Clinical Study Protocol

8400-211

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

Investigational Drug: IMO-8400

IND: 125410

Sponsor: Idera Pharmaceuticals, Inc.
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Protocol Number: 8400-211

Protocol Version: Version 6.0

Version Date: 27 January 2017

Protocol Approval Page

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Approved for the Sponsor by:

DocuSigned by:
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Joanna Horobin, MB, ChB
Senior Vice President, Chief Medical Officer
Idera Pharmaceuticals, Inc.

Signature Date (ddmmmyyyy)

REVISION HISTORY

Version	Date	Comment
1.0	11 June 2015	IND submission
2.0	22 July 2015	Revisions based on FDA review
3.0	26 August 2015	Revisions based on IRB/IEC reviews and operational considerations
4.0	29 February 2016	(No patients were enrolled under Protocol Version 4.0)
5.0	12 May 2016	Revisions based on FDA feedback
6.0	27 January 2017	Revisions based on investigator feedback and operational considerations

Study Contact Information

Any serious adverse event (SAE) must be reported within 24 hours. See Section 11.3 for detailed adverse event reporting procedures.

Table 1. Study Contact Information

Role in Study	Name, Title, Address	Telephone / fax / email
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1 ABBREVIATIONS AND TERMS

10MWR	10-meter walk-run test
A:G ratio	albumin: globulin ratio
ACTH	adrenocorticotropin
AE	adverse event(s)
ALD	aldolase
ALT	alanine transaminase
ANC	absolute neutrophil count
Anti-HBc	hepatitis B core antibody test
Anti-HCV	hepatitis C virus antibody test
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
AUC	area under the curve
BCG	Bacille Calmette-Guerin
C3	complement component 3
C4	complement component 4
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index
CFR	Code of Federal Regulations
CH50	hemolytic complement activity
CK	creatine kinase
C_{max}	maximum plasma concentration
CRO	clinical research organization
CRP	C-reactive protein
CS	clinically significant
CSMs	Core Set Measures
CSR	Clinical Study Report
CT	computed tomography
CXR	chest x-ray
DLBCL	diffuse arge B-cell lymphoma
DM	dermatomyositis
DMC	Data Monitoring Committee
DOI	definition of improvement
dsDNA	double-stranded deoxyribonucleic acid

ECG	electrocardiogram
eCRF	electronic case report form
EMG	electromyography
EOS	End-of-Study
EOT	End-of-Treatment
ET	Early Termination
EP	European Pharmacopeia
FDA	Food and Drug Administration
GCP	Good Clinical Practice
eGFR	estimated glomerular filtration rate
GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HBV	hepatitis B virus
HBsAG	hepatitis B surface antigen test
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus 1
HIV-2	human immunodeficiency virus 2
IBM	Inclusion Body Myositis
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IL	interleukin
IMACS	International Myositis Assessment Clinical Study
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
ISR	injection site reaction
ITT	Intent-to-Treat
IVIG	intravenous immunoglobulin
IXRS	Interactive voice/web-Response System
LDH	lactate dehydrogenase
LLN	lower limit of normal

mCDASIv2	Modified CDASI version 2
MedDRA	Medical Dictionary for Regulatory Activities
MMT/MMT8	Manual Muscle Testing
MRI	magnetic resonance imaging
NCS	not clinically significant
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B-cells
PD	pharmacodynamics
PET/CT	positron emission tomography and computed tomography
PK	pharmacokinetics
PP	per protocol
PPD	purified protein derivative
PSC	Patient Safety Committee
PT	prothrombin time
RMMM	repeated measures mixed model
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SF-36	Short Form-36 Health Survey
SOE	Schedule of Events
SRM	Study Reference Manual
STIR	short τ inversion recovery
T4	thyroxine
TB	tuberculosis
TLR	Toll-like receptors
T_{max}	time to maximum plasma concentration
TNFα	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UK	United Kingdom
US	United States
USP	United States Pharmacopeia
WBC	white blood cell
WM	Waldenström's macroglobulinemia

WNL	within normal limits

2 SYNOPSIS

Name of Sponsor/Company:
Idera Pharmaceuticals, Inc.

Name of Investigational Product:
IMO-8400 for Injection

Name of Active Ingredient:
IMO-8400

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

Study Sites: This study will be conducted at approximately 20 centers

Phase of Development: 2

Objectives:

Primary

- To assess the safety and tolerability of IMO-8400 in adult patients with active dermatomyositis (DM)
- To assess the effect of IMO-8400 on the cutaneous manifestations of DM

Exploratory

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

Methodology:

This is a 24-week, Phase 2, randomized, double-blind, placebo-controlled trial of IMO-8400 in adult patients with active DM. The trial is designed to assess the safety, tolerability, and treatment effect of IMO-8400 in these patients.

Eligible patients will be randomized to 1 of 3 groups to receive once weekly subcutaneous (SC) injections of: placebo (Sterile Saline for Injection, United States Pharmacopeia [USP]/European Pharmacopeia [EP]) or 0.6 mg/kg or 1.8 mg/kg of IMO-8400 and will be stratified by baseline Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)v2-Activity score (15 to 20 vs. ≥21).

Screening evaluations will be completed at Visit 1 or within 28 days prior to administering the first dose of study drug. On scheduled site visits (which will occur at least every 4 weeks) study drug will be administered at the study site along with all scheduled assessments. At the discretion of the Investigator, a visiting nurse who has been trained in the protocol and approved by the Sponsor may conduct the intervening weekly study visits outside of the clinic (e.g., at the patient's home or workplace); the visiting nurse may administer intervening doses of study drug, collect vital signs, and assess for adverse events (AEs) and concomitant medications.

Adverse events and concomitant medications will be monitored continuously; the timing and frequency of all other scheduled assessments is specified in the Schedule of Events (SOE).

Based on results from a 39-week nonclinical toxicology study in cynomolgus monkeys showing that adverse effects were reliably preceded by changes in complement and markers of acute phase reactions, serum levels of complement component 3 (C3), complement component 4 (C4), hemolytic complement activity (CH50), albumin, globulin, and albumin:globulin (A:G) ratio will be regularly monitored during this study and the following safety monitoring/stopping rules will apply:

- If either the C3 or C4 level *and* the A:G ratio are below the lower limit of normal (LLN), study drug administration will be discontinued.
- If either the C3 or C4 level *or* the A:G ratio are below the LLN, a Patient Safety Committee (PSC) consisting of the Investigator, Sponsor Medical Monitor, and Clinical Research Organization (CRO) Medical Monitor will convene within 7 days of abnormal laboratory report and review all available safety data for the patient; the outcome of the meeting may be to discontinue study drug, to conduct additional safety assessments, or to continue study drug without modification of the planned safety assessments.

Another oligonucleotide investigational product has been associated with clinically significant AEs of thrombocytopenia and renal abnormalities as well as injection site reactions (ISRs) in human clinical studies (FDA 2015). Given IMO-8400 is also an oligonucleotide investigational product, platelet counts, anti-platelet antibodies, urine protein, and renal function will be regularly monitored and the following safety monitoring rules will apply:

- If urinalysis results indicate urine protein is greater than + 2, or estimated glomerular filtration rate (eGFR) is below 50% of baseline, or platelet count is below 75,000/µL, study drug administration will be interrupted and a PSC consisting of the Investigator, Sponsor Medical Monitor, and CRO Medical Monitor will convene within 7 days of the abnormal laboratory report and review all available safety data for the patient. The outcome of the meeting may be to discontinue study drug, to conduct additional safety assessments, or to continue study drug without modification of the planned safety assessments.

To further ensure the safety of study participants, study drug administration will be discontinued in any patient who experiences a serious adverse event (SAE) that is assessed by the Investigator as possibly related or probably related to study drug.

In addition to the role of the PSC, a Data Monitoring Committee (DMC) will review unblinded safety data as outlined in the DMC charter. The DMC may also increase or alter safety monitoring, or recommend other modifications to ensure patient safety.

Because SC administration of IMO-8400 has been associated with potentially unblinding ISRs, skin activity assessments, manual muscle testing (MMT), 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. Patients will also be asked to wear clothing that covers injection sites whenever attending study site visits.

All patients will complete End-of-Treatment (EOT) assessments at Visit 26/Week 25 (7 days ± 2 from the last dose of study drug). For patients who discontinue study drug prematurely, an Early Termination (ET) Visit is required within 5 days of the notification of withdrawal; EOT and ET assessments are the same. With Investigator approval, patients who successfully complete the EOT assessments may continue receiving treatment with IMO-8400 (or for patients randomized to placebo in this study, initiate treatment with IMO-8400) if an extension study for this trial is initiated. Additional information regarding procedures to consent patients for participation will be provided if an extension study is initiated.

To protect patient safety and facilitate assessment of treatment effects, patients will be prohibited from receiving other investigational agents during the study. Moreover, pre-existing immunomodulatory regimens should be kept stable throughout the study.

Inclusion / Exclusion Criteria:

The eligibility criteria are designed to include only those patients with an established diagnosis of DM and documented skin involvement who are able to safely participate in all study procedures. Patients who do not qualify for enrollment at the Screening Visit based on these criteria may be further assessed for eligibility at any time during the Screening Period (within 28 days prior to Visit 2/Week 1, Day 1). Under some circumstances, patients who fail to meet eligibility criteria during the Screening Period may be rescreened for study entry following discussion with the CRO Medical Monitor.

Inclusion Criteria

A patient who meets all of the following criteria will be eligible for this study.

1. Has signed the current, approved Informed Consent Form (ICF).
2. Is 18 to 75 years of age (inclusive) at the time of consent.
3. Has definite or probable DM based on the criteria of Bohan and Peter (Appendix 3; 1975a, 1975b) **OR** those patients who have all other definite or probable Bohan and Peter criteria but do not have heliotrope rash and Gottron's signs/papules may still be included if they have one or more of the following:
    a) DM autoantibody (anti-Mi-2, anti-MDA5, anti-TIF1-gamma, anti-NXP-2, anti-Jo-1, anti-PL-12, anti-PL-7, anti-EJ, anti-KS, anti-OJ); at least 1 autoantibody must be present and documented in the patient's medical record
    b) A classic DM associated skin change including at least one of the following: malar rash without sparing nasolabial folds, Shawl sign, V neck rash, periungal erythema, or mechanic's hands; documented in the patient's medical record
4. Has a CDASIv2-Activity score ≥15 at Visit 2 (Baseline).
5. Patients with muscle weakness are eligible; however, having muscle weakness is not mandatory. These patients have documented assessment of active muscle involvement as indicated by clinical evidence of symmetrical proximal muscle weakness involving limb-girdle and/or anterior neck flexors within 16 weeks prior to Baseline and one or more of the following:
    a) Elevation of serum creatine kinase (CK) or serum aldolase (ALD) levels >1.5 times the upper limit of normal (ULN) during Screening or >1.5 times increase compared to a documented within normal limits (WNL) level obtained prior to disease onset or while in prior remission
    b) Electromyography (EMG) demonstrating one or more of the following within 16 weeks prior to Baseline:
        i. Fibrillation potentials (increased insertional irritability and spontaneous activity)
        ii. Positive sharp waves and complex repetitive discharges
        iii. Short duration, small amplitude motor unit action potentials
    c) Muscle biopsy demonstrating one or more of the following within 16 weeks prior to Baseline:
        i. Perimysial and/or perivascular infiltration of mononuclear cells
        ii. Perifascicular atrophy
        iii. Note: Patients with a muscle biopsy demonstrating rimmed vacuoles or other histologic findings of Inclusion Body Myositis (IBM) are excluded
    d) Magnetic resonance imaging (MRI) demonstrating evidence of disease activity and inflammation on the short τ inversion recovery (STIR) image within 16 weeks prior to Baseline.
6. If on permitted concomitant medications at Screening, the therapy regimen can include one or more of the following:
    a) Stable dose of prednisone (or other oral equivalent) ≤20 mg/day (or ≤140 mg/week) for ≥4 weeks
    b) Stable regimen that does not exceed the approved dosages for ≥12 weeks of no more than 1 of the following non-steroidal immunomodulatory medication(s): intravenous immunoglobulin (IVIG), mycophenolate mofetil, cyclophosphamide, cyclosporine, leflunomide, tacrolimus, methotrexate, azathioprine
    c) Stable regimen of topical treatments for scalp involvement for ≥3 weeks

7. Study participants must have a diagnostic evaluation for cancer if the diagnosis of DM was within 2 years prior to the Screening Visit. The evaluation should include either:
    a) All age- and gender-appropriate screening tests and a computed tomography (CT) of the chest, abdomen, and pelvis; OR
    b) Positron emission tomography and computed tomography (PET/CT) of the chest, abdomen, and pelvis.

    Note: If a diagnostic evaluation for cancer has not been performed within 2 years prior to the Screening Visit in patients for whom it is required, either a CT of the chest, abdomen, and pelvis should be performed, OR a PET/CT of the chest, abdomen, and pelvis if this is standard practice in the particular center. The diagnostic evaluation for cancer must be normal for a patient to meet this inclusion criterion.
8. Study participants must have no evidence of active or latent tuberculosis (TB) after a diagnostic evaluation with a chest x-ray (CXR) OR chest CT and 1 of the following: a) a purified protein derivative (PPD) skin test, b) a QuantiFERON blood test, or c) T-SPOT.TB blood test.

    If the diagnostic evaluation has not been performed within 12 weeks of the Screening Visit, it may be performed during the Screening Period (performed per Center for Disease Control [CDC] guidelines [http://www.cdc.gov/tb/topic/testing/default.htm]).

    For the patient to be eligible, the result of the diagnostic evaluation should include a negative chest image and 1 of the following: a) a PPD skin test with ≤5-mm induration, b) a negative (not detected) QuantiFERON result, or c) a negative T-SPOT.TB blood test. If the QuantiFERON result is indeterminate, the test may be repeated once. If the repeat QuantiFERON test result is indeterminate, then a PPD skin test result may be used to confirm patient eligibility. The PPD skin test is not an acceptable method of TB testing in Sweden.
9. Women of childbearing potential and men must agree to use effective contraceptive methods from Screening throughout the study and until at least 4 weeks after the last dose of study drug.
    Non-childbearing potential is defined as a female who meets ***either*** of the following criteria:
    a) postmenopausal state defined as no menses for 12 months without an alternative medical cause or b) documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy.
    Effective contraception methods that can achieve a failure rate of <1% per year when used consistently and correctly are considered highly effective birth control methods. Such methods are defined as ***1*** of the following:
    a) True abstinence, defined as refraining from heterosexual intercourse, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.
    b) Vasectomized partner (if that vasectomized partner is the sole sexual partner of the woman of childbearing potential and has received medical assessment of the surgical success of the vasectomy)
    c) An intrauterine hormone-releasing system (IUS)
    d) Oral, intravaginal or transdermal combined (estrogen and progesterone) implanted hormonal contraceptive
    e) NOTE: For patients in Sweden, low dose oral contraceptives are not permitted
    f) An intra uterine device (IUD)
10. Agrees to use a broad-spectrum (UVA/UVB) sunscreen with an SPF ≥15 daily (or a water-resistant, broad spectrum sunscreen with an SPF ≥30 for extended outdoor activity), and to not increase their normal sun exposure during the course of this study.
11. Is willing and able to comply with this protocol.

Exclusion Criteria

A patient who meets any of the following criteria will be excluded from this study.

1. Has ongoing severe dysphagia (e.g., requires a feeding tube) for the 3 months prior to Screening
2. Has known hypersensitivity to any oligodeoxynucleotide
3. Has a history of drug abuse within one year of screening, or evidence of drug abuse by urine drug screening
4. Has a history of alcohol abuse within one year of screening
5. Is pregnant (or intends to become pregnant within 6 months of last dose of study medication) or nursing
6. Has body weight >140 kg
7. Has any one of the following hepatitis serologic test results:
    a) Positive hepatitis B surface antigen test (HBsAg), or
    b) Positive hepatitis B core antibody test (anti-HBc) AND negative hepatitis B surface antibody (anti-HBs), or
    c) Positive hepatitis C virus antibody test (anti-HCV)
8. Has evidence of seropositive test in the patient's medical records or is currently receiving treatment for human immunodeficiency virus (HIV)-1 or HIV-2
9. Has screening safety laboratory test meeting any of the following criteria:
    a) Hemoglobin <10.5 g/dL
    b) White blood cell (WBC) count <3000/mm^3
    c) Absolute neutrophil count (ANC) <1.5 x 10^9/L (1500/mm^3)
    d) Platelet count <100,000/mm^3
    e) Serum creatinine >1.2 mg/dL in female patients and >1.5 mg/dL in male patients. Patients with serum creatinine values exceeding limits may be eligible for the study if their eGFRs are >60 mL/min
    f) Serum aspartate transaminase (AST) or serum alanine transaminase (ALT) >5 times ULN (unless considered consistent with muscle origin and accompanied by gamma-glutamyl transferase (GGT) <1.5 times ULN)
    g) Total bilirubin >1.5 times ULN
    h) Prothrombin time (PT) >1.5 times ULN
    i) C3 or C4 <LLN
    j) A:G ratio <LLN
    k) Urinalysis with proteinuria >1+
10. Has a diagnosis of Juvenile DM, IBM, drug-induced toxic myopathy, metabolic myopathy, dystrophy, cancer-associated DM , or connective tissue disease-associated DM (e.g., overlap syndrome)
11. Has received one or more of following prohibited treatments within the interval noted prior to Screening (Visit 1):
    a) Rituximab within 24 weeks (*Note: patients who received rituximab are only eligible for inclusion if B-cell counts are confirmed to be within normal limits*)
    b) Intravenous corticosteroids within 12 weeks
    c) Intravenous immunosuppressive drugs within 12 weeks
    d) Any other monoclonal antibody, biologic agent, or investigational agent within 12 weeks or 5 half-lives (whichever is longer)
    e) Antimalarials (e.g., hydroxychloroquine) within 36 weeks
    f) Topical corticosteroids (excluding scalp) within 2 weeks
12. Has evidence of or has required treatment for cancer (except for treated, non-invasive carcinoma of the skin or cured carcinoma-in-situ following discussion with Medical Monitor) within 5 years
13. Has other chronic or active significant medical conditions within 6 months prior to Screening including but

not limited to: allogeneic organ transplant (e.g., solid organ, bone marrow, or stem cells); cardiac disease (e.g., unstable angina, myocardial infarction, ventricular arrhythmia); congestive heart failure; liver disease; neurological disease; hematological disease; kidney disease; uncontrolled seizure disorder; uncontrolled pulmonary disease; uncontrolled gastrointestinal disease; uncontrolled endocrinological disease; uncontrolled psychiatric disease; or uncontrolled diabetes mellitus

14. Has interstitial lung disease requiring the use of supplemental oxygen
15. Has received or is expected to receive any live viral or bacterial vaccination within 3 months prior to Screening
16. Has received a Bacille Calmette-Guerin (BCG) vaccination within 12 months of Screening or is expected to receive it during the course of the study
17. Has a history of or ongoing active, chronic, or recurrent infection (including bacterial, viral, parasitic, protozoal, and/or fungal/granulomatous infections [e.g., histoplasmosis, coccidioidomycosis, aspergillosis]) requiring treatment with systemic antimicrobials, antivirals, antiparasitics, antiprotozoals, or antifungals within 12 weeks prior to Screening, or serious infection (including but not limited to pneumonia, sepsis, bone or joint infection) requiring hospitalization or treatment with IV antibiotics within 12 weeks prior to Screening
18. Has a history of opportunistic infection or non-tuberculosis mycobacterial infection within 9 months prior to Screening
19. Has any other condition that would, in the opinion of the Investigator, potentially compromise the safety or compliance of the patient or preclude the patient's successful completion of the study

Number of Patients:

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

Investigational Product, Dosage and Mode of Administration:

IMO-8400 for Injection will be supplied as a sterile, lyophilized powder for reconstitution using Sterile Saline for Injection, USP/EP or Sterile Water for Injection USP/EP. Details of the dose preparation procedure are provided in the Pharmacy Manual. 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. Injection volume will be based on patient weight with a maximum volume of 1.4 mL.

