PROTOCOL 8400-401

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 Waldenström's Macroglobulinemia
Investigational Drug:	IMO-8400
FDA IND:	119651
Sponsor:	Idera Pharmaceuticals, Inc. 167 Sidney Street Cambridge, MA 02139
Protocol Number:	8400-401
Protocol Version:	7.0
Date:	14 March 2016

Protocol Approval Page

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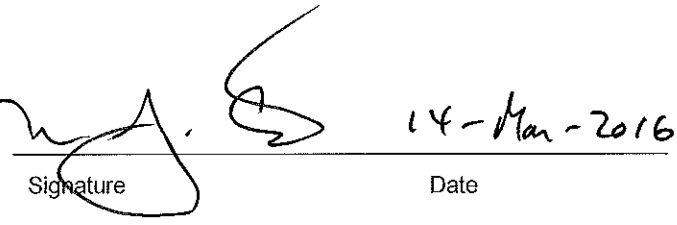
Approved by:

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



Signature Date

Revision History

Ver. No.	Date	Comment
1.0	11 Oct 2013	IND Submission
2.0	18 Nov 2013	Revisions based on FDA review
3.0	23 Jul 2014	Addition of home visits; addition of 150 mg vials; administrative clarifications
4.0	22 Sep 2014	Addition of IgM testing at Week 23; administrative clarifications
5.0	25 Feb 2015	Addition of assay for total IgM; addition of complement testing to safety assessments; guidance to Investigators for decrease in complement levels; statistical clarifications; administrative clarifications
6.0	13 Aug 2015	Allows patients deriving clinical benefit to continue IMO-8400 treatment on this study; elucidates timing and assessment of clinical and lab parameters; allows treatment past progressive disease; allows up to 49 patients to be enrolled in planned escalation and expansion cohorts; potential for additional patients in contingency cohorts or as replacements; administrative clarifications
7.0	14 Mar 2016	Adds additional dose escalation cohorts; revises method for calculating dose; eliminates upper weight limit dose cap of 125 kg; clarifies qualifying disease criteria and inclusion/exclusion criteria; adds safety procedures for patients with symptomatic thrombocytopenia and systemic injection reactions; 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.
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 Vice President & 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
Pharmacovigilance Contact	Theresa Wehrle, RN Sr. Safety Specialist, Safety and Pharmacovigilance INC Research, LLC 4800 Falls of the Neuse Road Raleigh, NC 27609	Office: +1 919 926 5732 email: twehrle@incresearch.com

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	8400-401
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 Waldenström's Macroglobulinemia
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 Waldenström's Macroglobulinemia
Number of Patients	Approximately 60 patients in planned escalation and expansion cohorts; potential for additional patients in contingency cohorts or as replacements
Number of Sites	Multiple Centers in the US
Date first patient enrolled	Q2 2014
Est. date last patient enrolled	Q4 2016
Est. date last patient last visit	Q2 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 Waldenström's Macroglobulinemia (WM).

1.2.2. Secondary Objectives

- To assess the treatment effect (clinical activity) of escalating dose levels of IMO-8400 using disease-specific international guidelines for classifying clinical response [1].
- To identify an optimal dose of IMO-8400 for further clinical evaluation.
- To characterize the pharmacokinetics (PK) 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 correlate the presence of myeloid differentiation primary response gene (88) L265P mutation with clinical outcome.
- To assess the potential immunogenicity of IMO-8400 administered by SC injection.

1.3. Study Design and Methodology

1.3.1. Brief Background and Rationale

IMO-8400 is a second-generation oligonucleotide antagonist of Toll-like receptors (TLR) 7, 8, and 9, which blocks immune activation mediated through those receptors. In a Phase 1 study IMO-8400 was administered to healthy adults by SC injection at single-doses and multiple-doses (once weekly for 4 weeks) up to 0.6 mg/kg (see Section 4.4 for details). All treatments were well-tolerated, with mild injection site reactions (ISRs) and no pattern of systemic reactions or laboratory changes.

In recent studies, a high frequency of mutation in the signaling pathway downstream of TLR7, 8, and 9 has been identified in patients with B-cell malignancies, including more than 90% of patients with WM [2]. In vitro studies of B-cell tumor lines indicate that such mutations are associated with an increase in cell activation, proliferation, and survival [3], and that 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 (see Investigator's Brochure for details).

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

1.3.2. Study Overview

This is an open-label, multiple-dose, dose escalation study of IMO-8400 in patients with relapsed or refractory WM.

1.3.3. Dose-escalation Cohorts

The dose-escalation cohorts (3 to 6 patients each) will systematically evaluate the safety and tolerability of IMO-8400 at increasing dose levels in order to identify the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D).

- The planned dose escalation cohort levels for IMO-8400 are 0.6, 1.2, 2.4, and 3.6 mg/kg administered once weekly and 1.2 mg/kg administered twice weekly (Table-3). Additional dose levels, schedules, and routes of administration may be evaluated based upon the emerging data. Weekly exposure is based on body weight (see Section 8.1 for details). Doses will be administered by SC injection.
- For Dose Level 3 (refer to Table-3), the total dose will be divided into 2 equal portions (1.2 mg/kg twice weekly), administered as separate SC injections over the course of the week, preferably 72 to 96 hours apart (minimum 48 hours) (see Section 8.4 for details).
- Once safety has been established for the 2.4 mg/kg/week as a divided weekly dose (1.2 mg/kg twice weekly), the same dose level of 2.4 mg/kg/week and subsequent dose levels will be given as a once weekly administration.
- Once the RP2D/MTD has been established, patients being treated at lower dose levels may have their doses escalated to the RP2D/MTD upon discussion and agreement between the Sponsor and the Investigator.

Table-3. Planned Dose Escalation Cohorts

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

1.3.4. Dose-escalation Procedures

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

- Explicit definitions for identifying suspected adverse reactions as dose-limiting toxicity (DLT) events (see Section 6.3.1 for details).
- Explicit definition for MTD (see Section 6.3.2).
- All injections of study medication will be administered by study personnel and all patients observed for 2 hours following the first injection (including the first injection of a new dose level in the case of intra-patient dose escalation) and for at least 30 min following all other injections.
- Detailed provisions for management of study drug in individual patients based on safety, tolerability, and disease response (see Section 6.5).
- Constitution of a Data Review Committee (DRC) 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 6.3.3).

1.3.5. Dose-escalation Enrollment and Review

Each dose-escalation cohort is expected to enroll at least 3 patients, with a maximum of 6.

- If the initial 3 patients all complete 4 weeks of treatment without a DLT event, the DRC will conduct a dose-escalation review.
- If 1 of the initial 3 patients experiences a DLT event prior to completing 4 weeks of treatment, then enrollment at that dose level will continue to a total of 6 patients and the dose-escalation review will be done when all 6 patients have completed 4 weeks treatment.
- If 2 patients at a dose-level experience DLT events during the first 4 weeks of treatment, then no further patients will be enrolled until the DRC completes a review, which should be done as soon as feasible.

The DRC review will include all safety data available for the cohort. The following represent anticipated outcomes for the review process.

- Dose escalation – progression to the next planned dose level.

- Continue cohort enrollment (applicable only to review after 3 patients) – enroll up to 6 patients at the current dose level to obtain additional safety data for subsequent review.
- Dose de-escalation – enrollment of intermediate dose levels for exploration of other schedules of administration (see Section 6.5.2).
- Approve enrollment in an expansion cohort at a selected dose level, if applicable (see Section 1.3.6).
- No further dose escalation enrollment – at this time the DRC will indicate the dose level that they consider represents the MTD.

1.3.6. Expansion Cohorts

The expansion cohorts provide for additional enrollment at agreed upon dose levels to assess the dose dependence of clinical response.

Once the MTD or a potential RP2D and/or schedule have been established during dose escalation, up to 22 patients will be treated at the RP2D level according to this schedule. The Sponsor may decide at any point during the expansion phase to modify the RP2D based on emerging data including, but not limited to, safety, DLTs, PK, and clinical activity. If such a change is made, enrollment may continue at the selected dose level in up to 22 patients.

1.3.7. Management of Study Treatment in Individual Patients

Each enrolled patient will receive IMO-8400 at the assigned dose level until the earliest of:

- *Clinical DLT event* – see Section 6.3.1.
  - Study treatment will be discontinued in patients determined to have a clinical DLT event until resolution and may only be resumed after discussion with an Idera Medical Monitor and agreement that it is in the patient's best interest to continue.
  - For a dose modifying event (DME), provision is made for interrupting dosing for up to 3 weeks and, if the acute toxicity improves sufficiently, resuming treatment at a lower dose level based on discussion between the sponsor's designated medical monitor and the treating physician.
  - For DLT laboratory 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 (see Section 6.5.2 for details).
  - The Investigator will review with the Medical Monitor decisions to discontinue, pause, and/or restart study treatment.
- *Disease progression* – based on scheduled assessments at Week 1 of each cycle. Unscheduled assessments may be conducted in response to new clinical observations. Disease status will be classified according to international guidelines [1] (see Section 9.5 for details).

- *Termination of participation in the study* – due to adverse event (AE), withdrawal of consent, intolerable toxicity, or loss to follow up.

In certain instances, patients may be deriving clinical benefit despite objective 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, provided the conditions in Section 6.5.1 are met.

1.4. Study Structure

- Screening will be done within 21 days prior to Day 1 (the first injection of study drug). See Section 9.2 for details of screening and Section 9.3 for details of the enrollment process.
- Treatment is scheduled to be administered in 8-week cycles until progressive disease, unacceptable toxicity, withdrawal of consent, or end of study.
- Assessments for treatment response (or disease progression) are scheduled every 8 weeks ± 1 week (at the start of a new cycle) for clinical assessments (see Section 9.4.1), and every 4 weeks ± 1 week for laboratory assessments (see Section 9.4.2).
- End-of-Treatment (EOT) visit will be performed within 5 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.

