PROTOCOL 8400-402

Study Title	Phase 1/2 Open-label, Multiple-dose, Dose-escalation Study to Evaluate the Safety and Tolerability of IMO-8400 in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma and Presence of the MYD88 L265P Mutation
Investigational Drug:	IMO-8400
FDA IND:	119651
Sponsor:	Idera Pharmaceuticals, Inc. 167 Sidney Street Cambridge, MA 02139
Protocol Number:	8400-402
Protocol Version:	4.0
Date:	29 Jan 2016

Protocol Approval Page

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Approved for the Sponsor by:

Mark Cornfeld, MD, MPH
Medical Lead, Oncology
Idera Pharmaceuticals, Inc.

Signature Date

Revision History

Ver. No.	Date	Comment
1.0	07 Mar 2014	Initial release
2.0	07 Nov 2014	Added: Pre-screening for L265P mutation, Revised: Assay for MYD88 L265P mutation advanced from commercial Clinical Laboratory Improvement Amendments (CLIA)-assays to Investigational Use Only (IUO) level assay; exclusion laboratory results: defined specific analytes and exclusionary values related to hematology, renal, hepatic and coagulation function. Deleted: Provision for self-administration of study drug; use of 50 mg vials of drug product; details of dose preparation (now in Study Pharmacy Manual) Administrative and technical clarifications Version 2.0 was not released.
2.1	12 Nov 2014	Technical revisions to specifications of MYD88 L265P assay This version tracks all changes from version 1.0.
3.0	09 Jun 2015	Addition of complement component 3 (C3) complement testing for safety assessments; establishes Cohort Review Committee in place of Dose Review Committee; changes dose-limiting toxicity (DLT) language; revises inclusion criteria to include a positive MYD88 L265P result from any CLIA-compliant assay; revises exclusion criteria to include diffuse large B-cell lymphoma (DLBCL) variants; revises dosing for expansion cohorts; removes extended treatment under a separate protocol and allows for responding or stable patients to remain on study until disease progression or intolerable toxicity; follows patients for survival.
4.0	29 Jan 2016	Updates patient population; clarifies and separates study by Phase 1 (dose escalation) and Phase 2 (dose expansion cohort); adds additional dose escalation cohorts; adds an interim analysis for futility in Phase 2; clarifies both study phases including dose escalation rules, number of patients expected to be enrolled, and rationale for enrollment; clarifies inclusion criteria; updates statistical analysis procedures and rationale, including determination of sample size; clarifies cohort review committee procedures and responsibilities; clarifies that bone marrow biopsy is optional and lymph node biopsy is required; adds safety procedures for patients with symptomatic thrombocytopenia; adds pre-treatment criteria; adds definition for other reportable events in safety analyses; other administrative and technical clarifications and procedural clarifications.

Contact Information

Any serious adverse event (SAE) must be reported within 24 hours using the study Electronic Data Capture (EDC) system.

See Section 10.5 for detailed reporting procedures.

Table 1: Emergency and Pharmacovigilance Contacts

Role in Study	Name, Title, Address	Telephone and Email
24-Hour Emergency Contact	Mark Cornfeld MD, MPH Medical Lead, Oncology Idera Pharmaceuticals, Inc. 505 Eagleview Blvd., Suite 212 Exton, PA 19341	Office: +1 484 348 1629 Cell: +1 609 240 7312 email: mcornfeld@iderapharma.com
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Table 2: Study Contact Information

Role in Study	Name, Title, Address	Telephone and Email
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1. SYNOPSIS

1.1. Protocol Information

Protocol Number	**8400-402**
Protocol Title	Phase 1/2 Open-label, Multiple-dose, Dose-escalation Study to Evaluate the Safety and Tolerability of IMO-8400 in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma and Presence of the MYD88 L265P Mutation
Sponsor	Idera Pharmaceuticals, Inc.
Name of Finished Product	IMO-8400 for Injection, 150 mg
Name of Active ingredient	IMO-8400
Phase of Development	1/2
Indication (Target)	Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL)
Number of Patients	Up to 30 patients in planned dose escalation cohorts and up to 29 patients in an expansion phase
Number of Sites	Multiple Centers in the US
Est. Date First Patient Enrolled	Q2 2014
Est. Date Last Patient Enrolled	Q2 2017
Est. Date Last Patient Last Visit	Q4 2017

1.2. Objectives

1.2.1. Primary Objective

- To evaluate the safety and tolerability of escalating dose levels of IMO-8400 administered by subcutaneous (SC) injection in patients with relapsed or refractory non-GCB subtype diffuse large B-cell lymphoma (DLBCL).

1.2.2. Secondary Objectives

- To assess the treatment effect (clinical activity) in patients with non-GCB subtype DLBCL with myeloid differentiation primary response gene (88) (MYD88) L265P mutations using disease-specific international guidelines for classifying clinical response [1].
- To identify an optimal dose of IMO-8400 for further clinical evaluation in B-cell malignancies.
- To characterize the pharmacokinetics of escalating dose levels of IMO-8400 administered by SC injection.

1.2.3. Exploratory Objectives

- To investigate associations between the treatment effect of IMO-8400 and selected biomarkers (e.g., serum cytokines).
- To assess the potential immunogenicity of IMO-8400 administered by SC injection.

1.3. Study Design and Methodology

1.3.1. Brief Background

IMO-8400 is a second-generation oligonucleotide antagonist of Toll-like receptors (TLRs) 7, 8 and 9, which blocks immune activation mediated through those receptors.

MYD88 is the initial linker protein in the TLR signaling pathway. Recent studies indicate a high frequency of mutation in MYD88 in patients with B-cell malignancies, particularly DLBCL subtypes with poor prognosis [2]. Specifically, the gain-of-function L265P mutation is found in almost a third of DLBCL with the activated B-cell (ABC) phenotype. *In vitro* studies of B-cell tumor lines indicate that (a) this mutation is associated with an increase in cell activation, proliferation, and survival [3], and (b) loss of endosomal TLRs results in markedly decreased cell proliferation and survival [4]. Data from Idera indicate that treatment of such cell lines with IMO-8400 has a similar effect [5].

Recently reported clinical experience with IMO-8400 in patients with Waldenström's Macroglobulinemia (WM), a B-cell malignancy almost always driven by the MYD88 L265P mutation [6], indicate that the treatment is active and well-tolerated at dose levels up to 1.2 mg/kg/twice weekly [7]. Dose escalation is continuing in that setting as the maximum tolerated dose (MTD) has not been reached.

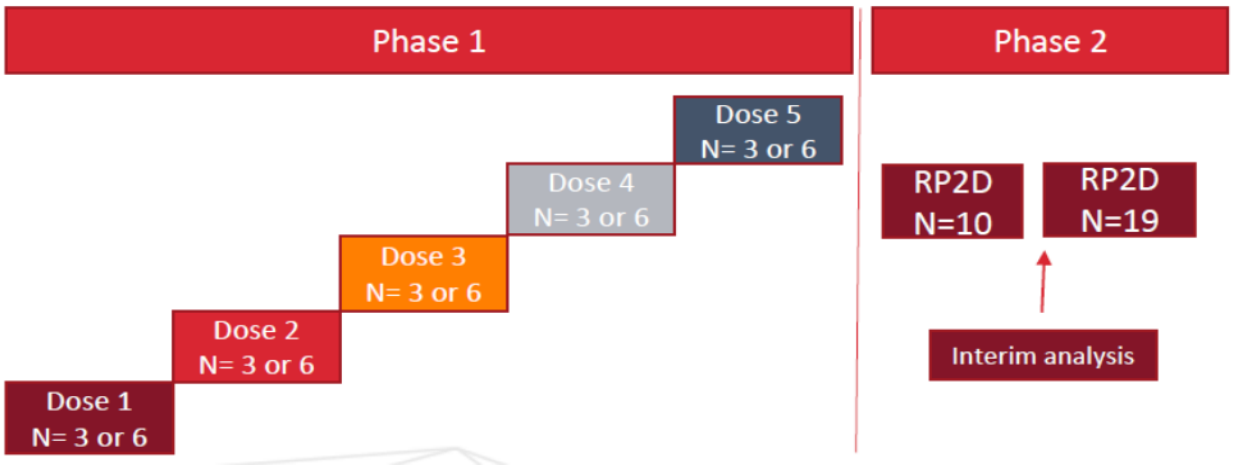
The current study represents the first clinical trial of IMO-8400 in patients with DLBCL.

1.3.2. Study Overview

This is an open-label, multiple-dose, dose escalation study of IMO-8400 in patients with relapsed or refractory DLBCL of non-GCB subtype. The study is a Phase 1/2 study in which Phase 1 will consist of a dose escalation to determine the recommended Phase 2 dose (RP2D). Phase 2 is a Simon two-stage design [8], consisting of an open-label treatment of patients at the RP2D. Initially 10 patients will be treated at the RP2D. If at least two of the 10 patients respond, the study will enroll 19 more patients, for a total of 29 patients in the Phase 2 portion.

A study schematic is represented in Figure 1.

Figure 1: Study Schematic



1.3.3. Phase 1: Dose Escalation

The dose escalation cohorts will permit systematic evaluation of the safety and tolerability of IMO-8400 at increasing dose levels in order to identify the maximum tolerated dose (MTD).

- The planned dose escalation cohort levels for IMO-8400 are 0.3, 0.6, and 1.2 mg/kg administered twice weekly and 2.4 and 3.6 mg/kg administered once weekly (Table 3). Additional dose levels, schedules, and routes of administration may be evaluated based upon the emerging data. Dosing is based on body weight (Section 8.1). Doses will be administered by SC injection.
- The Investigators and Sponsor will review available toxicity information (including adverse events [AEs] that are not dose-limiting toxicities [DLTs]), pharmacokinetic (PK) and activity data to determine the MTD (Section 1.3.5).

Table 3: Planned Dose Escalation Cohorts

Dose Level	IMO-8400 Dose (mg/kg)	Frequency	Initial Cohort Size
1 (starting dose)	0.3	Twice Weekly	3-6
2	0.6	Twice Weekly	3-6
3	1.2	Twice Weekly	3-6
4	2.4	Weekly	3-6
5	3.6	Weekly	3-6

Procedures for patient safety are summarized below and presented in detail in the sections indicated:

- Explicit definitions for identifying suspected adverse reactions as DLT events (Section 6.3.1).
- All injections of study medication will be administered by trained personnel. Patients will be observed for 2 hours following the first treatment and for at least 30 minutes following all other treatments (Section 8.4).
- Detailed provisions for management of study drug in individual patients based on safety, tolerability, and disease response (Section 6.5).
- Constitution of a Cohort Review Committee (CRC) comprised of the Idera Medical Monitor and Investigators from participating sites to decide whether to continue or halt dose escalation, or explore intermediate dose levels (Section 6.3.2).

1.3.4. Phase 2: Dose Expansion Cohort

Once the RP2D has been established, additional patients will be treated in a dose expansion phase that is designed to better characterize the safety, tolerability and preliminary anti-tumor activity of the study drug when provided at the RP2D to patients with non-GCB subtype DLBCL with MYD88 L265P mutations. Phase 2 utilizes a Simon two-stage design [8], consisting of an open-label treatment of patients at the RP2D. Initially 10 patients will be treated at the RP2D. If at least two of the 10 patients respond, the study will enroll 19 more patients, for a total of

29 patients in the Phase 2 portion. Additional dose-expansion cohorts may be added if clinical activity is seen during the dose escalation phase in tumors that lack this mutation.

1.3.5. Dose Escalation Enrollment and Review

Each dose escalation cohort is expected to enroll at least three patients, with a maximum of six patients. The number of patients enrolled in any of the planned dose escalation cohorts can be reduced if safety at that dose level has already been demonstrated in a related population (e.g., WM).

- If the initial three patients complete all 4 weeks of treatment without a DLT event, the CRC will conduct a dose escalation review.
- If one of the initial three patients experiences a DLT event prior to completing Cycle 1, then enrollment at that dose level will continue to a total of six patients and the dose escalation review will be done when all six patients have completed Cycle 1.
- If two patients at a dose-level experience DLT events during the Cycle 1, then no further patients will be enrolled until the CRC completes a review, which should be done as soon as feasible.
- Furthermore, cohorts may be expanded to include additional patients if such patients can be enrolled ≤7 days after the third (or sixth) patient was first dosed with IMO-8400.

The CRC review will include all available safety data. To facilitate standardizing the dose escalation reviews across different cohorts, the focus will be on observations from Cycle 1 at that dose level.

The following represent anticipated outcomes for the review process:

- Approval of enrollment in the expansion cohort at that dose level, if applicable.
- Dose escalation – progression to the next planned dose level.
- Continue cohort enrollment (applicable only to review after three patients) – enroll up to six patients at the current dose level to obtain additional safety data for subsequent review.
- Increase the number of patients treated at a given pre-specified or intermediary dose level to better define the safety profile of IMO-8400 and enhance the clinical experience at each participating site. Dose escalation decisions will be made once the last patient in a cohort completes Cycle 1.
- Dose de-escalation – enrollment of an intermediate level contingency cohort to facilitate identifying the MTD.
- No further dose escalation enrollment – at this time the CRC will indicate the dose level they consider represents the MTD.

The CRC comprises experienced clinicians, who will make recommendations based on their judgment. In consideration of the dynamic nature of early phase studies, those recommendations may include alternative courses of action not anticipated here.

1.3.6. Management of Study Treatment in Individual Patients

Each enrolled patient will receive IMO-8400 at the assigned dose level until disease progression, intolerable toxicity (despite dose modification), withdrawal of consent, start of another anti-cancer therapy, or study completion, whichever occurs first.

For DLT events, provision is made for pausing treatment for up to 3 weeks and, if the acute toxicity improves sufficiently, resuming treatment at a lower dose level (Section 6.5.2). Patients who are tolerating treatment at dose levels below those deemed acceptable by the CRC may be eligible for dose escalation upon discussion and approval with the Idera Medical Monitor.

1.4. Study Structure

- Pre-screening of patients who are deemed to be at high risk of recurrence can be performed by testing for the MYD88 L265P mutation at any point during the course of their disease. This would allow patients rapid access to study participation if they relapse or are refractory to standard therapy, without the delay associated with mutation testing.
- Screening will be done within 21 days prior to Cycle 1, Day 1 (the first treatment with study drug). See Section 9.2 for details of Screening and Section 9.4 for details of the enrollment process.
- Treatment is scheduled to be administered until disease progression, intolerable toxicity (despite dose modification), withdrawal of consent, start of another anti-cancer therapy, or study completion, whichever occurs first.
- Assessment for treatment response will continue throughout the patient's participation or until disease progression.
- End-of-Treatment (EOT) visit will be performed within 7 days of the decision to terminate treatment.
- End-of-Study (EOS) visit will be performed 30 to 35 days after the last dose of study drug.

Detailed schedules of events are presented in Section 1.9.

1.5. Diagnosis and Patient Selection Criteria

1.5.1. Pre-screening for MYD88 L265P Mutation

Patients with relapsed and refractory DLBCL have severe and progressive illness. Both Investigators and patients want to avoid delaying treatment for even the 7 to 10 days required for testing for the presence of the MYD88 L265P mutation, which is associated with poor prognosis, and increased risk for disease progression and death [9]. Available data indicate that the mutation is present at diagnosis and its impact on outcome can persist through current standard of care treatment [10].

Therefore, if a result for the MYD88 L256P mutation has already been identified using a Clinical Laboratory Improvement Amendments (CLIA)-compliant assay, then this result can be used for eligibility purposes so that the patient can continue additional screening procedures. Every

attempt will be made to gain access to additional lymphatic tissue in order to confirm the presence of the MYD88 L265P mutation using the Abbott Molecular tissue-based assay under development as a potential companion diagnostic. A blood sample will also be taken to explore the potential development of a plasma-based assay for detection of the MYD88 L265P mutation.

1.5.2. Inclusion Criteria

To be eligible for this study, a patient must meet ***all*** of the following criteria:

1. Have a primary diagnosis of DLBCL of non-GCB subtype, established according to the World Health Organization (WHO) criteria [11].
2. Be at least 18 years of age.
3. Have signed the current approved Informed Consent Form.
4. Have Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
5. Has, prior to enrollment, safety laboratory tests meeting the following criteria:
   - Hemoglobin ≥7.5 g/dL
   - Absolute neutrophil count (ANC) ≥1,000/μL
   - Platelets ≥50,000/μL
   - Serum creatinine ≤2.5x Upper limit of normal (ULN)
   - Serum aspartate transaminase (AST) ≤2.5x ULN
   - Serum alanine transaminase (ALT) ≤2.5x ULN
   - Total bilirubin ≤1.5x ULN
   - Prothrombin time (PT) ≤1.5x ULN
6. Have no history or current clinical evidence of lymphoma involvement in the central nervous system (CNS).
7. Have received at least one course of therapy consistent with the recommendations of the National Comprehensive Cancer Network [10].
8. Have either (a) received an autologous stem cell transplant, or (b) been assessed as ineligible for the procedure, or (c) declined the procedure.
9. Have relapsed or progressed ("refractory") based on the criteria for assessing response from the International Harmonization Project [1] (Section 9.6).
10. **Have tumor tissue that tests positive for a MYD88 mutation using a CLIA-compliant assay. (Note: patients whose tumors do not harbor MYD88 L265P mutations are eligible for the dose escalation phase of the study.)**
11. For women of childbearing potential and men, agree to use effective contraceptive methods from Screening, through the study, and for at least 4 weeks after the last dose of study drug. Effective birth control (contraception) methods are defined as ***one*** of the following:

- Abstinence.
- Condoms and spermicide.
- Diaphragm and spermicide.
- Oral or implanted hormonal contraceptive (e.g., Implanon™).
- An intra-uterine device.

Non-childbearing potential is defined as a female who meets ***either*** of the following criteria:

- Age ≥50 years and no menses for at least 3 years.
- Documented hysterectomy, bilateral tubal ligation or bilateral oophorectomy.

12. For women of childbearing potential, have a negative serum or urine pregnancy test prior to enrollment.
13. Have at least one site of measurable disease during dose expansion phase (patients with evaluable disease permitted during dose escalation).
14. Be willing and able to comply with this protocol.