Duration of Treatment:

The approximate duration of each patient's participation in the study is approximately 32 weeks, including 28 days of Screening, 24 weeks of study drug, an EOT Visit at 1 week after the last dose of study drug, and an End-of-Study (EOS) Visit for safety follow-up 4 weeks after the EOT Visit.

Reference Therapy, Dosage and Mode of Administration:

Placebo will be Sterile Saline for Injection, USP/EP, which will be indistinguishable in appearance to IMO-8400 injection solution and will be administered in the same manner.

Assessments

Safety:

- AEs, reported and observed
- Physical examination findings, including vital signs
- Standard laboratory safety tests including hematology, chemistry, coagulation and urinalysis
- Assessment of ISRs
- Electrocardiograms (ECG)
- Laboratory safety assessments including CH50, C3, C4, troponin, C-reactive protein (CRP), A:G ratio, proteinuria, eGFR, and platelet count

Efficacy:

- CDASI-Activity score (modified CDASI version 2, mCDASIv2)
- International Myositis Assessment Clinical Study (IMACS) "Core Set Measures" (CSMs):
  - Manual muscle testing-8 (MMT8)
  - Serum CK, ALD, lactate dehydrogenase (LDH), ALT, and AST
- Timed Function Tests
  - 10-meter walk-run test (10MWR)
  - Timed up and go test (TUG)
  - 4 stair climb test
- Short Form-36 Health Survey (SF-36)
- 5-D Itch Scale (5-D Pruritis Scale)

Pharmacokinetic:

- Blood samples for determination of IMO-8400 plasma concentrations (pre-dose and 2 hours [± 15 minutes] post-dose)

Pharmacodynamic:

- Skin biopsies (2 punch biopsies at each scheduled assessment) for: 1) Type 1 and Type 2 Interferon (IFN) gene expression signature, and 2) histology testing
- Whole blood samples for Type 1 and Type 2 IFN gene expression signature
- Serum samples for cytokines/chemokines panel

Disease-specific Autoantibodies :

- Serum samples for 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.

Immunogenicity:

- Serum samples for antibodies to IMO-8400 and antibodies to double-stranded deoxyribonucleic acid (dsDNA)

Statistical Methods

Determination of Sample Size

This study has approximately 80% power to detect a difference of 7 points in change from baseline on the mCDASIv2-Activity score at Week 25 using a 1-sided test with an alpha of 0.05.

Randomization

Randomization will be performed centrally in a 1:1:1 ratio (placebo or IMO-8400 at 0.6 mg/kg or 1.8 mg/kg) and will be stratified by baseline CDASIv2-Activity score (15 to 20 vs. ≥21).

Analysis Populations

- Safety Population and Intent-to-Treat Population (ITT): All patients who received at least 1 injection of study medication
- Per Protocol Population (PP): All patients who received at least 20 doses of study drug as assigned, completed the EOT Visit 26/Week 25, and had no major protocol violations that would potentially influence treatment effect (as determined by review by Idera prior to unblinding)

Safety analyses will be performed using the Safety Population. The efficacy, PD, disease-specific autoantibodies, and immunogenicity assessments will be analyzed for the ITT population; key endpoints may be also analyzed for the PP Population as specified in the Statistical Analysis Plan (SAP).

Primary Safety and Tolerability Endpoints

- Number of patients discontinuing treatment due to AEs

- Frequency and severity of AEs
- Physical examination findings, including vital signs
- Standard laboratory safety tests including hematology, chemistry, coagulation and urinalysis
- Assessment of ISRs
- ECG findings
- Laboratory safety assessments including CH50, C3, C4, troponin, CRP, albumin, globulin, A:G ratio, proteinuria, eGFR, and platelet count

Primary Efficacy Endpoint

- Change from baseline in mCDASIv2-Activity score

Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by event, grade, and relationship to study therapy. Safety analyses will be descriptive in nature; no statistical hypothesis testing will be performed.

Efficacy Analyses

The primary endpoint will be assessed via a repeated measures mixed model (RMMM). An appropriate covariance structure for repeated measures will be used. The difference between each IMO-8400 treatment group and placebo at Week 25 will be assessed. The overall alpha level will be controlled using the Bonferroni-Holm step-down method. Further details of this analysis will be described in the SAP. A sensitivity analysis to test the effect of important covariates on the effect of IMO-8400 will be performed using a RMMM. Differences in response rate between the IMO-8400 treatment groups and placebo will be assessed via logistic regression.

The MMT8, TUG, 4 stair climb test, timed 10MWR test, serum CK, ALD, LDH, AST, ALT, SF-36, and 5-D Itch Scale will be analyzed in a similar manner to the primary endpoint.

Continuous endpoints will be summarized descriptively. Categorical endpoints will be summarized by the number and percentage of patients in each category, and 95% confidence intervals for the proportion.

For the proportion of patients who meet the IMACS 2004 definition of improvement (DOI) (Rider 2004) at EOT, logistic regression will be performed. Other exploratory and sensitivity analyses will be specified in the SAP in addition to further details regarding the statistical methodology.

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 may be used to evaluate/interpret time-dependent trends.

Pharmacodynamic, Disease-specific Autoantibodies, and Immunogenicity Analyses

Pharmacodynamic, disease-specific autoantibodies, and immunogenicity study parameters will be summarized using descriptive statistics.

3 SCHEDULE OF EVENTS

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	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	
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	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		
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; C3 = complement component 3; C4 = complement component 4; CDASI = Cutaneous Disease and Activity Severity Index; Con Med = concomitant medication; CH50 = hemolytic complement activity; CRP = C-reactive protein; CT = computed tomography; D = day; dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End-of-Study; EOT = End-of-Treatment; ET = Early Termination; IFN = Type 1 and Type 2 interferon; Lab. = laboratory; MMT8 = manual muscle testing; PK = pharmacokinetic; PPD = purified protein derivative; SF-36 = 36-Item Short Form Health Survey; TB = tuberculosis; Wk = Week.
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 ET Visit will be performed within 5 days of the notification of withdrawal. The 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.
[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 ≤5-mm induration, b) a negative (not detected) QuantiFERON result, or c) T-SPOT. The PPD skin test is not an acceptable method of TB testing in Sweden.
[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.

4 BACKGROUND

4.1 Purpose of Study

The purpose of this Phase 2, randomized, double blind, placebo-controlled trial is to assess the efficacy, safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), disease-specific autoantibodies, and immunogenicity of IMO-8400 in adult patients with dermatomyositis (DM). Eligible patients will have confirmed skin involvement. Muscle involvement will be assessed but is not required. Enrolled patients will receive subcutaneous (SC) injections of 0.6 or 1.8 mg/kg of IMO-8400 or placebo (Sterile Saline for Injection, United States Pharmacopeia [USP]/European Pharmacopeia [EP]) once a week for 24 weeks. If an extension study for this trial is initiated, with Investigator approval, patients who successfully complete this study may be eligible to continue receiving treatment with IMO-8400 (or for patients randomized to placebo in this study, initiate treatment with IMO-8400).

4.2 Dermatomyositis Overview

Dermatomyositis is a rare, progressively debilitating, idiopathic inflammatory myopathy associated with significant morbidity and an increased risk of premature death. Affecting less than 70,000 people in the United States (US), it is approximately twice as common in women as men, with an age of onset that typically peaks between 45 to 65 years in adults, and 5 to 15 years in children (Prieto 2010).

Dermatomyositis is a multisystem disorder with a wide variety of clinical manifestations including lung, joint, esophageal, and cardiac findings; however, its hallmark features include the characteristic skin manifestations of Gottron's papules, Gottron's sign, and heliotrope rash, and progressive, symmetrical weakening of proximal muscles. Additional cutaneous symptoms may include photodistributed erythema, poikiloderma, nailfold changes, scalp involvement, and calcinosis cutis. Proximal muscle weakness, especially in the deltoids, hip flexors and neck flexors, may be associated with contractures and elevations in muscle enzymes, and often cause significant limitations on activities of daily living, such as difficulty climbing stairs, getting up from a chair, carrying heavy groceries, or picking up children. In more severe cases, respiratory and oropharyngeal muscle involvement can cause dysphagia, respiratory difficulties and *ab ingestis* pneumonia. Other symptoms of DM include fever, malaise, weight loss and arthralgias, heart failure, left ventricular diastolic dysfunction, hyperkinetic left ventricular contraction, and interstitial lung disease (Iaccarino 2014). While outcome studies in DM have primarily focused on the associated symptoms affecting the muscles in DM patients, the skin manifestations of DM can be a very active component of the disease. The skin manifestations of DM can be quite challenging to treat, and are often equally devastating to patients (Robinson 2015).

The diagnosis of DM is often based on its skin manifestations, which are easy to recognize upon physical examination. Moreover, Gottron and heliotrope rashes are DM-specific and usually do not require histological confirmation. The diagnostic criteria of Bohan and Peter, initially proposed in 1975, require a combination of skin and muscle symptoms to establish a diagnosis of DM and are still widely accepted today (Appendix 3; Bohan 1975a, Bohan 1975b).

Treatment for DM usually involves a combination of approaches with a focus on controlling the skin and muscle disease. Currently, there are only 2 drugs approved for the treatment of DM, Acthar gel (a highly purified sterile preparation of adrenocorticotropic hormone [ACTH]) and

prednisone; all other pharmacologic interventions are used off-label. Skin disease may be treated by avoiding sun exposure (as the cutaneous manifestations are extremely photosensitive) and/or with topical corticosteroids, antimalarial agents, immunomodulatory medications and intravenous immunoglobulin (IVIG) (Ang 2005, Levine 2012). Muscle weakness is also most commonly treated with corticosteroids, typically in conjunction with an immunosuppressive agent. Patients may also require assistive devices for ambulation, as well as adaptive strategies to minimize gastrointestinal complications secondary to esophageal muscle weakness, e.g., elevation of head of bed, avoidance of eating before bedtime.

Unfortunately, many patients do not achieve full control of symptoms with prednisone and/or experience intolerable side effects, including infection, weight gain, mood/behavioral changes, osteoporosis, Cushing's disease, and diabetes (Harris 2015). Glucocorticoids have also been associated with myopathy, which is a serious concern for patients with DM (Schakman 2009). Thus, there is an unmet medical need for safe and effective treatments for patients with DM.

4.3 IMO-8400 as a Potential Therapy for the Treatment of DM

While the initial cause of DM is not known, once inflammation is established, injured cells release nucleic acids, which in turn activate specific intracellular Toll-like receptors (TLRs 7, 8, and 9) expressed on the regenerating muscle cells, keratinocytes, and B-cells. Toll-like receptor activation in turn amplifies the inflammatory response, resulting in further damage to skin and muscle. Thus, blocking TLR activation represents a potential mechanism for interrupting the inflammatory cycle and offers a novel treatment approach for patients with DM.

Idera Pharmaceuticals, Inc. (Idera; Sponsor) is developing a SC formulation of IMO-8400, a novel synthetic phosphorothioate oligonucleotide antagonist to TLRs 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.

Moreover, in vivo studies have demonstrated IMO-8400's therapeutic potential in animal models for several autoimmune diseases including systemic lupus erythematosus, arthritis, psoriasis, and dermal inflammation.

5 STUDY OBJECTIVES

5.1 Primary

The primary objectives of this study are:

- To assess the safety and tolerability of IMO-8400 in adult patients with active DM
- To assess the effect of IMO-8400 on the cutaneous manifestations of DM

5.2 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 PD measures
- To assess plasma concentrations of IMO-8400 over time
- To characterize the enrolled population based on disease-specific autoantibody profiles for potential subgroup analyses
- To assess the immunogenicity of IMO-8400

6 STUDY ENDPOINTS AND DESIGN

6.1 Study Endpoints

6.1.1 Primary Endpoints

6.1.1.1 Primary Safety and Tolerability Endpoints

- Number of patients discontinuing treatment due to adverse event (AE)
- AEs, reported and observed
- Physical examination findings, including vital signs
- Standard laboratory safety tests including hematology, chemistry, coagulation and urinalysis
- Assessment of injection site reactions (ISRs)
- Electrocardiograms (ECG)
- 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 platelet count

6.1.1.2 Primary Efficacy Endpoint

- Change from baseline in Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)-Activity score (modified CDASI version 2 [mCDASIv2])

6.1.2 Exploratory Endpoints

6.1.2.1 Exploratory Efficacy Endpoints

- Change from baseline in the following International Myositis Assessment Clinical Study (IMACS) "Core Set Measures" (CSMs). Improvement will be assessed using the IMACS group definitions of improvement (DOIs) (2004 DOI [Rider 2004]):
  - 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:
  - 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)
- Change from baseline in the 5-D Itch Scale

6.1.2.2 Pharmacokinetic Endpoints

- IMO-8400 plasma concentrations pre-dose and 2 hours (± 15 minutes) post-dose to confirm systemic exposure

6.1.2.3 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
- Change from baseline in histology results, using skin biopsies.
- Change from baseline in DM relevant cytokines/chemokine levels, including interleukin (IL) 6, IL-8, IP-10, I-TAC, MCP-1, MCP-2, and tumor necrosis factor alpha (TNFα); additional or alternative cytokines or chemokines may be assessed.

6.1.2.4 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.

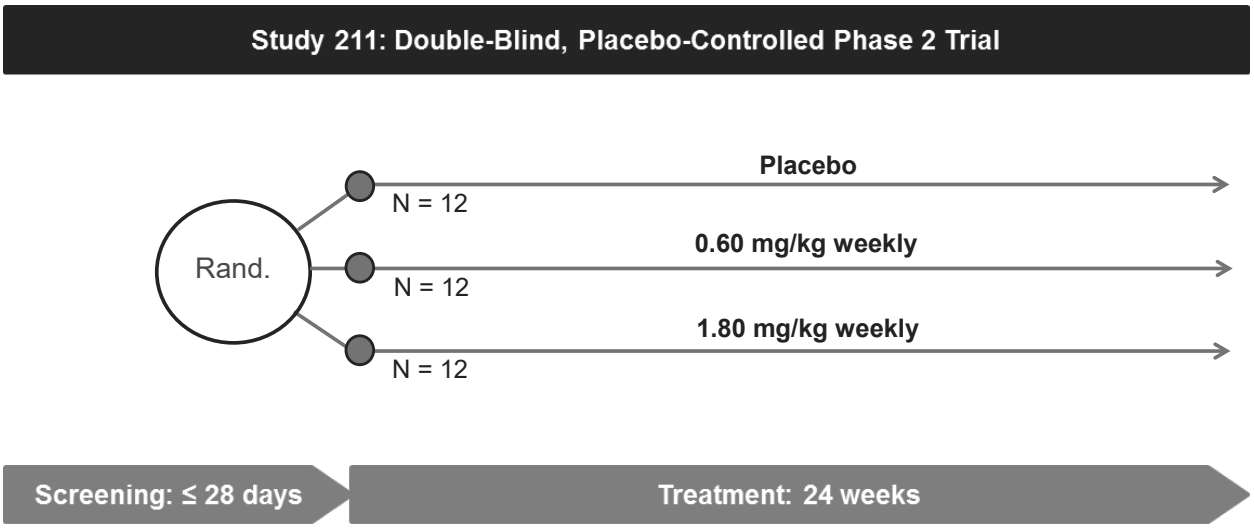
6.1.2.5 Immunogenicity Endpoint

- Change from baseline in presence of antibodies to IMO-8400 and anti-double-stranded deoxyribonucleic acid (dsDNA)

6.2 Study Design

This is a 24-week, Phase 2, randomized, double-blind, placebo-controlled trial of IMO-8400 in adult patients with DM with documented active skin disease. The trial is designed to assess the safety, tolerability, and treatment effect of IMO-8400 in these patients. The study scheme is shown in Figure 1.

Figure 1: Study Schematic



Eligible patients will be randomized to 1 of 3 treatment groups to receive once weekly SC injections of 0.6 or 1.8 mg/kg of IMO-8400 or placebo (Sterile Saline for Injection, USP/EP) and will be stratified by baseline CDASIv2-Activity score (15 to 20 vs. ≥21).

Screening evaluations will be completed at Visit 1 or within 28 days prior to the first dose of study drug at Visit 2/Week 1, Day 1. Study drug will be administered SC once a week. At scheduled site visits (which will occur at least every 4 weeks, i.e., at study Weeks 1, 5, 9, 13, 17, and 21) study drug will be administered at the study site along with all scheduled assessments. At the discretion of the Investigator, a visiting nurse who has been trained in the protocol and approved by the Sponsor may conduct the intervening weekly study visits outside of the clinic (e.g., at the patient's home or workplace); the visiting nurse may administer intervening doses of study drug, collect vital signs, and assess for AEs and concomitant medications.

Adverse events and concomitant medications will be monitored continuously; the timing and frequency of all other scheduled assessments is specified in the Schedule of Events (SOE) in Section 3.

