including a pathology report confirming the diagnosis of FL and MZL.

Bone marrow biopsies or aspirate performed as part of the subject's medical care that are within 12 weeks of C1D1 may be used for screening and eligibility determination, if necessary. Contrast-enhanced PET/CT or CT scans performed within 6 weeks of C1D1 may be used for screening and eligibility determination as long as they meet the minimum requirements per Lugano criteria (i.e., includes all appropriate anatomical areas of the body, a slice thickness ≤5 mm). This avoids unnecessary repeat tests and undue burden on subjects.

Eligibility must be verified by the Sponsor's medical monitor or designee (e.g., Contract Research Organization [CRO] Medical Monitor) prior to the initiation of dosing. Once the subject has been deemed eligible, the subject may be randomized and enrolled in the study. Dosing should be initiated within 3 days of randomization.

8.1.3. Randomization Assignment

After screening and meeting all eligibility criteria subjects will be randomized 1:1 based on stratification factors detailed in Section 4.1, using an Interactive Response Technology system into one of the two treatment arms of the study:

- Arm 1: R + zandelisib
- Arm 2: R-B or R-CHOP. Selection of therapy regimen will depend on prior therapy, specifically, if a subject had received anti-CD20 mAb in combination with B as a prior therapy, then the subject will receive R-CHOP if randomized to control arm. If a subject had received anti-CD20 mAb in combination with chemotherapy regimen (e.g., R-CHOP, R-CVP, FND-R, or similar regimen) or R-L, then the subject will receive R-B regimen if randomized to the control arm.

8.1.4. Treatment Period

Subjects meeting eligibility criteria will be randomized 1:1 to one of the two arms of the study and will start treatment on C1D1. It is important to assure that subjects continue to meet eligibility criteria prior to treatment initiation. Laboratory and general physical assessment of subjects to confirm eligibility should be performed prior to initial dosing on C1D1.

Study visits during the treatment period may be conducted remotely if a subject is unable to visit a study site due to COVID-19. In this situation, IP may be shipped directly to a subject if this is deemed appropriate by the PI and is acceptable per institutional guidelines and local regulations. If any study visits during the treatment period are conducted via telephone or a tele-health platform, this will be documented in the source and any missed visit procedures will be recorded as protocol deviations.

Refer to the Schedule of Assessments (Appendix 1) for details of treatment and timing of administration of various treatments.

8.1.5. Discontinuation of Treatment

Subjects will be discontinued from treatment for any of the following reasons:

- Progressive disease (PD)
- Completed treatment
- AE/SAE
- Start of non-protocol anti-cancer therapy
- Death
- Subject withdraws consent for further participation or follow-up
- Subject lost to follow-up

- Pregnancy
- Investigator decision

All efforts should be made to continue subject's participation in the clinical study with follow-up for efficacy and OS.

- Termination of study by the Sponsor
- Subjects who discontinue treatment for any reason except those who withdraw consent will be followed for safety as described in Sections 10.5 and 10.6. Subjects with PD are followed for survival and those who discontinue for reasons other than PD, are followed for response assessment until PD, then followed for survival. In case of termination of study, all follow-up will cease.
- Other

8.1.6. Early Discontinuation/Withdrawal of Subjects from Study

Subjects will be discontinued permanently from the study for any of the following reasons:

- Withdrawal of consent for further participation or follow-up
- Subject is lost to follow-up
- Termination of study by the Sponsor
- Death

8.1.7. End of Treatment Visit

The EOT visit will be performed within 7 days (±3 days) from the completion of the last dose or treatment discontinuation. The procedures to be performed at EOT visit are noted in the schedule of assessments (Appendix 1).

9. STUDY ASSESSMENTS

9.1. Assessment of Efficacy

Efficacy will be assessed based on radiological tumor evaluations of neck, chest, abdomen and pelvis by using IV (and oral, if indicated, per Imaging Manual) contrast-enhanced CT/MRI and/or PET-CT imaging modality. PET-CT imaging is the recommended method of assessment per Lugano Classification (Cheson 2014) for ^{18}F-fluorodeoxy glucose (FDG)-avid disease and will be performed at baseline, after 24 weeks (±1 week) on study, and for confirmation of CR/MCR (if initially assessed by CT scan only for FDG-avid disease). Contrast-enhanced CT scan or MRI scan to be done at screening and all other timepoints. Confirmation of PD can be done using CT or PET-CT scans. FDG-PET scan should be performed within 1 week (±3 days) of CT scan if it was not done at the same time. For subjects who have variable FDG-avid tumors, CT and/or MRI imaging can be used if PET-CT imaging is not optimal for assessment of disease status and response. To rule out a potential of false positive diagnosis of disease progression in ambiguous cases, it is highly recommended to repeat imaging assessments within 4–8 weeks after initial suspicion of PD. In addition, tumor biopsy may be performed to

confirm disease progression in existing or new lesions, or bone marrow involvement. The Investigator must review disease progression assessment with the Sponsor's medical monitor or designee.

During the treatment phase as well as during the active follow-up period, radiological tumor assessment by imaging scans will be performed every 12 weeks from C1D1 for the first 3 scans (weeks 12, 24 and 36 [±1 week]), followed by 3 scans every 16 weeks (weeks 52, 68 and 84 [±1 week]), a scan at week 104 (±1 week), and every 24 weeks (±2 weeks) thereafter.

Imaging scans will be evaluated locally at the study site. Scans will be submitted for an independent central review.

Response to treatment based on the Investigator evaluation of imaging scans will be the basis for subject management.

For the primary analysis, disease response assessment will be performed by an independent review blinded to the Investigator's assessment and treatment assignment.

Bone marrow biopsy and/or aspirate will be mandatory at screening if PET scan is not performed or is not evaluable. If the baseline biopsy is positive for lymphoma infiltration and PET scan is not utilized for response assessment, it will be mandatory to perform bone marrow biopsy again to confirm the first CR. Bone marrow biopsy is to include surgical pathology, immunohistochemistry, and flow cytometry as per institutional SOC. For MZL patients, if gastric involvement is suspected, an endoscopy at baseline should be obtained. At CR, endoscopy is required if not observed radiographically and the endoscopy was positive at baseline.

Response assessment will be performed based on modified Lugano Classification (Cheson 2014) described in Appendix 4, Table 3.

9.2. Assessment of Adverse Events

All AEs will be collected from start of treatment until 30 days after last dose of study drug or start of new anti-cancer treatment. For details of AE reporting see Section 10.

Any SAE due to protocol-mandated procedures will be collected from the time of informed consent. Other SAEs will be collected from the start of study drug administration. All SAEs will be reported and followed for up to 30 days after the last dose of study drug. After 30 days post last dose only SAEs deemed related to study drug will be reported to the Sponsor (see Section 10.6.3 for details).

9.3. Clinical Laboratory Tests

Laboratory tests listed on the Schedule of Assessments (Appendix 1) will be performed and analyzed at the investigative site's local laboratory and used in all safety analyses and response assessments (Appendix 4); PK samples discussed in Section 9.5 will be shipped to a central laboratory for analysis.

The following laboratory tests are to be performed (screening, Day 1 of the first 6 cycles, Day 1 from Cycle 7 to Cycle 10, Cycles 13, 17, 21, and 26 for Arm 1 subjects during zandelisib treatment period, and EOT, except as noted in the schedule of assessments (Appendix 1).

Hematology – Complete Blood Count	
• Hemoglobin (Hb) • Hematocrit (Hct) • Red blood cell (RBC) count • Mean corpuscular volume (MCV) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Platelet Count	• White blood cell (WBC) count and differential • Absolute neutrophil count • Absolute lymphocyte count • Absolute monocyte count • Absolute eosinophil count • Absolute basophil count
Chemistry – Metabolic Panel	
• Glucose • Calcium • Albumin • Total protein • Sodium • Potassium • Bicarbonate (total HCO_3) • Chloride • Urea or blood urea nitrogen (BUN) • Uric Acid	• Lactate dehydrogenase • Creatinine • Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Gamma-glutamyl transferase (GGT) • Total bilirubin • Direct bilirubin • Phosphorus
Coagulation	
• Activated partial thromboplastin time (aPTT) • Prothrombin time (PT)/ International Normalized Ratio (INR)	

Urinalysis	
• Specific Gravity • pH • Protein • Glucose • Ketones	• Blood (hemoglobin) • Leukocyte esterase • nitrite • Bilirubin • Urobilinogen • Microscopic examination [a]

[a] Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.

Urinalysis testing will be conducted using standard commercial test strips (urine dipstick). If urinalysis cannot be tested by dipstick, urinalysis for leukocytes can tested by microscopic examination.

Virus Tests at Screening and During the Study
• Hepatitis B Core antibody (HBc)[a] • Hepatitis B Surface Antigen (HBsAg)[a] • Hepatitis B PCR monitoring monthly while on treatment with rituximab or biosimilar monoclonal antibody is allowed if required per institutional standards • HCV antibody and HCV PCR testing • CMV serology and PCR[b]

[a] Hepatitis B PCR is required if hepatitis B core antibody and/or surface antigen is positive.
[b] CMV (PCR and antigen) testing may be performed at any time as clinically indicated.

- GFR calculation (screening only)
- Pregnancy test: hCG (screening, D1 of each cycle, and 30-day follow-up).

Unscheduled clinical laboratory assessments may be obtained at any time during the study to assess potential safety concerns.

9.4. Other Study Assessments

- Complete Physical Examination (Screening and EOT)
- Symptom-directed Physical Examination (Day 1 of the first 6 cycles, and Day 1 from Cycle 7 to Cycle 10, Cycles 13, 17, 21, and 26 for Arm 1 subjects during zandelisib treatment period)
- ECOG performance (screening, Day 1 of the first 6 cycles, and Day 1 from Cycle 7 to Cycle 10, Cycles 13, 17, 21, and 26 for Arm 1 subjects during zandelisib treatment period, EOT, and 30-day safety follow-up visit)
- Concomitant Medications (screening, Day 1 of the first 6 cycles, and Day 1 from Cycle 7 to Cycle 10, Cycles 13, 17, 21, and 26 for Arm 1 subjects during zandelisib treatment period), EOT, and the 30-day follow-up
- LVEF assessment by ECHO or MUGA per institutional standards for all subjects at baseline and as clinically indicated
- ECG assessment: Single tracing 12-lead ECGs performed at screening, pre-dose on Day 1 for the first 6 cycles of therapy, pre-dose Day 1 from Cycle 7 to Cycle 10, pre-dose Cycles 13, 17, 21, and 26 for Arm 1 subjects during zandelisib treatment period, at EOT visit, and as clinically indicated. On Day 1 of C1 and C3, additional ECGs will be performed 3-4 hours after zandelisib dose is taken.