1.5.3. Exclusion Criteria

Patients with any of the following will be excluded from enrollment in the study:

1. DLBCL of GCB subtype.
2. Due to their aggressive nature and/or occurrence in the setting of immunodeficiency (secondary to human immunodeficiency virus [HIV] or advanced age), the following B-cell neoplasms will be excluded:
   - Intravascular large B-cell lymphoma
   - Primary mediastinal (thymic) large B-cell lymphoma
   - Epstein-Barr virus (EBV) DLBCL of the elderly
   - Large B-cell lymphoma arising in human herpesvirus 8 (HHV-8)-associated Castleman disease
   - Plasmablastic lymphoma
   - Anaplastic lymphoma kinase (ALK)+ large B-cell lymphoma
   - Primary effusion lymphoma
   - Burkitt lymphoma
3. Has known hypersensitivity to any oligodeoxynucleotide.
4. Is nursing.
5. Has a body mass index (BMI) of >34.9 kg/m^2.
6. Has an indeterminate or positive result on screening test for antibody to

- Human immuno-deficiency virus (HIV-1 or -2)
- Hepatitis C virus (HCV), unless documented to have had a potentially curative course of anti-viral treatment and to have no detectable viremia at current screening.

7. Has a positive test for hepatitis B surface antigen (HBsAg).
8. Has known complement deficiency such as properdin deficiency or hereditary angioedema.
9. Is, at the initiation of study drug, receiving chronic systemic corticosteroid therapy >20 mg of prednisone daily (or equivalent); steroids administered topically or by inhalation are permitted.
10. Has, at the initiation of study drug, received cytotoxic chemotherapy within the past 3 weeks or rituximab within the past 2 months; for other anti-cancer therapies (approved or investigational) the interval will be determined in consultation with the Medical Monitor.
11. Has, at the initiation of study drug, an active infection requiring systemic antibiotics.
12. Has had within the 4 weeks prior to initiation of study drug, or is expected to have during the study period, surgery requiring general anesthesia.
13. Has life expectancy of less than 3 months.
14. Has heart failure of Class III or IV (New York Heart Association criteria).
15. Has other significant medical conditions (chronic or active within the past 6 months), including, but not limited to: cardiac disease (e.g., unstable angina, myocardial infarction, ventricular arrhythmia); uncontrolled seizure disorder; liver disease; uncontrolled diabetes.
16. Has another primary malignancy that has not been in remission for at least 3 years. The following are exempt from the 3-year limit: non-melanoma skin cancer, curatively treated, localized prostate cancer with non-detectable prostate-specific antigen (PSA), and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on a Pap smear.
17. Has any other condition that would, in the opinion of the Investigator, potentially compromise the patient's safety, compliance, or successful completion of the clinical trial.

1.6. Treatments

1.6.1. Investigational Product, Dosage and Mode of Administration

IMO-8400 administered as follows:

- Dose levels of 0.6 to 3.6 mg/kg/week by body weight at Screening to be given as SC injections (Section 8.4).
- Injection volume not to exceed 1.2 mL/site, with multiple sites used per dose as necessary.

- Dose to be recalculated if change in body weight from Screening exceeds 10% (±).
- Injections will be administered in the four quadrants of the abdomen or in the upper thighs, rotating injection site(s) each time IMO-8400 is administered (Section 8.4).

1.6.2. Reference Therapy, Dosage and Mode of Administration

Not applicable.

1.7. Criteria for Evaluation

1.7.1. Pharmacokinetics

Pharmacokinetic samples will be obtained as scheduled in relation to the first dose administered at each of Cycles 1, 2, 4, and 6 (Day 1 of each cycle). The following PK samples will be collected: pre-dose, at 1 (±5 minutes), 2 (±10 minutes), and 4 (±15 minutes) hours post-dose. Pharmacokinetic samples will also be taken at the EOT and EOS visits. Plasma samples will be analyzed for IMO-8400 concentration using a validated bioanalytical method.

For each cohort, the plasma IMO-8400 concentration data will be analyzed by non-compartmental PK analysis. The following parameters will be determined as appropriate: observed maximum plasma concentration (C_{max}), time of C_{max} (T_{max}), and area under the curve from 0 to last measurable plasma concentration (AUC_{0-t}). Pharmacokinetic parameters will be compared across IMO-8400 dose levels.

1.7.2. Safety

Assessments for safety include:

- Ongoing monitoring for clinical AEs and concomitant medications.
- Symptom review and vital signs at each scheduled visit.
- Physical exam and electrocardiogram (ECG) (Section 9.7).
- Laboratory safety tests (hematology, serum complement, clinical chemistry, coagulation, urinalysis) (Section 9.8).
- Injection site reactions (ISRs) (Section 9.7.5).
- Additional unscheduled assessments at Investigator's discretion.

1.7.3. Treatment Effect

A limited physical examination will be performed at every cycle focusing on known sites of disease. Assessments of disease status by radiological assessment for patients receiving IMO-8400 will be conducted every 8 weeks or as indicated based on new signs, symptoms or laboratory findings. During follow up (Section 6.5.6), patients discontinued from treatment for reasons other than progressive disease will be assessed per Revised Response Criteria for Lymphoma (Section 16.2) at a minimum of every 12 weeks for overall survival (OS) until documentation of progressive disease, initiation of new anti-cancer therapy, or the end of the study, whichever comes first. Following disease progression during survival follow up, patients

will be contacted every 12 weeks for the subsequent use of anti-cancer therapy as well as for survival until study completion. Disease status will be classified based on the criteria of the International Harmonization Project [1] (Section 9.6). Time to progression and duration of response will be measured as defined (Section 12.4).

1.8. Statistical Methods

Analysis Populations:

- DLT Evaluable Population: patients enrolled in the Phase 1 dose escalation portion of the study who receive all planned doses of study drug during the DLT observation period or who discontinue treatment due to AEs.
- Safety/Intent-to-Treat (ITT) Population: all patients who received at least one injection of study drug.
- Efficacy Evaluable (EE) Population: all patients who are MYD88 L265P mutation positive and have been treated at the RP2D.
- Per Protocol (PP) Population: all patients in the EE who had no major protocol violations that would potentially influence treatment effect.
- Pharmacokinetic (PK) Population: all patients who had both a pre-dose and at least one analyzable post-dose PK sample.

CRC review will be performed on the DLT Evaluable Population for the dose being considered. Safety analyses will be performed using the Safety/ITT Population. Efficacy endpoints (analysis of treatment effect [Section 12.4]) will be analyzed for the EE and PP Populations. Response will also be tabulated for the Safety/ITT Population. Pharmacodynamic and immunogenicity assessments will be analyzed for the Safety/ITT Population. Pharmacokinetic results will be analyzed by non-compartmental PK analysis. Descriptive statistics will be provided for all PK parameter values by dose and time, as appropriate.

Primary Safety and Tolerability Endpoints:

- Number of DLTs
- Frequency and intensity of AEs
- Physical examination findings, including vital signs
- Laboratory safety tests including hematology, chemistry, coagulation, urinalysis and complement levels
- Assessment of ISRs
- ECG findings

Primary Efficacy Endpoint:

- Proportion of responders at the RP2D with the MYD88 L265 mutation

Secondary Efficacy Endpoints:

- Duration of response

- Time to response
- Proportion of responders at all dose levels
- OS
- Progression-free survival

Safety Analyses

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 and tabulated by event, grade, and relationship to study treatment. Safety analyses will be descriptive in nature; no statistical hypothesis testing will be performed. Laboratory assessments for hematology, chemistry, coagulation, and special safety tests (C3, C4, and CH50) will be tabulated via shift tables, tabulating each patient's category at baseline via National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03 grading (normal and Grade 1 will be combined) versus their highest NCI-CTCAE grade on study. Injection site reactions will be summarized by incidence for each dose group and overall and by worst grade on study. Time-to-event analyses will be performed for ISRs.

Efficacy Analyses

The definition of a responder is a patient who achieves a complete response (CR) or partial response (PR) based on the Revised Response Criteria for Malignant Lymphoma proposed by the International Working Group [1] (Section 9.6 and Section 16.2).

As per the Simon two-stage design, after 10 subjects are treated at the RP2D until disease progression or clinical response, if one or fewer of those subjects respond, the study will end. If two or more of those initial 10 subjects respond, 19 more subjects will be enrolled. If six or more subjects out of 29 treated at the RP2D respond, then the null hypothesis will be rejected.

Secondary efficacy endpoints include the duration of response, time to response, proportion of responders at all dose levels, OS, and progression-free survival; these will be analyzed both globally across all cohorts and by dose level, reporting Kaplan-Meier estimated median, as well as the number of events and number of patients censored.

1.9. Schedule of Study Events

Table 4: Schedule of Study Evaluations

Visit[1]	Pre-screen[2]	Screen[3]	Treatment Period												EOT[4]	EOS[5]	F/U	Survival F/U
Cycle			**Cycle 1**				**Even Numbered Cycles**				**Odd Numbered Cycles**						**Every 12 wks. (±4 wks.)**	**Every 12 wks. (±4 wks.)**
Day		**≤21**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**				
Evaluation																		
Informed consent[6]	X	X																
Tumor genotyping[7]	X																	
Blood draw for genotyping	X																	
Inclusion/exclusion criteria		X																
Demography and medical history		X																
Physical exam[8]		X	X				X				X				X	X		
Vital signs[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy test[10]		X													X			
Radiologic imaging[11,12]		X								X					X			
Bone marrow biopsy[13]			X												X			
Lymph node biopsy		X[14]	X[15]															
Assessment of response[12]										X					X			
ECOG		X	X				X				X				X	X		
Hematology[16]		X	X		X		X		X		X		X		X	X		
Chemistry panel[16]		X	X		X		X		X		X		X		X	X		
Coagulation panel		X	X				X				X				X	X		
Complement		X	X				X				X				X	X		
Urinalysis		X	X				X				X				X	X		
12-lead ECG[17]		X	X				X				X				X	X		
Serology		X																
PK[18]			X				X				X				X	X		
PD and investigational studies[19]		X	X				X				X				X	X		
Study drug administration[20]			X	X	X	X	X	X	X	X	X	X	X	X				
Assessment of injection site(s)[20,21]			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AEs/concomitant medications[20]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

AE = adverse event; CLIA = Clinical Laboratory Improvement Amendments; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End-of-Study; EOT = End-of-Treatment; OS = overall survival; F/U = Follow up; PD = pharmacodynamic; PK = pharmacokinetic

1. All Days for a given Cycle are relative to the day of the first injection of study drug, designated Day 1 for that cycle; all times are relative to treatment, designated 0 hour; "pre-dose" vital signs are to occur within 1 hour prior to treatment; all other pre-dose procedures are to occur prior to treatment on the same calendar day.
2. Pre-screening procedures involve only tumor genotyping and require a separate consent (Section 9.2).
3. Screening procedures may be performed up to 21 days prior to Day 1.
4. If treatment is terminated prematurely for any reason, the EOT visit will be performed within 7 days of the decision to terminate.
5. EOS Visit will be performed 30 to 35 days after the last dose of study drug if treatment is terminated prematurely for any reason.
6. Informed consent must be signed prior to all study-specific pre-screening and/or screening procedures.
7. A tumor sample will be submitted to a central laboratory (Section 9.2) or alternatively previously confirmed by any outside CLIA-compliant assay and confirmed and approved by the Sponsor.
8. Physical exam includes body weight and, only at Screening, height; a directed physical examination at the discretion of the Investigator is acceptable while on study treatment. Complete physical examination is required prior to enrollment and EOT and EOS.
9. Vital signs comprise heart rate, blood pressure, respiratory rate and temperature. Vital signs will be obtained pre-dose (within 1 hour prior to treatment) and post-dose within 30 min (±5 min) of treatment. On Day 1 of Cycle 1, Week 1, post-dose vital signs will also be obtained at 2 hours (±20 min).
10. Serum or urine pregnancy testing for women of child-bearing potential.
11. Radiologic imaging of chest, abdomen, and pelvis, performed during the last week of even cycles (every 8 weeks [± 1 week]) while the patient is receiving IMO-8400; patients discontinued from treatment for reasons other than progressive disease will be assessed per Revised Response Criteria for Lymphoma [1] (Section 16.2) at a minimum of every 12 weeks (± 4 days) for OS until documentation of progressive disease, initiation of new anti-cancer therapy, or the end of the study, whichever comes first.
12. Assessment of response should be performed using the same imaging modalities throughout the study; assessment should be performed during the last week of all even numbered cycles (every 8 weeks [± 1 week]) while the patient is receiving active treatment with IMO-8400.
13. If available, bone marrow biopsy will be processed locally (see the Laboratory Manual for more details).
14. Archival or fresh tissue should be submitted for confirmation of diagnosis and exploratory analyses (see the Laboratory Manual for more details).
15. Should be collected at least once between 4 and 24 hours post-treatment (Section 9.5).
16. Hematology and chemistry full panels will be performed on Day 1 of each cycle; focused panels will also be performed on Day 15 of each cycle through Cycle 6. For Cycle 7 and on all testing will not be repeated on Day 15 unless more frequent monitoring is clinically indicated (refer to Section 9.8.1 for details).
17. If Screening and Day 1 Cycle 1 are performed within 24 hours then the 12-lead ECG will be performed only at Screening.
18. On Cycles 1, 2, 4, and 6 (Day 1 of each cycle): a pre-dose sample is required. Additionally, post-dose PK samples are obtained at 1 (±5 min), 2 (±10 min) and 4 hours (±15 min). Pharmacokinetic samples will also be taken at EOT and EOS (Sections 9.9).
19. Pharmacodynamic set involves one sample for serum cytokines and one sample for antibodies to IMO-8400 taken at Screening, pre-dose at Cycles 1, 2, 4, and 6 (Day 1 of each cycle), EOT, and EOS.
20. Except for Cycle 1 and study days that require a physical examination or laboratory safety tests to be performed, study drug administration, assessment of injection site(s), and assessment of AEs and con-meds may optionally be performed at a non-study site by a trained healthcare professional approved by the Sponsor, including at home by a visiting nurse (Section 8.6).
21. Assessment of all prior injection site(s) with grading and measurement of any reaction (Section 9.7.5). In addition, on dosing days, the planned injection site will be assessed to confirm it is appropriate for use.

Table 5: Estimation of Blood Volumes Required From Screening through End-of-Study[1]

Tests	Vol (mL)	Pre-screen	Screen	Maximum Volume Per Cycle (mL)	EOT (mL)	EOS (mL)
Safety Lab Tests	19		19	38	19	19
PK[2]	5			20	5	5
Serum Cytokines	4		4	4	4	4
Antibodies to IMO-8400	4		4	4	4	4
TLR Plasma	6	6				
Serology	10		10			
Total mL blood drawn	48	6	37	66	32	32

EOS = End-of-Study; EOT = End-of-Treatment; PD = pharmacodynamic; PK = pharmacokinetic; TLR = toll-like receptor; Vol = volume

1. The volumes shown are estimates; final volumes may vary, but will not be more than 15% greater than shown.
2. PK set involves a total of four samples: pre-dose, 1, 2, and 4 hours post-dose.

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3. LIST OF ABBREVIATIONS

Abbreviation	Explanation
ABC	Activated B-cell
ADL	Activity of daily living
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the curve from 0 to last measurable plasma concentration
BA	Bioavailability
BCR	B-cell receptor
BE	Bioequivalence
BMI	Body mass index
BP	Blood pressure
BTK	Bruton's tyrosine kinase
C3	Complement component 3
C4	Complement component 4
CBC	Complete blood count
CH50	50% hemolytic complement assay
CK	Creatine phosphokinase
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Observed maximum plasma concentration
CNS	Central nervous system
CPG	Cytosine guanine dinucleotide motifs
CR	Complete response
CRC	Cohort Review Committee
CRO	Clinical research organization
CRP	C-reactive protein
CS	Clinically significant
CSR	Clinical Study Report
CT	Computed tomography
DC	Dendritic cell
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid

EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic Data Capture
EE	Efficacy Evaluable
EHR	Electronic health record
EOS	End-of-Study
EOT	End-of-Treatment
FDA	Food and Drug Administration (US)
FDG	[^{18}F]fluorodeoxygluse
FFPE	Formalin-fixed, paraffin-embedded
GCB	Germinal center B-cell
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HHV-8	Human herpesvirus 8
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFN	Interferon
Ig	Immunoglobulin
ITT	Intent-to-Treat
IL	Interleukin
IND	Investigational New Drug
INR	International normalized ratio
IP-10	Interferon-inducible protein 10
IRAK	Interleukin receptor activated kinase
IRB	Institutional Review Board
ISR	Injection site reaction
ITT	Intent-to-Treat
IUO	Investigational Use Only
LDH	Lactate dehydrogenase

Jak	Janus kinase
LPS	Lipopolysaccharide
MALT	Mucosa-associated lymphoid tissue
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MTD	Maximum tolerated dose
MYD88	Myeloid differentiation primary response gene (88)
MZL	Marginal zone B-cell lymphoma
NA	Not applicable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Not clinically significant
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B-cells
NHL	Non-Hodgkin's lymphoma
OS	Overall survival
PD	Pharmacodynamic(s)
PET	Positron emission tomography
PHI	Protected health information
PK	Pharmacokinetic(s)
PP	Per Protocol
PR	Partial response
PSA	Prostate-specific antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cell
R-CHOP	Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCID	Severe combined immunodeficient
SD	Stable disease
STAT	Signal transducer and activator of transcription
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
Th1	T helper cell, type 1
TLR	Toll-like receptor

T_{max}	Time of observed maximum plasma concentration
TMF	Trial Master File
TNF	Tumor necrosis factor
ULN	Upper limit of normal
USP	United States Pharmacopeia
WBC	White blood cell
WHO	World Health Organization
WMA	World Medical Association
WM	Waldenström's Macroglobulinemia
β-hCG	Beta-human chorionic gonadotropin

4. INTRODUCTION

4.1. Diffuse Large B-cell Lymphoma: the Disease under Study

Hematological malignancies are cancers affecting blood, bone marrow, and lymph nodes; they may derive from either myeloid or lymphoid cell lines. Those arising from the lymphoid line may originate from lymphatic tissue within the bone marrow or outside it, including lymph nodes or lymphatic structures in the skin, gastrointestinal tract or other body sites (Table 6). Lymphoid tumors arising outside the bone marrow may spread to the marrow and impair the production of hematopoietic cells, resulting in pancytopenia.