A detailed schedule of events is presented in Table-4.

1.5. Diagnosis and Patient Selection Criteria

1.5.1. Qualifying Disease

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

1. Primary diagnosis established according to criteria of the Second International Workshop on WM [5] (see Section 16.1).
2. Has relapsed or progressed ("refractory") based on the criteria for assessing response from the VIth International Workshop on WM [1] (see Section 9.5).
3. Has, at Screening, serum monoclonal Immunoglobulin M protein ≥ 0.5 g/dL.

1.5.2. Inclusion Criteria

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

1. Be at least 18 years of age
2. Have signed the current approved informed consent form
3. Have an Eastern Cooperative Oncology Group Performance Status ≤ 2
4. Patients must meet the following laboratory criteria
   - Hemoglobin ≥ 7.5 g/dL
   - Absolute neutrophil count ≥ 1.0 x 10^9/L (1000/mm^3)
   - Platelets ≥ 50,000/μL
   - Serum creatinine ≤ 2.5 x the upper limit of normal (ULN)
   - Serum aspartate aminotransferase ≤ 2.5 x ULN
   - Serum alanine aminotransferase ≤ 2.5 x ULN
   - Total bilirubin ≤ 1.5 x ULN
   - Prothrombin time ≤ 1.5 x ULN
5. Life expectancy > 3 months
6. 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
7. For women of childbearing potential, have a negative serum pregnancy test at Screening
8. Be willing and able to comply with this protocol

1.5.3. Exclusion Criteria

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

1. Has known hypersensitivity to any oligodeoxynucleotide
2. Is nursing
3. Has body mass index > 34.9 kg/m^2
4. Has an indeterminate or positive test for antibody to human immunodeficiency virus (HIV-1 or -2) or hepatitis C virus
5. Has a positive test for hepatitis B surface antigen

6. Has known complement deficiency such as properdin deficiency or hereditary angioedema
7. 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
8. Has, at the initiation of study drug, received cytotoxic chemotherapy or a Bruton's tyrosine kinase (BTK)-inhibitor (e.g. ibrutinib) 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
9. Has, at the initiation of study drug, an active infection requiring systemic antibiotics
10. 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
11. Has active autoimmune cytopenia (anemia, thrombocytopenia, leukopenia) requiring concomitant therapy
12. Has heart failure of Class III or IV (New York Heart Association criteria)
13. Has sensory or motor neuropathy of Grade 4 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE v4.03 criteria])
14. 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; or uncontrolled diabetes
15. Has any other condition that would, in the opinion of the Investigator, potentially compromise the safety or compliance of the patient or may preclude the patient's successful completion of the clinical trial
16. History of another primary malignancy that has not been in remission for at least 3 years. The following are exempt from the 3 year limit: nonmelanoma skin cancer, curatively treated localized prostate cancer with nondetectable prostate specific antigen, and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on PAP smear
17. Lactating or pregnant women

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.
- Injection volume will not 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 4 quadrants of the abdomen or in the upper thighs, rotating injection site each time IMO-8400 is administered (see Section 8.4).
- Scheduled duration of study treatment is until withdrawn consent, progressive disease, end of study, or intolerable toxicity with provision for dose adjustment in the event of a laboratory DLT or occurrence of a DME (see Section 6.5).

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 first weekly dose administered on Day 1 of every cycle, at pre-dose and at 1 (± 5 minutes), 2 (± 10 minutes), and 4 (± 15 minutes) hours post-dose. A PK sample will also be taken at the EOT and EOS visits. Plasma samples will be analyzed for IMO-8400 concentration using a validated bioanalytical method. Pharmacokinetic analysis will be conducted on an individual basis.

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.
- Symptom review and vital signs at each scheduled visit.
- Physical exam and electrocardiogram (ECG) (see Section 9.6).
- Laboratory safety tests (hematology, serum complement, clinical chemistry, urinalysis) every 4 weeks (Section 9.7).
- Injection site reactions (see Section 9.6.5)
- Additional unscheduled assessments at Investigator's discretion.

Adverse events will be graded according to NCI CTCAE version 4.03. Adverse events will be coded using Medical Dictionary for Regulatory Activities version 16.0 and tabulated by event, grade, and relationship to study therapy. Laboratory results, vital signs, and ECG parameters will be summarized using descriptive statistics. Laboratory values will also be graded according to NCI CTCAE, version 4.03, and summarized using shift tables.

1.7.3. Treatment Effect

Assessments of disease status will be conducted at Screening, every 4 weeks ± 1 week (Week 1 and Week 5 of each cycle; for laboratory assessments, see Section 9.4.2), every 8 weeks

± 1 week (Week 1 of each cycle; for clinical assessments, see Section 9.4.1), every 12 weeks ± 4 weeks during the Follow-up Phase, at the EOT visit, and at the EOS visit. Disease assessments will be classified based on the guidelines of the VIth International Workshop [1]. Time to progression and duration of response will be measured as defined. See Section 9.5 for details. Patients discontinued from the study for reasons other than progressive disease will be assessed at a minimum of every 12 weeks ± 4 weeks until documentation of progressive disease, initiation of a subsequent anti-cancer therapy, or until the study ends, for up to 6 months from the first treatment (Cycle 1, Day 1) for the last patient enrolled, whichever comes first.

1.8. Statistical Methods

Safety observations will be analyzed using descriptive statistics and tabulation.

Following identification of the MTD/RP2D, up to an additional 22 patients will be enrolled at the MTD or proposed RP2D level. With a total sample size of 22 patients, there is a 90% probability to detect an AE with a true incidence rate of 10%. A secondary objective of this study is to determine the treatment effect of IMO-8400 in patients enrolled at the MTD/RP2D. Using the exact binomial distribution with a 1-sided test and an alpha of 0.05, there is 79% power to detect a response rate of 33% as compared to a null response rate of 10%.

1.9. Schedule of Assessments

Table-4. Schedule of Study Events

Visit[1]	Scrn[2]	Day 1	Treatment Period											EOT[3]	EOS[3]	F/U
Cycle			Cycle 1			Even Numbered Cycles				Odd Numbered Cycles						Every 12 weeks (± 4 weeks)
Week			2-4	5	6-8	1	2-4	5	6-8	1	2-4	5	6-8			
Evaluation																
Informed Consent[4]	X															Patients who discontinue for reasons other than progressive disease should be assessed per Response Assessment in WM[24] until documentation of progressive disease, start of new anti-cancer therapy, until the study ends, or for up to 6 months from the last patient's first treatment cycle, whichever one comes first.
Inclusion/Exclusion	X															
Medical History[5]	X															
Cryoglobulin & Cold Agglutinin Lab Tests[6]	X															
Physical examination[8]	X	X	X[8]	X		X		X		X		X		X	X	
Body weight[7]	X	X		X		X				X				X	X	
Height measurement	X															
Vital signs[9,10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical assessment for Tumor Status[11]	X	X				X				X				X	X	
Total IgM & Monoclonal Protein Lab Tests[12]	X	X		X		X		X		X		X		X	X	
ECOG[7]	X	X				X				X				X	X	
CT or MRI imaging[13]	X													X		
Safety Laboratory Tests[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[7]	X	X		X		X		X		X		X		X	X	
12-lead ECG[15]	X	X[15]		X[15]		X[15]		X[15]		X[15]		X[15]		X		
Pregnancy test (females only)[16]	X					X				X				X	X	
Serology	X															
PK[17]		X				X				X				X	X	
Serum Cytokines[18]		X				X				X				X	X	
Antibodies to IMO-8400[18]		X				X				X				X	X	
Serum NF-κB[19]		X				X				X				X	X	
Initial Dx Bone Marrow Slides[20]	X															
Bone Marrow Biopsy & Aspirate[21]	X													X		
Assessment of Injection Site[22]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Administration[10, 23]		X	X	X	X	X	X	X	X	X	X	X	X			
AE & Concomitant Med Monitoring	From Screening to EOS Visit															

Abbreviations: AE=adverse event; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOS=end-of-study; EOT=end-of-treatment; F/U=Follow-up; IgM=immunoglobulin M; NF-κB=nuclear factor kappa-light-chain-enhancer of activated B cells; PK=pharmacokinetic; MRI=magnetic resonance imaging; Scrn=Screening; WM=Waldenström's macroglobulinemia

[1] Day 1 is the day of the first injection of study drug. All weeks for a given cycle are relative to the day of the first injection of study drug for that Cycle and are defined as Day 1 through Day 7, inclusive; all times are relative to injection, designated 0 hour; "pre-dose" vital signs are to occur within 1 hour prior to injection; all other pre-dose procedures are to occur prior to injection on the same calendar day.

[2] Screening procedures may be performed up to 21 days prior to Day 1.

[3] If treatment is terminated prematurely for any reason, the EOT visit will be performed within 5 days of the decision to terminate; the EOS visit will be performed 30 to 35 days after the last dose of study drug.

[4] Informed consent must be signed prior to all study-specific screening procedures.

[5] Medical history includes, but is not limited to, a detailed review of the patient's malignancy, prior treatments, relevant current or past abnormalities or diseases, and signs and symptoms of WM at baseline.

[6] Cryoglobulin and cold agglutinin laboratory testing to be performed at Screening (local laboratory).

[7] To occur pre-dose.

[8] During Cycle 1 only, physical examination will be done on Week 2. In subsequent cycles, physical examinations will be done every 4 weeks.