Based on results from the 39-week nonclinical toxicology study in cynomolgus monkeys showing that adverse effects were reliably preceded by changes in complement and markers of acute phase reactions, serum levels of C3, C4, albumin, globulin, and A:G ratio will be regularly monitored during this study, and the following safety monitoring/stopping rules (fully defined in Section 8.3.2) will apply:

- If either the C3 or C4 level *and* the A:G ratio are below the lower limit of normal (LLN), study drug administration will be discontinued.
- If either the C3 or C4 level or the A:G ratio are below the LLN, a Patient Safety Committee (PSC) consisting of the Investigator, Idera Medical Monitor, and Clinical Research Organization (CRO) Medical Monitor will convene within 7 days of the abnormal laboratory test report and review all available safety data for the patient; the outcome of the meeting may be to discontinue study drug, to conduct additional safety assessments, or to continue study drug without modification of the planned safety assessments.

Another oligonucleotide investigational product has been associated with clinically significant AEs of thrombocytopenia and renal abnormalities as well as ISRs in human clinical studies (FDA 2015). Given IMO-8400 is also an oligonucleotide investigational product, platelet counts, anti-platelet antibodies, urine protein, and renal function will be regularly monitored and the following safety monitoring rules will apply:

- If urinalysis results indicate urine protein is greater than + 2, or eGFR is below 50% of baseline, or platelet count is below 75,000/µL, study drug administration will be interrupted and a PSC consisting of the Investigator, Sponsor Medical Monitor, and CRO Medical Monitor will convene within 7 days of the abnormal laboratory report and review all available safety data for the patient. The outcome of the meeting may be to discontinue study drug, to conduct additional safety assessments, or to continue study drug without modification of the planned safety assessments.

To further ensure the safety of study participants, study drug administration will be discontinued in any patient who experiences an serious adverse event (SAE) that is assessed by the Investigator as possibly related or probably related to study drug (see Section 8.3.5).

In addition to the PSC, a Data Monitoring Committee (DMC) will review unblinded safety data as outlined in the DMC charter. The DMC may also increase or alter safety monitoring, or recommend other modifications to ensure patient safety.

Because SC administration of IMO-8400 has been associated with potentially unblinding ISRs, the mCDASIv2, MMT8, and timed function tests (10MWR, TUG and 4 stair climb 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 other than administering the efficacy assessments. Patients will also be asked to wear clothing that covers injection sites when attending site visits.

All patients will complete End-of-Treatment (EOT) assessments at Visit 26/Week 25; (7 days ± 2 from the last dose of study drug). For patients who discontinue study drug prematurely, an Early Termination (ET) Visit is required within 5 days of the notification of withdrawal; EOT and ET assessments are the same.

If an extension study for this trial is initiated, with Investigator approval, patients who successfully complete this study may be eligible to continue receiving treatment with IMO-8400 (or for patients 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 prior to any extension study dosing at the EOT Visit 26/Week 25 (i.e., Visit 1/Week 1 of the extension study. All patients who discontinue study drug prematurely or decline participation in an extension study will undergo safety follow-up at the End-of-Study (EOS) Visit 27/Week 29, 4 weeks after completing EOT/ET assessments.

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

To protect patient safety and facilitate assessment of treatment effects, patients will be prohibited from receiving other investigational agents during the study. Moreover, pre-existing immunomodulatory regimens should be kept stable throughout the study (see Section 9.2 for additional guidance).

6.2.1 Benefits and Risk Assessment

Dermatomyositis is a rare, progressively debilitating, idiopathic inflammatory myopathy associated with significant morbidity and an increased risk of premature death. Unfortunately, many patients do not achieve full control of symptoms with prednisone and/or experience intolerable side effects, including infection, weight gain, mood/behavioral changes, osteoporosis, Cushing's disease, and diabetes (Harris 2015). Glucocorticoids have also been associated with myopathy, which is a serious concern for patients with DM (Schakman 2009). While the initial cause of DM is not known, once inflammation is established, injured cells release nucleic acids, which in turn activate specific intracellular TLRs (TLRs 7, 8, and 9) expressed on the regenerating muscle cells, keratinocytes, and B-cells. Toll-like receptor activation in turn amplifies the inflammatory response, resulting in further damage to skin and muscle. Thus, blocking TLR activation represents a potential mechanism for interrupting the inflammatory cycle and offers a novel treatment approach for patients with DM.

Toll-like receptors are a family of host sensors for "foreign" constituents (e.g., nucleic acids, lipopolysaccharides, peptidoglycans from viruses, bacteria, fungi) that "sound the alarm" and activate host immune defenses. The natural ligands for TLRs 7 and 8 are single-stranded ribonucleic acid from viruses, and for TLR9, unmethylated cytosine-guanine dinucleotide motifs, which are characteristic of bacterial DNA. Binding of the nucleic acid ligands to the cognate TLR results in intracellular signaling, generation of nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), and production of pro-inflammatory (T helper 1) chemokines and cytokines, including IFN-α, TNF-α, and IL-12. Toll-like receptors 7, 8, and 9 are located in the endosome whereas, most other TLRs are located on the host cell surface. In man, the endosomal TLRs are expressed primarily on dendritic cells and B-cells.

IMO-8400 is a selective antagonist of the endosomal TLRs 7, 8, and 9. The pharmacology of IMO-8400 has been examined using in vitro assays of mouse, monkey, and human cells; in vivo studies in healthy mice and monkeys; murine models of autoimmune disease; and in studies using human B-cell lymphoma lines both in vitro and in murine xenograft models. These studies demonstrate that IMO-8400 specifically inhibits the activity of TLRs 7, 8, and 9 agonists, and directly support the hypothesis that this effect has therapeutic potential in multiple autoimmune diseases and in B-cell malignancies characterized by the myeloid differentiation primary response gene 88 L265P oncogenic mutation.

The only secondary pharmacologic effect of IMO-8400 identified was activation of the complement pathway in non-human primates. Activation of the alternative complement pathway in non-human primates is a well-described effect of phosphorothioate oligonucleotides. This process has been related to the polyanionic nature of this class of agents and is independent of the intended pharmacological mechanism of action. IMO-8400 and other phosphorothioate oligonucleotides also activate the classical complement pathway in long-term toxicity studies in monkeys (39 weeks), which has been correlated with adverse treatment-related histological changes in this species. As of 01 February 2016, complement activation has not been seen in the 42 patients treated to date.

IMO-8400 is being developed as an immune modulator for the potential treatment of DM and other disorders. It offers multiple potential advantages:

- A novel target and mechanism of action
- Broader activity than currently available agents such as monoclonal antibodies to IFN-α or TNF-α, which block only 1 of the multiple cytokines induced by TLR activation (Celhar 2012, Means 2005)
- Greater specificity than such agents — the induction of those cytokines as critical host defenses is blocked only when the response is induced through TLRs 7, 8, or 9
- Could serve as an alternative or dose-sparing adjunct to currently available therapies

Overall, the adverse observations in nonclinical toxicity studies with IMO-8400 have been reported with other oligonucleotides. Adverse pathological findings of myocardial degeneration/necrosis, glomerulonephritis, and/or hepatocellular necrosis that were noted in non-human primates are thought to be the result of treatment-related vascular inflammation that was preceded by IMO-8400 treatment effects on serum complement (most notably C4) and acute phase response markers (most notably globulin and C-reactive protein) in affected animals. Such observations are reported in chronic toxicity studies in monkeys with other phosphorothioate oligonucleotides and have not been observed in humans or other species.

Frequent monitoring of serum complement (C3, C4, and CH50) and albumin:globulin ratio is included in clinical trials with IMO-8400 in order to determine the relevance of these findings to humans. Appropriate safety parameters are included in the PIONEER (8400-211) protocol (see Section 8.3.2). IMO-8400 was not mutagenic, clastogenic, or genotoxic in standard genotoxicity models.

Clinical studies of IMO-8400 have been completed in healthy subjects and patients with moderate to severe plaque psoriasis, and are currently ongoing in patients with Waldenström's macroglobulinemia (WM) and in patients with diffuse large B-cell lymphoma (DLBCL).

As of 22 November 2016, 104 subjects/patients have been exposed to IMO-8400, including 30 healthy subjects, 35 patients with psoriasis, 2 patients with DM, 31 patients with WM, and 6 patients with DLBCL. Subjects/patients have been exposed to doses ranging from 0.075 mg/kg/week to 2.4 mg/kg/week with a maximum duration of exposure of 91 weeks.

Data analyses in patients with psoriasis and WM have demonstrated clinical activity but no statistically significant treatment differences have been demonstrated. While statistical significance has not been demonstrated, these data do support the hypothesis that there is therapeutic potential for IMO-8400 where TLRs are implicated in the pathogenesis of the disease.

The safety profile in the 86 subjects exposed to repeat dosing of IMO-8400 at any dosage indicates that IMO-8400 has been generally well tolerated. There have been no treatment-related deaths and 3 drug-related SAEs were reported, which were a probable flare of pre-existing arthritis, arthralgia, and sepsis in Study 8400-401. Four subjects have discontinued treatment with IMO-8400 due to the following treatment-related AEs: chills, arthralgia, arthritis, and rash maculo-papular. There have been no other discontinuations due to drug-related treatment-emergent AEs. The most common adverse reactions seen with IMO-8400 include:

- Injection site reactions (e.g., erythema, induration, pruritus, tenderness, and pain). No blistering, ulceration, or necrosis have been observed.
- Non-specific, low grade symptoms (e.g., fever, chills, myalgias, headache, diarrhea, fatigue, and nausea). These typically had an onset approximately 8 hours post-injection and generally resolved in 1 to 2 days.

These events have been reported in most patients and are typically mild to moderate in intensity. The systemic symptoms have been readily managed with non-steroidal anti-inflammatory drugs. The ISRs have not required specific treatment; some subjects have reported benefit from ice packs.

No clinically relevant changes in laboratory values, vital signs, or ECGs have been noted in the completed studies, and based upon review of data from ongoing studies, no irreversible or unmanageable toxicities have been seen.

In summary, IMO-8400 has demonstrated biological and clinical activity supporting proof of mechanism and the adverse observations in nonclinical toxicity studies with IMO-8400 have been reported with other oligonucleotides. Safety parameters associated with toxicities identified in the nonclinical program can and will be monitored in the clinic. Further, IMO-8400 has been well tolerated to date with identified adverse reactions being reversible and manageable.

In summary, when the totality of the data are taken into account, the risk-benefit profile is acceptable. Refer to the IB for further information about IMO-8400.

6.3 Patient Study Participation and Study Completion

6.3.1 Patient Participation

The length of a patient's participation will be from the time the informed consent form (ICF) is signed until their last visit is complete and will be approximately 32 weeks, including screening up to 28 days prior to treatment, 24 weeks of study drug, an EOT Visit at 7 days ± 2 days after the last dose of study drug, and an EOS Visit for safety follow-up 4 weeks after the EOT Visit. Regardless of whether they have completed study treatment, a patient will be considered to have completed the study when they have either:

- Completed their EOT assessments at Visit 26 (Week 25) and enrolled in an extension study (if initiated)
- Completed EOT and EOS assessments at Visits 26 and 27 (Week 29), respectively

6.3.2 Premature Patient Discontinuation or Treatment Discontinuation

Patients are free to withdraw consent and/or discontinue participation in the study at any time, without prejudice to further medical care. Patients can also be withdrawn for the reasons specified in Section 11.5. Patients withdrawn from the study complete the EOT/ET Visit 26/Week 25 assessments (Section 10.1.4) and the EOS Visit 27/Week 29 assessments (Section 10.1.5) 4 weeks later.

6.3.3 Overall Study Completion

The study will be considered to be complete when the last patient has completed their EOT Visit 26/Week 25 assessments and has either enrolled in the extension study (if initiated) or has completed the EOS Visit 27/Week 29) assessments, whichever is last.

7 PATIENT POPULATION AND SELECTION

The eligibility criteria are designed to include only those patients with an established diagnosis of DM and documented skin involvement who are able to safely participate in all study procedures. Patients who do not qualify for enrollment at the actual Screening Visit based on these criteria may be further assessed for eligibility at any time during the Screening Period (within 28 days prior to Week 1, Day 1). Under some circumstances, patients who fail to meet eligibility criteria during the Screening period may be rescreened for study entry following discussion with the CRO Medical Monitor.

7.1 Inclusion Criteria

A patient who meets all of the following criteria will be eligible for this study.

1. Has signed the current, approved ICF.

2. Is 18 to 75 years of age (inclusive) at the time of consent.

3. Has definite or probable DM based on the criteria of Bohan and Peter (Appendix 3; 1975a, 1975b) **OR** those patients who have all other definite or probable Bohan and Peter criteria but do not have heliotrope rash and Gottron's signs/papules may still be included if they have one or more of the following:

    a) DM autoantibody (anti-Mi-2, anti-MDA5, anti-TIF1-gamma, anti-NXP-2, anti-Jo-1, anti-PL-12, anti-PL-7, anti-EJ, anti-KS, anti-OJ); at least 1 autoantibody must be present and documented in the patient's medical record

    b) A classic DM associated skin change including at least one of the following: malar rash without sparing nasolabial folds, Shawl sign, V neck rash, periungal erythema, or mechanic's hands; documented in the patient's medical record

4. Has a CDASIv2-Activity score ≥15 at Visit 2 (Baseline).

5. Patients with muscle weakness are eligible; however, having muscle weakness is not mandatory. These patients have documented assessment of active muscle involvement as indicated by clinical evidence of symmetrical proximal muscle weakness involving limb-girdle and/or anterior neck flexors within 16 weeks prior to Baseline and one or more of the following:

    a) Elevation of serum CK or serum ALD levels >1.5 times the upper limit of normal (ULN) during Screening or >1.5 times increase compared to a documented within normal limits (WNL) level obtained prior to disease onset or while in prior remission

    b) Electromyography (EMG) demonstrating one or more of the following within 16 weeks prior to Baseline:

        i. Fibrillation potentials (increased insertional irritability and spontaneous activity)

ii. Positive sharp waves and complex repetitive discharges

iii. Short duration, small amplitude motor unit action potentials

c) Muscle biopsy demonstrating one or more of the following within 16 weeks prior to Baseline:

i. Perimysial and/or perivascular infiltration of mononuclear cells

ii. Perifascicular atrophy

iii. Note: Patients with a muscle biopsy demonstrating rimmed vacuoles or other histologic findings of Inclusion Body Myositis (IBM) are excluded

d) Magnetic resonance imaging (MRI) demonstrating evidence of disease activity and inflammation on the short τ inversion recovery (STIR) image within 16 weeks prior to Baseline.

6. If on permitted concomitant medications at Screening, the therapy regimen can include one or more of the following:
   a) Stable dose of prednisone (or other oral equivalent) ≤20 mg/day (or ≤140 mg/week) for ≥4 weeks

   b) Stable regimen that does not exceed the approved dosages for ≥12 weeks of no more than 1 of the following non-steroidal immunomodulatory medication(s): IVIG, mycophenolate mofetil, cyclophosphamide, cyclosporine, leflunomide, tacrolimus, methotrexate, azathioprine (see Table 4)

   c) Stable regimen of topical treatments for scalp involvement for ≥3 weeks

7. Study participants must have a diagnostic evaluation for cancer if the diagnosis of DM was within 2 years of the Screening Visit. The evaluation should include either:

   a) All age- and gender-appropriate screening tests and computed tomography (CT) of the chest, abdomen, and pelvis; OR

   b) Positron emission tomography and computed tomography (PET/CT) of the chest, abdomen, and pelvis.
   Note: If a diagnostic evaluation for cancer has not been performed within 2 years prior to the Screening Visit in patients for whom it is required, either a CT of the chest, abdomen, and pelvis should be performed, OR a PET/CT of the chest, abdomen, and pelvis if this is standard practice in the particular center. The diagnostic evaluation for cancer must be normal for a patient to meet this inclusion criterion.
   Note: See Appendix 1 and Appendix 2 for guidelines on age and gender-appropriate workup.

8. Study participants must have no evidence of active or latent TB after a diagnostic evaluation with a chest x-ray (CXR) OR chest CT and 1 of the following: a) a purified protein derivative (PPD) skin test, b) a QuantiFERON blood test, or c) T-SPOT.TB blood test.

   If the diagnostic evaluation has not been performed within 12 weeks of the Screening Visit, it may be performed during the Screening Period (performed per Center for Disease Control [CDC] guidelines [http://www.cdc.gov/tb/topic/testing/default.htm]).

   For the patient to be eligible, the result of the diagnostic evaluation should include a negative chest image and 1 of the following: a) a PPD skin test with ≤5-mm induration, b) a negative (not detected) QuantiFERON result, or c) a negative T-SPOT.TB blood test. If the QuantiFERON result is indeterminate, the test may be repeated once. If the repeat QuantiFERON test is indeterminate, then a PPD skin test may be used to confirm patient eligibility. The PPD skin test is not an acceptable method of TB testing in Sweden.

9. Women of childbearing potential and men must agree to use effective contraceptive methods from Screening throughout the study and until at least 4 weeks after the last dose of study drug.

   Non-childbearing potential is defined as a female who meets ***either*** of the following criteria: a) postmenopausal state defined as no menses for 12 months without an alternative medical cause or b) documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy.

   Effective contraception methods that can achieve a failure rate of <1% per year when used consistently and correctly are considered highly effective birth control methods. Such methods are defined as ***1*** of the following:

   a) True abstinence, defined as refraining from heterosexual intercourse, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.

   b) Vasectomized partner (if that vasectomized partner is the sole sexual partner of the woman of childbearing potential and has received medical assessment of the surgical success of the vasectomy)

   c) An intrauterine hormone-releasing system (IUS)

   d) Oral, intravaginal, or transdermal combined (estrogen and progesterone) implanted hormonal contraceptive

   e) NOTE: For patients in Sweden, low dose oral contraceptives are not permitted

   f) An intra-uterine device (IUD)

10. Agrees to use a broad-spectrum (UVA/UVB) sunscreen with an SPF ≥15 daily (or a water-resistant, broad spectrum sunscreen with an SPF ≥30 for extended outdoor activity), and agrees to not increase their normal sun exposure during the course of this study.

11. Is willing and able to comply with this protocol.

7.2 Exclusion Criteria

A patient who meets any of the following criteria will be excluded from this study.

