PAREXEL International

Idera Pharmaceuticals

Protocol Number: 84011-211

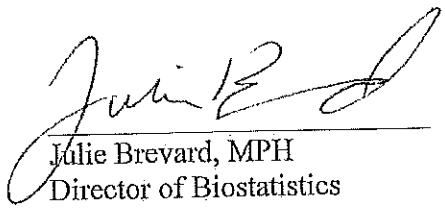
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial of IMO-8400 in Patients with Dermatomyositis

Statistical Analysis Plan

PAREXEL Project Number: 225244

SPONSOR SIGNATURE PAGE

Approved by:



Julie Brevard, MPH
Director of Biostatistics

26 APR 2018
Date

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LIST OF ABBREVIATIONS

10MWR	10-meter walk-run test
A:G ratio	albumin: globulin ratio
α	alpha
AE	adverse event(s)
ALD	Aldolase
ALT	alanine transaminase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
ATC	anatomic therapeutic class
BDR	Blind Data Review
C3	complement component 3
C4	complement component 4
CBC	complete blood count
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index
CH50	hemolytic complement activity
CI	confidence interval
CK	creatine kinase
Con Med	concomitant medications
CRO	clinical research organization
CRP	C-reactive protein
CSM	Core Set Measures
CSR	clinical study report
DM	Dermatomyositis
DMC	Data Monitoring Committee
DOI	definition of improvement
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
eDISH	evaluation of Drug Induced Serious Hepatotoxicity
EOS	End-of-Study
EOT	End-of-Treatment
ET	early termination
EP	European Pharmacopeia
FWER	family-wise error rate
HB	Hepatitis B
HC	Hepatitis C
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IMACS	International Myositis Assessment Clinical Study
INR	international normalized ratio
ISR	injection site reactions
IXRS	Interactive voice/web-response system

Kg	kilogram
LDH	lactate dehydrogenase
LLN	lower limit of normal
μ	mu (mean)
mCDASIv2	Modified CDASI version 2
MD	Myositis Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMT/MMT-8	Manual Muscle Testing
Mg	milligram
ml	milliliter
Ms	millisecond
PCS	Potentially Clinically Significant
PD	Pharmacodynamics
PDS	Protocol Deviation Specification
PK	Pharmacokinetics
PP	per protocol
PPD	purified protein derivative
PT	preferred term
QTcB	Corrected QT Interval Using Bazett's Formula
QTcF	Corrected QT Interval Using Fridericia's Formula
RBC	red blood cells
RMMM	repeated measures mixed model
SAE	serious adverse event
sAG	surface antigen
SAP	statistical analysis plan
SC	Subcutaneous
SD	standard deviation
SF-36	Short Form-36 Health Survey
SI	International System of Units
SOC	system organ class
SRM	Study Reference Manual
T4	Thyroxine
TB	Tuberculosis
TLR	toll-like receptor
TNFα	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
USP	United States Pharmacopeia
V	Visit
WBC	white blood cells
WHO	World Health Organization
WM	Waldenström's macroglobulinemia

1 INTRODUCTION

This statistical analysis plan (SAP) outlines the relevant analyses planned for data collected under Idera's clinical study protocol 8400-211. This is a phase 2, randomized, double blind, placebo-controlled clinical trial to assess the efficacy, safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), disease-specific autoantibodies, and immunogenicity of IMO-8400 in adult subjects with dermatomyositis (DM). The results of the analyses described herein will be summarized in the clinical study report.

DM is a rare, progressively debilitating, idiopathic inflammatory myopathy associated with significant morbidity and an increased risk of premature death. DM is a multisystem disorder with a wide variety of clinical manifestations including lung, joint, esophageal, and cardiac findings. Treatment for DM usually involves a combination of approaches with a focus on controlling the skin and muscle disease [1, 2].

Idera Pharmaceuticals, Inc. (Idera; Sponsor) is developing a subcutaneous (SC) formulation of IMO-8400, a novel synthetic phosphorothioate oligonucleotide antagonist to toll-like receptors (TLR) 7, 8, and 9, as a potential treatment for diseases in which TLR-mediated responses contribute to disease pathophysiology, including DM. Nonclinical studies using immune cells from mice, monkeys, and humans have confirmed IMO-8400's ability to selectively block the induction of pro-inflammatory cytokines and chemokines caused by administration of synthetic TLR7, TLR8, and TLR9 agonists.

[redacted] In summary, a total of 42 subjects have been exposed to IMO-8400 at dosages ≥0.6 mg/kg/week. As of 01 February 2016, 25 subjects have been exposed to IMO-8400 at 0.6 mg/kg/week, 5 subjects have been exposed to 1.2 mg/kg/week, and 12 subjects have been exposed to 2.4 mg/kg/week (divided as 1.2 mg/kg twice per week). Subjects have been exposed to IMO-8400 for up to 66 weeks with 12 subjects exposed for 24 weeks or longer at the following dosages: 0.6 mg/kg/week, 1.2 mg/kg/week, and 2.4 mg/kg/week (divided as 1.2 mg/kg/week). Patients with DM in this study will be given IMO-8400 at 0.6 or 1.8 mg/kg/week for 24 weeks.

This SAP is based upon the following study documents:

- Study Protocol, Version 5.0 (May 12, 2016)
- Electronic Case Report Form (eCRF), Version 3.0 (June 22, 2016)

2 STUDY OBJECTIVES

2.1 Primary

The primary objectives of this study are:

- To assess the safety and tolerability of IMO-8400 in adult subjects with DM with active skin and muscle disease
- To assess the effect of IMO-8400 on the cutaneous manifestations of DM

2.2 Exploratory

The exploratory objectives of this study are:

- To investigate associations between the treatment effect of IMO-8400 on indices of disease activity, patient-reported outcomes, and pharmacodynamics measures
- To assess the immunogenicity of IMO-8400
- To assess plasma concentrations of IMO-8400 over time
- To characterize the enrolled population based on disease-specific autoantibody profiles for potential subgroup analyses

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a 24-week Phase 2 randomized, placebo-controlled, double-blind, multi-center trial of IMO-8400 in adult subjects with DM who have documented active skin and muscle involvement. The trial is designed to assess the safety, tolerability, and treatment effect of IMO-8400 in these subjects.

IMO-8400 for Injection will be supplied as a sterile, lyophilized powder with Sterile Saline for Injection, United States Pharmacopeia (USP)/European Pharmacopeia (EP). The assigned dose of IMO-8400 will be administered as a single SC injection in the 4 quadrants of the abdomen. Injection site will be rotated with each injection. The total volume of the subject's dose will be based on their body weight at the most recent prior clinic study visit but may not exceed 1 ml (upper limit of subject weight is 140 kg).

Detailed study inclusion and exclusion criteria are given in the protocol.

Approximately 36 patients will be randomized to the three following cohorts in a 1:1:1 ratio:

- Once weekly SC injections of placebo (Sterile Saline for Injection, USP/EP)
- Once weekly SC injections of IMO-8400 at 0.6 mg/kg
- Once weekly SC injections of IMO-8400 at 1.8 mg/kg

Note: Patients enrolled under Protocol Version 3.0 who wish to remain on study must re-consent to follow all study procedures as defined by Version 5.0 of the study protocol (no patients were enrolled under Protocol Version 4.0); however, they must remain on the treatment assignment defined by Version 3.0 of the protocol.

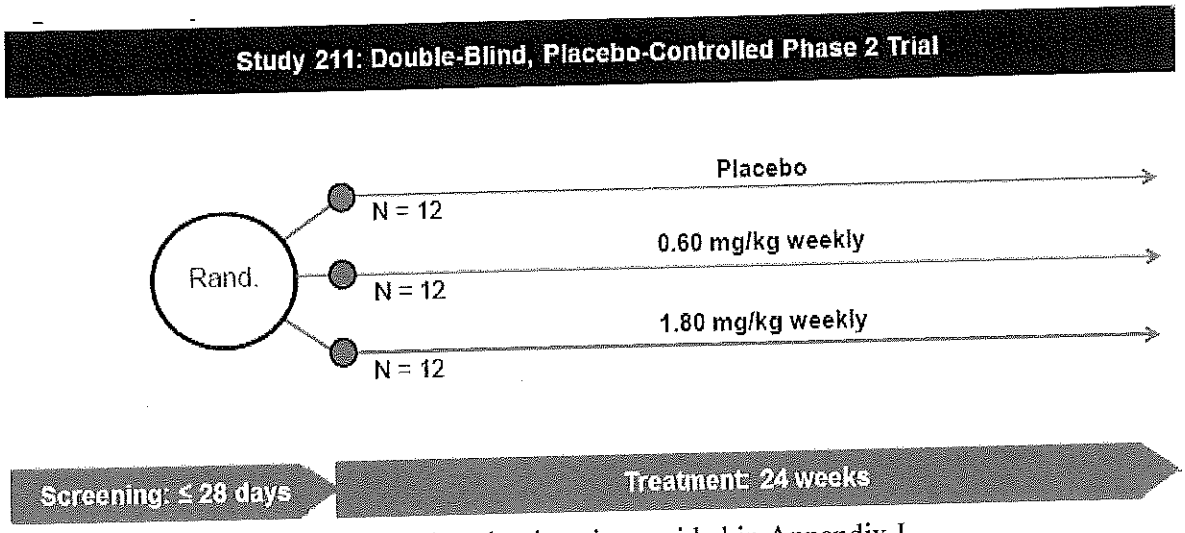
The study will be conducted at approximately 20 centers. Randomization will be performed centrally via an interactive voice/web-response system (IXRS). A permuted block randomization schedule will be employed. Blocks will be pre-allocated to the two CDASIv2-Activity strata (15 to 20 vs. $\geq$21) to achieve a balanced distribution of treatment assignments within those strata.

Study subjects, Investigators, and other site personnel will remain blinded to treatment assignment until the last subject to complete the study has either completed their end of study (EOS) assessments for Study 8400-211, and the database is locked, or has enrolled in an extension study if one is initiated.

The length of a subject's participation will be from the time the informed consent form is signed until their last visit is complete and will be approximately 33 weeks, including screening up to 28 days prior to treatment, 24 weeks of study drug, an End-of-Treatment (EOT) Visit at 7 days $\pm$ 2 days after the last dose of study drug and an End-of-Study (EOS) Visit for safety follow-up 4 weeks after the EOT Visit.

The study scheme is shown below in Figure 1.

Figure 1: Study Schematic



A schedule of study procedures and evaluations is provided in Appendix I.