[9] Vital signs comprise heart rate, blood pressure, respiratory rate and temperature. Vital signs will be obtained pre-dose (within 1 hour prior to injection) and post-dose at 30 (± 5) min after dosing. On Day 1 of Cycle 1, Week 1, post-dose vital signs will also be obtained at 2 hours (± 20 min).

[10] For patients who receive a second weekly dose, vital signs will be obtained pre-dose (within 1 hour prior to injection) and post-dose at 30 (± 5) min after dosing, and assessment of the injection site, as previously noted, will be conducted.

[11] Clinical assessment for tumor status will be conducted pre-dose on dosing visits and will include assessment for lymphadenopathy, hepatomegaly, and splenomegaly (see Section 9.4.1 for details).

[12] Assessments will be conducted pre-dose on dosing visits, and includes total serum IgM, monoclonal serum IgM, serum free light chains, urine free light chains, serum viscosity, and serum β2-microglobulin; see Section 9.4.2 for details.

[13] CT or MRI imaging of chest, abdomen, and pelvis with the same modality used for every assessment; see Section 9.4 for details.

[14] The full panel of safety laboratory tests (hematology, serum complement, chemistry and coagulation) will be done pre-dose on Day 1, and Weeks 1 and 5 of each cycle (including pre-treatment criteria presented in Section 8.4.1); a focused panel (hematology, selected chemistry) will be done pre-dose on Weeks 3 and 7 of each cycle; see Section 9.7.1 for details. Unscheduled tests to confirm decreases in serum complement levels will be performed (see Section 6.5.4).

[15] ECGs are to be performed pre-dose and 2 hours post-dose on Day 1 of Cycle 1 and pre-dose at the first dosing visit of Weeks 1 and 5 of each cycle thereafter. In addition, an ECG is to be performed at 2 hours post-dose on Day 1 of each odd-numbered cycle.

[16] Serum pregnancy testing will be done pre-dose and evaluated at the central laboratory.

[17] PK samples will be collected as scheduled in relation to the first dose administered on Day 1 of every cycle. Samples will be obtained pre-dose (within 1 hour prior to injection) and post-dose at 1 hour (± 5 min), 2 hours (± 10 min) and 4 hours (± 15 min) after dosing. PK samples will also be taken at EOT and EOS.

[18] Serum for cytokines and antibodies to IMO-8400 will be collected as scheduled in relation to the first dose administered on Day 1 of every cycle and will be obtained pre-dose (within 1 hour prior to injection).

[19] Serum samples for NF-κB analysis will be obtained pre-dose (within 1 hour prior to injection) and post-dose at 4 hours (± 15 min) (see Section 9.9 for details) and will be submitted to central laboratory.

[20] Bone marrow slides will be obtained from initial WM diagnosis.

[21] Bone marrow biopsy and aspirate will be collected at Screening, EOT, and to document complete response as appropriate (see Section 16.2) and submitted to central laboratory (see Section 9.4.4 and Section 12.4.1). If patients have a bone marrow biopsy within 4 weeks of EOT, the biopsy will not be repeated at EOT. The Screening Visit sample will also be assayed for the MyD88 L265P mutation.

[22] Assessment of all prior injection site(s) with grading and measurement of any reaction (see Section 9.6.5). In addition, on dosing days, the planned injection site will be assessed to confirm it is appropriate for use.

[23] Schedule applies to all patients receiving once weekly dosing and to the first weekly dose for all patients receiving twice weekly dosing (see Section 1.3.2 and Section 8.4 for details).

[24] Response assessment is summarized in Section 16.2 and includes total serum IgM, serum monoclonal IgM, bone marrow histology, adenopathy/organomegaly, cytopenias, and symptoms (see Section 9.5 for details). Total IgM and monoclonal protein lab tests (see Section 9.4.2 for details) will be submitted to central laboratory.

Table-5. Estimation of Blood Volumes Required From Screening through End-of-Study

Tests	Volume (mL)	Screening (mL)	Maximum Volume Per 8-week Cycle (mL)	EOT (mL)	EOS (mL)
Safety Lab Tests (full)	19	19	38	19	19
Safety Labs (focused)	10		20		
PK	2		8	2	2
Serum Cytokines	4	4	4	4	4
Antibodies to IMO-8400	4	4	4	4	4
Serum NF-κB	10		20	10	10
Tumor Assessments	15	15	30	15	15
Pregnancy test (F only) (extra blood volume is not required)	X	X	X	X	X
Serology	10	10			
Total mL blood drawn		52	124	54	54

Abbreviations: EOS=end-of-study; EOT=end-of-treatment; F=female; NF-κB=nuclear factor kappa-light-chain-enhancer of activated B cells; PK=pharmacokinetic

Note: The volumes shown are estimates; final volumes may vary, but will not be more than 15% greater than shown.

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3. LIST OF ABBREVIATIONS

Abbreviation	Explanation
ABC-DLBCL	Activated B-cell (type) Diffuse Large B-cell Lymphoma
AE	Adverse event
ALT	Alanine amino-transferase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate amino-transferase
β-hCG	Beta-human chorionic gonadotropin
BA	Bioavailability
BCR	B-cell receptor
BE	Bioequivalence
BP	Blood pressure
BTK	Bruton's tyrosine kinase
C3	Complement component 3
C4	Complement component 4
CBC	Complete blood count
CFR	Code of Federal Regulations
CH50	50% hemolytic complement assay
CK	Creatine phosphokinase
CNS	Central nervous system
CR	Complete response
CRP	C-reactive protein
CS	Clinically significant
CSR	Clinical Study Report
CT	Computed tomography
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DME	Dose modifying event
DNA	Deoxyribonucleic acid
DRC	Data Review Committee
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)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus

HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IFN	Interferon
IgM	Immunoglobulin M
IL	Interleukin
IND	Investigational new drug
INN	International nonproprietary name
INR	International normalized ratio
IP-10	Interferon-inducible protein-10
IRB	Institutional Review Board
ISR	Injection site reaction
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MTD	Maximum tolerated dose
MyD88	Myeloid differentiation primary response gene (88)
MR	Minor response
MRI	Magnetic resonance imaging
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NCS	Not clinically significant
PP	Per-protocol
PR	Partial response
PK	Pharmacokinetic(s)
PT	Prothrombin Time
RBC	Red blood cell
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TLR	Toll-like receptor
TMF	Trial master file
TNF	Tumor necrosis factor
ULN	Upper limit of normal
USP	United States Pharmacopeia
VGPR	Very good partial response
WBC	White blood cell
WM	Waldenström's macroglobulinemia
WMA	World Medical Association

4. INTRODUCTION

4.1. Waldenström's Macroglobulinemia (WM): 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. Malignancies arising from the myeloid line include acute and chronic myelogenous leukemia, myelodysplastic syndromes, and myeloproliferative diseases. Those arising from the lymphoid line include lymphoma, lymphocytic leukemia, multiple myeloma, and WM. 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.

Waldenström's macroglobulinemia is a distinct B-cell lymphoproliferative disorder characterized by a lymphoplasmacytic infiltrate in the bone marrow and high levels of a monoclonal immunoglobulin M (IgM) in the serum [6,7]. The disease can have a chronic, indolent course, with patients remaining asymptomatic for years. The principal complications include:

- Manifestations of the monoclonal gammopathy, including symptomatic hyperviscosity, cryoglobulinemia, and cold agglutinin disease.
- Disease-related cytopenia.
- Bulky adenopathy or organomegaly.
- Severe neuropathy.
- Amyloidosis.
- Disease transformation.

4.1.1. Current Standard of Care Therapy for WM

Current recommendations are that asymptomatic patients with WM are observed and that treatment should not be based on IgM levels alone. Treatment should be initiated in response to the clinical complications noted above [6,8]. Selection of therapeutic agents may be tailored to the disease manifestations. The most common first-line regimens are combinations including the following agents:

- Rituximab (anti-CD20 monoclonal antibody).
- Cyclophosphamide or chlorambucil (alkylating agents).
- Doxorubicin (anthracycline antibiotic).
- Vincristine (alkaloid).
- Prednisone (corticosteroid).
- Fludarabine or cladribine (nucleoside analogs).

Ibrutinib has recently received Food and Drug Administration approval for the treatment of WM on the basis of a response rate of 61.9% (including complete response [CR], very good partial response [VGPR], and partial response [PR]) in a Phase 2 study of 63 patients.

Plasmapheresis is used for symptomatic hyperviscosity and other complications of high serum levels of monoclonal IgM protein.

Salvage therapy for patients with refractory or relapsing disease is diverse and use of investigational agents is often considered appropriate. Approaches in current practice include (a) alternative combinations of the agents noted above, with the possible addition of bortezomib or thalidomide, and (b) transplantation with autologous stem cells or allogenic bone marrow [6,7].

Many of the agents used in refractory or relapsing WM are cytotoxic or sharply immunosuppressive and have substantial safety risks in elderly patients characteristic of this disease. A novel targeted agent that provided a beneficial treatment effect with a better tolerability profile would address an unmet need in WM.