9.5. Pharmacokinetics

PK sampling will only be performed in zandelisib arm according to the following schedule:

- C1D1: 2 samples – 2- and 4-hours (±30 min) post-dose of zandelisib
- C2D1: 1 sample – pre-dose (within 30-60 minutes)
- C3D1: 2 samples – pre-dose (within 30-60 minutes) and 3 hours (±30 min) post-dose of zandelisib
- C4D1: 1 sample – 3 hours (±30 min) post-dose of zandelisib

For better modeling of exposure-efficacy and exposure-safety, an accurate estimate of the time from drug intake to PK sample collection is needed. Collect accurate study drug dosing history (i.e., time of intake) within 48-72 hours (2-3 days) prior to days when PK samples are collected. The subject will be asked to record information on food intake on the day preceding and on the day of the visit on which blood samples are obtained for plasma concentrations measurement.

Detailed instructions on collection of plasma for determination of zandelisib PK will be provided in a study manual.

9.6. Patient Reported Outcomes

The effect of treatment on the physical symptoms of lymphoma is an important issue for patients; therefore, the collection of this information is a routine component in many protocols.

The main purpose of the symptom assessment in this study is to describe any differences between the treatment groups in (1) the time from randomization to deterioration in DRS-P of at least 3 points and (2) the time from randomization to improvement in DRS-P at least 3 points for subjects with a baseline DRS-P score 30 points or less. Physical symptoms of lymphoma will be assessed using the NCCN-FACT Lymphoma Symptom Index-18 (FLymSI-18), version 2 (Appendix 9) (NCCN-FACT: National Comprehensive Cancer Network - Functional Assessment of Cancer Therapy), and EQ-5D-3L (Appendix 10).

The FLymSI-18 is an instrument that was developed to assess symptoms of lymphoma, symptoms of treatment of lymphoma, and health related QoL of patients with lymphoma. The instrument was developed in accordance with the recent FDA 2009 PRO guidance (FDA 2009) for the development of instruments for symptom-specific patient-reported outcomes.

The instrument contains 18 items, each of which utilizes a Likert scale with 5 possible responses ranging from 0 “Not at all” to 4 “Very much”. Nine items reflect DRS-P, and the responses to the items are summed to calculate a DRS-P subscale score. Four items represent disease-related emotional symptoms (DRS-E), and the responses to those items will be used to calculate a DRS-E subscale score. Three items represent treatment side effects, and the responses to these items will be summed to calculate a treatment side-effect (TSE) subscale score. Finally, two items represent FWB, and responses to those items will be summed to calculate an FWB subscale score. The questionnaire allows for calculation of total score and four subscales: DRS-P, DRS-E, TSE and FWB.

In addition, EQ-5D-3L, utility score will be evaluated. EQ-5D-3L include 6 questions, where 5 questions measure functional and system attributes and one item. measures overall health assessment. This scoring system has been evaluated and endorsed as health utility standard by the European National Institute for Clinical Excellence and the US Agency for Healthcare Research and Quality (Askew 2011).

The EQ-5D-3L is a standardized instrument developed by the EuroQoL Group for use as a generic, preference-based measure of health outcome. It is applicable to a wide range of health conditions and treatments and is available in numerous languages. The EQ-5D-3L questionnaire captures 2 basic types of information, a descriptive “profile,” or “health state,” and an overall health rating using a visual analog scale. The health states include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which can be combined to produce a single weighted index score by applying coefficients from a validated value set. The visual analog scale (VAS) is a linear, thermometer like scale that respondents can use to rate their health status, with zero representing the worst imaginable health status and 100 the best (Scherber 2015). Estimated time to complete is approximately 8 minutes.

The FLymSI-18 and EQ-5D-3L and VAS will be administered according to the schedule specified in the study schedule of assessments (Appendix 1).

The FLymSI-18 and EQ-5D-3L and VAS should be completed at the start of the visit before the subject sees the physician and before any study-related procedure is conducted, so that any

interaction between the subject and physicians and knowledge of disease status does not influence the response to the FLymSI-18 and EQ-5D-3L questionnaires. Baseline assessment should occur during screening period prior to the time subject is randomized to treatment arm.

A PRO information sheet will be provided and completed by the study personnel at each visit at which the FLymSI-18 and EQ-5D-3L and VAS questionnaires are to be administered, regardless of whether or not the FLymSI-18 and EQ-5D-3L and VAS questionnaires are completed by the subject. This is to document information such as questionnaire completion, date of completion, and reasons for non-completed questionnaires.

9.6.1. Electronic Patient-reported Outcomes Evaluation

Electronic PRO (ePRO) devices will be implemented in the study. They will be used to complete the FLymSI-18 and EQ-5D-3L questionnaires. A Site Manual will be provided to sites to help them understand how the ePRO devices work and how to use them correctly.

9.7. Appropriateness of Measures

All study assessments have been well documented and are generally regarded as reliable, accurate, and relevant in this disease population. This includes health outcomes measures considered to be appropriate for evaluating changes in quality of life, global functioning, and disability.

9.8. Study Drug Administration

Study drugs will be administered according to the schedule shown in Appendix 1 (Study Drug Administration), detailed in Section 6.2.

10. ADVERSE EVENTS

An AE is any untoward medical event that occurs in a subject following the start of study drug administration, whether or not the event is considered drug-related. AEs can be:

- A pre-existing medical condition can be recorded as an AE if the condition worsens by at least one grade following the start of study drug administration and if the frequency, severity, or character of the condition worsens during the study. When recording on the eCRF it is important to capture applicable descriptors (e.g., more frequent arthritic pain).
- Disease-related out-of-range laboratory values will not be considered AEs/SAEs if there is no change from the screening laboratory values. Any deterioration in a laboratory value or other clinical test that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study product or deemed clinically significant by the Investigator will be considered an AE.

AEs will be recorded using the terminology defined in the NCI CTCAE v5.0.

A TEAE is defined as an AE starting or worsening in CTCAE grade after the first dose until 30 days after the last dose of study drug, or start of new anti-cancer therapy, whichever is earlier.

Death related to disease progression is not considered an AE. Signs and symptoms related to disease progression are not considered AEs. Anticipated fluctuations of pre-existing conditions,

including the disease under study that do not represent a clinically significant exacerbation or worsening, need not be considered AEs.

Only one AE term should be recorded in the event field on the AE eCRF if a specific AE is attributable to a primary diagnosis. Adverse events that are secondary to other events should be identified by their primary cause, with the exception of severe or serious secondary events. For example:

- If a subject initially had diarrhea and is subsequently diagnosed with colitis, these events should be consolidated to a single data point which would in this example be colitis
- If a subject had diarrhea that resulted in mild dehydration, only diarrhea should be reported in the eCRF
- If a subject who had diarrhea developed acute renal failure, both acute renal failure and diarrhea will be entered separately

For AEs, a diagnosis should be recorded on the AE eCRF rather than individual signs and symptoms (e.g., record only colitis rather than diarrhea, abdominal pain, decreased appetite). However, if a constellation of signs and symptoms cannot be medically characterized as a single diagnosis or syndrome, each individual event should be reported on the AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced on the AE eCRF based on a single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

10.1. Assessment of Severity

The term “severity” is used to describe the intensity of an AE. Severity will be graded according to NCI CTCAE v5.0.

10.2. Assessment of Causality

The Investigator is obligated to assess the relationship between study drug and the occurrence of each AE. The Investigator is to use his/her best medical judgement in determining the likely relationship of the AE to study drug. The relationship of an AE or SAE to study drug is to be classified as either ‘Related’ or ‘Not Related.’

10.3. Documenting Adverse Events

Adverse events should be documented in the source and entered on the subject’s CRF (or eCRF) with action taken with respect to the study drug and outcome.

10.4. Clinical Laboratory Changes

Clinical laboratory measurements are reported in the subject’s CRF (or eCRF). Laboratory abnormalities are to be reported as AEs only when deemed clinically significant, i.e., led to treatment interruption or discontinuation, associated with initiation of concomitant therapy or with hospitalization.

10.5. Adverse Event Follow-up

AEs occurring on study will be followed until resolution or return to baseline. AEs leading to discontinuation of study drug will be followed for minimum of 30 days after the last dose of study drug or until resolution, whichever comes first.

10.6. Serious Adverse Events

10.6.1. Definition

A SAE is any event that meets any of the following criteria:

- Adverse event resulting in death (Gr 5 toxicity)
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received any study drug.
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
    - Development of drug dependency or drug abuse

10.6.2. Definition of Terms

Life threatening: An AE is life threatening if the subject was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

If there is a question as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Disability/incapacitation: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

10.6.3. Reporting Serious Adverse Events

All SAEs must be reported to the Sponsor or Sponsor's designee (the CRO) within 24 hours of the Investigator becoming aware of the SAE.

To report an SAE, please refer to the applicable study manual or eCRF for SAE reporting instructions. For back up paper reporting, SAEs shall be reported to **MEI254808@Parexel.com**.

The 4 minimum criteria for a valid SAE report include:

- Study identifier
- Subject identifier
- Event term
- Study drug

All SAEs will be reported to the Sponsor's designee for up to 30 days after the last dose of study drug. After 30 days post last dose, only SAEs deemed related to study drug will be reported to the Sponsor's designee. The Investigator must report new significant follow-up information for these events to the Sponsor's designee immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant (requiring therapy or hospitalization) new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

All SAEs must be followed until resolution or death.

All SAEs also must be reported by each site to the appropriate IRB/EC in accordance with local requirements for reporting SAEs to their IRB/EC.

Reporting requirements will be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor.

All deaths should be recorded and reported to the Sponsor's designee. Disease progression, hospitalization to assess disease progression, and death due to disease progression as determined by the Investigator, are not considered SAEs. All other causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports for all deaths to the Sponsor's designee.

In the event of a medical emergency (requiring immediate attention regarding operation of the clinical study and/or the use of study product), study site staff will apply appropriate medical intervention according to current standards of care and will contact the Medical Monitor designee (e.g., CRO representative) for further consultation and guidance. The Sponsor will be reporting all AEs, SAEs, and expedited safety reports (suspected unexpected serious adverse reactions [SUSARs]) according to local regulatory requirements.

10.6.4. Overdose

Overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied in a single day. Symptomatic and non-symptomatic overdose must be reported in the drug administration form of eCRF. Any accidental or intentional overdose with zandelisib that is symptomatic only if fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hours) using the corresponding SAE form, and following the same process described for SAEs. If a study drug overdose occurs, patients should be clinically monitored as appropriate, managing symptoms and side effects that may occur. AEs associated with overdose should be reported on AE eCRF; overdose should be reported on drug administration eCRF.

Overdose is defined as administration of >120 mg of zandelisib in a single day because this dose is >2 times the planned starting dose of 60 mg QD.

The medical monitor must be contacted if a study drug overdose occurs.

10.6.5. Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported within 24 hours of learning of its occurrence. Pregnancy occurring up to 12 months after receiving the last dose of study drug must be reported.