1. Has ongoing severe dysphagia (e.g., requires a feeding tube) for the 3 months prior to screening

2. Has known hypersensitivity to any oligodeoxynucleotide

3. Has a history of drug abuse within one year of screening, or evidence of drug abuse by urine drug screening

4. Has a history of alcohol abuse within one year of screening

5. Is pregnant (or intend to become pregnant within 6 months of last dose of study medication) or nursing

6. Has body weight >140 kg

7. Has any one of the following hepatitis serologic test results:

    a) Positive hepatitis B surface antigen test (HBsAg), or

    b) Positive hepatitis B core antibody test (anti-HBc) AND negative hepatitis B surface antibody (anti-HBs), or

    c) Positive hepatitis C virus antibody test (anti-HCV)

8. Has evidence of seropositive test in the patient's medical records or is currently receiving treatment for human immunodeficiency virus (HIV)-1 or HIV-2

9. Has screening safety laboratory test meeting any of the following criteria:

    a) Hemoglobin <10.5 g/dL

    b) White blood cell (WBC) count <3000/mm^3

    c) Absolute neutrophil count (ANC) <1.5 x 10^9/L (1500/mm^3)

    d) Platelet count <100,000/mm^3

e) Serum creatinine >1.2 mg/dL in female patients and >1.5 mg/dL in male patients. Patients with serum creatinine values exceeding limits may be eligible for the study if their eGFR are >60 mL/min.

f) Serum AST or serum ALT >5 x ULN (unless considered consistent with muscle origin and accompanied by gamma-glutamyl transferase [GGT] <1.5 x ULN)

g) Total bilirubin >1.5 x ULN

h) Prothrombin time (PT) >1.5 x ULN

i) C3 or C4 <LLN

j) A:G ratio <LLN

k) Urinalysis with proteinuria >1+

10. Has a diagnosis of Juvenile DM, IBM, drug-induced toxic myopathy, metabolic myopathy, dystrophy, cancer-associated DM , or connective tissue disease-associated DM (e.g., overlap syndrome)

11. Has received one or more of following prohibited treatments within the interval noted prior to Screening (Visit 1):

a) Rituximab within 24 weeks (*Note: patients who received rituximab are only eligible for inclusion if B-cell counts are confirmed to be within normal limits*)

b) Intravenous corticosteroids within 12 weeks

c) Intravenous immunosuppressive drugs within 12 weeks

d) Any other monoclonal antibody, biologic agent, or investigational agent within 12 weeks or 5 half-lives (whichever is longer)

e) Antimalarials (e.g., hydroxychloroquine) within 36 weeks

f) Topical corticosteroids (excluding scalp) within 2 weeks

12. Has evidence of or has required treatment for cancer (except for treated, non-invasive carcinoma of the skin or cured carcinoma-in-situ following discussion with Medical Monitor) within 5 years

13. Has other chronic or active significant medical conditions within 6 months prior to Screening, including but not limited to: allogeneic organ transplant (e.g., solid organ, bone marrow, or stem cells); cardiac disease (e.g., unstable angina, myocardial infarction, ventricular arrhythmia); congestive heart failure; liver disease; neurological disease; hematological disease; kidney disease; uncontrolled seizure disorder; uncontrolled

pulmonary disease; uncontrolled gastrointestinal disease; uncontrolled endocrinological disease; uncontrolled psychiatric disease; or uncontrolled diabetes mellitus

14. Has interstitial lung disease requiring the use of supplemental oxygen

15. Has received or is expected to receive any live viral or bacterial vaccination within 3 months prior to Screening

16. Has received a Bacille Calmette-Guerin (BCG) vaccination within 12 months of Screening or is expected to receive it during the course of the study

17. Has a history of or ongoing active, chronic, or recurrent infection (including bacterial, viral, parasitic, protozoal, and/or fungal/granulomatous infections [e.g., histoplasmosis, coccidioidomycosis, aspergillosis]) requiring treatment with systemic antibiotics antimicrobials, antivirals, antiparasitics, antiprotozoals, or antifungals within 12 weeks prior to Screening, or serious infection (including but not limited to pneumonia, sepsis, bone or joint infection) requiring hospitalization or treatment with IV antibiotics within 12 weeks prior to Screening

18. Has a history of opportunistic infection or non-tuberculosis mycobacterial infection within 9 months prior to Screening

19. Has any other condition that would, in the opinion of the Investigator, potentially compromise the safety or compliance of the patient or preclude the patient's successful completion of the study

7.3 Patient Rescreening

Patients who do not qualify for enrollment at the actual Screening Visit based on the Inclusion/Exclusion criteria may be further assessed for eligibility at any time during the Screening Period (within 28 days prior to Visit 2/Week 1, Day 1). Under some circumstances, patients who fail to meet eligibility criteria during the Screening period may be rescreened for study entry following discussion with the CRO's Medical Monitor.

8 STUDY DRUG ADMINISTRATION

8.1 Treatments Administered

All patients will receive the investigational study drug, IMO-8400, at the dose level (total weekly exposure) of 0.6 or 1.8 mg/kg, or placebo once a week for 24 weeks. Patients will be randomized to one of the following groups in a 1:1:1 ratio.

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

8.2 Investigational Product(s)

IMO-8400 for Injection is supplied as sterile, lyophilized powder for reconstitution with Sterile Saline for Injection, USP/EP or Sterile Water for Injection USP/EP. Table 2 summarizes the physical and chemical properties of IMO-8400.

Table 2. Physical and Chemical Properties of Active Ingredient (Drug Substance)

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

8.2.1 Packaging and Labeling

The IMO-8400 drug product will be supplied as 25 mg/vial or 150 mg/vial lyophilized powder for reconstitution in a clear, round 5 mL glass vial with a rubber stopper and aluminum overseal. Each 5 mL glass vial contains IMO-8400 sodium salt equivalent to 25 or 150 mg/vial of free acid. All manufacturing, packaging, and labeling operations will be performed according to Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines, as well as local regulations.

Sterile Water for Injection, USP/EP and/or Sterile Saline for Injection, USP/EP will be supplied by the study site.

8.2.2 Storage

The sealed vials of drug product (IMO-8400 for Injection) should be stored at 2 °C to 8 °C (36 °F to 46 °F). See the Pharmacy Manual for further details on dose preparation and storage conditions prior to administration.

8.2.3 Preparation and Administration of the Product

Vials of IMO-8400 will be reconstituted using Sterile Saline for Injection USP/EP, or Sterile Water for Injection USP/EP, as described in the Pharmacy Manual. The total volume of the patient's dose will be based on their body weight at the most recent prior clinic study visit but may not exceed 1.4 mL (upper limit of patient weight is 140 kg). Dose preparation will be done by designated unblinded staff. Detailed dose-preparation instructions and flow sheets will be provided in the Pharmacy Manual.

Each dose of IMO-8400 or placebo will be administered as a single SC injection. The injection sites should be selected based on the following:

- Areas for injection are the 4 quadrants of the abdomen (upper and lower on the left and right).
- Injection sites will be rotated.

Blinded study personnel will administer all doses of study drug. Injections of study drug may be administered in 1 of 2 contexts: at the study site or outside of the clinic as described in Section 8.2.4. On study days when a physical examination is scheduled (see SOE in Section 3), it is expected that study drug will be administered at the study site.

8.2.4 Administration of the Product Outside the Clinic

With the agreement of the patient and the Investigator, doses may be administered outside of the clinic (e.g., at the patient's home or workplace) by a visiting nurse who has been trained in the protocol and approved by the Sponsor. In this event, the Sponsor or designee will arrange for a Central Pharmacy to prepare and dispense the patient's study treatment. Requirements for preparation of doses intended for shipment to patient's home will be detailed in the Pharmacy Manual. The study drug will be shipped by overnight courier in an appropriate insulated container that has been qualified to maintain the required storage condition (2 °C to 8 °C) with cooling packs. The used syringe and packaging materials will be disposed of or destroyed per policy of the Central Pharmacy. The visiting nurse will maintain appropriate source documents; the events will be entered into the electronic data capture (EDC) system and copies of the source documents provided to the site. The patient's vital signs, AEs (including assessment for ISRs), and concomitant medications will also be recorded by the visiting nurse.

8.2.5 Instructions for Delays in Dosing

As previously noted, doses must be administered once every 7 days ± 2 days, with at least 5 days between each dose administered. In the event of a missed dose, patients should resume once weekly injections.

8.3 Safety Monitoring and Drug Dose Interruption

Subjects must be monitored closely for AEs, including SAEs, and laboratory abnormalities during the course of the study. Patients will be monitored for approximately 4 hours after the first dose at the Baseline Visit.

Certain laboratory parameters have predefined monitoring and action procedures that must be followed (see Section 8.3.2, Table 3), and, as specified in Section 8.3.5, the occurrence of an SAE that is assessed by the Investigator as possibly or probably related to study drug will require discontinuation of study drug. For other AEs and for laboratory abnormalities not listed in Table 3, the Investigator should use his/her judgment in determining whether the event or abnormality is clinically significant, whether diagnostic evaluation is warranted, and whether potential interruption of study drug therapy is appropriate.

8.3.1 Laboratory Abnormalities and Adverse Events Requiring Evaluation and Potential Drug Interruption or Discontinuation

While specific monitoring, diagnostic testing, and supportive care measures must be instituted based on the clinical judgment of the Investigator, Investigators are encouraged to contact the CRO Medical Monitor to obtain guidance and to ascertain whether similar events are being seen at other sites.

The CRO Medical Monitor should be notified of any AE or laboratory abnormality (see Section 8.3.2) that leads to dose interruption and should be apprised of ancillary laboratory or other diagnostic findings and the evolving data from any work-up of the initial abnormality. The CRO Medical Monitor may suggest review of the case with expert consultants (either at the site or retained by Idera).

8.3.2 Laboratory Abnormalities Requiring Evaluation and Potential Drug Interruption or Discontinuation

Based on the findings of the toxicology program with IMO-8400 serum levels of C3, C4, CH50, and A:G ratio will be regularly monitored during this study. These parameters are being monitored due to the results from a 39-week nonclinical toxicology study in cynomolgus monkeys showing that adverse effects were reliably preceded by changes in complement and markers of acute phase reactions.

Another oligonucleotide investigational product has been associated with clinically significant AEs of thrombocytopenia and renal abnormalities as well as ISRs in human clinical studies (FDA 2015). Given IMO-8400 is also an oligonucleotide investigational product, platelet counts, anti-platelet antibodies, urine protein, and renal function will be regularly monitored.

A PSC consisting of the Investigator, CRO Medical Monitor, and Idera Medical Monitor will be formed to monitor abnormal laboratory test values as defined in Table 3, with information on actions to be taken in the event that abnormalities are noted in specified laboratory parameters.

If the PSC determines that it is in the patient's best interest to discontinue study drug because of a safety laboratory abnormality (Table 3) or because of a follow-up investigation, this would constitute a "withdrawal due to an AE of interest". For withdrawal due to abnormally low C3, C4 or A:G ratio, the Investigator must provide a narrative describing the history and reason for withdrawal (see Section 11.1.1).

Table 3. Safety Monitoring Parameters and Actions

Laboratory Values	Action to be Taken	Follow up Required (PSC Action)
C3 OR C4 below LLN AND A:G ratio below LLN	• Stop study drug immediately	• Confirm C3, C4 and A:G ratio values • Then start early termination process
C3 OR C4 below LLN OR A:G ratio below LLN	• Continue study drug	• Convene PSC within 7 days of abnormal laboratory test report • Confirm C3, C4 and A:G ratio values
Missing values on C3 OR C4 OR A:G ratio	• Continue study drug, for 1 additional week of dosing while missing value is being retrieved	• If missing value is not retrieved within 2 weeks, the subsequent scheduled dose cannot be administered. For example: if there is a missing value from Visit 6, the Visit 7 dose can be given, but the Visit 8 dose must be held until safety laboratory testing is completed
Urine protein above + 2	• Interrupt study drug administration	• Convene PSC within 7 days of abnormal laboratory test report • Review changes in serum creatinine and eGFR
eGFR[a] below 50% of baseline	• Interrupt study drug administration	• Convene PSC within 7 days of abnormal laboratory test report • Review changes in serum creatinine and urine protein
Platelet count below 75,000/µL	• Interrupt study drug administration	• Convene PSC within 7 days of abnormal laboratory test report • Review additional hematology laboratory values

A:G = albumin:globulin ratio; C = complement component; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; LLN = lower limit of normal; PSC = Patient Safety Committee
[a] eGFR (mL/min/1.73 m^2) = **175** x $(S_{cr, std})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African Ethnicity) (FDA 2010)

8.3.3 Instructions for Resuming Study Drug Administration after an Interruption for Safety Concerns Due to General Laboratory Abnormalities or Adverse Events

To decide about resuming study drug administration after a dose interruption for any clinically significant safety concern not related to the specified safety laboratories in Section 8.3.2, the Investigator, CRO Medical Monitor, and Idera Medical Monitor will together consider factors such as the type and severity of the AE or laboratory abnormality, the potential causal

relationship of study drug therapy, the patient's status in terms of DM or other health conditions, and the ability to monitor for recurrence of the event. Instructions for resuming study drug administration after an interruption for safety concerns due to the safety laboratory abnormalities noted in Section 8.3.2 are provided below in Section 8.3.4.

If study drug is re-initiated, it must be at the dose and at the same visit schedule to which the patient was randomized; no dose reductions are allowed.

8.3.4 Instructions for Resuming Study Drug Administration after an Interruption for Safety Concerns Due to Safety Laboratory Abnormalities

After a dose interruption due to an abnormality in safety laboratories as specified in Section 8.3.2, the PSC will together consider factors such as the type and severity of the AE or laboratory abnormality, the potential causal relationship of study drug therapy, the subject's status in terms of DM or other health conditions, and the ability to monitor for recurrence of the event.

The PSC will use their best judgment in determining whether to restart study drug. If study drug is re-initiated it must be at the dose to which the patient was randomized; no dose reductions are allowed.

If the PSC determines that it is in the patient's best interest to discontinue study drug because of a safety laboratory abnormality (Table 3) or because of a follow-up investigation, this would constitute a "withdrawal due to an AE of interest." For withdrawal due to abnormally low C3, C4 or A:G ratio, the Investigator must provide a narrative describing the history and reason for withdrawal (see Section 11.1.1).

8.3.5 Serious Adverse Events Requiring Discontinuation of Study Drug

To ensure the safety of study participants, study drug administration will be discontinued in any patient who experiences an SAE that is assessed by the Investigator as possibly related or probably related to study drug; the Investigator will assess if study drug administration will be discontinued in any patient who experiences an SAE that is assessed as not related to study drug.

The procedures for discontinuation of study drug and necessary follow-up and documentation are summarized in Section 8.3.6 and Section 11.5; also refer to Section 11.4 for instructions for completing the follow-up SAE form.

In addition, when a patient discontinues study drug secondary to the occurrence of a possibly related or probably related SAE, this is considered a "withdrawal due to an AE of interest", and the Investigator must provide a narrative describing the history and reason for withdrawal (see Section 11.1.1).

8.3.6 Instructions for Discontinuation of Study Drug Administration for Safety Concerns

See Section 11.5 for instructions upon a decision to permanently discontinue administration of study drug due to an AE, laboratory abnormality, or SAE. If permanent discontinuation of study drug is due to a reported SAE, a follow-up SAE report form should be completed (see Section 11.4).

8.4 Method of Assigning Patients to Treatment

8.4.1 Blinding and Randomization

8.4.1.1 Screening Procedures

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

8.4.1.2 Randomization

Randomization will take place using IXRS. Patients will be randomized after the Investigator has verified that they are eligible per criteria in Section 7. Patients will be randomized to receive either IMO-8400 at a dose of 0.6 or 1.8 mg/kg/week or placebo once a week for 24 weeks. Randomization will be performed centrally in a 1:1:1 ratio and will be stratified by baseline CDASIv2-Activity score (15 to 20 vs ≥21). A permuted block randomization schedule will be employed. Blocks will be pre-allocated to the two CDASIv2-Activity strata (15 to 20 vs. ≥21) to achieve a balanced distribution of treatment assignments within those groups.

8.4.1.3 Blinding

Every attempt should be made to preserve the integrity of study drug blinding. Except for cases of emergency unblinding as described in Section 8.4.2, the randomization code will remain unbroken for patients, parents/caregivers, and study personnel until the database has been locked.

Because SC administration of IMO-8400 has been associated with potentially unblinding ISRs, the mCDASIv2, MMT8, and timed function tests (10MWR, TUG, and 4 stair climb 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 other than administration of these efficacy assessments. In addition, patients will be asked to wear clothing that covers all injection sites whenever they visit the study site.

8.4.2 Emergency Unblinding

In the event of a medical emergency, laboratory abnormalities or 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 and in cases where an immediate need for unblinding exists for reasons of patient safety, the Investigator can unblind the patient's data at his/her discretion. When possible, the Investigator should consult the CRO Medical Monitor prior to unblinding to discuss the rationale for breaking the blind and the adverse consequences of the unblinding for the patient's continued participation in the study. The treatment assignment for that patient 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 electronic case report form (eCRF).

8.5 Treatment Compliance

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

9 PRIOR AND CONCOMITANT MEDICATIONS

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care. Information regarding any prior and concomitant medications will be collected and documented in the eCRF and in the source documents by the clinic staff as described in the explanation of study procedures.

9.1 Permitted Concomitant Medications

The following therapies are permitted for use during the 24 weeks of study drug treatment as detailed in Table 4:

- Corticosteroids
- Non-steroidal immunomodulatory medications - no more than 1 of the following: IVIG, mycophenolate mofetil, cyclophosphamide, cyclosporine, leflunomide, tacrolimus, methotrexate, azathioprine
- Topical corticosteroids for use on the scalp only

Any other treatments (including prescription drugs, non-prescription drugs, and herbal remedies), except those listed in the prohibited concomitant medications section (Section 9.3) should be taken as prescribed, per Investigator judgment.

9.2 Stabilization and Washout Period for Permitted Concomitant Medications

For patients who are on corticosteroids or non-steroidal immunomodulatory medications, a stable regimen should be established as described in Table 4 prior to Screening and maintained during the 24 weeks of study drug treatment. Adjustments in dosage for increases in body weight are permitted but are not mandatory.

Table 4. Stable Regimens of Permitted Concomitant Medications

Category	Medication	Dose	Duration of Stable Regimen Prior to Screening
Corticosteroids	Oral prednisone or equivalent	≤20 mg per day (or ≤140 mg/week)	≥4 weeks
Corticosteroids	Topical for scalp only	Limit to 2 applications per day	≥3 weeks
Non-steroidal immunomodulatory (limited to **one**)	Intravenous immunoglobulin	2 g/kg per month	≥12 weeks
	Oral mycophenolate mofetil	3 g per day	≥12 weeks
	Oral cyclophosphamide	5 mg/kg per day	≥12 weeks
	Oral cyclosporine	3 mg/kg per day	≥12 weeks
	Oral leflunomide	20 mg per day	≥12 weeks
	Oral tacrolimus	4 mg per day	≥12 weeks
	Oral or intramuscular methotrexate	25 mg per week	≥12 weeks
	Oral azathioprine	3 mg/kg per day	≥12 weeks

Interventions or potential dosage adjustments may be considered if a patient experiences a concerning AE related to the medications in Table 4.

