STATISTICAL ANALYSIS PLAN FOR INTERVENTIONAL STUDIES

A Multicenter, Open-Label, Single-Arm, Phase 2 Study of Zandelisib (ME-401) in Subjects with Follicular Lymphoma or Marginal Zone Lymphoma After Failure of Two or More Prior Systemic Therapies – The TIDAL Study

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REVISION HISTORY

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0.2	05-APR-2019	Gargi Patel	Added revisions based on sponsor comments on v0.1 / 29MAR
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1.1	12-Jun-2020	Fenfen Wang	Full version of SAP, update per protocol amendment 2
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3.0	21-Jun-2021	Joanne Li	Updated per Protocol Amendment 4

I confirm that I have reviewed this document and agree with the content.

APPROVALS

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LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BAT	Basophil activation test
BCRP	Breast cancer resistance protein transporter
BP	Blood Pressure
BTK	Bruton tyrosine kinase
BUN	Blood Urea Nitrogen
CAR T	Chimeric Antigen Receptor T-cell
CBC	Complete Blood Count
CI	Confidence Interval
CLL	Chronic lymphocytic leukemia
CMR	Complete metabolic response
CMV	Cytomegalovirus
CR	Complete Response/remission
CRi	Complete remission with incomplete marrow recovery
CS	Continuous Schedule
CT	Computed Tomography
CYP2C8	Cytochrome P450 2C8
CyTOF	Mass cytometry
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose Limiting Toxicity
DNA	Dexyribonucleic acid
DOR	Duration of Response
DORR	Duration of recaptured response
DSMB	Data Safety and Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
Emax	Maximum possible effect
FDA	Food and Drug Administration
FDG	18F-fluorodeoxyglucose

Abbreviation	**Description**
Abbreviation	**Description**
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognositc Index
GCP	Good Clinical Practice
GELF	Groupe d'Etudes des Lymphomes Folliculaires
GI	Gastrointestinal
HcT	Hematocrit
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IF	immunofixation
IND	Investigational New Drug
IRB	Institutional Review Board
IRRC	Independent Response Review Committee
IS	Intermittent Schedule
IV	intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
kg	kilogram
L	liter
mAb	monoclonal Antibody
MCL	mantle cell lymphoma
MCH	Mean Corpuscular Hemoglobin
MCR	Metabolic Complete Response
Min	Minimum
mm3	cubic millimeter
mg	milligram
mL	milliliter
MRD	minimal residual disease
MTD	Maximum tolerated dose
MUGA	Multigated Acquisition Scan
MZL	marginal zone lymphoma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ND	Not Detected
NDA	New Drug Application
NE	not evaluable
NHL	non-Hodgkin lymphoma
NIP	non-infectious pneumonitis
NMR	no metabolic response
NOAEL	no-observed-adverse-effect level
NOS	not otherwise specified
OI	Opportunistic Infection

Abbreviation	Description
OR	rates of overall response rate
Abbreviation	**Description**
ORR	Objective Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive disease
PET/CT	Positron Emission Tomography – Computed Tomography
PFS	Progression-free survival
PI3K	phosphatidylinositol 3-kinase
PI3Kδ	Phosphatidylinositol 3-kinase Delta
PJP	Pneumocystis jiroveci pneumonia
PK	Pharmacokinetics
PMD	progressive metabolic disease
PMR	partial metabolic response
POD24	progression of disease within 24 months of diagnosis after frontline treatment with chemoimmunotherapy
PR	Partial Response
QTc	QT corrected (corrected QT-interval)
QTcF	QT-interval corrected according to Fridericia's formula
R-bendamustine	rituximab, bendamustine
R-CVP	rituximab, cyclophosphamide, vincristine, prednisone
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvate transaminase
SLL	small lymphocytic lymphoma
SUSAR	suspected unexpected serious adverse reaction
TEAE	Treatment-emergent Adverse Event
TMP-SMX	trimethoprim-sulfamethoxazole
TREG	T regulatory cells
TTF	Time to Treatment Failure
ULN	upper limit of normal
US(A)	United States (of America)
WHO	World Health Organization

1. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

1.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings, except for the Population Pharmacokinetics (PK) and Exposure-Response analyses. A separate Population PK and Exposure-Response analysis plan will be developed by Nuventra for these analyses. MEI Pharma will review the statistical analyses and are responsible for final approval of all tables, figures and listings.

1.2. Timings of Analyses

The primary analysis for the primary efficacy endpoint of overall response rate (ORR) for the follicular lymphoma (FL) cohort (i.e., Primary Analysis for FL) will be triggered after all 91 subjects in the Primary Efficacy Population in FL (PEP FL) enrolled in the study (except those who discontinue early) have been followed for at least 6 months from the start of study drug.

The final analysis for DOR for follicular lymphoma (FL) to support the New Drug Application (NDA) initial filing for FL (i.e., NDA Analysis for FL) will be triggered after most responders in the Primary Efficacy Population have a minimum of 12 months of follow-up from first response.

The primary analysis for the primary efficacy endpoint of ORR for marginal zone lymphoma (MZL) (i.e., Primary Analysis for MZL) will be triggered after all subjects in the ITT MZL population enrolled in the study (except those who discontinue early) have been followed for at least 6 months from the start of study drug.

The final analysis for DOR for MZL to support the NDA filing for MZL (i.e., NDA Analysis for MZL) will be triggered after most responders in the ITT MZL population have a minimum of 12 months of DOR follow-up.

The final analysis includes all data collected through the time of the database lock. PK and Exposure-Response analyses will be performed by Nuventra, who will produce the analysis report.

An independent DSMB (Data Safety and Monitoring Board) will review descriptive summaries of accumulating safety, subject disposition, and limited efficacy data every 6 months. Further description of the DSMB analyses can be found in the DSMB charter.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To evaluate the objective response rate (ORR) of ME-401 in relapsed or refractory FL or MZL, defined as the best response rating of complete response (CR) or partial response (PR) based on the Lugano Response Criteria (Cheson 2014) as modified in

the study protocol, and as determined by an Independent Response Review Committee (IRRC).

2.2. Secondary Objectives

- To evaluate the efficacy of ME-401 as assessed by an IRRC:
  - Duration of response (DOR)
  - Complete response (CR) rate
  - Progression-free survival (PFS)
  - Time to treatment failure (TTF)
  - Recapture of response
  - Duration of recaptured response (DORR)
- To evaluate the efficacy of ME-401 as assessed by the Investigator:
  - Objective response rate (ORR)
  - Duration of response (DOR)
  - Complete response (CR) rate
  - Progression-free survival (PFS)
  - Time to treatment failure (TTF)
  - Recapture of response
  - Duration of recaptured response (DORR)
- To evaluate overall survival (OS)
- To evaluate the safety profile of ME-401
  - Overall incidence of treatment-emergent adverse events (TEAEs)
  - Incidence of adverse events of special interest (AESIs)
  - Time to occurrence of AESIs
- To evaluate the pharmacokinetics (PK) of ME-401

2.3. Brief Description

Under Protocol Amendment 2, this is a global, multicenter, open label, single-arm, phase 2 study of the PI3Kδ inhibitor ME-401 (zandelisib) in subjects with relapsed/refractory FL or MZL. ME-401 will be administered orally at a dose of 60 mg given once a day in 28-day cycles, with the first day of treatment designated as Day 1. Treatment with ME-401 can be administered based on a continuous schedule (CS) or an intermittent schedule (IS).

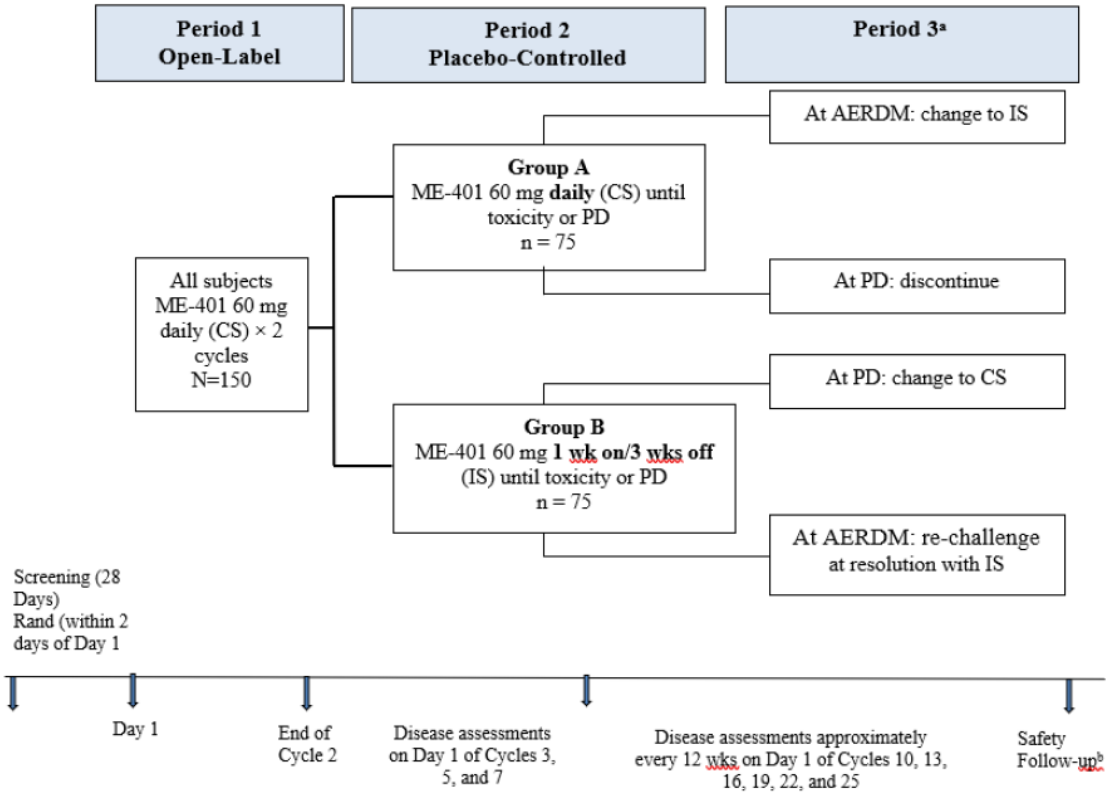
The CS (or Group A in Protocol Amendment 1) includes daily dosing for the whole duration of a treatment cycle until protocol-defined criteria is met for treatment interruption, modification to intermittent dosing to manage toxicity, or discontinuation.