3.2 Efficacy and Safety Variables

3.2.1 Primary Endpoints

3.2.1.1 Primary Efficacy Endpoint

- Change from baseline in mCDASIv2-Activity score as measured at Visits 2, 6, 10, 14, 18, 22 and 26 (EOT/ Week 25)

3.2.1.2 Primary Safety and Tolerability Endpoints

- Incidence of treatment-emergent adverse events (any, special interest, serious, leading to withdrawal, treatment-related and leading to death), recorded in an ongoing way throughout the duration of the study
- Observed and change from baseline in clinical laboratory parameters (hematology, chemistry, coagulation and urinalysis), as measured at Visits 1, 2, 6, 10, 14 ,18, 22, 26, and 27 (EOS/Week 29)
- Incidence of injection site reactions (ISR) by type, anatomic location, and overall, as measured at each visit beginning with the first dose administration
- Observed and change in electrocardiogram (ECG) parameters (heart rate, RR interval, PR interval, QRS interval, QT [uncorrected] interval, QTcB [Bazett's correction] interval and QTcF [Fridericia's correction] interval), as measured at Visits 1, 2, 6, 10, 14 ,18, 22, 26, and 27 (EOS/Week 29)
- Number and percentage of subjects exceeding thresholds based on International Council for Harmonisation (ICH) E14 [4] {HR (≥ 100) and QTcB/QTcF (>450, > 480, > 500)}, as measured at Visits 1, 2, 6, 10, 14, 18, 22, 26, and 27 (EOS/Week 29)

- Observed and change from baseline in laboratory safety assessments including hemolytic complement activity (CH50), complement component 3 (C3), complement component 4 (C4), troponin, C-reactive protein (CRP), albumin:globulin (A:G) ratio, proteinuria, estimated glomerular filtration rate (eGFR), and platelets, as measured at Visits 1, 2, 6, 10, 14, 18, 22, 26, and 27 (EOS/Week 29)
- Observed and change in vital signs, as measured at Visits 1, 2, 6, 10, 14 ,18, 22, 26, and 27 (EOS/Week 29)
- Incidence of usage of concomitant medications, recorded in an ongoing way throughout the duration of the study
- Pregnancy test results, as measured at Visits 1, 2, 6, 10, 14, 18, 22, 26, and 27 (EOS/Week 29)
- Physical examination results, as measured at Visits 1, 2, 6, 10, 14 ,18, 22, 26, and 27 (EOS/Week 29)

3.2.2 Exploratory Endpoints

3.2.2.1 Exploratory Efficacy Endpoints

- Change from baseline in IMACS Core Set Measures (CSMs) listed below, as measured at Visits 2, 6, 10, 14, 18, 22 and 26 (EOT/Week 25). Improvement will be also assessed using the 2004 IMACS group definitions of improvement (DOIs).
  - Manual Muscle Testing-8 (MMT8)
  - Serum creatine kinase (CK), aldolase (ALD), lactate dehydrogenase (LDH), alanine transaminase (ALT) and aspartate transaminase (AST)
- Change from baseline in the following Timed Function Tests, as measured at Visits 2, 6, 10, 14, 18, 22 and 26 (EOT/Week 25):
  - 10-meter walk-run test (10MWR)
  - Timed up and go test (TUG)
  - 4-stair climb test
- Change from baseline in the Short Form-36 Health Survey (SF-36), as measured at Visits 2, 10, 18 and 26 (EOT/Week 25):
  - Change from baseline in the SF-36 physical component summary score transformed using general US population norms
  - Change from baseline in the SF-36 mental component summary score transformed using general US population norms
- Change from baseline in the 5-D Itch Scale score, as measured at Visits 2, 6, 10, 14, 18, 22 and 26 (EOT/Week 25)

3.2.2.2 Pharmacokinetic Endpoints

- IMO-8400 plasma concentrations will be measured at pre-dose and 2 hours (± 15 minutes) post-dose to confirm systemic exposure. The PK parameters will be calculated from the plasma concentrations of IMO-8400 using non-compartmental analysis. The required PK parameters, as listed in section 4.9.1, are measured at Visits 2, 6, 14, 22 and 26 (Week 25)

3.2.2.3 Pharmacodynamic Endpoints

Note: the following analyses may be reported separately from the final Clinical Study Report (CSR).

- Change from baseline in Type 1 and Type 2 Interferon (IFN) gene expression signature using (a) whole blood and (b) skin biopsy, as measured at Visits 2, 6, 14, 22 and 26 (EOT/Week 25)
- Change from baseline in histology results, using skin biopsies, as measured at Visits 2 and 26 (EOT/Week 25)
- Change from baseline in DM relevant cytokines/chemokine levels including IL-6, IL-8, IP-10, I-TAC, MCP-1, MCP-2, and TNFα, as measured at Visits 2, 6, 14, 22 and 26 (EOT/Week 25); additional or alternative cytokines or chemokines may be assessed

3.2.2.4 Disease-specific Autoantibody Endpoint

- Presence of disease-specific autoantibodies at baseline and change from baseline in presence of autoantibodies associated with idiopathic inflammatory myopathies including, but not necessarily limited to, the following: anti-MDA-5, anti-Mi-2, anti-TIF1γ, anti-NXP2, anti-SAE1, anti-SAA 60, anti-Ro/SSA 52, anti-SSB/La, anti-Sm, anti-RNP, anti-Scl-70, anti-ribosomal-P, anti-chromatin, anti-Jo-1, anti-PL-7, and anti-PL-12 Note: only baseline autoantibody results will be reported in the CSR

3.2.2.5 Immunogenicity Endpoint

- Change from baseline presence of antibodies to IMO-8400 and anti-dsDNA, as measured at Visits 2, 6, 14, 22 26 and 27 (EOS/Week 29)

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

4.2 General Presentation Considerations

This section describes the analysis and data conventions that will be utilized for this study. All statistical analyses and summary information are to be generated according to this SAP. Any deviations from this SAP will be documented in the clinical study report.

4.2.1 General Definitions

'Baseline' is defined as the assessment which takes place during Visit 2/Week 1 Day 1, the last pre-treatment assessment. If a Visit 2/Week 1 assessment for a variable is missing then its Baseline value is the value from the last pre-treatment assessment prior to Visit 2/Week 1, Day 1.

4.2.2 Visit Windows

All visits during the treatment period of the study may have a visit window of ± 2 days. There must be at least 5 days between doses.

Assessments will be classified based on the visit information reflected on the eCRF. Assessments taken outside of protocol allowable windows will be displayed according to the nominal visit. If a subject withdraws early from the study, all efficacy and safety assessments captured at the early termination (ET) visit will be assigned to the next corresponding scheduled visit.

All subjects will complete end of treatment (EOT) assessments at Visit 26/Week 25 or, for subjects who discontinue study drug prematurely, an ET visit within 5 days of the decision to terminate; EOT and ET assessments are the same.

If an extension study for this trial is initiated, with Investigator approval, subjects who successfully complete this study may be eligible to continue receiving treatment with IMO-8400 (or for subjects randomized to placebo in this study, initiate treatment with IMO-8400). Signed informed consent for participation in any extension study will be obtained prior to assessments and extension study dosing at EOT Visit 26/Week 25.

All subjects who discontinue study drug prematurely or decline participation in an open-label IMO-8400 extension study must return for an EOS Visit 27/Week 29 at the investigational site 4 weeks (± 4 days) after completing EOT/ET assessments for final study-related evaluations.

Unscheduled visits and assessments may be conducted at Investigator discretion in response to new clinical observations or as follow-up to AEs. Unscheduled assessment, both efficacy and safety assessment, will be allocated to a scheduled visit according to visit window in Appendix IV. When both scheduled and unscheduled assessments exist in a specific visit window, the unscheduled assessment remains as unscheduled. When only unscheduled assessment exists in a specific visit window without scheduled assessment, the unscheduled assessment will be

assigned as scheduled assessment for analysis. Scheduled assessment will be included in the by visit analysis.

4.2.3 Presentation of Descriptive and Inferential Statistics

Continuous endpoints will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. In addition, geometric mean and the coefficient of variation (%CV) for geometric mean will also be calculated for $AUC_{0\text{-}inf}$, AUC_{last}, and C_{max}. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical endpoints will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n (the number of subjects providing data at the relevant time point) as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

The actual value and change from baseline of laboratory results for hematology, chemistry, urinalysis and coagulation and safety laboratory tests will be summarized using descriptive statistics by treatment group and visit. Shift tables will also be produced, comparing the category at baseline for each parameter (low, normal, high) to the worst value post-baseline. All laboratory test results will be listed, and values will be flagged that are above or below the normal range, and those judged by the Investigator to be clinically significant will also be flagged.

P-values greater than or equal to 0.001 will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001". Confidence interval limits and/or limits will be presented to one more decimal place than the raw data.

All report outputs will be produced using SAS® version 9.3 or a later version in a secure and validated environment. All report outputs will be provided to the Sponsor in a single Adobe PDF file. The PDF file will include a hyperlinked table of contents and hyperlinked bookmarks for ease of navigation.

4.3 Study Subjects

4.3.1 Disposition of Subjects

The following subject data will be presented by treatment group, including overall categories:

- The number of subjects screened (overall only)
- The number of subjects randomized

- The number of subjects treated
- The number and percentage of subjects who completed study (i.e., subject status recorded on Study Completion or Discontinuation CRF page as "Subject Completed")
- The number and percentage of subjects who discontinue study by primary reason

Number of subjects randomized will be presented by country, treatment group, site, and overall. Percentages of subjects will be based on the number of subjects randomized as 100%.

A listing will be provided for randomized subjects sorted by treatment group, site and subject. In addition, by-subject listings will be provided for subjects who discontinued the study early (post-randomization). The listing will display the reason for study discontinuation.

4.3.2 Protocol Deviations

Protocol deviations will be identified on an ongoing basis by the clinical study team based on the protocol deviation specification (PDS) document and assessed as "minor" or "major" in consultation with the Sponsor.

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. The impact of major protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis population (see Section 4.4), both including and excluding data potentially affected by major protocol deviations.

Details on major and minor protocol deviations, along with actions to be taken for analysis, can be found in the Protocol Deviation Specification. Other possible major deviations may be identified during the Blind Data Review (BDR) meetings.

Protocol deviations will be provided in a listing sorted by treatment group, site and subject. Major protocol deviations will also be summarized by treatment group.

4.3.3 Maintaining the Blind

A double-blind technique will be used. Study drug will be identical in appearance and will be packaged identically so that treatment blind is maintained. Neither the subject nor the investigational staff (Sponsor, Investigator, and evaluators) will know which treatment a subject is receiving.

All subjects who are screened (including screen failures) will be assigned a subject number by the Interactive voice/web-Response System (IXRS). The unique subject identification number will consist of 6-digits (XXX-XXX), with the first segment of the number representing the study site and the second segment of the number representing the subject at that study site. Any subject identification number that is assigned will not be reused even if the subject is not randomized.

Once a patient has met all eligibility criteria, the site representative should access the IXRS system and supply the necessary information to obtain a patient treatment assignment in anticipation of administration of the first dose of study drug at the Baseline Visit 2/Week 1, Day 1.

The blinding of efficacy assessor to potential injection site reactions requires the CDASI to be modified (mCDASIv2), eliminating the abdominal skin assessment from the overall score. Since SC administration of IMO-8400 has been associated with injection site reactions (ISRs) which may be potentially unblinding, skin activity assessments, manual muscle testing and timed function tests will be performed by qualified and trained raters who will be blinded to treatment assignment and study drug injection sites and who will have no other role or responsibility in the study beyond administering efficacy assessments. Subjects will also be asked to wear clothing that covers injection sites whenever attending study site visits.

In the event of a medical emergency, laboratory abnormalities or a serious adverse event (SAE) requiring cessation of treatment, unblinding is not required to provide effective medical intervention and support.

In the exceptional circumstance that knowledge of the study drug assignment appears essential for providing appropriate medical management, the Investigator and clinical research organization (CRO) medical monitor should discuss the rationale for breaking the blind and the adverse consequences of the unblinding for the subject's continued participation in the study. If the Investigator and CRO medical monitor believe that unblinding is warranted, the treatment assignment for that subject will be provided to the Investigator via the IXRS as described in the Study Reference Manual (SRM). No randomization lists or other unblinding information will be provided to the site.

After breaking the blind, the site staff should record details regarding the reasons for breaking the blind and any AEs leading to the breaking of the blind in the source documents and the appropriate eCRF.

4.4 Analysis Populations

Three populations are defined for the analyses:

- Modified Intent-to-Treat (mITT) population: All subjects who were randomized into the study and who received at least 1 injection of study medication. Subjects will be analyzed as randomized.
- Per-protocol (PP) population: All subjects belonging to the mITT Population who:
  - received at least 20 injections of study medication as assigned,
  - completed the EOT Visit 26/Week 25, and
  - had no major protocol violations that would potentially influence treatment effect (as determined by the Sponsor prior to unblinding).
- Safety population: All randomized subjects who received at least 1 injection of study medication. Subjects will be analyzed as treated.

For any patient enrolled into the study following Protocol Version 3.0 who was randomized to the placebo group or the 0.6 mg/kg IMO-8400 treatment group, assessment results will be presented in the tables, listings, and figures. However, if a patient was randomized into the 0.06 mg/kg or 0.20 mg/kg IMO-8400 treatment groups, the results will only be presented in the listings, and not summarized in tables and figures.

The efficacy, PD, disease-specific autoantibody, and immunogenicity assessments summaries and analyses will be based on the mITT population. The primary efficacy analysis will be repeated using the PP population. Exploratory efficacy analyses may also be repeated using the PP population. The safety summaries and analyses will be based on the Safety Population.

Protocol deviation and analysis population outputs will be produced and sent to Idera for review on a periodic basis. Prior to unblinding, an analysis population classification meeting will be arranged to discuss the protocol deviation listing and to decide which subjects and/or subject data will be excluded from certain analyses. Decisions made regarding the exclusion of subjects and/or subject data from analyses will be made prior to unblinding and will be documented and approved by the Sponsor.

The number and percentage of subjects in each analysis population will be presented by treatment group and overall.

In addition, a by-subject listing of analysis population details will be provided. This listing will be presented by treatment group and will include: center, subject identifier, inclusion/exclusion flag for each population and reason for exclusion from each population.

Table 1 below provides an overview of the analysis population to be used for each of the analyses.

Table 1. Summary of Analyses by Analysis Population

Analysis	Modified Intent-to-Treat	Safety	Per Protocol
Subject Evaluability and Disposition	✓		
Time to Study Discontinuation	✓		
Protocol Deviations	✓		
Demographics	✓		
Baseline Characteristics	✓		
Medical History	✓		
Primary Efficacy Endpoint	✓		✓
Exploratory Efficacy Endpoints	✓		
PD Endpoints	✓		
Disease-Specific Antibodies	✓		
Immunogenicity	✓		
PK Endpoints		✓	
Treatment Compliance / Dosing Information		✓	
Drug Exposure		✓	
AEs		✓	

Laboratory Parameters		✓	
Vital Signs		✓	
ECG		✓	
Concomitant Medications		✓	
Injection Site Reactions		✓	

4.5 Demographics, Baseline Characteristics and Baseline Disease Characteristics

Demographic and baseline characteristics data that will be summarized include age, sex, race, ethnicity, weight collected at Screening Visit (or Baseline Visit, if unavailable), height collected at Screening Visit (or Baseline Visit, if unavailable), and BMI calculated using weight and height from Screening Visit (or Baseline Visit, if unavailable). Baseline disease characteristics that will be summarized include baseline overall score for selected IMACS CSMs (MMT-8, serum muscle enzymes), baseline Timed Function Tests (TFTs), baseline 5-D Itch Scale, baseline CDASIv2-Activity Score category (15-20, ≥21), and baseline CDASIv2-Activity score. Subject demographics, baseline characteristics, and baseline disease characteristics will be summarized descriptively by treatment group for each country and all countries combined.

Separate listings of demographic data, baseline characteristics, and baseline disease characteristics will be presented sorted by treatment group, site and subjects.

For general medical history, all relevant medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 18.0) and summarized by system organ class (SOC), preferred term (PT) and treatment group, and an overall by-subject listing will also be provided. As part of the patient's medical history, documented evidence of cancer and tuberculosis screening are required.

4.6 Treatment Compliance and Exposure

4.6.1 Treatment Compliance

Treatment compliance will be assessed via compliance with scheduled weekly injections and documented on appropriate pages of the eCRF.

A subject is evaluated as compliant if the subject has received 80% to 105% of the expected 24 injections of the study drug. The number of injections administered, compliance rate and proportion of subjects considered as compliant will be summarized by treatment group.

The number of missed injections will be tabulated using the categories >= 22 doses, >= 20 to < 22 doses, >= 15 to < 20 doses, >= 10 to < 15 doses, >= 5 to < 10 doses and presented by treatment group.

4.6.2 Treatment Exposure

Study drug exposure will be tabulated as the number of injections of the study drug. Summary statistics for study drug exposure (i.e. total dose administered, total dose taken) will be presented by treatment group.

Total dose administered will be calculated by summing (Dose assigned*kg at visit) across all visits in which the subject was on treatment.

Treatment exposure and treatment compliance measures will be listed by subject within each treatment group.

4.6.3 Prior and Concomitant Medications

Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as Prior only, Prior and Concomitant, or Concomitant only. Medications starting after the study treatment withdrawal date will be classified and summarized, as well.

Medications that start and stop prior to the date of first dose of study medication will be classified as "Prior Only". Medications will be classified as "Concomitant Only" if they have a start and end date on or after the date of first dose of study medication. Medications that start before the date of first dose of study medication and end on or after the date of first dose of study medication will be classified as "Prior and Concomitant." Medication starts after last dose of study medication will be classified as "After Study Withdraw".

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be both Prior and Concomitant. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Dec 2014). Results will be tabulated by anatomic therapeutic class (ATC) and preferred term (PT).

Any medication 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 the end date. In case of repeated occurrences per subject, a medication will only be counted once per ATC Level 3/PT.

Medication use, including medication started after withdrawal date, will be summarized by ATC Level 3 term and PT for each treatment group. In addition to displaying the number and percentage of subjects who used each medication, a count of the total number of subjects receiving any medication for each treatment group will be included.

A listing of prior only, prior and concomitant, and concomitant only, medications will be provided sorted by treatment group, site and subject. A similar listing will be presented for medications started after completion/withdrawal date.

4.7 Efficacy Evaluation

4.7.1 Analysis and Data Conventions

This study is designed to test for superiority of each of the two IMO-8400 treatment group versus the placebo. For each IMO-8400 treatment group, the null hypothesis will be that there is no difference between the given IMO-8400 injection and placebo injection in mean mCDASIv2-Activity score. Symbolically, this is expressed as follows:

$$H_{i(0)}: \mu_i \text{ (IMO-8400 treatment group)} = \mu_0 \text{ (placebo group)}$$

$$H_{i(1)}: \mu_i \text{ (IMO-8400 treatment group)} \neq \mu_0 \text{ (placebo group)}$$

where i=0.6 mg/kg IMO-8400 treatment group or 1.8 mg/kg IMO-8400 treatment group, μ_i represents the mean mCDASIv2-Activity score for the IMO-8400 treatment group i, and μ_0 represents that for the placebo group.

For the primary efficacy analysis, a one-sided test will be performed with alpha set at 0.05. The overall alpha level will be controlled at 0.05 one-sided using the Bonferroni-Holm step-down method.

4.7.1.1 Multi-center Study

This is a multiple site/center study conducted under a single protocol. All data collected from participating centers will be monitored and reviewed according to a common set of guidelines and standard operating procedures.

4.7.1.2 Adjustments for Covariates

An overview of covariates to be used for each efficacy analysis is provided below.

Table 2. Parameterization of Efficacy Analysis Models

Dependent Variable	Covariates
Primary Analysis: mCDASIv2-Activity score across visits – mITT set	Baseline CDASIv2-Activity score, treatment group, visit week, treatment group*visit week
Sensitivity Analyses: mCDASIv2 Activity Score across visits – mITT set	All models: Baseline CDASIv2-Activity score, treatment group, visit week, treatment group*visit week, Unique: high steroid use at baseline, use of immune-modulating therapies at baseline, gender, ethnicity, baseline age, DM-associated

	antibody at baseline, baseline CDASIv2-Damage score, baseline serum CK, baseline MMT-8
Supportive analysis: Proportion of mCDASv2-Activity score responder – mITT Set	Baseline CDASIv2-Activity score, treatment group, visit week, treatment group*visit week
Supportive analysis: mCDASv2-Activity score across visits – PP set	Baseline CDASIv2-Activity score, treatment group, visit week, treatment group*visit week
MMT8 Score across visits – mITT Set	Baseline MMT8 Score, treatment group, visit week, treatment group*visit week
Completion time of 10MWR Test across visits – mITT Set	Baseline completion time of 10MWR Test, treatment group, visit week, treatment group*visit week
Completion time of TUG across visits – mITT Set	Baseline completion time of TUG, treatment group, visit week, treatment group*visit week
Completion time of 4 stair climb test across visits – mITT set	Baseline completion time of 4 stair climb, treatment group, visit week, treatment group*visit week
Serum CK across visits– mITT Set	Baseline Serum CK, treatment group, visit week, treatment group*visit week
Serum ALD across visits – mITT Set	Baseline Serum ALD, treatment group, visit week, treatment group*visit week
Serum LDH across visits – mITT Set	Baseline Serum LDH, treatment group, visit week, treatment group*visit week
Serum ALT across visits – mITT Set	Baseline Serum ALT, treatment group, visit week, treatment group*visit week
Serum AST across visits – mITT Set	Baseline Serum AST, treatment group, visit week, treatment group*visit week
SF-36 physical summary score across visits –	Baseline SF-36 physical summary score, treatment group, visit week, treatment

mITT Set	group*visit week
SF-36 mental summary score – mITT Set	Baseline SF-36 mental summary score, treatment group, visit week, treatment group*visit week
5-D Itch Scale score across visits – mITT Set	Baseline 5-D Itch Scale score, treatment group, visit week, treatment group*visit week

4.7.1.3 Handling of Dropouts or Missing Data

No imputation will be used for any missing data.

For variables that have composite scores, such as the MMT-8, a minimum of 50% of the components need to be non-missing for inclusion in analyses. In the event of missing subscores, total scores may be computed using the non-missing data and then weighting the score based off the number of components that were non-missing.

SF-36 scores will be calculated by OPTUM™.

The number and percentage of subjects with missing data for the primary endpoint will be summarized by treatment group and overall. If missing data is determined to be an issue at BDR, use of imputation methods will be explored. Details of the methods will be provided prior to database lock.

4.7.1.4 Multiple Comparisons/Multiplicity

One primary efficacy variable has been defined for this study, along with two treatment contrasts: 0.6 mg/kg IMO-8400 vs. placebo, and 1.8 mg/kg IMO-8400 vs. placebo. The other efficacy variables defined are intended to provide supportive evidence relating to the primary objective.

The Bonferroni-Holm step-down method will be used to adjust for multiple comparisons in the primary efficacy analyses. This method is a closed testing procedure and ensures that the family wise error rate (FWER) is controlled to be <= α for any subset of null hypotheses in the family. For this study the family wise error rate (FWER) is α=0.05, since the hypotheses are one-sided superiority hypotheses.

Using the Bonferroni-Holm step-down method, one-sided p-values of p_1, *and* p_2 are first determined, corresponding to the two null hypotheses $H_{i(0)}$ where i=0.6 mg/kg IMO-8400 treatment group or 1.8 mg/kg IMO-8400 treatment group. These p-values will then be sorted from lowest to highest, $p_{(1)} \leq p_{(2)}$ with associated null hypotheses being $H_{1(0)}$ and $H_{2(0)}$, respectively.

The significance of the hypotheses will be evaluated sequentially, consistent with the following rules: First, the null hypothesis $H_{1(0)}$ will be tested at $\alpha = 0.05/2 = 0.025$. If $p_{(1)} \geq 0.025$, then the hypothesis testing stops and none of the 2 hypotheses are rejected. It is concluded that, based upon data from this study, it is not reasonable to believe that any of the 2 treatments groups are superior to placebo.

If $p_{(1)} < 0.025$, then hypothesis $H_{1(0)}$ is rejected and the conclusion made that the associated treatment group is superior to placebo. Next, $H_{2(0)}$ alone will be evaluated for significance at $\alpha=0.05$.

Formally, this can be stated as follows:

For each step k = 1, 2, …, m in the sequentially rejective Holm's step down procedure:

- Let $p_{(k)}$ represent the p value with the minimal index for which $p_{(k)} > (\alpha) / (m - k +1)$ where α refers to the desired Type I error rate, and "m" represents the number of hypotheses to be tested;
- The hypotheses associated with $p_{(1)} \cdots p_{(k-1)}$ will be rejected, while those associated with $p_{(k)} \cdots p_{(m)}$ will not be rejected.

4.7.1.5 Handling of Outliers

Potential outliers detected during the review of the data, including extra assessments, will be investigated. Markedly abnormal laboratory results will be reported. Frequency and percentage of outlying values for the observed and baseline adjusted corrected and uncorrected QT parameters will be presented.

Identified outliers from safety assessment will be re-examined carefully for clinical relevance. If a subject has multiple records associated with a given visit, then only the first recorded observation to fall within the visit window will be included in the analysis. All records will be provided in listings.

4.7.1.6 Interim Analyses

There is no interim analysis for this study.

4.7.1.7 Examination of Subgroups

- Subgroups of interest will be explored by presenting treatment effect for each level of the subgroup, both in tabular and graphical forms. These subgroups will be selected via the sensitivity analysis, by identifying the covariate/s that had a test statistic p-value of <0.20 in the unique RMMM models described in section 4.7.2.3

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4.7.2 Primary Efficacy Variable

4.7.2.1 Definition

The primary variable for the assessment of efficacy is the change from Baseline in mCDASIv2-Activity score, as measured at Visits 2, 6, 10, 14, 18, 22 and 26 (EOT/Week 25).

The CDASIv2 is a clinician administered, one-page instrument designed to evaluate the cutaneous manifestations of DM (See # 1 in Appendix III). It includes separate measurements for disease activity and damage and yields a Total Score that captures overall disease state, an Activity Score that reflects the current inflammatory state of disease, and a Damage Score. Decreases in CDASI scores are indicative of improvement.

The CDASIv2-Activity is scored as follows: Across 15 anatomical locations, trained raters score the most severely affected DM skin lesion for:

- erythema (0 indicating absent, 1 indicating pink to 3, indicating dark red),
- scale (from 0, indicating absent, to 2, indicating lichenification), and
- erosion/ ulceration (0, indicating absent or 1, indicating present).

In addition, raters must assess a subject's hands, periungual changes, and presence of alopecia. The CDASIv2-Activity score can range from 0-100. For the CDASIv2-Damage Score, raters assess the presence of calcinosis and poikiloderma across the aforementioned anatomical locations. Scores can range from 0-32. Effectively, the total CDASIv2 score can range from 0-132. An improvement (i.e., decrease) in CDASI-Activity scores of 4 or 5 points in the CDASI-Activity Score is considered indicative of a clinically significant change [6, 7, 8, 9].

As discussed in section 3.1 and 4.3.3, this study will use the modified CDASIv2 (mCDASIv2)-Activity Score for post-baseline assessments, which excludes abdominal assessments. For the mCDASIv2, the Activity score can range from 0-94.

4.7.2.2 Analysis Methods

The mCDASIv2-Activity score will be summarized by treatment group and visit in terms of absolute values and changes from baseline. In addition, the least squared mean of mCDASIv2-Activity score with corresponding 90% CI will be estimated for each visit by treatment group and overall. The LS mean changes from baseline (90% CI) by treatment group will also be estimated.

A plot showing the median mCDASIv2-Activity score and change from baseline over time within each treatment group will be provided. The LS mean changes from baseline (90% CI) will be plotted by treatment group.

The primary efficacy endpoint will be assessed via a repeated measures mixed model (RMMM), using the mCDASIv2-Activity score as the dependent variable and treatment group, visit week, treatment group by time interaction, and baseline CDASIv2-Activity score as independent variables in the model. Subject will be modeled as a random effect, when applicable.

The structure of the model is as follows:

$$Y_{ijk} = \theta_0 \cdot y_{ij0} + T_i + V_k + TV_{ik} + s_{ij} + e_{ijk}$$

where

Y_{ijk} is the mCDASIv2-Activity score for the j^{th} subject of treatment group i at visit week k

y_{ij0} is the baseline CDASIv2-Activity score for the j^{th} subject of treatment group i

θ_0 is the unknown fixed slope for the baseline CDASIv2-Activity score

T_i is the unknown fixed effect of treatment group i

V_k is the unknown fixed effect of visit week k

TV_{ik} is the unknown fixed interaction effect of treatment group i and visit week k

s_{ij} is the random effect associated with the j^{th} subject of treatment group i

e_{ijk} is the error term for the j^{th} subject of treatment group i at visit week k

The covariance matrix for e is chosen to be block diagonal (with each block corresponding to a subject) with unstructured non-zero block diagonal elements as defaults. The spatial power law structure (which is a generalization of the autoregressive order one structure for unequally spaced data) will also be evaluated as a covariance structure. Akaike's Information Criteria (AIC) will be used to select the final covariance structure; the model with the smaller AIC will be used. If both the unstructured covariance matrix and spatial power law structure covariance matrix result in a lack of convergence, the autoregressive (1) covariance structure, followed by compound symmetry, will be used.

The Kenward-Roger approximation for the denominator degrees of freedom will be used. The p-values will be reported for the fixed effects. The least squared mean of mCDASIv2-Activity score with corresponding 90% CI will be estimated for each visit by treatment group and overall.

Pairwise contrasts of the least squares means will be performed between each IMO-8400 treatment group vs placebo. One sided p-values will be reported for each hypothesis test. The family-wise error rate will be controlled at 0.05, through the utilization of the Bonferroni-Holm step-down procedure, as discussed in section 4.7.1.4

The assumption of normality underlying the statistical model will be tested using the Shapiro-Wilk test. A p-value less than 0.05 will be taken to indicate evidence of non-normality. In addition, a normal probability plot of the studentized residuals will be used to investigate the normality assumption.

The assumption of homogeneity of variance of the treatment groups will be tested using Levene's test. A p-value less than 0.05 will be taken to indicate evidence of heterogeneity of variance.

If the assumptions of normality and/or homogeneity of variance underlying the statistical model are violated, the RMMM will instead be performed using rank transformed data. The treatment effect will be estimated using Hodges-Lehmann estimate of the difference in medians and corresponding 90% CI. The p-value from the hypothesis test of no difference in mCDASI-v2 Activity score between the IMO-8400 treatment group and placebo group will be presented.

A by-subject listing of the primary efficacy data will be provided, sorted by treatment group.

4.7.2.3 Sensitivity Analysis

Sensitivity analyses will be performed to test the effect of important covariates on the effect of IMO-8400. A set of RMMM's will be created using the factors described in section 4.7.2.2, along with one of the following covariates added to each unique model:high steroid use at baseline, use of immune-modulating therapies at baseline,, gender, ethnicity, age at baseline, DM-associated antibody at baseline, CDASI damage score at baseline, baseline serum CK, and MMT-8 at baseline. For each model, the estimated treatment effect, along with a 95% CI and nominal p-value, will be presented.

In addition, a single full RMMM, including the factors from section 4.7.2.2 and the ones mentioned in the above paragraph, will be created. Factors in the above paragraph will be included in the full model if p-value <0.20 in each unique model. Stepwise regression will performed to identify these covariates (i.e. those which yield a p-value < 0.20)

4.7.2.4 Supportive Analyses

The following supportive analyses will be performed:

- The primary analysis for the primary endpoint will be repeated for the per protocol population.
- To explore the proportion of subjects who responded (improvement of at least 4 points in mCDASIv2-Activity Score), a logistic regression model will be run, which will include baseline CDASIv2-Activity Score, treatment group as main effects. The proportion of subjects who responded will be presented by treatment group and visit. The odds ratios of response for each of the IMO-8400 treatment group vs. placebo group, along with 95% CI and nominal p-value, will be presented for each visit as well. In the event that the regression model fails to meet convergence criteria due to small-sample bias, alternate method such as Fisher's exact test may be utilized instead.

4.7.3 Exploratory Efficacy Variables

4.7.3.1 Efficacy Endpoint Utilizing Responder Definition

- Proportion of subjects who meet the IMACS 2004 DOI at EOT, using change from baseline in MMT-8 score and muscle enzymes.

Per IMACs, an increase from baseline in at least 2 of the following muscle enzymes is associated with a clinical improvement in DM: CK, LDH, AST, ALT, or ALD. Improvement is defined as changes from Baseline in LDH of ≥25%, and changes from Baseline in CK, AST, ALT, and ALD of ≥30%. In addition, MMT-8 score should improve by ≥15% to classify an adult DM/PM patient as improved [10]. DOI will be assessed at EOT Visit 26/Week 25. For the proportion of patients who meet the IMACS 2004 definition of improvement (DOI) (Rider 2004) at EOT, logistic regression will be performed, which will include baseline CDASIv2-Activity Score,

treatment group in model. The proportion of subjects who responded will be presented by treatment group. The odds ratios of response for each of the IMO-8400 treatment group vs. placebo group, along with 95% CI and nominal p-value.

The IMACS core set measures are validated and reliable clinical outcome measures used to evaluate multiple components of disease activity including muscle strength and laboratory enzymes. Following are the definitions of the subset of the core set measures that will be used in this study:

i. **Manual Muscle Testing-8 (MMT-8)**: an evaluation of the function and strength of individual muscles and muscle groups based on the effective performance of a movement against gravity or manual resistance. Within each of the 8 muscle groups, subjects are assigned a score between 0 (no contraction felt in muscle) and 10 (held test position against strong pressure), which is then summed for the total score. MMT-8 scores for all the proximal muscles and distal muscles on the right side, and then add the axial neck flexor group. If a right side score for a single muscle group is missing, substitute the left side score in for that muscle group.

ii. **Serum Levels**: Collection of blood samples for testing of muscle enzyme levels including CK, ALD, LDH, ALT and AST will be performed at the time points specified in the SOE. .

The proportion of subjects who meet the IMACS 2004 DOI at EOT will be analyzed using a logistic regression model with fixed effects for treatment group and baseline CDASIv2-Activity score.

The proportion of responders by treatment group will be presented. The odds ratio, 95% CI, and p-value testing the null hypothesis that the odds ratio is 1 will be presented for the pairwise comparisons between each of the IMO-8400 treatment groups and placebo group.

If the results of the primary efficacy endpoint analysis yield different conclusions for the mITT and PP analysis sets, then the above exploratory efficacy analysis will be repeated on the PP analysis set.

4.7.3.2 Efficacy Endpoints Evaluating Change from Baseline (Visit 2/Week 1, Day 1)

Exploratory efficacy endpoints evaluating change from baseline are listed as follows:

- Change in MMT-8 score, as measured at Visits 2, 6, 10, 14, 18, 22 and 26 (EOT/Week 25).
- Change in 10MWR score, as measured at Visits 2, 6, 10, 14, 18, 22 and 26 (EOT/Week 25).
- Change in TUG score, as measured at Visits 2, 6, 10, 14, 18, 22 and 26 (EOT/Week 25).
- Change in 4 Stair Climb Test score, as measured at Visits 2, 6, 10, 14, 18, 22 and 26 (EOT/Week 25).
- Change in 5-D Itch Scale score, as measured at Visits 2, 6, 10, 14, 18, 22 and 26 (EOT/Week 25).

- Change in serum CK, as measured at Visits 2, 6, 14, 22 and 26 (EOT/Week 25).
- Change in serum AST, as measured at Visits 2, 6, 14, 22 and 26 (EOT/Week 25).
- Change in serum ALT, as measured at Visits 2, 6, 14, 22 and 26 (EOT/Week 25).
- Change in serum ALD, as measured at Visits 2, 6, 14, 22 and 26 (EOT/Week 25).
- Change in serum LDH, as measured at Visits 2, 6, 14, 22 and 26 (EOT/Week 25).
- Change in SF-36, as measured at Visits 2, 10, 18, and 26 (EOT/Week 25)

Following are the definitions of the exploratory efficacy endpoints listed above:

i. **Manual Muscle Testing-8 (MMT-8)**: an evaluation of the function and strength of individual muscles and muscle groups based on the effective performance of a movement against gravity or manual resistance. Within each of the 8 muscle groups, subjects are assigned a score between 0 (no contraction felt in muscle) and 10 (held test position against strong pressure), which is then summed for the total score [11].

ii. **10 meter walk-run test (MWR):** This test measures, in seconds, the time it takes a subject to walk as quickly as they can along a marked path without assistance for 10 meters. The time taken to complete the task is measured with a stopwatch.

iii. **Timed Up and Go (TUG):** This test measures, in seconds, the time taken by an individual to stand up from a standard arm chair, walk a distance of 3 meters, turn, walk back to the chair, and sit down. The time taken to complete the task is measured with a stopwatch.

iv. **4-Stair Climb Test:** This test measures, in seconds, the time it takes the subject to climb up 4 standard-sized steps. The time taken to complete the task is measured with a stopwatch.

v. **5-D Itch Scale:** The 5-D itch scale is a brief multidimensional questionnaire to be completed by the subject. The five dimensions of itch- degree, duration, direction, disability and distribution- are achieved separately and then summed together to obtain a total 5-D score. 5-D scores can potentially range between 5 (no pruritus) and 25 (most severe pruritus). The questionnaire is provided in #3 of Appendix III.

vi. **Serum Levels**: Collection of blood samples for testing of muscle enzyme levels including CK, ALD, LDH, ALT and AST will be performed at the time points specified in the SOE.

vii. **SF-36:** The SF-36 is an extensively validated and widely used measure of quality of life that assesses subjects' perceptions of health status and its impact on their lives. It consists of 36 items organized into 8 scales (physical functioning, social functioning, role limitations physical, bodily pain, general medical health, mental health, role limitations emotional, and vitality). Two summary measures of physical and mental health, the Physical Component Summary and Mental Component Summary, respectively, are derived from scale aggregates. Higher scores are associated with better quality of life [12].

The same analytic approach used for the primary efficacy endpoint will be used for the 11 exploratory endpoints listed above. An RMMM with fixed effects for the variable's baseline value, treatment group, visit week, and treatment group by visit week interaction will be fitted, as outlined in Table 2. For each endpoint, pairwise comparisons of the least squares means will be performed between each of the IMO-8400 treatment groups and the placebo group for each change from baseline score. In addition, a nominal p-value will be reported for the associated hypothesis test of each exploratory endpoint.

For each endpoint, descriptive statistics for both the actual value and change from baseline value will be displayed by treatment group and visit. In addition, for continuous endpoints, box and whisker plots will be presented by treatment group and visit.

If the results of the primary efficacy endpoint analysis yield different conclusions for the mITT and PP analysis sets, then the above exploratory efficacy analyses will be repeated on the PP analysis set.

4.8 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in Section 4.4. In general, all data will be listed, sorted by treatment group, site, subject identification number and, when appropriate, by visit week/day within each subject. Safety analyses will be descriptive in nature; no statistical hypothesis testing will be performed.

4.8.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 and tabulated by event, severity, and relationship to study drug.

General Rules for Adverse Events:

1. An AE will be considered as treatment emergent (TE) if it begins on or after study drug dosing, or starts prior to dosing and increases in severity after dosing. In case of missing dates, an AE will be considered as treatment emergent. If AE start and/or stop dates are partial, the dates will be compared as far as possible with the date of first dose of study medication.
2. Subjects will be classified as having withdrawn from the study due to an AE if the subject had a study drug action taken recorded as 'drug withdrawn' on the Adverse Events page of the CRF and subject has a recorded 'No' for the study completion item with 'AE' as the primary reason of discontinuation on the study completion page of the CRF.
3. Events occurring during the pre-treatment phase will not be reported/summarized, since only treatment emergent adverse events (TEAE) will be summarized, but they will be listed.
4. If a subject experiences the same AE (i.e. same PT) more than once, they are only counted once under the count for PT.
5. If a subject experiences more than one AE in a particular system organ class, they will only be included once in the count for the system organ class, but will appear in the count for each appropriate preferred term within the system organ class (unless it is the same PT).

6. AEs related to study drug tables include only those AEs with a relationship to study drug of 'Possibly Related', 'Probably Related' or if there is a missing relationship on the AE page of the CRF.
7. For AE severity the following rules will be applied in determining the counts of AEs:
   - An individual subject who experiences two AEs of the same preferred term of the same severity will be included once in the appropriate severity count for the particular AE.
   - An individual subject who experiences two AEs of the SAME preferred term but different severity will be included once in the severity count for the higher severity but not in the count for the lesser severity.
   - In the total counts for each severity classification, an individual subject who experiences two AEs of different PT of the same severity will be included once in the total for the appropriate severity.
   - In the total counts for each severity classification, an individual subject who experiences two AEs of different PT of different severities will be included once in the total for the higher severity.

The following AE summary tables will be provided for by treatment group and overall:

- Any TEAEs (by PT only, sorted by frequency)
- Any TEAEs
- Any TEAEs of special interest (ISRs)
- Any Serious TEAEs
- TEAEs by severity
- TEAEs by relationship to study drug
- TEAEs leading to discontinuation of study drug
- TEAEs leading to death

The tabular presentation will include the number and percentage of patients experiencing this event. Within each table, AEs will be presented in descending frequency of SOC, and in descending frequency of PT within each SOC.

A listing of all adverse events (including non-treatment-emergent events) will be provided sorted by SOC. This listing will be presented by treatment group and will include: center, subject identifier, age, sex, race, adverse event (SOC, PT, and verbatim term), date of onset, severity, seriousness, action taken, outcome and causality.

4.8.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Deaths, SAEs, and other significant AEs, including those leading to discontinuation will be listed. A listing of verbatim AE terms and the MedDRA terms they are mapped to will be produced.

4.8.3 Clinical Laboratory Evaluation

4.8.3.1 Routine Safety Laboratory Assessments

All laboratory values will be reported in International System of Units (SI) units. Summary displays for laboratory safety data will be produced by treatment group and visit:

- Observed test results for each lab parameter
- Change from baseline for each lab parameter
- Percentage change from baseline for coagulation parameter

Unscheduled laboratory results will not be summarized for each scheduled visit, but will be included in listings. The following clinical parameters will be summarized:

Category	Analyte
Hematology	CBC: RBC, WBC, hemoglobin, hematocrit, platelet count Differential WBC count: neutrophils, monocytes, lymphocytes, eosinophils, basophils, abnormal cells Absolute cell counts: ANC
Coagulation	PT, activated partial thromboplastin time (aPTT), international normalized ratio (INR)
Clinical Chemistry Panel	Renal: Serum sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, creatinine, urea nitrogen
	Endocrine: Serum glucose, thyroxine (T4), thyroid stimulating hormone (TSH)
	Liver: serum ALT (SGTP), AST (SGOT), LDH, GGT, alkaline phosphatase, albumin, total protein, total bilirubin, direct bilirubin, indirect bilirubin
	Lipids: Serum cholesterol, LDL, HDL
Urinalysis	Routine and microscopic analyses
Hepatitis screen (At Screening Visit only)	Hepatitis B (HB) screen: HBsAg and anti-HBc Hepatitis C (HC) screen: anti-HCV
TB test (within 3 months prior to screening or during the Screening Period)	A negative chest x-ray and one of the following: a) a PPD skin test with ≤5-mm induration, OR b) a negative (not detected) QuantiFERON result. If the QuantiFERON result is indeterminate, the test may be repeated once (local testing), per Center for Disease Control (CDC) guidelines If the second QuantiFERON test is indeterminate, a PPD skin test may be used to confirm eligibility. (http://www.cdc.gov/tb/topic/testing/default.htm).
Drug abuse (At Screening Visit only)	Urine drug screen

ALT (SGPT) = alanine aminotransferase (serum glutamate-pyruvate transaminase); ANC = absolute neutrophil count; aPTT = activated Partial Thromboplastin Time; AST (SGOT) = aspartate transaminase (serum glutamic oxaloacetic transaminase); CBC = complete blood count; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; HDL = high-density lipoprotein; INR = International Normalized Ratio; LDH

= lactate dehydrogenase; LDL = low density lipoprotein; PPD = purified protein derivative; PT = prothrombin time; RBC = red blood cells; T4 = thyroxine; TB = tuberculin; TSH = thyroid stimulating hormone; WBC = white blood cells

Scatter plots of various laboratory parameters will be created plotting either the baseline value against the maximum or minimum value observed on study (as appropriate per parameter), or the value's fold increase above the test's upper limit of normal (ULN) at baseline versus the maximum observed on study.

The specific parameters to be plotted and the specifics of plotting are described in Table 3.

Table 3. Laboratory Parameters to be Plotted

Laboratory Parameter	Plot Specifications
ALT	-baseline fold >ULN vs. fold >ULN for maximum value on study
AST	-baseline fold >ULN vs. fold >ULN for maximum value on study
Total Bilirubin	-baseline fold >ULN vs. fold >ULN for maximum value on study
CK	-baseline fold >ULN vs. fold >ULN for maximum value on study
CRP	-baseline value vs. maximum value on study
CH50	-baseline value vs. minimum value on study
C3	-baseline value vs. minimum value on study
C4	-baseline value vs. minimum value on study
Troponin	-baseline value vs. maximum value on study
WBC	-baseline value vs. maximum value on study -baseline value vs. minimum value on study
Hemoglobin	-baseline value vs. maximum value on study -baseline value vs. minimum value on study
Creatinine	-baseline value vs. maximum value on study
Albumin: Globulin Ratio	-baseline value vs. minimum value on study
Platelets	-baseline value vs. maximum value on study -baseline value vs. minimum value on study
eGFR	-baseline value vs. minimum value on study

Laboratory values will be classified as normal, low, or high based on normal ranges supplied by the central laboratory. Laboratory categories will be expressed in terms of the L (below LLN), N (between LLN and ULN) and H (above ULN) classifications for numerical measurements and normal, abnormal for categorical measurements. The number and percentage of subjects with abnormal values will be summarized for each laboratory parameter by visit and treatment group. Shift tables will also be produced, comparing the category at baseline for each parameter (low, normal, high) to the worst value post-baseline.

Quantitative laboratory measurements reported as '< X', i.e. below the lower limit of quantification (BLQ), or '> X', i.e. above the upper limit of quantification (ULQ), will be

converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as '< X' or '> X' in the listings.

Values that meet the criteria provided below in Table 4 will be considered for potential clinical significance.

Table 4. Criteria for Potential Clinically Significant Laboratory Parameters

Hematology laboratory parameter	
Test	Criteria Value
Hemoglobin (g/dL)	Decrease > 2.0 and Value < 8.0
Hematocrit (%)	Value < 27
Total WBC ($x10^3/\mu L$)	Value < 2.0 or Value > 20.0
Eosinophils, absolute ($x10^3/\mu L$)	Percent increase ≥ 100 and Value > 0.8
Lymphocytes, absolute ($x10^3/\mu L$)	Percent decrease ≥ 33 and Value < 1.0
Neutrophils, absolute ($x10^3/\mu L$)	Percent decrease ≥ 33 and Value < 1.5
Platelets ($x10^3/\mu L$)	Percent decrease ≥ 50 and Value < 75
Clinical chemistry laboratory parameter	
Test	Criteria Value
Albumin (g/dL)	Decrease ≥ 1.0 and Value < 2.5
Alkaline phosphatase (IU/L)	Percent increase ≥ 100 and Value > 250
ALT (IU/L)	Percent increase ≥ 100 and Value > 150
AST (IU/L)	Percent increase ≥ 100 and Value > 150
Bicarbonate (mEq/L)	Value < 15 or Value > 35
BUN/Urea (mg/dL)	Percent increase ≥ 66 and Value > 40
Calcium (mg/dL)	(Increase ≥ 2.0 and Value > 11.5) or (Decrease ≥ 1.5 and Value < 7.5)
Chloride (mEq/L)	Value < 85 or Value > 120
Creatinine (mg/dL)	Percent increase ≥ 66 and Value > 2.5
Glucose (mg/dL)	(Percent Increase ≥ 100 and Value > 250) or (Percent decrease ≥ 33 and Value < 55)
Phosphate (mg/dL)	(Increase ≥ 2.5 and Value > 6.0) or (Decrease ≥ 1.0 and Value < 2.0)
Potassium (mEq/L)	(Increase ≥ 0.8 and Value > 5.5) or (Decrease ≥ 0.8 and Value < 3.0)
Sodium (mEq/L)	(Increase ≥ 10 and Value > 150) or (Decrease ≥ 5 and Value < 125)
Total Bilirubin (mg/dL)	<3 or >21 umol/L
Total protein (g/dL)	Value < 4.5 or Value > 10.0

All collected laboratory assessments, including serum calcium and pregnancy test results, will be listed.

Hy's Law, Temple's Corollary and Elevated LFT Results

Incidence of subjects with liver function test results satisfying the drug-induced liver injury (DILI) criterion defined as (> 3xULN for ALT/AST, > 2xULN for total bilirubin and ≤ 2xULN for alkaline phosphatase at the same time-point) will be presented by visit and treatment group. According to Hy's Law, a pure DILI case leading to jaundice, without a hepatic transplant, has a case fatality rate of 10% to 50%.

Incidence of subjects with liver function test results satisfying Temple's criterion defined as (> 3xULN for ALT/AST, ≤ 2xULN for total bilirubin and ≤ 2xULN for alkaline phosphatase at the same time-point) will be presented by visit and treatment group.

Evaluation of Drug Induced Serious Hepatotoxicity (eDISH) plots where the X-axis is the ULN value of AST and the Y-axis the maximum ULN value of total bilirubin will be produced. eDISH plots for ALT vs total bilirubin, AST vs CK, and ALT vs CK will also be produced.

In addition, incidence of elevated liver function test results will be presented at each visit by elevation criterion and treatment group. Elevation criteria are given as follows:

- ALT (ULN - ≤ 3xULN, > 3xULN - ≤ 5xULN, > 5xULN)
- AST (ULN - ≤ 3xULN, > 3xULN - ≤ 5xULN, > 5xULN)
- Total Bilirubin (ULN - ≤ 2xULN, > 2xULN)
- Alkaline Phosphatase (ULN - ≤ 2xULN, > 2xULN)

Identification of Hy's Law, Temple's Corollary and elevated function test results cases will be done for the entire duration of the study.

4.8.3.2 Special Safety Laboratory Assessments

The following safety laboratory parameters will also be summarized in a similar manner to the parameters in section 4.8.3.1:

Category	Analyte
Immune activation	Serum globulin, serum albumin, A:G ratio, CRP
Complement activation	C3, C4, CH50
Heart	Troponin

A:G albumin: globulin; C = complement factor; CH50 = hemolytic complement activity; CRP = C-reactive protein;

For C3, C4, albumin, globulin, platelets, eGFR, urine protein, and A:G ratio, per-patient line plots with reference lines of the normal limits will be produced with each dose in separate panels.

All laboratory data will be listed by dose, site, and subject, and flagged with H for values greater than the ULN and L for values less than the lower limit of normal (LLN).

4.8.4 Vital Signs, Physical Findings and Other Observations Related to Safety

4.8.4.1 Physical Examination and Vital Signs

Summaries of vital signs parameters (blood pressure, respiratory rate and temperature) will be presented by treatment group and visit. Summary statistics will be produced for both observed and change values from baseline for each parameter. LNH (low, normal, or high) classification of vital signs parameters will be based on the criteria in Table 5 below.

Table 5. Normal (Reference) Ranges and Markedly Abnormal Ranges for Vital Signs Parameters

Vital Sign Parameter	Below Normal	Normal (Reference) Range	Above Normal	Markedly Abnormal (High) Range	Units
Systolic blood pressure	<90	90-120	121-159	≥160	mmHg
Diastolic blood pressure	<50	50-80	81-99	≥100	mmHg
Respiratory rate	<12	12-18	19-24	≥25	Bpm
Temperature	<35.5	35.5-39.5	>39.5	NA	°C
Pulse	<51	51-99	100-119	≥120	bpm

The number and percentage of subjects with abnormal values will be summarized for each vital signs parameter by visit and treatment group. The number and percentage of subjects with MA observed values will be summarized for each vital signs parameter by visit and treatment group.

LNH shifts in vital sign from Baseline to each visit post first dosing will be summarized by visit and treatment group.

The change from baseline to lowest value on study and highest value on study will be summarized as shift tables, by treatment group, for all vital sign parameters. Graphical figures will be produced for each vital sign, showing a box and whisker plot representing the maximum absolute change from baseline by dose group.

Subjects with values outside the normal range, including those that meet the markedly abnormal criteria, will be flagged. A listing of all subjects meeting the criteria for abnormality at any time point will be provided. All collected vital signs assessment will be presented in a listing.

4.8.4.2 Electrocardiograms

Values and change from baseline for ECG parameters, including heart rate, PR interval, RR interval, QRS duration, QT interval, corrected QT interval using Bazett's formula [QTcB], and corrected QT interval using Fridericia's formula [QTcF], will be summarized by treatment group and visit. In addition, the change from baseline to lowest value on study and highest value on study will be summarized for all ECG parameters as shift tables. All ECG interval measurements will be given in [msec].

Bazett's formula is:

$$QTcB = QT^* (1000/RR)^{1/2}$$

Fridericia's formula is:

$$QTcF = QT^*(1000/RR)^{1/3}$$

Electrocardiographic parameter values are considered PCS if they meet the criteria listed in Table 6. The number and percentage of patients with PCS post-baseline ECG values will be tabulated by treatment group and visit. The percentages will be calculated relative to the number of patients with available baseline values and at least one post-baseline assessment. The numerator will be the total number of patients with available baseline values and at least one PCS post-baseline value. A supportive tabular display of patients with PCS post-baseline values will be provided, including the patient number, study center number, baseline, all post-baseline (including non-PCS) values, and change from baseline.

A shift table from baseline to the end of study in the Investigator's overall interpretation of the ECG will be presented by treatment group for the following categories: normal; abnormal, not clinically significant; and abnormal, clinically significant. A tabular display of patients with post-baseline clinically significant ECG abnormalities according to the Investigator's overall interpretation will be provided. Table 6 below provides criteria of interest for ECG parameters.

Table 6. Criteria for Potentially Clinically Significant Electrocardiograms

ECG Parameter	Criteria 1	Criteria 2
QT interval, QTcB, and QTcF		
Absolute values	> 450 msec	> 500 msec
Absolute change from baseline	> 30 msec	> 60 msec
QRS duration	≥ 100 msec	≥ 150 msec
PR interval	≥ 200 msec and an increase of ≥ 25% over baseline value	≥ 250 msec if baseline is < 250 msec
Heart Rate		
Tachycardia event	≥ 100 bpm	≥ 120 bpm
Bradycardia event	≤ 50 bpm	≤ 40 bpm

A listing of all observed ECG data will be displayed by treatment, site, subject, date/visit of collection, time, ECG results, interpretation, reason for abnormal interpretation and clinical significance.

4.8.4.3 Injection Site Reactions

The ISR verbatim terms of pain, tenderness, pruritis, induration, erythema, blisters, ulceration, and necrosis will be summarized by the greatest post-randomization severity for each symptom by table and bar graph. Incidence will be tabulated by type, anatomic location, severity and overall across treatment groups and overall. ISR's of induration, erythema, blisters, ulceration and necrosis will also be summarized by largest edge-to-edge lesion distance.

4.8.4.4 Pregnancy Test

Reported pregnancies will be listed.

4.8.5 Safety Monitoring (Data Monitoring Committee [DMC])

The DMC will operate under a charter developed as a collaborative document between the DMC and Idera. The primary responsibility of the DMC is to protect the safety and welfare of patients participating in this clinical study and to ensure the integrity of the clinical study.

In general, the DMC will be responsible for:

- Examining accumulated unblinded safety and other relevant data at prespecified points during the course of the study in order to make recommendations concerning continuation, termination, or modification of the study
- Reviewing the general progress of the study as regards such issues as patient accrual and protocol violations
- Providing expert advice to Idera on an ad hoc basis regarding matters such as safety concerns or diagnostic evaluations in individual patients

Based on the results of its deliberations, the DMC can recommend continuation of the study unchanged, study interruption, study termination, modification of the study, or alteration in the DMC monitoring plan.

The DMC will review unblinded safety data as outlined in the DMC Charter and SAP. The DMC may also increase or alter safety monitoring or recommend other modifications to ensure patient safety. The composition and specific responsibilities of the DMC are described in the DMC Charter, which is maintained as a separate document.

4.9 Other Analyses

4.9.1 Pharmacokinetic Analyses

Plasma concentrations of IMO-8400 will be determined pre-dose and 2 hours (± 15 minutes) post-dosing to confirm systemic exposure. Pre and post-dose plasma concentrations will be used to evaluate/interpret any time-dependent trends in safety or PD outcomes.

For each of the parameters listed below, except t_{max}, $t_{1/2}$, the following summary statistics will be calculated for the IMO-8400 dose group: median, maximum, minimum, arithmetic mean, standard deviation, %CV, geometric mean, 90% confidence interval (CI) for the geometric mean

and SD of logarithmically transformed data. For t_{max}, $t_{1/2}$, median maximum, minimum, arithmetic mean and SD will be calculated.

Parameter	Definition
AUC_{last} (ng·h/mL)	The area under the concentration-versus-time curve, from time 0 to the last quantifiable concentration sampling point
C_{max} (ng/mL)	Maximum (peak) observed plasma concentration
t_{max} (h)	The time of maximum observed concentration
$AUC_{0\text{-inf}}$ (ng·h/mL)	The area under the concentration-versus-time curve, from time 0 extrapolated to infinity
$t_{1/2}$ (h)	The apparent terminal elimination half-life
CL/F	The apparent clearance
V/F	The apparent volume of distribution based on the terminal phase

All calculations of non-compartmental parameters will be based on actual sampling times.

1. The first occurrence of the maximum observed plasma concentration C_{max} will be determined directly from the raw concentration-time data.
2. The time at which C_{max} is observed will be determined directly from the raw concentration-time data t_{max}.
3. AUC_{last} will be calculated using the linear-log trapezoidal rule as the area under the concentration-versus-time curve, from time 0 to the last quantifiable concentration sampling point.
4. $AUC_{(0\text{-inf})}$ will be calculated using the linear-log trapezoidal rule as the area under the concentration-versus-time curve, from time 0 extrapolated to infinity.
5. The apparent terminal elimination half-life ($t_{1/2}$) will be calculated as $0.693/\lambda z$, where λz will be estimated by linear regression of the terminal log-linear portion of the concentration-time curve.
6. The apparent clearance (CL/F) will be calculated as dose / $AUC_{(0\text{-inf})}$.
7. The apparent volume of distribution (V/F) will be calculated as dose / ($AUC_{0\text{-inf}} * \lambda z$).

Idera will be responsible for all PK Analysis and interpretations for trial 8400-211, which will be reported in an independent technical report.

4.9.2 Pharmacodynamic Analyses

Pharmacodynamic and investigational study parameters will be summarized using descriptive statistics. Figures presenting the median value of PD endpoints over time will be presented by treatment group.

Change from baseline in Type 1 and Type 2 Interferon (IFN) gene expression signature using (a) whole blood and (b) skin biopsy will be summarized by treatment group and visit.

Change from baseline in histology results, using skin biopsies, will be summarized by treatment group and visit.

Change from baseline in DM relevant cytokines/chemokine levels, including IL-6, IL-8, IP-10, I-TAC, MCP-1, MCP-2, and tumor necrosis factor alpha (TNFα) will be summarized by treatment group and visit; additional or alternative cytokines or chemokines may be assessed.

For each of the PD parameters: PT, aPTT, INR, TAFIa activity, clot lysis time, D-dimer, MCA recanalization assessed using reperfusion scores, the following will be summarized by treatment group, using mean, median, standard deviation, minimum, maximum:

- Observed values at each time point
- Absolute change from baseline to each time point
- Percent change from baseline to each time point (except MCA recanalization assessment using reperfusion score)

Box plot and mean profile plot will be generated for total TAFIa activity (%), clot lysis time (sec), D-dimer (mg/L [FEU]), TIMI reperfusion score by treatment group.

In addition, a comprehensive listing will be generated for each subject at each time point: raw values and absolute / percentage change from baseline in PT, aPTT, INR, total TAFIa activities, clot lysis time, D-dimer.

Note: PD results (IFN gene expression, histology, and cytokine/chemokine results) may be reported separately from the final CSR, and only the baseline autoantibody results will be reported in the CSR.

4.9.3 Autoantibodies

Blood samples will be collected at the time points specified in the SOE in Section 2 for assessment of autoantibodies associated with idiopathic inflammatory myopathies including, but not necessarily limited to: anti-MDA-5, anti-Mi-2, anti-TIF1γ, anti-NXP2, anti-SAE1, anti-SAA 60, anti-Ro/SSA 52, anti-SSB/La, anti-Sm, anti-RNP, anti-Scl-70, anti-ribosomal-P, anti-chromatin, anti-Jo-1, anti-PL-7, and anti-PL-12. Assessment of autoantibodies will help to characterize the enrolled population. The appropriate Laboratory Manual should be referenced for procedures on sample collection, handling, storage and shipping.

Presence of disease-specific autoantibodies at baseline and change from baseline in presence of autoantibodies associated with idiopathic inflammatory myopathies including, but not necessarily limited to, the following: anti-MDA-5, anti-Mi-2, anti-TIF1γ, anti-NXP2, anti-SAE1, anti-SAA 60, anti-Ro/SSA 52, anti-SSB/La, anti-Sm, anti-RNP, anti-Scl-70, anti-ribosomal-P, anti-chromatin, anti-Jo-1, anti-PL-7, and anti-PL-12.

Only baseline autoantibody results will be reported in the CSR.

4.9.4 Immunogenicity

Blood samples for assessment of antibodies to IMO-8400 and dsDNA will be collected at the time points specified in the SOE in Section 2. Analysis of Immunogenicity will be performed separately and not specified in this SAP.

4.10 Determination of Sample Size

A simulation was conducted in which one of the IMO-8400 groups exhibits a mean decrease of 7 points in CDASIv2-Activity score over 24 weeks, assuming a baseline mean of 25 and a standard deviation of 8.5 and the placebo group exhibits no mean decrease. Correlation between baseline CDASIv2-Activity score and Week 25 mCDASIv2-Activity score was assumed to be 0.4 for IMO-8400 treated patients and 0.7 for placebo treated patients. Using a repeated measures mixed model (RMMM) to analyze monthly mCDASIv2-Activity assessments, 10 patients with complete data yields 81.2% power to detect such a 7-point difference between groups at Week 25, using a 1-sided test with an alpha of 0.05. A 20% rate of patient dropout was assumed, yielding the final sample size of 12 subjects per treatment group.

4.11 Changes in the Conduct of the Study or Planned Analysis

Changes in the conduct of the study may be instituted through a protocol amendment. Planned analyses will be revised as appropriate. Similarly, planned analyses may be changed as a result of planned blinded data reviews. Changes will be finalized prior to database lock.

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Appendix I Schedule of Study Procedures and Evaluations

Event / Period	Screen[1]	Baseline	Treatment																								EOT / ET[2]	EOS[3]
Week[4]		Wk 1/ D1[2]	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	Wk 19	Wk 20	Wk 21	Wk 22	Wk 23	Wk 24	Wk 25	Wk 29
Visits[5]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27
Informed Consent[6]	X																										
Inclusion / Exclusion Criteria	X																										
Medical History	X																										
Physical Examination[7]	X	X				X				X				X				X				X				X	X
Skin Photography[8]	X	X																								X	
CDASIv2[9]	X	X				X				X				X				X				X				X	
Skin Biopsy[10]		X																								X[10]	
MMT8		X				X				X				X				X				X				X	
Muscle enzymes[11]		X				X				X				X				X				X				X	
SF-36		X								X								X								X	
Timed Function Tests[12]		X				X				X				X				X				X				X	
5-D Itch Scale		X				X				X				X				X				X				X	
Safety Labs[13]	X	X				X				X				X				X				X				X	X
12-Lead ECG[14]	X	X				X				X				X				X				X				X	X
Pregnancy Test[15]	X	X				X				X				X				X				X				X	X
IMO-8400 Plasma Concentration[16]		X				X								X								X				X	
Auto-Antibodies [17]		X																				X				X	
Anti-platelet antibodies[18]		X				X				X				X				X				X				X	
IFN Gene Expression		X				X								X								X				X	
Serum Cytokines [19]		X				X								X								X				X	X
Immunogenicity [20]		X				X								X								X				X	X
Vital Signs [21]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Injection Site(s)[22]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study Drug Admin [23, 24]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess AEs[25] & Con Meds[26]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: Admin. = administer; AE = adverse event; Con Med =concomitant medications; CDASI = Cutaneous Disease and Activity Severity Index; CT = computerized tomography; D = day; ECG = electrocardiogram; EOS = end-of-study; EOT = end-of-treatment; ET = early termination; IFN = Type 1 and Type 2 interferon; Lab. = laboratory; MMT8 = manual muscle testing; SF-36 = 36-Item Short Form Health Survey.

Note: Shaded columns in the Schedule of Events indicate study visits that may be performed by a visiting nurse outside of the clinic (e.g., patient's home or workplace), at the discretion of the Investigator.

Note: At Baseline, all assessments must be performed before study drug administration.

1 Screening will be performed within 28 days prior to Week 1/Day 1.

2 If treatment is terminated prematurely for any reason, the Early Termination (ET) Visit will be performed within 5 days of the notification of withdrawal. ET Visit assessments are the same as the EOT assessments (i.e., following 24 weeks of treatment).

3 The EOS Visit will be performed 4 weeks (± 4 days) after completion of the EOT assessments or the ET assessments.

4 All days are relative to the day of the prior visit.

5 Each visit has a window of ± 2 days.

6 Informed consent must be signed prior to conducting any study-specific procedures.

7 Physical examinations will include examination of general appearance, head, eyes, ears, nose, and throat (HEENT), heart, lungs, chest, abdomen, skin, lymph nodes, musculoskeletal, and neurological systems. Physical examination includes body weight with each exam and, at screening only, height.

8 Skin photography procedures are provided in the Study Reference Manual. No photographs will be taken of a patient's face, in order to maintain patient confidentiality.

9 Full CDASIv2 assessment at Screening and Baseline and modified CDASIv2 (mCDASIv2; i.e., no abdominal skin activity) assessment post-Baseline.

10 Two 4 mm punch biopsies will be taken at each of the Baseline Visit and the EOT Visit. Biopsies will be taken side by side on the upper back or upper arm of patients (whichever the Investigator feels has the most active skin disease at baseline) at the Baseline Visit and in an adjacent area at the EOT Visit. Sites where the baseline biopsy samples were taken should be photographed. Skin biopsies are not required for an ET Visit.

11 Serum muscle enzymes measured include creatine kinase, aldolase, lactate dehydrogenase, alanine transaminase, and aspartate transaminase.

12 Timed Function Tests include 10-meter walk-run test, timed up and go test, and 4 stair climb test

13 Routine safety laboratory tests include hematology, chemistry, coagulation, urinalysis, and a urine drug screen; safety laboratory assessments include CH50, C3, C4, CRP, troponin, albumin/globulin ratio. The urine drug screen and hepatitis B and C testing will be performed during the Screening Period only. Testing for TB should include a negative chest x-ray or chest CT and 1 of the following: a) a PPD skin test with h-mm induration, or b) a negative (not detected) QuantiFERON result.

14 ECGs will be performed only after the patient is positioned supine, resting, and quiet for a minimum of 5 minutes.

15 Urine pregnancy testing for women of child-bearing potential.

16 Sample for analysis of IMO-8400 plasma concentrations should be collected prior to dosing and 2 hours (± 15 minutes) post-dose at Visits 2 (Week 1), 6 (Week 5), 14 (Week 13), and 22 (Week 21). An additional sample will be collected as part of the EOT assessments (Visit 26/Week 25). If, at the EOT Visit, the patient is eligible for enrolment into an extension study, the EOT PK sampling will be done prior to extension study dosing at the EOT Visit, which will be the same as Visit 1/Week 1 of the extension study, if the extension study is initiated.

17 Serum samples for assay of autoantibodies.

18 Serum samples for anti-platelet antibodies.

19 Serum samples for assay of cytokines/chemokines .

20 Serum samples for immunogenicity assay (antibodies to IMO-8400 and dsDNA).

21 Vital signs include heart rate, respiration rate, blood pressure, and temperature and will be measured prior to study drug administration.

22 Assessment of all prior injection site(s). In addition, on dosing days, the planned injection site will be assessed to confirm it is appropriate for use.

23 ALL SCHEDULED ASSESSMENTS SHOULD BE PERFORMED PRIOR TO DOSING UNLESS OTHERWISE SPECIFIED. Patients will be monitored for approximately 4 hours after the first dose at the Baseline Visit.

24 THERE CAN NOT BE FEWER THAN 5 DAYS BETWEEN DOSES.

25 All AEs from the time the informed consent is signed through the EOS Visit 27/Week 29 will be recorded on the eCRF.

26 Stable regimens and washout periods for permitted concomitant medications are provided in Table 4 and Table 5, respectively. The washout period for prohibited concomitant medications is provided in Table 6.

Appendix II Prohibited Medications

The use of the following concomitant medications is prohibited during the 24 weeks of study drug treatment due to the possibility that they might confound interpretation of study results.

Prohibited Medication	Washout Period Prior to Screening[a]
Rituximab	At least 24 weeks **AND** B-cell counts (local testing) that are confirmed to be within normal limits
Intravenous corticosteroids	At least 12 weeks
Intravenous immunosuppressives	At least 12 weeks
Any other monoclonal antibody, biologic agent, or investigational agent	At least 12 weeks or 5 half-lives (whichever is longer)
Antimalarial agent(s)	At least 36 weeks
Topical corticosteroids (excluding scalp)	At least 2 weeks

[a] Medications are prohibited for at least the specified washout period immediately prior to screening

Appendix III Definition of Selected Efficacy Endpoints

1. CDASIv2- Activity Subscore

activity

Extent

Anatomical Location	Erythema	Scale	Erosion/ Ulceration
	0-absent 1-pink; faint erythema 2-red 3-dark red	0-absent 1-scale 2-crust; lichenification	0-absent 1-present
Scalp			
Malar Area			
Periorbital			
Rest of the face			
V-area neck (frontal)			
Posterior Neck			
Upper Back & Shoulders			
Rest of Back & Buttocks			
Abdomen			
Lateral Upper Thigh			
Rest of Leg & Feet			
Arm			
Mechanic's Hand			
Dorsum of Hands (not over joints)			
Gottron's – Not on Hands			

Gottron's – Hands

Examine patient's hands and double score if papules are present		Ulceration
0-absent 1-pink; faint erythema 2-red erythema 3-dark red		

Periungual

Periungual changes (examine)	
0-absent 1-pink; red erythema/microscopic telangiectasias 2-visible telangiectasias	

Alopecia

Recent Hair loss (within last 30 days as reported by patient)	
0-absent 1-present	

Total Activity Score
(For the activity score, please add up the scores of the left side, i.e. Erythema, Scale, Erosion/ Ulceration, Gottron's, Periungual, Alopecia)

2. CDASIv2- Damage Subscore

damage

Poikiloderma (Dyspigmentation or Telangiectasia)	Calcinosis	Anatomical Location
0-absent 1-present	0-absent 1-present	
		Scalp
		Malar Area
		Periorbital
		Rest of the face
		V-area neck (frontal)
		Posterior Neck
		Upper Back & Shoulders
		Rest of Back & Buttocks
		Abdomen
		Lateral Upper Thigh
		Rest of Leg & Feet
		Arm
		Mechanic's Hand
		Dorsum of Hands (not over joints)
		Gottron's – Not on Hands

Examine patient's hands and score if damage is present	
0-absent 1-dyspigmentation 2-scarring	

Total Damage Score
(For the damage score, add up the scores of the right side, i.e. Poikiloderma, Calcinosis, Gottron's)

3. **5-D Pruritus Scale (5-D Itch Scale)**

1. **Duration:** During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree:** Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction:** Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability:** Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

Appendix IV Visit Window of Endpoints

Visit window is calculated as the midpoint of two visit's target study day.

Study day is calculated as (Assessment date – first dose date + 1), if the assessment was performed on or after the first dose day; (Assessment date – first dose date), if the assessment was performed prior to the first dose date.

Visit window of Physical Examination, Safety Labs, 12-Lead ECG, Pregnancy Test

Scheduled Visit	Target Study Day	Time Interval (Study day)	
		Start	End
Visit 1		-28	0
Visit 2	Day 1	1	1
Visit 6	Day 29	2	42
Visit 10	Day 57	43	70
Visit 14	Day 85	71	98
Visit 18	Day 113	99	126
Visit 22	Day 141	127	154
Visit 26	Day 169	155	182
Visit 27	Day 197	183	

Visit window of CDASIv2

Scheduled Visit	Target Study Day	Time Interval (Study day)	
		Start	End
Visit 1		-28	0
Visit 2	Day 1	1	1
Visit 6	Day 29	2	42
Visit 10	Day 57	43	70
Visit 14	Day 85	71	98
Visit 18	Day 113	99	126
Visit 22	Day 141	127	154
Visit 26	Day 169	155	182

Visit window of MMT8, Muscle enzymes, Timed Function Tests, 5-D Itch Scale, Anti-platelet antibodies

Scheduled Visit	Target Study Day	Time Interval (Study day)	
		Start	End
Visit 2	Day 1	1	1
Visit 6	Day 29	2	42
Visit 10	Day 57	43	70
Visit 14	Day 85	71	98
Visit 18	Day 113	99	126
Visit 22	Day 141	127	154

Visit 26	Day 169	155	182

Visit window of SF36

Scheduled Visit	Target Study Day	Time Interval (Study day)	
		Start	End
Visit 2	Day 1	1	1
Visit 10	Day 57	2	84
Visit 18	Day 113	85	140
Visit 26	Day 169	141	182

Visit window of IMO-8400 Plasma Concentration, IFN Gene Expression, Serum Cytokines

Scheduled Visit	Target Study Day	Time Interval (Study day)	
		Start	End
Visit 2	Day 1	1	1
Visit 6	Day 29	2	56
Visit 14	Day 85	57	112
Visit 22	Day 141	113	154
Visit 26	Day 169	155	182

Visit window of Immunogenicity

Scheduled Visit	Target Study Day	Time Interval (Study day)	
		Start	End
Visit 2	Day 1	1	1
Visit 6	Day 29	2	57
Visit 14	Day 85	58	113
Visit 22	Day 141	114	154
Visit 26	Day 169	155	182
Visit 27	Day 197	183	

Visit window of Auto-Antibodies

Scheduled Visit	Target Study Day	Time Interval (Study day)	
		Start	End
Visit 2	Day 1	1	1
Visit 22	Day 141	2	154
Visit 26	Day 169	155	182

Visit window of Vital Signs

Scheduled Visit	Target Study Day	Time Interval (Study day)	
		Start	End
Visit 1		-28	0
Visit 2	Day 1	1	1
Visit 3	Day 8	2	11

Visit 4	Day 15	12	18
Visit 5	Day 22	19	25
Visit 6	Day 29	26	32
Visit 7	Day 36	33	39
Visit 8	Day 43	40	46
Visit 9	Day 50	47	53
Visit 10	Day 57	54	60
Visit 11	Day 64	61	67
Visit 12	Day 71	68	74
Visit 13	Day 78	75	81
Visit 14	Day 85	82	88
Visit 15	Day 92	89	95
Visit 16	Day 99	96	102
Visit 17	Day 106	103	109
Visit 18	Day 113	110	116
Visit 19	Day 120	117	123
Visit 20	Day 127	124	130
Visit 21	Day 134	131	137
Visit 22	Day 141	138	144
Visit 23	Day 148	145	151
Visit 24	Day 155	152	158
Visit 25	Day 162	159	165
Visit 26	Day 169	166	182
Visit 27	Day 197	183	