Upward adjustments in dose for reasons other than for change in body weight, or downward adjustments to prevent toxicities should be discussed with the CRO Medical Monitor. Patients who require interruption, dose modification, or re-initiation of the therapies in Table 4 may remain on blinded study drug therapy.

If a patient had been on more than one non-steroidal immunomodulatory medication, they must have stopped administration of the additional non-steroidal immunomodulatory medications for at least the washout periods listed in Table 5. Start and stop dates and dose/regimen for washout of these medications prior to Screening must be recorded on source documentation and eCRF.

Table 5. Washout Period for Prohibited Concomitant Medications

Prohibited Medication	Washout Period Prior to Screening[a]
Methotrexate	At least 4 weeks
Leflunomide, cyclophosphamide, intravenous immunoglobulin	At least 12 weeks
Any other non-steroidal immunosuppressive agent including azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus,	At least 8 weeks

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

9.3 Prohibited Concomitant 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.

- Rituximab
- Intravenous corticosteroids
- Intravenous immunosuppressive drugs
- Any other monoclonal antibody, biologic agent, or investigational agent
- Antimalarial agent(s)
- Topical corticosteroids (excluding scalp)
- Live viral or bacterial (including BCG) vaccination during the course of the study or within 3 months after the last dose of study medication

9.3.1 Washout Period for Prohibited Medications

Medications listed in Table 6 are prohibited within the indicated washout period immediately prior to Screening. Start and stop dates and dose/regimen for use of prohibited medications during the year prior to Screening (Visit 1) must be recorded on source documentation and eCRF.

Table 6. Washout Period for Prohibited Concomitant Medications

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

10 EXPLANATION OF STUDY PROCEDURES

10.1 Pretreatment, Treatment and Follow-up Periods

No study-related procedures should be performed prior to the signature of the informed consent document(s). After a patient has completed the necessary screening assessments and has been confirmed to be eligible by the Investigator, the Baseline Visit (Visit 2/Week 1, Day 1) for the patient can be scheduled.

10.1.1 Screening Visit (Visit 1) and Screening Period

Once written informed consent is obtained, patients will be screened for eligibility for entry into the study based on the inclusion and exclusion criteria detailed in Section 7. Screening includes, as indicated in the SOE in Section 3, a full medical/surgical history, including information relating to any prior or existing medical conditions/surgical procedures that may be relevant to the patient's experience in the study. Demographic data and DM-specific medical history information will also be recorded. Patients will also undergo a full physical examination, vital signs and a 12-lead ECG tracing will be obtained, and height and body weight will be measured. In addition, the full CDASIv2 will be performed and skin photographs will be taken. Blood and urine will be collected for standard safety laboratory assessments as well as pregnancy testing, hepatitis B and C screening, and other safety laboratory assessments (Section 8.3.2).

As part of the patient's medical history, documented evidence of cancer and TB screening are required. Study participants must have a diagnostic evaluation for cancer if the diagnosis of DM was within 2 years prior to the Screening Visit. The evaluation should include all age- and gender-appropriate screening tests and either a CT of the chest, abdomen, and pelvis OR, alternatively, a PET/CT of the chest, abdomen, and pelvis if this is standard practice in the particular center. If a diagnostic evaluation for cancer has not been performed in patients for whom it is required, a PET/CT (chest, abdomen, and pelvis) should be performed during the Screening Period. The diagnostic evaluation for cancer must be normal for a patient to meet this inclusion criterion. Study participants also must have no evidence of active or latent TB after a diagnostic evaluation with a CXR OR chest CT and 1 of the following: a) a PPD skin test, b) a QuantiFERON blood test, or c) T-SPOT.TB blood test. If the diagnostic TB evaluation has not been performed within 12 weeks prior to the Screening Visit, it may be performed during the Screening Period. For the patient to be eligible, the results of the diagnostic TB evaluation should include a negative chest image and 1 of the following: a) a PPD skin test with ≤5-mm induration, b) a negative (not detected) QuantiFERON result, or c) a negative T-SPOT.TB test. If the QuantiFERON result is indeterminate, the test may be repeated once. If the repeat QuantiFERON test is indeterminate, then a PPD skin test may be used to confirm patient eligibility. The PPD skin test is not an acceptable method of TB testing in Sweden.

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 (see Section 8.4) in anticipation of administration of the first dose of study drug at the Baseline Visit 2/Week 1, Day 1.

10.1.2 Baseline Visit (Visit 2, Day 1)

Before initiating treatment, each study participant will report to the clinic to complete study related procedures as outlined in the SOE in Section 3. Study drug will not be administered until all baseline assessments have been completed and collection of the pre-dose sample for determination of IMO-8400 plasma concentrations and baseline laboratory samples have been obtained. Baseline assessments include physical examination, vital signs, the full CDASIv2, IMACS CSMs, SF-36, Timed Function Tests, 5-D Itch Scale, 12-lead ECG, and skin biopsy. In addition, skin photographs will be taken. Subsequently the patient will receive the first dose of study drug, and the patient will have a 2-hour post-dose blood sample for determination of IMO-8400 plasma concentration. The patient will remain at the clinic until released by the Investigator approximately 4 hours after the first dose administration.

10.1.3 Treatment Period (Visit 2/Week 1 through Visit 25/Week 24)

The Baseline Visit 2/Week 1 is also Day 1 of the Treatment Period; patients will receive the first dose of study drug that day as described in Section 10.1.2. During the treatment period, each patient will return to the clinical research facility for Visit 6/Week 5, Visit 10/Week 9, Visit 14/Week 13, Visit 18/Week 17, and Visit 22/Week 21. During these visits patients will complete the assessments indicated in the SOE in Section 3. All scheduled assessments should be performed prior to dosing, unless otherwise specified. All CDASI assessments performed after the first dose of study drug will be done using the mCDASIv2.

With the agreement of the patient and the Investigator, doses during weeks not requiring clinic visits may be administered outside of the clinic (e.g., at the patient's home or workplace) by a visiting nurse who has been trained in the protocol and approved by Idera (Section 8.2.4). The patient's vital signs, AEs (including assessment for ISRs), and concomitant medications will be recorded by the visiting nurse during administration of study drug.

On dosing days, the planned injection site will be assessed for the presence of any ISRs to confirm the injection site is appropriate for use. All visits during the treatment period of the study have a visit window of ± 2 days. There must be at least 5 days between doses.

10.1.4 End-of-Treatment Visit (Visit 26) and Early Termination Visit

The patient will return to the clinical research facility at Week 25 ± 2 days (Visit 26) for the EOT Visit. If the patient discontinues prematurely (i.e., before Week 25) the procedures that would normally be performed at the Week 25 EOT Visit should be performed as an ET Visit before the patient leaves the study. Any patient who withdraws or is withdrawn from the study prematurely will be asked to complete the ET assessments (which are the same as the EOT Visit 26 assessments) within 5 days of the notification of withdrawal; these patients will also be asked to complete the EOS assessments (Visit 27/Week 29) 4 weeks (± 4 days) after completing the ET assessments.

It is intended that with Investigator approval, patients who successfully complete the EOT (Visit 26/Week 25 assessments may initiate receiving open-label IMO-8400 treatment upon signature of the informed consent document(s) if a separate open-label extension study is initiated. *Signed informed consent for participation in any extension study must be obtained prior to assessments and extension study dosing at Visit 26/Week 25.* Patients who do not enroll

in an extension study, including patients who withdraw from this study prematurely, will complete safety follow-up assessments at the EOS Visit (Visit 27/Week 29), 4 weeks (± 4 days) after completing EOT assessments.

10.1.5 End-of-Study Visit (Visit 27/Week 29)

All patients who discontinue study drug prematurely or decline participation in an open-label IMO-8400 extension study must return for an EOS Visit at the investigational site 4 weeks (± 4 days) after the last dose of study drug for final study-related evaluations.

10.1.6 Unscheduled Visits

Unscheduled visits and assessments may be conducted at Investigator discretion in response to new clinical observations or as follow-up to AEs.

10.2 Description of Assessments

The following sections describe the assessments that are necessary during the study. Rational for the appropriateness of selected assessments are provided in Section 17.

10.2.1 Informed Consent

The Investigator must inform each prospective patient of the nature of the study, explain the potential risks, and obtain written informed consent from the patient prior to performing any study-related screening procedures.

10.2.2 Inclusion/Exclusion Criteria

All patients must meet all of the inclusion criteria specified in Section 7.1 and none of the exclusion criteria specified in Section 7.2 to be enrolled in this study. As noted in Section 7.3, under some circumstances, patients who fail to meet eligibility criteria during the Screening Period may be rescreened for study entry following discussion with the CRO's Medical Monitor.

10.2.3 Demographic Information and Medical History

Basic demographic information (e.g., date of birth, age, sex, race) will be collected and a detailed medical history, including review of past and ongoing medications and therapies, history of alcohol use, and smoking history will be obtained at the Screening Visit as specified in the SOE in Section 3.

The Investigator should review the study candidate's medical history, including details relating to DM and any other medical conditions. As part of the patient's medical history, documented evidence of cancer and TB screening are required. Information regarding current medications must be captured on the eCRF. Details regarding any medication received within 3 months prior to screening will be collected on the eCRF. Information on permitted and prohibited medications, doses, and regimens are provided in Section 9.

10.2.4 Physical Examination Including Weight and Height

Physical examinations will be conducted at the time points specified in the SOE provided in Section 3. Physical examinations will be performed by the Investigator, an MD Sub-Investigator, a Nurse Practitioner, or a Physician's assistant (if licensed in the state to perform physical

examinations); if possible, the same person should perform all examinations for a given patient. 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.

Height is measured in centimeters, without shoes, at the Screening Visit only. Weight should be recorded in kg and will be measured during all physical examinations.

10.2.5 Skin Photography

Photography of the areas of the skin assessed in the CDASIv2 will be taken at Screening (Visit 1), Baseline (Visit 2/Week 1, prior to initiation of study drug treatment), and at the EOT/ET Visit 26/Week 25 as described in the SRM. Permission to perform photography will be requested in the informed consent document(s). Subjects who refuse being photographed may still participate in the study.

The SRM and additional documents will provide instructions on skin photography procedures.

10.2.6 Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)

The full CDASI version 2 (CDASIv2) assessment will be performed at the Screening and Baseline Visits. Subsequent CDASI assessments will be performed using the mCDASIv2, which eliminates the abdominal skin assessments post-injection. The mCDASIv2 will be performed by trained raters blinded to treatment assignment at the time points specified in the SOE in Section 3. To further decrease the risk of unblinding, patients will be provided with an abdominal covering to mask injection sites when the mCDASIv2 is performed

The CDASIv2 is a clinician administered, one-page instrument designed to evaluate the cutaneous manifestations of DM (see Appendix 4). Developed by leading academic dermatologists and rheumatologists with an expertise in DM, it takes approximately 5 minutes to complete and its validity and reliability have been demonstrated in multiple studies of DM patients (Klein 2008, Yassaee 2010, Goreshi 2012).

The CDASI 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.

10.2.7 Skin Biopsy

Skin biopsies will be performed at the Baseline Visit 2/Week 1, Day 1, and at the EOT Visit 26/Week 25. Two 4 mm punch 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 baseline and in an adjacent area at the EOT biopsy. Sites where the baseline biopsy samples were taken should be photographed **PRIOR** to the baseline biopsy (no photographs will be taken after the biopsy) to document the disease activity and to guide the EOT biopsy site. Biopsies can be performed with or without local anesthesia, as considered appropriate for a specific patient or study site. The skin samples should be prepared for analyses as per the procedures described in the Laboratory Manual. The skin biopsy is not required for a premature discontinuation visit.

10.2.8 International Myositis Assessment Clinical Study (IMACS) Core Set Measures

The IMACS Group, which includes more than 100 adult and pediatric rheumatologists, neurologists, dermatologists, rehabilitation medicine physicians, statisticians, nurses, and others with expertise in myositis, was founded in 2000 to facilitate clinical research for the idiopathic inflammatory myopathies including DM. The IMACS Group has identified a core set of outcome measures (the CSMs) to comprehensively describe myositis disease activity in juveniles and adults. The IMACS Group has also identified preliminary DOIs in disease activity (Rider 2004), which reflect clinically meaningful change in each of the CSMs. The subset of the CSMs identified by IMACS that will be used in this study are briefly described in Sections 10.2.8.1 and Section 10.2.8.2.

10.2.8.1 Manual Muscle Testing (MMT8)

Manual muscle testing will be performed by trained raters blinded to treatment assignment and who will have no other role or responsibility beyond administering efficacy assessments in the study at the time points specified in the SOE in Section 3.

Manual muscle testing assesses the function and strength of individual muscles and muscle groups based on the effective performance of a movement against gravity or manual resistance. A particular muscle or muscle group is first isolated, then an external force is applied and the patient's ability to complete the movement is graded by a trained therapist or clinician. This study will use an abbreviated MMT, the MMT8 (see Appendix 5), which was developed and validated by IMACS (Rider 2010). In the MMT8, 8 proximal, distal, and axial muscles including the deltoid, biceps, wrist extensors, quadriceps, ankle dorsiflexors, neck flexors, gluteus maximus, and gluteus medius, are evaluated unilaterally. Of note, the 8 muscle groups selected by expert consensus for inclusion in the MMT8 include 4 of the 5 weakest muscles in patients with idiopathic inflammatory myopathies (i.e., the neck flexor, deltoid, gluteus maximus, and gluteus medius) (Harris-Love 2009).

10.2.8.2 Muscle Enzymes

The activity of serum enzymes derived from muscle in myositis patients has long been used as an indicator of myositis disease activity in clinical practice. 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 in Section 3 (see Appendix 6).

10.2.9 Short Form-36 Health Survey

The SF-36 will be completed by the patient at the time points specified in the SOE in Section 3.

The SF-36 is an extensively validated and widely used measure of quality of life that assesses patients' perceptions of health status and its impact on their lives (Ware 1992). 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 (see Appendix 7).

10.2.10 Timed Function Tests

The 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 assignment beyond administering these efficacy assessments (see Section 8.4.1) at the time points specified in the SOE in Section 3.

Timed function tests will include time taken to walk/run 10 meters, time taken to stand from a seated position, and time taken to climb 4 standard-sized stairs (Mendell 1989, Griggs 1991, Beenakker 2005, Pradhan 2006, Podsiadlo 1991, Rao 2009) (see the SRM). These tests provide additional measures of muscle strength and functional capability in patients with DM. Decreases in time taken to complete these tasks are considered to be indicative of patient improvement.

10.2.10.1 Timed 10-meter Walk-run Test (10MWR)

This test measures, in seconds, the time it takes a patient 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.

10.2.10.2 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.

10.2.10.3 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.

10.2.11 5-D Itch Scale (5D Pruritis Scale)

The 5-D Itch Scale will be completed by the patient at the time points specified in the SOE in Section 3.

The 5-D Itch Scale is a brief multidimensional questionnaire for use in clinical trials (see Appendix 8). The five dimensions of itch include degree, duration, direction, disability, and distribution. The duration, degree and direction domains each include one item, while the disability domain has 4 items. All items of these first 4 domains are measured on a 5-point Likert scale. The distribution domain includes 16 potential locations of itch, including 15 body part items and one point of contact with clothing or bandages. The scores of each of the 5 domains 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).

10.2.12 Clinical Laboratory Tests

Blood and urine samples for routine (Table 7) and safety laboratory (Table 8) tests will be collected at the time points specified in the SOE in Section 3 and analyzed by an accredited central laboratory selected by Idera. The appropriate Laboratory Manual should be referenced for procedures on sample collection, handling, storage, and shipping.

Any value outside of the current reference ranges for the laboratory performing the test will be flagged on the laboratory results. The Investigator will score all abnormal assessment results as either clinically significant (CS), or not clinically significant (NCS). See Section 8.3.2 for guidelines on actions for safety laboratory results.

10.2.12.1 Routine Safety Laboratory Assessments

Table 7. Routine Safety Laboratory Assessments

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 virus (HBV) screen: HBsAg and anti-HBc Hepatitis C virus (HCV) 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, OR c) a negative T-SPOT.TB test. 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

Note: The PPD skin test is not an acceptable method of TB testing in Sweden.

10.2.12.2 Safety Laboratory Assessments

Table 8. Safety Laboratory Assessments

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 component; CH50 = hemolytic complement activity; CRP = C-reactive protein

10.2.13 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be obtained at the time points specified in the SOE in Section 3 at the study site. ECGs will be performed only after the patient is positioned supine, resting, and quiet for a minimum of 5 minutes. The ECG will be reviewed and interpreted by medically qualified personnel. The Investigator will review the results of the ECG report, document the interpretation and designate the findings as normal or abnormal (CS or NCS), and report changes from previous readings.

10.2.14 Pregnancy test

Urine samples for pregnancy testing will be collected on all women of childbearing potential at the time points specified in the SOE in Section 3.

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

- Postmenopausal state defined as no menses for 12 months without an alternative medical cause.
- Documented hysterectomy, bilateral tubal ligation or bilateral oophorectomy.

10.2.15 IMO-8400 Plasma Concentration

Blood samples for determination of IMO-8400 plasma concentrations will be collected prior to administration of study drug pre-dose and 2 hours (± 15 minutes) post-dose at Visit 2/Week 1, Day 1, Visit 6/Week 5, Visit 14/Week 13, and Visit 22/Week 21. An additional sample will be collected as part of the EOT Visit 26/Week 25 assessments.

If an extension study is initiated and the patient is enrolled, the EOT PK sample will be the same as the Visit 1/Week 1, Day 1 pre-dose sample for the extension study. The appropriate Laboratory Manual should be referenced for procedures on sample collection, handling, storage, and shipping.

10.2.16 Autoantibodies

Blood samples will be collected at the time points specified in the SOE in Section 3 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; subgroup analyses may be performed according to the autoantibody profile. Additional serum for anti-platelet antibodies will also be collected at the time points specified in the SOE in Section 3. The appropriate Laboratory Manual should be referenced for procedures on sample collection, handling, storage and shipping.

10.2.17 Interferon (IFN) Gene Expression

Blood samples and a skin biopsy for analysis of Type 1 and Type 2 IFN gene expression profiles will be obtained at the time points specified in the SOE in Section 3. Guidance on performing the skin biopsy is provided in Section 10.2.7 and in the SRM.

