STATISTICAL ANALYSIS PLAN

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

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Name of Test Drug:	IMO-8400
Phase:	Phase 1/2
Methodology:	Open-label, Multiple-dose, Dose-escalation, Multicenter
Sponsor:	Idera Pharmaceuticals, Inc. 167 Sidney Street Cambridge, MA 02139
Sponsor Representatives:	Suzanne Swann, PhD Principal Statistician Idera Pharmaceuticals, Inc.
Statistical Analysis Plan Date:	11 November 2016
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APPROVAL SIGNATURE PAGE

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Sponsor: Idera Pharmaceuticals, Inc.
167 Sidney Street
Cambridge, MA 02139

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Veristat, LLC. Author:

Debora Manning, MPH
Biostatistician
Veristat, LLC
118 Turnpike Road
Southborough, MA 01772

Signature:_____

Date:_____

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

Suzanne Swann, PhD
Principal Statistician
Idera Pharmaceuticals, Inc.

Signature:_____

Date:_____

TABLE OF CONTENTS

Section **Page**

TABLES AND FIGURES INCLUDED IN THE TEXT

Table/Figure **Page**

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABC	Activated B-cell
AE	Adverse event
ATC	Anatomic Therapeutic Class
BCR	B-cell receptor
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CRC	Cohort review committee
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOS	End of study
EOT	End of treatment
GCB	Germinal center B-cell
ICH	International Conference on Harmonisation
IRB	Institutional review board
ISR	Injection site reaction
ITT	Intent-to-treat
IWG	International Working Group
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MyD88	Myeloid differentiation primary response gene (88)
NCI	National Cancer Institute
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B-cells
NHL	Non-Hodgkin’s lymphoma
PD	Pharmacodynamic

Abbreviation	Definition
PK	Pharmacokinetic(s)
QTcF	QT interval corrected for heart rate using Fridericia's formula
Rel Day	Relative study day
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TLR	Toll-like receptors
WHO	World Health Organization
WM	Waldenström's macroglobulinemia

2. STATISTIAL ANALYSIS PLAN OBJECTIVES

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objectives. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives and analyses than those planned in the study protocol.

3. INFORMATION FROM THE STUDY PROTOCOL

3.1. Introduction and Objectives

3.1.1. Introduction

Non-Hodgkin lymphomas (NHL) represent a heterogenous group of lymphoid malignancies. Current estimates for the United States are approximately 70,000 new cases of NHL annually and 19,000 deaths (NCI, 2013). The primary differentiation is based on lymphocyte cell type: B-cell, T-cell, or NK-cell. Approximately 85% of NHL arises from B-cells and the most common of the mature B-cell malignancies is diffuse large B-cell lymphoma (DLBCL), representing ~31% of all cases. DLBCL is considered an aggressive lymphoma with the potential for rapid disease progression.

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 subcutaneous (SC) injection at single doses and multiple doses (once weekly for 4 weeks) up to 0.6 mg/kg (see Protocol Section 4.4.1 for details). All treatments were well tolerated, with mild injection site reactions and no pattern of systemic reactions or laboratory changes.

Myeloid differentiation primary response gene (88) (MyD88) is the initial linker protein in the TLR signaling pathway. Recent studies indicate a high frequency of mutations in MyD88 in patients with B-cell malignancies, particularly DLBCL subtypes with poor prognosis (Ngo, 2011). Specifically, the gain-of-function L265P mutation is found in almost a third of DLBCL with the activated B-cell (ABC) phenotype. In vitro studies of B-cell tumor lines indicate that (a) this mutation is associated with an increase in cell activation, proliferation, and survival, and (b) loss of endosomal TLRs results in markedly decreased cell proliferation and survival (Young and Staudt, 2013; Lim, 2013). Data from Idera indicate that treatment of such cell lines with IMO-8400 has a similar effect (Bhagat, 2014).

Recently reported clinical experience with IMO-8400 in patients with Waldenström's macroglobulinemia (WM), a B-cell malignancy almost always driven by the MYD88 L265P mutation, indicate that the treatment is active and well tolerated at dose levels up to 1.2 mg/kg twice weekly (Treon, 2012; Thomas, 2015). Dose escalation is continuing in that setting as the maximum tolerated dose (MTD) has not been reached.

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

On September 26, 2016, accrual to this trial was suspended by the Sponsor after 5 patients had been enrolled and treated. No further patients will be enrolled. As a result, limited efficacy results will be presented.

3.1.2. Study Objectives

3.1.2.1. Primary Objective

The primary objective is to evaluate the safety and tolerability of escalating dose levels of IMO-8400 administered by SC injection in patients with relapsed or refractory non-germinal center B-cell (GCB) subtype DLBCL.