Table 6: Broad Classification of Hematologic Malignancies

Cell Line of Origin	Site of Origin	General Classes	Examples
Myeloid	Bone Marrow	Leukemia	Acute Myelogenous Leukemia Chronic Myelogenous Leukemia
		Myelodysplasia	Myelodysplastic Syndrome Myeloproliferative Disease
Lymphoid	Bone Marrow[1]	Leukemia	Lymphocytic Leukemia Lymphoblastic Leukemia
	Extra-marrow[1,2]	Hodgkin Lymphoma	Nodular Sclerosing Hodgkin Lymphoma
		Non-Hodgkin Lymphoma	Lymphoplasmacytic Lymphoma (Waldenström's Macroglobulinemia) Diffuse Large B-cell Lymphoma

1. Lymphoid malignancies arising in the marrow are also referred to as "precursor cell neoplasms" and those arising outside the marrow as "mature cell neoplasms."
2. Sites of origin outside the bone marrow include lymph nodes or lymphatic structures in the skin, gastrointestinal tract, and other body sites.

Non-Hodgkin lymphomas (NHL) represent a heterogenous group of lymphoid malignancies. The primary differentiation is based on lymphocyte cell type: B-cell, T-cell, NK-cell. The complete World Health Organization (WHO) classification currently includes over 30 specific mature B-cell neoplasms [11] (Section 16.1) distinguished by multiple different factors, including:

- Histologic appearance, e.g., follicular, mantle cell, diffuse large B-cell
- Tissue or structure of origin or primary involvement: spleen, mucosa-associated lymphoid tissue (MALT), marginal zone, mediastinum (thymus), skin (cutaneous), intravascular
- Immunoglobulin production: Waldenström's Macroglobulinemia (WM) (immunoglobulin [Ig]M), multiple myeloma (IgG, IgA), heavy chain diseases
- Associated virus, e.g., Epstein-Barr virus (EBV), human herpesvirus 8 (HHV-8), Human immunodeficiency virus (HIV)

Current estimates for the United States are approximately 70,000 new cases of NHL annually and 19,000 deaths [12]. The incidence of NHL rises steadily with advancing age from rates of 2.4 cases per 100,000 in the 20- to 24-year age-group, to 8 cases per 100,000 for 35- to

39-year-olds, to 119.4 cases per 100,000 among those age 80- to 84-years. The median age at diagnosis is ~70 years old.

Among the cases of NHL, ~85% arise from B-cells and the most common of the mature B-cell malignancies is diffuse large B-cell lymphoma (DLBCL), representing ~31% of all NHL. Some rare forms of diffuse large B-cell tumors are recognized as specific diagnoses, including:

- DLBCL associated with chronic inflammation
- Primary cutaneous DLBCL, leg type
- Intravascular large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- T-cell/histiocyte rich large B-cell lymphoma
- Primary mediastinal (thymic) large B-cell lymphoma
- EBV-positive DLBCL of the elderly
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease

Recent molecular analyses have proposed subtyping DLBCL based on gene expression profiles into two classes designated activated B-cell subtype ([ABC]; representing ~28% of DLBCLs) and germinal center B-cell (GCB) subtype (representing most of the remaining DBLCLs)[13]. Germinal center B-cell subtype-DLBCL has been associated with a higher response rate to standard treatments and an overall improved prognosis, with 60% five-year survival, compared to 39% for patients with non-GCB tumor profiles [13]. The ABC phenotype, which is driven by myeloid differentiation primary response gene (88) (MYD88) mutation in a significant proportion of patients (Table 7), has a particularly poor prognosis when compared with GCB subtype-DLBCL, and thus represents an important unmet medical need [14].

4.1.1. Current Standard of Care Therapy for NHL

Treatment strategies in NHL vary depending on the specific disease and stage. Diffuse large B-cell lymphoma is considered an aggressive lymphoma with the potential for rapid disease progression. Intensive chemotherapy is typically the initial treatment of choice; rituximab (an anti-CD20 monoclonal antibody) plus combination cytotoxic chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) represents the most commonly used regimen.

Options for treating relapsed or refractory disease include:

- Bone marrow or stem cell transplantation
- Repeat of initial therapy
- Other combinations of rituximab and chemotherapy
- Radiolabeled monoclonal antibodies
- Immunomodulatory drugs (e.g., lenalidomide)

In some reports, these strategies have improved progression-free survival for patients with relapsed/refractory NHL, but definitive survival advantage is less clear and most patients die from the disease. New treatments are needed for advanced, recurrent B-cell malignancies and current practice guidelines recommend inclusion of these patients in investigational trials [10].

4.2. Toll-like Receptors – Overview

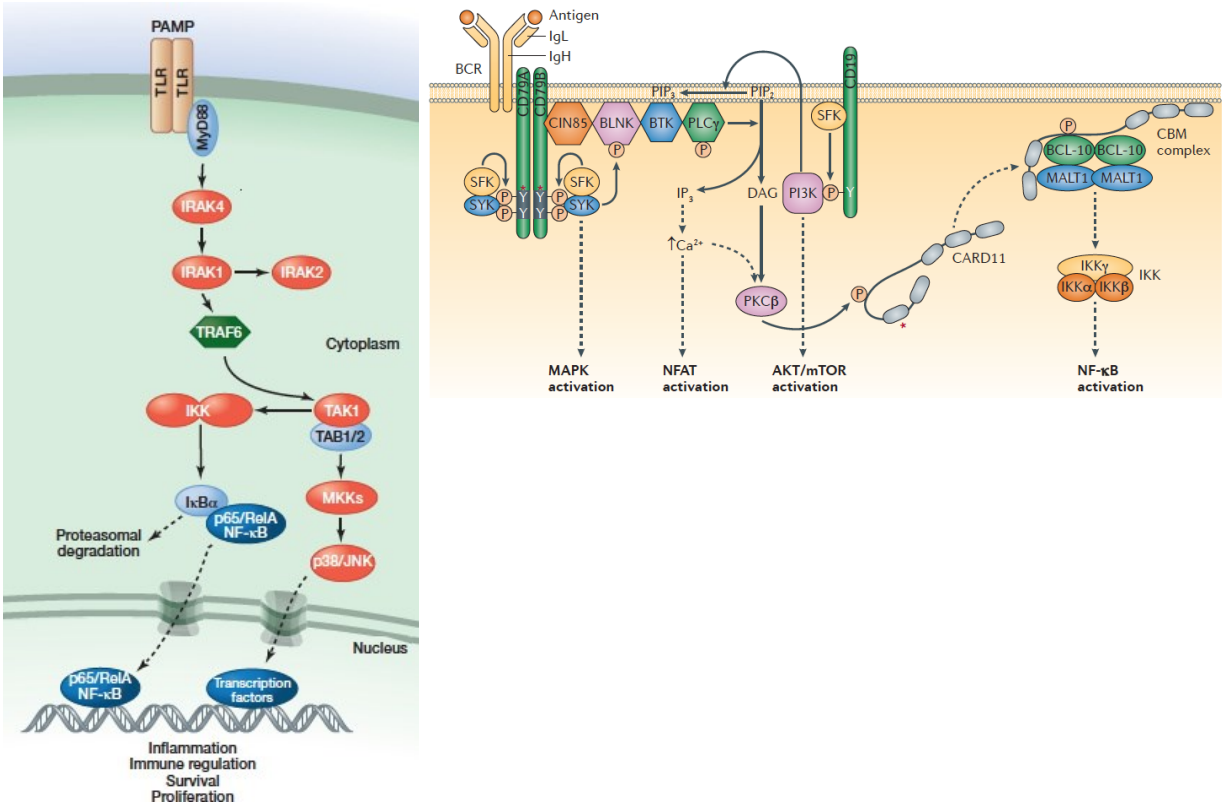
Toll-like receptors (TLRs) are a family of host sensors for "foreign" constituents (e.g., nucleic acids, lipopolysaccharides, peptidoglycans from viruses, bacteria, fungi) that "sound the alarm" and activate host immune defenses. The natural ligands for TLR7 and 8 are single-stranded ribonucleic acid (RNA) from viruses, and for TLR9, unmethylated cytosine-guanine dinucleotide motifs (CpG), which are characteristic of bacterial deoxyribonucleic acid (DNA). Binding of these ligands to the cognate receptor results in intracellular signaling, generation of nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), and production of pro-inflammatory (Th1) chemokines and cytokines, including interferon (IFN)-α, tumor necrosis factor (TNF-α) and interleukin (IL)-12. Of note, TLRs 7, 8, and 9 are located in the endosome, whereas most other TLRs are located on the host cell surface. In man, the endosomal TLRs are constitutively expressed primarily on dendritic cells (DCs) and B-cells.

Although foreign constituents are the intended ligands for the nucleic acid TLRs, multiple studies indicate that activation by endogenous nucleic acids is central to the development and persistence of autoimmunity and inflammatory diseases [15, 16, 17, 18, 19]. As detailed below, recent evidence suggests this process can also contribute to the malignant phenotype of B-cell tumors.

The TLR signaling pathway (Figure 2, left panel) comprises a series of cytoplasmic proteins that result in generation of NF-κB, which translocates to the nucleus and mediates increased expression of genes involved in cell survival, proliferation, and cytokine production. In B-cells, the other major mechanism for activation is binding of specific antigen to the B-cell receptor (BCR). There are several signaling pathways associated with the BCR (Figure 2, right panel), including one that generates increased NF-κB. The constituents of that BCR signaling pathway are, in general, distinct from those of the TLR pathway.

Figure 2: TLR and BCR Signaling Pathways in B-cells.

TLR signaling **BCR signaling [3]**



4.3. Toll-like Receptors in B-cell Malignancy

A central feature of malignant cell transformation is the development of dysregulated or autonomous cell activation resulting in increased cell proliferation and survival. This can be the result of specific 'oncogene' mutations or defects in the control of the expression of critical genes. Chromosomal abnormalities, both point mutations and translocations, are common among hematological malignancies, have an established role in diagnosis, and are increasingly used in guiding specific approaches to treatment.

Studies of B-cell malignancies have identified changes in the BCR signaling pathway, and more recently in the TLR signaling pathway, that drive NF-κB expression and the malignant phenotype. These changes include:

- Mutations in MYD88, the adapter (linker) protein that binds to TLRs [20].
- Mutations in BCR signaling pathway genes, including CD79A/B and CARD11 [3].
- Increased expression of MYD88 [21].

The most common alteration identified to date in MYD88 is the L265P mutation. This mutation is present in over 90% of WM, in ~30% of ABC-DLBCL, and at lower frequencies in other, more common lymphomas (Table 7). Among patients with DLBCL, both increased expression of MYD88 [21] and the L265P mutation [9] have been associated with markedly poorer outcomes.

Table 7: Incidence of MYD88 L265P Mutation in Selected B-cell Malignancies

Disease	Incidence of Disease (2014[1])	MYD88 L265P Mutation		Reference for Frequency of L265P
		% Patients	Incidence (Est. 2013[2])	
DLBCL	17,387	10%	1,739	[9]
ABC-DLBCL[3]	4,868	29%	1,412	[2]
Waldenström's Macroglublinemia	876	91%	797	[22]
Chronic Lymphocytic Leukemia	14,586	5%	729	[23,24]
Primary CNS Lymphoma	1,200	37%	444	[25,26]
Marginal Zone Lymphoma[4]	4,868	6.5%	316	[2,27]

ABC-DLBCL = Activated B-cell (type) Diffuse Large B-cell Lymphoma; CNS = central nervous system; DLBCL = Diffuse Large B-cell Lymphoma; MALT = Mucosa-Associated Lymphoid Tissue Lymphoma; NHL = Non-Hodgkin's lymphoma; SEER = Surveillance Epidemiology and End Results dataset

1. Diagnosis-specific 2014 incidence is based on the age-adjusted annual US incidence of 70,800 NHL cases estimated using the SEER[28], and the relative counts of specific diagnoses within the dataset.
2. Estimated incidence of L265P mutation is based on 2011 disease incidence and the reported frequency of the mutation in the disease.
3. ABC-type represents ~28% of all DLBCL. In studies subtyping DLBCL, most instances of L265P mutations have been in those with ABC-subtype.
4. Marginal Zone Lymphoma is also referred to as MALT.

Recent *in vitro* studies of B-cell tumor lines with L265P mutation suggest that TLR signaling directly contributes to the malignant phenotype of these cells [4]. Specifically, cell proliferation and survival decreased markedly under the following conditions:

- Impaired expression of endosomal TLRs, using an inhibitory RNA.
- Enzymatic elimination of endogenous nucleic acids in the culture supernatant.

Idera Pharmaceuticals, Inc. has conducted independent studies using B-cell tumor lines, including LY10, a cell line with the L265P mutation and increased MYD88 expression. LY10 cells cultured *in vitro* with IMO-8400 demonstrate decreased growth and survival. Severe combined immunodeficient (SCID) mice inoculated with LY10 developed progressive disease and died. Treatment with IMO-8400 prolonged median survival from 33 to 48 days [5].

4.4. Rationale for the Current Study

Taken together, the above data directly support the hypothesis that an antagonist of TLR7, 8, and 9 would have a therapeutic effect in patients with B-cell malignancies, specifically, those characterized by MYD88 L265P mutation or increased MYD88 expression.

IMO-8400 is a synthetic oligonucleotide that functions as an antagonist for TLRs 7, 8, and 9 and blocks cell activation mediated through ligand binding. In human studies, IMO-8400 has been administered once weekly by subcutaneous (SC) injection in two completed clinical trials, including a 4-week Phase 1 study of healthy adults administered 0.3 or 0.6 mg/kg (Study 8400-001) and a 12-week Phase 2a study of patients with moderate to severe plaque psoriasis administered 0.075, 0.15, 0.3, or 0.6 mg/kg (Study 8400-201). All treatments were well-tolerated. There were no deaths, serious adverse events (SAEs), discontinuations due to

treatment-related adverse events (TEAEs), and no clinically meaningful changes in laboratory measurements, 12-lead electrocardiograms (ECGs), or physical examination findings in either study.

IMO-8400 is also currently being evaluated in an ongoing, open-label study at weekly dose levels of 0.6 mg/kg/week, 1.2 mg/kg/week, or 2.4 mg/kg/week (1.2 mg/kg twice weekly) in patients with WM (Study 8400-401) as well as in an extension study for patients completing Study 8400-401 (Study 8400-404) (see Section 4.4.1 and Investigator Brochure [IB] for study details). Recently reported interim results from Study 8400-401 show that IMO-8400 is well-tolerated and demonstrate evidence of clinical activity [7]. Dose escalation is ongoing in this study as a maximum tolerated dose (MTD) has not been reached.

The current study represents the first use of IMO-8400 in patients with DLBCL.

4.4.1. Overview of IMO-8400

IMO-8400 was created by Idera Pharmaceuticals, Inc. using a structure-activity approach to design synthetic oligonucleotide drug candidates that target TLRs. IMO-8400 is designed as an antagonist for endosomal TLR7, TLR8, and TLR9. Non-clinical studies (reviewed in detail in the IB) demonstrated that IMO-8400 has the following characteristics:

- Acts as an antagonist for activation of TLR7, 8 and 9, specifically blocking the activity of agonists for those receptors, including inhibiting generation of NF-κB and induction of cytokines and chemokines (e.g., TNF-α, IL-12, IL-1β, interferon inducible protein 10 [IP-10], IL-6, IFN-α).
- Has no agonist activity; that is, does not induce Th1 cytokines/chemokines.
- Is specific for endosomal TLRs 7, 8, and 9; that is, has no effect on activation of other unrelated TLRs, such as TLR4, whose natural ligand is bacterial lipopolysaccharide (LPS).
- Has potent therapeutic activity in animal models of autoimmune diseases to inhibit the progression or reverse the clinical and immunologic manifestations of disease.

Further, Idera has recently completed studies both *in vitro* and in mice examining the effect of IMO-8400 on human lymphoma B-cell lines, including cell lines with and without mutations in the TLR signaling pathway. These studies demonstrate that IMO-8400 has the following effects:

- Inhibits constitutive activation of cell signaling pathways, including NF-κB, interleukin receptor activated kinase (IRAK), signal transducer and activator of transcription (STAT)-3, Janus kinase (Jak)/STAT, and Bruton's tyrosine kinase (BTK), in human lymphoma cell lines with the MYD88 L265P mutation.
- Decreases *in vitro* cell survival and proliferation in a time- and concentration-dependent manner in human lymphoma cell lines with the MYD88 L265P mutation.
- Decreases tumor cell growth *in vivo*, as indicated by decreased serum levels of tumor-secreted human cytokine and increased mouse survival time in a disseminated

xenograft model using OCI-Ly10, a human lymphoma cell line with the MYD88 L265P mutation.

- Decreases tumor growth and serum levels of tumor-secreted human IL-10 in an SC xenograft mouse model using OCI-Ly10, a human lymphoma cell line with the MYD88 L265P mutation.
- Does not impact tumor growth and tumor-secreted human cytokines in an SC xenograft mouse model using SU-DHL-6, a human lymphoma cell line with wild-type MYD88.
- Clinical studies with IMO-8400 are summarized in Table 8, and the IB. Clinical experience with IMO-8400 related to the rationale for the dosing regimen in the current study is provided in Section 6.10.2.1.

Table 8: Clinical Studies with IMO-8400

Protocol No.	Protocol Title	Status
8400-001	A Phase 1, Single-Dose Escalation and 4-week Multiple-Dose Escalation Study of the Safety and Pharmacokinetics of IMO-8400 in Healthy Volunteers	Completed
8400-201	A Randomized, Double-Blind, Placebo-Controlled, 12-week Dose-Ranging Trial of IMO-8400 in Patients with Moderate to Severe Plaque Psoriasis	Completed
8400-401	Phase 1/2 Open-label, Multiple-dose, Dose escalation Study to Evaluate the Safety and Tolerability of IMO-8400 in Patients with Relapsed or Refractory Waldenström's Macroglobulinemia	Ongoing
8400-404	An Extension Study to Evaluate the Long-Term Safety, Tolerability, and Clinical Activity of IMO-8400 in Patients with Relapsed or Refractory Waldenström's Macroglobulinemia who Completed Study 8400-401	Ongoing
8400-211	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial of IMO-8400 in Patients with Dermatomyositis	Ongoing

5. STUDY OBJECTIVES

5.1. Primary Objective

- To evaluate the safety and tolerability of escalating dose levels of IMO-8400 administered by SC injection in patients with relapsed or refractory non-GCB subtype DLBCL.

5.2. Secondary Objectives

- To assess the treatment effect (clinical activity) in patients with non-GCB subtype DLBCL with MYD88 L265P mutations using disease-specific international guidelines for classifying clinical response [1].
- To identify an optimal dose of IMO-8400 for further clinical evaluation in B-cell malignancies.
- To characterize the pharmacokinetics of escalating dose levels of IMO-8400 administered by SC injection.