The IS (or Group B in Protocol Amendment 1) includes:

- continuous daily therapy for the initial 2 cycles (~56 days) of treatment
- the intermittent treatment begins at Cycle 3, with ME-401 administered daily for the first 7 days of every 28-day cycle (7 days on treatment and 21 days off treatment)

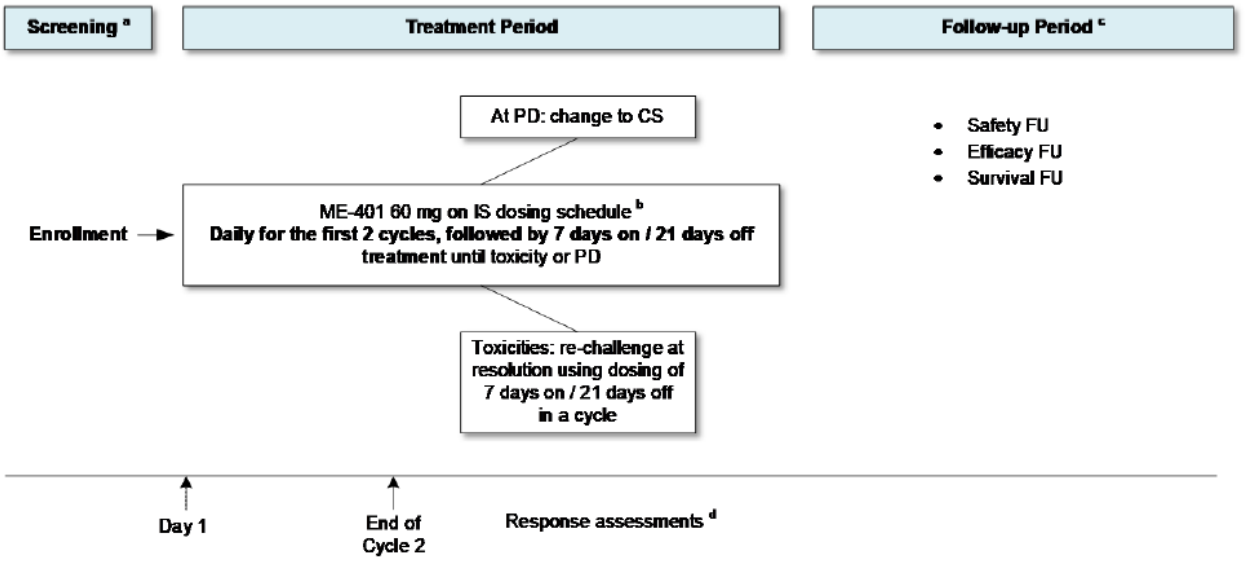
Under Protocol Amendment 1 (Figure 1a), subjects were randomized 1:1 to receive CS or IS. Since Protocol Amendment 2 (Figure 1b), the initial CS treatment arm was terminated, and all new subjects were enrolled to receive therapy on the IS only. If CS subjects already completed 2 initial cycles of therapy, they were switched to IS dosing after they complete therapy in the ongoing cycle of treatment, and if they had not completed the first 2 cycles of therapy they were switched to IS dosing after completion of the first two cycles of therapy on CS. Subjects who progress on IS dosing may be switched to CS dosing. Subjects will continue to receive study drug in accordance with the IS dosing regimen (or CS dosing regimen if switched from IS after disease progression [PD]) until investigator-assessed disease progression or unmanageable toxicity requiring treatment discontinuation, subject's decision to withdraw their consent to participate on study, or study closure by the Sponsor.

Figure 1a: Study Schema (Protocol Amendment 1)



Abbreviations: AERDM = AEs requiring dose modification or drug discontinuation; Rand = randomization.
[a] For subjects who require study drug interruption to manage ME-401 related toxicity or have disease progression.
[b] Safety follow up will occur 30 days (±3 days) from the last day of study drug treatment. Post-treatment follow-up will be conducted every 3 months to obtain data regarding disease progression, improvement in disease response, start of subsequent lymphoma therapy and death.

Figure 1b: Study Schema (Protocol Amendments 2 and 3)



Abbreviations: EOT = End of Treatment; FU = follow up; PD = progressive disease.

[a] Screening from Day -28 to Day -1.

[b] IS dosing schedule: 60 mg daily for the first 2 cycles (56 days) followed by 60 mg daily for 7 days of every 28-day cycle (7 days on / 21 days off treatment).

[c] Follow-up Period will include: 1) EOT/30-Day Safety Follow-up visit will occur 30 (±3) days from the last day of study drug treatment. 2) Efficacy Follow-up - for subjects who discontinue study treatment due to reasons other than disease progression or death, response follow up will occur until PD of the start of a new anti-cancer therapy. 3) Survival Follow-up visits will occur every 3 months until death, and will continue for up to 3 years after the last subject was enrolled in the study.

[d] Response assessments will be performed every 2 months (±7 days) for the first 6 months of therapy, every 3 months (±7 days) during the following 12 months, and every 6 months (±14 days) thereafter (starting with month 18).

Subjects who discontinue study drug will remain in the study with follow-up conducted every 3 months from the last dose of study drug to obtain post-treatment long-term follow-up information on disease status (i.e., change in disease response, progression), start of subsequent therapy, and survival (death). During this post-treatment follow-up phase, all subjects who discontinued treatment due to reasons other than PD must continue imaging tests to assess disease status, performed per the original protocol-defined schedule for disease/response assessment, or earlier if clinically indicated. Imaging test results will no longer be collected when a subject starts a new therapy or disease progression occurs and is documented in the post-treatment long-term follow-up phase. Survival follow-up will continue for up to 3 years after the last subject is enrolled in the study.

Individual subject participation in the study will include 28 days for screening, approximately 18 months of dosing with study drug, and follow-up for survival after discontinuation of study drug. Actual subject participation in the study may be shorter or longer depending on disease response, tolerability to therapy, and duration of long-term follow-up. The study will continue until all enrolled subjects (except those who discontinue early) have been followed for at least 6 months from the start of study drug.

2.4. Determination of Sample Size

Sample Size for FL

The study will test the null hypothesis that the IRRC-reviewed ORR is ≤48% against the alternative hypothesis that it is ≥65.5%. The sample size for the primary efficacy population for FL is estimated to be 91 subjects, with at least 90% power and 1-sided alpha = 0.025.

Safety analysis will be performed based on the Safety Population, with analysis focused on the IS FL subjects at the primary analysis database lock for FL submissions. With a total sample size of 120 FL subjects treated with ME-401 IS dosing regimen, if ≤15 subjects experience Grade ≥3 AESIs (i.e., subject incidence rate of ≤12.5% with 95% CI of 7.2–19.8%), the study can rule out the possibility of having an incidence rate ≥20% for Grade ≥3 AESIs with the IS dosing regimen. In addition, with a total sample size of 120 FL subjects, if ≤5 subjects experience a particular type of events (i.e., subject incidence rate of ≤4.2% with 95% CI 1.4-9.5%), the study can rule out the possibility of having an incidence rate of ≥10% for this AE.

Sample Size for MZL

The study will test the null hypothesis that the IRRC-reviewed ORR is ≤46% against the alternative hypothesis that it is ≥66.5%. The sample size for the MZL population is estimated to be 64 subjects, with at least 90% power and 1-sided alpha = 0.025.

For the supplement submission for MZL indication, safety analysis will be focused on all subjects treated with ME-401 IS dosing regimen. With a total sample size of 184 subjects treated with the ME-401 IS dosing regimen in both the FL and MZL subjects, if ≤25 subjects experience Grade ≥3 AESIs (i.e., subject incidence rate of ≤13.6% with 95% CI of 9.0 – 19.4%), the study can rule out the possibility of having an incidence rate ≥20% for Grade ≥3 AESIs with the IS dosing regimen. In addition, with a total sample size of 184 subjects treated with the ME-401 dosing regimen in both the FL and MZL populations, if ≤9 subjects experience this type of adverse events (i.e., subject incidence rate of ≤4.9% with 95% CI 2.3-9.1%), the study can rule out the possibility of having an incidence rate of ≥10% for this AE.

2.5. Treatment Assignment

Under Protocol Amendment 1 (Figure 1a), subjects are randomized 1:1 to Group A (CS) or Group B (IS), stratified accordingly to tumor bulk (largest lymphoid mass <5 cm vs. ≥5cm) and disease response to last therapy (relapse vs. refractory).

Since Protocol Amendment 2 (Figure 1b), this is an open-label and single-arm phase 2 study that all new subjects will be enrolled and treated by IS dosing only. During the first 2 cycles, subjects will receive open-label ME-401 administered at 60 mg once daily. After completing 2 cycles of daily therapy, subjects will continue ME-401 administered at 60 mg daily for the first 7 days of every 28-day cycle (7 days on treatment and 21 days off treatment). Subjects who progress disease on IS dosing have the option to have their ME-401dosing switched to CS dosing.

Since Protocol Amendment 2, the initial CS treatment arm was terminated, and switched to IS dosing. For CS Subjects from Protocol Amendment 1, those who already completed 2 initial cycles of therapy were switched to IS dosing once they complete the ongoing cycle; those who had not completed the first 2 cycles were switched to IS dosing after the first 2 cycles.

For subjects who experience toxicity during the first 2 cycles while receiving daily therapy with ME-401, dose interruption followed by a switch to the intermittent schedule daily dosing for the first 7 days of every 28-day cycle is allowed. Subjects who experience toxicities on the IS will be managed by the instructions for management of potential drug-related toxicity (Protocol Amendment 3, Table 4), which may include dose interruption or permanent discontinuation of ME-401.