10.2.18 Histology

A second skin biopsy will be obtained for histology analysis at the same time points as the IFN skin biopsies, as specified in the SOE in Section 3. Guidance on performing the skin biopsy is provided in Section 10.2.7 and in the SRM.

10.2.19 Serum Cytokines

Blood samples for analysis of DM-relevant cytokines/chemokine levels (including IL-6, IL-8, IP-10, I-TAC, MCP-1, MCP-2, and TNFα; additional or alternative cytokines or chemokines may be assessed) will be obtained at the time points specified in the SOE in Section 3. The appropriate Laboratory Manual should be referenced for procedures on sample collection, handling, storage and shipping.

10.2.20 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 3. The appropriate Central Laboratory Manual should be referenced for procedures on sample collection, handling, storage and shipping.

10.2.21 Vital Signs

Vital signs (temperature [oral or tympanic], pulse rate, respiratory rate, and blood pressure) will be measured at the time points specified in the SOE in Section 3. Vital signs will be measured prior to injection. All assessments will be performed after patients have remained seated for 5 minutes. Temperature should be recorded in degrees Celsius (°C), and pulse rate and respiratory rate should be measured over 1 minute.

10.2.22 Concomitant Medications/Therapies/Procedures During Treatment

Review of all concomitant medications, therapies and procedures, and changes in dosage of concomitant medications will be assessed at each visit as specified in the SOE in Section 3. Data on pharmacological and non-pharmacological treatments will be recorded on an eCRF page. At

each study visit, the patient will be asked about any additional treatments or any changes in regimen or dosages since the last visit. Indications for any new medications or therapies during the study period will be recorded as an AE. Further detail on concomitant medications is provided in Section 9.

10.2.23 Blood Volume Collection Summary

An estimated 20 to 55 mL of blood is required to be drawn at clinic visits, with an estimated total of 350 mL expected during this study (refer to details in the Laboratory Manual).

11 ADVERSE EVENT REPORTING

At each study visit, patients will be evaluated for new AEs and the status of existing AEs. All AEs from the time the informed consent is signed through the EOS Visit 27/Week 29 will be recorded on the eCRF.

11.1 Definition of Adverse Events

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study patient, whether or not the event is considered causally related to the investigational product. An AE can be a new occurrence or an existing process that increases significantly in severity or frequency.

Adverse events include:

- Symptoms described by the patient or signs observed by the Investigator or medical staff
- Test abnormalities (laboratory tests, ECG, x-rays, etc.) that result in an alteration in medical care (diagnostic or therapeutic)
  - Abnormally low values for C3, C4 or A:G ratio may result in discontinuation of study treatment. Patients who discontinue due to these laboratory test abnormalities will be classified as "withdrawals due to adverse events" and a narrative describing their history and reason for withdrawal will be prepared by the Investigator.
  - Abnormally low eGFR or platelet count or abnormally high urine protein as described in Table 3 may result in discontinuation of study treatment. Patients who discontinue due to these laboratory test abnormalities will be classified as "withdrawals due to adverse events".
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs. The outcome of the accident (hip fracture secondary to the fall) should be recorded in source documents.

Abnormalities present at Baseline are considered AEs only if they reoccur after resolution or worsen in severity or frequency during the study.

Each AE is to be classified as serious or nonserious.

11.1.2 Serious Adverse Events (SAE)

An AE is serious when the patient outcome, regardless of whether or not it is considered related to the study medication, is one or more of the following:

- Death
- Life threatening, per the Investigator, the patient was at immediate risk of death from the event at the time that the event occurred. It does not include an event that hypothetically might have caused death if it had occurred in a more severe form

- Hospitalization, initial or prolonged, meaning that a hospital admission and/or prolongation of a hospital stay was required for the treatment of the AE, or occurred as a consequence of the event. It does not include a pre-planned elective hospital admission for treatment or diagnostic procedures
- Disability or incapacity that is persistent or significant
- Congenital anomaly or birth defect that occurs in the offspring of a patient exposed to the study drug
- Important medical event that, although not immediately life-threatening, requires intervention in order to prevent one of the other serious outcomes listed above

11.1.3 Suspected and Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is defined as an SAE that meets ***both*** the following criteria with respect to study drug:

- *Suspected* — is assessed as related or possibly related to study drug (see Section 11.2.3)
- *Unexpected* — compared to the study drug-related AEs described in Investigator's Brochure, the event meets ***any*** of the following criteria:
  - The event was not previously described;
  - The event is now characterized as more severe (see Section 11.2.4)
  - The event is now characterized more specifically (e.g., an event of "interstitial nephritis" in a patient receiving an agent previously described as associated with "acute renal failure").

11.2 Evaluation of Adverse Events

All AEs/SAEs experienced by the patient will be recorded in the eCRF and will include a concise description of: the event; date and time of event onset and resolution; relationship to study drug; severity; management of study medication; management of the AE/SAE, and outcome as described in Sections 11.2.1 through 11.2.7.

Abnormalities in vital signs, laboratory results, and other safety assessments will be recorded as an AE if they meet the definition of an AE (Section 11.1).

When possible, a diagnosis should be recorded as an AE, rather than symptoms or isolated laboratory abnormalities related to that diagnosis.

A medical or surgical procedure is not an AE; rather the condition leading to the procedure should be recorded as the AE. If the condition is not known, the procedure must be reported as an AE instead.

Similarly, death is not an AE, but is rather the outcome of the AE(s) that resulted in death. If the AE(s) leading to death are not known, then death must be reported as an AE.

11.2.1 Description of Event

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

11.2.2 Date and Time of Onset

The date and time at which the event was first apparent. The time of onset of symptoms may be appreciably earlier than the date and time the Investigator becomes aware of the event. Some events may be apparent to the patient and Investigator independently, and information from each may contribute to the final report. For example, a patient may report the onset of a rash two days before being seen by a physician who makes a diagnosis of herpes zoster based on appearance and laboratory confirmation. In that case, there is a single AE, with the date of onset based on the date of the initial observation by the patient and a specific description (herpes zoster) based on the clinical exam and tests.

11.2.3 Relationship to Study Drug

A causality assessment must be provided for all AEs. This assessment must be made by the Investigator and recorded on the eCRF (SAE form, as appropriate). The definitions for the causality assessment are provided below.

- **Not related**: The AE is clearly not related to study drug
- **Possibly related**: There is some evidence supporting the possibility of a causal relationship between study drug and the AE, i.e., the event follows a reasonable temporal sequence from the time of study drug administration and/or follows a known response pattern to the study drug, but could also have been attributed to other factors. AEs that are deemed by the Investigator to be possibly related to study drug shall be considered related to study drug.
- **Probably Related**: There is strong evidence that there is a causal relationship between study drug and the AE

As previously noted in Section 8.3.5, any SAE assessed by the Investigator as possibly related or probably related to study drug will require discontinuation of study drug administration according to the procedures outlined in Section 11.5; the Investigator will assess if study drug administration will be discontinued in any patient who experiences an SAE that is assessed as not related to study drug.

11.2.4 Severity

The severity of all AEs will be assessed by the Investigator as mild, moderate, or severe using the following criteria:

- **Mild**: An AE that is transient, requires minimal or no treatment, and does not interfere with the patient's daily activities

- **Moderate**: An AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant
- **Severe**: An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention

Changes in the severity of an AE must be recorded in the eCRF to allow an assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of onset and duration of each episode if the severity of the intermittent event changes.

11.2.5 Action Taken with Study Medication upon Occurrence of an Adverse Event

For each AE the Investigator will be required to document the action taken regarding study drug in response to the AE. Options include:

- **Discontinued (withdrawn)**: Study drug was stopped permanently due to the AE
- **Dosing Interrupted**: Study drug regimen was modified by being temporarily halted, i.e., one or more doses were not administered, but drug was not stopped permanently
- **Dose Not Changed (none)**: No change in the administration of study mediation

11.2.6 Actions Taken for Management of AE

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

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

- **Concomitant medication**: One or more medications (prescription or over-the-counter) were started or increased in dose; non-medication actions may also have been ordered
- **Other action**: Non-medication action(s) were ordered as management of the AE (e.g., bed placed in Trendelenburg position, warm compresses applied to IV access site)
- **No action**: No actions were ordered for management of the AE

11.2.7 Outcome of AEs

If possible, AEs will be followed until resolved (synonyms: recovered, recuperated, ended) either with or without sequelae, or the Investigator assesses them as chronic or stable.

The outcome of each event (including date and time) will be described using the following categories:

- **Recovered**: The event resolved and patient returned to baseline
- **Recovered With Sequelae**: The event resolved but the patient is left with residual problems (e.g., functional deficits, pain)

- **Not Recovered**: At the last observation, the event was unchanged
- **Death (Fatal)**: To be used for the one AE which, in the judgment of the Investigator, was the primary cause of death
- **Unknown**: There were no observations after the onset (initial observation or report) of the event

A patient withdrawn from the study because of an AE must be followed by the Investigator until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. Follow-up may need to continue after the patient has discontinued from the study, and additional investigations may be requested by the Investigator. (see Section 11.4 for additional details on AE/SAE follow-up requirements).

11.2.8 Injection Site Reactions

New ISRs will be captured in AE reporting, and assessment of all previously used injection site(s) will be made at all clinic and non-clinic visits before and after dosing, and at the EOT and EOS Visits. In addition, on dosing days, the planned injection site will be assessed to confirm it is appropriate for use. ISRs that are reported by the patient or observed by the Investigator will be recorded by verbatim term, onset date, resolution date, anatomical location, and the visit number or date of the injection associated with the reaction. The verbatim terms of pain, tenderness, pruritis, induration, erythema, blisters, ulceration, and necrosis will be offered in the eCRF to simplify data collection and reporting, and Investigators will rate the severity as mild, moderate, or severe. An ISR may be composed of more than one AE using more than one verbatim term.

For ISRs of induration, erythema, blisters, ulceration, and necrosis, Investigators will measure and record the largest edge-to-edge lesion distance in millimeters.

11.3 Reporting Serious Adverse Events

The Investigator will review each SAE and evaluate the severity and the causal relationship of the event to study drug. All SAEs will be recorded from signing of informed consent until the EOS Visit 27/Week 29. Serious AEs occurring after the EOS Visit and coming to the attention of the Investigator must be reported only if there is (in the opinion of the Investigator) reasonable causal relationship with the study drug.

The Investigator is responsible for providing notification to the CRO of any SAE, whether deemed study drug-related or not, that a patient experiences during their participation in study within 24 hours of when he or she became aware of the event.

As a minimum requirement, the initial notification should provide the following information:

- Study number
- Patient number
- Name of Investigator
- Adverse event
- Criterion for classification as ‘serious’

- Study drug name
- Causality assessment (if sufficient information is available to make this classification)
- Identifiable reporter of event

CRO Safety personnel will request clarification of omitted or discrepant information from the initial notification. The Investigator or an authorized delegate is responsible for sending the requested information within 24 hours.

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g., hospital reports, consultant reports, autopsy reports), with the study patient's personal identifiers removed. If a new SAE Report Form is sent, then the Investigator must sign and date the form. The CRO may also request additional information on the SAE, which the Investigator or an authorized delegate must send to the SAE contact information below.

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

PAREXEL Clinical Studies Safety Center

United States (US) Telephone number/SAE Hotline: Durham, NC +1-919-294-5268

Fax number: +1-919-544-3572

US Email: NorthAmerica_Medical@parexel.com

United Kingdom (UK) Telephone number/SAE Hotline: Uxbridge +44 1895 273434

Fax number: Uxbridge +44 1895 231847

UK Email: DrugSafety@parexel.com

Provide the name of the Investigator, your name, the telephone number where you can be reached, and the protocol number and title.

11.4 Follow Up of Adverse Events/Serious Adverse Events

All AEs/SAEs documented at a previous visit/contact that are designated as not recovered will be reviewed by the Investigator at subsequent visits/contacts.

All AEs will be followed until the resolution of AE, completion of the patient's participation, or study termination, whichever occurs first.

Serious AEs will be followed until resolution, the condition stabilizes, or the Investigator and Sponsor agree that follow up is no longer necessary. Rules for AE/SAE follow up apply to all patients, including those withdrawn from the study prematurely to the extent allowed by the patient's consent. The Investigator will ensure that follow up includes further investigations consistent with appropriate medical management and patient consent to determine the nature and/or causality of the AE/SAE.

11.5 Other Reportable Events

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

- Pregnancy exposure (patient becomes pregnant while taking study drug). Should a female patient or partner of a male patient become pregnant during the study, the patient will inform the Investigator. The patient will be asked to follow up with the study site to report the eventual outcome of the pregnancy. The information will be tracked by the Sponsor.
- Overdose of study medication (defined as dosing ≥2 fold above intended weekly dose) occurring as a result of dosing amount error or timing error should be reported on the eCRF. The CRO Medical Monitor should be contacted if an overdose occurs. Any adverse outcomes of overdose should be recorded as AEs/SAEs according to the procedures described in Section 11.2.
- Lactation exposure (subject was taking study drug while nursing an infant)
- Accidental exposure (someone other than the study subject was exposed to study drug)
- Other medication errors that potentially place subjects at greater risk of harm than was previously known or recognized (e.g., study drug was administered via an incorrect route)

12 WITHDRAWAL OF PATIENTS

All patients who receive study drug should remain in the study whenever possible. However, patients are free to withdraw consent and/or discontinue participation in the study at any time, without prejudice to further medical care.

A patient's treatment and participation in the study may also be discontinued at any time at the discretion of the Investigator, CRO Medical Monitor, or Idera. Justifiable reasons to discontinue a patient from treatment and the study may include, but are not limited to the following:

- The patient was erroneously included in the study (i.e., did not meet eligibility criteria)
- The patient experiences an SAE assessed as possibly or probably related to study drug
- The patient is unable to comply with the requirements of the protocol
- The patient participates in another investigational study
- The patient withdraws consent
- The patient becomes pregnant
- A patient for whom the blind is intentionally broken

Patients who are withdrawn from treatment should complete the EOT/ET Visit 26/Week 25 assessments within 5 days of notification of withdrawal and the EOS Visit 27/Week 29 at 4 weeks (± 4 days) after the ET Visit (see Sections 10.1.4 and 10.1.5 for information regarding the EOT/ET and EOS Visits, respectively). A patient who completes the initial portion of the study (through the EOT Visit 26/Week 25) and is then lost to follow-up will not be considered to have prematurely withdrawn.

A patient will be considered "discontinued due to an AE" if they withdraw from the study due to any AE, regardless of whether or not the AE is considered related to investigational product. If the patient withdraws from the study due to an AE, the Investigator should arrange for the patient to be followed appropriately until the AE has resolved or stabilized (in the opinion of the Investigator).

The Investigator will document the reason(s) for treatment or study discontinuation on the eCRF. Idera and the CRO Medical Monitor should be informed when a patient is withdrawn from the study.

13 DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

13.1 Data Collection and Recording

The Investigator or personnel designated by the Investigator will perform primary data collection based on source document hospital or clinic records or other source documentation. All required study information must be recorded on the appropriate eCRF. The study monitor will review eCRFs for accuracy and completeness to ensure maximum data integrity. In addition, as the person ultimately responsible for the accuracy of all eCRF data, the Investigator will provide electronic endorsement that the data on the eCRFs are accurate and complete. Data processed at a central laboratory (e.g., safety laboratory tests and bioanalytical data) will be transferred electronically. An IXRS will be used to allocate the randomized treatments to patients as they are enrolled. The randomized treatment assignments will be transferred electronically for integration with the clinical study data at the appropriate time.

13.2 Data Quality Assurance

The eCRFs will be reviewed by a CRO study monitor against the source notes for identification and clarification of any discrepancies. Automated quality assurance programs will be in place to identify discrepancies, such as missing data, selected protocol violations, out of range data, and other data inconsistencies. Requests for data clarification or correction will be documented using an electronic data query and forwarded to the Investigator or study coordinator for resolution. All changes to the eCRFs will be tracked to provide an audit trail.

The Investigator must make study data accessible to the study monitor, to other authorized representatives of Idera, and to the appropriate regulatory authority inspectors. Audits for quality assurance of the database may be performed according to relevant standard operating procedures within the CRO or at the request of Idera.

13.3 Data Management

Idera, in close collaboration with any designee, will be responsible for:

- database creation and validation
- eCRF review and data validation
- query resolution
- data analysis and reporting

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

13.4 Protocol Violations

Prior to unblinding the study, Idera will review the protocol violations that occur during the study. A determination will be made as to which violations are considered to be major or would potentially impact efficacy assessments. Patients with such violations will not be included in the Per Protocol analysis, as per Section 14.3.

Examples of violations that would be considered to impact efficacy assessments would be:

- Change in background DM therapy during the study period
- Wrong study treatment was given
- Receiving <80% of planned doses of study treatment while on study.

14 STATISTICAL METHODS AND PLANNED ANALYSES

14.1 General Considerations

Continuous endpoints will be summarized descriptively. Categorical endpoints will be summarized by the number and percentage of patients in each category and 95% confidence intervals for the proportion.

14.2 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.

14.3 Analysis Sets

Safety Population and Intent-to-Treat Population (ITT) — all patients who received at least 1 injection of study medication.

Per Protocol Population (PP) — all patients who received at least 20 doses of study drug as assigned, completed the EOT Visit 26/Week 25, and had no major protocol violations that would potentially influence treatment effect (as determined by review by Idera prior to unblinding).

Safety analyses will be performed using the Safety Population. The efficacy, PD, disease-specific autoantibody, and immunogenicity assessments will be analyzed for the ITT population; key endpoints may be also analyzed for the PP Population as specified in the Statistical Analysis Plan (SAP). Analyses will be performed comparing the IMO-8400 treatment groups with placebo. Details will be provided in the SAP.

14.4 Statistical Analyses

14.4.1 Demographic and Baseline Characteristics

Patient demographics and baseline characteristics will be summarized descriptively by treatment group.

14.4.2 Study Conduct and Patient Disposition

The number of patients who enrolled in the study, the number randomized to each group, and the number in each analysis set will be summarized descriptively. The number of patients who completed the study will be summarized, and for those who terminated study participation before study completion, the reason for early termination will be tabulated by treatment group.

14.4.3 Treatment Compliance

Study drug exposure will be tabulated by the number of doses of study drug received. The number of and reason for missed doses will be tabulated categorically by treatment group.

14.4.4 Efficacy Analyses

The primary efficacy endpoint will be assessed via an RMMM. An appropriate covariance structure for repeated measures will be used. The difference between each IMO-8400 treatment group and placebo at Week 25 will be assessed. The overall alpha level will be controlled using the Bonferroni-Holm step-down method. Further details of this analysis will be described in the SAP. A sensitivity analysis will be performed to test the effect of important covariates on the effect of IMO-8400 using an RMMM.