5.3. Exploratory Objectives

- To investigate associations between the treatment effect of IMO-8400 and selected biomarkers (e.g., serum cytokines).
- To assess the potential immunogenicity of IMO-8400 administered by SC injection.

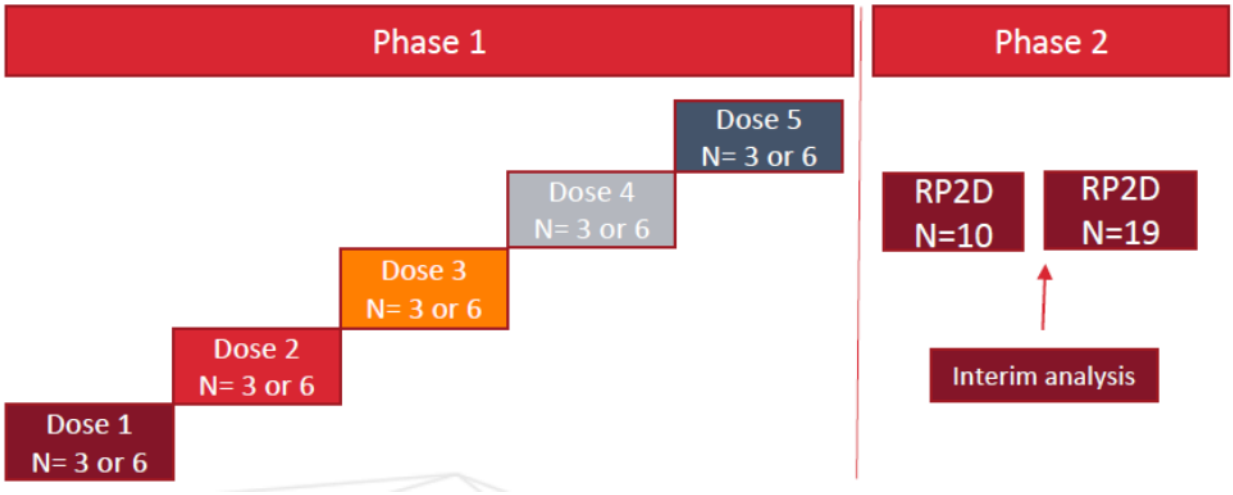
6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is an open-label, multiple-dose, dose escalation study of IMO-8400 in patients with relapsed or refractory DLBCL of non-GCB subtype. The study is a Phase 1/2 study in which Phase 1 will consist of a dose escalation to determine the recommended Phase 2 dose (RP2D). Phase 2 is a Simon two-stage design [8], consisting of an open-label treatment of patients at the RP2D. Initially 10 patients will be treated at the RP2D. If at least two of the 10 patients respond, the study will enroll 19 more patients, for a total of 29 patients in the Phase 2 portion.

A study schematic is represented in Figure 3.

Figure 3: Study Schematic



6.2. Phase 1: Dose Escalation

The dose escalation cohorts will systematically evaluate the safety and tolerability of IMO-8400 at increasing dose levels in order to identify the MTD.

- The planned dose escalation cohort levels for IMO-8400 are 0.3, 0.6, and 1.2 mg/kg administered twice weekly and 2.4 and 3.6 mg/kg administered once weekly (Table 3). Additional dose levels, schedules, and routes of administration may be evaluated based upon the emerging data. Dosing is based on body weight (Section 8.1). Doses will be administered by SC injection.
- The Investigators and Sponsor will review available toxicity information (including AEs that are not dose-limiting toxicities [DLTs]), pharmacokinetic (PK) and activity data to determine the MTD (Section 6.3.3).

6.3. Dose Escalation Procedures

6.3.1. Definition of a Dose-Limiting Toxicity

The safety and tolerability of IMO-8400 will be assessed using reported and observed AEs as well as scheduled safety observations including vital signs, physical examination, laboratory safety tests (hematology, serum complement, chemistry, and coagulation), urinalysis, and ECGs.

A DLT can be either a clinical or laboratory AE.

A potential DLT event is defined as a TEAE (Section 10.1) that meets protocol-defined criteria for events of hematological and non-hematological origin. It must be related to study treatment (assessed as not related to disease, intercurrent illness, or concomitant medication). For the purposes of dose escalation and determination of the MTD, only DLTs that occur during the first cycle of treatment will be necessarily considered for discussions regarding dose escalation. Clinically significant toxicities or TEAEs that meet the definition of dose limiting but occur after Cycle 1 (dose modifying events) may be considered when determining the RP2D.

Protocol-defined hematologic DLT criteria:

- Grade 4 neutropenia lasting ≥ 7 days
- Grade 3 or 4 neutropenia with fever ≥38.5°C
- Grade 3 thrombocytopenia with bleeding that requires transfusion therapy
- Grade 4 thrombocytopenia

Protocol-defined non-hematologic DLT criteria:

- Grade 3 vomiting or nausea despite the use of optimal anti-emetic treatments
- Grade 3 diarrhea despite the use of optimal anti-diarrheal treatments
- Serum creatinine ≥ 3.0x upper limit of normal (ULN)
- Bilirubin ≥ 3.0x ULN
- Bilirubin 2.0-3.0x ULN with ≥ Grade 2 ALT in patients without liver metastases
- Bilirubin 2.0-3.0x ULN with ≥ Grade 3 ALT or ALT > 5x ULN in patients with liver metastases
- Other non-hematologic toxicities of ≥ Grade 3 except for the following:
  - AEs related to underlying disease
  - Fatigue
  - Alopecia
  - Isolated, asymptomatic elevations in biochemistry laboratory values lasting ≤7 days. This includes electrolyte abnormalities that respond to medical intervention.

The Cohort Review Committee (CRC) will review all DLTs to assess causality, i.e., relationship to study drug (Section 10.4.3).The definition of DLT event will be applicable in the following contexts:

- CRC review determining dose escalation (Section 6.3.2).
- CRC review in defining the MTD.
- Investigator (and Medical Monitor) review for determining discontinuation of study treatment in individual patients.

6.3.2. Cohort Review Committee

The CRC is comprised of the Idera Medical Monitor and Investigators from participating sites. Once the last patient in a given cohort has completed a cycle of study treatment, a CRC meeting will be convened to review all safety data and decide whether to continue or halt dose escalation, further expand individual dose levels to gain additional safety data, or explore lower or intermediate dose levels.

The CRC will conduct a review of safety data upon completion of each dose escalation cohort and periodically during Dose Expansion (Phase 2).

In addition to end-of cohort meetings, the CRC will convene periodically to review safety data for ongoing patients and patients in follow up.

The roles of the CRC are to:

- Review and provide definitive adjudication on individual DLTs, if needed (Section 6.3.1).
- Perform dose escalation review and make specific recommendations for the progress of the study (Section 6.3.3).
- Determine the MTD.

6.3.3. Dose Escalation Enrollment and Review

Each dose escalation cohort is expected to enroll at least three patients, with a maximum of six patients. The number of patients enrolled in any of the planned dose escalation cohorts can be reduced if safety at that dose has already been demonstrated in a related population (e.g., WM).

- If the initial three patients complete all 4 weeks of treatment without a DLT event, the CRC will conduct a dose escalation review.
- If one of the initial three patients experiences a DLT event prior to completing Cycle 1, then enrollment at that dose level will continue to a total of six patients and the dose escalation review will be done when all six patients have completed Cycle 1.
- If two patients at a dose-level experience DLT events during the Cycle 1, then no further patients will be enrolled until the CRC completes a review, which should be done as soon as feasible.

- Furthermore, cohorts may be expanded to include additional patients if such patients can be enrolled ≤7 days after the third (or sixth) patient was first dosed with IMO-8400.

The CRC review will include all available safety data. To facilitate standardizing the dose escalation reviews across different cohorts, the focus will be on observations from Cycle 1 at that dose level.

The following represent anticipated outcomes for the review process:

- Approval of enrollment in the expansion cohort at that dose level, if applicable.
- Dose escalation – progression to the next planned dose level.
- Continue cohort enrollment (applicable only to review after three patients) – enroll up to six patients at the current dose level to obtain additional safety data for subsequent review.
- Increase the number of patients treated at a given pre-specified or intermediary dose level to better define the safety profile of IMO-8400 and enhance the clinical experience at each participating site. Dose escalation decisions will be made once the last patient in a cohort completes Cycle 1.
- Dose de-escalation – enrollment of an intermediate level contingency cohort to facilitate identifying the MTD.
- No further dose escalation enrollment – at this time the CRC will indicate the dose level they consider represents the MTD.

The CRC comprises experienced clinicians, who will make recommendations based on their judgment. In consideration of the dynamic nature of early phase studies, those recommendations may include alternative courses of action not anticipated here.

6.4. Phase 2: Dose Expansion Cohort

Once the RP2D has been established, additional patients will be treated in a dose expansion phase that is designed to better characterize the safety, tolerability and preliminary anti-tumor activity of the study drug when provided at the RP2D to patients with non-GCB subtype DLBCL with MYD88 L265P mutations. Phase 2 utilizes a Simon two-stage design [8], consisting of an open-label treatment of patients at the RP2D. Initially 10 patients will be treated at the RP2D. If at least two of the 10 patients respond, the study will enroll 19 more patients, for a total of 29 patients in the Phase 2 portion. Additional dose-expansion cohorts may be added if clinical activity is seen during the dose escalation phase in tumors that lack this mutation.

Treatment will continue until disease progression, intolerable toxicity (despite dose modification), withdrawal of consent, start of another anti-cancer therapy, or study completion, whichever occurs first.

6.5. Management of Individual Patients

6.5.1. Duration of Treatment

Each enrolled patient will receive IMO-8400 at the assigned dose level until disease progression, intolerable toxicity (despite dose modification), withdrawal of consent, start of another anti-cancer therapy, or study completion, whichever occurs first.

Patients discontinued from treatment for reasons other than progressive disease will be assessed at a minimum of every 12 weeks for overall survival (OS) until documentation of progressive disease, initiation of new anti-cancer therapy, or the end of the study, whichever comes first. Patients who are tolerating treatment may be escalated to any dose level that has been deemed safe by the CRC upon discussion and approval with the Idera Medical Monitor. In certain instances, patients may be deriving clinical benefit despite objectives signs of progressive disease such as radiologic progression. It can be anticipated that based on the study drug's mechanism of action, through an immunologic mediated effect, signs of radiologic response may be delayed. Based on these considerations, continuing to treat some patients past progressive disease may be considered after discussion between the Sponsor and Investigator.

6.5.2. Dose Modification in Patients with DLT Events

Patients determined to have a DLT event may resume treatment at the next lowest dose level (Table 3) after dose interruption and with dose modification if *all* of the following criteria are met:

- The patient is receiving >0.6 mg/kg/week; patients receiving 0.6 mg/kg/week will be discontinued.
- The patient has not previously had dose interruption and/or adjustment for a DLT event.
- Both the Investigator and the Medical Monitor consider that continued treatment with study drug is in the patient's interest.
- The DLT event improves at least two grades or returns to baseline within 14 days of the last dose administered.

Patients who do not resume treatment within 21 days of their last dose will have treatment discontinued permanently and will proceed to End-of-Treatment (EOT) and End-of-Study (EOS) visits.

6.5.3. Procedures for Assessment of Patients with Decreases in Complement Levels

Activation of complement in non-human primates is a well-described effect of phosphorothioate oligonucleotides, including IMO-8400. Monkeys are thought to be particularly sensitive to oligonucleotide-induced complement activation and a similar direct oligonucleotide-induced complement activation has not been observed in humans or other species. Specifically, in a 39 week chronic toxicity study conducted in cynomolgus monkeys, 3 of 28 animals administered IMO-8400 at dose levels ≥ 6 mg/kg/week were found dead or sacrificed moribund during the study with necropsy findings of myocardial degeneration/necrosis, glomerulonephritis, and/or hepatocellular necrosis. Adverse microscopic findings were also noted in two 6 mg/kg/week-

treated animals that survived to the terminal sacrifice. Findings consisted of minimal degeneration/necrosis of the myocardium in one animal and slight subacute vasculitis in the heart of the other. Of the five animals on study with adverse, treatment-related, anatomic pathology findings, all had perturbations in serum complement and serum chemistry parameters consistent with an acute phase response (most notably globulin and C-reactive protein [CRP]) in the weeks and months prior to either their unscheduled deaths or the scheduled terminal necropsy. Effects on clinical pathology parameters associated with the target organ toxicity in these animals (increased troponin I concentrations, liver enzyme activities, and/or urine protein:urine creatinine ratio) occurred later in the study when compared to effects on serum complement and serum chemistry parameters that were consistent with an acute phase response.

If at any time during study participation, a patient experiences an acute drop in complement component (CH50, C3 or C4) levels, defined as ≥ 50% with reference to baseline testing or most recent values on study or a drop to an absolute value of < 10 mg/dL, the following procedures and testing should be performed:

1. Hold study drug treatment
2. Repeat the serum complement test to confirm decreased complement levels
3. Query patient for recent change in signs or symptoms suggestive of a rheumatologic or vasculitic event, i.e., recent appearance of a rash or bruising, new onset symptoms such as fever, arthralgias, or fatigue
4. Perform physical examination with careful attention to findings suggestive of vasculitis; i.e., rash, palpable purpura, petechiae
5. Perform repeat complete blood count (CBC) with platelets, or review most recent CBC/platelets
6. Perform repeat urinalysis, or review most recent urinalysis with special attention to findings suggestive of glomerulonephritis; i.e., presence of protein, blood, red blood cell (RBC) casts or white blood cell (WBC) casts
7. Perform an ECG

Based on the results of this work-up and the patient's disease assessment/response to study drug, the Investigator in discussion with the Sponsor's medical monitor, will determine the patient's risk/benefit profile and discuss appropriate next steps regarding the patient's continued participation in the study.

6.5.4. Procedures for Assessment of Patients with Symptomatic Thrombocytopenia

Severe thrombocytopenia has been reported in clinical studies with another oligonucleotide [29]. Most of these patients had confirmed anti-platelet antibodies. These cases occurred 14 to 26 months after the onset of treatment, suggesting that risk increases with duration of exposure. In the event of a precipitous drop in platelet counts (i.e., to $<25 \times 10^9$/L), treatment with IMO-8400 should be held and an anti-platelet antibody count obtained. Treatment can be resumed once pre-treatment criteria (Section 8.4.1) are met. Antiplatelet, thrombolytic, or anticoagulant drugs should be used with caution.

6.5.5. Classification of Patients at Termination of Treatment

To provide for consistent accounting of patient disposition when study treatment is discontinued in an individual patient for any reason, the Investigator will complete the appropriate electronic case report form (eCRF) and select the primary reason for discontinuation of treatment from the following standard categories:

- *DLT event* – defined above.
- *Disease progression* – as defined above.
- *AE, other than DLT* – this includes any AE (clinical or laboratory; serious or non-serious; regardless of relation to study drug), that represents the reason study drug was discontinued, including:
  - The medical judgment of the Investigator based on the best interests of the patient.
  - The patient's request based on any AE.
- *Withdrawal of consent* – the patient desired to withdraw from further participation in the study in the absence of a clinical issue. If the patient gave a reason for withdrawing (e.g., leaving area), it should be recorded in the eCRF.
- *Lost to follow up* – the patient stopped coming for visits.
- *Study termination* – by the Sponsor, for any reason.

When study treatment is discontinued prematurely for any reason, the EOT and EOS visits will be performed as specified (Section 1.4). If a patient cannot be seen, attempts will be made to contact the patient by telephone to inquire about reasons for stopping participation and get updated information on any unresolved AEs.

6.5.6. Study Duration

The study will end following completion of the response assessment in the expansion phase or approximately 6 months after the last patient has begun treatment. Study treatment may be discontinued in an individual patient before this planned duration as described in Section 6.5.5.

Follow up:

All treated patients will have an EOT visit within 7 days of the decision to discontinue treatment to collect data for safety, PK, progressive disease, immunogenicity and tumor response. An EOS visit will occur 30-35 days after the patient's last administration of study drug. Additionally, patients discontinued from treatment for reasons other than progressive disease will be assessed per Revised Response Criteria for Lymphoma (Section 16.2) at a minimum of every 12 weeks for OS until documentation of progressive disease, initiation of new anti-cancer therapy, or the end of the study, whichever comes first.

Survival follow up:

Following disease progression, patients will be contacted every 12 weeks for the subsequent use of anti-cancer therapy as well as for survival until study completion.

6.6. Criteria for Replacement of Patients

6.6.1. Definition of a Evaluable Patient

A patient will be considered evaluable for purposes of CRC review if they meet *either* of the following criteria:

- Received at least one dose of study drug and had treatment discontinued because of a DLT event as defined in Section 6.3.1; *or*
- Completed Cycle 1 successfully as scheduled and completed Cycle 2, Day 1 assessment procedures.

See Section 12 for additional discussion of analysis for safety and efficacy.

6.6.2. Replacement of Patients

A patient who does not meet criteria for "evaluable" may be replaced to assure the requirements for completing the cohort are met. Replacement patients will be identified by distinctive patient numbers and will receive the same dose level as the patient being replaced.

6.7. Maximum Number of Patients

The maximum exposures to IMO-8400, the investigational agent in this study, will be as follows:

- Maximum number of patients: Up to 59 patients in planned escalation and expansion cohorts; potential for additional patients in contingency cohorts or as replacements.
- Treatment is until progression or intolerable toxicity, therefore the maximum number of dose levels is not pre-specified.

6.8. Treatment Assignment

Enrollment procedures are presented in Section 9.4.

6.9. Criteria for Study Termination

The Sponsor reserves the right to discontinue or suspend the study at any time, at an individual site or overall, for safety or for administrative reasons. In the event of such action, the Sponsor will:

- Promptly inform the impacted Investigators and institutions, the regulatory authorities, and the Institutional Review Board (IRB) of the action and the reason(s) for the action.
- Arrange for all study documentation to be archived at the site (Section 11.9) or returned to the Sponsor, as appropriate; and for any remaining study medication to be properly disposed of (Section 8.7.1).

6.10. Discussion of Study Design and Treatment Regimens

This protocol represents the first clinical trial of IMO-8400 in patients with DLBCL.

6.10.1. Rationale for Study Design

The open-label study design is consistent with both the study objectives and current principles for the evaluation of investigational drugs in patients with advanced malignancy.

The dose escalation design with enrollment guided by safety experience and reviewed by a CRC are standard for a Phase 1 study and serve to minimize the number of patients required and to assure patient safety is protected.