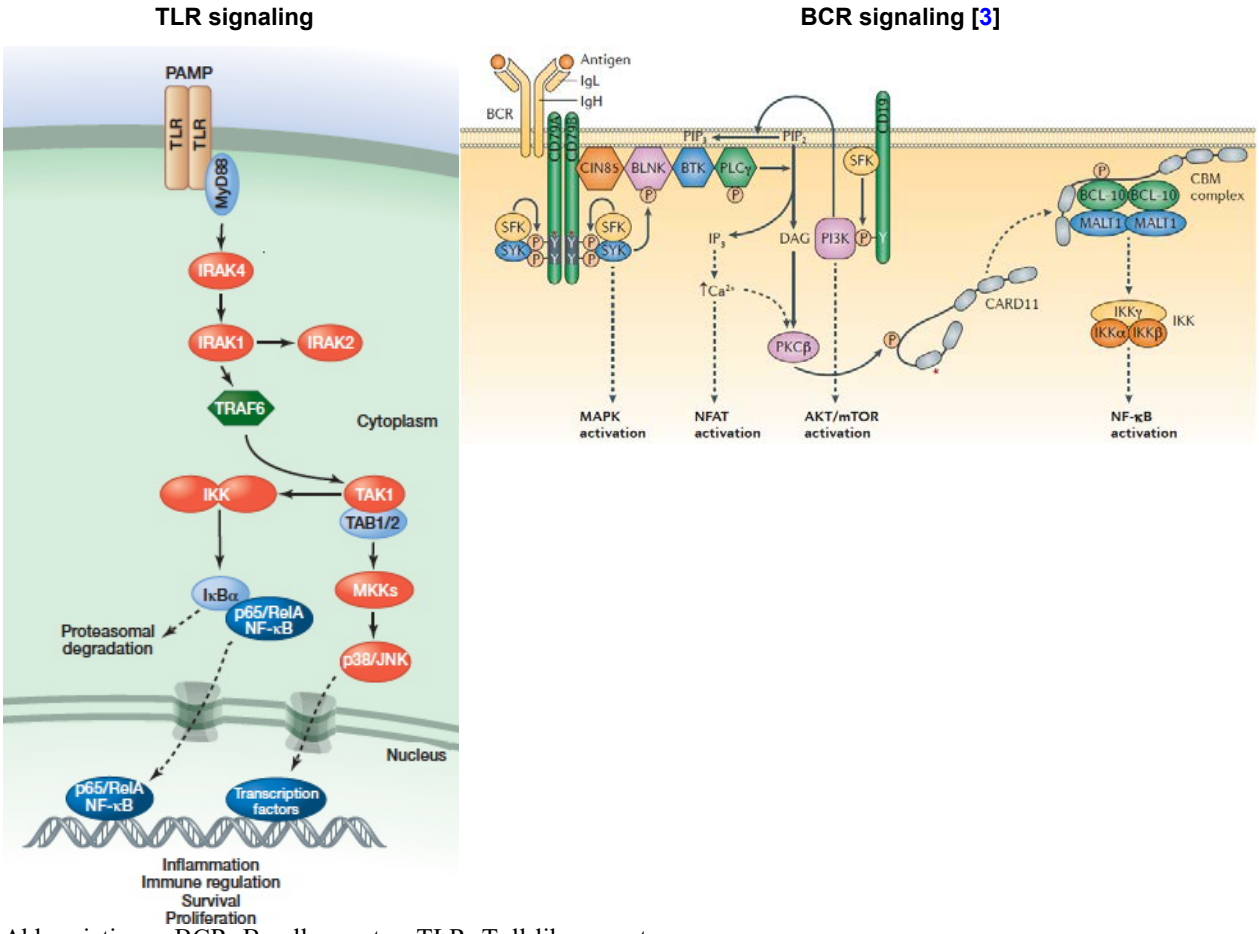
4.2. Role of Toll-like Receptors (TLRs) in B-cell Malignancy

Toll-like receptors 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, which are located on the host cell surface. In man, the endosomal TLRs are expressed primarily on dendritic cells 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. [9,10,11,12,13].

The TLR signaling pathway (Figure-1, 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-1, 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-1. TLR and BCR Signaling Pathways in B-cells



Abbreviations: BCR=B-cell receptor; TLR=Toll-like receptor

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. 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 BCR pathway genes, including CD79A/B and CARD11 [3].
- Increased expression of myeloid differentiation primary response gene (88) (MyD88), the adapter (linker) protein that binds to TLRs [14].
- Mutations in MyD88 [15].

The most common alternation identified to date in MyD88 is the L265P mutation. Table-6 displays the frequency of MyD88 L265P among B-cell malignancies and proliferative diseases. The mutation is present in over 90% of WM, in ~30% of Activated B-cell-like Diffuse Large B-cell Lymphoma, and at lower frequencies in other, more common lymphomas.

Table-6. Incidence of MyD88 L265P mutation in selected B-cell malignancies

Disease	Incidence of Disease (SEER 2001)	% Patients with MYD88 L265P mutation	Estimated Incidence 2013[a] (New cases/year)	Reference for MyD88 frequency
ABC-DLBCL	6,789[b]	29%	2,150	[16]
Waldenström's macroglobulinemia	1,144	91%	1,200	[2]
Chronic Lymphocytic Leukemia	16,984	3%, 7%	925	[17,18]
Primary CNS Lymphoma	1,200	36%, 38%	480	[19,20]
Marginal Zone Lymphoma[c]	3,247	9%, 4%	225	[16,21]

Abbreviations: ABC-DLBCL=Activated B-cell (type) Diffuse Large B-cell Lymphoma; CNS=central nervous system; DLBCL=Diffuse Large B-cell Lymphoma; MyD88=Myeloid differentiation primary response gene (88); SEER=Surveillance Epidemiology and End Results

a. New cases/year are adjusted + 10% due to population growth since data collection [22,23]

b. Incidence of DLBCL, 24,246; ABC-type represents 28% of all DLBCL.

c. Marginal Zone Lymphoma is also referred to as MALT, Mucosa-Associated Lymphoid Tissue Lymphoma

Recent in vitro studies of B-cell tumor lines with L265P mutation suggest that increased TLR signaling 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 demonstrated decreased growth and survival (see Investigator Brochure for details). Severe combined immunodeficient mice inoculated with LY10 developed progressive disease and died. Treatment with IMO-8400 prolonged median survival from 33 to 48 days (see Investigator's Brochure for details).

Taken together, these data directly support the hypothesis that an antagonist of TLR7, 8, and 9 would have a therapeutic effect in patients with B-cell malignancies, particularly those characterized by MyD88 L265P mutation or increased MyD88 expression.

4.3. Rationale for the Current Study

IMO-8400 is a synthetic oligonucleotide that blocks activation mediated through TLR7, 8 and 9; that is, it functions as an antagonist for those receptors.

To date, IMO-8400 in doses up to 0.6 mg/kg once weekly has been administered for 4 weeks in healthy volunteers and for 12 weeks in a completed Phase 2 psoriasis study (see Section 4.4 for details). All treatments were well-tolerated, with mild injection site reactions and no pattern of systemic reactions or laboratory changes.

As detailed above, recent studies indicate a role for TLR activation and subsequent signal amplification by MyD88 L265P mutation in the activation, proliferation, and increased survival of malignant B-cells.

The current protocol represents the first use of IMO-8400 in patients with a B-cell malignancy.

4.4. Overview of IMO-8400

IMO-8400 has been created by Idera Pharmaceuticals, Inc. using a structure-activity approach to design TLR-targeted drug candidates. IMO-8400 is a synthetic oligonucleotide designed to inhibit immune responses mediated through endosomal TLR7, TLR8, and TLR9.

Non-clinical studies (reviewed in detail in the Investigator's Brochure) have demonstrated that IMO-8400 is an immunomodulatory agent with 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, IFN-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.
- 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 laboratory 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 constitutively active cell signaling pathways, including NF-κB, IRAK, STAT-3, Jak/Stat, and 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 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 IL-10 in a subcutaneous (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 cytokines in a 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-7 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.

Table-7. Clinical Studies with IMO-8400 in Addition to This Study

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
8400-402	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	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

Abbreviations: MyD88=Myeloid differentiation primary response gene (88)

4.4.1. Clinical Experience with WM

As of August 2015, 19 patients have been treated in this Phase 1 study with IMO-8400 at doses of 0.6, 1.2, and 2.4 mg/kg/week. IMO-8400 was generally well tolerated at all dose levels. Most reported adverse events (AEs) deemed related or possibly related to study drug were mild or moderate (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] grade 1 or 2). The most common AEs observed were fatigue, injection site erythema, headache, injection site pain, nausea, and pain in extremity. Reported injection site reactions included grade 1 erythema, grade 1 pain, and grade 1 induration. No injection site blistering, necrosis, pruritus, ulceration, or tenderness were reported. Grade 3 AEs reported as possibly or probably related to study drug included neutropenia, anemia, and arthritis. One of 88 patients treated at the 2.4 mg/kg dose level experienced a dose-limiting toxicity (DLT) that was deemed possibly related to study drug; this patient experienced a grade 3 probable flare of pre-existing arthritis. No deaths or grade 4 events were reported.

Early signals of efficacy include 3 responses among 11 patients treated at the 0.6 and 1.2 mg/kg dose levels. Among 6 evaluable patients treated at the highest dose level (2.4 m/kg), 3 had responses and 2 had stable disease [24].

4.4.2. Benefit/Risk Aspects

The starting dose level for the present study (0.6 mg/kg once weekly by SC injection) has been well tolerated for up to 4 weeks in healthy volunteers and up to 12 weeks in patients with moderate to severe psoriasis. The majority of treatment-emergent adverse events (TEAEs) are mild injection site reactions; there were no treatment-related serious adverse events (SAEs) or discontinuations due to AEs. This starting dose is, therefore, considered to represent minimal risk.

In the context that patients enrolled in this study have no therapeutic options likely to extend their survival, the clinical and safety profile demonstrated thus far with IMO-8400 justifies their inclusion and their treatment until progression.

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 WM.

5.2. Secondary Objectives

- To assess the treatment effect (clinical activity) of escalating dose levels of IMO-8400 using disease-specific international guidelines for classifying clinical response [1].
- To identify an optimal dose of IMO-8400 for further clinical evaluation.
- To characterize the pharmacokinetics (PK) 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 correlate the presence of MyD88 L265P mutation with clinical outcome.
- 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 WM.