3.1.2.2. Secondary Objectives

The secondary objectives are as follows:

- To assess the treatment effect (clinical activity) in patients with non-GCB subtype DLBCL with MYD88 L265P mutations using disease-specific international guidelines for classifying clinical response (Cheson, 2007)
- To identify an optimal dose of IMO-8400 for further clinical evaluation in B-cell malignancies
- To characterize the pharmacokinetics (PK) of escalating dose levels of IMO-8400 administered by SC injection

3.1.2.3. Exploratory Objectives

The exploratory objectives are as follows:

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

3.2. Study Design

3.2.1. Synopsis of Study Design

This is an open-label, multiple-dose, dose escalation study of IMO-8400 in patients with relapsed or refractory DLBCL of non-GCB subtype. The study is a Phase 1/2 study. Phase 1 consists of a dose escalation to determine the recommended Phase 2 dose (RP2D). Phase 2 uses a Simon 2-stage optimal design to evaluate open-label treatment of patients at the RP2D (Simon, 1989). Initially, 10 patients will be treated at the RP2D. If at least 2 of the 10 patients respond, the study will enroll 19 more patients, for a total of 29 patients in the Phase 2 portion.

A study schematic is represented in Figure 1 of the protocol.

Patients are eligible to enroll on the basis of a positive MYD88 L265P mutation assay performed using any Clinical Laboratory Improvement Amendments (CLIA) compliant assay at any point during the course of their disease. Patients whose tumors do not harbor MYD88 L265P mutations are eligible for the dose escalation phase of the study only (Phase 1), but the L265P mutation is required to be eligible for the expansion phase of the study (Phase 2).

3.2.1.1. Phase 1: Dose Escalation

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

- The planned dose escalation cohort levels for IMO-8400 are 0.3, 0.6, and 1.2 mg/kg administered twice weekly and 2.4 and 3.6 mg/kg administered once weekly (Table 3-1). One or more dosing levels may be skipped based on demonstration of safety from other studies concurrently conducted on IMO-8400. Additional dose levels, schedules, and routes of administration may be evaluated based upon the emerging data. Dosing is based on body weight (see Protocol Section 8.1). Doses will be administered by SC injection.
- The Investigators and Sponsor will review available toxicity information (including adverse events [AEs] that are not dose-limiting toxicities [DLTs]), PK and activity data to determine the MTD (see Section 3.2.5.1).

Table 3-1 Planned Dose Escalation Cohorts

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

Each dose escalation cohort is expected to enroll at least 3 patients, with a maximum of 6 patients. The number of patients enrolled in any of the planned dose escalation cohorts can be reduced if safety at that dose level has already been demonstrated in a related population (e.g., WM). A cohort review committee (CRC) comprised of the Idera Medical Monitor and Investigators from participating sites will decide whether to continue or halt dose escalation, or explore intermediate dose levels (see Section 3.2.3).

The following dose escalation procedures will be used:

- If the initial 3 patients complete all 4 weeks of treatment without a DLT event, the CRC will conduct a dose escalation review.
- If 1 of the initial 3 patients experiences a DLT event prior to completing Cycle 1, 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 Cycle 1.
- If ≥2 patients at a dose-level experience DLT events during the Cycle 1, then no further patients will be enrolled until the CRC completes a review, which should be done as soon as feasible.
- Furthermore, cohorts may be expanded to include additional patients if such patients can be enrolled ≤7 days after the third (or sixth) patient was first dosed with IMO-8400.

To facilitate standardizing the dose escalation reviews across different cohorts, the focus will be on observations from Cycle 1 at that dose level.

3.2.1.2. Phase 2: Dose Expansion Cohort

Once the RP2D has been established, additional patients will be treated in a dose expansion phase that is designed to better characterize the safety, tolerability, and preliminary anti-tumor activity of the study drug when provided at the RP2D to patients with non-GCB subtype DLBCL with MYD88 L265P mutations. Phase 2 will use a Simon 2-stage design. Patients from Phase 1 treated at the RP2D, who are non-GCB subtype and MYD88 L265P mutation positive, will be included in the Phase 2 dose-expansion phase. Additional patients will be enrolled in the cohort until a total of 10 patients are treated at the RP2D. If at least 2 of the 10 patients respond, the study will enroll 19 more patients, for a total of 29 patients in the Phase 2 portion. Additional dose-expansion cohorts may be added if clinical activity is seen during the dose escalation phase in tumors that lack this mutation.

3.2.2. Stopping Rules

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

will promptly inform the impacted Investigators and institutions, the regulatory authorities, and the Institutional Review Board (IRB) of the action and the reason(s) for the action.

3.2.2.1. Stopping Rules for Individual Patients

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

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

3.2.3. Cohort Review Committee (CRC)

The CRC is comprised of the Idera Medical Monitor and Investigators from participating sites. Once the last patient in a given cohort has completed a cycle of study treatment, a CRC meeting will be convened to review all safety data and decide whether to continue or halt dose escalation, further expand individual dose levels to gain additional safety data, or explore lower or intermediate dose levels. In addition to end-of-cohort meetings, the CRC will convene periodically, including during Dose Expansion (Phase 2), to review safety data for ongoing patients and patients in follow up.

The roles of the CRC are to:

- Review and provide definitive adjudication on individual DLTs, if needed (see Section 3.2.5.1.1)
- Perform dose-escalation review and make specific recommendations for the progress of the study (see Section 3.2.1.1)
- Determine the MTD (see Section 0)

A patient will be considered evaluable for purposes of CRC review if they meet the criteria to be included in the DLT Evaluation Population defined in Section 4.1.

3.2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 3-2. The schedule is presented relative to the day and time of dosing.

Table 3-2 Schedule of Study Evaluations

Visit[1]	Pre-Screen[2]	Screen[3]	Treatment Period												EOT[4]	EOS[5]	F/U	Survival F/U
Cycle			**Cycle 1**				**Even Numbered Cycles**				**Odd Numbered Cycles**						**Every 12 wks. (+/- 4 wks.)**	**Every 12 wks. (+/- 4 wks.)**
Day		**≤ 21**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**				
Evaluation																		
Informed Consent[6]	X	X																
Tumor genotyping[7]	X																	
Blood draw for genotyping	X																	
Inclusion/Exclusion criteria		X																
Demography and medical history		X																
Physical exam[8]		X	X				X				X				X	X		
Vital Signs[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test[10]		X													X			
Radiologic Imaging[11,12]		X								X					X			
Bone Marrow Biopsy[13]			X												X			
Lymph Node Biopsy		X[14]	X[15]															
Assessment of Response[12]										X					X			
ECOG		X	X				X				X				X	X		
Hematology[16]		X	X		X		X		X		X		X		X	X		
Chemistry panel[16]		X	X		X		X		X		X		X		X	X		
Coagulation panel		X	X				X				X				X	X		
Complement		X	X				X				X				X	X		
Urinalysis		X	X				X				X				X	X		
12-lead ECG[17]		X	X				X				X				X	X		

Visit[1]	Pre-Screen[2]	Screen[3]	Treatment Period												EOT[4]	EOS[5]	F/U	Survival F/U
Cycle			**Cycle 1**				**Even Numbered Cycles**				**Odd Numbered Cycles**						**Every 12 wks. (+/- 4 wks.)**	**Every 12 wks. (+/- 4 wks.)**
Day		**≤ 21**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**				
Evaluation																		
Serology		X																
PK[18]			X				X				X				X	X		
PD and Investigational Studies[19]		X	X				X				X				X	X		
Study Drug Administration[20]			X	X	X	X	X	X	X	X	X	X	X	X				
Assessment of Injection Site(s)[20,21]			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AEs/concomitant medications[20]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

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

1. All days for a given Cycle are relative to the day of the first injection of study drug, designated Day 1 for that cycle; all times are relative to treatment, designated 0 hour; "pre-dose" vital signs are to occur within 1 hour prior to treatment; all other pre-dose procedures are to occur prior to treatment on the same calendar day.
2. Pre-screening procedures involve only tumor genotyping and require a separate consent (protocol Section 9.2).
3. Screening procedures may be performed up to 21 days prior to Day 1.
4. If treatment is terminated prematurely for any reason, the EOT visit will be performed within 7 days of the decision to terminate.
5. EOS Visit will be performed 30 to 35 days after the last dose of study drug if treatment is terminated prematurely for any reason.
6. Informed consent must be signed prior to all study-specific pre-screening and/or screening procedures.
7. A tumor sample will be submitted to a central laboratory (protocol Section 9.2) or alternatively previously confirmed by any outside CLIA-compliant assay and confirmed and approved by the Sponsor.
8. Physical exam includes body weight and, only at Screening, height; a directed physical examination at the discretion of the Investigator is acceptable while on study treatment. Complete physical examination is required prior to enrollment and EOT and EOS.
9. Vital signs comprise heart rate, blood pressure, respiratory rate and temperature. Vital signs will be obtained pre-dose (within 1 hour prior to treatment) and post-dose within 30 min (±5 min) of treatment. On Day 1 of Cycle 1, Week 1, post-dose vital signs will also be obtained at 2 hours (±20 min).
10. Serum or urine pregnancy testing for women of child-bearing potential.
11. Radiologic imaging of chest, abdomen, and pelvis, performed during the last week of even cycles (every 8 weeks [± 1 week]) while the patient is receiving IMO-8400; patients discontinued from treatment for reasons other than progressive disease will be assessed per Revised Response Criteria for Lymphoma (protocol Section 16.2) at a minimum of every 12 weeks (± 4 days) for OS until documentation of progressive disease, initiation of new anti-cancer therapy, or the end of the study, whichever comes first.
12. Assessment of response should be performed using the same imaging modalities throughout the study; assessment should be performed during the last week of all even numbered cycles (every 8 weeks [± 1 week]) while the patient is receiving active treatment with IMO-8400.
13. If available, bone marrow biopsy will be processed locally (see the Laboratory Manual for more details).
14. Archival or fresh tissue should be submitted for confirmation of diagnosis and exploratory analyses (see the Laboratory Manual for more details).

15. Should be collected at least once between 4 and 24 hours post-treatment (protocol Section 9.5).
16. Hematology and chemistry full panels will be performed on Day 1 of each cycle; focused panels will also be performed on Day 15 of each cycle through Cycle 6. For Cycle 7 and on all testing will not be repeated on Day 15 unless more frequent monitoring is clinically indicated (refer to protocol Section 9.8.1 for details).
17. If Screening and Day 1 Cycle 1 are performed within 24 hours then the 12-lead ECG will be performed only at Screening.
18. On Cycles 1, 2, 4, and 6 (Day 1 of each cycle): a pre-dose sample is required. Additionally, post-dose PK samples are obtained at 1 (±5 min), 2 (±10 min) and 4 hours (±15 min). Pharmacokinetic samples will also be taken at EOT and EOS (protocol Sections 9.9).
19. Pharmacodynamic set involves one sample for serum cytokines and one sample for antibodies to IMO-8400 taken at Screening, pre-dose at Cycles 1, 2, 4, and 6 (Day 1 of each cycle), EOT, and EOS.
20. Except for Cycle 1 and study days that require a physical examination or laboratory safety tests to be performed, study drug administration, assessment of injection site(s), and assessment of AEs and con-meds may optionally be performed at a non-study site by a trained healthcare professional approved by the Sponsor, including at home by a visiting nurse (protocol Section 8.6).
21. Assessment of all prior injection site(s) with grading and measurement of any reaction (protocol Section 9.7.5). In addition, on dosing days, the planned injection site will be assessed to confirm it is appropriate for use.

3.2.5. Safety, Efficacy, and Pharmacokinetic Parameters

3.2.5.1. Safety Parameters

The safety and tolerability of IMO-8400 will be assessed using reported and observed AEs and injection site reactions (ISRs) as well as scheduled safety observations including vital signs, physical examination, laboratory tests (hematology, serum complement, chemistry, coagulation, urinalysis, and pregnancy tests [for females only]), and electrocardiograms (ECGs).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0. Laboratory values will be graded according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

3.2.5.1.1. Definition of Dose Limiting Toxicity and Maximum Tolerated Dose

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

Protocol-defined hematologic DLT criteria:

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

Protocol-defined non-hematologic DLT criteria:

- Grade 3 vomiting or nausea despite the use of optimal anti-emetic treatments
- Grade 3 diarrhea despite the use of optimal anti-diarrheal treatments
- Serum creatinine ≥ 3.0 x ULN
- Bilirubin ≥ 3.0 x ULN
- Bilirubin 2.0-3.0 x ULN with ≥ Grade 2 ALT in patients without liver metastases
- Bilirubin 2.0-3.0 x ULN with ≥ Grade 3 ALT or ALT > 5 x ULN in patients with liver metastases
- Other non-hematologic toxicities of ≥ Grade 3 except for the following:
  - AEs related to underlying disease
  - Fatigue
  - Alopecia

- Isolated, asymptomatic elevations in biochemistry laboratory values lasting ≤ 7 days. This includes electrolyte abnormalities that respond to medical intervention.

The CRC will review all DLTs to assess causality, i.e., relationship to study drug. The definition of a DLT event will be applicable in the following contexts:

- Cohort Review Committee review determining dose escalation.
- Cohort Review Committee review in defining the MTD.
- Investigator (and Medical Monitor) review for determining discontinuation of study treatment in individual patients.

The MTD is the 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.

3.2.5.2. Efficacy Parameters

As no further enrollment into Protocol 8400-402 is planned after 5 patients (see Section for further detail), only one efficacy parameter will be assessed: distribution of best overall response per the International Working Group (IWG) response criteria (Cheson, 2007). Due to limited data, no other efficacy endpoints will be analyzed.

3.2.5.3. Pharmacokinetic Parameters

Blood samples for plasma levels of IMO-8400 will be collected as scheduled (Table 3-2). Samples will be analyzed for IMO-8400 concentration using a ligand binding (hybridization) bioanalytical method (estimated sensitivity, 20 ng/ml). Pharmacokinetic (PK) parameters and details for analysis will be described in a separate analysis plan.

3.2.5.4. Pharmacodynamic Parameters

Pharmacodynamic assessments as described in the protocol were not all performed due to the early termination of the trial. All PD data that was collected, which includes nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-kB) and cytokine data, will be listed.

4. PATIENT POPULATION

4.1. Population Definitions

The following patient populations will be evaluated and used for presentation and analysis of the data:

- DLT Evaluable Population: All patients enrolled in the Phase 1 dose escalation portion of the study who receive all planned doses of study drug during the DLT observation period or who discontinue treatment due to AEs.
- Safety Population: All patients who received at least 1 injection of study treatment.

The CRC review will be performed on the DLT Evaluable Population for the dose being considered. Safety analyses will be performed using all available information for the Safety Population. The limited efficacy data will also be presented using the Safety Population.

4.2. Protocol Deviations

All protocol deviations will be presented in a data listing.

Relevant Output

Listing 16.2.2.3 Protocol Deviations

5. GENERAL STATISTICAL METHODS

5.1. Sample Size Justification

To identify the MTD/RP2D of IMO-8400 in this population, the sample size in the Phase 1 portion of the study will start with 3 patients, and expand as described in Section 3.2.1.1. The maximum number of patients expected in the dose escalation cohort is approximately 30 patients, and will be dependent upon tolerability results observed at each dose level.

Following identification of the MTD, up to 29 additional patients will be enrolled at the RP2D. Simon's two-stage optimal design will be used to test the response rate at the RP2D (Simon, 1989). The null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. In the first stage, 10 patients will be accrued. If there is at most 1 response in these 10 patients, the study will be stopped. Otherwise, 19 additional patients will be accrued for a total of 29. The null hypothesis will be rejected if 6 or more responses are observed in 29 patients. This design yields a type I error rate of 4.7% and power of 80.5% when the true response rate is 30%.

5.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). For the purpose of analysis, relative study day is defined as follows:

- Rel Day 1 is defined as the calendar day of the first injection of study drug.
- The days prior to Rel Day 1 are designated Rel Day –1, Rel Day –2, etc; there is no Rel Day 0.
- The days following the day of the first injection of study drug are designated Rel Day 2, Rel Day 3, 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 subcutaneous injection of study drug), which is designated as t = 0 (zero). Thus, 15 minutes prior to dosing is t = –15 min; 2 hours after dosing is designated t = 2 h.

All output will be produced as Microsoft Word files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented.

Data will be presented by patient and summarized by dose level and overall, including a pooled cohort of all IMO-8400 dosed groups. Only dose groups that enrolled at least 1 patient will be presented.

Relevant Output

Table 14.0.1 Treatment Codes Applicable to Tables and Listings

5.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.3 or above, unless otherwise noted.

5.4. Baseline Definitions

For all analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug.

5.5. Methods of Pooling Data

Data will be pooled across all study sites.

5.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

5.7. Multiple Comparisons

No adjustments for multiple comparisons will be made. As the primary purpose of this study is to assess the safety and tolerability of IMO-8400, efficacy assessments are secondary and the type I error rate will not be adjusted.

5.8. Subpopulations

No analyses of subpopulations are planned.

5.9. Withdrawals, Dropouts, Loss to Follow-up

During Phase 1, a patient who does not meet the criteria to be included in the DLT Evaluable Population defined in Section 4.1 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.

5.10. Missing Data

Missing data will not be imputed, except as described in this section. All the data recorded on the eCRF will be included in data listings that will accompany the CSR.

When tabulating AE data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the first date of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A missing onset date will be coded as the first day of treatment. Listings will present all data as reported (i.e., without imputations).

5.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule; visits outside of this schedule will be listed as a protocol deviation. Data will be tabulated by nominal visit and a windowing strategy will not be employed.

Unscheduled assessments will not be summarized in tabulations that present data by visit. However, in shift tables or summaries of best response, data from unscheduled assessments will be included. All data from unscheduled assessments will be listed.

In data listings, the relative day of all dates will be presented.

5.12. Interim Analyses

Interim safety data will be examined on an ongoing basis to ensure patient safety and to comply with the clinical trial dose escalation rules.

The protocol-specified interim analysis of efficacy in Phase 2 will not be conducted due to the early termination of the study.

6. STUDY ANALYSES

6.1. Patient Disposition

By-patient listings of patient disposition, inclusion and exclusion criteria, reasons for screen failure, and study populations will be produced.

Relevant Output

Listing 16.2.1.1	Patient Disposition
Listing 16.2.1.2	End of Treatment (EOT) Visit Status
Listing 16.2.1.3	End of Study (EOS) Visit Status
Listing 16.2.2.1	Listing of Inclusion/Exclusion Criteria Not Met
Listing 16.2.2.2	Listing of Reasons for Screen Failure
Listing 16.2.3.1	Study Populations

6.2. Demographics, Baseline Characteristics, and Medical History

Demographics, baseline characteristics, medical history, disease history, MyD88L265P mutation status, and prior treatments will be listed. Medical history will be coded using MedDRA version 16.0 (or later).

Relevant Output:

Listing 16.2.4.1	Demographic Characteristics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3A	Disease History: Part 1
Listing 16.2.4.3B	Disease History: Part 2
Listing 16.2.4.4	Prior Therapy
Listing 16.2.4.5	MyD88 L265P Mutation Status

6.3. Safety Analyses

Safety analyses will be conducted using the Safety Population, and presented by dose level and overall. Safety data will be analyzed using descriptive statistics and tabulation. No formal statistical comparisons are planned. All safety data will be presented in listings.

6.3.1. Study Drug Exposure

Study drug exposure will be tabulated by the number of weeks of study drug received, where a week of study drug received is defined as any week during which the patient received at least 1 dose. Cumulative dose (mg) will be summarized using descriptive statistics, where cumulative dose is the actual dose injected summed across all visits. The actual dose for each injection will be presented in mg/kg and calculated as follows, using body weight measured at screening: dose (mg/kg) = dose volume (mL) × dose concentration (mg/mL) / body weight (kg)

The number of missed doses will be tabulated, as well as the reason the dose was missed per patient (i.e. if a patient missed multiple doses for the same reason, they will only be counted once for that reason). Dosing information for each patient will be presented in a data listing.

Relevant Output:

Table 14.3.5.1 Study Drug Exposure (Safety Population)

Listing 16.2.5.1 Study Drug Exposure

6.3.2. Adverse Events

Adverse events will be coded using the MedDRA coding system and displayed in tables and data listings using SOC and preferred term.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as:

- any AE with onset after the first administration of study medication (Day 1) through the end of study (EOS) visit,
- any AE that was present at baseline but worsened in intensity, or
- any AE with missing onset date.

TEAEs will be summarized by patient incidence rates; therefore, in any tabulation, a patient contributes only once to the count for a given TEAE (SOC or preferred term), regardless of the number of episodes of a particular AE term reported. No formal hypothesis-testing analysis of TEAE incidence rates will be performed.

In an overview of TEAEs, a summary of the number and percentage of patients with any TEAE, TEAE related to study drug, TEAE ≥ Grade 3, serious adverse event (SAE), DLT, TEAE leading to discontinuation of study treatment, TEAE leading to dose modification, and TEAE leading to death will be produced.

Summary tables by preferred term will be produced for the following:

- All TEAEs (this summary will also be produced by SOC and preferred term)
- All TEAEs by relationship to study drug (drug-related, not drug-related) where drug-related AEs include events with probable, possible, and missing relationships
- All TEAEs by maximum severity grade (i.e. Grade 1, Grade 2, Grade 3, Grade 4, or Grade 5)
- All SAEs
- All non-serious TEAEs
- TEAEs leading to discontinuation of study treatment
- TEAEs leading to dose modification

Observed ISRs ≥ Grade 2 will be summarized by dose level and overall, by worst grade on study. Pain, tenderness, pruritus, and induration will be summarized using number and percentage of patients by toxicity grade. Induration and erythema measurements (mm) will be summarized descriptively, including quartiles and 90th percentiles. Blisters, ulceration and necrosis measurements (mm) will be summarized descriptively, including quartiles and 90th percentiles, as well as categorically by grade. For each summary, the worst grade is counted per patient and symptom.

All AEs occurring from the time of signing informed consent will be listed. Additionally, a glossary of AE verbatim terms by preferred term and SOC will be provided.

By-patient listings will also be provided for the following: AEs leading to death, SAEs, TEAEs leading to discontinuation of study treatment, TEAEs leading to dose-modification, and DLTs.

Relevant Output:

Table 14.3.1.1	Overview of Adverse Events (Safety Population)
Table 14.3.1.2A	Incidence of Adverse Events by MedDRA Preferred Term (Safety Population)
Table 14.3.1.2B	Incidence of Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.3	Incidence of Adverse Events by Relationship to Study Drug and by MedDRA Preferred Term (Safety Population)
Table 14.3.1.4	Incidence of Adverse Events by Maximum Severity Grade and by MedDRA Preferred Term (Safety Population)
Table 14.3.1.5	Incidence of Serious Adverse Events by MedDRA Preferred Term (Safety Population)
Table 14.3.1.6	Incidence of Non-Serious Adverse Events by MedDRA Preferred Term (Safety Population)
Table 14.3.1.7	Incidence of Adverse Events Leading to Discontinuation of Treatment by MedDRA Preferred Term (Safety Population)
Table 14.3.1.8	Incidence of Adverse Events Leading to Dose Modification by MedDRA Preferred Term (Safety Population)
Table 14.3.1.9	Incidence of Observed Injection Site Reactions ≥ Grade 2 by Worst Grade Post Baseline (Safety Population)
Table 14.3.2.1	Listing of Adverse Events Leading to Death
Table 14.3.2.2	Listing of Serious Adverse Events
Table 14.3.2.3	Listing of Adverse Events Leading to Discontinuation of Treatment
Table 14.3.2.4	Listing of Adverse Events Leading to Dose Modification
Listing 16.2.7.1	Adverse Events by Patient and MedDRA System Organ Class / Preferred Term
Listing 16.2.7.2	Adverse Events by MedDRA Preferred Term and Patient
Listing 16.2.7.3	Glossary of Adverse Event Verbatim Terms by MedDRA System Organ Class, Preferred Term, and Patient
Listing 16.2.7.4A	Injection Site Reactions: Part 1 – Assessments
Listing 16.2.7.4B	Injection Site Reactions: Part 2 – Patient Reported Reactions
Listing 16.2.7.4C	Injection Site Reactions: Part 3 – Observed Reactions

6.3.3. Laboratory Data

Clinical laboratory values will be reported in conventional International System of Units (SI) units.

Shift tables relative to the CTCAE grade and, for laboratory results not graded by the CTCAE, relative to the normal range, will be produced for hematology, chemistry, coagulation, and serum complement parameters.

Laboratory CTCAE grades shift from baseline to the worst grade post baseline over all visits (scheduled and unscheduled) will be tabulated using number and percentage of patients. Laboratory parameters that do not have CTCAE grades will be summarized by shift from baseline to the worst-case post baseline relative to the normal range (i.e. to highest increase and lowest decrease from baseline) for all visits (scheduled and unscheduled), again tabulated using number and percentage of patients.

All laboratory data will be listed, including serum complement data, urinalysis, serologic tests (for screening only), and pregnancy tests (females only). Abnormal laboratory values will be flagged and the CTCAE grade included.

Relevant Output:

Table 14.3.5.2A	Shifts from Baseline to Worst CTCAE Grade Post-Baseline in Hematology Parameters by Dose Group (Safety Population)
Table 14.3.5.2B	Shifts from Baseline to Worst CTCAE Grade Post-Baseline in Chemistry Parameters by Dose Group (Safety Population)
Table 14.3.5.2C	Shifts from Baseline to Worst CTCAE Grade Post-Baseline in Coagulation Parameters by Dose Group (Safety Population)
Table 14.3.5.3A	Shifts from Baseline to Lowest Decrease or Highest Increase Post-Baseline Relative to the Normal Range in Hematology Parameters by Dose Group (Safety Population)
Table 14.3.5.3B	Shifts from Baseline to Lowest Decrease or Highest Increase Post-Baseline Relative to the Normal Range in Chemistry Parameters by Dose Group (Safety Population)
Table 14.3.5.3C	Shifts from Baseline to Lowest Decrease or Highest Increase Post-Baseline Relative to the Normal Range in Coagulation Parameters by Dose Group (Safety Population)
Table 14.3.5.3D	Shifts from Baseline to Lowest Decrease or Highest Increase Post-Baseline Relative to the Normal Range in Serum Complement Parameters by Dose Group (Safety Population)
Listing 16.2.8.1A	Central Laboratory Results: Hematology
Listing 16.2.8.1B	Local Laboratory Results: Hematology
Listing 16.2.8.2A	Central Laboratory Results: Chemistry
Listing 16.2.8.2B	Local Laboratory Results: Chemistry
Listing 16.2.8.3A	Central Laboratory Results: Urinalysis
Listing 16.2.8.3B	Local Laboratory Results: Urinalysis
Listing 16.2.8.4A	Central Laboratory Results: Coagulation
Listing 16.2.8.4B	Local Laboratory Results: Coagulation
Listing 16.2.8.5	Central Laboratory Results: Serum Complement
Listing 16.2.8.6A	Central Laboratory Results: Serology
Listing 16.2.8.6B	Local Laboratory Results: Serology
Listing 16.2.8.7	Urine Pregnancy Test Results

6.3.4. Vital Signs

Bi-directional shift tables from baseline to worse value post-baseline relative to the normal range will be tabulated using number and percentage of patients, separately by increases or decreases in value for each parameter (i.e. to highest increase and lowest decrease from baseline). This summary will include values from unscheduled visits.

Vital sign measurements will be listed.

Relevant Output:

Table 14.3.5.4	Shifts from Baseline to Lowest Decrease or Highest Increase Post-Baseline Relative to the Normal Range for Vital Signs (Safety Population)

Listing 16.2.9.1 Vital Signs

6.3.5. Physical Examination

All physical examination findings and ECOG Performance Status will be listed.

Relevant Output:

Listing 16.2.9.2 Physical Examination Findings
Listing 16.2.9.3 ECOG Performance Status

6.3.6. Electrocardiogram

Electrocardiogram results will be summarized descriptively, including the number and percentage of patients with a QT interval corrected for heart rate using Fridericia's formula (QTcF) > 400 msec, > 450 msec, > 480 msec, and > 500 msec and increase from baseline QTcF of ≥ 30 msec and ≥ 60 msec. QTcF will be derived for all patients using the formula: QT/(RR^(1/3)), where RR = 60/heart rate if not collected separately.

All ECG data will be listed.

Relevant Output:

Table 14.3.5.5 Summary of Maximum QTc Interval Prolongation and Change from Baseline in QTc Interval (Safety Population)

Listing 16.2.9.4 12-Lead Electrocardiogram Interval and Overall Assessment

6.3.7. Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version Q12013 (or later).

Any medications that did not end prior to first dose will be classified as a concomitant medication, as well as medications that are ongoing or those missing an end date.

Concomitant medications will be listed.

Relevant Output:

Listing 16.2.9.5 Concomitant Medication

6.4. Efficacy Analyses

Best overall response, summarized by the number and percentage of patients in each best overall response category, will be presented using the Safety Population. No other efficacy analyses will be presented.

All efficacy data will be listed.

Relevant Output:

Table 14.2.1 Summary of Best Overall Response (Safety Population)

Listing 16.2.6.1 Disease Response
Listing 16.2.6.2 Tumor Assessment
Listing 16.2.6.3A Radiological Imaging: Part 1 – General Assessment
Listing 16.2.6.3B Radiological Imaging: Part 2 – Lesion Assessment
Listing 16.2.6.3C Radiological Imaging: Part 3 – Spleen and Liver Assessment
Listing 16.2.6.4 Bone Marrow Biopsy Results

6.5. Pharmacokinetic Analyses

All PK analyses will be conducted outside the scope of this analysis plan. Date and time of PK data collection will be listed.

Relevant Output

Listing 16.2.5.2 Pharmacokinetic Collection Dates

6.6. Pharmacodynamic Analyses

Pharmacodynamic collection dates and any corresponding results, including serum cytokine results, will be listed.

Relevant Output

Listing 16.2.5.3 Pharmacodynamic Collection Dates and Results
Listing 16.2.5.4 Serum Cytokines

7. CHANGES TO PLANNED ANALYSES

The protocol describes efficacy parameters for this study in Sections 1.8, 12.4, and 12.5. Due to the premature closure of the study, this document states that the only efficacy summary will be best overall response. No additional summaries of efficacy will be presented. Sections 1.8 and 12.3 of the protocol also describe time-to-event analyses for ISRs; this safety analysis is not included in this document.

Sections 1.8 and 12.2 of the protocol defines an Intent-to-treat/Safety Population. This population is renamed to "Safety Population" for this document, as described in Section 4.1. Section 12.2 of the protocol also describes a Per-Protocol and Efficacy Evaluable Population to be evaluated. Due to the limited enrollment in this study, and the lack of efficacy summaries, the Safety Population will be used for presentation of efficacy data.

If additional 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.

8. REFERENCES

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9. CLINICAL STUDY REPORT APPENDICES

9.1. Statistical Tables and Figures to be Generated

9.2. Data Listings to be Generated

10. REVISION HISTORY

Not applicable; this is the first draft of this document.