The Phase 2 portion of the study is designed to test whether the clinical activity of IMO-8400 is greater than a null response rate of 10% (see Section 12.1 for sample size analysis). It is designed with an interim analysis for futility. Results from this study will guide further development of IMO-8400 in oncology/hematology.

6.10.2. Rationale for Treatment Regimens in Current Protocol

6.10.2.1. Dosing Regimen

Starting dose/Safety. Following the completion of Study 8400-001 performed in healthy volunteers, Study 8400-201 was conducted in patients with moderate to severe plaque psoriasis. A total of 46 patients were enrolled in the study and treatment with IMO-8400 was administered SC weekly for 12 weeks. Thirty five patients were treated with IMO-8400 at dose levels 0.075, 0.15, 0.3, or 0.6 mg/kg/week, and eleven patients were randomized to placebo (saline). IMO-8400 was safe and well-tolerated in doses up to 0.6 mg/kg/week in patients with psoriasis.

A concurrent Phase 1/2 study of IMO-8400 is ongoing in patients with relapsed/refractory WM (Study 8400-401). This is an open-label, multiple-dose, dose escalation study and is evaluating the safety, tolerability, and preliminary clinical activity of IMO-8400. As of the most recent interim analysis from September 2015, 19 patients have been enrolled at dose levels up to 1.2 mg/kg given twice weekly. The most frequently noted AEs (>10%) were fatigue, injection site erythema, headache, injection site pain, nausea, and pain in extremity, all of which were low-grade. Grade 3 AEs were limited to neutropenia (two patients), anemia (2), and arthritis (1). No Grade 4 AEs were reported. A single episode of DLT (arthritis flare) was reported in one of eight patients enrolled in the 1.2 mg/kg/twice weekly cohort. Dose escalation is ongoing as the MTD has not been reached [7].

Dose regimen. The initial clinical indications for development of IMO-8400 were autoimmune diseases, where TLR antagonism serves to modulate the immune system and decrease inappropriate immune activation. In this context, once weekly dosing was assessed as appropriate and sufficient.

In B-cell malignancies, cell responses, proliferation, and survival are abnormal. *In vitro* studies with cell lines bearing the MYD88 L265P indicate pathologic activation of TLR signaling pathways, with apparent overreaction to TLR ligands. The application of TLR antagonism in this context is expected to require more sustained receptor blockade than physiologic immunomodulation. Therefore, in this initial trial of DLBCL, a life-threatening, aggressive malignancy, more intensive dosing is considered appropriate.

As noted the starting regimen (0.3 mg/kg twice weekly) represents simple dose fractionation of the total weekly exposure that has been observed to be well-tolerated in healthy volunteers and in

patients with psoriasis (0.6 mg/kg once weekly). Dose escalation will proceed based on review of safety experience with dose fractionation at this level.

Dose Escalation. Sequential dose escalation is consistent with current practices and is supported by dose response in the dose escalation Study 8400-401 that is ongoing in patients with WM.

Study Population. Patients with non-GCB subtype DLBCL have a poor prognosis following relapse with presence of the MYD88 L265 mutation being an independent predictor of poor outcome [9]. IMO-8400 has been shown to be effective in pre-clinical lymphoma models that carry this mutation [5]. Preliminary evidence for clinical activity has also been established in a related B-cell malignancy (WM) in patients both with and without MYD88 L265 mutations [7].

7. SELECTION OF PATIENTS

7.1. Source of Patients and Recruitment Methods

Following receipt of IRB approval, the Investigator may initiate patient recruitment (Section 13). To reach an economically and socially diverse population, the study may be announced in newspapers and on relevant Internet websites; prior to use, the form and content of such announcements will be submitted to the IRB for approval (Section 13).

7.2. Presence of MYD88 L265P Mutation

Detection of the MYD88 L265P mutation in the patient's tumor is based on analysis either by an assay performed at a central laboratory approved by the Sponsor or from a prior result using a Clinical Laboratory Improvement Amendments (CLIA)-compliant assay (Section 9.3). Additional immunophenotype, genotype, and gene expression data that has been determined by the site will be collected and may be used to justify inclusion (Section 1.5.2).

7.3. Patient Restrictions during the Conduct of the Study

In the interest of their safety and to facilitate assessment of both safety and treatment effect, the patients participating in this study will be requested to agree to the following restrictions during the study:

- Not start any new prescription medications, except as prescribed or approved by their Investigator or if required in an emergency.
- Not take any over-the-counter medications, herbal medications, or experimental medicines except as instructed or approved by their Investigator.

8. STUDY TREATMENT

8.1. Study Treatments to be Administered

All patients will receive the investigational study drug, IMO-8400, at the weekly exposure level designated for the cohort in which they are enrolled. Instructions for dose preparation are provided in the Pharmacy Manual. Weekly exposure levels are calculated as mg/kg based on body weight at Screening. The dose is to be recalculated if change in body weight from Screening exceeds 10% (±). Dose volume per injection site should not exceed 1.2 mL/site, with multiple sites used per dose as necessary.

8.2. Description and Manufacture of Study Drug

All manufacture, packaging and labeling operations will be performed according to Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines, as well as US regulations.

Table 9: Physical and Chemical Properties of Active Ingredient (Drug Substance)

Name	**IMO-8400**
Drug Class	Oligonucleotide antagonist of Toll-like receptors (TLRs) 7, 8 and 9
INN	NA
Molecular Formula	$C_{179}H_{216}N_{52}Na_{17}O_{101}P_{17}S_{17}$ (sodium salt)
Molecular Weight	6174 (sodium salt)
Appearance	Hygroscopic white to off-white amorphous solid obtained by lyophilization
Solubility	Freely soluble in aqueous media
Melting Point	Amorphous powder, decomposes without a defined melting point.

Table 10: Formulation of IMO-8400 for Injection (Drug Product)

Name	**IMO-8400 for Injection, 150 mg**
Active Ingredient	IMO-8400
Excipients	Each vial contains nitrogen (National Formulary).
How Supplied	Sterile, lyophilized powder for reconstitution packaged in a clear, round 5-mL glass vial with a rubber stopper and aluminum overseal. Each vial contains 150 mg (as labeled) IMO-8400 free acid, corrected for moisture and impurities.
Storage	The sealed vials of formulated drug product should be stored at 2-8°C.
Preparation and Handling	For dose levels of 0.6 mg/kg *per injection* or lower, vials are reconstituted using Sterile Saline for Injection, United States Pharmacopeia (USP); for higher dose levels, using Sterile Water for Injection, USP (to be provided by study site). Formulations used for dose levels of 2.4 mg/kg or higher will be prepared with 200 mg/mL active drug concentration. Detailed dose preparation instructions and flow sheets will be provided in the Pharmacy Manual.
Administration	The dose is administered as SC injection(s), not to exceed 1.2 mL/site, with multiple sites used per dose as necessary, using a fresh sterile needle (approximately 26 g); see Section 8.4 regarding the site of injection.

8.3. Reconstitution of IMO-8400 for Injection

IMO-8400 is provided as 150 mg of lyophilized powder in a 5-mL vial, to be reconstituted into solution for injection prior to use. The active drug concentration for all dose levels of 2.4 mg/kg/dose and higher will be 200 mg/mL. Detailed dose preparation instructions and flow sheets are provided in the Pharmacy Manual.

8.4. Administration of Study Treatments

Each dose of IMO-8400 will be administered as SC injection(s), not to exceed 1.2 mL/site, with multiple sites used per dose as necessary. For example, a 300 mg dose would be administered as two separate injections of 0.75 mL. The injection sites should be selected based on the following:

- There are six potential areas for injection: the four quadrants of the abdomen (upper and lower on the left and right) and the thigh of each leg.
- Injection site(s) should be rotated; that is, assuming all injection areas are suitable, each area would be used once every six dose injections.

If, because of injury or other issue, an injection site area will be used more frequently than once every 2 weeks, the Investigator should discuss the situation with the Medical Monitor.

8.4.1. Pre-Treatment Criteria

IMO-8400 should not be administered until the following conditions are met:

- Hemoglobin ≥7.5 g/dL
- ANC ≥1,000/μL
- Platelets ≥50,000/μL
- All other laboratory abnormalities to baseline or grade ≤1

8.4.2. Variances in Dose Administration Schedule

Dosing should ideally be performed on the same day each week; however, allowances of up to 48 hours (±) will be made for unavoidable scheduling conflicts.

If, for any reason (e.g., scheduling or toxicity), dosing is interrupted more than five calendar days beyond expected, then the next dose should be administered as soon as feasible and the schedule reset.

If, for any reason, dosing is interrupted more than 21 calendar days, the patient should be discontinued from study treatment and should complete EOT and EOS visits.

8.5. Prior and Concomitant Medications

Prior treatments for DLBCL will be recorded in the eCRF as well as treatments for any significant illness in the past year.

Any concomitant medication used from time of Screening through last study visit will be recorded in the eCRF, including dose, dosage regimen, and indication (reason for its prescription).

8.5.1. Prohibited Treatments

The exclusion criteria specify treatments prohibited at the time of study entry (Section 1.5.3).

While patients are receiving study treatment, other treatments for DLBCL are prohibited. Patients who discontinue treatment prematurely and have completed the EOT visit, may receive available or investigational treatment for their disease at any time based on the judgment of their physician. If such treatment is initiated prior to the EOS visit (scheduled for 30 to 35 days after last dose of study drug), this will be recorded in concomitant medications and considered in assessment of any new AEs.

8.6. Treatment Compliance

All doses of study drug will be administered by trained personnel. Injections of study drug may be administered in one of two contexts:

- ***Study site*** – defined as the site designated by the participating Investigator. On study days when a physical examination or laboratory safety test is scheduled it is expected that study drug will be administered at the study site.
- ***Non-study site administration by a visiting nurse*** – With the agreement of the patient and the Investigator, doses not administered at the study site may be administered by a visiting nurse who has been trained in the protocol and approved by the Sponsor.

The Sponsor will arrange for a Central Pharmacy to prepare and dispense the patient's study treatment, which will be packaged as required and shipped to the patient by overnight delivery service. To protect the integrity of the treatment, patients will be instructed to hold the shipping container unopened in a cool, dry, protected place.

  - The visiting nurse will open the container, inspect the materials, confirm they are correct, and proceed with pre-dose procedures, study drug administration, and post-dose procedures.

The used syringe and packaging materials will be disposed of per policy of the Central Pharmacy.

The visiting nurse will maintain appropriate source documents; the events will be entered into the Electronic Data Capture (EDC) system and copies of the source documents provided to the site.

8.7. Accountability of Investigational Drug Supplies

Study drug will be provided by the Sponsor. The Investigator at each study site and a designated pharmacist at the Central Pharmacy are responsible for the control of the study drug, and will identify trained and experienced personnel to handle it in accordance with the protocol and appropriate GCP and GMP principles. (Central Pharmacy will be responsible for study drug stored at Central Pharmacy and dispensed to patients for non-study site administration). This includes:

- Storing the drug in a secure, controlled-access location.

- Storing the drug under the specified conditions, including daily monitoring and recording of storage temperature.
- Maintaining records of the receipt of study drug and providing acknowledgement of receipt.
- Dispensing and administering study drug only in accordance with the protocol, including proper labeling of individual doses prepared in syringes ready for use.
- Maintaining drug accountability records indicating the disposition of study drug, including a Drug Dispensing Log containing the following information:
- Identification of the patient to whom the study drug was dispensed.
- Date(s) and quantity of the study drug dispensed to the patient.
- Having all records and drug supplies available for inspection by the study monitor.

Treatment administered to patients at non-study sites by a visiting nurse will be prepared by a Central Pharmacy from supply provided by the Sponsor. The Central Pharmacy is also required to comply with the specifications above.

8.7.1. Disposition of Study Drug

At any time during or after completion of the study, the site must obtain written authorization from the Sponsor regarding the final disposition of any remaining study drug; that disposition must be appropriately documented. Typical procedures for handling any remaining study drug include the following:

- Returning study drug to the Sponsor.
- Destroying study drug at the study site according to the site's institutional standard operating procedure.

9. STUDY EVENTS AND EVALUATIONS

9.1. Schedule of Events

The schedules for all study evaluations are detailed in Table 4. An estimate of blood volumes required is shown in Table 5.

The schedule is presented relative to the day and time of dosing. All days are relative to the calendar day of the first treatment of study drug, designated Cycle 1, Day 1. All times are relative to treatment, designated 0 hour. "Pre-dose" vital signs are to occur within 1 hour prior to treatment; all other pre-dose procedures are to occur prior to treatment on the same calendar day.

9.2. Screening, including Sequence of Procedures

Pre-screening for the MYD88 L265P mutation may be performed as detailed in Section 1.5.1. Protocol screening may be initiated up to 21 days prior to dosing. Written informed consent will be obtained before any study-specific procedures are performed and will be recorded in source documentation. The site will maintain a Patient Identification Log indicating all consented patients. Patients being considered for Phase 2 (Dose Expansion) should not undergo any additional screening work-up unless the MYD88 L265P mutation has already been documented (local or central lab; Section 1.5.1).

9.3. Determination of Presence or Absence of MYD88 L265P Mutation in DLBCL

Prior to enrolling a patient into the study, the patient's tumor is to be tested for the MYD88 L265P mutation using a CLIA-compliant assay performed at any point during the course of the patient's disease. If this has not been done, tumor may be sent to the Sponsor's designated central laboratory to perform testing for the presence of the mutation. If this analysis had been previously performed using a CLIA-compliant assay, all attempts should be made to procure either the original tumor tissue (previously collected at the time of diagnosis or at any point during the course of the patient's disease) or a fresh biopsy, if tissue is readily available (e.g., a superficial lymph node), to repeat/confirm the mutation testing at the Sponsor's designated central laboratory and to perform other investigational studies (Section 9.10). The sample will comprise formalin-fixed, paraffin-embedded (FFPE) tissue that is known to have a meaningful proportion of representative tumor cells and is submitted either as a cell block or as unstained sections. The latter should include the following:

- At least two unstained, mounted sections, 3 to 4 µm thick (to be processed for routine histology).
- Unmounted sections ("curls" or "slices") totaling 20 µm thick (e.g., five curls each 4 µm thick or two curls each 10 µm thick). The curls will be placed in a labeled microfuge tube for transport.

The sample will be analyzed using an assay from Abbott Molecular in development as a potential companion diagnostic, and the results reported as either "MYD88 L265P mutation detected" or "L265P mutation not detected". Samples may be retained for up to 1 year after the

end of the study (i.e., last patient, last visit) to support possible future development of a companion diagnostic assay.

9.4. Enrollment Procedure

The following procedure is to assure that patients enrolled across multiple sites are assigned to the appropriate cohort and receive the appropriate dose level. Patients who have completed all screening procedures will have eligibility data entered into the study EDC (electronic data capture) system, including the Investigators assessment of the patient's eligibility. The Sponsor or Sponsor's designated representative will review the data; the patient's assigned dose level will then be provided in writing (by email and/or fax) to both the Investigator and the site pharmacy.

9.5. Disease Evaluations

Radiologic Imaging – Radiographic tumor evaluation by PET/computed tomography (CT) scan or CT scan of chest, abdomen, and pelvis will be performed within 21 days prior to first dose of study treatment.

Repeat, radiologic assessments will be performed every 8 weeks while the patient is receiving active treatment with IMO-8400. Patients discontinued from treatment for reasons other than progressive disease will have radiologic tumor assessments performed every 12 weeks as a part of follow up (Section 6.5.6) until documentation of progressive disease, initiation of new anti-cancer therapy, or the end of the study, whichever comes first. The same radiographic assessments used at Screening should be used at all subsequent radiographic evaluations. Interim scans may be done at the request of the Investigator based on new clinical indications, signs or symptoms. Copies of the radiologic reports and images may be requested by the Sponsor for central review.

Lymph node biopsy – Archival or fresh tumor tissue should be submitted to the central lab for confirmation of diagnosis and exploratory analyses (as described in Section 9.10). At least one post-treatment biopsy should also be performed in order to evaluate target engagement. These should be collected between 4 and 24 hours post-treatment and may be obtained at any time during study participation. Instructions for submitting biopsy sections are provided (see the Laboratory Manual for more details).

9.6. Assessment of Response to Treatment

Following enrollment, the patient's disease status will be assessed every 8 weeks during study treatment, and at the EOT visit to permit evaluation of the response to treatment. In addition to routine clinical examination, these assessments will include PET\CT scanning or CT alone, and lymph node biopsy, as detailed in Section 9.5.

Table 11 summarizes the criteria for response to treatment. The full text of the International Working Group classification [1] is provided in Section 16.2.

Table 11: Summary of Evaluation of Response to Treatment and Disease Status

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
Complete Response (CR)	Disappearance of all evidence of disease	No residual FDG-avid or PET-positive nodes; PET-negative mass of any size permitted	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, IHC should be negative
Partial Response (PR)	Regression of measurable disease and no new sites	>50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes	>50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
Stable Disease (SD)	Failure to attain CR/PR or progressive disease	PET-positive at prior sites of disease and no new sites		
		a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET		
		b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Progressive Disease	Any new lesion or increase by >50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, *or* >50% increase in SPD of more than one node, *or* >50% increase in longest diameter of a previously identified node >1 cm in short axis	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
		Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy		

FDG = [^{18}F]fluorodeoxyglucose; PET = positron emission tomography; CT = computed tomography; IHC = immunohistochemistry; SPD = sum of the products of the diameters.
See Section 16.2 for the complete, original table.

9.7. General Clinical Assessments

9.7.1. Medical History, including DLBCL

Prior to enrollment, the Investigator will obtain a comprehensive medical history to ensure eligibility of the patients, including the following items:

- A detailed review of the course of the patient's malignancy, including clinically significant complications such as systemic infections, bleeding events, etc.
- Prior treatments, including supportive therapy (agent, best clinical response, AEs related to treatment, and reason for discontinuation).

- Relevant current or past abnormalities or diseases (including surgical procedures) of the following systems: allergic (including drug sensitivity), cardiovascular, dermatologic, endocrine/metabolic, gastrointestinal, gynecologic, hematologic/lymphatic, hepatic/biliary, immunologic, infectious, musculoskeletal, neurologic/psychiatric, renal, and respiratory.

Past history should include all significant illnesses that the patient has experienced during the 12 months prior to obtaining informed consent, including illnesses that have resolved as well as those that are active. Illnesses active at the time of informed consent will be regarded as concomitant illnesses. After obtaining informed consent, concomitant illnesses that worsen or new illnesses that emerge will be documented as AEs (Section 10).