6.2. Dose-escalation Cohorts

The dose escalation cohorts (3 to 6 patients each) will systematically evaluate the safety and tolerability of IMO-8400 at increasing dose levels in order to identify the MTD/recommended Phase 2 dose (RP2D).

- The planned dose escalation cohort levels for IMO-8400 are 0.6, 1.2, 2.4, and 3.6 mg/kg administered once weekly and 1.2 mg/kg administered twice weekly (Table-8). Additional dose levels, schedules, and routes of administration may be evaluated based upon the emerging data. Weekly exposure is based on body weight (see Section 8.1 for details). Doses will be administered by SC injection.
- For Dose Level 3 (refer to Table-8), the total dose will be divided into 2 equal portions (1.2 mg/kg twice weekly), administered as separate SC injections over the course of the week, preferably 72 to 96 hours apart (minimum 48 hours) (see Section 8.4 for details).
- Once safety has been established for the 2.4 mg/kg/week as a divided weekly dose (1.2 mg/kg twice weekly), the same dose level of 2.4 mg/kg/week and subsequent dose levels will be given as a once weekly administration.
- Once the RP2D/MTD has been established, patients being treated at lower dose levels may have their doses escalated to the RP2D/MTD upon discussion and agreement between the Sponsor and the Investigator.

Table-8. Planned Dose Escalation Cohorts

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

6.3. Dose-escalation Procedures

6.3.1. Definition of a Dose-Limiting Toxicity and Dose Modifying Event

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 tests (hematology, chemistry, and coagulation), urinalysis, and electrocardiograms (ECGs).

A DLT can be either a clinical or laboratory AE.

A potential DLT event is defined as a treatment-emergent AE (see Section 10.1) which occurs within the first 5 weeks of treatment and meets *any* of the following criteria using NCI CTCAE grading (see Section 10.4.4):

- Is a clinical event of Grade 3 or higher severity, except for the following:
  - Alopecia
  - Grade 3 fatigue
  - Grade 3 nausea/vomiting that has not been treated with optimal anti-emetic treatments
  - Grade 3 diarrhea that has not been treated with optimal anti-diarrheal treatments
  - AE related to the underlying disease
- Is a confirmed laboratory finding of Grade 3 or higher severity (see Section 10.4.5) and has been assessed as related to IMO-8400 (any relationship other than "not related") with the exceptions of neutropenia and thrombocytopenia. DLTs with respect to neutropenia/thrombocytopenia are outlined below:
  - Grade 4 neutropenia lasting > 7 days
  - Grade 3 or 4 neutropenia with a sustained temperature > 101.3º F
  - Grade 3 thrombocytopenia associated with clinically significant bleeding that requires transfusion therapy
  - Grade 4 thrombocytopenia

Clinically significant toxicities or TEAEs that meet the definition of dose-limiting but occurring after Week 5 of Cycle 1 are defined as dose modifying events (DMEs) and may be considered when determining the RP2D.

The Data Review Committee (DRC) is comprised of the Idera Medical Monitor and Investigators from participating sites. The DRC will review all potential DLT events to assess causality, i.e., relationship to study drug (see Section 10.4.3). Events will be considered DLT events unless they are unanimously assessed as "Not related," that is, a factor other than study drug is the cause of the event (see Section 10.4.3).

The definition of a DLT event will be applicable in the following contexts:

- DRC review determining dose escalation (see below).
- DRC review in defining the MTD (see below) or RP2D.

- Investigator (and Medical Monitor) review for determining pausing or discontinuation of study treatment in individual patients (see Section 6.5).

6.3.2. Definition of Maximum Tolerated Dose and Recommended Phase 2 Dose

The MTD is the highest dose level meeting *both* of the following criteria:

- It is below the level at which 2 or more patients experienced DLTs during the first 4 weeks of treatment;
- It is a dose level at which no more than 1 patient experienced DLTs during the first 4 weeks of treatment.

The RP2D will be a dose at or below the MTD based on clinical data.

6.3.3. Dose-escalation Enrollment and Review

Each dose-escalation cohort is expected to enroll at least 3 patients, with a maximum of 6.

- If the initial 3 patients all complete 4 weeks of treatment without a DLT event, the DRC will conduct a dose-escalation review.
- If 1 of the initial 3 patients experiences a DLT event prior to completing 4 weeks of treatment, then enrollment at that dose level will continue to a total of 6 patients and the dose-escalation review will be done when all 6 patients have completed 4 weeks treatment.
- If 2 patients at a dose level experience DLT events during the first 4 weeks of treatment, then no further patients will be enrolled until the DRC completes a review, which should be done as soon as feasible.

Once the last patient in a given cohort has a completed 4 weeks of study treatment, a DRC meeting will be convened to review all safety data and to decide whether to continue or halt dose escalation, or explore intermediate dose levels. To facilitate standardizing the dose-escalation reviews across different cohorts, the focus will be on observations from the first 4 weeks of treatment at that dose level.

The following represent anticipated outcomes for the review process (refer to DRC Charter for full details):

- Dose escalation – progression to the next planned dose level.
- Continue cohort enrollment (applicable only to review after 3 patients) – enroll up to 6 patients at the current dose level to obtain additional safety data for subsequent review.
- Dose de-escalation – enrollment of intermediate dose levels for exploration of other schedules of administration (see Section 6.5.2).
- Approve enrollment in an expansion cohort at a selected dose level, if applicable (see Section 6.4).
- No further dose escalation enrollment – at this time the DRC will indicate the dose level that they consider represents the MTD.

6.4. Expansion Cohorts

The expansion cohorts provide for additional enrollment at agreed upon dose levels to assess the dose dependence of clinical response.

Once the MTD or a potential RP2D and/or schedule have been established during dose escalation, up to 22 patients will be treated at the RP2D level according to this schedule. The Sponsor may decide at any point during the expansion phase to modify the RP2D based on emerging data including, but not limited to, safety, DLTs, PK, and clinical activity. If such a change is made, enrollment may continue at the selected dose level in up to 22 patients.

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 the earliest of:

- *Clinical DLT event* – see Section 6.3.
  - Study treatment will be discontinued in patients determined to have a clinical DLT event until resolution and may only be resumed after discussion with an Idera Medical Monitor and agreement that it is in the patient's best interest to continue.
  - For a DME, provision is made for interrupting dosing for up to 3 weeks and, if the acute toxicity improves sufficiently, resuming treatment at a lower dose level based on discussion between the sponsor's designated medical monitor and the treating physician.
  - For DLT laboratory 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 (see Section 6.5.2 for details).
  - The Investigator will review with the Medical Monitor decisions to discontinue, pause, and/or restart study treatment.
- *Disease progression* – based on scheduled assessments at Week 1 of each cycle. Unscheduled assessments may be conducted in response to new clinical observations. Disease status will be classified according to international guidelines [1] (see Section 9.5 for details).
- *Termination of participation in the study* – due to AE, withdrawal of consent, intolerable toxicity, or loss to follow up.

In certain instances, patients may be deriving clinical benefit despite objective 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, provided the following conditions are met:

- Patient has not achieved an objective response on study and then developed progressive disease;

- Patient has not experienced a period of clinically significant stable disease on study and then developed progressive disease;
- Patient must be re-evaluated 4 to 6 weeks after initial progression in order to confirm progressive WM disease;
- If the follow-up assessment does not confirm progressive disease, patient may resume regularly scheduled follow-up per protocol;
- Patient must not have symptoms/signs indicative of clinically significant disease progression;
- Patient must not have a decline in Eastern Cooperative Oncology Group (ECOG) performance status;
- Patient must not have rapidly progressive disease or tumor progression at critical anatomic sites (e.g., cord compression) requiring urgent medical intervention.

6.5.2. Dose Modification in Patients with Laboratory DLT Events or DMEs

Patients determined to have a laboratory DLT event or DME (Section 6.3.1) may resume treatment 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 laboratory DLT event or DME.
- Both the Investigator and the Medical Monitor consider that continued treatment with study drug is in the patient's interest.
- The abnormal laboratory parameter(s) representing the DLT event or DME improve at least 2 grades or back to baseline within 14 days of the last dose administered.

If, for any reason, dosing is interrupted more than 21 calendar days due to toxicity, the patient should be discontinued from study treatment unless the Investigator and the Idera Medical Monitor agree that it is in the patient's best interest to continue.

If dose modification is required, patients should resume dosing at the next lowest dosing level (see Table-8).

6.5.3. Management of Systemic Injection Reactions

Fever, chills, and rigors have been reported in the first 24 hours following IMO-8400 injection. These symptoms have responded well to symptomatic measures without long-term consequences. Prophylaxis with acetaminophen and diphenhydramine may be considered for patients who experience these symptoms with prior injections. Treatment should be discontinued for patients who experience more significant reactions (e.g., anaphylaxis or cardiovascular collapse) and full supportive care provided, as per institutional practice.

6.5.4. Procedures for Assessment of Patients with Changes 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. These findings correlated with changes in serum complement levels. Alterations in serum complement in these animals were noted in the weeks to months preceding their unscheduled deaths.

If at any time during study participation, a patient experiences an acute drop in complement (50% hemolytic complement assay [CH50], complement component 3 [C3], or complement component 4 [C4]) levels ≥ 50% or a drop to an absolute value below the lower limit of normal with reference to baseline testing or most recent values on study, 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 casts or white blood cell 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.

6.5.5. Procedures for Assessment of Patients with Symptomatic Thrombocytopenia

Severe thrombocytopenia has been reported in clinical studies with another oligonucleotide [25]. 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.