2.6. Study Procedures and Flowchart

All study assessments for procedures will be performed at the visits and time points outlined in the Schedule of Assessments (Table 1).

Table 1: Schedule of Assessments (Amendment 4)

Assessment/Procedure	Screening [b]	Cycle 1			Cycle 2		Cycle 3	Cycle 4		Cycle 5	Cycle 6		Cycle 7	Cycles 10, 13, 16, 19, 22, 25 [d]…	EOT/30-Day Safety Follow-up [e]	Post-Treatment Long-Term Follow-up
Day(s) of Cycle	-28 to -1	1 [c]	8	15	1	15	1	1	7	1	1	7	1	1	30 (± 3) days post last dose or treatment discontinuation	Every 3 Months
Study Day(s)	-28 to -1	1	8	15	29	43	57	85	91	113	141	147	169	253, 337, 421, 505, 589…		
Visit Window (days) [a]			±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7 [a]		
Informed consent form (ICF)	X															
Medical history [f]	X															
Physical examination	X	X			X		X	X		X	X		X	X	X	
Symptom-directed exam [g]			X	X		X										
Vital signs [h]	X	X	X	X	X	X	X	X		X	X		X	X	X	
Height	X															
Weight	X	X			X		X	X		X	X		X	X	X	
ECOG performance status	X	X			X		X	X		X	X		X	X	X	
Pregnancy test [i]	X	X			X		X	X		X	X		X	X	X	
HIV testing [j]	X															
Hepatitis B and C testing [k]	X															
Adverse events [l]		X	X	X	X	X	X	X		X	X		X	X	X	
Concomitant medication [m]	X	X	X	X	X	X	X	X		X	X		X	X	X	
ECG [n]	X	X					X				X			X	X	
CBC with differential [o]	X	X	X	X	X	X	X	X		X	X		X	X	X	
Serum chemistry [p]	X	X	X	X	X	X	X	X		X	X		X	X	X	
Coagulation [q]	X	X			X		X			X			X	X	X	
PCR test for CMV	X	X			X		X	X		X	X		X	X		
Urinalysis (Dipstick) [r]	X	X			X		X	X		X	X		X	X	X	

Assessment/Procedure	Screening [b]	Cycle 1			Cycle 2		Cycle 3	Cycle 4		Cycle 5	Cycle 6		Cycle 7	Cycles 10, 13, 16, 19, 22, 25 [d]…	EOT/30-Day Safety Follow-up [e]	Post-Treatment Long-Term Follow-up
Day(s) of Cycle	**-28 to -1**	**1 [c]**	**8**	**15**	**1**	**15**	**1**	**1**	**7**	**1**	**1**	**7**	**1**	**1**	**30 (± 3) days post last dose or treatment discontinuation**	**Every 3 Months**
Study Day(s)	**-28 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**85**	**91**	**113**	**141**	**147**	**169**	**253, 337, 421, 505, 589…**		
Visit Window (days) [a]			**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7 [a]**		
COVID-19 test [s]	X															
Issue and assess compliance diary [t]		X			X		X	X		X	X		X	X		
Dispense study drug [u]		X			X		X	X		X	X		X	X		
PK Sampling [v]		X		X[w]	X				X			X				
Echocardiogram or MUGA [x]	X														X	
Correlative immune study (pre-dose) [y]		X		X	X		X			X			X	X	X	
Opportunistic infection monitoring [z]		X			X		X	X		X	X		X	X	X	
Post-Treatment Follow-up procedures [aa]																X

Response Assessment [bb,cc]	Screening	Every 2 Months for the First 6 Months			Every 3 Months for the Next 12 Months (through 18 Months)				Every 6 Months Thereafter
Study Day		**61**	**121**	**182**	**274**	**365**	**456**	**547**	**730, 912, 1095…**
Visit Window (days)		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±14**
CT neck/chest/abdomen/pelvis [dd]	X	X	X	X	X	X	X	X	X
FDG-PET scan [ee]	X		X			X			
Bone marrow biopsy/aspirate [ff]	X								
Endoscopy with biopsy [gg]	X								

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; CBC = complete blood count; CMV = cytomegalovirus; CMR = complete metabolic response; CO2 = carbon dioxide; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FDG-PET = 18F-fluorodeoxyglucose positron emission tomography; HcT = hematocrit; HGB = hemoglobin; HIV = human immunodeficiency virus; HR = heart rate; ICF = informed consent form; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MUGA = multigated acquisition scan; PCR = polymerase chain reaction; PK = pharmacokinetic; PT = prothrombin time; RBC = red blood cell; SOC = standard of care; WBC = white blood cell.

[a.] **Study Assessment Day(s)** – There is ±3-day window allowable for each clinic visit for Cycle 1 Day 8 and Cycle 1 Day 15. For Cycles 2 through 25, the allowable window is ±7 days. After Cycle 25, 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 enrollment. Upon confirmation of meeting eligibility criteria, subjects should be treated within a reasonable time frame (within 5 days). If there are >7 days between screening laboratory assessments and expected Cycle 1 Day 1 dosing, then the laboratory assessments should be repeated and reviewed prior to the first dose of ME-401. Some tests performed prior to obtaining ICF (e.g., CT scan, bone marrow biopsy) may not need to be repeated for the study as long as they were performed within the allowed screening window.

[c.] **Cycle 1 Day 1** – Physical examination need not be repeated on Cycle 1 Day 1 if performed within 7 days prior to start of treatment. Laboratory assessments (CBC with differential, serum chemistry, coagulation, urinalysis) need not be repeated on Cycle 1 Day 1 if performed within 7 days prior to start of treatment.

[d.] **Cycle 25+ –** Subjects who remain on study after 25 cycles (approximately 2 years) will visit the clinic every 3 months (±1 month), with a response assessment performed every 6 months as per standard of care.

[e.] **EOT/30-Day Safety Follow-up –** Visit will be completed 30 (±3) days post last dose of study drug administration (or prior to starting a new treatment if urgent treatment is required) or from study drug discontinuation.

[f.] If known, record in the medical history information on COVID-19 vaccination administered at any time prior to subject consent to participate in the study.

[g.] **Symptom-directed exam –** Performed on Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 2 Day 15, only as needed/indicated, based on interim history.

[h.] **Vital signs** – BP, HR, temperature.

[i.] **Pregnancy test** – The screening serum pregnancy test in females of childbearing potential must be completed within 28 days prior to Cycle 1 Day 1. Urine or serum pregnancy test must be performed on study Day 1. For women of childbearing potential, a monthly serum or urine pregnancy test will be conducted every dosing cycle and 30 days after discontinuation of dosing.

[j.] **HIV testing** – HIV antibody is required.

[k.] **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 C PCR is required if hepatitis C antibody is positive.

[l.] **Adverse events** – Recorded from the time of the first dose of study drug on Cycle 1 Day 1 and continues until 30 days after the last dose of study drug or start of new anti-cancer treatment.

[m.] **Concomitant medications** – Recorded from 28 days prior to Cycle 1 Day 1 until the EOT/30-Day Safety Follow-up visit, or start of new anti-cancer treatment. Please, record information about COVID-19 vaccination, if performed.

[n] **ECG** – 12-lead ECGs performed at screening; Cycle 1 Day 1 pre-dose (unless the Screening visit is within 3 days prior to Day 1); pre-dose on Day 1 of Cycles 3, 6, 13, 19, and 25, and every 6 months thereafter; at the EOT/30-Day Safety Follow-up visit, and as clinically indicated. ECGs should be performed pre-dose. For Cycle 1 Day 1 and Cycle 3 Day 1, ECGs should be taken pre-dose and at expected C_{max} (3–5 hours after dosing).

[o] **CBC with differential** – WBC, ANC, RBC, HGB, HcT, lymphocytes, eosinophils, monocytes, basophils, platelets, and MCH. Screening labs must be repeated if performed >7 days prior to Cycle 1 Day 1.

[p] **Serum chemistry** – Glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, ALP, AST, ALT, total bilirubin, total protein, albumin, LDH, and phosphorous. Screening labs must be repeated if performed >7 days prior to Cycle 1 Day 1.

[q] **Coagulation** – aPTT, PT/INR. Screening labs must be repeated if performed >7 days prior to Cycle 1 Day 1.

[r] **Urinalysis** – Dipstick or urine test (pH, specific gravity, glucose, ketones, blood, and protein). Screening labs must be repeated if performed >7 days prior to Cycle 1 Day 1.

[s] **COVID-19 test results –** Please record COVID-19 test results in the AE CRF page, if positive.

[t] **Issue and Assess Compliance Diary** – Compliance diary to record daily study drug administration. Returned diaries are to be assessed for study product compliance. New compliance diary is to be issued with each dispensing of ME-401.

[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 intake or 2 hours after food intake at the same time each day. On days of PK sampling, instruct subjects to not take study drug until after the pre-dose PK sample is drawn. Compliance diary and count of returned capsules are performed on each day of dispensing study drug.

[v] **PK sampling** – Pre-dose PK samples are to be obtained within 1 hour before study drug administration on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 7, and Cycle 6 Day 7. Pre-dose PK samples collected after Cycle 1 Day 1 are to be obtained within ±60 minutes of the scheduled time, which is based on the Cycle 1 Day 1 dosing time.

[w] **PK Sampling** – **Cycle 1 Day 15** – pre-dose and 3 hours (±30 min) post intake of study drug. Collect data regarding food and drink intake 4 hours prior to study drug intake.

[x] **Echocardiogram or MUGA** – Performed at screening, EOT/30-Day Safety Follow-up visit, and as clinically indicated. The same methodology (echocardiogram or MUGA) should be used throughout the study.

[y] **Correlative Sample Study** – US Sites only. Samples will be obtained pre-dose on Day 1 of Cycle 1, and then pre-dose on the following visits: Day 15 of Cycle 1; Day 1 of Cycles 2, 3, 5, 7, 10; then every 3 cycles thereafter; and at the EOT/30-Day Safety Follow-up visit. Fresh blood samples will be collected and shipped overnight to a central laboratory for analysis. Samples may be shipped only Monday to Thursday. Samples may not be shipped for delivery on weekends or holidays. If possible, a sample will also be obtained when a subject develops a late onset Grade 2 AE of diarrhea/colitis, rash/mucositis, transaminase elevation, or non-infectious pneumonitis, or when a subject discontinues study drug permanently for another reason. Samples will be collected at the first visit of the adverse event, at the time when treatment is held, and at the time when treatment is resumed.

[z] **Opportunistic Infection Monitoring** – Prior to start of every cycle of treatment with ME-401, monitoring will be conducted, and for subjects with identified risk factors and those who developed an OI while on study treatment, additional assessments should include: CD4 and CD8 count and ratio, c-reactive protein, blood cultures, any additional laboratory and diagnostic methods according to local SOC reported as unscheduled laboratory and diagnostic methods of assessment, radiological imaging (i.e., chest X-ray or CT scans). Note: Treatment of the OI that started while on study should be based on local SOC.

[aa] **Post-treatment Follow-up Procedures** – Every 3 months from the last dose of study drug to obtain data regarding changes in efficacy assessments, death or subsequent therapy based on standard of care assessments. Imaging tests to assess disease status will be performed at least once every 6 months or earlier as indicated per standard of care. Any AE that has not returned to baseline or Grade ≤2 should be followed until it has returned to baseline or better, the event is assessed as stable by the Investigator, the subject is lost to follow up, or the subject withdraws consent. Survival follow-up will continue for up to 3 years after the last subject is enrolled in the study.

[bb] **Response assessment** – Imaging scans, physical examination, bone marrow aspirate/biopsy (if applicable), and laboratory evaluation as appropriate for individual subjects.

[cc] **Response assessment at the EOT/30-Day Safety Follow-up visit** – Perform imaging test (CT scan or PET/CT scan) only if last imaging tests outside the window noted for CT scan or PET-CT.

[dd] **CT Scan** – CT of the neck, chest, abdomen, and pelvis must be obtained at screening (within 6 weeks prior to Cycle 1 Day 1). CT scans must be performed using IV contrast. For subjects who are intolerant to contrast agents, the CT scan will be performed with oral contrast or MRI scans will be used.

[ee] **PET/CT** – FDG-PET scan must be obtained at screening (within 6 weeks prior to Cycle 1 Day 1), as indicated, and to confirm CR/CMR. PET/CT imaging is no longer needed once a CMR has been achieved and a CT scan is an appropriate imaging test.

[ff] **Bone marrow biopsy/aspirate** – Bone marrow biopsy/aspirate is obtained at screening and to confirm CR if PET scans were not performed or were not evaluable to assess bone marrow involvement. In addition, it can be performed as clinically indicated at the discretion of the Investigator.

gg. **Endoscopy with biopsy** – For subjects with gastric MZL, endoscopy with biopsy to be performed to confirm CR.

3. ENDPOINTS

3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is ORR, defined as the proportion of subjects achieving the best response rating of CR or PR based on the Modified Lugano Classification (response criteria summarized in Appendix 5 of Protocol Amendment 2), as determined by IRRC.

For both Primary Analysis and NDA Analysis for FL, ORR will include best response of PR and/or CR prior to first PD that is reported before the data cutoff date for FL Primary Analysis, among all patients in the Primary Efficacy Population in FL (PEP FL).

As supportive analyses for NDA Analysis for FL, ORR will be summarized by 1) including PR or CR achieved that is reported before the data cutoff date for NDA Analysis for FL, among all patients in the Primary Efficacy Population in FL; 2) including PR or CR achieved that is reported before the data cutoff date for NDA Analysis for FL, among all patients in the ITT FL Population.

Time to response will be assessed to provide supportive information for the primary endpoint of ORR. It is defined as the time from the first dose of study drug to the first objective response for the subjects who achieved best response of CR or PR.

3.2. Secondary Efficacy Endpoints

The analysis of secondary efficacy endpoints, DOR, CR rate, PFS, TTF, recapture of response, DORR will be performed accordingly to the disease assessment reported by the IRRC. Analysis of ORR, DOR, CR rate, PFS, TTF, recapture of response, DORR will also be performed using Investigator assessment of disease response. In addition, the overall survival will be analyzed. Recapture of analysis and DORR will only be summarized for the IS patients who switched back to CS after PD.

3.2.1. Objective Response Rate (ORR) by Investigator

ORR defined as the proportion of subjects achieving the best response rating of CR or PR based on the Lugano Classification, as determined by the Investigator.

3.2.2. Duration of Response (DOR) and Duration of Recaptured Response (DORR)

DOR is defined as time from first (CR or PR) response to the time of first PD (based on the Modified Lugano Response Criteria) or the date of death due to any cause (whichever occurs earlier).

For Primary Analysis and NDA Analysis for FL, DOR will be analyzed based on the patients who achieved PR or CR prior to first PD, that is reported before the data cutoff date for the FL Primary Analysis.

As a supportive analysis for NDA Analysis for FL, DOR will be analyzed based on all patients who achieved PR or CR prior to first PD, that is reported before the data cutoff date for the NDA Analysis for FL submission.

To evaluate the duration of response for subjects who had recapture of response on the CS dosing (Section 3.2.6), DORR is defined as the time from recapture of response (CR or PR) to the time of second PD or the date of death due to any cause (whichever occurs earlier).

Detailed censoring rules are specified in Table 2 (FDA guidance [FDA 2015] and [FDA 2018]). In general, in primary analysis for DOR and analysis for DORR, subjects will be censored at the date of last adequate assessment with evidence of no progression by the IRRC, 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 scheduled visits.

Supportive analysis for DOR will be conducted to evaluate the robustness of the primary analysis result for DOR, by considering all progressions and deaths as events per 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 (Table 3).

For subjects in IS dosing switching to the CS at PD, both DOR and DORR will be estimated.

Table 2: Censoring Rules for the Primary Analysis of DOR and DORR

Situation	Date of Event or Censoring	Outcome
Progression documented	Date of earliest assessment which revealed progression determined by the IRRC	Event
Death before first PD assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event
No progression, nor death	Date of last adequate assessment with evidence of no progression by the IRRC	Censored
Discontinuation for any reason other than documented PD or death	Date of last adequate assessment with evidence of no progression by the IRRC	Censored
Loss to follow-up	Date of last adequate assessment with evidence of no progression by the IRRC	Censored
Switching back to CS dosing schedule without evidence of PD by IRRC prior to switching	Date of last adequate assessment with evidence of no progression by the IRRC before switching back to the CS dosing schedule	Censored
New anti-lymphoma treatment started without evidence of PD by IRRC	Date of last adequate assessment with evidence of no progression by the IRRC before the start of new anti-lymphoma treatment	Censored
Death or progression after two or more consecutive missed scheduled visits	Date of last adequate assessment with evidence of no progression by the IRRC	Censored

Table 3: Censoring Rules for the Supportive Analysis of DOR

Situation	Date of Event or Censoring	Outcome
Progression documented	Date of earliest assessment which revealed progression determined by the IRRC	Event
Death before first PD assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event
No progression, nor death	Date of last adequate assessment with evidence of no progression by the IRRC	Censored
Treatment discontinuation for any reason other than documented PD or death	Date of last adequate assessment with evidence of no progression by the IRRC	Censored
Loss to follow-up	Date of last adequate assessment with evidence of no progression by the IRRC	Censored
Switching back to CS dosing schedule without evidence of PD by IRRC prior to switching *	Date of earliest assessment which revealed progression determined by the IRRC or death after switching to CS	Event
New anti-lymphoma treatment started *	Date of earliest assessment which revealed progression determined by the IRRC or death	Event
Death or progression after two or more consecutive missed scheduled visits *	Date of earliest assessment which revealed progression determined by the IRRC or death	Event
Investigator claim of clinical progression leading to treatment discontinuation *	Date of clinical progression	Event

* Outcome definitions are different from primary analysis of DOR

3.2.3. Complete Response (CR) Rate

CR rate is defined as the proportion of subjects achieving the best response rating of CR based on the Lugano Classification, as determined by IRRC or Investigator.

The primary analysis for CR will include CR prior to first PD.

As a supportive analysis, CR will be summarized by including CR achieved overall.
i.e, throughout the duration of the study for subjects in IS group switching to CS group.

3.2.4. Progression-Free Survival (PFS)

PFS is defined as time from first dose of study drug until first disease progression or death from any cause for all groups. Disease progression criteria are defined per Modified Lugano Response Criteria and will be assessed by IRRC and Investigator, independently.

As supportive analysis, PFS2 will be defined as time from first dose of CS after switching until disease progression or death from any cause, and PFS3 will be defined as time from first dose of study drug until disease progression or death from any cause after switching back to the CS. PFS2 and PFS3 are only defined for patients in the ITT IS Population (Section 4.2) who switched back to the CS.

The censoring rule for PFS will be the same as the ones for primary analysis for DOR (Table 3), with the exception that subjects with Incomplete or no baseline tumor assessments or no additional follow-up data obtained will be censored at first dose date.

3.2.5. Time to Treatment Failure (TTF)

Time to treatment failure is defined as time from the first dose of study drug to treatment failure. Treatment failure is defined as any treatment discontinuation due to PD, toxicity, or death.

Censoring rule for TTF:

- Subjects who are still alive and on treatment will be censored at the last disease assessment date indicating the absence of progression;
- Subjects who have treatment discontinued for reasons other than PD, AE, or death, will be censored at the treatment discontinuation date.

3.2.6. Recapture of Response

Recapture of response is defined as achieving a second documented CR or PR after experiencing the first PD. The CT scan at PD will be used as new baseline for assessing disease response to ME-401.

Recapture of response rate (RRR) is defined as the proportion of subjects who achieved a CR or PR followed by a PD during IS dosing and subsequently switched to CS dosing and achieved a second documented CR or PR.

Time to recapture of response is defined as the time from the first PD until the second documented CR or PR. Subjects who do not have the second documented CR or PR will be censored at last time of response assessment.

3.2.7. Overall Survival (OS)

OS is defined as time from date of first dose of study drug until death from any cause. OS will be censored at the last date the subject is known to be alive when the confirmation of death is absent or unknown.

3.3. Safety Endpoints

3.3.1. Overall Incidence Rate of Treatment-Emergent Adverse Events (TEAEs)

A TEAE is defined as any new or worsening adverse event occurred after first dose of study drug until 30 days after last dose of ME-401.

The overall incidence rate of TEAEs is calculated as the proportion of subjects with at least one TEAE.

The overall incidence rate of serious adverse events (SAEs) will also be calculated.

3.3.2. Incidence Rate of Adverse Event of Special Interests (AESIs)

The rate of AESIs is calculated as the proportion of subjects with at least one AESI.

3.3.3. Time to Occurrence of Adverse Event of Special Interests (AESIs)

Time to occurrence of AESIs is defined as the time from first dose of study drug to first occurrence of an AESI.

Censoring rules for time to occurrence of AESIs:

- Subjects without AESI who are still on treatment will be censored at the data cutoff date;
- Subjects without AESI who discontinue from treatment will be censored at the treatment discontinuation date.

3.3.4. Other Safety Endpoints

Other safety endpoints include:

- Laboratory test
- Vital signs
- Electrocardiogram (ECG)
- Physical examination

4. ANALYSIS POPULATIONS AND ANALYSIS SETS

4.1. Safety Population

The Safety Population will include all FL and MZL subjects who received at least one dose of study drug. The safety population will be used for analyses of safety endpoints for the Final Analysis for the NDA submission.

4.2. Intent-to-Treat (ITT) Population

The ITT FL population will include all FL subjects randomized per Protocol Amendment 1 (two-arm design with randomization), and all enrolled FL subjects who received at least one dose of study drug per Protocol Amendment 2 or later amendment (single-arm, open-label design).

The ITT IS FL Population is defined as all FL subjects who are intended to receive ME-401 IS regimen, either per Protocol Amendment 1 or per Protocol Amendment 2 or later amendments, including subjects who:

- Were randomized to the ME-401 IS dosing regimen group (Group B) per Protocol Amendment 1
- Were randomized to the ME-401 CS dosing regimen group (Group A) per Protocol Amendment 1, but re-consented to Protocol Amendment 2 (for IS dosing regimen) prior to or on their Cycle 3 visit date
- Were enrolled per Protocol Amendment 2 or later amendment who received ME-401 IS dosing regimen.

The ITT CS Group in the ITT FL Population is defined as all FL subjects who are randomized to the ME-401 CS regimen group (Group A) per Protocol Amendment 1, and did not switch to IS dosing regimen at Cycle 3 visit per Protocol Amendment 2. More specifically, this population includes subjects who were originally randomized to the ME-401 CS dosing regimen group (Group A) per Protocol Amendment 1, had their Cycle 3 visits prior to when the subjects re-consented to Protocol Amendment 2, or discontinued treatment without being re-consented under Protocol Amendment 2.

The ITT MZL population is defined as all enrolled MZL subjects who received at least one dose of ME-401.

Subjects' original treatment assignments are documented in IVRS vendor's randomization listings.

- If the FL patients' ORIGINAL_TREATMENT="ME-401 60 mg 1 wk on/3 wks off" or "Open Label Treatment", they will be included in ITT IS FL Population;
- If the FL patient's ORIGINAL_TREATMENT="ME-401 60 mg daily", and
    - If VISIT_TYPE="Cycle 3 Day 1" and VISIT DATE >= the date when subjects re-consented to Protocol Amendment 2 from Inform Consent CRF data from EDC, they will be included in ITT IS FL Population;
    - If VISIT_TYPE="Cycle 3 Day 1" and VISIT DATE < the date when subjects re-consented to Protocol Amendment 2 from Inform Consent CRF data from EDC, the subject will be included in ITT CS Population;
    - If patients were never consented to Protocol Amendment 2, they will be included in ITT CS Population.

The ITT FL population and ITT MZL population will be used for the analyses of disposition, baseline characteristics, and efficacy endpoints. The overall ITT population (including both ITT FL and ITT MZL populations) will be used for the presentation of subjects in all subject listings.

To evaluate the impact of the covid-19 pandemic on ORR, a Modified ITT (mITT) Population is defined as all ITT FL or ITT MZL patients excluding who discontinued from treatment early due to covid-19 deaths with no post-baseline efficacy assessment.

4.3. Efficacy Analysis Populations and Analysis Sets

The primary efficacy population in FL (PEP FL) is defined as the initial 91 consecutive subjects enrolled in the ITT IS FL Population.

The DOR Primary Analysis Set for FL will include subjects in the PEP FL who achieved PR or CR prior to first PD, that is reported before the data cutoff date for the FL Primary Analysis.

The DOR Supportive Analysis Set for FL will include subjects in the ITT IS FL who achieved PR or CR prior to first PD, that is reported before the data cutoff date for the NDA Analysis for FL.

The DOR Analysis Set for MZL will include subjects in the ITT MZL FL who achieved PR or CR prior to first PD, that is reported before the data cutoff date for the MZL Primary Analysis.

The efficacy evaluable (EE) population will include all subjects who received at least one dose of study drug and had at least one response assessment post baseline.

Subjects will be analyzed by randomized group per Protocol Amendment 1 and by enrolled group (IS dosing) per Protocol Amendments 2 and 3. EE population will be used for selected efficacy analyses.

4.4. Pharmacokinetic (PK) Population

The PK population will include all subjects who received at least one dose of ME-401 and who had evaluable PK data, i.e. quantifiable ME-401 concentrations. The PK population will be used for the analyses of PK endpoints. PK Analysis will be performed separately by central Lab (LGC).

4.5. Per Protocol (PP) Population

The per protocol population will include all subjects who received at least one dose of study drug, had at least one response assessment after Day 1, and did not have any major protocol deviation during the study. Subjects will be analyzed by randomized group per Protocol Amendment 1 and by enrolled group (IS dosing) per Protocol Amendments 2 and 3. PP population will be used for primary efficacy analyses.

4.6. Protocol Deviations

Study protocol deviations will be identified by the clinical team and assigned within the appropriate deviation category. All protocol deviations will be collected separately from the database, and graded as minor or major before the database lock. A summary table for number

and percentage of subjects with major protocol will be summarized by type of deviation and treatment group. A listing will be generated for protocol deviations.

5. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

5.1. General Methods

- All statistical analyses and summaries will be performed using SAS® 9.4 or higher.
- Unless otherwise specified, safety summarized will be presented for all dosed patients by actual dose schedule (CS and IS). For IS group, the safety tables further have 3 sub-columns: FL, MZL, and all IS.
- Detailed types of analyses and corresponding populations for planned Primary Analysis and NDA Analysis for FL is shown in Table 4.
- Unless otherwise specified, descriptive statistics for continuous data will include the number of subjects (n), mean, standard deviation (SD), minimum and maximum. For discrete variables, frequency count and percentages will be computed. Percentages based on frequency counts will be based on available data, and denominators will generally exclude missing values, unless otherwise stated. All percentages will be presented with one decimal, unless otherwise specified. Percentages equal to 100 will be presented as 100, and percentages will not be presented for zero frequencies.
- The same number of decimal places as in the raw data will be presented when reporting min and max, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD. If the raw data has 3 decimal places or more, 3 decimal places will be presented for mean, median, Q1/Q3, and SD. For continuous variables assessed at baseline and post-baseline, the change from baseline summary statistics will also be presented.
- Subject listings of all data in the database will be provided, including data collected in the electronic case report form (eCRF) as well as data transferred electronically. Measurements from subjects excluded from the pre-defined analysis populations or extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables unless specified otherwise, but will be included in the subject listings. Listings will be sorted by treatment groups, subject number, and visit/collection date/time if applicable, unless otherwise stated.
- All fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12 - 0.30, not .12 - .30).

Table 4: Types of Analyses and Corresponding Populations for Planned Primary Analysis and NDA Analysis for FL

Planned Analysis	Type of Analysis	Population	Analysis Set / Group
Primary Analysis for FL	Baseline disposition and demographics	ITT IS FL	ITT IS FL Total
	Primary endpoint ORR	PEP FL[1]	PEP FL
	Secondary endpoint DOR	PEP FL	DOR Primary Analysis Set for FL
	Selected Critical Secondary endpoints (PFS, OS)	PEP FL	PEP FL
	Selected Safety endpoints	Safety IS FL population	Safety IS FL Total
NDA Analysis for FL	Baseline disposition and demographics	ITT FL	PEP FL, ITT IS FL, ITT CS, ITT FL Total
	Primary endpoint ORR (Primary Analysis) and all secondary endpoints	PEP FL[1]	PEP FL
	Primary endpoint ORR (Supportive Analysis)	PEP FL[2]	PEP FL
	Primary endpoint ORR (Supportive Analysis)	ITT FL[3]	PEP FL, ITT IS FL, ITT CS, ITT FL Total
	Secondary endpoint DOR (Primary Analysis)	PEP FL	DOR Primary Analysis Set for FL
	Secondary endpoint DOR (Supportive Analysis)	ITT IS FL	DOR Supportive Analysis Set for FL
	Selected critical efficacy endpoints (PFS, OS, etc.)	ITT FL	PEP FL, ITT IS FL, ITT CS, ITT FL Total
	Safety endpoints	Safety population	IS FL, IS MZL[4], IS Total, CS
Primary Analysis and NDA Analysis for MZL	Baseline disposition and demographics	ITT MZL	ITT MZL
	Primary endpoint ORR and all secondary endpoints (except DOR)	ITT MZL	ITT MZL
	Secondary endpoint DOR	ITT MZL	DOR Analysis Set for MZL
	Safety endpoints	Safety population	IS FL, IS MZL, IS Total, CS

[1] Primary analysis for ORR will include best response of PR and/or CR prior to first PD that is reported before the data cutoff date for FL Primary Analysis, among all patients in the Primary Efficacy Population in FL (PEP FL).
[2] Supportive analysis for ORR will include PR or CR achieved that is reported before the data cutoff date for NDA Analysis for FL, among all patients in the Primary Efficacy Population in FL.
[3] Supportive analysis for ORR will include PR or CR achieved that is reported before the data cutoff date for NDA Analysis for FL, among all patients in the ITT FL Population.
[4] Including MZL patients in the Safety Population who were dosed prior to the data cutoff date for the NDA Analysis for FL.

5.2. Key Definitions

5.2.1. Baseline

Unless otherwise specified, baseline is defined as the last non-missing assessment prior to the first dose date of study drug and within 28 days of first dose date. In cases where measurements are taken on the same day as the first dose of study drug and no times are reported, it will be assumed that these measurements are taken prior to study drug being administered therefore can be defined as baseline measurements.

5.2.2. Change from Baseline

Change from baseline will be calculated as post-baseline value – baseline value. If either the baseline or post-baseline value is missing, the change from baseline is set to "missing".

Percentage change from baseline will be calculated as [(Post baseline value – Baseline value)/Baseline value] ×100.

5.2.3. Study Day

Study day will be calculated from first dose as:

Study day = date of assessment – date of first dose +1 if the date of assessment is later than the date of first dose; Otherwise Study day = date of assessment – date of first dose.

One cycle corresponds to 28-days, with the first day of treatment designated as Day 1. For subjects who are randomized/enrolled but not dosed, Day 1 will be the randomization/enrollment day.

5.3. Missing Data

Missing efficacy data will not be imputed.

5.3.1. Handling of Missing Dates/Months/Years for All Adverse Events

If the start/end date of an AE is partially missing, the date will be compared as far as possible with the first dose date of study drug. The AE will be assumed as treatment emergent if it cannot be definitively shown that the AE did not occur or worsen during the treatment-emergent period, from first dose of study drug to 30 days after last dose of study drug (worst case approach).

- Start dates:
  - For missing start day only: Day will be imputed as the first day of the month (i.e., 01) with the following exception: if the partial date falls in the same month and year as first dose date, then the partial date will be imputed to equal first dose date.
  - For missing start day and month: Day and month will be imputed as the first day of the year (i.e., 01 January) with the following exception: if the partial date falls in the same year as first dose date, then the partial date will be imputed to equal first dose date.
  - For missing start day, month, and year: Date will be imputed to the first dose date.

- Imputed start dates must be prior to the discontinuation date or completion date.

- Stop dates:
  - For missing stop day only: Day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31).
  - For missing stop day and month: Day and month will be imputed as the last day of the year (i.e., 31 December).
  - For missing stop day, year, and month: Date will be imputed as date of discontinuation or completion.
  - Imputed dates should not extend beyond the date of completion or discontinuation.
  - Imputed stop dates must be on or after the start date.

5.3.2. Handling of Missing Dates/Months/Years for Concomitant Medications

Prior or concomitant medications with incomplete dates will be handled as follows for the sole purpose of determining whether a non-study medication is a concomitant medication. If the start/stop date of a medication is partially missing, the date will be compared as far as possible with the first dose date of study drug and the medication will be assumed as concomitant if it cannot be definitively shown that the stop date is before the start of administration of study drug, or the start date is after the last visit of the study.

- If the start and stop dates are both completely missing, a medication will be considered concomitant.

- Start date:
  - For missing start day only: Day will be imputed as the first day of the month (i.e., 01).
  - For missing start day and month: Day and month will be imputed as the first day of the year (i.e., 01 January).
  - Missing start dates will not be imputed.

- Stop date:
  - For missing stop day only: Day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31).
  - For missing stop day and month: Day and month will be imputed as the last day of the year (i.e., 31DEC).
  - Imputed stop dates must be on or after the start date.

The original partial or missing date will be shown in listings of all non-study medications.

5.4. Visit Windows

For study assessment days, there is ± 3-day window allowable for each clinic visit during Cycle 1. For Cycles 2 through 25, the allowable window is ± 7 days. After Cycle 25, the allowable window is ± 1 month for each clinic visit and its associated assessments.

There is no plan to re-assign visits based on actual visit dates. The analysis will be based nominal visit/time points collected.

5.5. Subgroups

- Tumor bulk (largest lymphoid mass <5 cm vs. ≥5 cm)
- Tumor bulk (largest lymphoid mass <7 cm vs. ≥7 cm)
- Prior use of lenalidomide in combination of rituximab (yes vs. no)
- Disease response to last therapy (relapse vs. refractory)
- Disease response to prior anti-CD monoclonal antibodies (relapse vs. refractory)
- Disease response to prior alkylating agents (relapse vs. refractory)
- Disease response to prior bendamustine (relapse vs. refractory)
- Disease response to prior immunochemotherapy (relapse vs. refractory)
- Number of prior lines of systemic cancer treatments (2 vs. >2)
- Number of prior lines of chemo regimens (1, 2-3, 4+)
- PD within 24 months of first line immunochemotherapy (POD24) (yes vs. no)
- Age (<65 vs. ≥65)
- Sex (Male vs. Female)
- Region (North America, Europe, Asia-Pacific)
- Race (Caucasian, Black, Asian, Other)
- Baseline Eastern Cooperative Oncology Group (ECOG) (0 vs. ≥1)
- Disease stage at diagnosis (1-2 vs 3-4)
- Disease stage at study enrollment (1-2 vs 3-4)
- Duration of treatment-free interval from the last lymphoma-directed therapy: ≤6 months, >6 months
- Baseline lactate dehydrogenase (LDH) (normal vs abnormal)
- History of bone marrow involvement (yes vs. no)
- Extra-nodal disease (yes vs. no)

6. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

6.1. Subject Eligibility, Disposition and Protocol Deviations

The subject disposition table will summarize the number of subjects screened, the number and percentage of subjects in each analysis set, the number and percentage of subjects who

discontinued treatment, along with reasons of treatment discontinuation, and the number and percentage of subjects who discontinued study, along with reasons of study discontinuation. The summary tables will be generated separately for all subjects, ITT FL Population, and ITT MZL Population.

Separate by-subject listings will be provided for subject disposition, eligibility, analysis populations, and protocol deviations.

Subject follow-up time (months) on study will be provided in disposition summaries. It is defined as (date of data cutoff – date of first dose + 1) / 30.4375 for patients remaining on study, and (End of Study date – date of first dose + 1) / 30.4375 for patients who discontinued from study.

6.2. Demographic and Other Baseline Characteristics

Descriptive statistics will be presented for continuous variables including age, height, weight, body mass index (BMI) at baseline. The frequency and percentage of subjects will be tabulated for categorical variables including age group (<65 vs. ≥65), sex, child-bearing potential, race, ethnicity, and region of enrollment at baseline. The summary tables will be produced separately for Safety Population, ITT FL Population, and ITT MZL Population.

All demographic data at baseline will be listed.

6.3. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall for Safety Population, ITT FL Population, and ITT MZL Population.

- Tumor bulk (largest lymphoid mass <5 cm vs. ≥5 cm, and 7 cm vs. ≥7 cm)
- Disease response to last therapy (relapse vs. refractory)
- Disease response to specific prior cancer therapies (relapse vs. refractory)
    - Anti-CD20 monoclonal antibodies
    - Alkylating agents
    - Bendamustine
    - Immunochemotherapies
- Stage at diagnosis (I, II, III, IV), stage at study entry (I, II, III, IV), and grade at study entry (1, 2, 3a)
- POD24 (yes vs. no)
- Baseline ECOG (0 vs. ≥1)
- Duration of treatment-free interval from the last lymphoma-directed therapy: ≤6 months, >6 months
- Baseline LDH (normal vs abnormal)

Disease response to prior therapy is defined as follows:

- Relapsed disease: disease progression after a response (CR or PR) lasting ≥6 months

6.4. Refractory Disease: No Response to Therapy (no CR or PR) or Response Lasting <6 months Medical History and Concomitant Diseases

Medical History will be coded into system organ class (SOC) and preferred term (PT) by Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 or later. Medical history will be listed but not summarized.

Medical history data listings will be produced.

6.5. Prior and Concomitant Medications

All prior and concomitant medications and therapies will be recorded from 28 days prior to Cycle 1 Day 1 through 30 days after last dose of ME-401, treatment discontinuation, or until a subsequent anti-cancer therapy is initiated. Medications will be coded by World Health Organization Drug Dictionary (WHO DD) Version Global B3 Sep2018 or later.

Prior medications are medications which stop before the start of study drug. Concomitant medications are medications which start or stop on or after the start of study drug.

For the classification of prior medications vs. concomitant medications, incomplete start or stop dates of medications will be imputed using the algorithm in Section 5.3.2. The medication will be assumed as concomitant if it cannot be definitively shown that the stop date is before the first dose date of study drug.

Prior and concomitant medications will be coded into Anatomical Therapeutic Chemical (ATC) classification levels and preferred term. All prior and concomitant medications will be listed but not summarized.

6.6. Prior Therapies

The following prior therapies will be summarized using the number and percentage of subjects with each therapy type using Safety Population.

- Prior cancer surgery for follicular lymphoma
- Prior radiotherapy
- Prior transplant
- Prior Cancer therapy
    - Anti-CD20 monoclonal antibodies
    - Alkylating agents
    - Bendamustine
    - Immunochemotherapies
    - Lenalidomide in combination of rituximab

- Number of prior lines of cancer therapies (2 vs. >2)
- Number of prior lines of chemo regimens (1, 2-3, 4+)

The data of prior therapies will also be listed.

6.7. Concomitant Procedures

The concomitant medical procedures will be listed but not summarized.

7. EFFICACY ANALYSIS

7.1. Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint is ORR, defined as the proportion of subjects achieving the best response rating of CR or PR based on the Modified Lugano Classification, assessed by IRRC.

For Primary Analysis and NDA Analysis for FL, ORR will be evaluated by summarizing the number and percentage of subjects with the best overall response (CR/PR) prior to first PD as assessed by IRRC that is reported before the data cutoff date for the Primary Analysis, along with 2-sided 95% exact Clopper-Pearson confidence interval (CI). The primary efficacy analysis will be based on the Primary Efficacy Population for FL (PEP FL).

As a supportive analysis for NDA Analysis for FL, ORR will be analyzed

- using the ITT FL Population by including the PEP FL, ITT IS FL, ITT CS, ITT FL Total patients
- by summarizing the number (percentage) of patients who achieved PR or CR before the data cutoff date for the NDA Analysis for FL submission.

As sensitivity analyses, the above analyses in Section 7.1 will be repeated for EE population and PP population.

All subjects who did not meet the criteria for an objective response by the analysis cut-off date will be considered non-responders.

To evaluate the impact of the covid-19 pandemic on efficacy of ME-401, the above analyses in Section 7.1 will also be conducted using the Modified ITT Population in IS FL patients, i.e., patients who discontinued from treatment early due to covid-19 deaths with no post-baseline efficacy assessment will be excluded from the analysis.

Subgroup analysis of ORR (the proportion of subjects with the best overall response [CR/PR] prior to first PD as assessed by IRRC), that is reported before the data cutoff date for the Primary Analysis, will be performed by the subgroups defined in Section 5.5, based on PEP FL and ITT MZL population. Forest plots will be provided for ORR and 95% CI in selected subgroups.

Waterfall plots of maximum percentage decrease in sum of the products of longest diameters (SPD) measured by the IRRC will be provided for the patients in the PEP FL and ITT MZL population.

7.2. Secondary Efficacy Endpoints and Analyses

7.2.1. Objective Response Rate (ORR) by Investigator

Secondary analysis of the ORR, as determined by the investigator, will be repeated as described above for the analyses of primary efficacy endpoint in Section 7.1.

The concordance in best overall response between IRRC and Investigator assessments will be summarized.

Waterfall plots of maximum percentage decrease in sum of the products of longest diameters (SPD) measured by the investigator will be provided for the patients in the PEP FL and ITT MZL population.

7.2.2. Duration of Response (DOR) and Duration of Recaptured Response (DORR)

DOR is the time from first response (CR or PR) to the time of first PD or the date of death due to any cause (whichever occurs earlier).

For Primary Analysis and NDA Analysis for FL, DOR will be analyzed using the DOR Primary Analysis Set for FL.

As a supportive analysis for NDA Analysis for FL, DOR will be analyzed using the DOR Supportive Analysis Set.

For the Primary and NDA Analysis for MZL, DOR will be analyzed using the DOR Analysis Set for MZL.

Subgroup analysis of DOR using the DOR Primary Analysis Set for FL and the DOR Analysis Set for MZL will be performed by the subgroups defined in Section 5.5.

DORR is the time from recapture of response (CR or PR) to the time of second PD or the date of death due to any cause (whichever occurs earlier).

The assessment of DOR and DORR assessed by IRRC and by Investigator will be summarized separately.

DOR and DORR will be summarized using Kaplan-Meier (KM) summary statistics. The min, max, median duration of response with 95% CI (based on the LOGLOG transformation), number of events, number censored with types of censoring and, KM plot for cumulative probability of DOR and DORR over time will be presented. DOR and DORR will be reported in months. Only subjects who had a response will be included in this summary table, and the denominator will be all subjects in each population who had a documented CR or PR response. Estimates and 95% CIs for DOR rates at 3 months, 6 months, 9 months and 12 months, and, median with 95% CI of the follow-up time (months) based on reverse KM estimate of the DOR time (by reversing the censoring/event status) will be summarized.

KM estimates of DOR will be provided by best response type (CR vs PR).

Forest plots will be provided for median DOR and 95% CI in different subgroups.

7.2.3. Complete Response (CR) Rate

The CR rate is proportion of subjects achieving the best response rating of CR, and will be assessed separately by IRRC and investigator.

For FL Primary Analysis and Final Analysis, the CR rate will include CR prior to first PD that is reported before the data cutoff date for Primary Analysis.

As a supportive analysis in Final Analysis, CR rate will be summarized by including CR achieved that is reported before the data cutoff date for NDA Analysis for FL.

For CR rate, the number and percent (%) of subjects with 2-sided 95% exact Clopper-Pearson CIs will be summarized for subjects in PEP FL, ITT MZL population, ITT FL population (for NDA Analysis for FL only), EE population, and PP Population.

7.2.4. Progression Free Survival (PFS)

PFS is the time from first dose of study drug until first disease progression or death from any cause. The analysis of PFS will be performed based on the assessment by IRRC and investigator, separately.

PFS will be summarized using Kaplan-Meier summary statistics for PEP FL, ITT MZL population, and ITT FL population (for NDA Analysis for FL only). The min, max, and median PFS with 95% CI (based on the LOGLOG transformation), number of events, number censored with types of censoring, and KM plot for cumulative probability of PFS over time will be presented. PFS will be reported in months. Estimate and 95% CI for PFS rates at 6 months, 12 months, 18 months and 24 months, and median with 95% CI of the follow-up time (months) based reverse KM estimate of the PFS time (by reversing the censoring/event status) will be summarized.

KM estimates of PFS will be provided by best response type (CR, PR and non-responders).

7.2.5. Time to Treatment Failure (TTF)

TTF is the time from the first dose of study drug to treatment failure (any treatment discontinuation due to PD, toxicity, or death). The analysis of TTF will be performed based on the assessment by IRRC and investigator, separately.

TTF will be summarized using Kaplan-Meier summary statistics for PEP FL and ITT MZL population. The median TTF with 95% CIs (Brookmeyer and Crowley method), number of events, number censored, and KM plot of proportion of subjects without treatment failure over time will be presented. TTF will be reported in months. Estimate and 95% CI for 1-year TTF rate, and reverse KM estimate median with 95% CI for follow-up time (months) will be summarized.

7.2.6. Recapture of Response Rate (RRR)

RRR is the proportion of subjects who achieved a CR or PR followed by a PD during IS dosing and subsequently switched to CS dosing and achieved a second documented CR or PR. The analysis of RRR will be performed based on the assessment by IRRC and investigator, separately.

For RRR, the number and percent (%) of subjects with 2-sided 95% exact Clopper-Pearson CIs will be summarized for subjects who achieved a CR or PR followed by a PD during IS dosing and subsequently switched to CS dosing, in PEP FL and ITT MZL population.

7.2.7. Time to Recapture of Response

Time to recapture of response is the time from the first PD until the second documented CR or PR. The analysis of time to recapture of response will be performed based on the assessment by IRRC and investigator, separately.

Time to recapture of response will be summarized using Kaplan-Meier summary statistics only for subjects who achieved a CR or PR followed by a PD during IS dosing and subsequently switched to the CS dosing, in PEP FL and ITT MZL population. The median time to recapture of response with 95% CI (Brookmeyer and Crowley method), number of events, number censored and, and KM plot of proportion of subjects without recapture of response over time will be presented. Time to recapture of response will be reported in months. Estimate and 95% CI for 1-year rate of time to recapture of response, and reverse KM estimate median with 95% CI for follow-up time (months) will be summarized.

7.2.8. Overall Survival (OS)

OS is the time from date of first dose of study drug until death from any cause, and will be summarized by Kaplan-Meier summary statistics for PEP-FL, ITT MZL population, ITT FL population (for NDA Analysis for FL only).

Kaplan-Meier plots of OS will be presented. Summaries of the number and percentage of subjects who had died, were still in survival follow-up, were lost to follow-up and had withdrawn consent will be provided along with the median OS times and 95% CIs (Brookmeyer and Crowley method). Overall survival will be reported in months. Estimate and 95% CI for 1-year OS rate, and reverse KM estimate median with 95% CI for follow-up time (months) will be summarized.

8. SAFETY ANALYSES

Safety analyses will be presented and summarized in the safety population for the Primary Analysis for FL and NDA Analysis for FL, and include overall IS group, IS FL, MZL, and CS group.

Safety IS FL population will be used to analyze safety endpoints for the FL Primary Analysis.

8.1. Extent of Exposure

Exposure to ME-401 will be evaluated by duration of study drug exposure (months), actual dose intensity, and relative dose intensity for the safety population.

Descriptive statistics will be presented for continuous exposure variables: duration of exposure, actual dose intensity, and relative dose intensity. The number and percentage of subjects with dose schedule modified or dose interrupted due to AE or progressive disease will be summarized. The number and percentage of subjects with dose missed will be summarized by

reason. For subjects on study drug at the time of the ORR analysis, the data cut-off (DCO) date will be used to calculate exposure.

- Duration of exposure (months) = (Date of last non-zero dose – Date of first non-zero dose +1) /30.4375.
- Duration of exposure on the CS (months)
  - = (Date of last non-zero CS dose – Date of first non-zero CS dose +1) /30.4375 for subjects who never switched dosing regimen; or
  - = sum of (Date of last non-zero CS dose – Date of first non-zero CS dose +1) /30.4375 from each CS dosing interval for subjects who switched dosing regimens; date of first or last CS dose can be derived based on the switching date.
- Duration of exposure on the IS (months)
  - = (Date of last zero/non-zero IS dose – Date of first non-zero IS dose +1) /30.4375
- Actual total dose exposed (mg) is defined as the sum of 'total mg' of study drug received.
- Total dose intended (mg) is defined as the sum of 'total mg' of study drug planned.
  - Total dose intended for the CS is estimated to be 60 mg x Duration of exposure on the CS (months) x 30.4375
  - Total dose intended for the IS is estimated to be (60 mg /4) x Duration of exposure on the IS (months) x 30.4375
- Actual dose intensity (mg/month) = 30.4375 x Actual total dose exposed (mg) ÷ [(Date of last dose, zero or non-zero dose of study drug) – (Date of first non-zero dose of study drug) + 1]
- Intended dose intensity (mg/month) = 30.4375 x Total dose intended (mg) ÷ [(Date of last dose, zero or non-zero dose of study drug) – (Date of first non-zero dose of study drug) + 1]
- Relative dose intensity (RDI) (%) is the percentage of the actual dose intensity delivered relative to the intended dose intensity through to study drug discontinuation. RDI (%) = (actual dose intensity) ÷ (intended dose intensity) x 100

8.2. Treatment Compliance

The study drug compliance (%) will be calculated as:

- Overall Compliance (%) = [total dose exposed (mg) / total dose intended (mg)] x 100
- Compliance (%) on the CS = [Total dose exposed (mg) on the CS / total dose intended (mg) on the CS] x 100
- Compliance (%) on the IS = [Total dose exposed (mg) on the IS / total dose intended (mg) on the IS] x 100

For subjects on study drug at the time of the ORR analysis, the data cut-off (DCO) date will be used to calculate compliance.

8.3. Adverse Events and Adverse Events of Special Interest

Adverse events (AEs) will be captured from the first dose of study drug and continue until 30 days after the last dose of study drug. All AEs will be classified to SOC and PT by MedDRA Version 21.1 or later.

The Investigator will assess AEs for severity and relationship to study drug and determine if an AE meets the criteria for a SAE. The relationship of an AE to study drug is to be classified as 'Related', 'Possibly Related', or 'Not Related' by investigators. The study drug related AEs include both 'Related' and 'Possibly Related' AEs. Each AE will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. For the purpose of the summaries, AEs with missing relatedness will be considered to be related ME-401. AEs with missing severity (CTCAE grade) will be considered grade 3 (severe).

All AE listings will include the date of onset, date of resolution (if AE is resolved) and investigator's assessment of severity and relationship to study drug. Missing (partial) start/stop dates will appear as missing (partial) in the subject data listings, but will be imputed to permit proper tabulation of AE data (See Section 5.3.1).

AEs will be summarized descriptively by number and percentage (%) of subjects with an event (n (%)), and number of events [e], by MedDRA SOC/PT and CTCAE grade.

A subject will be counted once at the SOC level and once at PT level. For summaries by SOC, PT, and intensity, a subject will be counted only at the maximum intensity level. Summaries by relatedness would be handled similarly to the summaries by intensity. Summaries by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT. Summaries of PT will be ordered in descending frequency of PT.

8.3.1. Treatment-Emergent Adverse Event (TEAE)

TEAE is any new or worsening AE that started after the first dose of study drug until 30 days after the last dose of study drug. Treatment emergence will be determined by comparing the AE onset date with first dose date. If AE onset date is incomplete, treatment emergence will be imputed according to the algorithm in Section 5.3.1. In general, only TEAEs will be included in the AE summaries but all AEs will be included in the listings.

8.3.2. Adverse Events of Special Interest (AESI)

AESIs are events of scientific and medical interest specific to the further understanding of the ME-401 safety profile. For ME-401, AESIs will comprise of (see study protocol Section 5.3.2):

- Cutaneous reactions, including skin rash Grade ≥2
- Oral mucositis or stomatitis Grade ≥2
- Diarrhea/colitis Grade ≥2
- AST/ALT Grade ≥2
- Non-infectious pneumonitis (NIP) of any grade
- Lung infection/pneumonia Grade ≥2
- Cardiomyopathy of any grade

AESI will be summarized by selected subgroups.

8.3.3. Summaries of Incidence of Adverse Events

The number and percentage of subjects reporting TEAEs and AESIs will be summarized as below:

- Overall summary of TEAEs and AESIs
- TEAEs by SOC and PT
- TEAEs by PT
- TEAEs of Grade 3 and above by PT
- TEAEs by maximum grade and PT
- TEAEs leading to treatment discontinuation by PT
- TEAEs related to ME-401 leading to treatment discontinuation by PT
- TEAEs leading to treatment interruption by PT
- TEAEs related to study drug by PT
- AEs leading to death by PT
- Treatment-related AEs leading to death by PT
- Treatment-Emergent SAEs by SOC and PT
- Treatment-Emergent SAEs by PT
- Treatment-Emergent SAEs by maximum grade and PT
- Treatment-emergent AESIs by AESI Type and PT
- Treatment-emergent Grade 3 and Above AESIs by AESI type and PT
- Covid-19 events by grade
- Other important safety events including opportunistic infection, CMV infection, PJP infection, and fungal infection, cytopenia event, pulmonary event by maximum grade and PT

Selected analysis on TEAEs will be summarized by subgroups.

Listings will be produced for all AEs, TEAEs, SAEs, AEs leading to treatment discontinuation, AEs leading to death, AESI, and for subjects with grade 3 and above AEs.

8.3.4. Analysis of Time to Occurrence of AESIs

As primary analysis, time to occurrence of AESIs is the time from first dose of study drug to first occurrence of AESI.

As a supportive analysis, time to first occurrence of Grade 3 and above AESIs will be analyzed similarly.

Kaplan-Meier summary statistics median time to occurrence of AESI and 95% CI (Brookmeyer and Crowley method), number of events, number censored and, KM figures will be presented by dosing group. Time to occurrence of AESI will be reported in weeks. A separate listing of time to occurrence of AESI will be created. Reverse KM estimate median with 95% CI for follow-up time (months) will be summarized.

8.4. Laboratory Evaluations

Lab evaluations will include hematology (including coagulation), serum chemistry, urinalysis, pregnancy test, HIV testing, Hepatitis B and Hepatitis C testing, bone marrow aspiration/biopsy, PCR tests for CMV and opportunistic infection (OI) monitoring.

For statistical and graphical summaries of the laboratory tests, values below or above the limit of detection (e.g., '< 3' or '>500') are substituted with the lower limit of detection minus 1% for values below the lower limit and are substituted with the upper limit of detection plus 1% for values above the upper limit (e.g., '< 3' is substituted by '2.97', '> 500' is substituted by '505'). In data listings, the values are shown including the < or > sign.

Results from the hematology, chemistry, and urinalysis will be summarized by visit using descriptive statistics, including the observed values and change from baseline values for numeric parameters and distribution of categories for categorical parameters. Boxplots by visit will be generated for selected hematology/chemistry parameters.

In addition, the incidence rate of grade 3 and above toxicity for selected hematology and chemistry parameters will be summarized by visit. Separate listings will be produced for subjects with grade 3 and above toxicity for selected hematology and chemistry parameters.

Treatment-emergent toxicities are defined as the worsening of lab toxicity grade comparing to the baseline. The incidence rate of treatment-emergent grade 3 and above toxicity for hematology and chemistry parameters will be summarized by visit.

By-subject listings of hematology, serum chemistry, and urinalysis tests, including lab normal ranges, will be provided. Derived CTCAE grades will be included in listings, as applicable.

The following lab data will be listed only: pregnancy test, HIV, Hepatitis B and Hepatitis C tests, bone marrow aspiration/biopsy, CMV titers, and OI monitoring.

8.5. Vital Signs

Vital sign measurements will include the measurement of height, weight, and systolic and diastolic blood pressure, heart rate, and body temperature.

Results from each parameter will be summarized by visit using descriptive statistics, including the observed values and changes from baseline.

All vital signs data will be listed.

8.6. Cardiac Evaluations

12-lead ECGs parameters including hear rate, RR interval, PR interval, QRS interval and QTcF will be assessed. For each parameter, the observed values and change from baseline will be summarized by visit.

The overall ECGs interpretations will be collected as 'Normal', 'Abnormal, not clinically significant' and 'Abnormal, clinically significant. Shift tables from baseline will be produced based on these categories for each post-baseline. In addition, the incidence rate of grade 3 and above QT prolongation will be summarized by visit.

All 12-lead ECG data will be listed. In addition, the results of echocardiogram will be listed.

8.7. Physical Examination

The physical examination will include examination of all organ systems. A symptom-directed exam will be performed only if needed/indicated, based on interim history. Skin assessments will be required for subjects who developed a rash.

Listings will be produced for physical examination and skin assessments.

8.8. Eastern Co-operative Oncology Group (ECOG)

ECOG performance status data will be summarized by visit, and listed.

9. INTERIM ANALYSES

No formal interim analysis is planned for this study.

An independent DSMB (Data Safety and Monitoring Board) will review descriptive summaries of accumulating safety, subject disposition and limited efficacy data every 6 months. Further description of the DSMB analyses are included in the DSMB charter.

10. CHANGES FROM ANALYSIS PLANNED IN PROTOCOL

No changes from planned analysis in protocol.

11. REFERENCE LIST

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol. 2014;32(27):3059–67.

EMA (2013) Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man (CHMP/EWP/205/95 Rev.4): methodological considerations for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials. EMA/CHMP/27994/2008/Rev.1.

FDA 2015 Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics.

FDA 2018 Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

12. PROGRAMMING CONSIDERATIONS

12.1. General Considerations

- One SAS program can create several outputs.
- One output file can contain several outputs.
- Output files will be delivered in Word format (.rtf) which enable pasting to Word document with minimal formatting required / portable document format (.pdf).
- Numbering of TLFs will follow International Conference on Harmonization (ICH) E3 guidance.

12.2. Table, Listing, and Figure Format

12.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font or Times New Roman, size 9.
- The data displays for all TLFs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font or Times New Roman, size 9.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified.
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.
- Tables and listing should not have vertical grid lines or borders, but only horizontal lines on the header rows and bottom row.

12.2.2. Headers

- All output should have the following header at the top left of each page:

  MEI Pharma; Protocol No.: ME-401-003
  Draft/Final Run

- All output should have Page n of N at the top or bottom right corner of each page. TLFs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date output was generated should appear along with the program name as a footer on each page.

12.2.3. Display Titles

- Each TLF is identified by the designation and a numeral. (i.e., Table 14.1.1). The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

12.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

12.2.5. Body of the Data Display

12.2.5.1. General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

12.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter.
  If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.

- P-values are output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value is returned as >0.999, then present as >0.999
- Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group will be the denominator.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(count)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

12.2.5.3. Listing Conventions

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display and date the program was run (i.e., 'Program : xxx.sas Table Generation: DDMMMYYYY').

13. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.