9.7.2. Physical Examination and Body Weight

Complete physical examinations will include examination of general appearance, skin, neck (including thyroid), eyes, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, reproductive (in event of recent history, symptoms, or AEs related to reproductive system) and nervous system and measurement of body weight. Complete physical examination is required prior to enrollment and EOT and EOS. Directed physical examinations may be performed while on study treatment at the discretion of the Investigator. Exam of reproductive system, when needed, may be performed by the Investigator or delegated to a specialist.

Height and weight will be evaluated prior to enrollment and the BMI will be calculated.

Any clinically significant changes in physical exam identified after obtaining informed consent will be reported as AEs (Section 10).

9.7.3. Vital Signs

Vital signs include heart rate (HR), blood pressure (BP), respiratory rate (RR), and temperature. Vital signs will be performed once weekly for patients receiving once weekly dosing and twice weekly for patients receiving twice weekly dosing, immediately before each administration (within 1 hour of treatment) and post-dose (within 30 min [±5 min] of treatment). Vital signs should be after the patient has been sitting comfortably for 5 minutes with the BP cuff in place on the non-dominant arm. Blood pressure and HR measurements will be taken first and may be done manually or by automated recorder; RR will be determined by observation for at least 30 seconds; temperature will be obtained using an electronic (rapid reading) device.

Vital sign measurements will be assessed by the Investigator as either ‘normal’, ‘abnormal, not clinically significant’, or ‘abnormal, clinically significant’. Clinically significant abnormal vital sign measurements will be reported as an AE, and, if possible, should be repeated at clinically relevant intervals until resolved or stabilized.

9.7.4. Electrocardiogram

Standard 12-lead ECG will be obtained after the patient has been semi-recumbent for ~10 minutes. The following ECG parameters will be recorded: ventricular rate, RR interval, PR interval, QRS interval, and QT interval; also QTc, if available, including method of calculation.

9.7.5. Injection Site Reaction Assessments

Injection site reactions will be documented in detail for each individual injection as described in Table 12 and recorded in the injection site assessment form in the eCRF.

The Investigator will assess the injection site as scheduled and perform the following:

- Pain, tenderness, pruritus and induration: grade using the scale provided;
- For induration, also record the actual maximal linear diameter as a continuous variable;
- Erythema, record the actual maximal linear diameter as a continuous variable;
- Blisters, ulceration, necrosis: indicate presence or absence and record the maximal linear diameter, if applicable.

Table 12: IMO-8400 Subcutaneous Injection Site Grading (Local Reactions)

Finding	Mild	Moderate	Severe
Pain	Present; no limitations in ADL	Limitations in age-appropriate instrumental ADL *or* requires repeated non-narcotic pain reliever	Limitations in self-care ADL *or* interferes with sleep, *or* requires repeated narcotic pain reliever
Tenderness	Mild discomfort with pressure	Discomfort with touch	Discomfort elicited by clothing or bedsheets
Pruritus (itch)	Present, but minimally distracting	Present, distracting during routine activities	Interferes with sleep
Induration (swelling, edema)	Present; no limitations in ADL	Limitations in age-appropriate instrumental ADL *or* requires repeated treatment (excluding systemic steroids).	Limitations in self-care ADL *or* requires treatment with systemic steroids

Pain: discomfort or unpleasant feeling (e.g., headache) experienced while at rest or with activity; in addition to location, the patient's description may include intensity as well a distinctive quality (e.g., burning, stabbing).
Tenderness: discomfort elicited when the area is touched either intentionally or accidently.
Pruritus (itch): an unpleasant sensation that evokes the desire or reflex to scratch. (In contrast, pain and tenderness evoke a reflex to withdraw.)
Activities of daily living (ADL) are classified into two subsets:
– instrumental ADL, e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money;
– self-care ADL, e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

Injection site reactions may also be captured on the AE form. When reporting injection site reactions as an AE, the Investigator should report in the verbatim term the words "injection site reaction," along with the specific reaction symptom (such as erythema), and select the severity grade based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) guidelines which are presented in Table 13.

Table 13: Intensity of AE of Injection Site Reaction[a]

Mild	Moderate	Severe	Life-threatening
Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated

a. Based on NCI-CTCAE v.4.03. Definition of Injection Site Reaction: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.

9.8. Safety Laboratory Studies

Safety laboratory tests (with the exception of serum complement testing) indicated below will be performed by a local laboratory. Serum complement procedures for collecting, processing, and transporting the required blood sample will be detailed in the laboratory manual.

The Investigator may order additional local laboratory tests consistent with their routine standard of care.

9.8.1. Safety Laboratory Tests

Hematology Panel

*Hemoglobin
*Hematocrit
*Red blood cell count (RBC)
*White blood cell (WBC) count
*Platelet count
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Mean corpuscular volume (MCV)
*WBC differential (absolute cell counts):
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Clinical Chemistry Panel

*Glucose	Calcium	*Alanine aminotransferase (ALT)
*Urea	Magnesium	*Aspartate aminotransferase (AST)
*Creatinine	Phosphate	*Alkaline phosphatase (AP)
*Sodium	Uric Acid	*Total bilirubin
*Potassium	Cholesterol	Total protein
*Chloride	Triglycerides	Albumin
*Bicarbonate	LDL	Lactate dehydrogenase (LDH)
	HDL	Creatine phosphokinase (CK)
	CRP	β-2-microglobulin

* Laboratory tests comprising the focused panel to be performed during Cycles 1-6 on Day 15 of each Cycle. Hematology and Chemistry full panels will be performed on Day 1 of each Cycle. For Cycle 7 and subsequent cycles, testing will not repeated on Day 15 unless more frequent monitoring is clinically indicated.

Serum Complement Testing

Complement component 3 (C3)
Complement component 4 (C4)
50% hemolytic complement (CH50)

Coagulation Panel

Prothrombin Time (PT)	International normalized ratio (INR)
Activated partial thromboplastin time (aPTT)	Fibrinogen

Urinalysis

Specific gravity, pH, ketones, glucose, protein, blood (commercial dipstick may be used); microscopic examination, including quantitation of WBCs and RBCs.

Serologic tests (Screening only)

Hepatitis B surface antigen (HBsAg)	Antibody to HIV-1 and HIV-2	Antibody to hepatitis C virus (HCV)

Pregnancy tests (females only)

beta-human chorionic gonadotropin (β-hCG)

Females of child-bearing potential (defined in Section 1.5.2) must have a negative pregnancy test within 21 days of the first dose of study drug (Cycle 1, Day 1).

9.8.2. Reporting of Safety Laboratory Tests

Procedures for the Investigator assessment of the results are detailed in Section 10.2. Procedures for the analysis of laboratory data are described in Section 10.4.5.

9.8.3. Repeating Abnormal Laboratory Tests

Laboratory tests showing abnormal or exclusionary values prior to enrollment may be repeated no more than once, except non-negative screening serology results will be exclusionary and will not be repeated. After dosing, abnormal laboratory tests assessed as "clinically significant" values may be repeated as often as deemed clinically necessary by the Investigator until the test values are clinically acceptable or until an explanation other than drug effect is given.

9.9. Pharmacokinetic Assessments

Blood samples for plasma levels of IMO-8400 will be collected as scheduled (Table 4). Samples will be analyzed for IMO-8400 concentration using a validated bioanalytical method. For each cohort, the plasma IMO-8400 concentration data will be analyzed by non-compartmental PK analysis. The following parameters will be determined as appropriate: observed maximum plasma concentration (C_{max}), time of C_{max} (T_{max}), and AUC from 0 to last measurable plasma concentration (AUC_{0-t}). Pharmacokinetic parameters will be compared across IMO-8400 dose levels. Descriptive statistics will be provided for all PK parameter values by dose and time, as appropriate.

9.10. Pharmacodynamic and Investigational Studies

The central laboratory will distribute samples to the specialty laboratories that will perform the following studies on the tumor sample and on serum and plasma samples collected as scheduled to assess the pharmacologic effects of the investigational agent; to maximize consistency, tests may be batched. The clinical significance of these tests is unknown at this time and therefore the results will not be assessed by the Investigator.

Tumor cells (from archival or fresh sample of tumor or from the bone marrow biopsy) may be assayed for:

- Presence of somatic mutations in other genes encoding proteins in the TLR and BCR signaling pathways (e.g., CARD11, IRAK4, Btk).

Pre-dose serum samples will be assayed for:

- Levels of cytokines such as IL-6, IL-12, IL-17, IP-10; additional or alternative cytokines may be assessed using the samples collected.
- Antibodies to IMO-8400.

Plasma samples will be assayed for MYD88 L265P mutation and may be assayed for additional mutations.

Bone marrow biopsy – Bone marrow aspirate and/or biopsy is not required for disease assessment and is an optional procedure; however, any available specimens may be submitted for exploratory analyses whenever marrow is obtained. Instructions for submitting to the central laboratory are provided (see the Laboratory Manual for more details).

10. SAFETY ASSESSMENTS

10.1. Definition of AEs

10.1.1. Adverse Event

An AE is any untoward medical occurrence temporally associated with the use of a medical product in a patient, ***whether or not*** the event is considered causally related to the medical product.[1] An AE can be a new occurrence or an existing process that increases significantly in intensity or frequency.

An AE in a clinical trial may be ***any*** of the following:

- Unfavorable and unintended *symptom reported by the patient* — patients will be encouraged to report treatment-emergent AEs spontaneously; general, non-directed questioning may also be used to elicit reports of AEs.
- Clinical *sign detected by the Investigator* — observations by other study personnel will be reported to the Investigator for evaluation.
- Abnormal result from a *laboratory study* or other *diagnostic procedure* that meets at least one of the following criteria:
  - Results in termination of study drug.
  - Leads to treatment.
  - Leads to further diagnostic tests (other than a single repeat for confirmation).
  - Is assessed as "clinically significant" by the Investigator (Section 10.2).

10.1.2. Serious Adverse Event

An AE is **serious** when the patient outcome is one or more of the following:

- Death.
- Life-threatening, meaning that the patient was at immediate risk of death from the event at the time that the event occurred. It does not include an event which hypothetically might have caused death if it occurred in a more severe form.
- Hospitalization, initial or prolonged, meaning that a hospital admission and/or prolongation of a hospital stay was required for the treatment of the AE, or occurred as a consequence of the event. It does not include a pre-planned elective hospital admission for treatment or diagnostic procedures, or, in general, a hospital admission of less than 24 hours duration.
- Disability or incapacity that is persistent or significant.
- Congenital anomaly or birth defect.

[1] A medical product may be a drug or a device being used either prior to or after regulatory approval. The medical product in this protocol will hereafter be referred to as study drug (synonym: investigational agent).

- Important medical event that, although not immediately life-threatening, requires intervention in order to prevent one of the other serious outcomes listed above. Examples of such events are allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.

10.1.3. Suspected, Unexpected Serious Adverse Reaction

A suspected, unexpected serious adverse reaction (SUSAR) is defined as an SAE that meets ***both*** the following criteria with respect to study drug:

- *Suspected* — is assessed as related or possibly related to study drug (Section 10.4.3).
- *Unexpected* — compared to the study drug-related AEs described in the IB, the event meets ***any*** of the following criteria:
  - The event was not previously described.
  - The event is now characterized as more severe (Section 10.4.4).
  - The event is now characterized more specifically (e.g., an event of "interstitial nephritis" in a patient receiving an agent previously described as associated with "acute renal failure").

In clinical trials involving ill patients, events considered related to the natural history of the disease under study or to lack of efficacy (that is, the event is considered more likely related to those factors than to other factors, including study drug) are not considered "unexpected". Lack of efficacy is recorded as specified elsewhere in the protocol.

10.2. Investigator Assessment of Safety Laboratory Tests

The Investigator will review the results of all Safety Laboratory tests (Section 9.8.2) and designate any results outside of the reference range as ***either*** of the following:

- Abnormal, not clinically significant (NCS).
- Abnormal, clinically significant (CS).

In making this judgment, the Investigator will consider all available information, including the patient's clinical condition, all available laboratory results (central and local), and the potential for false positive test results. In addition, laboratory studies that result in the actions specified in Section 10.1.1 will be classified as CS.

Any result assessed as CS will be recorded as an AE *unless* it is consistent with one or more of the following:

- Process noted in the medical history.
- Ongoing AE already recorded.
- Expected course of the primary disease under study.

10.3. Recording Adverse Events

Procedures for the collection and recording of AEs are as follows:

- From obtaining informed consent through EOS, there will be active surveillance to identify all AEs. Events will be recorded in the AE portion of the EDC, with particular attention to whether the onset of the event was before or after the administration of the first dose of study drug. All recorded events will be included in applicable line listings, but only events with onset after administration of the first dose will be included in summaries of TEAEs (Section 12.3).
- After the EOS, surveillance will be passive (only events brought to the Investigator's attention will be considered) and only events assessed as SUSARs will be recorded (Section 10.1.3).
- In accordance with FDA Guidance Document – Safety Reporting Requirements for Investigational New Drugs (INDs) and Bioavailability/Bioequivalence (BA/BE) Studies, disease progression does not require reporting as an AE or SAE. However, signs and symptoms related to disease may be reported at the discretion of the Investigator.

10.4. Characterizing Adverse Events

For each AE recorded the following characteristics will be noted.

10.4.1. Description of Event

The diagnosis or description will be as specific and complete as possible (i.e., "lower extremity edema", rather than just "edema"). Whenever possible, signs and symptoms due to a common etiology will be reported as an integrated diagnosis; for example, cough, runny nose, sneezing, sore throat and head congestion would be reported as "upper respiratory infection".

10.4.2. Date and Time of Onset

The date and time at which the event was first apparent. Table 14 summarizes the basis for reporting the date and time of onset for the different types of AEs.

Table 14: Reporting the Date and Time of Onset of AE for Different Types of Events

Type of Event	Examples	Source of Date and Time of Onset
Symptom	Headache, feverish, paresthesiae	When first experienced by the patient
Sign (Finding)	Elevated BP, enlarged liver on physical exam	When first observed by the Investigator or other study staff
Laboratory / diagnostic result	Neutropenia, hyperglycemia, lesions on brain scan	When lab sample was obtained or diagnostic study performed

The time of onset of symptoms may be appreciably earlier than the date and time the Investigator becomes aware of the event. Some events may be apparent to the patient and Investigator independently, and information from each may contribute to the final report. For example, a patient may report the onset of a rash 2 days before being seen by a physician who makes a diagnosis of herpes zoster based on appearance and laboratory confirmation. In that case, there is

a single AE, with the date of onset based on the date of the initial observation by the patient and a specific description (herpes zoster) based on the clinical exam and tests.

10.4.3. Relationship to Study Drug

This determination is based on the Investigator's clinical judgment regarding the likelihood that the study drug caused the AE and may include consideration of some or all of the following factors:

- Alternative possible causes of the AE, including the patient's underlying disease or co-morbid conditions, other drugs, other host and environmental factors.
- Temporal sequence between the exposure to study drug and the AE.
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or toxicity of the study drug.
- Whether the AE resolved or improved with decreasing the dose or stopping the study drug (i.e., dechallenge); or recurred or worsened with re-exposure to the drug (i.e., rechallenge).

The relationship between the study drug and the AE will be described using one of the following categories:

- ***Related*** — the study drug is more likely the cause of the AE than other factors.
- ***Possibly related*** — there is a *reasonable* possibility that the study drug is the cause of the AE, including that the study drug and another factor(s) are equally likely as causes of the AE.
- ***Unlikely related*** — another factor is considered more likely the cause of the AE than the study drug.
- ***Not related*** — another factor is considered to be the cause of the AE.

Related and possibly related AEs may result during the use of the study drug as planned (per protocol), or from abuse, withdrawal or over-dosage of the agent.

10.4.4. Intensity (Severity)

The intensity (synonym: severity) of clinical AEs (i.e., symptoms reported by the patient and/or signs observed by the Investigator) will be assessed using the guidelines summarized in Table 15 [30].

Table 15: Estimating Severity Grade

Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
Moderate	Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.
Severe	Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalizations possible.
Life-threatening	Extreme limitation in activity; significant assistance required; significant medical intervention/therapy required; hospitalization or hospice.

10.4.5. Grading of Laboratory Safety Tests for Reporting and Analysis

Treatment-emergent abnormal laboratory results will be handled as follows:

- Graded using NCI-CTCAE Version 4.03 criteria
- Assessed as potential DLT events based on pre-specified criteria (Section 6.3.1).
- Reported as AEs when assessed as "clinically significant" using the procedures and criteria detailed in Section 10.2.

10.4.6. Management of Study Drug upon Occurrence of an AE

For each AE the Investigator will indicate which one of the following actions regarding the administration of study drug was taken because of that AE:

- ***Discontinued (withdrawn)*** — study drug was stopped permanently due to the AE.
- ***Dosing Interrupted*** — study drug regimen was modified by being temporarily halted, i.e., one or more doses were not administered, but drug was not stopped permanently.
- ***Dose Decreased*** — study drug regimen was modified by subtraction, i.e., by decreasing the frequency, strength or amount.
- ***None*** — no change in the administration of study medication.

For patients whose treatment is paused and then resumed at a lower dose level as detailed in Section 6.5.2, the management of study drug will be recorded as "Dose Decreased".

10.4.7. Actions Taken for Management of AE

Adverse events will be followed and managed by the Investigator, including obtaining any supplemental studies needed to define the nature and/or cause of the event (e.g., laboratory tests, diagnostic procedures, consultation with other health care professionals).

For each AE the Investigator will categorize as follows the actions taken to manage the AE:

- ***Concomitant medication*** — one or more medications (prescription or over-the-counter) were started or increased in dose; non-medication actions may *also* have been ordered.

- ***Other action*** — *only* non-medication action(s) were ordered as management of the AE (e.g., bed placed in Trendelenburg position, warm compresses applied to SC access site).
- ***No action*** — no actions were ordered for management of the AE.

10.4.8. Follow up and Outcome of AEs

If possible, AEs will be followed until resolved (synonyms: recovered, recuperated, ended) either with or without sequelae, including for patients who prematurely discontinue treatment. For AEs that are assessed as not drug-related and are not resolved at the EOS visit, follow up may be limited with the approval of the Medical Monitor.

The outcome of each event will be described using the following categories:

- ***Resolved without sequelae*** — the event resolved and patient returned to baseline.
- ***Resolved with sequelae*** — the event resolved but the patient is left with residual problems (e.g., functional deficits, pain).
- ***Resolving*** — at the last observation, the event was improving.
- ***Not resolved*** — at the last observation, the event was unchanged.
- ***Death (Fatal)*** — to be used for the *one* AE which, in the judgment of the Investigator, was the *primary* cause of death.
- ***Unknown*** — there were no observations after the onset (initial observation or report) of the event.

Note: Resolving and Not Resolved may also be used for AEs that were unresolved at the time a patient died, but were *not* assessed as the primary cause of death.

10.4.9. Date and Time of Outcome

For each class of outcome as defined above, Table 16 indicates the date and time to be recorded. As discussed in detail for date / time of onset (Section 10.4.2), determining the date/ time an event resolved (ended) should reflect the type of event and the source of the information.

Table 16: Date and Time of Outcome for AE by Outcome Class

Outcome assigned to AE	Date and Time to be Recorded
Resolved (with or without sequelae)	Date and time event observed or reported as resolved
Death	Date and time of death
Resolving or Not Resolved	Date and time of last observation
Unknown	None (see definition above)

10.5. Reporting Adverse Events

10.5.1. Where to Report SAEs

Serious AE reporting will be performed by the site using the EDC system; detailed training will be provided during site initiation. Reports and supporting materials relating to SAEs will be scanned and uploaded into the EDC system. Contact information for the Medical Monitor and the Pharmacovigilance service is provided in Table 1 and Table 2.

In the event an SAE cannot be submitted via EDC, contact information is provided in Table 1 for alternative submission methods.

10.5.2. Procedures for Reporting SAEs to the Sponsor

The ***initial notification*** of each SAE will be entered into the EDC system ***within 24 hours*** of the time the Investigator (or the Investigator's designee) becomes aware that the event has occurred. The following items will be entered into the appropriate EDC section (any items not available should be explicitly noted):

- Protocol number, study site, patient number.
- Investigator’s name and contact information (phone, email).
- Date of the first treatment with study drug.
- Date of the last treatment with study drug prior the event.
- Description of the event (i.e., date and time of onset, initial assessment, treatments and course).
- Current status of the patient and the event.
- Criteria by which the event was assessed as serious.
- Assessment of relationship of study drug to the event.
- Whether the study drug was discontinued or adjusted as a result of the event.

The following ***additional*** information will be entered within 2 days for death and life-threatening events and within 4 days for all other SAEs:

- Narrative summary of the event — to include specific information that will assist in understanding the event, e.g., relevant medical history, co-morbid conditions, physical exam, diagnostics, assessment, treatments (including concomitant medications), response to treatment, course, and outcome (if known).
- Copies of relevant medical reports — including diagnostic procedures (e.g., laboratory, ECG, x-ray), surgical procedures, and consultations.

Thereafter, ***supplemental (follow up) reports*** will be submitted via the EDC system as any additional information (e.g., more definitive outcome regarding events previously reported as ongoing or unknown outcome) becomes available to the Investigator (either directly or as a result of investigation into a query).

10.5.3. Other Reportable Events

Certain events that occur in the absence of an AE should be reported to the Sponsor. These include the following:

- Pregnancy exposure (patient becomes pregnant while taking study drug). Should a female patient or partner of a male patient become pregnant during the study, the patient will inform the Investigator. The patient will be asked to follow up with the study site to report the eventual outcome of the pregnancy. The information will be tracked by the Sponsor.
- Lactation exposure (patient was taking study drug while nursing an infant).
- Accidental exposure (someone other than the patient was exposed to study drug).
- Overdose (patient received more than the prescribed dose of study drug within a given timeframe).
- Other medication errors that potentially place patients at greater risk of harm than was previously known or recognized (e.g., study drug was administered via incorrect route).

10.5.4. Requirements for Expedited and Periodic Reporting of AEs

Suspected unexpected serious adverse reactions are required to be reported rapidly to regulatory authorities and to IRBs (typically within 7 days for fatal or life-threatening SUSARs; within 14 days for all other SUSARs). The Sponsor and the Investigator will work together to meet these reporting requirements.

10.5.5. Notification of SUSARs to the Investigator by the Sponsor

In accordance with regulatory requirements, the Sponsor will notify the Investigator of the occurrence of SUSARs reported by other Investigators in this or in other studies involving the study drug. The Investigator will promptly inform his/her IRB of such communications from the Sponsor and will document that notification in the Investigator's Regulatory Binder.

11. DATA QUALITY ASSURANCE

11.1. Compliance

The Sponsor and the Investigator will conduct the study in accordance with:

- The protocol — as approved by applicable regulatory authorities.
- Ethical standards and procedures — as detailed in Section 13.
- "Good Clinical Practices" and "Good Manufacturing Practices" — as detailed in documents issued by the International Council for Harmonisation (ICH).
- Applicable national regulations — e.g., in the US, 21 CFR.

11.2. Training and Qualifications of Site Personnel

All site personnel involved in the study will be trained regarding the protocol and the study drug. This includes, but is not limited to, pharmacy, nursing and medical personnel involved in handling and administering the study drug, monitoring the patients and collecting clinical data.

The Sponsor (or designee) will provide formal training sessions either off-site (e.g., Investigators Meeting) or on-site (e.g., site initiation visit). Topics covered will include, but not be limited to, background of the investigational drug, the protocol, study events, study procedures, data collection and recording, expedited and routine reporting of AEs, and regulatory requirements. It is the responsibility of the Investigator to document that all participating study personnel have received adequate training.

11.3. Source Documents

Source documents are the originals of any documents used by the Investigator, hospital, or institution that verify the existence of the patient and substantiate the integrity of the data collected during the trial.

11.3.1. Medical Records

Medical records related to the patient's routine clinical care, including prior to or during the study:

- Information obtained from the patient's personal physicians or other third parties regarding the patient's medical history or prior physical condition.
- Reports of imaging studies, hospitalizations, surgical procedures.
- Laboratory reports, including clinical pathology and diagnostic histologic pathology.
- Medication prescription and administration records.
- Data and reports from automated instruments (e.g., ECGs, cardiac monitors, vital signs).
- Medical records relating to scheduled and unscheduled clinical visits.

It is expected that Investigator's clinical practice will include medical records that meet current best practices for readability and documentation. Electronic health record (EHR) systems should meet current regulatory requirements for "protected health information" (PHI), including, at a minimum, security requirements for electronic signature and audit trails for changes.

11.3.2. Study-Specific Source Documents

Study-specific source documents include, but are not limited to, the following:

- The Informed Consent Form (ICF), signed and dated by the patient.
- The site patient identification log.
- Any reports noted above that are scheduled as part of the protocol and have been annotated to indicate the significance of any abnormal findings (Section 10.4.5).
- Concomitant medication prescription and administration records;
- Records relating to scheduled and unscheduled study visits, including, but not limited to, results of examinations, observations relating to AEs, and concomitant medications.

Study-specific source documents must meet the following requirements:

- Be prepared at the time of the events or activities described (i.e., contemporaneously).
- Indicate both the date and time recorded.
- Identify the source of all recorded information (e.g., the patient, direct observations of the recorder, lab reports, external / historical sources).
- Have text that is readable, unambiguous, and applies best medical record practices (e.g., minimal use of abbreviations; proper numerical, dose, and posology formats).
- Have all entries signed and dated by the recorder.

Study-specific paper documents must meet the following additional requirements:

- Be written legibly in dark ink (preferably black), including signature and date.
- In the event that any entry needs to be changed, a single line will be made through the original entry, the correct information added next to it, and the action initialed, dated, and explained (if appropriate). The original entry must not be obscured or obliterated by multiple cross-out, correction fluid or overlay of other material.

Study-specific source document forms created by the site must be reviewed by the Sponsor prior to use.

11.4. Electronic Case Report Forms

The Sponsor will provide a regulatory-compliant EDC system for reporting study data to a central facility holding the trial database. All study personnel will be trained on the system and each will have a unique login password and electronic signature.

The Investigator (or qualified sub-Investigator approved by the Sponsor) will review all eCRFs and indicate their concurrence by (electronic) signature.

11.5. Protocol Deviations

A protocol deviation is defined as an event in which the Investigator or site personnel did not conduct the study according to the Protocol, including compliance requirements and agreements. Guidelines for minor procedural variations (e.g., collection time of blood samples) will be agreed to and documented by the Investigator and the Sponsor prior to starting the study. Events conforming to those guidelines will not be considered deviations.

For protocol deviations relating to individual patients, the event and relevant circumstances will be recorded on source documents and on the appropriate eCRF; reported to the Sponsor in a timely manner; and presented in the Clinical Study Report (CSR).

Deviations that are not patient-specific (e.g., unauthorized use of an investigational agent outside the protocol, either human administration or laboratory use) will be reported to the Sponsor in writing and copies placed in the Trial Master File (TMF).

Deviations that can be anticipated should, if possible, be discussed with the Sponsor before being implemented.

11.6. External Review of the Study Conduct at Participating Sites

All study-related materials at the site are subject to external review to ensure the safety of the patients, the integrity of the study data, and compliance with all applicable regulatory and oversight requirements.

There are several different classes of review:

- Monitoring — review by the Sponsor or authorized representatives, typically from the clinical research organization (CRO) coordinating the clinical conduct of the trial. As detailed below, visits may be conducted before, during, and after the conduct of the study.
- Audits — systematic, independent review by the quality assurance department of the Sponsor or authorized representatives, potentially from an organization not involved in the clinical conduct of the study.
- Regulatory review — performed by representatives of regulatory authorities with responsibility for oversight of the trial or approval of the investigational agent. These authorities may be from the country where the site is located or from another country.

Monitoring and auditing visits on behalf of the Sponsor will be scheduled with the Investigator in advance and will be conducted at a reasonable time. To facilitate these visits, the Investigator will assure that the following are available:

- Appropriate space, facilities and access to all source documents (including access to computerized records either electronically or as complete print outs).
- Consent forms, eCRFs, SAE forms, and medical records for all screened and enrolled patients.

- Timely access to site personnel, including the Investigator, sub-Investigator(s), and other study personnel on the day of the visit to resolve any questions that arise.

Regulatory authorities may visit and review the site and/or Investigator during or after the study and may or may not notify the Investigator or the Sponsor in advance. The Investigator will fully cooperate with regulatory audits conducted at a reasonable time in a reasonable manner. The Investigator will notify the Sponsor immediately of any contact by or communication from regulatory authorities regarding the study.

11.7. Study Monitoring Visits

11.7.1. Site Qualification and Initiation Visits

Before an investigational site can enter a patient into the study, a representative of Idera Pharmaceuticals, Inc. will visit the site to perform the following:

- Inspect the facilities (e.g., clinical and administrative areas, pharmacy, laboratory).
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, as well as the responsibilities of Idera and its representatives.
- Review the site TMF, including documentation related to the protocol, the Investigator, and other study site personnel; correspondence to and from the IRB, the Sponsor, and their representatives.
- Review the standard operating procedures and current practices relating to clinical and pharmacy activities, data handling, the IRB oversight and the informed consent process.

11.7.2. Interim Monitoring Visits

During the study, a monitor from or representing Idera will visit the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product is being appropriately handled and accounted for.
- Perform source data verification, including verifying the data in the eCRFs against the relevant source documents (Section 11.3) and resolving any discrepancies noted.
- Record and report any protocol deviations.
- Confirm that AEs and SAEs have been properly documented on eCRFs; that any SAEs have been forwarded to Idera Pharmaceuticals, Inc.; and that SAEs meeting criteria for reporting have been forwarded to the IRB.

Between visits the monitor will be available as needed to provide information or support to the Investigator(s) or other staff.

11.7.3. Study Closeout Visit

The study will be considered complete when all of the following have occurred:

- All treated patients have completed all scheduled visits plus any unscheduled follow up required by AEs.
- All eCRFs have been completed, submitted and all queries resolved.
- The trial database has been locked.

The Sponsor or designee will then conduct a study closeout visit, which may include, but is not limited to, the following:

- Review the site TMF to assure all required regulatory documents are current and complete.
- Resolve any open issues from prior monitoring, audit or inspection visits.
- Review the site's provisions for meeting the requirements for retention study records.
- Discuss possible future site audits.
- Review the Sponsor's publication policy.
- Confirm compliance with requirements for notifying the IRB of study events, including closure.
- Collect any unused study materials for either return to the Sponsor or disposal in a manner approved by the Sponsor.

11.8. Resolution of Deficiencies

The Investigator agrees to take promptly any reasonable steps requested by the Sponsor to resolve any deficiencies identified as a result of monitoring, audits, inspections, protocol deviations, or review of any other study documentation. Failure to take adequate remedial action can result in suspension or termination of the study at the site.

11.9. Retention of Records

All study-related materials at the site (e.g., source documents, eCRFs, TMF) will be retained according to ICH guidelines and applicable regulations.

The study drug is being developed under a US IND application; regulations require all study-related materials be retained for at least 2 years after one of the following events:

- Approval of a New Drug Application based on this study.
- Notification by the Sponsor that no further application will be filed.

The Investigator will use the following procedures regarding retained records:

- Contact the Sponsor ***before*** destructing any records pertaining to the study.
- Provide the Sponsor an opportunity to collect the records.
- Obtain written permission from the Sponsor to destroy the records.

- Notify the Sponsor if the Investigator plans to leave the institution so that arrangements can be made for the transfer of records.

Clinical and laboratory samples that are unstable may be disposed with the written approval of the Sponsor.

11.10. Data Management

A detailed Data Management Plan will be prepared separately and approved by the Sponsor.

12. STATISTICAL METHODS

The sections below indicate the overall structure and approach to the analysis of this study. A detailed Statistical Analysis Plan (SAP) incorporating these sections below will be prepared separately and approved by the Sponsor. The SAP will define populations for analysis, outline all data handling conventions, including software, and specify additional statistical methods to be used for analysis of safety, efficacy and PK.

12.1. Sample Size Determination and Study Power

Following identification of the RP2D, up to an additional 29 patients will be enrolled at the RP2D.

Simon's two-stage design [8] will be used to test the response rate at the RP2D. The null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. In the first stage, 10 patients will be accrued. If there are one or fewer responses in these 10 patients, the study will be stopped. Otherwise, 19 additional patients will be accrued for a total of 29. The null hypothesis will be rejected if six or more responses are observed in 29 patients. This design yields a type I error rate of 4.7% and power of 80.5% when the true response rate is 30%.

12.2. Analysis Populations

Analysis Populations:

- DLT Evaluable Population: patients enrolled in the Phase 1 dose escalation portion of the study who receive all planned doses of study drug during the DLT observation period or who discontinue treatment due to AEs.
- Safety/Intent-to-Treat (ITT) Population: all patients who received at least 1 injection of study drug.
- Efficacy Evaluable (EE) Population: all patients who are MYD88 L265p mutation positive and are treated at the RP2D.
- Per Protocol (PP) Population: all patients in the EE who had no major protocol violations that would potentially influence treatment effect.
- Pharmacokinetic (PK) Population: all patients who had both a pre-dose and at least one analyzable post-dose PK sample.

CRC review will be performed on the DLT Evaluable Population for the dose being considered. Safety analyses will be performed using the Safety/ITT Population. Efficacy endpoints will be analyzed for the EE and PP Populations. Response will also be tabulated for the Safety/ITT Population. Pharmacodynamic and immunogenicity assessments will be analyzed for the Safety/ITT Population.

12.3. Analysis of Safety

Safety analyses will be performed on the Safety/ITT Population. Safety observations will be analyzed using descriptive statistics and tabulation. No formal statistical comparisons are

planned. All safety data will be presented in listings. Only TEAEs (onset after the administration of the first dose of study drug) will be summarized in the Tables.

Primary Safety and Tolerability Endpoints:

- Number of DLTs
- Frequency and intensity of AEs
- Physical examination findings, including vital signs
- Laboratory safety tests including hematology, chemistry, coagulation, urinalysis and complement levels
- Assessment of injection site reactions (ISRs)
- ECG findings

Safety Analyses

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 and tabulated by event, grade, and relationship to study treatment. Safety analyses will be descriptive in nature; no statistical hypothesis testing will be performed. Laboratory assessments for hematology, chemistry, coagulation, and special safety tests (C3, C4, and CH50) will be tabulated via shift tables, tabulating each patient's category at baseline via National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03 grading (normal and Grade 1 will be combined) versus their highest NCI-CTCAE grade on study. Injection site reactions will be summarized by incidence for each dose group and overall and by worst grade on study. Time-to-event analyses will be performed for ISRs.

12.4. Analysis of Treatment Effect

Analyses of treatment effect will be performed on both the EE and the PP Populations.

12.4.1. Assessments

Patients will be assessed as per the schedule of events. Response status will be classified using disease-specific criteria as proposed by the International Working Group [1] (Section 9.6 and Section 16.2).

12.4.1.1. Primary Treatment Effect Parameter

The primary treatment effect parameter is the proportion of responders at the RP2D with the MYD88 L265 mutation. The definition of a responder is a patient who achieves a complete response (CR) or partial response (PR) based on the Revised Response Criteria for Malignant Lymphoma proposed by the International Working Group [1] (Section 9.6 and Section 16.2).

As per the Simon two-stage design, after 10 subjects are treated at the RP2D until disease progression or clinical response, if one or fewer of those subjects respond, the study will end. If two or more of those initial 10 subjects respond, 19 more subjects will be enrolled. If six or more subjects of 29 treated at the RP2D respond, the null hypothesis that $P_{response} \leq 10\%$ may be rejected.

12.4.1.2. Secondary Treatment Effect Parameters

The International Working Group specifies a number of outcome metrics related to time [1] (Section 16.3). The parameters considered most relevant to this study are: duration of response, time to response, proportion of responders at all dose levels, OS, and progression-free survival; these will be analyzed both globally across all cohorts and by dose level, reporting Kaplan-Meier estimated median, as well as the number of events and number of patients censored.

12.5. Exploratory Analyses

The following investigational factors will be analyzed with regard to response status:

- Presence or absence of MYD88 L265P mutation in tumor cells.
- Serum cytokine levels.
- Serum levels of antibody to IMO-8400.

12.6. Identification of Study Event Days and Times

Study events will be recorded using the calendar date and (where applicable) the time to the nearest minute.