Differences in response rate between the IMO-8400 treatment groups and placebo will be assessed via logistic regression.

The MMT8, TUG, 4 stair climb test, timed 10MWR test, serum CK, ALD, LDH, AST, ALT, SF-36, and 5-D Itch Scale will be analyzed in a similar manner to the primary endpoint.

For the proportion of patients who meet the IMACS 2004 DOI (Rider 2004) at EOT, logistic regression will be performed.

All efficacy endpoints will also be summarized descriptively by treatment group and nominal visit. Other exploratory and sensitivity analyses will be specified in the SAP in addition to further details regarding the statistical methodology.

14.4.5 Safety Analyses

Safety analyses will be descriptive in nature; no statistical hypothesis testing will be performed.

14.4.5.1 Physical Examination and Vital Signs

Physical examination data will list whether changes were noted. Changes in physical examination post baseline will be recorded as AEs. The actual value and change from baseline of vital signs will be summarized descriptively by treatment group and nominal visit. 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.

14.4.5.2 Clinical Laboratory Tests

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 nominal 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.

14.4.5.3 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by event, severity, and relationship to study therapy. Listings of SAEs and AEs

leading to study discontinuation will be produced. A listing of verbatim AE terms and the MedDRA terms they are mapped to will be produced.

14.4.5.4 Electrocardiograms

The actual value and change from baseline of ECG parameters will be summarized descriptively by treatment group and nominal visit. The number of patients experiencing QTC changes greater than 30 and 60 ms will be tabulated, as well as the number of patients with a QTC value greater than 450 and 500 ms.

14.4.5.5 Concomitant Medications and Therapies

Concomitant medications will be coded using the WHO Drug Dictionary. Results will be tabulated by anatomic therapeutic class and preferred term.

14.4.5.6 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.

14.4.6 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 may be used to evaluate/interpret any time-dependent trends in safety or PD outcomes.

14.4.7 Pharmacodynamic, Disease-specific Autoantibodies, and Immunogenicity Analyses

Pharmacodynamic, disease-specific autoantibodies, and immunogenicity study parameters will be summarized using descriptive statistics.

Details of the association between change in PD endpoints, clinical outcome measures, and dose received will be described in the SAP.

Figures presenting the median value of PD endpoints over time will be presented by treatment group.

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.

14.5 Significance Levels

Statistical analyses will use a 1-sided test with alpha set at 0.05.

14.6 Missing or Invalid Data

No missing data will be imputed. If any data are found to be invalid after database lock, the data will be hard-coded and a listing of all hard-coded values will be included in the CSR.

15 STUDY COMMITTEES

15.1 Data Monitoring Committee (DMC)

A DMC, operating autonomously from Idera, will be responsible for providing independent recommendations to Idera about evolving risk-benefit observed in the course of the study and any modifications required during the course of the study. The DMC will comprise at least 1 physician experienced in treating DM, and a biostatistician. The DMC will be chaired by one of these individuals. DMC members must not be actively involved in study design, conduct, or daily management of this study and must not have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making. Specialists may be invited to participate as non-voting members at any time if additional expertise is desired.

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. 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.

15.2 Patient Safety Committee (PSC)

A PSC consisting of the Investigator, CRO Medical Monitor and Idera Medical Monitor will be formed to monitor abnormal laboratory test values. See Sections 8.3.2 and 8.3.4 for actions to be taken in the event that abnormalities are noted in specified laboratory parameters.

16 SPECIAL REQUIREMENTS AND PROCEDURES

16.1 Compliance with Ethical and Regulatory Guidelines

This study was designed and will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in conformance with International Council for Harmonisation (ICH) GCP E6 guidance documents. The study will comply with the requirements that are enunciated in the US Code of Federal Regulations (CFR) related to the protection of human subjects (21 CFR Part 50), Institutional Review Boards (IRBs) (21 CFR Part 56) and investigational new drug applications (INDs) (21 CFR Part 312), electronic records and electronic signatures (21 CFR 11) and financial disclosure (21 CFR 54).

16.2 Institutional and Ethics Review

This protocol and a patient ICF, participant information sheet, and any proposed advertising material, must be reviewed and approved by an IRB/independent ethics committee (IRB/IEC), applicable regulatory authorities, and host institution(s) for written approval (where applicable) before enrollment of patients and release of investigational product. Documentation of IRB/IEC approval and the approved consent form must be received by the CRO prior to obtaining the patient's informed consent. Amendments to the original approved documents, where applicable, will also be submitted to and approved by the above parties. Investigators will comply with the appropriate IRB/IEC reporting requirements.

16.3 Confidentiality

All information regarding the nature of the proposed investigation that is provided to the Investigator by Idera or the CRO with the exception of information that is required by law or regulations to be disclosed to the IRB or the appropriate regulatory authority, must be kept in confidence by the Investigator in accordance with current Health Insurance Portability and Accountability Act standards.

Research records will be collected and stored in a manner that protects the confidentiality of patient information. The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by Idera (or its authorized designee). The names and identities of the patients need not be divulged; however, the records must nevertheless be inspected. This will be accomplished by blanking out the patient's name and replacing the name with the patient's study identification number on any record provided to or retained by Idera (or designee). The ICF must include appropriate statements explaining these requirements.

By signing this protocol, the Investigator affirms to Idera that the Investigator will maintain, in confidence, information furnished by Idera and will divulge such information to the IRB/IEC under an appropriate understanding of confidentiality with such board.

16.4 Changes to the Conduct of the Study or Protocol

Any changes in the study protocol, such as changes in the study design, objectives or endpoints, inclusion and exclusion criteria, and/or procedures (except to eliminate an immediate hazard) will be implemented only after the mutual agreement of the Investigator and the Sponsor or designee. All protocol changes must be documented in protocol amendment(s). Protocol

amendment(s) must be signed by the Investigator and approved by the IRB/IEC and Competent Authorities (CA), if applicable, prior to implementation. If a protocol amendment requires changes in the informed consent documents (if applicable), the revised documents must be reviewed and approved by the CRO Medical Monitor before review and approval by the IRB.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular patient and that are deemed by the Investigator as crucial for the safety and wellbeing of that patient may be instituted for that patient only. The Investigator will contact the CRO Medical Monitor as soon as possible regarding such a departure. These departures do not require preapproval by the IRB; however, the IRB and CRO Medical Monitor must be notified in writing as soon as possible in accordance with the IRB policies after the departure has been made. In addition, the Investigator will document the reasons for the protocol deviation and the ensuing events in the patient's eCRF. Documentation of IRB approval of any amendments must be returned to CRO.

16.5 Investigator Responsibilities

16.5.1 Patient Informed Consent

Investigators must adhere to GCP, which includes ethical principles that have their origin in the Declaration of Helsinki, when developing the patient ICF and when obtaining consent from the patient. By signing the Statement of Investigator (Food and Drug Administration [FDA] Form 1572), the Investigator assures that informed consent will be obtained from each patient prior to study entry and that the informed consent will be obtained in accordance with current regulations.

The Investigator will give each patient full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. An informed consent document will be provided to each patient in a language in which the patient is fluent. This information must be provided to the patient prior to undertaking any study-related procedure.

It is the responsibility of the Investigator to document the consent process within the source documents and obtain consent using an IRB/IEC-approved consent form.

16.5.2 Case Report Forms

The Investigator will make available copies of pertinent records in connection with the study, including all source documents, to Idera or the CRO upon request with due precaution towards protecting the privacy of the patient.

Under direction of the Investigator, data will be entered by the site onto the eCRFs in the electronic data capture system. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made on the eCRFs should be corrected. Changes made to the data after initial entry into the eCRF will be captured via an electronic audit trail, and should include the reason for change. Incomplete entries or entries needing additional explanation will be highlighted or queried to the Investigator for clarification.

After database lock, the Investigator will receive an electronic copy of the patient data for archiving at the investigational site. At all times, the Principal Investigator has final

responsibility for the accuracy and authenticity of all clinical data entered into the eCRFs and/or reported to Idera from the Investigator's site.

16.5.3 Record Retention

The Principal Investigator(s) must maintain all Essential Documents (as listed in the ICH Guideline for GCP) until notified by Idera and in accordance with all local laws regarding retention of records.

The Investigator must obtain written permission from Idera before disposing of any records. In order to avoid any possible errors, the Investigator will contact Idera prior to the destruction of any study records. The Investigator will promptly notify Idera in the event of accidental loss or destruction of any study records. If the Investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another Investigator, another institution, or to Idera.

16.5.4 Monitoring and Auditing

An Idera or CRO representative will visit the Investigator periodically at mutually convenient times, before, during, and after completion of the study, for the purpose of monitoring the progress of this study in accordance with the protocol, GCP, and local regulations. Non-compliance with the protocol, GCP, and local regulations will be documented and corrective actions implemented, as necessary. It is the responsibility of the Investigator to be present or available for consultation during monitoring visits. During these routine visits, all data pertaining to a patient's participation in this clinical investigation must be made available to the monitor.

At any time prior to, during, or after completion of the clinical study, an audit may be performed by Idera, CRO, or a representative of a national regulatory agency may choose to inspect a study site. Investigators should notify Idera upon notification of inspection by a representative of a national regulatory agency. A Sponsor or designee representative will be available to assist in the preparation for study site inspections. All pertinent study data should be made available for verification, audit, or inspection purposes.

16.5.5 Study or Site Termination

If Idera, the Investigator, or regulatory authorities discover any conditions during the study that indicate that the study or study site should be terminated, this action may be taken after appropriate consultation between the Sponsor and the Investigator. The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, which may include the following:

- The incidence and severity of AEs in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting this study

- Submission of knowingly false information from the study site to the Sponsor or regulatory authorities

In the event that the study is terminated early, Idera will provide specific guidance to investigational sites regarding the EOS procedures.

16.5.6 Investigational Product Control

16.5.6.1 Accountability of Study Drug

The study site (under direction of the Investigator) must maintain accurate records demonstrating dates and amount of study drug received, to whom dispensed (patient-by-patient accounting), any amount returned, and accounts of any study drug accidentally or deliberately destroyed. Study drug accountability should be performed for placebo as well. Unless otherwise notified, all vials both used and unused, must be saved for study drug accountability. At the end of the study, a final reconciliation must be made between the amount of study drug supplied, dispensed, and subsequently destroyed or returned to Idera. A written explanation will be provided for any discrepancies. The Investigator must ensure that the study drug is maintained in a controlled location, with limited access, and under adequate storage conditions.

16.5.6.2 Disposition of Unused Study Drug

All unused investigational products must be maintained under adequate storage conditions in a limited-access area. If any unused material is remaining upon completion of the study, the Investigator will return unused material to Idera or destroyed after accountability has been performed by CRO representative.

16.5.6.3 Product Handling and Complaints Reporting

If there are any issues during the course of the study related to the quality of the investigational product, the clinical site pharmacist or pharmacy designee should contact the CRO Medical Monitor.

16.5.7 Public Notification of Study Conduct

Consistent with Section 113 of the Food and Drug Modernization Act of 1997 (FDAMA) and with requirements of the International Committee of Medical Journal Editors (ICJME) as a condition of consideration for publication of study results, Idera will be responsible for ensuring that this protocol is listed at the ClinicalTrials.gov website and that information at the website relating to study design and conduct is appropriately updated during the course of the study. In order to facilitate this process, Investigators will need to supply Idera with appropriate contact information for study site personnel.

16.5.8 Dissemination of Results

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

To allow for the use of the information derived from this clinical study and to insure compliance with current regulations, the Investigator is obliged to provide Idera with complete test results and all data developed in this study. The information obtained during this study may be made

available to other physicians who are conducting similar studies and to the FDA or other regulatory authorities. Such information may be disclosed as deemed necessary by Idera.

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

16.5.9 Clinical Study Report

A study Investigator will be designated to review and sign the completed CSR(s).

16.5.10 Communication with Regulatory Authorities

Idera and CRO will assume responsibility for regulatory interactions with the FDA, the European Medicines Evaluation Agency (EMEA) and/or other regulatory authorities. In this regard, Idera will maintain an Investigational New Drug (IND) for IMO-8400 in support of the study. In fulfilling this responsibility, Idera and CRO will collect, assemble, and communicate all required regulatory documents (e.g., Form FDA 1572, Investigator financial disclosure forms, protocol and protocol amendments, investigator brochures, informed consent documents, annual reports) as required by regulation. Idera and CRO will also assume responsibility for AE reporting to regulatory authorities.

17 STUDY RATIONALE

This Phase 2 study was designed to build on prior clinical experience with IMO-8400, and to safely and efficiently generate critical dosing, safety, and efficacy data to support continued development of IMO-8400 for the treatment of DM and autoimmune diseases in which TLR receptors play a pivotal role.

IMO-8400 is a synthetic oligonucleotide that acts as a specific antagonist for TLRs 7, 8, and 9. It inhibits cell activation by agonists of those TLRs, including generation of NF-κB and the induction of cytokines and chemokines such as TNFα, IL-12, IL-1β, IP-10, IL-6, and IFN-α. IMO-8400 does not interfere with the immune stimulation mediated through other TLRs.

In murine models of autoimmune disease in which activation of TLRs play a critical pathogenic role including psoriasis, lupus, rheumatoid arthritis, and dermal inflammation, IMO-8400 has shown potent ability to inhibit the development of disease or to reduce ongoing signs and symptoms. Given that there is no animal model of human DM available for testing therapeutic agents (Katsumata, 2008) these models serve as surrogate DM mouse models that demonstrate the therapeutic effects of IMO-8400 in analogous diseases where inflammation due to TLR activation is implicated in pathogenesis.

Taken together, these studies support the hypothesis that IMO-8400 represents a novel approach to the treatment of diseases in which activation of endosomal TLRs is part of the pathophysiology, including DM. Current treatment options for DM often have significant adverse effects and/or are limited in the extent or duration of their impact. Thus IMO-8400 has the potential to address a substantial unmet medical need.

17.1 Study Design

The randomized, double-blind, placebo-controlled nature of the design was intended to eliminate bias in treatment assignment, facilitate blinding of study treatment, eliminate placebo effects, and ensure the reliability and validity of the study data. Randomization will be stratified by baseline CDASIv2 Activity score (15 to 20 vs. ≥21). The inclusion of multiple study sites is intended to enhance study accrual from this limited patient population while providing reassurance that the results are likely to have general applicability.

Selection of placebo as the reference arm in the proposed study is clearly appropriate given that this is a first-in-class approach to DM and that no approved standard therapy exists. Use of placebo provides an opportunity to obtain information regarding the full treatment effect size for IMO-8400. Comparison of IMO-8400 to corticosteroids is inappropriate because corticosteroids have a different mechanism of action and may have different clinical effects relative to IMO-8400.

Mandating that patients not receive prednisone or oral immunosuppressive therapy is not feasible as it would be potentially unethical to withdraw these therapies from patients who are benefiting from their use and would also shrink the pool of eligible patients.

17.2 Selection of Study Population

The entry criteria were designed to enroll only those patients with a confirmed diagnosis of DM in conjunction with documented evidence of skin involvement that could reasonably be expected to safely complete the study and provide interpretable data.

Bohan and Peter's diagnostic criteria, proposed in 1975, are still widely accepted, however, they are unable to differentiate DM from inclusion body myopathy or dystrophies for which the investigation of myositis specific autoantibodies and MRI must be performed (Iaccarino 2014). Therefore, supplemental criteria are provided in the inclusion criteria to ensure that appropriate patients with confirmed DM are enrolled.

17.2.1 Baseline Disease Activity Assessment

Baseline CDASI is likely to have prognostic significance for the primary assessment of skin activity. Changes in CDASI over 12 and 24 weeks for a convenience sample of 115 patients were analyzed by baseline score (unpublished data). Approximately 30% of patients showed improvement in CDASI scores by at least 4 points (clinically relevant changes) at both the 12- and 24-week assessment. Improvements are assumed to result from current standard care, although no data on treatments during the 24 weeks were collected. Patients with a high baseline CDASI score experienced larger decreases in CDASI at 24 weeks than those with a low baseline score. To control for possible effects of baseline disease activity on the results, randomization will be stratified by baseline CDASIv2-Activity score (15-20 vs. ≥21), and the study will be powered to detect a 7 point treatment effect, a therapeutic effect beyond that of the standard of care.

17.2.2 Dose Selection

17.2.2.1 Estimation of Human Equivalent Dosages from Animal Models of Autoimmune Disease

In the absence of an animal model of DM, the activity of IMO-8400 was tested in murine models of autoimmune diseases where, like DM, pathologic products that activate endosomal TLRs are formed endogenously. In the NZBW/F1 lupus mouse model, IMO-8400 demonstrated a dose-dependent improvement in inflammatory markers and renal impairment. Dose-dependent activity in animal models of arthritis, psoriasis, and dermal inflammation has also been seen with IMO-8400. Using a data-driven, systemic exposure-based dosage conversion for oligonucleotides as described in Yu et al (Yu 2015), the range of IMO-8400 dosages with therapeutic response in the NZBW/F1 mouse (3.8 to 7.5 mg/kg/week) extrapolates to a 0.76 to 1.5 mg/kg/week human equivalent dosage range. An exposure-based comparison between humans and mice in clinical and nonclinical studies conducted with IMO-8400 yields a similar dosage conversion from mice to humans as that described in Yu et al. The IMO-8400 doses being tested in this protocol, 0.6 mg/kg/week and 1.8 mg/kg/week, span the human equivalent dose range estimated from the NZBW/F1 lupus mouse model and the 1.8 mg/kg/week dose is within the estimated active dose range predicted by the other animal models of autoimmune disease.

17.2.2.2 Safety Profile of Selected Doses

Patients with DM in this study will be given IMO-8400 at 0.6 or 1.8 mg/kg/week for 24 weeks. In clinical trials as of 22 November 2016, IMO-8400 has been generally well tolerated. There were no treatment-related SAEs or fatalities, except 3 patients with WM with SAEs reported as a significant exacerbation of the subject's arthritis, arthralgia, and sepsis. Further description about all reported SAEs and AEs can be found in the Investigator's Brochure. In summary, a total of

60 subjects have been exposed to IMO-8400 at dosages ≥0.6 mg/kg/week. As of 22 November 2016, 32 subjects have been exposed to IMO-8400 at 0.6 mg/kg/week, 6 subjects have been exposed to 1.2 mg/kg/week, and 21 subjects have been exposed to 2.4 mg/kg/week Subjects have been exposed to IMO-8400 for up to 91 weeks.