Study drug must be discontinued in a subject who becomes pregnant. The pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Subjects must be followed at least 8 weeks after giving birth to a child.

Pregnancy in and of itself is not an AE; however, certain situations and/or outcomes of pregnancy can be (see below). Any pregnancies should be recorded on a Pregnancy Form and reported by the Investigator to the Sponsor or designee. Pregnancy follow-up should be recorded and should include an assessment of the possible relationship to the study product of any pregnancy outcome. Examples of pregnancy outcomes that are SAEs include reports of:

- Congenital anomalies or developmental delay in the fetus or the child
- Fetal death or spontaneous abortion
- Suspected adverse reactions in the neonate that are classified as serious

Pregnancy case information will be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

11. STATISTICS

Full details of all statistical methods will be included in the study Statistical Analysis Plan (SAP).

11.1. Study Populations

- The intent-to-treat (ITT) population is defined as all subjects who are randomized.
- Efficacy Evaluable (EE) Population includes all subjects who receive at least one dose of study drug and have at least one evaluable post-baseline response assessment.
- The safety population is defined as all subjects who were randomized and received at least 1 dose of any study drug.
- The PK population is defined as all subjects who had at least two PK samples collected and analyzed.
- Per Protocol (PP) Population will include all subjects who receive at least one dose of study drug, have at least one evaluable post-baseline response assessment, and do not have any major protocol deviation that affects the efficacy analysis during the study.

11.2. Sample Size and Power Considerations

It is estimated that approximately 534 subjects will be randomized into this study.

Assuming a hazard ratio (HR) of 0.70, approximately 330 PFS events at primary analysis are required to yield 87.5% power to detect superiority of zandelisib in combination with rituximab over standard immunochemotherapy.

An interim analysis is planned to take place after approximately 248 (75% of the 330 planned) IRRC assessed PFS events have occurred. If the statistical significance for PFS is not achieved at the interim analysis, the primary PFS analysis will be performed after IRRC assessed 330 PFS events have been observed.

Assuming that the median time to PFS for the control group is 24 months, the accrual duration is 36 months, and the annual dropout rate is 3%, a total sample size of 534 for the primary analysis with 28 months minimal follow-up time after last patient's enrollment is required.

11.3. General Considerations

Study disposition, subject demographic and baseline characteristic will be analyzed using the ITT population.

Efficacy analyses will be performed in the ITT population.

Selected key efficacy analyses will be performed in the EE population and PP population.

Safety analyses will be performed on the Safety Population.

PK analysis will be performed for all subjects in the PK population.

Unless otherwise noted, efficacy analyses will be performed by randomized treatment and safety data will be summarized by actual treatment group.

Because the objective of the study is to test the hypothesis that zandelisib in combination with rituximab has better clinical activity and risk/benefit profile compared to standard 2nd line immunochemotherapy (R-CHOP/R-B) in subjects with relapsed FL or MZL, all tests of treatment effects will be conducted as 1-sided test with family-wise type I error alpha controlled at 0.025.

Primary efficacy and safety analyses will be conducted comparing the 2 treatment groups . Exploratory analyses may be conducted to assess any clinically meaningful differences in treatment effect between zandelisib plus R vs. immunochemotherapy in each subgroup defined by prior therapy. If differences are present, sensitivity analyses will be performed to account for the heterogeneity in different subgroups in order to ensure the overall consistency and robustness of the primary analysis.

11.4. Statistical Methods

11.4.1. Primary Endpoint

Progression Free Survival (PFS)

The primary endpoint in this study is PFS as determined by the IRRC. PFS is defined as the time from randomization date until the date of disease progression, or death from any cause. Subjects who have not progressed and are still alive at the time of analysis will be censored at the last disease assessment date indicating the absence of progression.

The PFS analysis to test the superiority of zandelisib in combination with rituximab to standard immunochemotherapy in prolonging PFS time will use the log-rank test stratified by the following randomization factors:

- Prior treatment regimen: anti-CD20 mAb in combination with non-bendamustine chemotherapy regimen or R-L vs. anti-CD20 mAb with B
- Number of prior lines of therapy: 1 vs. >1
- NHL histology: FL vs. MZL
- Duration of treatment-free interval from the last lymphoma-directed therapy: ≤24 months vs. >24 months

The Kaplan-Meier (KM) method will be used to estimate the median PFS time with 95% CI. PFS rates at milestone time periods will be estimated for each treatment group.

The Cox proportional hazard model will be used to estimate the hazard ratio and corresponding 95% confidence interval with Wald's test p-value after stratifying for the same randomization factors.

Censoring rules for the primary endpoint, PFS, will be detailed in the SAP, following FDA guidance (FDA 2015, FDA 2018). In general, in the primary analysis, subjects will be censored at the date of last adequate assessment by the IRRC with evidence of no progression in the following situations:

- No progression nor death
- Discontinuation for any reason other than IRRC documented PD or death, including loss to follow-up, toxicity, withdrawal of consent, etc.
- Start of new anti-lymphoma treatment without evidence of IRRC documented PD
- Death or progression after two or more consecutive missed or inadequately scheduled tumor response assessments.

Supportive analyses will be conducted to evaluate the robustness of the primary analysis results, by considering all progressions and deaths as PFS events per the European Medicines Agency (EMA) guidance (EMA 2013), regardless of whether they occurred after initiating next anti-lymphoma treatment, after 2 or more consecutive missed scheduled assessments, or being reported as clinical (non-IRRC reviewed radiographic) progression.

Subjects who discontinue study treatment for any reason other than PD, start new anti-lymphoma therapy, or death, will be followed for PFS, unless the subject withdraws consent (Section 7.7). Every effort will be made to minimize missing data for PFS assessment. The follow-up time will be summarized by treatment arm, and the reason for censoring will be tabulated. Supportive analysis will be conducted to evaluate the robustness of the primary analysis results.

In addition, to account for violation of the assumption of proportional hazards and considering potential delayed treatment effect, sensitivity analysis may be conducted using weighted log-rank test which allocates appropriate weights to different time periods. The weight function will be pre-specified in the SAP.

A group-sequential design by including 1 interim analysis and 1 primary analysis is planned for this study. At each analysis, the hypothesis for the primary endpoint IRRC assessed PFS will be tested using a 1-sided with the overall family-wise error rate alpha of 0.025 controlled to adjust for multiplicity, utilizing Lan-DeMets O'Brien-Fleming approximation spending function.

The interim analysis is planned to take place after approximately 248 (75% of the 330 planned) IRRC assessed PFS events have occurred. If the statistical significance for PFS is not achieved at the interim analysis, the primary PFS analysis will be performed after 330 IRRC assessed PFS events have been observed. The alpha-spending for the interim and primary analyses will be 0.0096 and 0.0221 if the two analyses are performed at exactly 248 and 330 IRRC assessed PFS events, respectively. The actual boundary for the final analysis will be calculated based on the actual number of events observed at the time of each analysis using software that implements the alpha-spending scheme noted above (for example SAS or similar software).

Once statistical significance is successfully met at the interim analysis or the primary analysis, the study will be declared positive based on the primary endpoint of PFS, and the testing of selected secondary endpoints will proceed. Details of the testing strategy and control of family-wise error rate alpha at one-sided 0.025 will be provided in the SAP.

The requirement for unblinding the Sponsor at the interim analysis is described in Section 11.4.6.

11.4.2. Secondary Endpoints

Secondary endpoints include ORR as determined by the IRRC, CRR as determined by the IRRC, TTNT, PFS2, time to deterioration and time to improvement in the 9-item DRS-P subset of FlymSI-18, FWB score and change from baseline in the DRS-P and FWB subscales and total score of FlymSI-18 at specified study visits, change from baseline in EQ-5D-3L total score and VAS 18 at specified study visits, and OS.

If the statistical significance is successfully met at the interim analysis or the primary analysis, the testing of selected secondary endpoints (ORR, CRR, FlymSI-18 DRS-P, and OS) will proceed, by utilizing a hierarchical testing procedure to account for multiplicity and maintain the overall family-wise error rate alpha at 0.025 one-sided (detailed in the Statistical Analysis Plan).

Differences in ORR and CRR between treatment groups will be tested using Cochran-Mantel-Haenszel (CMH) method stratified by the randomization factors.

OS, and time to deterioration and time to improvement in the 9-item DRS-P subset of FlymSI-18 assessment will be tested between the two treatment groups using stratified log-rank test. The KM method will be used to estimate the median OS, and median time to deterioration and median time to improvement in the 9-item DRS-P subset of FlymSI-18 with 95% CI. OS rates will be estimated for each treatment group at Years 1, 2, 3, etc.

Change from baseline in the DRS-P and FWB subscales and the total score of FlympSI-18, and EQ-5D-3L total score and VAS at specified study visits will be compared between the two treatment groups using ANCOVA model.

Endpoint Definitions

Overall response rate

ORR is defined as the proportion of subjects who have a best overall response of CR or PR according to the Lugano Classification over the entire duration of the study, including the efficacy follow-up period.

Complete response rate

CRR is defined as the proportion of subjects who have a best overall response of CR during the study (i.e., up to time of analysis of PFS).

Time to Next Anti-lymphoma Treatment

TTNT is defined as the time from date of randomization to date of first documented administration of a new anti-lymphoma treatment (including but not limited to chemotherapy, radiotherapy, radioimmunotherapy or immunotherapy).

PFS on next anti-lymphoma treatment (PFS2)

PFS2 is defined as the time from the date of randomization to the first documented disease progression as reported by the investigator after the initiation of a new anti-lymphoma therapy, death from any cause, or start of a third anti-lymphoma therapy, whichever occurs first.

Overall survival

OS is defined as the time (in days) from randomization until death from any cause. For subjects alive at the time of analysis, they will be censored at the last documented alive date.

Time to deterioration in the 9-item DRS-P subset of FlymSI-18

Time to deterioration in the 9-item DRS-P subset of FlymSI-18 is defined as time from randomization to first decrease of DRS-P score from baseline of ≥3 points.

Sensitivity analysis may be conducted by using difference threshold other than 3 points on this endpoint, considering forthcoming research findings in external emerging data. Additional analyses are described in the Supplemental SAP for PRO analysis.

Time to improvement in the 9-item DRS-P subset of FlymSI-18

Time to improvement in the 9-item DRS-P subset of FlymSI-18 is defined as time from randomization to first increase of DRS-P score from baseline of ≥3 points in patients with a

baseline DRS-P score 30 or less (i.e., patients who still have room for improvement in symptoms).

Sensitivity analysis may be conducted by using different threshold on this endpoint, considering forthcoming research findings in external emerging data.

FWB score and Change from baseline in the FWB subscale and Total Score of FlymSI-18

Change from baseline in the DRS-P scale of FlymSI-18 is calculated as the FlymSI-18 DRS-P score at specific study visits minus the baseline score.

Change from baseline in the FWB scale of FlymSI-18 is calculated as the FlymSI-18 FWB score at specific study visits minus the baseline score.

Change from baseline in FlymSI-18 total score is calculated as the FlymSI-18 total score at specific study visits minus the baseline score.

Change from baseline in EQ-5D-3L Total Score and VAS Score

Change from baseline in EQ-5D-3L total score is calculated as the EQ-5D total score at specific study visits minus the baseline score.

Change from baseline in EQ-5D-3L VAS score is calculated as the EQ-5D-3L VAS score at specific study visits minus the baseline VAS score.

11.4.3. Exploratory Endpoints

CRR and ORR as determined by the Investigator, and ORR during the first 24 weeks on study determined by both the IRRC and the investigator will be analyzed using the CMH method stratified by the randomization factors.

PFS as determined by the Investigator, DOR and TTP as determined by both the IRRC and the Investigator, will be summarized by stratified log-rank test, KM method, and Cox proportional hazard model.

Additional PRO endpoints and analyses will be specified in the Supplemental SAP for PRO analysis.

The relationship of plasma zandelisib exposure to efficacy and safety will be explored by PK/PD modeling.

ORR at Week 24

ORR at Week 24 is defined as the proportion of subjects who have a response of CR or PR according to the Lugano Classification up to the Week 24 assessment.

Duration of Response

DOR is defined as the time from first observed tumor response (CR, PR) until PD, or death from any cause. Subjects without PD or death at the time of analysis will be censored at the date of their last documented tumor assessment. DOR will only be analyzed for subjects with at least one CR or PR.

Time to Progression

TTP is defined as the time from randomization to PD. TTP does not include deaths. Analyses will be performed using both PD as assessed by the IRRC and the Investigator.

Zandelisib Area Under the Curve (AUC)

Zandelisib exposure will be estimated by determination of AUC by population PK method and the relationship between exposure and efficacy and exposure and safety will be assessed. The results of exposure-response assessments will be presented in a separate report.

11.4.4. Analysis of Safety

All safety summaries and analyses will be based on the Safety Population, defined as all randomized subjects receiving at least 1 dose of any study drug. Safety analyses will be performed by actual treatment group. Overall summary of safety will include but not limited to the following analyses:

- TEAEs, including severity and possible relationship to study drug and/or study treatment
- AESIs
- Treatment-emergent SAEs
- Discontinuations from study treatment due to AEs
- Treatment-emergent changes in laboratory values

Time to AESIs will be calculated from randomization date to first occurrence of AESI, utilizing KM methodology.

Due to likely imbalance of treatment duration between 2 treatment arms, exposure-adjusted analysis may be performed for safety endpoints. The exposure-adjusted event rate is defined as the total number of specified events over the total exposure duration.

Clinical laboratory values will be graded according to NCI CTCAE Version 5.0 for applicable tests. Shift from baseline to worst severity grade observed during the treatment will be displayed by treatment group.

Vital signs abnormality will be presented by treatment group. Normal ranges of vital signs will be defined in the SAP.

11.4.5. Study Variables

All study variables, e.g., demographic and baseline characteristics, previous therapy, concomitant medications, etc., will be summarized for the ITT population by treatment arm.

Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages. Time-to-event variables will be summarized using KM methods (median, 95% CI, number of events, number censored, KM figures). Data listings will be created to support data review.

11.4.6. Interim Analysis

The interim analysis is planned to take place after approximately 248 (75% of the 330 planned) IRRC assessed PFS events have occurred. The objective of this interim analysis is to examine the efficacy to allow an early declaration of success. If the statistical significance for PFS is not achieved at the interim analysis, the primary PFS analysis will be performed after IRRC assessed 330 PFS events have been observed. The alpha-spending for the interim and primary analyses will be 0.0096 and 0.0221, respectively. The interim PFS analysis will be performed by the DMC.

If statistical significance is successfully met at the interim analysis or the final analysis, the study will be declared positive based on the primary endpoint of PFS, and the testing of selected secondary endpoints will proceed, by utilizing a hierarchical testing procedure to account for multiplicity and maintain the overall family-wise error rate alpha at 0.025 at one-sided (detailed in the Statistical Analysis Plan).

Based on our estimated recruitment rate and PFS event rates, the planned interim analysis is projected to occur after all subjects have been enrolled and a projected median time on study of approximately 30 months (range: 12-48). Also, it is anticipated that all subjects randomized to the control arm would have completed their treatment regimen at the planned interim analysis.

12. ETHICS AND GOVERNANCE

12.1. Good Clinical Practice

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and the Investigator abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g., IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the Investigator may not modify or alter the procedures described in this protocol.

All the changes to the study protocol will be done through protocol amendment. The Investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the Investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 7.9.

12.1.1. Study Personnel

The list of all study personnel will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the Principal Investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The Principal Investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g., health authority, ethics committee, sponsor) before subject recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the Principal Investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the Sponsor's study file.

12.2. Financial Disclosure

Investigators must maintain compliance with the current country-specific guidelines and regulations concerning financial disclosure.

12.3. Institutional Review Board/Independent Ethics Committee

Approval of this study will be obtained from an IRB/EC prior to enrolling subjects and will be reviewed and approved on an annual basis by the IRBs/ECs representing the participating institutions. Such IRBs/ECs must be appropriately constituted and meet all requirements as described in Title 21, Part 56 of the Code of Federal Regulations, and any applicable country and/or regional requirements. The review must include the protocol, subject recruitment materials, the IB, the ICF, and any other study-specific material that will be provided to subjects (including study product compliance diaries). A copy of the letter or notice of approval from the IRB/EC must be received by the Sponsor or designee prior to shipment of drug supplies to the Investigator. The IRB/EC membership list or Federal Wide Assurance number must be submitted to the Sponsor or designee with the written IRB approval, and lists must be updated, if applicable.

12.4. Informed Consent

All relevant information on the study will be summarized in an integrated information sheet for trial subjects and the ICF provided by the sponsor or the study center. A sample information sheet for subjects and ICF is provided as a document separate to this protocol.

Based on this information sheet, the Investigator or designee will explain all relevant aspects of the study to each subject/legal representative or proxy consenter (if the subject is under legal protection), prior to his/her entry into the study (i.e., before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The Investigator will also mention that written approval of the IRB/IEC has been obtained.

Each subject/legal representative or proxy consenter will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's consent covers end-of-study examinations as specified in the visit description described in Section 8.1.7 to be conducted after withdrawal of consent.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g., image reading); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The subject has the right to object to the generation and processing of this post-withdrawal data. For this, the subject's oral objection may be documented in the subject's source data. Each subject/legal representative or proxy consenter will have ample time and opportunity to ask questions.

Only if the subject/legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the Investigator will personally sign and date the form. The subject/legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the subject's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures. Certain results from diagnostic testing performed as part of the standard of practice prior to the informed consent date and time may be used to fulfill screening criteria. This includes results from tumor scans (CT/MRI and/or PET-CT), bone marrow sample, HIV testing which may also be used provided that they fall into the protocol-specified time window. Tumor scans must also meet the quality standards of the Imaging Manual.

If the subject is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the Sponsor and the Investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

For adults under legal protection, consent shall be given by the legal guardian(s). The consent of an adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

The ICF and any other written information provided to subjects, legal representatives, or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and/or the written informed consent form. The Investigator will inform the subject/legal representative or proxy consenter of changes in a

timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB's approval / favorable opinion in advance of use.

12.5. Records Management

Study data will be stored and transmitted using electronic case report forms (eCRFs), using a system determined by the Sponsor. The Sponsor or designee will provide secure access and eCRF completion guidelines, as well as study-specific training, as needed, to each site. The eCRFs should be completed as soon as possible after each study visit or contact.

12.6. Source Documentation

Data recorded in the eCRFs must be supported by information captured in source documents, which must be available at all times for inspection by authorized representatives of the Sponsor, the FDA, or other regulatory agencies.

12.7. Study Files and Record Retention

The Investigator will retain the records of the study for two (2) years following the last date that a marketing application for zandelisib is approved in any ICH region, or if marketing approval is not obtained, for two (2) years after the Investigational New Drug (IND) application for zandelisib has been closed in the US or until there are no pending contemplated marketing applications in an ICH region. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Sponsor will notify Investigators when study records retention is no longer required.

The site will retain copies of all versions of the protocol, IB, correspondence with the IRB/EC (including submission and approval letters, approved ICFs), curricula vitae and medical licenses of the Investigator and sub-Investigator(s), Form FDA 1572 or similar forms, correspondence, laboratory documentation (including accreditation documents, reference ranges, and manuals), Delegation of Authority Log (documenting procedures delegated by the Investigator to be performed by study staff), IP study product records (including receipt, storage, dispensing, and return records), source documents (including clinic charts, medical records, laboratory results, radiographic reports), training records, screening/enrollment logs, monitoring visit logs, and study procedure manuals.

Should the Investigator leave the institution or otherwise withdraw from the investigation or should there be any changes in the archival arrangements for the study records, the Sponsor will be notified. The Sponsor will be notified of the identity of any individual assuming responsibility for maintaining the study records and the location of their storage. If no other individual at the investigational site is willing to assume this responsibility, the Sponsor will assume responsibility for maintaining the study records.

12.8. Auditing and Monitoring

A Sponsor-designated study monitor will conduct a site initiation visit (SIV) prior to the first subject signing the ICF. The SIV may be conducted in person or as a 'virtual' visit. The study monitor will conduct routine monitoring visits at periodic intervals during the course of the

study, including a visit shortly after enrollment of the first subject, as per the study-specific monitoring plan. Monitoring visits may be conducted in person or remotely.

The primary purposes of the site visits are to:

1. Ensure the safety and welfare of study subjects
2. Ensure the accuracy and completeness of eCRF entries, as verified against the source documentation
3. Verify that the conduct of the study adheres to the written protocol approved by the IRB/EC, as well as regulatory requirements
4. Verify that regulatory and other study-specific documentation is maintained and current
5. Perform study drug product accountability (reconcile study product receipt, storage, dispensing, and return records)

Site audits and vendor audits may be performed by the Sponsor at any time during the study and at the time of site or vendor closure to ensure adherence to the protocol and GCP quality standards.

12.9. Quality Assurance

Quality assurance is maintained using risk-based approaches and is documented in written procedures that ensure trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). Written agreements are established with vendors, investigators, and CROs, to ensure proper execution of trials and allow direct access to all trial-related sites, source data/documents, and reports to ensure oversight of monitoring, periodic auditing, and inspections by applicable regulatory authorities. Quality checks are applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

12.10. Amendments

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the Investigator must await approval before implementing the changes. The Sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the Investigator, and/or the Sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

12.11. Study Discontinuation

Both the Sponsor, and the Principal Investigator reserve the right to terminate the study at the Investigator's site at any time. Should this be necessary, the Sponsor, or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the IRB/IEC of the same. In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

12.12. Confidentiality

The Principal Investigator and designees, employees, and agents involved with this study will comply with relevant local, state, federal and regional laws, as applicable, relating to the confidentiality, privacy, and security of subjects' health information.

Subject names will not be supplied to the Sponsor. Only the subject number will be recorded in the CRF, and if the subject's name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the Sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

12.13. Publication Policy

The Sponsor will make the information regarding the study protocol and results publicly available on the internet at www.clinicaltrials.gov and the relevant European competent authorities in the European Clinical Trials register (https://www.clinicaltrialsregister.eu/).

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the Sponsor will fulfill its obligations according to all applicable laws and regulations. The Sponsor is interested in the publication of the results of every study it performs.

The Sponsor recognizes the right of the Investigator to publish the results upon completion of the study. However, the Investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the Sponsor on the intended publication manuscript before its submission. To this end, the Investigator must send a draft of the publication manuscript to the Sponsor within a time period specified in the contract. The Sponsor will review the manuscript promptly and will discuss its content with the Investigator to reach a mutually agreeable final manuscript.

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14. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment/Procedure	Screening [b]	Cycle 1			Cycle 2 to Cycle 6		Cycle 7 - 10, Cycles 13, 17, 21 and 26	End of Treatment (EOT) [c]	30-Day Safety Follow-up [d]	Post-Treatment Long-Term Follow-up [e]
Cycle Day(s) [a]	**-28 to -1**	**1**	**2**	**8, 15, 22**	**1**	**2**	**1**			
Screening and Enrollment										
Eligibility/ICF	X									
Medical history	X									
Pregnancy test [f]	X	X			X		X[f]		X	
Randomization	X									
Vital signs/Weight [g]	X	X	X [g]	X	X	X[g]	X	X	X	
Hepatitis B and C testing [h]	X	X			X			X		
GFR calculation	X									
Complete Physical Examination [i]	X							X		
Symptom Directed Physical Examination [j]		X			X		X			
ECOG performance status	X	X			X		X	X	X	
Adverse events [k]	X	X	X	X	X	X	X	X	X	
Concomitant medication [l]	X	X			X		X	X	X	
Compliance Diary [m]		X			X		X	X		
12-lead ECG [n]	X	X			X		X [n]	X		
LVEF by ECHO or MUGA [o]	X									
CBC with differential [p]	X	X			X		X [p]	X	X	
Serum chemistry [q]	X	X			X		X [q]	X	X	
Coagulation [r]	X	X						X		
CMV testing [s]	X	X			X [s]		X [s]			
Urinalysis [t]	X	X			X		X [t]	X		
Dispense study drug [u]		X			X		X			

APPENDIX 1. SCHEDULE OF ASSESSMENTS (CONTINUED)

Assessment/Procedure	Screening [b]	Cycle 1			Cycle 2 to Cycle 6		Cycle 7 - 10, Cycles 13, 17, 21 and 26	End of Treatment (EOT) [c]	30-Day Safety Follow-up [d]	Post-Treatment Long-Term Follow-up [e]
Cycle Day(s) [a]	**-28 to -1**	**1**	**2**	**8, 15, 22**	**1**	**2**	**1**			
PRO Questionnaires (FLymSI-18) and EQ-5D-3L and VAS [v]	X	X [v]			X [v]		X [v]	X [v]	X [v]	
PK Sampling [w]		X [w]			X [w]					
Survival follow-up [x]										X

Efficacy Assessments									
Response Assessment [y]	**Screening**	**Week 12 (±1 week)**	**Week 24 (±1 week)**	**Week 36 (±1 week)**	**Week 52 (±1 week)**	**Week 68 (±1 week)**	**Week 84 (±1 week)**	**Week 104 (±1 week)**	**Every 24 weeks thereafter (±2 weeks)**
CT/PET/MRI [y,z]	X	X	X	X	X	X	X	X	X
Bone marrow biopsy/aspirate [aa]	X								
Endoscopy with biopsy [bb]	X								

APPENDIX 1. SCHEDULE OF ASSESSMENTS (CONTINUED)

Study Drug Administration												
Zandelisib+ R (q4w) 28-day cycle [cc]	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6 to 26**	
Rituximab IV 375 mg/m^2 (maximum 6 cycles)	D1, D8, D15, D22				D1		D1		D1		C6 D1 only	
Zandelisib 60 mg QD orally	Every day				D1 to D7 then 21 days off		D1 to D7 then 21 days off		D1 to D7 then 21 days off		D1 to D7 then 21 days off	
R-B (q4w) 28-day cycle [dd]	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**	
Rituximab IV 375 mg/m^2	D1		D1		D1		D1		D1		D1	
Bendamustine IV 90 mg/m^2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2
R-CHOP (q3w) 21-day cycle [ee]	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**	
Rituximab IV 375 mg/m^2	D1		D1		D1		D1		D1		D1	
Cyclophosphamide IV 750 mg/m^2	D1		D1		D1		D1		D1		D1	
Doxorubicin IV 50 mg/m^2	D1		D1		D1		D1		D1		D1	
Vincristine IV 1.4 mg/m^2	D1		D1		D1		D1		D1		D1	
Prednisone 100 mg daily orally	D1 to D5		D1 to D5		D1 to D5		D1 to D5		D1 to D5		D1 to D5	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; C = cycle; CBC = complete blood count; CMV = cytomegalovirus; HCO_3 = Bicarbonate dioxide; CT = computed tomography; D = day; ECG = electrocardiogram; ECHO = echocardiography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FDG = ^{18}F-fluorodeoxy glucose; GFR = glomerular filtration rate; GGT = gamma-glutamyl transferase; Hct = hematocrit; Hb = hemoglobin; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; HrRt = heart rate; ICF = informed consent form; INR = international normalized ratio; IV = intravenous; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; MCH = mean corpuscular hemoglobin; MCR = metabolic complete response; MDP = metabolic disease progression; MUGA = multigated acquisition scan; PCR = polymerase chain

reaction; PK = pharmacokinetic; PRO = patient reported outcome; PT = prothrombin time; RBC = red blood cell; SOC = standard of care; TTNT = time to next anti-lymphoma treatment; WBC = white blood cell

a. **Study Assessment Day(s)** –Visits will occur based on assigned treatment schedule. For assessment timing, a window relative to Cycle 1 Day 1 is allowed starting on Cycle 2. If a cycle is missed, it will be skipped to the next cycle. For Cycles 2 through 26, the allowable window is ±7 days. For post treatment long term follow-up, the allowable window is ±1 month for each clinic visit and its associated assessments.

b. **Screening** – Screening assessments are to be performed within 28 days prior to randomization. After confirmation of eligibility, subjects should be treated within 3 days of randomization. It is important to assure that subjects continue to meet eligibility criteria prior to treatment initiation. Laboratory and general physical assessment of subjects to confirm eligibility should be performed prior to initial dosing on C1D1. Laboratory assessments need not be repeated on C1D1 if performed within 3 days prior. Physical examination need not be repeated on C1D1 if performed within 7 days prior. Some tests performed prior to obtaining ICF (e.g., CT scan, bone marrow biopsy/aspirate) may not need to be repeated for the study as long as they were performed within the allowed screening window.

c. **EOT visit** – Performed within 7 days (±3 days) from the last dose or treatment discontinuation.

d. **30-Day safety follow-up visit** – Visit will be completed 30 (±3) days post last dose of study drug (or prior to starting a new anti-cancer treatment if urgent treatment is required) or from study drug discontinuation.

e. **Post-treatment long-term follow-up procedures** - During the treatment phase as well as during the active follow-up period, subjects will be followed for response assessments every 12 weeks for the first 3 scans (weeks 12, 24, and 36 [±1 week]), followed by 3 scans every 16 weeks (weeks 52, 68, and 84 [±1 week]), a scan at week 104 (±1 week), and every 24 weeks (±2 weeks) thereafter. Survival follow up will be every 3 months for 5 years after the last patient's randomization.

f. **Pregnancy test** – The screening serum pregnancy test for human chorionic gonadotropin (hCG) in females of childbearing potential must be completed within 7 days prior to C1D1. A urine or serum pregnancy test must also be performed on C1D1. For women of childbearing potential, serum or urine pregnancy test will be conducted on D1 of every dosing cycle (when a subject has a visit) and 30 days after discontinuation of dosing.

g. Day 2 vital signs and weight to be recorded for R-B arm only

h. **Hepatitis B and C testing** – Hepatitis B core antibody, Hepatitis B surface antigen and hepatitis C antibody are required. Hepatitis B PCR is required if hepatitis B core antibody and/or surface antigen is positive. Hepatitis B PCR monitoring monthly while on treatment with rituximab or biosimilar monoclonal antibody is allowed if required per institutional standards. Post-treatment monitoring is per institutional standards. Hepatitis C PCR is required if hepatitis C antibody is positive. Prophylactic therapy for hepatitis is recommended per institutional standards.

i. **Complete physical exam** – Only at screening and EOT. If physical exam is performed >7 days prior to C1D1 it must be repeated on C1D1.

j. **Brief symptom-directed physical exam** – Performed on Day 1 of Cycles 1 to 6 only as clinically indicated, based on interim history. For zandelisib arm, Day 1 of Cycles 1 to 6, and then every 2 to 3 months (when a subject has a visit).

k. **Adverse events** – AEs will be collected continuously from start of dosing until the 30-Day safety follow-up visit or start of new anti-cancer treatment, whichever occurs first (AEs that may be related to screening procedures will be collected from baseline). SAEs will be followed until resolution. All SAEs must be reported and followed for 30 days after the last dose of study drug. After 30 days, only SAEs deemed related to study drug will be reported to the Sponsor. AEs leading to discontinuation of study drug will be followed for minimum of 30 days after the last dose of study drug or until resolution, whichever comes first. AEs will be assessed at all site visits.

l. **Concomitant medications** – Recorded from Screening until the 30-Day Safety Follow-up visit, or start of new anti-cancer treatment, whichever occurs first.

m. **Issue and review compliance diary for zandelisib** – Compliance diary to record daily study drug administration will be issued on Day 1 of each cycle

(when a subject has a visit). Returned diaries are to be assessed for study product compliance. New compliance diary is to be issued with each dispensing of zandelisib.

n. **ECG** – Single tracing 12-lead ECGs performed at screening, pre-dose on Day 1 for the first 6 cycles, pre-dose on Day 1 from Cycle 7 to Cycle 10, pre-dose Cycles 13, 17, 21 and 26 for Arm 1 subjects during zandelisib treatment period, at EOT visit, and as clinically indicated. On Day 1 of C1 and C3, additional ECGs will be performed 3-4 hours after zandelisib dose is taken.

o. **LVEF** – to be measured using ECHO or MUGA at screening and at any time if clinically indicated. The Investigator must discuss decisions leading to treatment changes, interruptions due to LVEF abnormalities with the Sponsor's medical monitor or designee.

p. **CBC with differential** – WBC, ANC, RBC, HGB, HcT, lymphocytes, eosinophils, monocytes, basophils, platelets, MCV, MCH, and MCHC. Screening labs must be repeated if performed >7 days prior to C1D1. If screening labs are drawn within 3 days of C1D1, they do not need to be repeated on C1D1 . During C7 to C26, to be done on D1 of C7-C10, C13 C17, C21, C26, and EOT.

q. **Serum chemistry** – Glucose, BUN or urea, uric acid, creatinine, sodium, potassium, chloride, calcium, bicarbonate, ALP, AST, ALT, GGT, LDH, total bilirubin, direct bilirubin, total protein, phosphorous, and albumin. Screening labs must be repeated if performed >7 days prior to C1D1. Need not be performed on C1D1 if screening labs were done within 3 days of C1D1. During C7 to C26, to be done on D1 of C7-C10, C13 C17, C21, C26, and EOT.

r. **Coagulation** – aPTT, PT, INR, to be performed at screening, EOT, and as clinically indicated per the institutional standard of care. Screening labs must be repeated if performed >7 days prior to C1D1. Need not be performed on C1D1 if screening labs were done within 3 days of C1D1.

s. **CMV testing –** At screening, C1D1, C3D1, C6D1, and D1 of Cycles 9, 13, 17, 21, 26 for Arm 1 subjects during zandelisib treatment period until subject discontinues treatment, and as clinically indicated. CMV testing at screening must include CMV serology (IgG, IgM) and CMV DNA PCR testing. Subject must have a negative result for CMV DNA PCR, which is below the limit of quantitation at screening to be eligible for the study. Prophylactic therapy for CMV is allowed.

t. **Urinalysis** – Dipstick or urine test (pH, specific gravity, glucose, ketones, blood, leukocyte esterase, bilirubin, urobilinogen, protein, and microscopic examination). Screening labs must be repeated if performed >7 days prior to C1D1. Need not be performed on C1D1 if screening labs were done within 3 days of C1D1. During C7 to C26, to be done on D1 of C7-C10, C13 C17, C21, C26, and EOT.

u. **Dispense study drug** – Study drug is to be taken orally once a day on an empty stomach at least 1 hour prior to food at the same time each morning. On days of PK sampling, subjects are instructed to not take study drug at home; on these days study drug will be administered at the clinic in relation to the timing of the PK sample collection.

v. **Patient Reported Outcome (PRO) (FlymSI 18 and EQ-5D-3L and VAS)** - Baseline assessment should occur during screening period prior to the time subject is assigned to treatment arm. Subjects in both arms will complete the questionnaires on D1 of every cycle of therapy during first 6 cycles of therapy. After first 6 months of therapy, subjects will complete the FLymSI-18 and EQ-5D-3L and VAS questionnaires at the same visits as follow-up tumor assessments: week 36, 52, 68, 84, 104 and then every 24 weeks until response assessment is performed. PRO assessments also will be done at the EOT, and at the 30-day safety follow-up visit for subjects in each treatment arm. (for more detail see Section 9.6).

w. **PK sampling** – PK samples are to be collected only in the zandelisib arm:

- C1D1: 2 samples – 2- and 4-hours (±30 min) post-dose of zandelisib
- C2D1: 1 sample – pre-dose (within 30-60 minutes)
- C3D1: 2 samples – pre-dose (within 30-60 minutes) and 3 hours (±30 min) post-dose of zandelisib
- C4D1: 1 sample – 3 hours (±30 min) post-dose of zandelisib

Note: On days of PK sampling when a pre-dose sample is drawn, subjects are instructed to not take study drug until after pre-dose PK sample is drawn.

x. After treatment discontinuation, all subjects will be followed for OS every 3 months for 5 years after the last subject's randomization, except for subjects who withdraw consent. Subjects or their healthcare providers will be contacted either in person, by telephone, or e-mail. During OS follow-up, TTNT will be recorded.

y. **Response assessment (CT and PET scans) –** Response assessment will be performed every 12 weeks (from C1D1) for the first 3 scans (weeks 12, 24 and 36 [±1 week]), followed by 3 scans every 16 weeks (weeks 52, 68 and 84 [±1 week]), a scan at week 104 (±1 week), and every 24 weeks (±2 weeks) thereafter.

z. **PET/CT/MRI** – PET/CT at baseline, week 12, week 24 (after completion of treatment in control arm and initial 6 cycles of therapy in study arm), and for confirmation of CR/MCR (if initially assessed by CT scan only for FDG-avid disease). FDG-PET scan should be performed within 1 week (±3 days) of CT scan if it was not done at the same time. Contrast-enhanced CT scan to be done at screening and all other timepoints. PET and/or CT scan can be used to confirm PD. Scans will be evaluated locally at the study site for response assessment. Scans will be submitted for an independent central review. If a subject is intolerant to contrast agent then MRI can be used consistently throughout the study for that subject.

aa. **Bone marrow biopsy** – Bone marrow biopsy/aspirate will be mandatory at screening and to confirm CR if PET scan is not performed or is not evaluable and the patient had bone marrow involvement at screening.

bb. For subjects with MZL having gastric involvement an endoscopy at baseline should be obtained. At CR, endoscopy is required if not observed radiographically and the endoscopy was positive at baseline.

cc. **Zandelisib + R:**

- Zandelisib 60 mg QD orally for the first 2 cycles of therapy (56 days), then 60 mg for 7 days followed by 21 days off treatment in every 28-day cycle.
- Rituximab IV 375 mg/m^2 on D1, D8, D15 and D22 of C1 and then on D1 of C3, C4, C5, and C6 for up to a total of 8 doses in 6 cycles. Rituximab infusion should start approximately one hour after zandelisib on clinic days, and on PK collection days infusion can be prior to the post dose PK collection for zandelisib.

dd. **R-B** will be administered every 4 weeks (q4w) as follows: rituximab IV 375 mg/m^2 body surface on Day 1 (D1) and B administered IV 90 mg/m^2 body surface on D1 and D2 of each cycle for 6 cycles

ee. **R-CHOP** will be administered once every 3 weeks (q3w) as follows: rituximab IV 375 mg/m^2 body surface on D1; cyclophosphamide IV 750 mg/m^2 body surface on D1; doxorubicin IV 50 mg/m^2 body surface on D1; Vincristine IV 1.4 mg/m^2 body surface (maximum dose 2.0 mg) on D1, prednisone 100 mg daily orally (PO) from D1 to D5 of each cycle for 6 cycles

APPENDIX 2. COCKCROFT-GAULT EQUATION FOR ESTIMATED CREATININE CLEARANCE

Estimate the subject's creatinine clearance using the serum creatinine value provided by the local laboratory, actual body weight, and the appropriate Cockcroft-Gault formula (if necessary, convert serum creatinine values from µmol/L to mg/dL by dividing by 88.4; for example, 100 µmol/L divided by 88.4 equals 1.131 mg/dL):

Estimated Creatinine Clearance (C_{Cr}) by the Cockcroft-Gault Equation:

$$C_{Cr} = \frac{(140 - age\ in\ years)\ \times\ (weight\ in\ kg)}{72\ \times (serum\ creatinine\ in\ mg/dL)} \times (0.85\ if\ female)$$

Abbreviation: C_{Cr} = creatinine clearance (in mL/minute)

APPENDIX 3. GUIDELINES FOR WOMEN OF CHILDBEARING POTENTIAL AND FERTILE MALE SUBJECTS

For females of childbearing potential, defined as all premenopausal women capable of becoming pregnant, must agree to use a medically effective contraceptive method (has a failure rate of <1% per year) starting with the first dose of study drug through 12 months after the last dose of study drug.

Postmenopausal women are defined as no menstrual periods for at least 12 consecutive months OR FSH greater than 40 IU/L on at least two occasions.

Fertile male subjects, defined as all males physiologically capable of conceiving offspring who are sexually active with a female partner of child-bearing potential, must agree to use a medically effective contraceptive method and to refrain from donating sperm for at least 6 months after the last dose of study drugs, CHOP, zandelisib or bendamustine, and 12 months after the last dose of rituximab, whichever is longest.

Men/women should also seek advice about sperm/oocyte preservation before treatment if desired, because of possible irreversible infertility due to study drugs.

Acceptable Contraception Methods:

Highly effective contraception is defined as:

True Abstinence	When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
Sterilization	When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
Male Partner Sterilization	When the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

Use of a combination of any two of the following (one from a + one from b):	a. Placement of an intrauterine device (IUD) or intrauterine system or established use of oral, injected, or implanted hormonal methods of contraception b. Barrier methods of contraception: Male Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Unacceptable Contraception Methods:

Unacceptable contraception methods include:

c. IUD progesterone T
d. Female condom
e. Natural family planning (rhythm method) or breastfeeding
f. Fertility awareness
g. Withdrawal
h. Cervical shield

Pregnancy in a subject on study treatment must be reported within 24 hours of learning of its occurrence. Pregnancy occurring up to 12 months after receiving the last dose of study drug must be reported to the sponsor.

APPENDIX 4. LYMPHOMA RESPONSE CRITERIA

SELECTION OF TARGET LESIONS

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

1. Clearly measurable in two diameters (longest diameter and shortest diameter) at baseline
    a. All nodal lesions must measure >1.5 cm in longest diameter regardless of short axis measurement
    b. All measurable extranodal lesions should have a longest tumor diameter >1.0 cm
2. All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-target lesions
3. If possible, the lesions should be from disparate regions of the body
4. Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

SELECTION OF NON-TARGET LESIONS

Non-target lesions will be qualitatively assessed at each subsequent timepoint. All of the sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that were not chosen as target lesions.

Examples of non-target lesions include:

1. All bone lesions, irrespective of the modality used to assess them
2. Lymphangitis of the skin or lung
3. Cystic lesions
4. Irradiated lesions
5. Measurable lesions beyond the maximum number of six
6. Groups of lesions that are small and numerous
7. Pleural/pericardial effusions and/or ascites
    a. Effusions, ascites, or other fluid collections will be followed as non-target lesions
    b. At each assessment point, radiologists will check for the presence or absence of effusions/ascites. If there is a significant volume increase in the absence of a benign etiology, progression can be assessed
    c. Significant new effusions, ascites, or other fluid collections, which are radiographically suggestive of malignancy should be recorded as new lesions and should be assessed

Response should be determined on the basis of radiographic and clinical evidence of disease. For subjects who achieve a CR by CT criteria, an FDG-PET will be performed. FDG-PET scan should be performed within 1 week (±3 days) of CT scan if they were not done at the same time. Assessment by FDG-PET should follow the criteria described by Cheson 2014 which is summarized in Table 3.

Overall response should be determined based upon the Modified Lugano response criteria (Table 3).

SPLEEN INVOLVEMENT

Splenomegaly defined as enlargement of spleen measured by vertical (cranial or caudal) length of >13 cm. Measurable lesions in spleen defined as extra-nodal lesions can be selected and followed as target, non-target or new lesions.

LIVER INVOLVEMENT

CT measurements used for qualitative assessment of liver involvement, and FDG-PET used for assessment of response (e.g., new uptake indicative of disease progression). Measurable lesions in liver defined as extra-nodal lesions can be selected and followed as target, non-target or new lesions.

Table 3: Modified Lugano Response Criteria

Morphologic Response	Metabolic Response	Bone Marrow Biopsy/Aspirate	Prior Combined Response	Lugano Combined Response
NE/No CT	CMR			CR[a]
	PMR			SD unless the previous CT scan indicated CR or PR, then combined response is PR[b]
	NMR			SD
	PMD			PD
	NE/No PET			NE
PD	CMR			PD
	PMR			PD
	NMR			PD
	PMD			PD
	NE/No PET			PD
SD	CMR			CR
	PMR			SD[b]
	NMR			SD
	PMD			PD
	NE/No PET[c]			SD
PR	CMR			CR
	PMR			PR
	NMR			PR[b]
	PMD			PD
	NE/No PET[c]			PR

Table 3: Modified Lugano Response Criteria (Continued)

Morphologic Response	Metabolic Response	Bone Marrow Biopsy/Aspirate	Prior Combined Response	Lugano Combined Response
CR	CMR			CR
	PMR			PR
	NMR			PR
	PMD			PD
	NE/No PET		No prior PET response	PR
	NE/No PET		No prior response and prior PET was negative	CR
	NE/No PET		SD	PR
	NE/No PET		PR	PR
	NE/No PET		CR	CR
	NE/No PET		PD and prior evaluable PET was not PMD	PR
	NE/No PET[c]		PD and prior PET was PMD	NE
	NE/No PET	CR[d]		CR

Abbreivations: BMB = bone marrow biopsy; CMR = complete metabolic response; CR = complete response; CT = computed tomography; NE = not evaluated; NMR = no metabolic response; PD = progressive disease; PET = positron emission tomography; PMD = progressive metabolic disease; PMR = partial metabolic response; PR = partial response; SD = stable disease

a If the lesion(s) on CT were non-FDG avid at baseline, the assessment will be based on a prior morphological response.

b Lugano combined response criteria for this response combination has been modified per FDA request.

c When a timepoint does not have an evaluable PET scan, the morphologic response is not PD, and the most recent evaluable PET scan indicated a metabolic response of PMD, then the combined response will be NE. An improved combined response without evidence that the findings in the prior PET scan have resolved isn't justified. However, there is not PET-based evidence that the subject has continuing PMD, so the response is designated as NE.

d When a PET scan is not acquired or not evaluable, a bone marrow biopsy (BMB)/aspirate is required to confirm a CR by CT. If no BMB is taken (and no PET can be acquired for this time point), the best possible overall response is a PR unless the prior overall response meets either criteria: prior overall response was CR or there was no prior overall response and the baseline/prior PET was negative.

APPENDIX 5. ECOG PERFORMANCE STATUS CRITERIA

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self- care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

References: Oken 1982.

APPENDIX 6. LIST OF CYP2C8 INHIBITORS AND INDUCERS

Following is a table of known inducers and inhibitors of CYP2C8.

Inhibitors of CYP2C8 can be classified by their potency, such as:

- **Strong inhibitor** being one that causes at least a 5-fold increase in the plasma AUC values, or more than 80% decrease in clearance.
- **Moderate inhibitor** being one that causes at least a 2-fold increase in the plasma AUC values, or 50–80% decrease in clearance.
- **Weak inhibitor** being one that causes at least a 1.25-fold but less than 2-fold increase in the plasma AUC values, or 20–50% decrease in clearance.

Inhibitors	Inducers
Strong inhibitor gemfibrozil **Moderate inhibitor** trimethoprim glitazones montelukast quercetin	**Unspecified potency** rifampin

Note: Medicines on this list must be reviewed by Principal Investigators on an ongoing basis to assure updates.

Please note the following: This is not an exhaustive list. For an updated list, see the following links:

- https://www.fda.gov/drugs/development-resources/drug-interactions-labeling
- http://medicine.iupui.edu/clinpharm/ddis/main-table/

APPENDIX 7. LIST OF CYP3A INHIBITORS AND INDUCERS

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Moderate CYP3A Inhibitors
CYP3A4, CYP3A5, CYP3A7
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole, clotrimazole
Protease inhibitors: amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir
Calcium channel blockers: diltiazem, verapamil
Tyrosine kinase inhibitors (anticancer): imatinib, crizotinib
Food products: grapefruit juice (*citrus paradisi* juice)
Herbal medications: Schisandra sphenanthera
Others: amiodarone, aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam

	Strong inducers	Moderate inducers	Weak inducers
CYP3A	apalutamide, carbamazepine[(e)], enzalutamide[(g)], mitotane, phenytoin[(b)], rifampin[(a)], St. John's wort[(h)]	bosentan, efavirenz[(f)], etravirine, phenobarbital, primidone	armodafinil, modafinil[(i)], rufinamide

Abbreviations: CYP = cytochrome P450
Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for CYP3A inhibition or induction risks or contact the medical monitor of the protocol.
Source: Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine.
Note: Strong, moderate, and weak inducers are drugs that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥80%, ≥50% to <80%, and ≥20% to <50%, respectively.
This table provides examples of clinical index inducers and not intended to be an exhaustive list.
http://medicine.iupui.edu/flockhart/table.htm
Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers | FDA

APPENDIX 8. LIST OF DRUGS KNOWN TO PROLONG QT/QTC INTERVAL

The table below includes a list of drugs known to prolong QT/QTc interval from https://www.cpsbc.ca/files/pdf/Methadone-Drugs-QT-Interval-Prolongation.pdf

Note: Medicines on this list must be reviewed by Principal Investigators on an ongoing basis to assure updates.

Generic Name	Brand Names (Partial List)
Alfuzosin	Uroxatral®
Amantadine	Symmetrel®, Symadine®
Amiodarone	Cordarone®, Pacerone®, Nexterone®
Amisulpride (Only on Non US Market)	Solian®, Supitac®, Soltus®, Amitrex®, Amazeo®
Amitriptyline	Elavil® (Discontinued 6/13), Tryptomer®, Tryptizol®, Laroxyl®, Saroten®, Sarotex® Lentizol®, Endep®
Anagrelide	Agrylin®, Xagrid®
Apomorphine	Apokyn®, Ixense®, Spontane®, Uprima®
Aripiprazole	Abilify®, Aripiprex®
Arsenic trioxide	Trisenox®
Artenimol+piperaquine	Eurartesim®
Asenapine	Saphris®, Sycrest®
Astemizole (Removed from Market)	Hismanal®
Atazanavir	Reyataz®
Atomoxetine	Strattera®
Azithromycin	Zithromax®, Zmax®
Bedaquiline	Sirturo®
Bepridil (Removed from Market)	Vascor®
Bortezomib	Velcade®, Bortecad®
Bosutinib	Bosulif®
Ceritinib	Zykadia®
Chloral hydrate	Aquachloral®, Novo-Chlorhydrate®, Somnos®, Noctec®, Somnote®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®, Largactil®, Megaphen®
Cilostazol	Pletal®
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®
Cisapride (Removed from Market)	Propulsid®
Citalopram	Celexa®, Cipramil®

APPENDIX 8. LIST OF DRUGS KNOWN TO PROLONG QT/QTC INTERVAL (CONTINUED)

Generic Name	Brand Names (Partial List)
Clarithromycin	Biaxin®, Prevpac®
Clomipramine	Anafranil®
Clozapine	Clozaril®, Fazaclo®, Versacloz®
Cocaine	Cocaine
Crizotinib	Xalkori®
Cyamemazine (cyamepromazine) (Only on Non-US Market)	Tercian®
Dabrafenib	Tafinlar®
Dasatinib	Sprycel®
Degarelix	Firmagon®
Delamanid (Only on Non-US Market)	Deltyba®
Desipramine	Pertofrane®, Norpramine®
Dexmedetomidine	Precedex®, Dexdor®, Dexdomitor®
Diphenhydramine	Benadryl®, Nytol®, Unisom®, Sominex®, Dimedrol®, Daedalon®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Dolasetron	Anzemet®
Domperidone (Only on Non-US Market)	Motilium®, Motillium®, Motinorm Costi®, Nomit®
Donepezil	Aricept®
Doxepin	Sinequan®, Silenor®, Aponal®, Adapine®, Doxal®, Deptran®, Sinquan®
Dronedarone	Multaq®
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®
Eribulin mesylate	Halaven®
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)
Famotidine	Pepcid®, Fluxid®, Quamatel®

APPENDIX 8. LIST OF DRUGS KNOWN TO PROLONG QT/QTC INTERVAL (CONTINUED)

Generic Name	Brand Names (Partial List)
Felbamate	Felbatol®
Fingolimod	Gilenya®
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®
Fluconazole	Diflucan®, Trican®
Fluoxetine	Prozac®, Sarafem®, Fontex®
Foscarnet	Foscavir®
Furosemide (frusemide)	Lasix®, Fusid®, Frumex®
Galantamine	Reminyl®, Nivalin®, Razadyne-ER®,
Gatifloxacin (Removed from Market)	Tequin®
Gemifloxacin	Factive®
Granisetron	Kytril®, Sancuso®, Granisol®
Grepafloxacin	Raxar®
Halofantrine	Halfan®
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®
Hydrochlorothiazide	Apo-Hydro®, Aquazide H®, BP Zide®, Dichlotride®, Hydrodiuril®, HydroSaluric®, Hydrochlorot®, Microzide®, Esidrex®, Oretic®
Hydrocodone - ER	Hysingla™ ER, Zohydro ER
Hydroxychloroquine	Plaquenil®, Quineprox®
Hydroxyzine	Atarax®, Vistaril®, Aterax®, Alamon®, Durrax®, Equipose®, Masmoran®, Orgatrax®, Paxistil® Quiess®, Tran-Q®, Tranquizine®
Ibutilide	Corvert®
Iloperidone	Fanapt®, Fanapta®, Zomaril®
Imipramine (melipramine)	Tofranil®
Indapamide	Lozol®, Natrilix®, Insig®
Isradipine	Dynacirc®
Itraconazole	Sporanox®, Onmel®
Ivabradine	Procoralan®, Coralan®, Corlentor®, Coraxan®, Ivabid®, Bradia®
Ketoconazole	Nizoral®, Sebizole®, Ketomed®, Keton®
Lapatinib	Tykerb®, Tyverb®
Lenvatinib	Lenvima®

APPENDIX 8. LIST OF DRUGS KNOWN TO PROLONG QT/QTC INTERVAL (CONTINUED)

Generic Name	Brand Names (Partial List)
Leuprolide	Lupron®, Eligard®, Viadur®, Carcinil®, Enanton®, Leuplin®, Lucrin®, Procren®, Prostap® and others
Levofloxacin	Levaquin®, Tavanic®
Levomepromazine (Only on Non-US Market)	Nosinan®, Nozinan®, Levoprome®
Levomethadyl (Removed from Market)	Orlaam®
Lithium	Eskalith®, Lithobid®
Mesoridazine (Removed from Market)	Serentil®
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®
Metoclopramide	Reglan®, Afipran®, Maxolon®, Cerucal®, Clopamon®, Clopra®, Maxeran®, Maxolon®, Metozolv®, Plasil®, Pramin®, Primperan®, Perinorm®
Metronidazole	Flagyl® and many others
Mifepristone	Korlym®, Mifeprex®
Mirabegron	Myrbetriq®
Mirtazapine	Remeron
Moexipril/HCTZ	Uniretic®, Univasc®
Moxifloxacin	Avelox®, Avalox®, Avelon®
Nelfinavir	Viracept®
Nicardipine	Cardene®
Nilotinib	Tasigna®
Norfloxacin	Noroxin®, Ambigram®
Nortriptyline	Pamelor®, Sensoval®, Aventyl®, Norpress®, Allegron®, Noritren®, Nortrilen®
Ofloxacin	Floxin®
Olanzapine	Zyprexa®, Zydis®, Relprevv®
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®
Osimertinib	Tagrisso®
Oxaliplatin	Eloxatin®
Oxytocin	Pitocin®, Syntocinon®
Paliperidone	Invega®, Xepilon®
Panobinostat	Farydak®
Pantoprazole	Protonix® and others
Papaverine HCl	none

APPENDIX 8. LIST OF DRUGS KNOWN TO PROLONG QT/QTC INTERVAL (CONTINUED)

Generic Name	Brand Names (Partial List)
Paroxetine	Paxil®, Aropax®, Pexeva®, Seroxat®, Sereupin®
Pasireotide	Signifor®
Pazopanib	Votrient®
Pentamidine	Pentam®
Perflutren lipid microspheres	Definity®
Pimozide	Orap®
Pipamperone (Only on Non-US Market)	Dipiperon (E.U), Propitan (Japan)
Posaconazole	Noxafil®, Posamol®
Probucol (Removed from Market)	Lorelco®
Procainamide	Pronestyl®, Procan®
Promethazine	Phenergan®
Propofol	Diprivan®, Propoven®
Quetiapine	Seroquel®
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®
Quinine sulfate	Qualaquin®
Ranolazine	Ranexa®, Ranozex®
Rilpivirine	Edurant®, Complera®, Eviplera®
Risperidone	Risperdal®
Ritonavir	Norvir®
Roxithromycin (Only on Non-US Market)	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®, Biaxsig®, Roxar®, Roximycinv®, Roxomycin®, Rulid®, Tirabicin®, Coroxin®
Saquinavir	Invirase®(combo)
Sertindole (Only on Non-US Market)	Serdolect®, Serlect®
Sertraline	Zoloft®, Lustral®, Daxid®, Altruline®, Besitran®, Deprax®, Elrval®, Emergen®, Gladem®, Implicane®, Sedoran®, Sealdin®, SerivoLowfin®, Stimuloton®, Tresleen®, Sertralin Bluefish®
Sevoflurane	Ulane®, Sojourn®
Solifenacin	VESIcare®
Sorafenib	Nexavar®
Sotalol	Betapace®, Sotalex®, Sotacor®
Sparfloxacin (Removed from Market)	Zagam®
Sulpiride (Only on Non-US Market)	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®

APPENDIX 8. LIST OF DRUGS KNOWN TO PROLONG QT/QTC INTERVAL (CONTINUED)

Generic Name	Brand Names (Partial List)
Sunitinib	Sutent®
Tacrolimus	Prograf®, Prograf®, Advagraf®, Protopic®
Tamoxifen	Nolvadex®(discontinued 6/13), Istubal®, Valodex®
Telaprevir	Incivo®
Telavancin	Vibativ®
Telithromycin	Ketek®
Terfenadine (Removed from Market)	Seldane®
Tetrabenazine	Nitoman®, Xenazine®
Thioridazine	Mellaril®, Novoridazine®, Thioril®
Tizanidine	Zanaflex®, Sirdalud®
Tolterodine	Detrol®, Detrusitol®
Toremifene	Fareston®
Torsemide	Demadex®, Diuver®, Examide®
Trazodone	Desyrel® (discontinued 6/13), Oleptro®, Beneficat®, Deprax®, Desirel®, Molipaxin®, Thombran®, Trazorel®, Trialodine®, Trittico®, Mesyrel®
Trimipramine	Surmontil®, Rhotrimine®, Stangyl®
Tropisetron (Only on Non-US Market)	Navoban®, Setrovel®
Vandetanib	Caprelsa®
Vardenafil	Levitra®
Vemurafenib	Zelboraf®
Venlafaxine	Effexor®, Efexor®
Voriconazole	VFend®
Vorinostat	Zolinza®
Ziprasidone	Geodon®, Zeldox®

APPENDIX 9. NCCN-FACT FLYMSI-18 (VERSION 2)

Please circle or mark one number per line to indicate your response as it applies to <u>the past 7 days</u>.

			Not at all	A little bit	Some-what	Quite a bit	Very much
	GP1	I have a lack of energy.....	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
D	C2	I am losing weight	0	1	2	3	4
R	Leu1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
S	BMT6	I get tired easily	0	1	2	3	4
P	BP1	I have bone pain	0	1	2	3	4
	HI8	I have trouble concentrating	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
D	GE6	I worry that my condition will get worse	0	1	2	3	4
R	BRM9	I have emotional ups and downs	0	1	2	3	4
S	Leu4	Because of my illness, I have difficulty planning	0	1	2	3	4
E		for the future					
	Leu5	I feel uncertain about my future health.....	0	1	2	3	4
T	GP2	I have nausea	0	1	2	3	4
S	N3	I worry about getting infections	0	1	2	3	4
E	GP5	I am bothered by side effects of treatment	0	1	2	3	4
FW	GF3	I am able to enjoy life	0	1	2	3	4
B	GF7	I am content with the quality of my life right now	0	1	2	3	4

Abbreviations: DRS-P = Disease-Related Symptoms Subscale – Physical; DRS-E = Disease-Related Symptoms Subscale – Emotional; TSE = Treatment Side Effects Subscale; FWB = Function and Well-Being Subscale English (Universal) 03 March 2010 Copyright 2001

APPENDIX 10. EQ-5D-3L HEALTH QUESTIONNAIRE

EQ-5D Health Questionnaire

Client ID ☐ New User ☐ Existing User ☐

Date ☐

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

Self-Care

I have no problems with self-care ☐

I have some problems with washing or dressing myself ☐

I am unable to wash or dress myself ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

Pain / Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety / Depression

I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

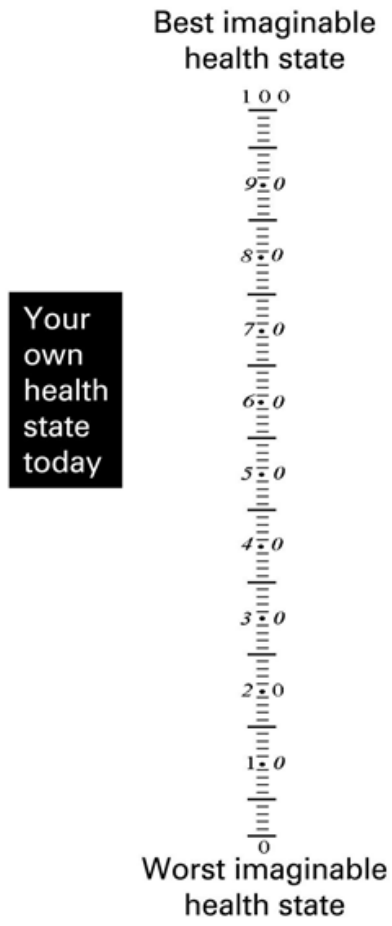
APPENDIX 10. EQ-5D-3L HEALTH QUESTIONNAIRE (CONTINUED)

Visual Analogue Scale

Please indicate on this scale how good or bad your own health state is today.

The best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

Please draw a line from the box to the point on the scale that indicates how good or bad your health state is today.



Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

APPENDIX 11. EVALUATION OF TOLERABILITY OF ZANDELISIB IN COMBINATION WITH RITUXIMAB IN JAPANESE SUBJECTS

Evaluation Part 1:

Tolerability of zandelisib in combination with R in Japanese subjects will be evaluated in the first 3 Japanese subjects who are randomized to the zandelisib in combination with R arm. The Safety Review Committee (SRC), which is composed of the Sponsor/in-country caretaker, person designated by the Medical Monitor (person in charge from CRO), and the Principal Investigators/Investigators, will discuss and evaluate the tolerability of zandelisib in combination with R based on the adverse events reported in Cycle 1. Tolerability will be evaluated according to the criteria and procedures specified in the SRC Charter. Subject enrollment in Japan will be suspended when the start of administration is confirmed for the first 3 Japanese subjects in the zandelisib in combination with R arm. If zandelisib in combination with R is tolerated in these 3 Japanese subjects, enrollment of Japanese subjects in this study will resume. Subjects who signed the ICF at the time the first 3 Japanese subjects received zandelisib in combination with R can then be enrolled in the study following confirmation of eligibility. Henceforth, if a subject is randomized to the zandelisib in combination with R arm, tolerability of zandelisib in combination with R will be evaluated in the subject.

Evaluation Part 2:

If it is deemed necessary to evaluate tolerability in additional subjects, according to the procedures described in Evaluation Part 1, subject enrollment in Japan will be suspended again following confirmation that 3 additional subjects were randomized to the zandelisib in combination with R arm. Tolerability of zandelisib in combination with R in Evaluation Part 2 will be evaluated in a total of 6 subjects consisting of 3 subjects in Evaluation Part 1 and 3 additional subjects in Evaluation Part 2.

The SRC, will discuss and evaluate the tolerability of zandelisib in combination with R based on adverse events reported in Cycle 1. Tolerability will be evaluated according to the criteria and procedures specified in the SRC Charter. If zandelisib in combination with R is tolerated, enrollment of Japanese subjects in this study will resume. Subjects who signed the ICF at the time the first 3 Japanese subjects in the zandelisib in combination with R arm of this Part can then be enrolled in the study. Henceforth, if a subject is randomized to the zandelisib in combination with R arm, tolerability of zandelisib in combination with R will be evaluated in the subject.

Details for the safety evaluations are described in the SRC Charter.

Signature Page for VV-CLIN-000217 v4.0

Approval	Richard Ghalie Clinical 22-Sep-2021 18:51:36 GMT+0000

Approval	Staci Ellis Regulatory 22-Sep-2021 20:27:32 GMT+0000

Signature Page for VV-CLIN-000217 v4.0