For purposes of post-study analysis (e.g., tables and listings), study days will be designated as follows:

- Day 1 is defined as the calendar day of the first treatment with study drug.
- The days prior to Day 1 are designated Day –1, Day –2, etc.; there is no Day 0.
- The days following the day of the first treatment with study drug are designated Day 2, Day 3, etc.
- The day of the last treatment with study drug is indicated by adding the suffix "L", e.g., if the last treatment is administered on Day 43, it will be displayed as "Day 43L".
- The days following the last treatment with study drug are designated Day 1P, Day 2P, etc.

The times of events related to dosing of study drug will be designated as minutes or hours before or after the time of dosing (i.e., the SC injection of study drug), which is designated as t = 0 (zero). Thus, 15 minutes prior to dosing is t = –15 min; 2 hour after dosing is designated t = 2 h.

12.7. Interim Analysis

An interim analysis is planned after 10 patients are treated at the RP2D. If fewer than two patients respond, the study will stop. If two or more patients respond, the study will continue until 29 patients are enrolled and treated at the RP2D.

12.8. Handling Missing Data

Missing data will not be imputed. In time-to-event analyses using Kaplan-Meier methodology, patients who do not experience the event of interest will be censored. Rules for censoring of data will be described in the SAP.

Further details for handling of missing, duplicated or unscheduled data will be given in the SAP.

12.9. Changes in the Planned Analyses

If changes to the analyses planned in the protocol are made, then these will be listed in the CSR, along with an explanation as to why they occurred.

13. ETHICAL CONSIDERATIONS

The study will be conducted in accordance with:

- The current version of "Ethical Principles For Medical Research Involving Human Subjects" as adopted by the World Medical Association (WMA)[31].[2]
- Local laws and regulations for the use of investigational therapeutic agents.

13.1. Independent Ethics Committee

13.1.1. Initial Review Prior to Study Initiation

Prior to initiating the study, the Investigator will submit the following to an Independent Ethics Committee (IEC)[3] for approval:

- Study protocol.
- Investigator's Brochure.
- Informed Consent Form and any other written documents to be given to the patient;
- Details of any compensation to participants.
- Copies of any proposed public announcements of the trial (e.g., advertisements, web postings).
- Any other requested document(s).

The study will not commence until the IEC has issued a letter of approval signed and dated by the IEC chair or authorized person which includes the following items:

- Protocol number, full title, version number and date.
- Version date of the ICF.
- Version date of the applicable IB.
- Date the protocol and consent form were reviewed and approved by the IEC.

The Sponsor or designee will be provided copies of all correspondence between the Investigator and the IEC. In addition, prior to study initiation, the Sponsor will be provided *one* of the following to verify that the IEC was appropriately qualified to approve the protocol:

[2] This document, commonly referred to as the "Declaration of Helsinki", was issued in 1964 and has been amended or clarified at subsequent WMA Assemblies. Only the current document is considered official by WMA. The most recent version was approved in October 2013 (Fortaleza, Brazil).

[3] ICH E6, which specifies GCP, requires "an independent body (a review board or a committee, institutional, regional, national or supernational) …. whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial…" In this protocol, the body performing this function will be referred to as the IEC (Independent Ethics Committee); in practice, many alternative designations are used, e.g., Institutional Review Board (IRB).

- Documentation that on the date of the approval, the IEC met all currently applicable regulatory requirements for policies and procedures (e.g., membership, quorum, and approval procedures).
- A memo listing the voting members of the IEC who were present at the meeting the protocol was approved, including their titles, occupations, and institutional affiliations.

13.1.2. Subsequent Submissions to the IEC

After the initial approval, the Sponsor and Investigator will submit the following to the IEC:

- Any new information that may be relevant to a patient's willingness to initiate or continue participation in the trial.
- Any proposed amendments to the protocol.
- Proposed revisions to the ICF that incorporate new information or procedures.
- Copies of any proposed public announcements of the trial.
- At least annually, a report of the study's progress.
- Notification of any decision by the Investigator or Sponsor to suspend or terminate the study and the reason(s) for such action.

13.2. Written Informed Consent

Informed Consent Forms submitted to the IEC must be (a) based on a master document provided by the Sponsor and (b) reviewed and approved by the Sponsor prior to submission to the IRB. The Sponsor must also review and approve any changes requested by the IRB prior to the ICF being used.

Informed consent will be obtained prior to conducting any study procedures that are not part of the patient's routine medical care. During the consent process, each patient will:

- Be advised of the nature and risk of the study by the Investigator or designated study personnel.
- Be given full opportunity to read the ICF, ask any questions, and consider whether to participate.
- Provide informed consent voluntarily.

The ICF will be signed and dated by the patient and by the person who provided the information. A copy of the signed ICF will be provided to the patient; the original will be retained by the Investigator as a source document. The informed consent process will be noted in the source documents.

The patient will be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. Communication of this information to the patient will be noted in the source documents.

13.2.1. Obtaining Informed Consent from Patients Who Are Not Literate

If the site proposes to enroll patients who are not literate, or who are literate in a language other than English, then the operating guidelines of the approving IRB should specify appropriate regulatory-compliant procedures.

Typically, if a patient is not literate, then ICF must be signed (or marked) by the patient *and* signed by an *impartial* witness who was present during the *entire* informed consent process. For patients who are literate in a language other than English, the consent process typically includes either:

- An approved translation of the ICF in the appropriate language.
- Presentation by an approved translator who presents the required consent information in the patient's native language *plus* the patient signing a generic ("short form") consent in their native language indicating that the study-specific information has been presented to them verbally in their native language and they have had the usual opportunity to have any questions answered.

13.2.2. Special Informed Consent Situations Not Applicable to This Protocol

Patients may not be enrolled if they meet ***any*** of the following conditions which require specific provisions and approvals not provided for in this protocol:

- Are not able to provide informed consent (e.g., are acutely or permanently impaired).
- Are at increased risk of coercion (e.g., prisoners, institutionalized persons).

13.2.3. Protection of Patient Information

The identity and collected data of each patient ("protected health information") will be kept confidential and will be protected in accordance with applicable local regulations, including:

- Each patient will be assigned a unique patient number, which will be used on the eCRF in place of the patient's name.
- Computer systems for collecting and analyzing the data will have restricted access.
- In publications, aggregate data will be used wherever possible; any individual data will be redacted of unique identifying characteristics.

The informed consent process will comply with local requirements relating to (a) disclosure of the data to be collected and (b) authorization for its use. When permitted, these issues will be included in the ICF. In the event a separate form is required, the following will apply:

- The Sponsor must review and approve the separate form.
- The form will be signed and dated by, and copies provided to, the required parties.
- A completed copy of the form will be placed in the trial files with the completed ICF.

14. STUDY ADMINISTRATION

14.1. Registration of Study

The Sponsor will register the trial on clinicaltrials.gov in accordance with applicable US regulatory requirements and the guidelines of the International Committee of Medical Journal Editors (ICMJE) regarding registration of controlled clinical trials ("clinically directive trials").

14.2. Changes in the Conduct of the Study

After the protocol has been approved by the governing IEC and regulatory authority, substantial changes in the conduct of the study will only be made as formal protocol revisions, which must be reviewed and approved by the Sponsor and the Investigator prior to submission to the applicable IEC and regulatory body. Changes will only be implemented after the revised protocol is approved as required.

Changes to contract information or designated study personnel (page 4) may be handled administratively.

14.3. Confidentiality

This protocol, the applicable IB, the results of the study and other related information provided by the Sponsor represent confidential and proprietary material of the Sponsor. They will be available only to the Investigator, personnel directly involved in the study, and authorized members and staff of the applicable IEC. These parties agree not to disclose these materials to others.

14.4. Financial Disclosure

In compliance with US 21 CFR 54.4, any listed or identified Investigator or Sub-investigator (including the spouse and any dependent children of said individuals) directly involved in the treatment or evaluation of research patients will disclose the following information for the time period during which the Investigator is participating in the study and for 1 year following completion of the study:

- Any financial arrangement between Idera Pharmaceuticals, Inc. and the Investigator in which the value of the compensation to the Investigator for conducting the study could be impacted by the outcome of the study.
- Payments (exclusive of the costs of conducting this or other clinical studies) by Idera Pharmaceuticals, Inc. totaling >$10,000, including, but not limited to, grants to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.
- Any proprietary interest held by the Investigator in the product being evaluated.
- Equity interest in Idera Pharmaceuticals, Inc. that exceeds $10,000, including ownership interest, stock options, or other financial interest whose value cannot be determined through reference to public prices.

14.5. Publication Policy

Idera Pharmaceuticals, Inc. recognizes the importance of communicating the results of scientific studies, including clinical trials, and, therefore, encourages their publication in reputable scientific journals and presentation at seminars or conferences. Idera also has legitimate corporate and shareholder responsibilities, including, but not limited to, protecting confidential information about its proprietary products and obtaining patent protection for its intellectual property.

Therefore, the following procedures apply to any communication (including written, oral, or electronic; manuscript, abstract, other publication, or presentation) of results or information arising from this study (including any ancillary studies involving trial patients) to any third parties:

- The proposed communication will be prepared in collaboration with the Sponsor.
- The final proposed version must be submitted to Idera for review and comment at least 30 days prior to presentation, submission for publication or other dissemination.
- In the event Idera reasonably determines that a proposed communication contains confidential or patentable material, they may require *either* of the following:
  - The material be removed from the communication;
  - The communication be delayed for up to 60 additional days to permit filing the appropriate intellectual property protection.

These procedures apply regardless of whether the study is completed as planned or is terminated prematurely for any reason.

The first publication from this study is expected to be a summary of all protocol results, jointly produced by the Sponsor and the participating Investigators.

14.6. Authorship and Acknowledgement

All publications will give Idera Pharmaceuticals, Inc. and/or their personnel appropriate credit (i.e., authorship or acknowledgement) for any direct contribution made by them.

Authorship will be decided jointly by the Investigators and the Sponsor. Manuscripts will conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, including, but not limited to, the standards for authorship contained therein.

15. LIST OF REFERENCES

1 Cheson B, Pfistner B, Juweid ME et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007; 25(5):579-586.
2 Ngo VN, Young RM, Schmitz R, et al. Oncogenically active MyD88 mutations in human lymphoma. Nature. 2011; 470(7332): 115–119.
3 Young RM, Staudt LM. Targeting pathologic B cell receptor signaling in lymphoid malignancies. Nature Rev Drug Discovery. 2013; 12:229-243.
4 Lim K-H, Barton GM, Staudt LM. Oncogenic MyD88 mutants require Toll-like receptors. Amer Assoc Cancer Res, 2013 Annual Meeting, Abstract 2332.
5 Bhagat L, Wang D, Jiang W, et al. IMO-8400, a selective antagonist of TLRs 7, 8 and 9, inhibits MYD88 L265P mutation-driven signaling and cell survival: A potential novel approach for treatment of B-cell lymphomas harboring MYD88 L265P mutation. Abstract, AACR Annual Meeting 2014, San Diego, California, April 5-9, 2014.
6 Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. N Engl J Med 2012; 367:826-33.
7 Thomas, S, Harb W, Beck T, et al. Interim Results From a Phase 1/2, Open-Label, Dose-Escalation Trial of IMO-8400 in Patients with Relapsed or Refractory Waldenström's Macroglobulinemia Abstract, ASH Annual Meeting 2015
8 Simon R. Optimal two-stage design for phase II clinical trials. Control Clin Trials. 1989; 10(1):1-10.
9 Fernandez-Rodriguez C, Bellosillo B, Garcia-Garcia M, et al. MyD88 (L265P) mutation is an independent prognostic factor for outcome in patients with diffuse large B-cell lymphoma. Leukemia 2014; 28, 2104–2106.
10 NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphoma. Version 2.2013. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf. Accessed on-line 5 Nov 2013
11 Campo E, Swerdlow SH, Harris NL, et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2008; 17(19):5019-5032.
12 SEER Cancer Statistics Factsheets: Non-Hodgkin Lymphoma. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/nhl.html. Accessed 5 November 2013.
13 Hill BT, Sweetenham J. Clinical implications of the molecular subtypes of diffuse large B-cell lymphoma. Leuk Lymphoma. 2012;53:763-769.
14 Lenz, G, Wright G, Dave SS, et al. Stromal Gene Signatures in Large-B-Cell Lymphomas N Engl J Med. 2008; 359:2313-23.
15 Green N, Marshak-Rothstein A. Toll-like receptor driven B cell activation in the induction of systemic autoimmunity. A Sem Immunol. 2011; 23:106-112.
16 Marshak-Rothstein A, Rifkin I. Immunologically Active Autoantigens: The Role of Toll-Like Receptors in Development of Chronic Inflammatory Disease. Ann Rev Immunol. 2007; 25:419-441.
17 Sun S, Rao N, Venable J, et al. TLR7/9 Antagonists as Therapeutics for Immune-Mediated Inflammatory Disorders. Inflamm Alerrgy Drug Targets. 2007; 6:223-235.
18 Cros J, Cagnard N, Woollard K, et al. Human CD14dim Monocytes Patrol and Sense Nucleic Acids and Viruses via TLR7 and TLR8 Receptors. Immunity. 2010; 33:1-12.
19 Demaria O, Pagni P, Traub S, et al. TLR8 deficiency leads to autoimmunity in mice. J Clin Invest. 2010; 120:3651-3662.

20 Wang JQ, Jeelall YS, Horikawa K. Emerging targets in human lymphoma: targeting the MyD88 mutation. Blood Lymph Cancer 2013;3:53–61.
21 Choi JW, Kim Y, Lee J-H, Kim Y-S. MyD88 expression and L265P mutation in diffuse large B-cell lymphoma. Hum Pathol. 2013; 44:1375-1381.
22 Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med. 2012;367(9):826–833
23 Puente XS, Pinyol M, Quesada V, et al. Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia. Nature. 2011;475(7354):101–105.
24 Wang L, Lawrence MS, Wan Y, et al. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. N Engl J Med. 2011;365(26):2497–2506.
25 Montesinos-Rongen M, Godlewska E, Brunn A, Wiestler OD, Siebert R, Deckert M. Activating L265P mutations of the MyD88 gene are common in primary central nervous system lymphoma. Acta Neuropathol. Dec 2011;122(6):791–792.
26 Gonzalez-Aguilar A, Idbaih A, Boisselier B, et al. Recurrent mutations of MyD88 and TBL1XR1 in primary central nervous system lymphomas. Clin Cancer Res. Oct 1, 2012;18(19):5203–5211.
27 Li ZM, Rinaldi A, Cavalli A, et al. MyD88 somatic mutations in MALT lymphomas. Br J Haematol. 2012;158(5):662–664.
28 Ries LAG, Eisner MP, Kosary CL, eds. SEER Cancer Statistics Review, 1975-2011. Bethesda, MD: National Cancer Institute. Available at: http://seer.cancer.gov/csr/1975_2011/. Accessed 6 July 2014.
29 FDA Briefing Document: Peripheral and Central Nervous System Drugs Advisory Committee Meeting. NDA 206031. Drisapersen. 2015 Nov.
30 Common Terminology Criteria for AEs (CTCAE). Version 4.0, 28 May 2009. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. NIH Publication No. 03-5410.
31 Ethical Principles For Medical Research Involving Human Subjects. World Medical Association. Available at (accessed 8 October 2013) http://www.wma.net/en/30publications/10policies/b3/.

16. DIAGNOSTIC AND RESPONSE CLASSIFICATIONS CITED

16.1. WHO Classification of Mature B-cell neoplasms [11]

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Splenic lymphoma/leukemia, unclassifiable
  - Splenic diffuse red pulp small B-cell lymphoma
  - Hairy cell leukemia-variant
- Lymphoplasmacytic lymphoma
  - Waldenström's Macroglobulinemia
- Heavy chain diseases
  - Alpha heavy chain disease
  - Gamma heavy chain disease
  - Mu heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone B-cell lymphoma (MZL)
  - Pediatric type nodal MZL
- Follicular lymphoma
  - Pediatric type follicular lymphoma
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
  - T cell/histiocyte rich large B-cell lymphoma
  - Primary DLBCL of the CNS
  - Primary cutaneous DLBCL, leg type

  - Epstein-Barr virus (EBV)-positive DLBCL of the elderly
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- Anaplastic lymphoma kinase (ALK)+ large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

See Section 1.5 for specific diagnoses eligible for and excluded from this study.

16.2. Classification of Disease Response for DLBCL

Reproduced from Reference [1].

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

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

16.3. Efficacy End Point Definitions

Reproduced from Reference [1].

Table 3. Efficacy End Points

End Point	Patients	Definition	Measured From
Primary			
Overall survival	All	Death as a result of any cause	Entry onto study
Progression-free survival	All	Disease progression or death as a result of any cause	Entry onto study
Secondary			
Event-free survival	All	Failure of treatment or death as a result of any cause	Entry onto study
Time to progression	All	Time to progression or death as a result of lymphoma	Entry onto study
Disease-free survival	in CR	Time to relapse or death as a result of lymphoma or acute toxicity of treatment	Documentation of response
Response duration	In CR or PR	Time to relapse or progression	Documentation of response
Lymphoma-specific survival	All	Time to death as a result of lymphoma	Entry onto study
Time to next treatment	All	Time to new treatment	End of primary treatment

Abbreviations: CR, complete remission; PR, partial remission.

17. INVESTIGATOR'S AGREEMENT

I have read the foregoing protocol (Protocol 8400-402, Version 4.0) and agree to the following:

- The protocol contains all necessary details for carrying out this study.
- I will conduct the study as detailed in the protocol and will abide by all its provisions.
- I will conduct the study in compliance with ICH Guidelines for Good Clinical Practice, the requirements of the IRB and all applicable government regulations.
- I will train and supervise all individuals delegated to assist me in conducting this study, including providing copies of the protocol and all pertinent information and discussing the material with them to ensure they are fully informed regarding the investigational drug, the protocol and their responsibilities and obligations.
- I will use only the current informed consent form approved by the Sponsor (or their designee) and by the IRB responsible for this study.
- I will fulfill all requirements for submitting pertinent information to the IRB and to the Sponsor, including reportable serious AEs.
- I will complete all case report forms, including resolution of queries, in a timely manner.
- I will provide the Sponsor (or their designee) with access to any source documents from which case report form information may have been derived.
- I will provide the Sponsor with complete, signed statements of financial disclosure as required.
- I understand that the information in this protocol and the referenced Investigator's Brochure is confidential and that its disclosure to any third parties (other than those approving or conducting the study) is prohibited. I will take the necessary precautions to protect this information from loss, inadvertent disclosure or access by third parties.

Signature of Investigator **Date**

Investigator (printed name): _____

Title: _____

Address: _____

Facility / Site of Investigation: _____

Facility address: _____