6.5.6. 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 from the following standard categories:

- *DLT event* – defined above.
- *Disease progression* – as defined above.
- *Adverse Event, 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 for any reason, the End-of-Treatment (EOT) and End-of-Study (EOS) visits will be performed as specified (see 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.

6.6. Criteria for Replacement Patients

6.6.1. Definition of a Evaluable Patient

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

- Received at least 1 dose of study drug and had treatment discontinued because of a DLT event as defined in Section 6.3.1; *or*
- Received all doses of study drug in the first 4 weeks of treatment and completed Week 5 assessment procedures.

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

6.6.2. Replacement 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 and Maximum Exposures

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

- Maximum number of patients: Approximately 60 patients in planned escalation and expansion cohorts; potential for additional patients in contingency cohorts or as replacements.
- Maximum dose level: Undefined (pending dose escalation results). The planned dose escalation cohort levels for IMO-8400 are 0.6, 1.2, 2.4, and 3.6 mg/kg administered once weekly and 1.2 mg/kg administered twice weekly
- Maximum duration of exposure: undefined (treatment is until study completion or until the patient experiences intolerable toxicity, disease progression, or withdraws consent, whichever comes first as defined in Section 6.10.2.2).

6.8. Treatment Assignment

See Section 9.3.

6.9. Criteria for Study Termination

The study ends approximately 6 months following enrollment of the last patient. The Sponsor reserves the right to discontinue or suspend the study earlier for safety or administrative reasons at any time, at an individual site or overall. Should the study be terminated and/or the site closed for whatever reason, all study documentation must be archived and study medication must be destroyed according to local policy or returned to the Sponsor or its representative per Sponsor's instructions.

If the trial is terminated prematurely or suspended, the Sponsor will promptly inform the participating Investigators and institutions, the regulatory authorities, and the Institutional Review Board (IRB) of the termination or suspension and the reason(s) for the action.

6.10. Discussion of Study Design and Treatment Regimens

This protocol represents the first clinical trial of IMO-8400 in patients with B-cell malignancies and the third clinical trial of IMO-8400 overall.

6.10.1. Rationale for Study Structure

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 DRC are standard for a Phase 1 study and serve to minimize the number of patients required and to assure patient safety is protected.

The expansion cohorts will permit preliminary signal-seeking and 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. The proposed starting dose (0.6 mg/kg/week) is consistent with the safety experience in protocol 8400-001, the Phase 1 study, in which that dose was administered for 4 weeks without incident to healthy volunteers; and in protocol 8400-201, the Phase 2a study, in which that dose was administered for 12 weeks to patients with moderate to severe plaque psoriasis. The primary TEAEs observed were mild injection sites reactions; there were no treatment-related changes in laboratory studies, including tests of liver and renal function.

Dosing interval. Once and twice weekly dosing are supported by animal studies of autoimmune diseases and in vivo tumor growth.

Dose escalation. Numerically larger increases in hemoglobin and a faster time to response were seen in patients dosed at the highest dose level studied in the current trial [24]. In the absence of dose-limiting toxicity, further dose escalation to determine the extent of disease control that can be attained is appropriate and consistent with standard oncology Phase 1 trial design.

6.10.2.2. Duration of Treatment

Treatment with IMO-8400 will continue until study completion or until the patient experiences intolerable toxicity, disease progression, or withdraws consent, whichever comes first.

Follow-Up. Additionally, patients who have discontinued study treatment for reasons other than progressive disease will be assessed per Response Assessment in WM from the VIth International Workshop, at a minimum of every 12 weeks (± 4 weeks) until documentation of progressive disease, start of new anti-cancer therapy, or until study completion, for up to 6 months from the last patient's first treatment (Cycle 1, Day 1), whichever comes first.

7. SELECTION OF PATIENTS

7.1. Source of Patients and Recruitment Methods

Following receipt of IRB approval, the Investigator may initiate patient recruitment (see 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 (see Section 13).

7.2. 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, 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 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.

Abbreviations: INN=international nonproprietary name; NA=not applicable; TLR=Toll-like receptor

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 IMO-8400 free acid, as labeled, corrected for moisture and impurities.
Storage	The sealed vials of formulated drug product should be stored at 2-8°C.
Preparation and handling	Vials are reconstituted using Sterile Saline or Sterile Water for Injection, USP (to be provided by study site). The choice of diluent and the reconstitution volume are determined by the vial strength and the dose level assigned; see Pharmacy Manual for details.
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.

Abbreviations: SC=subcutaneous; USP=United States Pharmacopeia

8.3. Reconstitution of IMO-8400 for Injection

Detailed dose-preparation instruction 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 1.5 mL dose volume would be administered as two separate injections of 0.75 mL. The injection sites should be selected based on the following:

- Areas for injection are the 4 quadrants of the abdomen (upper and lower on the left and right) and the upper thigh of each leg.
- Injection sites should be rotated, that is, no injection area used more than once every 6 injections.

In the event these guidelines cannot be accommodated due to injury or other issue, the Investigator should discuss the situation with the Idera 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

These parameters will be measured at local laboratories at Week 1 and Week 5 of each cycle.

8.4.2. Variances in Dose Administration Schedule

Once weekly dosing: for patients assigned to dose levels of 0.6, 1.2, 2.4, or 3.6 mg/kg/week. The expectation is that patients will be dosed each week on the same day of the week. To allow for holidays and other scheduling issues, individual doses may be administered up to 2 calendar days earlier or later than expected, while remaining on the same schedule. Doses should not be administered fewer than 5 calendar days after the preceding dose.

If, for any reason (e.g., scheduling or toxicity), dosing is interrupted more than 2 calendar days beyond expected, then the next dose should be administered as soon as feasible and the schedule reset to once weekly on the next convenient weekday.

Twice weekly dosing: for patients assigned to the dose level of 1.2 mg/kg twice weekly (2.4 mg/kg/week). The total weekly exposure will be administered as a 2 separate SC injections of 1.2 mg/kg per injection, respectively, over the course of the week. The expectation is that patients will be dosed twice each week on the same day of the week, with (approximately) 72 or 96 hours (3 or 4 calendar days, respectively) between injections. The minimum interval between successive doses may not be less than 48 hours (2 calendar days). If, for any reason (e.g., scheduling or toxicity), the interval between successive doses is 6 or more calendar days, then the next dose should be administered as soon as feasible and the twice weekly dosing schedule resumed.

Extended dosing interruptions. If, for any reason, dosing is interrupted for more than 21 calendar days due to toxicity, the patient should be discontinued from study treatment unless

the Investigator and the Idera Medical Monitor agree that it is in the patient's best interest to continue.

8.5. Assigning Patients to Treatment Groups

See Section 9.3.

8.6. Prior and Concomitant Medications

Prior treatments for WM 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).

8.6.1. 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 WM 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 days after last dose of study drug), this will be recorded in concomitant medications and considered in assessment of any new AEs.

8.6.2. Other restrictions

None.

8.7. Treatment Compliance

All doses of study drug will be administered by study 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 is scheduled (that is, at Day 1 and at the first weekly doses of Weeks 2 and 5 of Cycle 1 and at Weeks 1 and 5 of additional cycles), 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 by overnight delivery service. To protect the integrity of the treatment, the shipping container must be held 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.

8.8. Accountability of Investigational Drug Supplies

Study drug will be provided by the Sponsor. The Investigator at each study site is 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 the patient). 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.
- 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.

8.8.1. 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 schedule for all study events is detailed in Table-4. Table-5 gives an estimate of blood volumes required.

The schedule is presented relative to the day and time of dosing. All Days are relative to the calendar day of the first injection of study drug, designated Day 1. All weeks are relative to Week 1 of each cycle, defined as Day 1 through Day 7, inclusive. All times are relative to injection, designated 0 hour; "pre-dose" vital signs are to occur within 1 hour prior to injection; all other pre-dose procedures are to occur prior to injection on the same calendar day.

9.2. Screening Procedure

The screening evaluation may be performed up to 21 days prior to dosing. Written informed consent will be obtained before any study-specific procedures are performed. The consent procedure must be recorded in source documentation. All patients who sign an informed consent form (ICF) will be entered into the EDC system within 48 hours of consent. To minimize patient risk and discomfort, the radiologic imaging and bone marrow biopsy scheduled at Screening will be performed only *after* the patient meets all other inclusion and exclusion criteria.

Waldenström's macroglobulinemia is a rare disease and patients often travel considerable time and distance to be managed at tertiary referral centers. To facilitate rapid completion of screening and enrollment and thereby avoid the need for multiple trips, Investigators may, with the approval of the Sponsor, perform screening laboratory studies at their local laboratory, including safety labs (see Section 9.7), cryoglobulins and cold agglutinins, and qualifying total serum IgM and monoclonal serum IgM protein levels (see Section 9.4.2). In such cases, central laboratory tests scheduled at Screening will be handled as follows:

- Concurrent safety labs (see Section 9.7) will not be submitted to the central lab.
- Blood and urine samples will be submitted to the central lab for the tests relating to monoclonal protein (see Section 9.4.2) and to Investigational studies (see Section 9.9) to support longitudinal data analysis.

Pre-dose on Day 1, safety labs will be sent to the central laboratory for *all patients* as scheduled and used as the baseline (pre-treatment) safety laboratory values to support longitudinal analysis.

9.3. 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 and are assessed as eligible by the Investigator will be reviewed with the Sponsor or the Sponsor's designated representative. After acceptance, the Investigator and site pharmacy will be provided the following information in writing (by email and/or fax):

- The patient's assigned unique study number, to be marked on all study-specific documents.
- The patient's assigned dose level.

9.4. Assessments of Waldenström's Macroglobulinemia

Laboratory assessments for disease status (see Section 9.4.2) will be conducted at Screening, every 4 weeks ± 1 week (Week 1 and Week 5 of each cycle), every 12 weeks ± 4 weeks during the Follow-up Phase, at the EOT visit, and at the EOS visit.

Clinical assessments for disease status (see Section 9.4.1) will be conducted at Screening, every 8 weeks ± 1 week (Week 1 of every cycle), every 12 weeks ± 4 weeks during the Follow-up Phase, at the EOT visit, and at the EOS visit.

Radiologic imaging will be performed at Screening and at EOT visit or as clinically indicated.

Bone marrow biopsy and aspirate will be performed at Screening, EOT, and to document complete response as appropriate (see Section 16.2).

A medical history specific to WM will be collected at Screening and will include, but is not limited to: a detailed review of the patient's malignancy, prior treatments, relevant current or past abnormalities or diseases, and signs and symptoms of WM at baseline (Section 9.6.1).

9.4.1. Clinical Assessments

- ECOG performance status.
- Clinical assessment for tumor status including assessment of lymphadenopathy, hepatomegaly and splenomegaly.

9.4.2. Laboratory Assessments Relating to Total IgM and Monoclonal Protein

The following laboratory assessments will be performed by a central laboratory approved by the Sponsor. As noted above, patients being enrolled on the basis of local lab data may be qualified based on local results for serum IgM monoclonal protein levels, but at the time of Screening they will still have blood and urine samples submitted so that the panel below may be performed at the central lab.

- Total serum IgM by nephelometry (i.e., total IgM or IgM).
- Quantification of serum IgM monoclonal and total protein by densitometry, i.e., Serum Protein Electrophoresis with immunofixation (i.e., monoclonal IgM or M-spike).
- Serum Free Light Chains (sFLC) and ratio.

- Serum β2-microglobulin.
- Serum viscosity.
- Urine Free Light Chains (uFLC) and ratio.

9.4.3. Radiologic Imaging

Computed tomography or magnetic resonance imaging scan of chest, abdomen and pelvis to assess for lymphadenopathy and organomegaly. Modality of the scan must be consistent throughout the study. Interim scans may be performed at the request of the Investigator and with the approval of the Idera Medical Monitor based on new signs or symptoms.

9.4.4. Bone marrow biopsy and aspirate

The procedures for collecting, processing, and transporting bone marrow biopsy and aspirate specimens will be detailed in the Bone Marrow Biopsy manual. Bone marrow biopsy and aspirate specimens will be sent to the central pathologist for confirmation of disease status, flow cytometry, and to the central laboratory for investigational studies of tumor cells (see Section 9.9). The percent lymphoplasmacytic cell involvement will be noted for each biopsy performed. Bone marrow biopsy and aspirate will be performed at Screening, EOT, and to document complete response as appropriate (see Section 16.2).

9.5. Evaluation of Response to Treatment and Disease Status

The criteria for response to treatment are provided in Section 16.2 (based on the full text of the VIth International Workshop classification [1]). Central laboratory serum total IgM and serum monoclonal IgM values are to be used to evaluate response to treatment (refer to Section 9.4.2).

The Third International Workshop for WM also defined the following categories [26]:

Not evaluable response: Reserved for situations in which there is insufficient data for a determination of response to treatment.

Delayed response: A delayed response is described particularly after treatment with purine analogue or monoclonal antibody. The recommendation was that patients should be followed for at least 12 weeks after treatment initiation to be considered unresponsive to therapy.

9.6. General Clinical Assessments

9.6.1. Medical History, including WM

At the Screening visit, 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, duration, 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.

- A separate eCRF will be provided to record signs and symptoms of WM at Baseline, including but not limited to: bleeding events, fatigue, anemia, thrombocytopenia, leukemia/neutropenia, fever, hyperviscosity, neuropathy, lymphadenopathy, weight loss, headache, night sweats, and vision changes.

Past history should include all significant illnesses that the patient has experienced and have resolved within the 12 months prior to signing informed consent. Illnesses active at the time of informed consent will be regarded as concomitant illnesses. Concomitant illnesses that worsen or illnesses with onset after obtaining informed consent will be recorded on the AE form in the EDC (see Section 10), with particular attention to whether the onset was before or after administration of the first dose of study drug. If a WM sign or symptom recorded at Screening worsens, it will be captured as an AE.

9.6.2. 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. Exam of reproductive system when needed may be performed by the Investigator or delegated to a specialist.

Height and weight will be evaluated at Screening and the body mass index will be calculated.

Any clinically significant changes in physical exam identified after obtaining informed consent will be recorded using the AE form in the EDC (see Section 10).

9.6.3. Vital Signs

Vital signs include heart rate (HR), blood pressure (BP), respiratory rate, and temperature. Where feasible, vital signs should be measured before blood is drawn and 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. Respiratory rate 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.

9.6.4. 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, QT interval, QTc interval, and QTc method. Electrocardiograms are to be performed at Screening, at pre-dose and 2 hours post-dose on Day 1 of Cycle 1, and pre-dose at

the first dosing visit of Weeks 1 and 5 of each cycle thereafter. In addition, an ECG is to be performed at 2 hours post-dose on Day 1 of each odd-numbered cycle.

9.6.5. Injection Site Reaction (ISR) Assessments

Injection site reactions will be documented in detail for each individual injection as described in Table-11. Each ISR shall also be captured on the AE 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-11. 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.

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-12.

Table-12. 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.

9.7. Safety Laboratory Studies

The laboratory tests indicated below will be performed by a central laboratory designated by the Sponsor (except for sites approved to use local laboratory results for screening as detailed in Section 9.2). The procedures for collecting, processing, and transporting the required blood samples will be detailed in the laboratory manual.

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

9.7.1. 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
*Urea
*Creatinine
*Sodium
*Potassium
*Chloride
*Bicarbonate
C-reactive protein (CRP)
Magnesium
Calcium
Phosphate
Uric Acid
Cholesterol
Triglycerides
Low density lipoprotein (LDL)
High density lipoprotein (HDL)
*Alanine aminotransferase (ALT)
*Aspartate aminotransferase (AST)
*Alkaline phosphatase (AP)
*Total bilirubin
Total protein
Albumin
Lactate dehydrogenase (LDH)
Creatine phosphokinase (CK)

* Laboratory tests comprising focused panel to be performed on Weeks 3 and 7 of each cycle.

Serum Complement Testing

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

Coagulation Panel

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

Urinalysis

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

Serologic tests (Screening only)

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

Pregnancy tests (Females only)

beta-human chorionic gonadotropin (β-hCG)

9.7.2. Reporting of Safety Laboratory Tests

Results of safety laboratory tests are expected to be available to the Investigator within 48 hours. 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.

9.7.3. Repeating Abnormal Laboratory Tests

Laboratory tests showing abnormal or exclusionary values at Screening may be repeated no more than once. 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.

9.8. Pharmacokinetic Assessments

Blood samples for plasma levels of IMO-8400 will be collected as scheduled. Samples will be analyzed for IMO-8400 concentration using a validated bioanalytical method (estimated sensitivity, 20 ng/mL). Pharmacokinetic data will be analyzed on an individual basis.

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.

9.9. Investigational Laboratory Studies

The following laboratory studies relate to assessing the pharmacologic effects of the investigational agent. Samples will be collected as scheduled and sent to the Central Lab, where they will then be sent to Sponsor-designated qualified labs for testing. 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 the bone marrow biopsy samples will be assayed for:

- Presence of MyD88 L265P mutation, and, if indicated, other somatic mutations in genes encoding proteins in the TLR and BCR signaling pathways (e.g., CARD11, IRAK4, BTK). Samples will be retained for up to 1 year after completion of the study to support possible future development of a companion diagnostic assay.

Serum samples will be assayed for:

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

10. SAFETY ASSESSMENTS (ADVERSE EVENTS)

10.1. Definition of Adverse Events

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 TEAEs 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 (see 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.

[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).

- Congenital anomaly or birth defect.
- 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 (SUSAR)

A 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 (see Section 10.4.3);
- *Unexpected* — compared to the study drug-related AEs described in Investigator's Brochure, the event meets ***any*** of the following criteria:
  - The event was not previously described;
  - The event is now characterized as more severe (see 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 (see Section 9.7.2) 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 (see Section 12.2).
- 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 (see Section 10.1.3).
- In accordance with the 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-13 summarizes the basis for reporting the date and time of onset for the different types of AEs.

Table-13. Reporting the Date and Time of Onset of adverse events 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 blood pressure, 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. Severity

The 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-14 [27].

Table-14. Estimating Severity Grade

Grade 1/Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living[a]
Grade 3/Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living[b]
Grade 4/Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5/Death	Death related to adverse event

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, ect.
b. Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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 (see 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 Adverse Event

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., 1 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 mediation.

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*** — 1 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 study participation. 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-15 indicates the date and time to be recorded. As discussed in detail for date/time of onset (see 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-15. Date and Time of Outcome for Adverse Event by Outcome Class

Outcome assigned to Adverse Event	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 services is provided in Table-1 and Table-2.

In the event a 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).
- 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.
- Date of the first injection of study drug.
- Date of the last injection of study drug prior to the event.
- 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.

Additional documentation may be submitted as part of a follow-up report.

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 Adverse Events

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 SAEs to the Investigator by the Sponsor

In accordance with regulatory requirements, the Sponsor or designee 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 Code of Federal Regulations (CFR).
- FDA guidance document: Safety Reporting Requirements for INDs and BA/BE Studies

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. 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.
- Medication prescription and administration records.
- Laboratory reports, including clinical pathology and diagnostic histologic pathology.
- Reports of imaging studies.
- 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," including, at a minimum, security requirements for electronic signature and audit trails for changes.

11.3.1. Study-Specific Source Documents

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

- The ICF, signed and dated by the patient.
- The site screening log.
- Any clinical reports noted above that are scheduled as part of the protocol and have been annotated to indicate the significance of any abnormal findings (see 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);
- Text should be readable and unambiguous, including application of best medical record practices (e.g., minimal use of abbreviations; proper numerical, dose and posology formats);
- Entries will be signed and dated by the recorder.

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

- Be written legibly in dark (preferably black) ink, 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 contract 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 Pharmaceuticals, Inc. 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 Pharmaceuticals, Inc. 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 (see 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 Investigational New Drug 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. STATISTICS

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 MTD/RP2D, up to an additional 22 patients will be enrolled at the MTD or proposed RP2D level. With a total sample size of 22 patients, there is a 90% probability to detect an AE with a true incidence rate of 10%. A secondary objective of this study is to determine the treatment effect of IMO-8400 in patients enrolled at the MTD/RP2D. Using the exact binomial distribution with a 1-sided test and an alpha of 0.05, there is 79% power to detect a response rate of 33% as compared to a null response rate of 10%.

12.2. Analysis Populations

Safety/Intent-to-treat (ITT) Population — all patients who received at least 1 dose of study treatment.

Efficacy Evaluable (EE) Population – all patients who completed ≥1 cycle of therapy or those who discontinued due to progressive disease or DLT.

Per-Protocol (PP) Population — all patients who have adequate data at baseline and at 1 or more scheduled post-treatment tumor assessment and have no major protocol deviations. For patients who discontinue study treatment for any reason and start another treatment of their malignancy, no subsequent response assessments will be used for efficacy evaluation.

12.3. Analysis of Safety

Safety analyses will be conducted 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.

- Safety Endpoints
  - AEs.
  - Concomitant medications.
  - Clinical observations (e.g., vital signs, physical examination).
  - Laboratory tests, (e.g., clinical chemistry, hematology, coagulation, urinalysis).
  - ECGs.
  - Injection site reactions.

- Analyses
  - TEAEs: by dose level, intensity, and relationship to investigational product.
  - Treatment-emergent changes in severity grade of laboratory tests (see Section 10.4.5) will be summarized as "shift tables."
  - Descriptive statistics will be summarized for vital signs and ECG parameters by dose level and visit.
  - Concomitant medications will be summarized by WHO Drug Class and ATC text.
  - Injection site reactions will be summarized by incidence for each dose group and overall by worst grade on study. Time-to-event analyses will be performed for injection site reactions.

12.4. Analysis of Treatment Effect

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

12.4.1. Assessments

Laboratory assessments for disease status (see Section 9.4.2) will be conducted at Screening, every 4 weeks ± 1 week (Week 1 and Week 5 of each cycle), every 12 weeks ± 4 weeks during the Follow-up Phase, at the EOT visit, and at the EOS visit. Clinical assessments for disease status (see Section 9.4.1) will be conducted at Screening, every 8 weeks ± 1 week (Week 1 of every cycle), every 12 weeks ± 4 weeks during the Follow-up Phase, at the EOT visit, and at the EOS visit. Radiologic imaging will be performed at Screening and at EOT visit or as clinically indicated. Bone marrow biopsy and aspirate will be performed at Screening, EOT, and to document complete response as appropriate (see Section 16.2).

12.4.1.1. Primary Treatment Effect Parameter

The primary treatment effect parameter is objective response rate, defined as the occurrence of CR, VGPR, PR, or MR.

12.4.1.2. Secondary Treatment Effect Parameters

The VIth International Workshop specifies a number of outcome metrics related to time [1] (see Section 16.3). The following parameters are considered most relevant to this time-limited study and will be analyzed both globally across all cohorts and by dose level.

- Distribution of response categories by treatment group and overall.
- Time to progression – Time from the initiation of treatment to disease progression with deaths due to unrelated causes censored.
- Progression-free survival – Time from the initiation of treatment to disease progression or death from any cause.
- Time to best observed response – Time from the initiation of treatment to best observed category of response.

- Percent and absolute change in quantitative serum levels of monoclonal and total IgM.

Kaplan-Meier analyses will be used to analyze time to event data. Analysis of IgM data will be performed using a repeated measures mixed model. MyD88 L265P mutation status will be used as a covariate in statistical analyses.

12.5. Exploratory Analyses

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

- Presence or absence of MyD88 L265P mutation in tumor cells.
- Serum cytokine levels.
- Serum levels of antibody to IMO-8400.
- NF-κB inhibition.

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 injection of 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 injection of study drug are designated Day 2, Day 3, etc.
- The day of the last injection of study drug is indicated by adding the suffix "L," e.g., if the last injection is administered on Day 43, it will be displayed as "Day 43L."
- The days following the last injection of 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. 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.

12.8. 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)[28];[2]
- local laws and regulations for the use of investigational therapeutic agents.

13.1. Independent Ethics Committee (IEC)

13.1.1. Initial Review Prior to Study Initiation

Prior to initiating the study, the Investigator will submit the following to an IEC[3] for approval:

- Study protocol;
- Investigator's Brochure;
- ICF 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 Investigator's Brochure;
- Date the protocol and consent form were reviewed and approved by the IEC.

[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).

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:

- 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 IEC. 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 sufficient opportunity to read the ICF, to ask any questions, and to 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 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.

Note that this process is *not* applicable to patients who are literate in a language other than English; they must be provided an approved, certified translation of the ICF in that language.

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);
- Are less than 18 years of age.

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.

Methods to be used to protect the data will include the following:

- 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 3) may be handled administratively.

14.3. Confidentiality

This protocol, the applicable Investigator's Brochure, 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

The information developed during the conduct of this clinical study is considered confidential by Idera. This information may be disclosed as deemed necessary by Idera.

To allow for the use of the information derived from this clinical study and to ensure compliance with current regulations, the Investigator is obliged to provide Idera with complete test results and all data developed in this study. The information obtained during this study may be made available to other physicians who are conducting similar studies and to the FDA or other regulatory authorities. Such information may be disclosed as deemed necessary by Idera.

Idera intends that the data from this study will be presented and published. The Idera staff in collaboration with the Investigator will be responsible for writing presentations and manuscripts for publication. Investigators will not be allowed to publish or present the data from this study without prior agreement with Idera.

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

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16. CRITERIA FROM THE INTERNATIONAL WORKSHOPS

16.1. Diagnostic Criteria for Waldenström's Macroglobulinemia

The following is reproduced from the "Recommendations from the Second International Workshop on Waldenström's Macroglobulinemia" [5].

Table 2. Proposed Diagnostic Criteria for WM

- IgM monoclonal gammopathy of any concentration
- Bone marrow infiltration by small lymphocytes showing plasmacytoid/plasma cell differentiation
- Intertrabecular pattern of bone marrow infiltration
- Surface IgM^{+}, CD5$^{\pm}$, CD10^{-}, CD19^{+}, CD20^{+}, CD22^{+}, CD23^{-}, CD25^{+}, CD27^{+}, FMC7^{+}, CD103^{-}, CD138^{-} immunophenotype*

* Variations from this immunophenotypic profile can occur. However, care should be taken to satisfactorily exclude other lymphoproliferative disorders. This is most relevant in CD5^{+} cases, for which chronic lymphocytic leukemia and mantle cell lymphoma require specific exclusion before a diagnosis of WM can be made.

16.2. Classification of Disease Response for Waldenström's Macroglobulinemia

Reproduced from Reference [1].

Table I. Categorical response definitions.

Response category	Definition
Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)	Monoclonal IgM protein is detectable $\geq$90% reduction in serum IgM level from baseline* Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Partial response (PR)	Monoclonal IgM protein is detectable $\geq$50% but<90% reduction in serum IgM level from baseline* Reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Minor response (MR)	Monoclonal IgM protein is detectable $\geq$25% but<50% reduction in serum IgM level from baseline* No new signs or symptoms of active disease
Stable disease (SD)	Monoclonal IgM protein is detectable <25% reduction and <25% increase in serum IgM level from baseline* No progression in extramedullary disease, i.e., lymphadenopathy/splenomegaly No new signs or symptoms of active disease
Progressive disease (PD)	$\geq$25% increase in serum IgM level* from lowest nadir (requires confirmation) and/or progression in clinical features attributable the disease

*Sequential changes in IgM levels may be determined either by M protein quantitation by densitometry or total serum IgM quantitation by nephelometry.

16.3. Efficacy Measure Definitions

Reproduced from Reference [1].

Table II. Efficacy measure definitions.

Endpoint	Definition
Overall survival	Time from the initiation of treatment to death from any cause
Cause-specific survival	Time from the initiation of treatment to death censoring for deaths from unrelated causes
Progression-free survival (PFS)	Time from the initiation of treatment to disease progression or death from any cause
Time to progression (TTP)	Time from the initiation of treatment to disease progression with deaths due to unrelated causes censored
Disease-free survival (DFS)	Time from the first documentation of complete response to disease progression with deaths due to unrelated causes censored
Duration of response (DOR)	Time from the first documentation of response to disease progression with deaths due to unrelated causes censored
Time to next treatment (TTNT)	Time from the initiation of treatment to next therapy

17. INVESTIGATOR'S AGREEMENT

I have read the foregoing protocol (Protocol 8400-401, Version 7.0) 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 GCP, 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 ICF 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 SAEs.
- 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 (dd-mmm-yyyy)**

Investigator (printed name): _____

Title: _____

Address: _____

Facility / Site of Investigation: _____

Facility address: _____