17.3 Appropriateness of Efficacy Assessments

Dermatomyositis is a multisystem disorder with a wide variety of clinical manifestations. Characteristic skin findings are a hallmark of the disease as well as muscle weakness. Therefore endpoints have been selected that have a logical connection to the skin and muscle disease symptoms. The effects of IMO-8400 on the skin and muscle manifestations of DM will be primarily evaluated using the CDASI, which has been used in other studies of DM and is a reliable and valid assessment for these purposes. The blinding of efficacy assessor to potential ISRs requires the mCDASIv2, eliminating the abdominal skin assessment from the overall score.

Most of the other efficacy measures included in this study (including muscle enzyme levels and MMT8) were specifically recommended for inclusion in clinical trials of DM by the IMACS coalition of health care providers and researchers with experience and interest in the myositis syndromes (Rider 2004). Timed function tests, including the 10MWR, TUG and 4 stair climb test were added as exploratory endpoints to evaluate the potential effects of IMO-8400 on functional outcome measures (as opposed to rating scales) and the 5-D Itch Scale, a reliable and validated assessment of pruritis, was added to evaluate the ability of IMO-8400 to address this symptom.

17.3.1 CDASI

The CDASI is a one-page instrument designed to evaluate the cutaneous manifestations of DM. Developed by leading academic dermatologists and rheumatologists with an expertise in DM, the validity and reliability have been demonstrated in multiple studies of DM patients (Klein 2008, Yassaee 2010, Goreshi 2012).

To determine the minimal difference in CDASI scores associated with clinically significant change, a 2-center, prospective study of 199 patients with DM was conducted. Patients were evaluated with the CDASI, a PGA of disease severity, and a PGA of disease change since the last visit (improved, worse, no change) over the course of 12 visits. Clinical response was defined as a rating of "improved" on the PGA of disease change or a 3-point/2 cm change on the PGA of disease severity. Data were analyzed with logistic regression models using generalized estimating equations to account for correlation among patients. Based on the results, 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 (Anyanwu 2013).

Of note, clinically significant change in cutaneous manifestations of DM, as indicated by decreases in CDASI-Activity scores ≥4, were associated with statistically significant increases in quality of life as measured by the Skindex-29 and patient-reported itch and pain on a 10-point visual analogue scale (Robinson, 2015).

The CDASI has been used as a clinical endpoint in a least 1 clinical trial, a 52-week randomized, double-blind, placebo-controlled trial of etanercept in DM subjects. While treatment with etanercept was not associated with statistically significant changes in CDASI-Activity scores,

etanercept-treated patients demonstrated mean changes from baseline in CDASI-Activity scores of -4.9 after 24 weeks, while placebo-treated controls had a mean change of +1.5, confirming the responsiveness of the CDASI to changes in disease activity over time (Amato 2011).

The original CDASI had 4 activity and 2 damage measures. Yassaee et al (2010) created a second version of the CDASI (CDASIv2) and validated the new version in order to simplify and improve the tool for clinical research and care. The modified CDASI has 3 activity and 2 damage measures, and results of the research efforts by Yassaee et al indicated that all scores of the original and the modified CDASI correlated perfectly with each other.

In this study, the full CDASIv2 assessment will be performed at the Screening and Baseline Visits. Subsequent CDASI assessments will be performed using a mCDASIv2, which eliminates the abdominal skin assessments post-injection to decrease the risk of unblinding.

17.3.2 IMACS

The IMACS CSMs are validated and reliable clinical outcome measures used to evaluate multiple components of disease activity including muscle strength and laboratory enzymes. Analyses of the CSMs have been defined as: Change from baseline in the IMACS CSMs. Improvement will be assessed using the IMACS group DOIs (2004 DOI [Rider 2004]).

17.3.2.1 Manual Muscle Testing (MMT8)

Manual muscle testing is used to evaluate the function and strength of individual muscles and muscle groups based on the effective performance of a movement against gravity or manual resistance and is 1 of the IMACS CSMs for DM. The MMT has been widely used in myositis therapeutic trials and clinical studies (Feldman 2008, Jain 2006, Amato 2011) and its reliability and validity have been demonstrated repeatedly (Cuthbert 2007, Rider 2011). Moreover, the IMACS group identified muscle strength assessment as a key measure for clinical trials (Miller 2001).

The MMT8 is less physically and mentally taxing for the patient and clinician, has excellent internal and inter-rater reliability, and performs as well as or better than Total MMT in terms of responsiveness, content validity, and construct validity, it is expected to be an even more reliable indicator of muscle strength than the full MMT and has been incorporated into the IMACS CSM (https://www.niehs.nih.gov/research/resources/imacs/diseaseactivity/). While an absolute value for the minimal clinically important difference has not been determined for the MMT or MMT8, a group of adult and pediatric rheumatologists and neurologists have reached consensus that MMT should improve by ≥15% to classify an adult DM/PM patient as improved and should improve by ≥18% to classify a juvenile DM/PM patient as improved (Rider 2004).

17.3.2.2 Muscle Enzyme Levels

Muscle enzyme levels are another of the IMACS CSMs. Per IMACS, increases 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% (Rider 2004).

17.3.3 Timed Function Tests

Timed function tests (TFTs) will include time taken to run/walk 10 meters (10MWR), time taken to stand from a seated position (Timed Up and Go [TUG]), and time taken to climb 4 standard-sized stairs. Commonly used in assessment of neuromuscular diseases, these tests are relevant to DM in that they assess functional aspects of proximal muscle strength required for everyday ambulation (Brooke 1989, Podsiadlo 1991, Rao 2009). TFTs are reproducible, simple to administer, and have documented response to therapeutic intervention including corticosteroid therapy (Mendell 1989, Griggs 1991, Beenakker 2005). They are easy to perform functional assessments that usually take less than 5 minutes and provide adjunct functional assessment to the CDASI and IMACS.

17.3.4 5-D Itch Scale (5-D Pruritis Scale)

The 5-D Itch Scale is a validated patient-reported outcome measure that evaluates the 5 dimensions of itch (degree, duration, direction, disability and distribution) (Elman 2010). The evaluation is sensitive and able to measure multidimensional aspects of pruritus, including severity and impact on quality of life with demonstrated content validity, test-retest reliability, and internal consistency. The test can detect changes over time in patients with chronic pruritus and has been shown to have applicability in multiple diseases including skin disease, liver disease, kidney disease, HIV/AIDS, and burns (Elman 2010).

17.3.5 SF-36

SF-36 scores can be transformed using general US population norms so that all scales have a mean of 50 and a standard deviation of 10 as described in the SF-36 User's Manual (Ware 2001). Therefore, scores can be directly compared across scales, as well as to the general population norm of 50.

17.4 Safety Monitoring

The safety measures used in this study are available as standard laboratory tests and reflect appropriate monitoring of adult subjects receiving an investigational drug. Although no such events have been observed in clinical studies to date, adverse effects of myocardial degeneration/necrosis, glomerulonephritis, and/or hepatocellular necrosis were observed in cynomolgus monkeys treated with ≥6 mg/kg/week of IMO-8400 for up to 39 weeks (see the Investigator's Brochure for further detail). Changes in serum C3, C4 and the A:G ratio were sensitive predictors of toxicity in the 39-week monkey toxicology study, but several animals with no pathological changes at necropsy had abnormally low C3, C4, or A:G ratio, indicating a low specificity for the individual assays. Combining the data for these assays results in improved predictive power; using a compound rule of "low C3 or low C4 AND low A:G ratio" had a sensitivity of 100% and specificity of 74% for the prediction of adverse histological findings at necropsy.

All five monkeys with histological evidence of toxicity met the compound rule of abnormally low pre-dose C3 or C4 levels AND low A:G ratios several weeks to months prior to their unscheduled deaths or necropsy. Six of the animals in the recovery group met the compound rule during the dosing period. As five out of the fourteen monkeys (36%) that met the compound rule during the dosing period had histological evidence of toxicity at the primary or unscheduled

necropsy, it was estimated that two or three of the six monkeys in the recovery group with low pre-dose C3 or C4 levels AND low A:G ratios would have been expected to have had histological evidence of toxicity at the end of treatment. Because none of the monkeys had adverse microscopic findings at the end of their recovery period, it is concluded that the adverse histopathological findings would be avoidable or reversible if dosing were interrupted based on the compound rule.

In addition to the usual monitoring of AEs and laboratory data, Idera will monitor C3, C4, and the A:G ratio every 4 weeks in an effort to avoid toxicity in study subjects. (Subjects must have normal C3, C4 and A:G ratio for inclusion in the study).

Another oligonucleotide investigational product has been associated with clinically significant AEs of thrombocytopenia and renal abnormalities as well as ISRs in human clinical studies (FDA 2015). Given IMO-8400 is also an oligonucleotide investigational product, platelet counts, anti-platelet antibodies, urine protein, and renal function will be regularly monitored.

Stopping rules for abnormal safety laboratory test results are defined in Section 8.3.2. In addition, a DMC will review unblinded safety and efficacy data as outlined in the DMC Charter.

17.5 Overview of Human Safety Experience

In studies to date, IMO-8400 was safe and well tolerated in adult human subjects/patients at dose levels up to 2.4 mg/kg/week. Refer to Section 17.2.2 and the Investigator's Brochure for more detailed safety data.

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APPENDIX 1. AGE AND GENDER-APPROPRIATE CANCER WORK-UP GUIDELINES FOR WOMEN

Recommended Test & Schedule	**Age (years)**										
	18-19	**20**	**21-29**	**30-39**	**40-49**	**50-54**	**55-59**	**60-65**	**66-69**	**70-74**	**75**
Periodic health exams, including physical examination for signs of cancer of the: • Thyroid • Oral cavity • Skin • Lymph nodes • Ovaries		X	X	X	X	X	X	X	X	X	X
Pap test every 3 years			X								
Clinical breast exam every 3 years			X	X							
Pap test every 3 years OR Pap test and HPV test every 5 years [a]				X	X	X	X	X [b]			
Clinical breast exam yearly					X	X	X	X	X	X	
Mammography [c] yearly or every 2 years					X	X	X	X	X	X	
Communicate risks and symptoms of endometrial cancer [d]					----------Starting at the time of menopause----------						
Flexible sigmoidoscopy, double-contrast barium enema, or CT colonography every 5 years [e], OR Colonoscopy every 10 years						X	X	X	X	X	X
Guaiac-based fecal occult blood test or fecal immunochemical test yearly [e,f]						X	X	X	X	X	X
Low-dose CT (lungs) yearly, if patient • Is in fairly good health, *and* • Has a 30 pack per year smoking history, *and* • Is still smoking or has quit within the last 15 years							X	X	X	X	

[a] A woman who has had her uterus removed (and also her cervix) for reasons not related to cervical cancer and who has no history of cervical cancer or serious pre-cancer should not be tested.

[b] Women over age 65 who have had regular cervical cancer testing with normal results should not be tested for cervical cancer. Once testing is stopped, it should not be started again. Women with a history of a serious cervical pre-cancer should continue to be tested for at least 20 years after that diagnosis, even if testing continues past age 65.

[c] Some women – because of family history, a genetic tendency, or certain other factors – should be screened with MRI in addition to mammograms.

[d] Women should report any unexpected bleeding or spotting to their doctors. Some women – because of their history – may need to consider having a yearly endometrial biopsy.

[e] If the test is positive, a colonoscopy should be done.

[f] Highly-sensitive versions of these tests should be used with the take-home multiple sample method. One test done by the doctor in the office is not adequate for testing.

CT = computed tomography; HPV = human papilloma virus; MRI = magnetic resonance imaging
Note: Guidelines are based on recommendations from the American Cancer Society and the US Preventative Services Task Force. This is US guidance only; EU countries should follow local guidance.

APPENDIX 2. AGE AND GENDER-APPROPRIATE CANCER WORK-UP GUIDELINES FOR MEN

Recommended Test & Schedule	**Age (years)**										
	18-19	**20**	**21-29**	**30-39**	**40-49**	**50-54**	**55-59**	**60-65**	**66-69**	**70-74**	**75**
Periodic health exams, including physical examination for signs of cancer of the: • Thyroid • Oral cavity • Skin • Lymph nodes • Testes		X	X	X	X	X	X	X	X	X	X
PSA blood test with or without rectal exam [a]						X	X	X	X	X	X
Flexible sigmoidoscopy, double-contrast barium enema, or CT colonography every 5 years [b] OR Colonoscopy every 10 years						X	X	X	X	X	X
Guaiac-based fecal occult blood test or fecal immunochemical test yearly [c]						X	X	X	X	X	X
Low-dose CT yearly, if patient • Is in fairly good health, *and* • Has a 30 pack per year smoking history, *and* • Is still smoking or has quit within the last 15 years							X	X	X	X	

[a] Starting at age 50, men should talk to a doctor about the risks and possible benefits of testing and treatment. If they are African American or have a father or brother who had prostate cancer before age 65, men should have this talk with a doctor starting at age 45. For men who decide to be tested, the frequency of testing will depend on PSA level.

[b] If the test is positive, a colonoscopy should be done.

[c] Highly-sensitive versions of these tests should be used with the take-home multiple sample method. One test done by the doctor in the office is not adequate for testing.

CT = computed tomography; PSA = prostate-specific antigen

Note: Guidelines are based on recommendations from the American Cancer Society and the US Preventative Services Task. This is US guidance only; EU countries should follow local guidance.

APPENDIX 3. BOHAN AND PETER DIAGNOSTIC CRITERIA FOR DERMATOMYOSITIS

A	Symmetric proximal muscle weakness determined by physical examination
B	Elevation of serum skeletal muscle enzymes, including CK, aldolase, serum glutamate oxaloacetate and pyruvate transaminases, and lactate dehydrogenase
C	The electromyographic triad of short, small, polyphasic motor unit potentials; fibrillations, positive sharp waves, and insertional irritability; and bizarre, high-frequency repetitive discharges
D	Muscle biopsy abnormalities of degeneration, regeneration, necrosis, phagocytosis, and an interstitial mononuclear infiltrate
E	Typical skin rash of DM. Including a heliotrope rash and Gottron's sign/papules
Criteria for DM: • Definitive: Three criteria (A, B, C or D) + E • Probable: Two criteria (A, B, C or D) + E • Possible: One criterion (A, B, C or D) + E	

From Bohan 1975a and Bohan 1975b

APPENDIX 4. CUTANEOUS DERMATOMYOSITIS DISEASE AREA AND SEVERITY INDEX (CDASI) VERSION 2

Source: PCI Licensing Group, Perelman School of Medicine

Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) *ver02*

Select the score in each anatomical location that describes the most severely affected dermatomyositis-associated skin lesion

activity ⟷ **damage**

Extent ↕

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

Gottron's – Hands

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

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, Excoriation, Ulceration, Gottron's, Periungual, Alopecia)

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

NOTE: The CDASIv2 has been modified for this study such that abdominal assessments will not be performed after the first injection of study drug, to avoid unblinding the raters. Therefore, post-injection score totals will not include scores for the abdomen.

APPENDIX 5. IMACS FORM 04: MANUAL MUSCLE TESTING 8 SCORING SHEET

Source: http://www.niehs.nih.gov/research/resources/imacs/diseaseactivity/index.cfm

Patient number _____

Assessor _____

Date of Assessment (mm/dd/yy) _____

Visit number _____

	Function of the Muscle	**Grade**
No Movement	No contractions felt in the muscle	0
	Tendon becomes prominent or feeble contraction felt in the muscle, but no visible movement of the part	0
Test Movement	**MOVEMENT IN HORIZONTAL PLANE**	
	Moves through partial range of motion	1
	Moves through complete range of motion	2
	ANTIGRAVITY POSITION	
	Moves through partial range of motion	3
Test Position	Gradual release from test position	4
	Holds test position (no added pressure)	5
	Holds test position against slight pressure	6
	Holds test position against slight to moderate pressure	7
	Holds test position against moderate pressure	8
	Holds test position against moderate to strong pressure	9
	Holds test position against strong pressure	10

MMT8 is a set of 8 designated muscles tested unilaterally (potential score 0 – 80), test on right side (use left side if right side cannot be tested).

Position	Order of Testing
Sitting	
Deltoid middle (shoulder abductors)	1
Biceps brachii (elbow flexors)	2
Wrist extensors (extensor carpi ulnaris/radialis)	3
Quadriceps femoris (knee extensors)	4
Ankle dorsiflexors (tibialis anterior)	5
Supine	
Neck flexors (scalenes, sternocleidomastoid)	6
Deltoid middle (G.E. test if needed)	-
Gluteus medius (G.E. test if needed)	-
Sidelying (lying on left side-right muscles tested)	
Gluteus medius (hip abductors)	7
Gluteus maximus (G.E. test if needed)	-
Biceps brachii (G.E. test if needed)	-
Neck flexors (G.E. test if needed)	-
Prone	
Gluteus maximus (hip extensors)	8

Scoring Area

Muscle Groups	Right (0 – 10)	Left (0 – 10)	Axial (0 – 10)
Axial Muscles (0 – 10)			
Neck flexors	-	-	
Proximal Muscles (0 – 100)			
Deltoid middle			-
Biceps brachii			-
Gluteus maximus			-
Gluteus medius			-
Quadriceps			-
Distal Muscles (0 – 40)			
Wrist extensors			-
Ankle dorsiflexors			-
MMT- 8 score (0 – 80)			

APPENDIX 6. IMACS FORM 06: SERUM LEVELS OF MUSCLE ENZYMES

Source: http://www.niehs.nih.gov/research/resources/imacs/diseaseactivity/index.cfm

Patient number _____

Date of Assessment (mm/dd/yy) _____

Visit number _____

Blood laboratories:	Result	Normal Range
Creatine kinase (IU/L)		
Aldolase (IU/L)		
Aspartate transaminase (IU/L)		
Alanine transaminase (IU/L)		
Lactate dehydrogenase (IU/L)		
Creatinine (mg/dL)		

APPENDIX 7. SF-36 HEALTH SURVEY

Source: Quality Metric: http://www.qualitymetric.com/products/descriptions/sflicenses.shtml

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Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

APPENDIX 8. 5-D ITCH SCALE (ALSO KNOWN AS THE 5-D PRURITIS SCALE)

Source: Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. Br J Dermatol. 2010 Mar;162(3):587-93.

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 9. INVESTIGATOR'S AGREEMENT

I have read the foregoing protocol (Protocol 8400-211) and agree to the following:

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

Signature of Investigator **Date (dd-mmm-yyyy)**

Investigator (printed name):

Facility / Site of Investigation: