KZR-616-003

A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF KZR-616 IN THE TREATMENT OF PATIENTS WITH ACTIVE POLYMYOSITIS OR DERMATOMYOSITIS

Clinicaltrials.gov Identifier	*NCT04033926*
Release date of report:	*01 March 2019*

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2 Randomized, Double-blind, Placebo-controlled, Crossover Multicenter Study to Evaluate the Safety and Efficacy of KZR-616 in the Treatment of Patients with Active Polymyositis or Dermatomyositis
Protocol Number:	KZR-616-003
Investigational Medicinal Product:	KZR-616
Indications:	Polymyositis (PM) and Dermatomyositis (DM)
Development Phase:	2
US IND Number:	[redacted]
Sponsor:	Kezar Life Sciences, Inc. 4000 Shoreline Court, Suite 300 South San Francisco, CA 94080 Telephone: [redacted]
Original Protocol Date:	01 March 2019

Confidentiality Statement:

The concepts and information contained herein are confidential and proprietary and shall not be disclosed in whole or part without the express written consent of the Sponsor.

Compliance Statement:

This study will be conducted in accordance with this protocol, the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

PROTOCOL APPROVAL PAGE

I have read the document described above, and my signature below indicates my approval:

[redacted]

04 March 2019

Date

PROTOCOL ACCEPTANCE PAGE

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the International Conference on Harmonisation Guideline (ICH) for Good Clinical Practice (GCP), the Declaration of Helsinki, all local, regional, and national regulatory requirements (including the Code of Federal Regulations [CFR] Title 21 for US Investigators), requirements of the applicable Institutional Review Board/Independent Ethics Committee, and the clinical trial protocol. I agree to conduct the trial according to these regulations and guidelines, to appropriately direct and assist the staff under my control that will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Investigator's Name: _____

Name of Institution/Site: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

INVESTIGATIONAL PRODUCT (IP)	
Name of IP	KZR-616
Name of Active Ingredient	KZR-616
CLINICAL CONDITION(S)/INDICATION(S) • Polymyositis (PM) • Dermatomyositis (DM)	
PROTOCOL ID	KZR-616-003
PROTOCOL TITLE	A Phase 2 Randomized, Double-blind, Placebo-controlled, Crossover Multicenter Study to Evaluate the Safety and Efficacy of KZR-616 in the Treatment of Patients with Active Polymyositis or Dermatomyositis
Short Title	A Phase 2 Study of KZR-616 to Evaluate Safety and Efficacy in Patients with Active Polymyositis or Dermatomyositis
STUDY PHASE	Phase 2
STUDY OBJECTIVES	
Primary Objective • Evaluate efficacy of KZR-616 in patients with PM or DM.	
Secondary Objective(s) • Evaluate safety and tolerability of KZR-616 in patients with PM or DM • Evaluate pharmacokinetics (PK) of KZR-616 in patients with PM or DM.	
Exploratory Objectives • Evaluate biomarkers related to efficacy and safety of KZR-616 in patients with PM or DM • Evaluate the PK and pharmacodynamic (PD) relationship of KZR-616 in patients with PM or DM.	
STUDY DESIGN	
Study Type	Interventional
Allocation	Randomized
Intervention model	Crossover
Blinding/Masking	Double-blind
Primary Purpose	Treatment
Planned Duration of Patient Participation	Up to 44 weeks: 4-week Screening Period, 32-week Treatment Period, and 8-week Safety Follow-up (SFU)

Study Design

This is a Phase 2 randomized, double-blind, placebo-controlled, crossover, multicenter study to evaluate the safety, tolerability, efficacy, PK and PD of treatment with KZR-616 in patients with active PM or DM. Patients will be evaluated for eligibility during the Screening Period. Eligible patients will be randomized 1:1 to Arm A or Arm B of the study. Patients will be stratified by their diagnosis of PM or DM.

During the 32-week treatment period, patients will receive study drug subcutaneously (SC) once weekly. The 16 weeks of dosing during Treatment Period 1 begins at Week (W) 0 and continues through W15 (ie, ends immediately before dosing at Week 16 [approximately Day 113]); patients allocated to Arm A will receive KZR-616 and those in Arm B will receive placebo. The 16 weeks of dosing during Treatment Period 2 begins with administration of the first dose at W16 and continues through W31 (ie, ends immediately before Week 32); patients allocated to Arm A will receive placebo and those in Arm B will receive KZR-616.

This study will be conducted on an outpatient basis. Study visits will occur at Screening, W0, W4, W8, W12, W16, W20, W24, W28, W32, W36, and W40. Day 1 of W0 will be defined as Baseline. The W36 and W40 visits will comprise the Safety Follow-up (SFU).

Randomized patients who withdraw from the study prior to W32 will be requested to undergo the Early Termination Visit (ETV) procedures, and all patients who withdraw prematurely also will be requested to return for a SFU visit 9 weeks (W40 visit procedures) after receipt of their last dose of the study drug.

Efficacy assessments will be performed for all patients, unless indicated otherwise, and will include: International Myositis Assessment and Clinical Studies Group (IMACS) core set Activity and Damage measures (Manual Muscle Testing-8 Muscle Groups [MMT-8]; Physician and Patient Global Assessments of Disease Activity [MDGA and PtGADA, respectively]; Health Assessment Questionnaire-Disability Index [(HAQ-DI]; muscle enzymes [clinical laboratory assessments]: creatine phosphokinase [CK], aldolase, lactate dehydrogenase [LDH], alanine aminotransferase [ALT], and aspartate aminotransferase [AST]; Myositis Disease Activity Assessment Tool [MDAAT, 2005 version]; Myositis Damage Index [MDI]; and the Patient Global Assessment of Disease Damage [PtGADD]), Functional Index-2 (FI-2; performed for the dominant side only), Functional Index-3 (FI-3; 30-second chair stand test, timed up and go test, and 6-minute walk distance), Physician Global Impression of Change (MDGIC), and Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI; performed only for patients with DM).

Additional patient reported outcome measures (PROMs) will be performed for all patients, unless indicated otherwise, and will include: Patient Reported Outcomes Measurement Information System 29-item Short Form Profile Version 2.1 (PROMIS-29), EuroQoL 5-dimension 5-level (EQ-5D-5L), Healthcare Resource Utilization (HRU), Treatment Satisfaction Questionnaire for Medication Version II (TSQM), Patient Global Impression of Change (PGIC), and the Peak Pruritus Numeric Rating Scale (NRS; performed only by patients with DM).

Safety will be assessed throughout the study by monitoring vital signs (blood pressure, pulse rate, temperature, and respiration rate), physical examination, electrocardiograms (ECGs), clinical laboratory tests (hematology, chemistry, urinalysis, immunoglobulins), and by recording and analyzing all adverse events (AEs) and serious adverse events (SAEs).

Biopsies will be collected from a subset of enrolled patients; skin biopsies will be performed only for selected patients with DM, and muscle biopsies will be performed for selected patients with PM or DM. For selected patients, biopsies will be collected from skin and/or muscle at Baseline, W16, and optionally at W32. The tissue samples may be used for exploratory investigations of treatment-related changes and regulation of inflammatory pathways.

Efficacy Endpoints

The primary efficacy endpoint is:

- Mean change from start to end of KZR-616 treatment in the Total Improvement Score (TIS), which ranges from 0 to 100.

Secondary efficacy endpoints are:

- Proportion of patients with an increase ≥20 points on the TIS from start to end of KZR-616 treatment. The categories and ranges of scores for improvement are: 20-39 points being minimal improvement, 40-59 points being moderate improvement, and ≥60 points being major improvement
- Proportion of patients from start to end of KZR-616 treatment meeting IMACS Definition of Improvement (DOI). The IMACS DOI is ≥20% improvement in at least 3 of 6 core set activity measures, with no more than 2 core set activity measures (CSAMs) worsening by ≥25% (the MMT-8 cannot be a worsening measure)
- Absolute change and percent change from start to end of KZR-616 treatment in the IMACS individual CSAMs
- For patients with DM, the mean change from start to end of KZR-616 treatment in the CDASI
- For patients with DM, the mean change from start to end of KZR-616 treatment in the Peak Pruritus NRS.

Exploratory efficacy endpoints are:

- Mean change over time from start to end of KZR-616 treatment in the TIS in all patients, patients with DM only, and in patients with PM only
- Proportion of patients over time with an increase of ≥20, ≥40, or ≥60 points on the TIS from start to end of KZR-616 treatment in all patients, in patients with DM only, and in patients with PM only
- For patients with an increase of ≥20 points on the TIS from Baseline to W16, the proportion of patients with no change or increase in their TIS at W32 for all patients, in patients with DM only, and in patients with PM only

- Mean change and mean percent change over time from start to end of KZR-616 treatment in the IMACS individual CSAMs and core set damage measures (CSDMs) for all patients, in patients with DM only, and in patients with PM only
- Mean change from Baseline over time from start to end of KZR-616 treatment in the FI-2, the FI-3 and the individual components of the FI-3 for all patients, in patients with DM only, and in patients with PM only
- For patients with DM, mean change over time from start to end of KZR-616 treatment in the CDASI
- For patients with DM, the proportion over time with ≥7 points improvement in the CDASI from start to end of KZR-616 treatment
- For patients with DM, the mean change over time from start to end of KZR-616 treatment in the Peak Pruritus NRS
- Mean change over time from start to end of KZR-616 treatment in the individual domains of the PROMIS-29 for all patients, in patients with DM only, and in patients with PM only
- Mean change over time in TSQM from start to end of KZR-616 treatment for all patients, in patients with DM only, and in patients with PM only
- The change in quality of life over time from start to end of KZR-616 treatment as measured by the EQ-5D-5L for all patients, in patients with DM only, and in patients with PM only
- The HRU over time from start to end of KZR-616 treatment for all patients, in patients with DM only, and in patients with PM only
- The MDGIC over time from start to end of KZR-616 treatment for all patients, in patients with DM only, and in patients with PM only
- The PGIC over time from start to end of KZR-616 treatment for all patients, in patients with DM only, and in patients with PM only.

Note: The primary analysis period is from start to end of KZR-616 treatment for both sequence arms combined. A secondary analysis comparing KZR-616 to parallel placebo will be confined to the Baseline to Week 16 period. Lastly, the usual crossover analysis comparing placebo to KZR-616 will be carried out as an exploratory analysis approach. The rationale for this priority order is as follows. The usual crossover analysis for this design is prespecified as exploratory since it is unknown whether that analysis would be confounded by carryover effect. In order to maximize the precision for assessment of KZR-616 effect, it is assessed primarily via all patients' start to end of KZR-616 treatment, and secondarily by the Treatment Period 1 between-treatment comparison.

Safety Endpoints

- Incidence, nature, and severity of AEs
- Incidence, nature, and severity of SAEs
- Incidence and severity of infection-related AEs and SAEs
- Incidence and severity of AEs with onset within 24 hours from the start of dosing with any study drug
- Incidence of AEs leading to study drug discontinuation
- Changes in standard laboratory parameters, vital signs, and ECGs.

Pharmacokinetic and Pharmacodynamic Endpoints

The secondary PK endpoint will:

- Evaluate the plasma PK parameters for KZR-616 and its metabolite KZR-59587.

The exploratory PK/PD endpoints will:

- Evaluate the relationships between KZR-616 PK, clinical efficacy, clinical safety, and various PD endpoints including proteasome inhibition and changes in circulating cytokine and immune cell profiles
- Evaluate the relationships between KZR-616 PK, clinical efficacy, clinical safety, and various PD endpoints related to skin and muscle biopsy histology and gene expression profiles.

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION

Active Product	**Dosage form:** KZR-616 Lyophile, 125 mg/vial, is supplied as a refrigerated lyophilized drug product containing 125 mg of KZR-616 (150 mg of KZR-616 maleate) and [redacted] (inactive excipient) in single-use 3.0-mL borosilicate glass vial. **Dose and dose frequency**:

	The study consists of 2 arms: Arm A: • Treatment Period 1: KZR-616 30 mg SC weekly for 2 weeks (W0-W1), then 45 mg SC weekly for 14 weeks (W2-W15) • Treatment Period 2: Placebo SC weekly for 16 weeks (W16-W31). Arm B: • Treatment Period 1: Placebo SC weekly for 16 weeks (W0-W15) • Treatment Period 2: KZR-616 30 mg SC weekly for 2 weeks (W16-W17), then 45 mg SC weekly for 14 weeks (W18-W31).
Control/Comparator	A placebo control will be used to maintain blinding and will be sterile water for injection (WFI). Dose and dose frequency: Refer to the dose and dose frequency of the active product, KZR-616.
PATIENT SELECTION	
Targeted Accrual	Approximately 24 enrolled patients; it is anticipated 40 patients will be screened to achieve 24 patients enrolled
Number of Arms	Two with approximately 12 patients in each arm
Planned Number of Sites	Up to approximately 18 sites

Inclusion Criteria

1. Adult patients at least 18 years of age at the time of signing informed consent at Screening
2. Body Mass Index (BMI) of 18 to 40 kg/m^2
3. Diagnosis of probable or definite DM or PM by the 2017 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) Classification Criteria
4. Must have their data reviewed by an adjudication committee to confirm eligibility unless at least 1 of the following is present:
    a. Muscle biopsy with evidence of active myositis within the last 6 months prior to or at Screening
    b. Electromyography or magnetic resonance imaging (MRI) with evidence of active myositis within the last 6 months prior to Screening
    c. A CK ≥4 × upper limit of normal (ULN).
5. Must have demonstrable muscle weakness as measured by the MMT-8 with a score ≥80/150 but ≤136/150 units and any 2 of the following:
    a. MDGA visual analog scale (VAS) ≥2 cm
    b. PtGADA VAS ≥2 cm
    c. At least one muscle enzyme laboratory measurement (ie, CK, aldolase, LDH) ≥1.3 × ULN
    d. MDAAT Extramuscular Global Activity VAS ≥1 cm.
6. Documented inadequate response to a 12-week trial of corticosteroids or at least 1 immunosuppressant (eg, methotrexate [MTX], mycophenolate mofetil [MMF], mycophenolate sodium [MPS], azathioprine [AZA], leflunomide [LEF], tacrolimus, cyclosporine [CyA]) OR have demonstrated significant documented toxicity or intolerance to such therapies
7. Has had age-appropriate cancer screening that is up to date and negative for evidence of malignancy as per local standard of care (see Appendix A)

8. Female patients of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline and must agree to employ adequate birth control measures for the duration of the study.
   Women of childbearing potential (WOCBP) must use highly effective and medically acceptable methods of contraception to prevent pregnancy during Screening and must agree to continue to practice adequate contraception during the study and for 4 weeks after administration of the last dose of the study drug.
   For the purposes of this study, WOCBP are defined as: all postpubescent female patients, unless the patient is postmenopausal (defined by amenorrhea for at least 2 years or amenorrhea for at least 1 year with confirmatory follicle stimulating hormone [FSH] level in the postmenopausal range as documented historically or measured by the central laboratory at Screening and if patient is not on supplementary hormonal therapy) or if the patient is surgically sterile (ie, tubal ligation, hysterectomy, bilateral salpingoophorectomy).
   Highly effective contraception is defined as the use of 2 barrier methods (eg, female diaphragm and male condom), 1 barrier method with spermicide, intrauterine device, or hormonal contraceptives (eg, implant or oral). If using a hormonal form of contraception, it must have been stable for at least 4 weeks prior to Screening, and if using concomitant mycophenolate, the patient must use another nonhormonal form of highly effective contraception. Abstinence will be acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation) and withdrawal are not acceptable methods of contraception
9. Male patients must be either congenitally sterile or surgically sterile (vasectomy with documented confirmation of aspermia) or willing to use a condom in addition to having their female partner use another form of contraception (such as an intrauterine device, barrier method with spermicide, or hormonal contraceptive [eg, implant, injectable, patch, or oral]) from Screening until 12 weeks after the last dose of study drug, unless their partners are infertile or surgically sterile
10. Willing and able to comply with the requirements of the protocol
11. Provide written informed consent prior to any study-related procedure.

Exclusion Criteria

1. Has significant muscle damage (eg, severe muscle atrophy, end-stage disease, postmyopathic DM) per Investigator opinion or has a muscle damage VAS score ≥5 cm on the MDI
2. Any other form of myositis or myopathy other than PM or DM (eg, metabolic or drug-induced myopathy, drug-induced myositis, juvenile PM or DM, inclusion body myositis, cancer-associated myositis [myositis diagnosed within 3 years, either before or after, of a diagnosis of any malignancy except for squamous or basal cell carcinoma of the skin or cervical carcinoma in situ], myositis in overlap with another connective disease [eg, systemic lupus erythematosus{SLE}, systemic sclerosis, rheumatoid arthritis {RA}], or muscular dystrophy); patients with secondary Sjogren's syndrome, necrotizing myopathy, or antisynthetase syndrome are permitted to participate in this study
3. Any condition (eg, severe arthritis with limited range of motion or severe calcinosis) that, in the Investigator's opinion, precludes the ability to quantitate muscle strength
4. Has severe interstitial lung disease per Investigator opinion or has a pulmonary damage VAS score ≥5 cm on the MDI
5. Presence of autoinflammatory disease (eg, psoriatic arthritis, axial spondyloarthropathy, inflammatory bowel disease)
6. Has received treatment with any of the following:
   a. Oral prednisone (or prednisone equivalent) >20 mg/day at Screening or during the Screening Period, or initiation of oral prednisone during the Screening Period. If oral prednisone is being used at Screening, use should be stable during the 2 weeks prior to Baseline
   b. Use of nonsteroidal immunosuppressants other than oral MMF or MPS (≤3 g/day or 2160 mg/day, respectively); oral, intramuscular (IM), or SC MTX (≤25 mg/week); AZA (≤2.5 mg/kg/day); LEF (≤20 mg/day); tacrolimus (≤3 g/day); or concurrent use of more than 1 nonsteroidal immunosuppressant at Baseline. If a permitted nonsteroidal immunosuppressant is being used, it must have used for at least 12 weeks and must have been taken at a stable dose (including stable route of administration) for the last 4 weeks prior to Screening. If MMF, MPS, MTX, AZA, LEF, or tacrolimus is being discontinued, it must be discontinued at least 4 weeks prior to Baseline

c. Antimalarials exceeding the recommended doses (hydroxychloroquine up to 400 mg/day or 6.5 mg/kg/day, whichever is less; chloroquine up to 250 mg/day, or quinacrine up to 100 mg/day are permitted) or taken at an unstable dose during the 12 weeks prior to Screening. If an antimalarial is being discontinued, it must be discontinued at least 4 weeks prior to Baseline. Antimalarials are considered distinct from corticosteroids in (a) and nonsteroidal immunosuppressants in (b) above
d. Initiation of or use of an unstable dose of topical therapy (eg, corticosteroids, pimecrolimus) in the 4 weeks prior to Screening. If topical therapy is being discontinued, it must be discontinued at least 4 weeks prior to Baseline.

7. Receipt of any of the following treatments within the following timeframes before Screening:
   a. Oral corticosteroids at doses ≥1 mg/kg/day prednisone or equivalent: 4 weeks
   b. Intravenous or IM corticosteroids: 4 weeks
   c. Intra-articular therapies, such as corticosteroids or hyaluronic acid preparations: 4 weeks
   d. Intravenous, SC, or IM Ig: 4 weeks
   e. Cyclophosphamide or chlorambucil: 24 weeks
   f. Prohibited nonbiologic nonsteroidal immunosuppressants or targeted therapies including, but not limited to, CyA, dapsone, tofacitinib, baricitinib: 8 weeks
   g. Cytokine or integrin antagonists or selective costimulation modulators including, but not limited to, interleukin (IL)-1, IL-6, IL-17, IL-12/23, IL-23, interferon (IFN), integrin, and tumor necrosis factor (TNF)α antagonists or abatacept: 12 weeks
   h. B cell-depleting or -modulating therapies (eg, rituximab, ofatumumab, obinutuzumab, ocrelizumab, belimumab, atacicept): 24 weeks
      For those patients who have used an anti-cluster of differentiation (CD) 20 drug at ≥24 weeks and <48 weeks before Screening, they must have levels of circulating CD19+ B cells ≥the lower limit of normal (LLN). A CD19 count is not required for patients with prior use of an anti-CD20 drug ≥48 weeks prior to Screening
   i. Previous treatment with the following cell-depleting therapies, including investigational agents or approved therapies: alemtuzumab, anti-CD4, anti-CD5, or anti-CD3: at any time
   j. Other biologics or investigational drugs: 8 weeks or 5 half-lives, whichever is longer
   k. Transfusion with blood, packed red blood cells, or platelets or treatment with plasmapheresis or plasma exchange: 6 weeks
   l. Creatine dietary supplements: 4 weeks.
8. Initiation of an exercise program (including physical therapy or occupational therapy) for muscle strengthening within 4 weeks of Screening or initiation planned during the study. Any exercise program or regimen that was initiated >4 weeks prior to Screening must be continued in a stable manner during Screening and the study
9. Patient has had recent serious or ongoing infection, or risk for serious infection, including:
   a. Acute or chronic infection defined as any infection requiring systemic antibiotic, antifungal, or antiviral (antimicrobial) therapy within 2 weeks of Baseline
   b. Hospitalization or receipt of a course of IV antimicrobial therapy within 24 weeks prior to Screening or during the Screening Period
   c. Symptomatic herpes zoster or herpes simplex infection (HSV) (not including simple oral HSV lesions) within 12 weeks prior to Screening or during the Screening Period
   d. History of severe and/or disseminated viral infections, and/or opportunistic infections
   e. Known seropositivity for or active infection by human immunodeficiency virus (HIV)
   f. Active, chronic, or resolved hepatitis B or hepatitis C infection (hepatitis B core antibody or surface antigen positive, or hepatitis C antibody positive at Screening)
   g. History of progressive multifocal leukoencephalopathy
   h. Active or untreated latent tuberculosis (TB), as suggested by chest radiograph performed within the 12 weeks prior to or at Screening (see Section 7.2.6.3) or positive (or 2 indeterminate or borderline) results of an approved TB test at Screening (see Section 7.2.6.1). Patients with a history of latent TB with documented completed treatment per Centers for Disease Control and Prevention guidelines and no known exposures post treatment are allowed to participate
   i. Receipt of a live-attenuated vaccine within 4 weeks of Screening

j. Primary immunodeficiency (unless otherwise considered, in the opinion of the Investigator or the Sponsor, to confer a clinically insignificant infection risk, such as deficiency in immunoglobulin A [IgA], C1q, C2, or C4 without a history of recurrent infections [3 or more infections in 1 year that required antimicrobial therapy])
k. History of recurrent infections [3 or more infections in 1 year that required antimicrobial therapy] in the 12 months prior to Baseline
l. Prior hematopoietic cell or solid organ transplant.

10. History of any concurrent illness (eg, asthma) that has required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 24 weeks prior to Screening
11. Any of the following laboratory values at Screening:
    a. Estimated glomerular filtration rate <45 mL/min by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation
    b. Hemoglobin <10 g/dL
    c. White blood cell (WBC) count $<3.0 \times 10^9$/L
    d. Absolute neutrophil count (ANC) $<1.5 \times 10^9$/L (1500/mm^3)
    e. Platelet count $<100 \times 10^9$/L
    f. Serum AST or serum ALT >2.5 × ULN (unless considered consistent with muscle origin)
    g. Serum alkaline phosphatase >2.5 × ULN
    h. Total bilirubin >1.5 × ULN (3 × ULN for patients with documented Gilbert's syndrome)
    i. Thyroid stimulating hormone outside of the central laboratory normal range
    j. Immunoglobulin G (IgG) <500 mg/dL.
12. Presence of New York Heart Association Class III or IV heart failure, or uncontrolled blood pressure (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg at rest), or QT interval with Fredericia's correction (QTcF) or Bazett's correction (QTcB) >480 msec on ECG
13. Major surgery within 12 weeks before Screening, major surgery planned during the study period, or any surgery planned during the study period that would require an alteration of concomitant immunosuppressant or corticosteroid therapy or additional corticosteroid therapy
14. Clinical evidence of significant unstable or uncontrolled diseases (eg, cardiac [including congestive heart failure, hypertension, angina, or recent {<6 months prior to Screening} myocardial infarction], pulmonary [including chronic obstructive pulmonary disease, asthma requiring systemic corticosteroid therapy, pulmonary hypertension, or interstitial lung disease], hematologic, gastrointestinal, endocrinologic [eg, hypothyroidism, diabetes], hepatic, renal, neurological, or infectious) that, in the opinion of the Investigator or Sponsor, could confound the results of the study, put the patient at undue risk, or interfere with protocol adherence
15. Evidence of current or previous clinically significant disease, medical condition (including abnormal laboratory values), or finding in the medical examination that in the Investigator's or Sponsor's opinion would compromise the safety of the patient or the ability to interpret the data
16. Any active or suspected malignancy, including myeloproliferative or lymphoproliferative disorder, or history of documented malignancy within the last 5 years before Screening or within 3 years of diagnosis of myositis, except appropriately excised and cured cervical carcinoma in situ or basal or squamous cell carcinoma of the skin; patients with a history of basal or squamous cell carcinomas of the skin must have had 3 or fewer in their lifetime to be eligible
17. Alcohol abuse or drug abuse in the last 1 year prior to Screening in the opinion of the Investigator
18. Women who are pregnant, lactating, or discontinued lactation less than 12 weeks prior to Screening, or who plan to become pregnant or initiate lactation during the study
19. Patients unable to comply with the protocol in the Investigator's or Sponsor's opinion.

STATISTICAL ANALYSIS

Planned Statistical Analysis

The Safety Analysis Set consists of all patients who receive at least one dose of study drug. The Full Analysis Set (FAS) consists of all patients who received at least one dose of study drug and have a Baseline and post-Baseline observation. This is the primary efficacy analysis set for the study. The Per Protocol Analysis Set consists of all patients who received at least one dose of KZR-616 and for whom the PK data are considered sufficient. Since this is a Phase 2 study, all analyses and summaries will be based on the actual test treatment the respective patients received.

Efficacy Analysis

The primary endpoint is mean change from start to end of KZR-616 treatment in TIS.[2] For the continuous efficacy parameters, within patient changes will be analyzed as follows:

- (1: primary) by comparing the Baseline and post-Baseline observations within patients for the KZR-616 treatment periods combined, ie, W16 versus W0 for patients allocated to the randomized treatment sequence KZR-616 followed by placebo and W32 versus W16 for patients allocated to the randomized treatment sequence placebo followed by KZR-616, combined;
- (2: secondary) by comparing the change from Baseline in Treatment Period 1 between treatments, ie, change from W0 to W16 for patients allocated to the randomized treatment sequence KZR-616 followed by placebo versus change from W0 to W16 for patients allocated to the randomized treatment sequence placebo followed by KZR-616; and
- (3: exploratory) by comparing the last response on test treatment between treatments via a crossover design analysis, ie, W16 for patients allocated to the randomized treatment sequence KZR-616 followed by placebo and W32 for patients allocated to the randomized treatment sequence placebo followed by KZR-616, combined, versus W16 for patients allocated to the randomized treatment sequence placebo followed by KZR-616 and W32 for patients allocated to the randomized treatment sequence KZR-616 followed by placebo, combined.

The rationale for this priority order is as follows. The usual crossover analysis for this design is prespecified as exploratory since it is unknown whether that analysis would be confounded by carryover effect. In order to maximize the precision for assessment of KZR-616 effect, it is assessed primarily via all patients' Baseline versus post-Baseline KZR-616 assessment and secondarily by the Treatment Period 1 between-treatment comparison. Summary statistics, including 95% confidence intervals, will be provided for each treatment for each of the 3 types of analysis. Within-patient changes will be analyzed via paired t-tests and corroborated by signed rank tests. Between-patient differences will be analyzed via analysis of covariance, with Baseline as a covariate. The crossover analysis will be via a mixed model repeated measures analysis. Normality will be assessed graphically and via the Shapiro-Wilk statistic. If substantial departure from normality is observed, transformations, eg, natural log and rank, will be explored. P values will be 2-sided with the type 1 error level at 0.05.

Binary endpoints will be summarized by counts and percent and 95% confidence intervals via Clopper-Pearson method. Additional analyses will be specified in the Statistical Analysis Plan (SAP).

Safety Analysis

The safety analysis set will be used for all presentations of safety endpoints. No statistical testing will be used to compare treatment arms for different safety endpoints. Safety data will be summarized descriptively for each test treatment. All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment emergent AEs will be presented within summary presentations by MedDRA system organ class and preferred term, cohort, and treatment arm.

Pharmacokinetic and Pharmacodynamic Analyses

Blood samples for assay of KZR-616 plasma concentrations will be collected periodically. The plasma concentrations of KZR-616 and its metabolite KZR-59587, and PK parameters will be listed and summarized by appropriate summary statistics (eg, geometric means, natural log-scale standard deviation [SD], medians, quartiles). Whole blood samples for determination of proteasome activity will be collected periodically and processed to washed whole blood and isolated peripheral blood mononuclear cell (PBMC) pellets. Chymotrypsin-like (CT-L) activity and proteasome subunit active site occupancy in each compartment will be assessed and presented as absolute and predose normalized values. Pharmacodynamic data will be listed for each individual and summarized by nominal sampling time point and treatment group with descriptive statistics (eg, sample size, arithmetic mean, SD, median, minimum, maximum).

Sample Size Calculation

Prior summary statistics on change from Baseline in TIS score are not available. Hence, statistical power is quantified via standardized effect size (mean difference divided by pooled SD). A sample size of 24 patients has 80% power to yield a statistically significant (alpha=0.05 2-sided) improvement from Baseline if the true underlying effect size is 0.6 (90% power if true effect size is 0.7). The minimum observed effect size that would yield statistical significance is 0.42. This level of statistical precision is thought to be adequate for this initial trial of KZR-616 in PM and DM.

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LIST OF ABBREVIATIONS

Abbreviation or term	Definition
6MWD	6-minute walk distance
ACR	American College of Rheumatology
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AZA	azathioprine
BMI	body mass index
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
CD	cluster of differentiation
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index
CFR	Code of Federal Regulations
CGI	Clinical Global Impressions scale
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum concentration
CRP	C-reactive protein
CSAM	core set activity measures
CSDM	core set damage measures
CT-L	chymotrypsin-like
CyA	cyclosporine
CYC	cyclophosphamide
DOI	Definition of Improvement
DM	dermatomyositis
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate

ELISA	enzyme-linked immunosorbent assay
EMG	electromyography
EQ-5D-5L	EuroQoL 5-dimension 5-level
ESR	erythrocyte sedimentation rate
ETV	Early Termination Visit
EULAR	European League Against Rheumatism
FAS	full analysis set
FDA	Food and Drug Administration
FI	Functional Index
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HAQ-DI	Health Assessment Questionnaire-Disability Index
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HRU	Healthcare Resource Utilization
HSV	herpes simplex virus
HUS	hemolytic uremic syndrome
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IM	intramuscular
IMACS	International Myositis Assessment and Clinical Studies Group
IND	Investigational New Drug
IRB	Institutional Review Board
ISR	injection site reaction
IV	intravenous
IVIg	intravenous immunoglobulin

LDH	lactate dehydrogenase
LEF	leflunomide
LLN	lower limit of normal
LMP	low-molecular mass polypeptide
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean cell volume
MDAAT	Myositis Disease Activity Assessment Tool
MDGA	Physician Global Assessment
MDGIC	Physician Global Impression of Change
MDI	Myositis Damage Index
MECL-1	multicatalytic endopeptidase complex-like 1
MedDRA	Medical Dictionary for Regulatory Activities
Mg	magnesium
MHC	major histocompatibility complex
MITAX	Myositis Intention to Treat Activity Index
MMF	mycophenolate mofetil
MMT-8	Manual Muscle Testing-8 Muscle Groups
MPS	mycophenolate sodium
MRI	magnetic resonance imaging
MTX	methotrexate
N	sample size
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
NRS	Numeric Rating Scale
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PGIC	Patient Global Impression of Change
P-gp	P-glycoprotein
PK	pharmacokinetic
PM	polymyositis
ProCISE	proteasome constitutive/immunoproteasome subunit ELISA
PROM	patient reported outcome measures

PROMIS-29	Patient Reported Outcomes Measurement Information System 29-item Short Form Profile Version 2.1
PtGADA	Patient Global Assessments of Disease Activity
PtGADD	Patient Global Assessment of Disease Damage
QTcB	QT interval with Bazett's correction
QTcF	QT interval with Fredericia's correction
RA	rheumatoid arthritis
RBC	red blood cell
RNA	ribonucleic acid
RTSM	Randomization and Trial Supply Management system
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SFU	Safety Follow-up
SLE	systemic lupus erythematosus
STS	sit-to-stand
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TEAE	treatment emergent adverse event
Th	T helper cell
TIS	Total Improvement Score
TMA	thrombotic microangiopathy
T_{max}	time to maximum concentration
TNFα	tumor necrosis factor alpha
Treg	regulatory T cell
TSQM	Treatment Satisfaction Questionnaire for Medication Version II
TTP	thrombotic thrombocytopenic purpura
TUG	timed up and go
ULN	upper limit of normal
US	United States
VAS	visual analog scale
W	Week
WBC	white blood cell
WFI	water for injection

WHO	World Health Organization
WOCBP	women of childbearing potential

1. BACKGROUND

1.1. Study Diseases and Description of the Population under Study

1.1.1. Polymyositis

Polymyositis (PM) is an inflammatory autoimmune myopathy that affects striated muscle with a subacute onset of a few weeks to months[15] and affects adults over 18 years of age. The estimated incidence of PM in the United States (US) ranges from 2.5 to 3.8 cases per 100,000 person-years, with the peak incidence occurring in those 65 years of age and over.[19,46] It presents with symmetrical weakness of the proximal muscles, sparing the facial and eye muscles. Muscle weakness manifests as difficulty in climbing steps, rising from a chair, lifting objects, and combing hair.[12,16] The diagnosis of PM is based on history and physical examinations, which are confirmed by laboratory examination. Laboratory findings include elevated serum levels of muscle associated enzymes (eg, creatine kinase [CK], aldolase, lactate dehydrogenase [LDH]), electromyography (EMG) consistent with myopathy,[16,34] and muscle biopsy demonstrating primary inflammation with the presence of cluster of differentiation (CD)8+ lymphocytes invading muscle fibers expressing major histocompatibility complex (MHC) class I antigens and the absence of vacuoles. Myositis specific and myositis associated antibodies, eg, anti-Jo-1 or anti-SSA, present in about 60% of patients, may help to confirm the diagnosis.[14]

Although the exact etiology of PM is not yet fully understood, several risk factors have been associated with disease pathogenesis. Genetic risk factors include human leukocyte antigen (HLA) alleles found on chromosome 6 (HLA-DQA1*0501 and HLA-DRB1*0301) and polymorphisms in tumor necrosis factor alpha (TNFα). Environmental risk factors that have been implicated comprise infectious agents including vaccinations, medications (eg, penicillamine, 3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors), and occupational exposures (eg, silica).[12]

The aim of treatment for PM is to suppress inflammation, increase muscle strength, and prevent long-term damage to muscles and extramuscular organs.[12] Initial treatment includes high doses of systemic corticosteroids such as prednisone; intravenous (IV) methylprednisolone may be required in severe cases. With improvement, the dose can be tapered to reach an adequate maintenance dose. Immunosuppressive agents such as methotrexate (MTX) and azathioprine (AZA) alone or in combination may be added to the drug regimen when there is poor response to corticosteroids. Other drugs that may be considered include mycophenolate mofetil (MMF), cyclophosphamide (CYC), rituximab, or IV immunoglobulin (Ig).[12] Physical therapy is recommended to maintain a full range of joint movement. Scoring systems may be used to assess improvement, stability or deterioration in symptoms and can help guide therapeutic choices.[12]

1.1.2. Dermatomyositis

Dermatomyositis (DM) is a multifactorial, chronic autoimmune disorder distinguished by inflammation involving the muscle and the skin. Dermatomyositis affects both children (juvenile DM) and adults. Although some overlap between disease characteristics exist, adult

and juvenile DM are separate entities with variable features. Adult DM is most often observed over age 40 years.[43] The estimated incidence of adult DM in the US is approximately 1.5 cases per 100,000 person-years.[19,46]

Proximal symmetrical skeletal muscle weakness is the most common feature of DM. Skin involvement may present concurrently with, precede, or postdate myositis, and a small percentage of patients never develop myositis. Other organ systems may be involved including blood vessels, joints, esophagus, lungs, and heart.[43] Up to 40% of patients may develop interstitial lung disease, which may be associated with rapidly progressive pulmonary failure and death.[43] Several factors have been implicated in the disease pathogenesis, including genetic, environmental, and immune mediated factors.[43] A small percentage of patients with DM have been reported to have a concomitant diagnosis of another connective tissue disorder, particularly scleroderma.[16,49]

Treating DM is difficult because it affects multiple organ systems and has a variable clinical presentation. Systemic corticosteroids, particularly prednisone, are considered first-line therapy. However, since long-term corticosteroid therapy can be associated with several adverse effects, an immunosuppressive agent (eg, MTX, cyclosporine [CyA], AZA, or MMF) is often introduced early during disease management. Antimalarials such as hydroxychloroquine and chloroquine may be effective but carry a cumulative risk of ocular toxicity with prolonged use and are associated with exacerbation of cutaneous symptoms in about one-third of patients. High-dose IV Ig (IVIg) has proved beneficial for refractory cases in the short term. Rituximab has been shown to improve muscle strength but has mixed results in controlling skin disease. Other therapies for skin disease include avoiding sun exposure and use of topical corticosteroids.[9,43]

1.2. 26S Proteasome

The 26S proteasome is a ubiquitously expressed protein complex responsible for the homeostatic control of protein turnover and regulated degradation of proteins involved in most cellular functions.[11,13,51] The proteasome exists in 2 forms, the constitutive proteasome and the immunoproteasome. The immunoproteasome is expressed primarily in hematopoietic cells (eg, lymphocytes and monocytes) and is induced in cytokine-exposed nonhematopoietic cells.[21,35,37] In the immunoproteasome, low-molecular mass polypeptide 7 (LMP7), LMP2, and multicatalytic endopeptidase complex-like 1 (MECL-1) replace β5, β1, and β2, respectively. The LMP7 subunit has a similar substrate preference as β5 and is, thus, referred to as the chymotrypsin-like (CT-L) subunit of the immunoproteasome.

The proteasome has been validated as a therapeutic drug target through regulatory approval of the 3 nonselective proteasome inhibitors, bortezomib (VELCADE®), carfilzomib (KYPROLIS®), and ixazomib (NINLARO®), for use in the treatment of the plasma cell neoplasm, multiple myeloma.

1.3. KZR-616

KZR-616 is a tripeptide ketoepoxide-based selective inhibitor of the immunoproteasome. The nonselective proteasome inhibitors, such as bortezomib, carfilzomib, and ixazomib, are

cytotoxic and equipotent inhibitors of the 2 forms of proteasomes found in cells, namely the constitutive proteasome and the immunoproteasome.[30,31] Selective inhibitors of the immunoproteasome such as KZR-616 have no cytotoxic potential.[39]

In vitro, KZR-616 demonstrates potent and selective inhibition of the LMP7 subunit of the immunoproteasome and can target multiple subunits of the immunoproteasome. Inhibition of immunoproteasome active site subunits by KZR-616 occurs through an irreversible mechanism, similar to that for carfilzomib [7,26]. Peptide ketoepoxides show no off-target activity,[5,31] and KZR-616 has been found to exhibit no activity in a broad diversity panel of biochemical assays that included 110 receptor/ligand and enzyme assays.

The safety of KZR-616 has been demonstrated in Good Laboratory Practice (GLP)-compliant toxicity studies in rats, rabbits, and monkeys. In repeat dose studies, KZR-616 was administered by subcutaneous (SC) injection once weekly for 13 consecutive weeks in rats and monkeys and for 26 consecutive weeks in rats. For both species, KZR-616 was well tolerated at doses expected to result in potent and selective inhibition of the immunoproteasome. In rats, the target organs identified at the no observed adverse effect level (NOAEL) were mostly similar between animals dosed for 13 or 26 weeks. Injection site reactions (ISRs) were noted in both species at the NOAEL. Lymphoid depletion in lymph nodes, thymus, and spleen were noted in rats only; however, none of these findings were considered adverse due to the low magnitude and severity. In rats, higher doses of KZR-616, including those that resulted in mortality, induced potent inhibition of both proteasome types, a profile equivalent to carfilzomib. It should be noted that in rats, administration of carfilzomib and bortezomib induced mortality in rats at doses ~20% and 30% below the labeled dose and administration for each compound respectively.[17,38] This suggests that rats are significantly more sensitive to dual proteasome inhibition than humans.

The safety, pharmacokinetics (PK), and proteasome inhibition level of KZR-616 has been studied in healthy volunteers in a Phase 1 trial, KZR-616-001. Subcutaneous administration of KZR-616 was well tolerated at doses of 30 mg and 45 mg, which resulted in potent and selective inhibition of the immunoproteasome. Adverse events (AEs) were generally mild and transient and were predominantly ISRs. Following 4 weeks of treatment with KZR-616, there were no clinically significant laboratory abnormalities that are commonly seen with the dual-targeting proteasome inhibitors. Subcutaneous administration of KZR-616 resulted in consistent, dose-proportional PK and pharmacodynamics (PD). At all dose levels, KZR-616 was rapidly absorbed and cleared with no accumulation following weekly repeat doses with dose-dependent inhibition of peripheral blood mononuclear cell (PBMC) CT-L activity (predominantly immunoproteasome). At doses of ≥30 mg, mean inhibition of PBMC CT-L activity 4 hours postdose exceeded 80% with significant but not complete recovery within 6 days of dosing. Mean inhibition of whole blood CT-L activity (predominantly constitutive proteasome) was less than 43% for all doses. No difference in the level of immunoproteasome inhibition was seen after the fourth weekly dose relative to the first dose suggesting that there is no accumulation of proteasome inhibition. From a PK and PD perspective, weekly SC administration of KZR-616 is tantamount to serial episodic dosing.

Ongoing studies include KZR-616-002, “A Phase 1b/2 Study of KZR-616 in Patients with Systemic Lupus Erythematosus (SLE) with and without Nephritis.”; and Study

KZR-616-004, "A Phase 1, Randomized, Double-Blind, Placebo Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of KZR-616 in Healthy Female Subjects". No reportable data are yet available for Study KZR-616-004. In Study KZR-616-002, as of 31 January 2019, weekly administration of KZR-616 up to 45 mg (Cohort 1) for 13 weeks was well tolerated in patients with active SLE. For this cohort, treatment emergent AEs (TEAEs) predominantly consisted of ISRs that were mild. There were no moderate or severe AEs or serious adverse events (SAEs) reported for the cohort. All 3 patients who discontinued the study were due to withdrawal of consent. In patients who received an initial dose of 60 mg of KZR-616, all 5 patients who were enrolled reported some combination of Grade 1 or Grade 2 AEs of nausea, vomiting, dizziness, or chills that started approximately 8 to 24 hours after receiving their first injection. One patient who received a second dose of 60 mg had recurrent nausea and vomiting starting at approximately 8 hours and resolved by approximately 24 hours. These AEs were similar to those encompassed by the preferred term of adverse drug reaction reported for the 60 mg dose in the KZR-616-001 study. Preliminary analysis of the laboratory data, vital signs, and ECG data for both cohorts demonstrated no concerning trends. To see if 60 mg is a dose at which KZR-616 could be administered routinely, a third cohort (Cohort 2a) is being enrolled to receive a step up dosing regimen of KZR-616 (30 mg, then 45 mg, then 60 mg) to potentially tolerize patients to receiving higher doses of KZR-616.

In Study KZR-616-002, 2 SAEs have been reported to date in the open-label Phase 1b portion of the study: 1 event of thrombotic microangiopathy (TMA) (Cohort 2, 60 mg) and 1 event of shingles (localized herpes zoster) (Cohort 2a, post receipt of 2 doses of 30 mg and 1 dose of 45 mg). While both events may have been related to the patient's underlying condition of SLE or other risk factors present, causality cannot be ruled out, especially as these events have also been reported to occur with the nonspecific proteasome inhibitors.

Please refer to the Investigator's Brochure (IB) for further information on KZR-616.

1.4. Rationale for Use in the Proposed Study Populations

Idiopathic inflammatory myopathies such as PM are characterized by inflammatory infiltrates in the skeletal muscle. Innate and adaptive immune mechanisms (eg, macrophages, autoreactive lymphocytes, autoantibodies, pro-inflammatory cytokine production) as well as intrinsic defects in skeletal muscle contribute to muscle weakness and damage in myositis. For example, regulatory T cells (Treg) are considered instrumental for healing via interactions with muscle stem cells, whereas accumulation of CD4+ and CD8+ T lymphocytes are associated with further immune-mediated injury as occurs in inflammatory myositis and some muscular dystrophies.[44] The immunoproteasome has also been shown to be upregulated in the muscle of patients with PM and DM and the skin in patients with DM.[8,20] Further, increased levels of circulating proteasomes, likely reflecting immunoproteasomes, have been observed in patients with inflammatory myositis and appear to be associated with disease markers such as CK and myoglobin levels.[18]

In vitro, KZR-616 and other immunoproteasome inhibitors block cytokine production across multiple immune cell types, reduce the activity of inflammatory T helper (Th) cell subsets,

increase the number of Tregs, and block plasma cell formation and autoantibody production.[27,28,36] KZR-616 does not induce cytotoxicity in vitro, has demonstrated promising therapeutic activity in animal models of rheumatoid arthritis (RA) and SLE/lupus nephritis, and has a favorable safety profile in healthy volunteers. Because of these characteristics, KZR-616 represents a new agent with a novel mechanism of action that may have broad therapeutic potential across autoimmune conditions, including PM and DM. As patients exist who have an inadequate response to currently available treatments, unmet medical need remains for new therapies for the treatment of PM and DM.

1.5. Risk/Benefit Assessment

The safety profile of KZR-616, a selective and irreversible inhibitor of the immunoproteasome, is distinct from dual proteasome inhibitors, such as carfilzomib and bortezomib, which induce thrombocytopenia, anemia, and neutropenia within 1 month of dosing[10,25] and are associated with constitutional toxicities such as prolonged fatigue, myalgia, and gastrointestinal toxicities.

Adverse events most often associated with KZR-616 treatment at doses of 30 mg and 45 mg are ISRs that are transient, generally mild, and do not appear to increase in severity or frequency with repeat dosing. All healthy volunteers and most patients who received repeat doses of ≥30 mg experienced ISRs. At higher doses (ie, 60 mg), AEs included transient rash and an event with the preferred term adverse drug reaction in healthy volunteers and nausea, vomiting, chills, headache and dizziness in patients with SLE. These AEs were similar to the dermatomyositsequelae of events associated with infusion reactions seen with carfilzomib. In healthy volunteers in cohorts evaluating doses of 30 mg and/or 45 mg, which utilized prophylactic antihistamine and corticosteroids and/or intrasubject dose escalation, and that achieved similar levels of exposure and target inhibition, AEs of adverse drug reaction were not reported. Similarly, transient AEs of nausea, vomiting, headache, chills, and dizziness each were seen in 25% or less of the patients with active SLE receiving 45 mg.

Aside from the 2 SAEs reported with preferred term of adverse drug reaction in healthy volunteers in Study KZR-616-001, there have been 2 related SAEs, each in 1 patient, reported in ongoing Study KZR-616-002 of KZR-616 in patients with active SLE. The SAEs of TMA and shingles, while both potentially attributable to the patients' underlying condition of SLE and other risk factors that were present, have also been described in the prescribing information of 1 or more of the nonselective proteasome inhibitors.

Thorough monitoring and assessment of all AEs will be performed in this study, and safety assessments according to the protocol will include physical examination, vital sign measurements, electrocardiograms (ECGs), and clinical laboratory tests. Guidance is provided to monitor for TMA, and occurrence of such an event will be reported as an AE of special interest (AESI) and trigger a prompt review of safety data by the Data Monitoring Committee (DMC). In addition, related to herpes zoster, patients who have had a recent episode of herpes zoster will be excluded, and vaccinations are recommended to be up to date. Patients who discontinue KZR-616, whether or not prematurely, will be monitored for worsening of disease and may receive rescue therapy as clinically appropriate. Generally, safety data will be reviewed and recommendations regarding protocol conduct will be made

by a DMC comprising a participating Investigator, a Medical Monitor, and a Kezar representative or designee. Supportive measures, such as IV or oral hydration, diuresis, transfusions, growth factor support, and/or prophylactic antimicrobials will be recommended to be considered when clinically appropriate.

Based on nonclinical studies with KZR-616 and the safety of KZR-616 at 45 mg in healthy volunteers, the potential benefit from anti-inflammatory activity induced by immunoproteasome inhibition may include an improvement in patients with PM and DM. These benefits are anticipated to outweigh the known risks of associated with KZR-616 administration to date.

Refer to the IB for further guidance regarding the risks and potential toxicities of KZR-616, which are based on current clinical trial data, nonclinical toxicology studies conducted in rodents and monkeys, as well as known safety risks of currently marketed proteasome inhibitors.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- Evaluate the efficacy of KZR-616 in patients with PM or DM.

2.1.2. Secondary Objectives

- Evaluate the safety and tolerability of KZR-616 in patients with PM or DM
- Evaluate the PK of KZR-616 in patients with PM or DM.

2.1.3. Exploratory Objectives

- Evaluate biomarkers related to efficacy and safety of KZR-616 in patients with PM or DM
- Evaluate the PK and PD relationship of KZR-616 in patients with PM or DM.

2.2. Study Endpoints

2.2.1. Efficacy Endpoints

The primary efficacy endpoint is:

- Mean change from start to end of KZR-616 treatment in the Total Improvement Score (TIS), which ranges from 0 to 100.

Secondary efficacy endpoints are:

- Proportion of patients with an increase ≥20 points on the TIS from start to end of KZR-616 treatment. The categories and ranges of scores for improvement are: 20-39 points being minimal improvement, 40-59 points being moderate improvement, and ≥60 points being major improvement
- Proportion of patients from start to end of KZR-616 treatment meeting International Myositis Assessment and Clinical Studies Group (IMACS) Definition of Improvement (DOI). The IMACS DOI is ≥20% improvement in at least 3 of 6 core set activity measures, with no more than 2 core set activity measures (CSAMs) worsening by ≥25% (the Manual Muscle Testing-8 Muscle Groups [MMT-8] cannot be a worsening measure)
- Absolute change and percent change from start to end of KZR-616 treatment in the IMACS individual CSAMs
- For patients with DM, the mean change from start to end of KZR-616 treatment in the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)
- For patients with DM, the mean change from start to end of KZR-616 treatment in the Peak Pruritus Numeric Rating Scale (NRS).

Exploratory efficacy endpoints are:

- Mean change over time from start to end of KZR-616 treatment in the TIS in all patients, patients with DM only, and in patients with PM only
- Proportion of patients over time with an increase of ≥20, ≥40, or ≥60 points on the TIS from start to end of KZR-616 treatment in all patients, in patients with DM only, and in patients with PM only
- For patients with an increase of ≥20 points on the TIS from Baseline to W16, the proportion of patients with no change or increase in their TIS at W32 for all patients, in patients with DM only, and in patients with PM only
- Mean change and mean percent change over time from start to end of KZR-616 treatment in the IMACS individual CSAMs and core set damage measures (CSDMs) for all patients, in patients with DM only, and in patients with PM only
- Mean change from Baseline over time from start to end of KZR-616 treatment in the FI-2, the FI-3 and the individual components of the FI-3 for all patients, in patients with DM only, and in patients with PM only
- For patients with DM, mean change over time from start to end of KZR-616 treatment in the CDASI
- For patients with DM, the proportion over time with ≥7 points improvement in the CDASI from start to end of KZR-616 treatment
- For patients with DM, the mean change over time from start to end of KZR-616 treatment in the Peak Pruritus NRS
- Mean change over time from start to end of KZR-616 treatment in the individual domains of the Patient Reported Outcomes Measurement Information System 29-item Short Form Profile Version 2.1 (PROMIS-29) for all patients, in patients with DM only, and in patients with PM only
- Mean change over time in Treatment Satisfaction Questionnaire for Medication Version II (TSQM) from start to end of KZR-616 treatment for all patients, in patients with DM only, and in patients with PM only
- The change in quality of life over time from start to end of KZR-616 treatment as measured by the EuroQoL 5-dimension 5-level (EQ-5D-5L) for all patients, in patients with DM only, and in patients with PM only
- Healthcare Resource Utilization (HRU) over time from start to end of KZR-616 treatment for all patients, in patients with DM only, and in patients with PM only
- Physician Global Impression of Change (MDGIC) over time from start to end of KZR-616 treatment for all patients, in patients with DM only, and in patients with PM only
- Patient Global Impression of Change (PGIC) over time from start to end of KZR-616 treatment for all patients, in patients with DM only, and in patients with PM only.

Note: The primary analysis period is from start to end of KZR-616 treatment for both sequence arms combined. A secondary analysis comparing KZR-616 to parallel placebo will be confined to the Baseline to Week 16 period. Lastly, the usual crossover analysis comparing placebo to KZR-616 will be carried out as an exploratory analysis approach. The rationale for this priority order is as follows. The usual crossover analysis for this design is prespecified as exploratory since it is unknown whether that analysis would be confounded

by carryover effect. In order to maximize the precision for assessment of KZR-616 effect, it is assessed primarily via all patients' start to end of KZR-616 treatment, and secondarily by the Treatment Period 1 between-treatment comparison.

2.2.2. Safety Endpoints

Safety endpoints are:

- Incidence, nature, and severity of AEs
- Incidence, nature, and severity of SAEs
- Incidence and severity of infection-related AEs and SAEs
- Incidence and severity of AEs with onset within 24 hours from the start of dosing with any study drug
- Incidence of AEs leading to study drug discontinuation
- Changes in standard laboratory parameters, vital signs, and ECGs.

2.2.3. Pharmacokinetic and Pharmacodynamic Endpoints

The secondary PK endpoint will:

- Evaluate the plasma PK parameters for KZR-616 and its metabolite KZR-59587.

The exploratory PK/PD endpoints will:

- Evaluate the relationships between KZR-616 PK, clinical efficacy, clinical safety, and various PD endpoints including proteasome inhibition and changes in circulating cytokine and immune cell profiles
- Evaluate the relationships between KZR-616 PK, clinical efficacy, clinical safety, and various PD endpoints related to skin and muscle biopsy histology and gene expression profiles.

3. STUDY DESIGN

3.1. Type and Design of Study

This is a Phase 2 randomized, double-blind, placebo-controlled, crossover, multicenter study designed to evaluate the safety, tolerability, efficacy, PK, and PD of treatment with KZR-616 in patients with active PM or DM.

Patients will be evaluated for eligibility during the Screening Period. Eligible patients will be allocated in a 1:1 fashion to a randomized treatment arm (Arm A or Arm B). Patients will be stratified by their diagnosis of PM or DM.

During the 32-week treatment period, patients will receive study drug SC once weekly. The 16 weeks of dosing during Treatment Period 1 begins at Week (W) 0 and continues through W15 (ie, ends immediately before dosing at Week 16 [approximately Day 113]); patients allocated to Arm A will receive KZR-616 and those in Arm B will receive placebo. The 16 weeks of dosing during Treatment Period 2 begins with administration of the first dose at W16 and continues through W31 (ie, ends immediately before Week 32); patients allocated to Arm A will receive placebo and those in Arm B will receive KZR-616.

This study will be conducted on an outpatient basis. Study visits will occur at Screening, W0, W4, W8, W12, W16, W20, W24, W28, W32, W36, and W40. Day 1 of W0 will be defined as Baseline. The W36 and W40 visits will comprise the Safety Follow-up (SFU).

Randomized patients who withdraw from the study prior to W32 will be requested to undergo the Early Termination Visit (ETV) procedures, and all patients who withdraw prematurely also will be requested to return for a SFU visit 9 weeks (W40 visit procedures) after receipt of their last dose of the study drug.

Efficacy assessments will be performed for all patients, unless indicated otherwise, and will include:

- IMACS core set Activity and Damage measures
    - MMT-8
    - Physician Global Assessment (MDGA)
    - Patient Global Assessments of Disease Activity (PtGADA)
    - Health Assessment Questionnaire-Disability Index (HAQ-DI)
    - Muscle enzymes (clinical laboratory assessments): CK, aldolase, LDH, alanine aminotransferase (ALT), and aspartate aminotransferase (AST)
    - Myositis Disease Activity Assessment Tool (MDAAT, 2005 version)
    - Myositis Damage Index (MDI)
    - Patient Global Assessment of Disease Damage (PtGADD).
- Functional Index-2 (FI-2, performed for the dominant side only).
- Functional Index-3 (FI-3) assessments:
    - 30-second chair stand test

  - Timed up and go test
  - 6-minute walk distance.

- MDGIC
- CDASI, performed only for patients with DM.

Additional patient reported outcome measures (PROMs) will be performed by all patients, unless indicated otherwise, and will include:

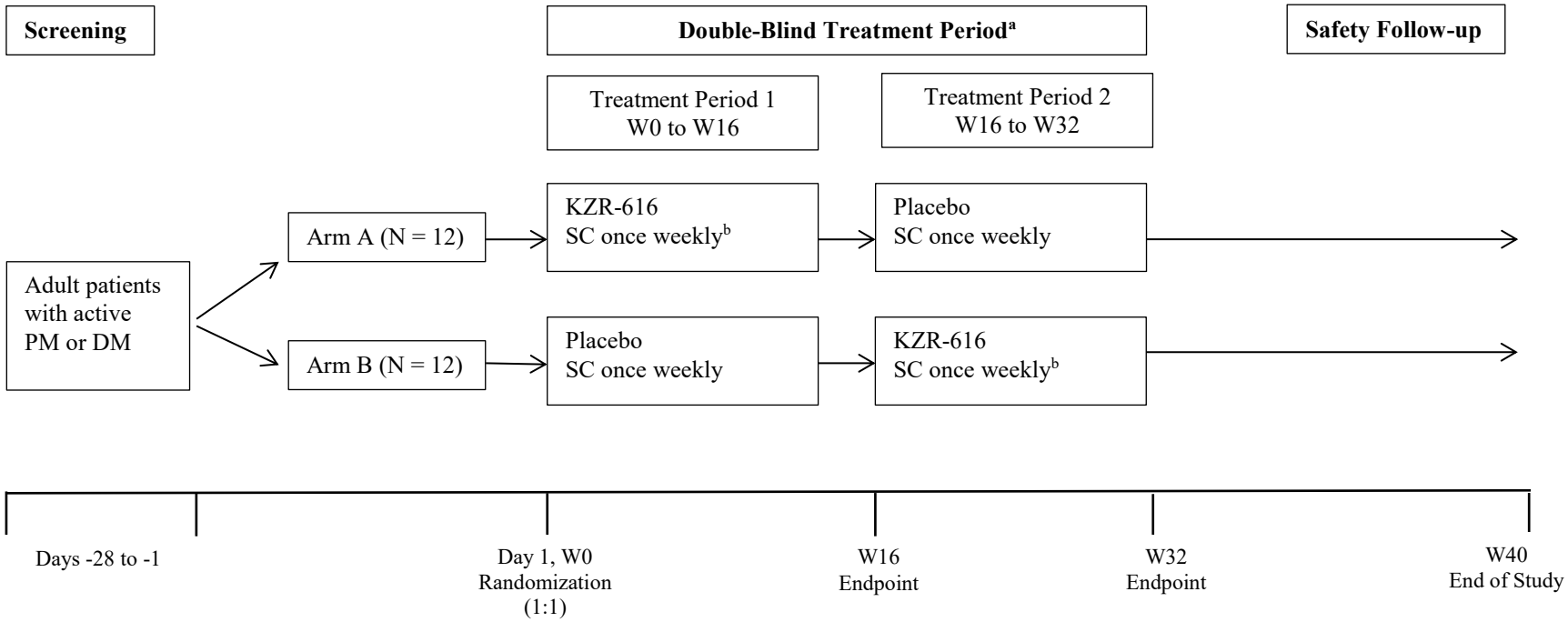
- PROMIS-29
- EQ-5D-5L
- HRU
- TSQM
- PGIC
- Peak Pruritus NRS, performed only by patients with DM.

Safety will be assessed throughout the study by monitoring of vital signs (blood pressure, pulse rate, temperature, and respiration rate), laboratory tests (hematology, chemistry, urinalysis, immunoglobulins), ECGs, and physical exams; and by recording and analyzing all AEs and SAEs.

Biopsies will be collected from a subset of enrolled patients; skin biopsies will be performed only for selected patients with DM, and muscle biopsies will be performed for selected patients with PM or DM. For selected patients, biopsies will be collected from skin and/or muscle at Baseline, W16, and optionally at W32. The tissue samples will be used for exploratory investigations of treatment-related changes and regulation of inflammatory pathways. Complete instructions for the collection and processing of biopsy samples will be included in the Laboratory Manual.

The study design schema is presented in Figure 1.

Figure 1 Study Design Schema



a Treatment Period 1 is from Day 1 of Week 0 and continues until immediately before dosing at Week 16 (approximately Day 113). Treatment Period 2 begins with administration of the first dose at Week 16 and continues through Week 32.

b In Treatment Periods 1 and 2, KZR-616 30 mg will be administered for the first 2 doses of each treatment period followed by administration of KZR-616 45 mg for the remaining 14 doses of each Treatment Period.

3.1.1. Sequence and Duration of Study Periods

The study comprises a 4-week Screening Period, a 32-week Treatment Period divided into two 16-week periods, and an 8-week SFU.

Individual patients will participate for approximately 44 weeks, inclusive of the Screening and SFU Periods.

3.1.2. Dose and Regimen Rationale

The planned doses of KZR-616 for administration in this study are 30 and 45 mg SC once weekly for 16 consecutive weeks; 30 mg doses will be administered the first 2 weeks (ie, the first 2 doses of the Treatment Period) followed by administration of 45 mg doses for the remaining 14 weeks of the Treatment Period.

In a Phase 1 study in healthy volunteers and a Phase 1b study in SLE patients, weekly SC administration of 45 mg was determined to be tolerated and resulted in potent and selective inhibition of the immunoproteasome. Anticipated levels of exposure with KZR-616 45 mg SC once weekly are lower than those achieved at the NOAEL for rats and monkeys. The profile of immunoproteasome inhibition at this dose correlated with anti-inflammatory activity in nonclinical models at the minimally efficacious dose.

The duration of dosing per treatment period will be 16 weeks. This is to allow adequate time to detect a change in muscle strength while minimizing the time patients spend on placebo.

3.1.3. Study Design Rationale

This placebo-controlled double-blind crossover study is designed to minimize bias in the evaluation of KZR-616 in patients with DM/PM and to maximize the opportunity for each patient to contribute data. All patients may still receive background treatment in the form of the allowed concomitant therapies as described in the study exclusion criteria (Section 4.3). A crossover design was selected for use in this study to:

- Increase the power of the study because not only will there be the opportunity for evaluation of between-group comparisons, but the patients initially treated with placebo can serve as their own controls
- Data for bortezomib allude to maintenance of effect of proteasome inhibition postdosing.[3] The Treatment and SFU Periods allow for evaluation of the treated population after drug discontinuation in terms of both safety and efficacy; these data are best obtained from those patients that start on KZR-616 first and then cross over to placebo.

3.2. Minimization of Bias

3.2.1. Randomization

Patients will be allocated to a randomized treatment sequence (Arm A: KZR-616 followed by placebo; Arm B: placebo followed by KZR-616) in a 1:1 fashion. Patients will receive the first assigned study drug treatment in Treatment Period 1 (W0 through before dosing at W16)

and cross over to receive the next study drug treatment beginning on the first day of Treatment Period 2 (administration of the first dose at W16 through W32). Patients will be stratified according to their diagnosis of PM or DM. Patients will be stratified by their diagnosis of DM or PM.

3.2.2. Blinding

This is a double-blind study. The Sponsor, Investigator, study personnel, and patients will not make any efforts to determine which study drug is being received. Unblinded pharmacy (or other qualified site) personnel will be utilized in this study to prepare the study drug, and unblinded study personnel (eg, Clinical Pharmacologist required for conducting any PK analyses and Statistician) may be utilized in this study.

3.2.3. Breaking the Blind

If the treatment allocation for a patient becomes known to the Investigator or other study staff involved in the management of study patients, the Sponsor must be notified immediately by the Investigator.

Patients should not be routinely unblinded to treatment assignment. Only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific patient, may the Investigator unblind a patient's treatment assignment. The unblinding of the patient's treatment assignment can be completed through the use of the electronic data capture (EDC) Randomization and Trial Supply Management (RTSM) system to determine treatment and institute appropriate follow-up care. However, prior to any unblinding, the Investigator is strongly advised to discuss options with the Medical Monitor or appropriate Sponsor study personnel. As soon as possible and without revealing the patient's study treatment assignment (unless important to the safety of patients remaining in the study), the Investigator must notify the Sponsor if the blind is broken for any reason. The Investigator will record in source documentation the date and reason for unblinding and the names and roles of personnel unblinded. The reason for unblinding will be captured directly within the EDC system prior to the unblinding as well. The EDC system will automatically store the date and time of the unblinding.

All unblinding events (with the exception of those by pharmacovigilance for regulatory reporting purposes) must be reported to the Sponsor's Medical Monitor and designee promptly.

Patients who have been unblinded for pharmacovigilance reporting purposes only will not, based on the unblinding alone, be discontinued from further receipt of investigational product.

3.3. Number of Sites

Up to approximately 18 sites are planned to participate in this study.

4. PATIENT SELECTION AND ENROLLMENT

4.1. Number of Patients

Approximately 24 patients are planned for enrollment. It is anticipated that 40 patients will be screened to achieve 24 patients enrolled.

4.1.1. Patient Screening

Study participation begins once written informed consent is obtained (see Section 11.3 for details). The Investigator will ensure that the patient has provided written informed consent before performing any study-related assessments.

Once informed consent is obtained, a sequential patient identification number will be assigned by the site, and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The patient identification number will be used to identify the patient during the screening process and throughout study participation, if applicable.

Screening assessments (see the Schedule of Assessments [Table 2]) for this study should be performed between Day -28 and Day -1. The Screening Period can be extended to 35 days upon Sponsor or designee approval only. Patients who fail Screening or do not meet inclusion/exclusion criteria may be rescreened 1 time.

Only individuals who fulfill all of the inclusion criteria and none of the exclusion criteria may be enrolled into the study. Data collected at Screening will be reviewed by the Sponsor, designee(s), or adjudication committee (as defined in the Study Manual) to confirm eligibility, of the patient to be enrolled.

4.2. Inclusion Criteria

1. Adult patients must be at least 18 years of age at the time of signing informed consent at Screening
2. Body Mass Index (BMI) of 18 to 40 kg/m^2
3. Diagnosis of probable or definite DM or PM by the 2017 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) Classification Criteria
4. Must have their data reviewed by an adjudication committee to confirm eligibility unless at least 1 of the following is present:
   a. Muscle biopsy with evidence of active myositis within the last 6 months prior to or at Screening
   b. Electromyography or magnetic resonance imaging (MRI) with evidence of active myositis within the last 6 months prior to Screening
   c. A CK ≥4 × upper limit of normal (ULN).
5. Must have demonstrable muscle weakness as measured by the MMT-8 with a score ≥80/150 but ≤136/150 units and any 2 of the following:
   a. MDGA visual analog scale (VAS) ≥2 cm
   b. PtGADA VAS ≥2 cm

c. At least one muscle enzyme laboratory measurement (ie, CK, aldolase, LDH) ≥1.3 × ULN
d. MDAAT Extramuscular Global Activity VAS ≥1 cm.

6. Documented inadequate response to a 12-week trial of corticosteroids or at least 1 immunosuppressant (eg, MTX, MMF, mycophenolate sodium [MPS], AZA, leflunomide [LEF], tacrolimus, CyA) OR have demonstrated significant documented toxicity or intolerance to such therapies
7. Has had age-appropriate cancer screening that is up to date and negative for evidence of malignancy as per local standard of care (see Appendix A)
8. Female patients of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline and must agree to employ adequate birth control measures for the duration of the study.
   Women of childbearing potential (WOCBP) must use highly effective and medically acceptable methods of contraception to prevent pregnancy during Screening and must agree to continue to practice adequate contraception during the study and for 4 weeks after administration of the last dose of the study drug.
   For the purposes of this study, WOCBP are defined as: all postpubescent female patients, unless the patient is postmenopausal (defined by amenorrhea for at least 2 years or amenorrhea for at least 1 year with confirmatory follicle stimulating hormone [FSH] level in the postmenopausal range as documented historically or measured by the central laboratory at Screening and if patient is not on supplementary hormonal therapy) or if the patient is surgically sterile (ie, tubal ligation, hysterectomy, bilateral salpingoophorectomy).
   Highly effective contraception is defined as the use of 2 barrier methods (eg, female diaphragm and male condom), 1 barrier method with spermicide, intrauterine device, or hormonal contraceptives (eg, implant or oral). If using a hormonal form of contraception, use must have been stable for at least 4 weeks prior to Screening, and if using concomitant mycophenolate, the patient must use another nonhormonal form of highly effective contraception. Abstinence will be acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation) and withdrawal are not acceptable methods of contraception
9. Male patients must be either congenitally sterile surgically sterile (vasectomy with documented confirmation of aspermia) or willing to use a condom in addition to having their female partner use another form of contraception (such as an intrauterine device, barrier method with spermicide, or hormonal contraceptive [eg, implant, injectable, patch, or oral]) from Screening until 12 weeks after administration of the last dose of the study drug, unless their partners are infertile or surgically sterile
10. Willing and able to comply with the requirements of the protocol
11. Provide written informed consent prior to any study-related procedure.

4.3. Exclusion Criteria

1. Has significant muscle damage (eg, severe muscle atrophy, end-stage disease, postmyopathic DM) per Investigator opinion or has a muscle damage VAS score ≥5 cm on the MDI
2. Any other form of myositis or myopathy other than PM or DM (eg, metabolic or drug-induced myopathy, drug-induced myositis, juvenile PM or DM, inclusion body

myositis, cancer-associated myositis [myositis diagnosed within 3 years, either before or after, of a diagnosis of any malignancy except for squamous or basal cell carcinoma of the skin or cervical carcinoma in situ], myositis in overlap with another connective disease [eg, SLE, systemic sclerosis, RA], or muscular dystrophy); patients with secondary Sjogren's syndrome, necrotizing myopathy, or antisynthetase syndrome are permitted to participate in this study

3. Any condition (eg, severe arthritis with limited range of motion or severe calcinosis) that, in the Investigator's opinion, precludes the ability to quantitate muscle strength
4. Has severe interstitial lung disease per Investigator opinion or has a pulmonary damage VAS score ≥5 cm on the MDI
5. Presence of autoinflammatory disease (eg, psoriatic arthritis, axial spondyloarthropathy, inflammatory bowel disease)
6. Has received treatment with any of the following:
    a. Oral prednisone (or prednisone equivalent) doses >20 mg/day at Screening or during the Screening Period, or initiation of oral prednisone during the Screening Period. If oral prednisone is being used at Screening, use should be stable during the 2 weeks prior to Baseline
    b. Use of nonsteroidal immunosuppressants other than oral MMF or MPS (≤3 g/day or 2160 mg/day, respectively); oral, intramuscular (IM), or SC MTX (≤25 mg/week); AZA (≤2.5 mg/kg/day); LEF (≤20 mg/day); tacrolimus (≤3 g/day); or concurrent use of more than 1 nonsteroidal immunosuppressant at Baseline. If a permitted nonsteroidal immunosuppressant is being used, it must have used for at least 12 weeks and must have been taken at a stable dose (including stable route of administration) for the last 4 weeks prior to Screening. If MMF, MPS, MTX, AZA, LEF, or tacrolimus is being discontinued, it must be discontinued at least 4 weeks prior to Baseline
    c. Antimalarials exceeding the recommended doses (hydroxychloroquine up to 400 mg/day or 6.5mg/kg/day, whichever is less; chloroquine up to 250 mg/day, or quinacrine up to 100 mg/day are permitted) or taken at an unstable dose during the 12 weeks prior to Screening. If an antimalarial is being discontinued, it must be discontinued at least 4 weeks prior to Baseline. Antimalarials are considered distinct from corticosteroids in (a) and nonsteroidal immunosuppressants in (b) above
    d. Initiation of or use of an unstable dose of topical therapy (eg, corticosteroids, pimecrolimus) in the 4 weeks prior to Screening. If topical therapy is being discontinued, it must be discontinued at least 4 weeks prior to Baseline.
7. Receipt of any of the following treatments within the following time frames before Screening:
    a. Oral corticosteroids at doses ≥1 mg/kg/day prednisone or equivalent: 4 weeks
    b. Intravenous or IM corticosteroids: 4 weeks
    c. Intra-articular therapies, such as corticosteroids or hyaluronic acid preparations: 4 weeks
    d. Intravenous, SC, or IM Ig: 4 weeks
    e. Cyclophosphamide or chlorambucil: 24 weeks
    f. Prohibited nonbiologic nonsteroidal immunosuppressants or targeted therapies including, but not limited to, CyA, dapsone, tofacitinib, baricitinib: 8 weeks

g. Cytokine or integrin antagonists or selective costimulation modulators including, but not limited to, interleukin (IL)-1, IL-6, IL-17, IL-12/23, IL-23, interferon (IFN), integrin, and tumor necrosis factor (TNF)α antagonists or abatacept: 12 weeks
h. B cell-depleting or modulating therapies (eg, rituximab, ofatumumab, obinutuzumab, ocrelizumab, belimumab, atacicept): 24 weeks
For those patients who have used an anti-CD20 drug at ≥24 weeks and <48 weeks before Screening, they must have levels of circulating CD19+ B cells ≥the lower limit of normal (LLN). A CD19 count is not required for patients with prior use of an anti-CD20 drug ≥48 weeks prior to Screening
i. Previous treatment with the following cell-depleting therapies, including investigational agents or approved therapies: alemtuzumab, anti-CD4, anti-CD5, or anti-CD3: at any time
j. Other biologics or investigational drugs: 8 weeks or 5 half-lives, whichever is longer
k. Transfusion with blood, packed red blood cells, or platelets or treatment with plasmapheresis or plasma exchange: 6 weeks
l. Creatine dietary supplements: 4 weeks.

8. Initiation of an exercise program (including physical therapy or occupational therapy) for muscle strengthening within 4 weeks of Screening or initiation planned during the study. Any exercise program or regimen that was initiated >4 weeks prior to Screening must be continued in a stable manner during Screening and the study
9. Patient has had recent serious or ongoing infection, or risk for serious infection, including:
a. Acute or chronic infection defined as any infection requiring systemic antibiotic, antifungal, or antiviral (antimicrobial) therapy within 2 weeks of Baseline
b. Hospitalization or receipt of a course of IV antimicrobial therapy within 24 weeks prior to Screening or during the Screening Period
c. Symptomatic herpes zoster or herpes simplex infection (HSV) (not including simple oral HSV lesions) within 12 weeks prior to Screening or during the Screening Period
d. History of severe and/or disseminated viral infections, and/or opportunistic infections
e. Known seropositivity for or active infection by human immunodeficiency virus (HIV)
f. Active, chronic, or resolved hepatitis B or hepatitis C infection (hepatitis B core antibody or surface antigen positive, or hepatitis C antibody positive at Screening)
g. History of progressive multifocal leukoencephalopathy
h. Active or untreated latent tuberculosis (TB), as suggested by chest radiograph performed within the 12 weeks prior to or at Screening (see Section 7.2.6.3) or positive (or 2 indeterminate or borderline) results of an approved TB test at Screening (see Section 7.2.6.1). Patients with a history of latent TB with documented completed treatment per Centers for Disease Control and Prevention guidelines and no known exposures post treatment are allowed to participate
i. Receipt of a live-attenuated vaccine within 4 weeks of Screening

j. Primary immunodeficiency (unless otherwise considered, in the opinion of the Investigator or the Sponsor, to confer a clinically insignificant infection risk, such as deficiency in IgA, C1q, C2, or C4 without a history of recurrent infections [3 or more infections in 1 year that required antimicrobial therapy])
k. History of recurrent infections [3 or more infections in 1 year that required antimicrobial therapy] in the 12 months prior to Baseline
l. Prior hematopoietic cell or solid organ transplant.

10. History of any concurrent illness (eg, asthma) that has required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 24 weeks prior to Screening
11. Any of the following laboratory values at Screening:
    a. Estimated glomerular filtration rate <45 mL/min by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation
    b. Hemoglobin <10 g/dL
    c. White blood cell (WBC) count $<3.0 \times 10^9$/L
    d. Absolute neutrophil count (ANC) $<1.5 \times 10^9$/L (1500/mm^3)
    e. Platelet count $<100 \times 10^9$/L
    f. Serum AST or serum ALT >2.5 × ULN (unless considered consistent with muscle origin)
    g. Serum alkaline phosphatase >2.5 × ULN
    h. Total bilirubin >1.5 × ULN (3 × ULN for patients with documented Gilbert's syndrome)
    i. Thyroid stimulating hormone outside of the central laboratory normal range
    j. IgG <500 mg/dL.
12. Presence of New York Heart Association Class III or IV heart failure, or uncontrolled blood pressure (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg at rest), or QT interval with Fredericia's correction (QTcF) or Bazett's correction (QTcB) >480 msec on ECG
13. Major surgery within 12 weeks before Screening, major surgery planned during the study period, or any surgery planned during the study period that would require an alteration of concomitant immunosuppressant or corticosteroid therapy or additional corticosteroid therapy
14. Clinical evidence of significant unstable or uncontrolled diseases (eg, cardiac [including congestive heart failure, hypertension, angina, or recent {<6 months prior to Screening} myocardial infarction], pulmonary [including chronic obstructive pulmonary disease, asthma requiring systemic corticosteroid therapy, pulmonary hypertension, or interstitial lung disease], hematologic, gastrointestinal, endocrinologic [eg, hypothyroidism, diabetes], hepatic, renal, neurological, or infectious) that, in the opinion of the Investigator or Sponsor, could confound the results of the study, put the patient at undue risk, or interfere with protocol adherence
15. Evidence of current or previous clinically significant disease, medical condition (including abnormal laboratory values), or finding in the medical examination that in the Investigator's or Sponsor's opinion would compromise the safety of the patient or the ability to interpret the data
16. Any active or suspected malignancy, including myeloproliferative or lymphoproliferative disorder, or history of documented malignancy within the last

5 years before Screening or within 3 years of diagnosis of myositis, except appropriately excised and cured cervical carcinoma in situ or basal or squamous cell carcinoma of the skin; patients with a history of basal or squamous cell carcinomas of the skin must have had 3 or fewer in their lifetime to be eligible

17. Alcohol abuse or drug abuse in the last 1 year prior to Screening in the opinion of the Investigator
18. Women who are pregnant, lactating, or discontinued lactation less than 12 weeks prior to Screening, or women who plan to become pregnant or initiate lactation during the study
19. Patients who are unable to comply with the protocol in the Investigator's or Sponsor’s opinion.

5. STUDY DRUG INFORMATION

Instructions for the receipt, inspection, storage, preparation, administration, and disposal of KZR-616 are to be provided in a separate Pharmacy Manual at each clinical site.

5.1. Physical Description of the Study Drugs

KZR-616 Lyophile, 125 mg/vial, is supplied as a refrigerated lyophilized drug product containing 125 mg of KZR-616 (150 mg of KZR-616 maleate) and [redacted] (inactive excipient) in single use 3.0-mL borosilicate glass vial. Each vial is reconstituted with sterile water for injection (WFI) prior to administration.

Placebo will be sterile WFI and will be supplied by the individual clinical sites.

5.2. Packaging and Labeling

The lyophilized drug product will be supplied in 3-mL single-use vials packaged in multivial cartons.

The Sponsor or its representatives will be responsible for labeling according to local regulatory requirements.

All packaging and labeling operations will be performed according to Good Manufacturing Practice (GMP) for Medicinal Products and the relevant regulatory requirements.

5.3. Supply, Dispensing, Storage, and Investigational Product Accountability

The Sponsor or its representatives will supply KZR-616 Lyophile to the investigational site. The study drug supplies provided for this study will be manufactured under current GMP, will be subject to release, and will be suitable for human use.

Only participants enrolled in the study may receive study drug and only authorized staff may supply or administer study drug.

KZR-616 Lyophile must be stored in a refrigerator at 2°C to 8°C. Reconstituted study drug can be stored until use in a refrigerator (recommended) controlled at 2°C to 8°C for a maximum of 24 hours or at room temperature at 15°C to 30°C for a maximum of 4 hours, or until use, whichever occurs first. All study drug should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions. Access to study drug must be limited to the Investigator and authorized study personnel.

Further information of the storage, preparation, and administration of study drug will be provided in a Pharmacy Manual.

On receipt of the study drug, the Investigator (or designee) will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts.

The study monitor may check the study supplies at each study center at any time during the study.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

It is the responsibility of the study monitor to ensure that the Investigator (or designee) has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The study monitor will perform an inventory of study drug at the closeout visit to the study center. All discrepancies must be accounted for and documented.

6. DOSAGE AND STUDY DRUG ADMINISTRATION

6.1. Study Drug Administration

KZR-616 and matching placebo will be administered by SC injection once weekly according to the randomized treatment schedule shown in Table 1. Patients should be monitored for 2 hours after dosing at W0 and W16.

Further details regarding drug product formulation, preparation, and administration of KZR-616 will be provided in a separate Pharmacy Manual.

Table 1 Study Drug Administration

	Study Drug Administered	
	Treatment Period 1 [a]	**Treatment Period 2** [a]
Treatment Arm	**Week 0 to Week 16** [b]	**Week 16 to Week 32** [b]
Arm A	**KZR-616** W0 and W1: 30 mg W2-W15: 45 mg	**Placebo**
Arm B	**Placebo**	**KZR-616** W16 and W17: 30 mg W18-W31: 45 mg

a Treatment Period 1 is from the time of dosing on Day 1 of Week 0 and continues until immediately before dosing at Week 16 (approximately Day 113). Treatment Period 2 begins with administration of the first dose at Week 16 and continues through Week 32.

b Study drug will be administered via subcutaneous injection once weekly. Patients need to be monitored for 2 hours after dosing at Week 0 and at Week 16. The last dose of study drug is at W15 for Treatment Period 1 and at W31 for Treatment Period 2.

6.1.1. Dosing Criteria

All patients must meet the following criteria before each dose:

- Absolute neutrophil count $\geq 1.0 \times 10^9$/L as of the most recent laboratory testing
- Hemoglobin ≥8.0 g/dL and ≤16.5 g/dL as of the most recent laboratory testing
- Platelets $\geq 50{,}000/mm^3$ and $\leq 1{,}000{,}000/mm^3$ as of the most recent laboratory testing
- Serum ALT or AST ≤3 × ULN and total bilirubin <2 × ULN
- Non-ISR AEs ≤Grade 2.

Dosing should be held until the AE improves to ≤Grade 2 or the laboratory abnormality is within the range to allow dosing (please see Section 6.1.4.2 regarding missed doses), unless there is Medical Monitor or Sponsor approval to permit dosing. Any laboratories with values that preclude dosing should be repeated as soon as possible (as per Section 7.2.6.10).

6.1.2. Administrative Site

A different SC injection site should be used for each administration. Injection sites should be rotated (eg, 4 abdominal quadrants, posterior upper arms, anterior thighs), and a minimum of 4 weeks should separate injections to the same site.

6.1.3. Monitoring of Dose Administration

Systemic injection reactions have been observed with KZR-616 and other proteasome inhibitors; the following guidance is based on these known experiences[45,23] and may be modified as clinical experience with KZR-616 evolves and matures.

In KZR-616-001, 4 of 12 healthy volunteer subjects who received 60 mg KZR-616 SC experienced AEs with the preferred term of adverse drug reaction; consisting of hypotension, tachycardia, nausea, vomiting, rigors, and/or chills, associated with an acute phase-like response, including leukocytosis and elevated C-reactive protein (CRP), which occurred approximately 8 to 12 hours after dosing. These events are similar to the infusion-related reactions observed with the currently marketed proteasome inhibitor carfilzomib, which generally occur in the first cycle of dosing.

Systemic injection reactions with other proteasome inhibitors include a number of signs and symptoms, including fever, chills, myalgia, facial swelling or flushing, vomiting, weakness, hypotension, chest tightness, and shortness of breath, as well as abnormalities in laboratory values (eg, creatinine, transaminases). However, the relative roles of the immunoproteasome versus constitutive proteasomes to these specific events are not known. The individual signs/symptoms of systemic injection reactions must be reported as AESIs within 24 hours using the AE electronic case report form (eCRF) (refer to Section 9.5.1).

With other proteasome inhibitors, prophylactic measures such as predose hydration and low-dose dexamethasone (4 mg) reduce the incidence and severity of infusion-related reactions. Therefore, upon the development of signs and/or symptoms suggestive of a systemic drug reaction, the following interventions are suggested:

- Supportive measures, including the administration of oral and/or IV fluids, antiemetics, acetaminophen, antihistamines and/or systemic corticosteroids (eg, prednisone 25 mg – equivalent to 4 mg of dexamethasone)
- Collection of serum and/or plasma samples for analysis of potentially elevated levels of eg, cytokines, histamines
- For patients who develop signs and/or symptoms that may be consistent with a cardiac etiology (eg, hypo- or hypertension, tachycardia, arrhythmia, or abnormal cardiac enzymes), the following should be obtained to rule out cardiac toxicity which has been described with proteasome inhibitors:
    - Serial ECGs, cardiac enzymes (eg, CK-MB, troponins, B-type natriuretic peptide [BNP]) to rule out myocardial infarction
    - Echocardiogram, unless heart failure can otherwise be ruled out by the preceding investigations.

- Prophylactic measures may be considered at the time of the first dose, or with subsequent doses if signs and/or symptoms consistent with a systemic drug reaction develop, including:
    - Fluid hydration, eg, 30 mL/kg orally at least 48 hours prior to dosing; and/or 250 to 500 mL IV after dosing if symptoms are present
    - Antiemetics, acetaminophen, and antihistamines
    - Systemic corticosteroids (eg, dexamethasone 4 mg or prednisone 25 mg) prior to subsequent doses. Use of systemic corticosteroids for prophylaxis should be discussed in advance with the Medical Monitor as their use could confound efficacy assessments.

6.1.4. Dose Modification Guidelines for KZR-616

6.1.4.1. Dose Reduction

Patients who experience a KZR-616-related AE are permitted to undergo dose reduction of KZR-616 in a blinded manner for subsequent doses at the discretion of the Investigator or upon recommendation by the DMC as per Section 8.1.2; written Medical Monitor approval must be obtained in advance of implementing dose reduction. Any dose modifications should be documented in the eCRF as per Section 9.1.4. Patients must continue to fulfill the Dosing Criteria in Section 6.1.1 prior to each dose. After dose reduction is implemented, patients who are currently on treatment with KZR-616 will remain on 30 mg throughout the relevant Treatment Period if the dose reduction occurs at W1 (Treatment Period 1) or W17 (Treatment Period 2); they will have their dose reduced to 30 mg from 45 mg if the dose reduction occurs at or after W2 (Treatment Period 1) or W18 (Treatment Period 2). Once the dose has been reduced, it will remain at the reduced dose level only for the duration of the Period during which the dose was reduced.

6.1.4.2. Missed Doses

Doses should be administered within the visit windows as per the Schedules of Assessments (Section 7.1). Any doses administered outside of the visit window will be considered a protocol deviation, but if necessary to avoid missing a dose, doses can be administered up to 3 days from the date of scheduled administration per Section 7.1 with a minimum of 4 days required between doses.

Patients who do not fulfill Dosing Criteria (Section 6.1.1) or who meet Individual Patient Stopping Rules (Section 8.1.2) may miss up to 2 consecutive doses, or patients may miss up to 4 total doses for any reason (eg, AE, scheduling, emergency). Upon resumption of dosing, subsequent doses should be timed according to the original dosing schedule based on Day 1. If more than 2 consecutive doses or more than 4 total doses were missed, then the patient should be discussed with the Medical Monitor to evaluate if KZR-616 should be discontinued. Any dose modifications should be discussed with the Medical Monitor and documented in the eCRF as per Section 9.1.4. Patients who are discontinued for missed doses should have their discontinuation per Section 8.2 recorded in the eCRF based on the reason the doses were missed, eg, AE, protocol noncompliance.

If study medication is permanently discontinued due to an AE, the planned assessments (see Schedule of Assessments) should continue for the protocol specified time period.

6.2. Prior and Concomitant Treatments

Any concomitant therapies must be recorded on the eCRF. A concomitant therapy is any therapy that may be used, eg, transfusions, physical therapy, surgery, medication. A concomitant medication is any prescription or over-the-counter preparation, including vitamins and supplements. Except as described below, prior and concomitant medication use will be recorded for the 60 days prior to screening until the last follow-up visit. Details to be recorded include, but are not limited to, the concomitant medication generic name, dose, route, frequency of administration, and indication. Prior to study initiation, the Sponsor will specify which version of the drug dictionary is to be used.

All prior DM/PM medications (eg, corticosteroids, immunosuppressants, antimalarials, biologics) regardless of time frame of use will be recorded.

Background medication(s) will not be provided by the Sponsor unless required by local legislation.

6.2.1. Permitted Concomitant Medications

6.2.1.1. Myositis Disease-related Concomitant Medications

Patients should continue all concomitant medications related to myositis therapy throughout the study, as outlined in the Inclusion/Exclusion Criteria (Section 4.2 and Section 4.3) at a stable dose, without modification throughout the study, unless there is documented toxicity, intolerability, or lack of availability. No new immunomodulatory therapies, including investigational agents, are permitted to be introduced during the study. If a concomitant treatment for myositis needs to be decreased or discontinued for safety reasons, the reason must be documented in the eCRF and should be discussed with the Medical Monitor (and discussed in advance where possible).

The permitted medications for myositis include the use of the following:

- Oral prednisone (or prednisone equivalent) dose ≤20 mg/day. If used, it must have been present at Screening, used at a stable dose for the 2 weeks prior to Baseline.
- The use of a maximum of 1 of the following immunosuppressants is allowed:
  - Oral MMF or MPS (≤3 g/day or 2160 mg/day, respectively)
  - Oral, IM, or SC MTX (≤25 mg/week)
  - Oral AZA (≤2.5 mg/kg/day)
  - LEF (≤20 mg/day)
  - Tacrolimus (≤3 g/day).

If a permitted immunosuppressant is being used, it must have used for at least 12 weeks and must have been taken at a stable dose (including stable route of administration) for the last 4 weeks prior to Screening.

- The use of the following antimalarials is allowed if present at a stable dose for at least 12 weeks prior to Screening:
  - Hydroxychloroquine up to 400 mg/day or 6.5 mg/kg/day, whichever is less
  - Chloroquine up to 250 mg/day
  - Quinacrine up to 100 mg/day.
- Continued use of a stable dose of topical therapy (eg, corticosteroids, pimecrolimus) is allowed.

6.2.1.2. Other Concomitant Medications

Hormonal contraception is allowed; if used by a WOCBP, it should be used and have been stable as described in Section 4.2 and continued for the duration of the study. If hormonal contraception is discontinued for safety reasons, the Investigator should ensure that the patient is using another acceptable form of contraception.

Other concomitant therapies for comorbid conditions, such as antihypertensives or lipid lowering agents, are permitted. The patient should be advised to maintain a stable dosage regimen for lipid lowering agents (such as statins) and nonsteroidal anti-inflammatory drugs (NSAIDs) unless dosage adjustment is clinically necessary.

KZR-616 is a substrate of the P-glycoprotein (P-gp) transporter. Given the rapid clearance of the drug (half-life <2 hours), it is unlikely that inhibitors of P-gp will affect drug exposure. However, no formal interaction studies with P-gp inhibitors have been performed. Therefore, KZR-616 should be administered at least 4 hours after drugs that are known inhibitors of P-gp (eg, atorvastatin, azithromycin, colchicine, omeprazole).

6.2.1.3. Vaccinations

It is strongly recommended that patients be up-to-date on immunizations per the Centers for Disease control (https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html) or current 2015 American College of Rheumatology guidelines for RA. Vaccinations received at any time documenting that the patient is up to date on vaccines should be recorded in the eCRF.

Note: Patients who received a live-attenuated vaccine within 4 weeks of Screening will be excluded from participation in the study as per Section 4.3.

6.2.2. Rescue Therapy

Rescue therapy is defined as any modification to the background DM or PM treatment, including dose or frequency increases of concomitant medications or initiation of a new medication. Rescue medications may include, but are not limited to IVIg, topical calcineurin inhibitors, systemic corticosteroids, or nonsteroidal immunosuppressants. While rescue therapy is typically restricted or prohibited therapy per protocol (Section 6.2.3), patients may receive rescue therapy during the study at the discretion of the Investigator when deemed medically necessary for the safety of the patient, eg, hospitalization for worsening DM or PM.

If an Investigator determines that a patient needs rescue therapy, the Medical Monitor should be informed; where possible, a discussion should occur between the Investigator and Medical Monitor prior to implementation of the rescue therapy.

Any rescue medications administered should be recorded in the eCRF under concomitant medications. Patients who receive rescue therapy may continue in the study upon Medical Monitor approval but will be considered nonresponders from the timepoint of receipt or rescue therapy forward (as per Section 6.2).

6.2.2.1. Nonpharmacologic Therapies

Patients who are receiving physical or occupational therapy or exercising should have had a stable treatment or exercise regimen for at least 4 weeks prior to Screening as per Section 4.3 and remain on a stable regimen throughout the duration of the study. A regimen should not be initiated during the study.

6.2.3. Restricted or Prohibited Therapies

Use of the following is prohibited during the study and as described in Section 4.3:

- Oral prednisone (or prednisone equivalent) doses >20 mg/day
- Intravenous or IM corticosteroids
- Initiation of IV, SC, or IM Ig
- Immunosuppressants (other than as presented in Section 6.2.1)
- Antimalarials at doses that exceed the recommended dose (see Section 6.2.1)
- Topical therapy (other than as presented in Section 6.2.1)
- Intra-articular therapy (eg, corticosteroids or hyaluronic acid preparations)
- Cyclophosphamide or chlorambucil
- Nonbiologic immunosuppressants or targeted therapies including, but not limited to, CyA, dapsone, tofacitinib, baricitinib
- Cytokine or integrin antagonists or selective costimulation modulators including, but not limited to, IL-1, IL-6, IL-17, IL-12/23, IL-23, IFN, integrin, and TNFα antagonists or abatacept
- B cell-depleting or modulating therapies (eg, rituximab, ofatumumab, obinutuzumab, ocrelizumab, belimumab, atacicept)
- Cell-depleting therapies, including investigational agents or approved therapies, alemtuzumab, anti-CD4, anti-CD5, or anti-CD3
- Any other biologics or investigational drug(s)
- Transfusion with blood, packed red blood cells, or platelets or treatment with plasmapheresis or plasma exchange
- Creatine dietary supplements
- Live-attenuated vaccines
- Major surgery during the study period, or any surgery planned during the study period that would require an alteration of concomitant immunosuppressant or corticosteroid therapy or additional corticosteroid therapy.

6.2.4. Other Restrictions and Prohibitions

Participants should not donate blood or blood products during the study and continuing through 4 weeks after administration of the last dose of the study drug. Female participants should not donate eggs during the study and continuing through 4 weeks after administration of the last dose of the study drug. Male participants should not donate sperm during the study and continuing through 12 weeks after administration of the last dose of the study drug.

7. STUDY EVALUATIONS

7.1. Schedules of Assessments

The Schedule of Assessments for Screening and Treatment Period 1 is presented in Table 2 and the Schedule of Assessments for the study drug administration visits during Treatment Period 1 is presented in Table 3.

The Schedule of Assessments for Treatment Period 2, the ETV, and SFU is presented in Table 4 and the Schedule of Assessments for the study drug administration visits during Treatment Period 2 is presented in Table 5.

Please refer to the Laboratory Manual for details regarding the specific blood draw requirements for each visit.

For details regarding visit windows, refer to the Schedule of Assessments (Table 2, Table 3, Table 4, and Table 5).

7.1.1. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted. During an unscheduled visit, the following information will be required to be collected:

- Concomitant medications
- AEs

Any of the other procedures listed for the W32 visit may also be performed at the Investigator's discretion.

Table 2 Schedule of Assessments for Screening and Treatment Period 1

Study Period	Screening	Treatment Period 1				
Visit Number	1	2		6	10	14
Start of Week	-4	0		4	8	12
Day ± Window	-28 to -1	1		29±1	57±1	85±1
PK and PD assessments		Predose	Postdose			
Informed consent	X					
Informed consent for genotyping	X					
Informed consent for biopsies	X					
Inclusion/exclusion criteria[a]	X	X				
Demographic data	X					
PM and DM classification criteria[b]	X					
Medical history (including procedures, prior therapy, social history)	X					
Concomitant therapy		←				→
Randomization		X				
Tuberculosis assessment[c]	X					
Viral serology (HIV/HBV/HCV)[d]	X					
Chest radiograph[e]	X					
Follicle stimulating hormone[f]	X					
Coagulation, thyroid, APLA[g]	X					
Pregnancy test[h]	X	X		X	X	X
Physical examination[i]	X	X			X	
Vital signs, weight, and height[j]	X	X		X	X	X
12-lead ECG[k]	X	X		X		X
MMT-8[l]	X	X		X	X	X
MDAAT, MDGA, MDGIC[l]	X	X		X	X	X
FI-2 (dominant side only)[l]	X	X				
FI-3[l]	X	X			X	
Sit-to-stand test[l]	X			X		X
MDI[l]	X	X				
CDASI[l, m]	X	X		X	X	X
PtGADA, HAQ-DI, PGIC[n]	X	X		X	X	X
PROMIS-29, EQ-5D-5L[n]	X	X		X		
HRU[n]		X			X	
PtGADD[n]	X	X				
Peak Pruritus NRS[m, n]	X	X		X	X	X
TSQM[n]				X		
Hematology, chemistry[o], CRP, and aldolase	X	X		X	X	X

Study Period	Screening	Treatment Period 1				
Visit Number	1	2		6	10	14
Start of Week	-4	0		4	8	12
Day ± Window	-28 to -1	1		29±1	57±1	85±1
PK and PD assessments		Predose	Postdose			
Erythrocyte sedimentation rate[p]	X	X		X	X	X
CD19 count[q]	X					
Urinalysis[r]	X	X		X		X
Quantitative immunoglobulins[s]	X	X				
Autoantibodies[t]	X					
PK assessment[u]		X	X			
PD assessment[v]		X	X			
Cytokines/proteomics and leukocyte subsets[w]		X		X		
Gene expression and DNA methylation profiling (RNA)[x]		X		X		
Genotyping (DNA)[x]		X				
Skin and/or muscle biopsies[y]	X					
Study drug administration[z]		X		X	X	X
Adverse events	←					→

Abbreviations: APLA=antiphospholipid antibodies; CD19=cluster of differentiation 19; CDASI=Cutaneous Dermatomyositis Disease Area and Severity Index; CRP=C-reactive protein; DM=dermatomyositis; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EQ-5D-5L=EuroQoL 5-dimension 5-level; FI-2=Functional Index-2; FI-3=Functional Index-3; HAQ-DI=Health Assessment Questionnaire-Disability Index; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRU=healthcare resource utilization; MDAAT=Myositis Disease Activity Assessment Tool; MDGA=Physician Global Assessment; MDI=Myositis Damage Index; MDGIC=Physician Global Impression of Change; MMT-8=Manual Muscle Testing-8 Muscle Groups; NRS=numeric rating scale; PD=pharmacodynamics; PK=pharmacokinetics; PROMIS-29=Patient Reported Outcomes Measurement Information System 29-item Short Form Profile Version 2.1; PtGADA=Patient Global Assessment of Disease Activity; PtGADD=Patient Global Assessment of Disease Damage; PGIC=Patient Global Impression of Change; RNA=ribonucleic acid; TSQM=Treatment Satisfaction Questionnaire for Medication Version II.

Note: Chest radiograph and ECG (as well as other assessments approved by the Medical Monitor) may be performed as needed to confirm findings requiring confirmation on the MDAAT.

a. Eligibility criteria for this study should be assessed only after signing of informed consent for this study. All data from Screening and all data except for central laboratory results from the Day 1 visit should be used to confirm patient eligibility.
b. Classification criteria and web calculator located at: https://www niehs.nih.gov/research/resources/imacs/classificationcriteria/index.cfm.
c. Tuberculosis assessment includes an interferon gamma release assay. If indeterminate or borderline on first assessment, it may be repeated. A positive or second indeterminate result is exclusionary. Test may be performed locally or centrally.
d. Human immunodeficiency viruses 1 and 2, hepatitis B virus core antibody and surface antigen, and hepatitis C virus antibody.
e. Chest radiograph should be performed at Screening (posteroanterior view) if findings from a radiograph obtained within 12 weeks before Screening are not available.
f. Follicle stimulating hormone may be drawn to confirm postmenopausal status in female patients.
g. Coagulation: prothrombin time, international normalized ratio, activated partial thromboplastin time, lupus anticoagulant panel; thyroid function: thyroid stimulating hormone, free T4, free T3; APLA: antiphospholipid antibodies (anti-β_2 glycoprotein I IgG and IgM, anticardiolipin IgG and IgM).
h. A serum pregnancy test should be performed at Screening and a urine pregnancy test will be performed at all other visits.
i. A complete physical examination should be performed at Screening, Week 16, W32/Early Termination Visit, and End of Study Visit (see Table 4). Physical examinations at all other time points may be limited in nature.

j. Vital signs and weight will be measured at all visits; height will be measured at Screening only. Blood pressure and pulse rate should be collected after the patient has had at least 5 minutes of rest in the seated position. If the blood pressure is elevated on the first measurement at Screening or Baseline, it should be repeated after an additional 5 minutes of rest. It is recommended that blood pressure is measured using the same arm at each assessment.
k. 12-lead ECG should be performed after at least 5 minutes of rest in a supine position.
l. Should be completed by qualified personnel, and it is recommended that the same individual performs the assessment at all visits.
m. Should be performed only in those patients with DM.
n. Patient reported outcome measures are recommended to be completed first at each visit where performed, ie, prior to any other procedures or assessments other than signing of informed consent.
o. Hematology: hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count (total and differential), and platelet count.
Clinical chemistry: creatinine, creatine kinase, urea (or blood urea nitrogen), aspartate aminotransferase, alanine aminotransferase, gamma glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, uric acid, total cholesterol, magnesium, calcium, phosphorus.
p. Erythrocyte sedimentation rate should be performed locally.
q. CD19 count is required to be performed only for those patients being evaluated for eligibility who had their last dose of rituximab ≥24 and <48 weeks before Screening.
r. Urinalysis: color, appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite, leukocyte esterase with reflex testing for microscopic parameters.
s. Quantitative immunoglobulins: IgG, IgM, IgA.
t. Autoantibodies could potentially include the following: myositis autoantibodies: anti-Jo-1, anti-PL-7, anti-PL12, anti-EJ, anti-OJ, anti-SRP, anti-Mi-2α, anti-Mi-2β, anti-MDA-5, anti-TIF-1γ, anti-NXP-2, anti-HMGCR; other autoantibodies: anti-PM-Scl, anti-U1RNP, anti-SSA, anti-SSB, anti-Ku, anti-SAE, anticentromere, antinuclear.
u. Pharmacokinetics will be performed as sparse sampling before dosing and at 0.5 (±5 minutes) and 4 hours (±10 minutes) after dosing in all patients at Week 0 and at Week 16 (see Table 4). In addition, a PK sample will be obtained at 0.25 (±5 minutes), 1 (±10 minutes), or 2 hours (±10 minutes) after dosing at Weeks 0 and 16 (see Table 4) based on the random assignment of a patient via the Randomization and Trial Supply Management system to PK Cohort A, B, or C.
v. Blood sampling for PD (proteasome inhibition) will be performed in all patients before dosing and at 4 hours after dosing at Week 0 and at Week 16 (see Table 4).
w. Blood sampling will be performed before dosing to measure cytokines including IFNα, IFNβ, IFNγ, IL-2, IL-6, IL-12, IL-17A, IL-21, IL-23, CXCL10, BLyS, TNFα, TGFβ; and to profile immune cells including B cell subgroups (naïve, activated, memory), plasma cell subgroups (long, short-lived), T cell subgroups (CD4 [Th1, Th17, all, naïve, activated], CD8 [memory], Treg).
x. Will be performed in patients who have provided the proper informed consent for genetic analyses.
y. Patients who do not have a muscle biopsy will be permitted to get one during the Screening Period if needed to determine eligibility. Skin and/or muscle biopsies for histology and gene expression analysis will be performed in consenting patients at qualified centers. Patients who agree to participate in the biopsy substudy will have biopsies obtained at the time points as specified.
z. Patients need to be monitored for 2 hours after dosing at Week 0 and at Week 16 (see Table 4). Patients will receive study drug weekly. Home health service will be arranged for patients who choose not to return to investigative site for study drug administration weekly according to Table 3.

Table 3 Schedule of Assessments for the Study Drug Administration Visits during Treatment Period 1

Study Period	Treatment Period 1											
Visit No.	3	4	5	7	8	9	11	12	13	15	16	17
Start of Week	1	2	3	5	6	7	9	10	11	13	14	15
Day	8±1	15±1	22±1	36±1	43±1	50±1	64±1	71±1	78±1	92±1	99±1	106±1
Vital signs[a]	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration	X[b]	X	X	X	X	X	X	X	X	X	X	X

Note: Home health service will be arranged for patients who choose not to return to investigative site for study drug administration weekly.

a. Vital signs will be collected before dosing. Blood pressure and pulse rate should be collected after the patient has had at least 5 minutes of rest in the seated position. It is recommended that blood pressure is measured using the same arm at each assessment.

b. Patients need to be monitored for 2 hours after dosing at Visit 3.

Table 4 Schedule of Assessments for Treatment Period 2 and Safety Follow-up

Study Period	Treatment Period 2					SFU		
Visit No. and or Name	18		22	26	30	34/ETV[a]	35	36/EOS
Start of Week	16		20	24	28	32	36	40
Day	113±1		141±1	169±1	197±1	225±2	253±3	281±3
PK and PD assessments	Predose	Postdose						
Concomitant therapy	←						→	
Pregnancy test[b]	X		X	X	X	X		
Physical examination[c]	X			X		X		X
Vital signs and weight[d]	X		X	X	X	X	X	X
12-lead ECG[e]	X		X			X		X
MMT-8[f]	X		X	X	X	X	X	X
MDAAT, MDGA, MDGIC[f]	X		X	X	X	X	X	X
FI-2 (dominant side only)[f]	X					X		X
FI-3[f]	X			X		X		X
Sit-to-stand test[f]			X		X		X	X
MDI[f]	X					X		
CDASI[f,g]	X		X	X	X	X	X	X
PtGADA, HAQ-DI, PGIC[h]	X		X	X	X	X	X	X
PROMIS-29, EQ-5D-5L[h]	X		X			X		X
HRU[h]	X			X		X		X
PtGADD[h]	X					X		X
TSQM[h]	X		X			X		X
Peak Pruritus NRS[g,h]	X		X	X	X	X	X	X
Hematology, chemistry[i], CRP, and aldolase	X		X	X	X	X	X	X
Erythrocyte sedimentation rate[j]	X		X	X	X	X	X	X
Urinalysis[k]	X		X	X	X	X	X	X
Quantitative immunoglobulins[l]	X					X		X
Autoantibodies[m]	X					X		
PK assessment[n]	X	X						
PD assessment[o]	X	X				X		
Cytokines/proteomics and leukocyte subsets[p]	X		X			X		
Gene expression and DNA methylation profiling (RNA)[q]	X		X			X		
Skin and/or muscle biopsies[r]	X					X		
Study drug administration[s]	X[s]		X	X	X			
Adverse events	←						→	

Abbreviations: CDASI=Cutaneous Dermatomyositis Disease Area and Severity Index; CRP=C-reactive protein; DM=dermatomyositis; ECG=electrocardiogram; EOS=End of Study; EQ-5D-5L=EuroQoL 5-dimension 5-level; ETV=Early Termination Visit; FI-2=Functional Index-2; FI-3=Functional Index-3; HAQ-DI=Health Assessment Questionnaire-Disability Index; HRU=healthcare research utilization; MDGIC=Physician Global Impression of Change; MDAAT=Myositis Disease Activity Assessment Tool;

MDGA=Physician Global Assessment; MDI=Myositis Damage Index; MMT-8=Manual Muscle Testing-8 Muscle Groups; NRS=numeric rating scale; PD=pharmacodynamics; PK=pharmacokinetics; PROMIS-29=Patient Reported Outcomes Measurement Information System 29-item Short Form Profile Version 2.1; PtGADA=Patient Global Assessment of Disease Activity; PtGADD=Patient Global Assessment of Disease Damage; PGIC=Patient Global Impression of Change; RNA=ribonucleic acid; SFU=Safety Follow-up; TSQM=Treatment Satisfaction Questionnaire for Medication Version II.
Note: Chest radiograph and ECG (as well as other assessments approved by the Medical Monitor) may be performed as needed to confirm findings requiring confirmation on the MDAAT.

a. Patients withdrawing prior to Week 32 visit should complete all Early Termination Visit (Week 32) assessments for their early termination visit. It is requested that these patients return for their Safety Follow-up Visit 9 weeks after administration of the last dose of the study drug.
b. A urine pregnancy test will be performed.
c. A complete physical examination should be performed at the W32/Early Termination Visit and End of Study Visit. Physical examinations at all other time points may be limited in nature.
d. Vital signs and weight will be measured at all visits. Blood pressure and pulse rate should be collected after the patient has had at least 5 minutes of rest in the seated position. If the blood pressure is elevated on the first measurement at Screening or Baseline, it should be repeated after an additional 5 minutes of rest. It is recommended that blood pressure is measured using the same arm at each assessment.
e. 12-lead ECG should be performed after at least 5 minutes of rest in a supine position.
f. Should be completed by qualified personnel, and it is recommended that the same individual performs the assessment at all visits.
g. Should be performed only in those patients with DM.
h. Patient reported outcome measures are recommended to be completed first at each visit where performed, ie, prior to any other procedures or assessments other than signing of informed consent.
i. Hematology: hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count (total and differential), and platelet count.
   Clinical chemistry: creatinine, creatine kinase, urea (or blood urea nitrogen), aspartate aminotransferase, alanine aminotransferase, gamma glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, uric acid, total cholesterol, magnesium, calcium, phosphorus.
j. Erythrocyte sedimentation rate should be performed locally.
k. Urinalysis: color, appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite, leukocyte esterase with reflex testing for microscopic parameters.
l. Quantitative immunoglobulins: IgG, IgM, IgA.
m. Autoantibodies could potentially include the following: myositis autoantibodies: anti-Jo-1, anti-PL-7, anti-PL12, anti-EJ, anti-OJ, anti-SRP, anti-Mi-2α, anti-Mi-2β, anti-MDA-5, anti-TIF-1γ, anti-NXP-2, anti-HMGCR; other autoantibodies: anti-PM-Scl, anti-U1RNP, anti-SSA, anti-SSB, anti-Ku, anti-SAE, anticentromere, antinuclear.
n. Pharmacokinetics will be performed as sparse sampling before dosing and at 0.5 (±5 minutes) and 4 hours (±10 minutes) after dosing in all patients at Week 16. In addition, a PK sample will be obtained at 0.25 (±5 minutes), 1 (±10 minutes), or 2 hours (±10 minutes) after dosing at Weeks 16 based on the random assignment of a patient via the Randomization and Trial Supply Management system to PK Cohort A, B, or C.
o. Blood sampling for PD (proteasome inhibition) will be performed in all patients before dosing and at 4 hours after dosing at Week 16 and at Week 32.
p. Blood sampling will be performed before dosing at Weeks 16 and 20 and at Week 32 to measure cytokines including IFNα, IFNβ, IFNγ, IL-2, IL-6, IL-12, IL-17A, IL-21, IL-23, CXCL10, BLyS, TNFα, TGFβ; and to profile immune cells including B cell subgroups (naïve, activated, memory), plasma cell subgroups (long, short-lived), T cell subgroups (CD4 [Th1, Th17, all, naïve, activated], CD8 [memory], Treg).
q. Will be performed patients who have provided the appropriate informed consent for genetic analyses.
r. Skin and or muscle biopsies for histology and gene expression analysis will be performed in consenting patients at qualified centers. Patients who agree to participate in the biopsy substudy will have biopsies obtained at the time points as specified. The collection at W32 will be optional.
s. Patients need to be monitored for 2 hours after dosing at Week 16. Patients will receive study drug weekly. Home health service will be arranged for patients who choose not to return to investigative site for study drug administration weekly according to Table 5.

Table 5 Schedule of Assessments for the Study Drug Administration Visits during Treatment Period 2

Study Period	Treatment Period 2											
Visit No.	19	20	21	23	24	25	27	28	29	31	32	33
Start of Week	17	18	19	21	22	23	25	26	27	29	30	31
Day	120±1	127±1	134±1	148±1	155±1	162±1	176±1	183±1	190±1	204±1	211±1	218±1
Vital signs[a]	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration	X[b]	X	X	X	X	X	X	X	X	X	X	X

Note: Home health service will be arranged for patients who choose not to return to investigative site for study drug administration weekly.

a. Vital signs will be collected before dosing. Blood pressure and pulse rate should be collected after the patient has had at least 5 minutes of rest in the seated position. It is recommended that blood pressure is measured using the same arm at each assessment.

b. Patients need to be monitored for 2 hours after dosing at Visit 19.

7.2. Study Procedures and Assessments

All patients must be provided a consent form describing the study with sufficient information for patients to make an informed decision regarding their participation as per Section 11.3.

All study procedures and assessments will be performed according to the schedules presented in Table 2, Table 3, Table 4, and Table 5.

7.2.1. Demographic Data

Demographic data will be recorded at Screening and will include date of birth, age (calculated), sex, ethnicity, and race.

7.2.2. PM/DM Classification

Patients will be classified as having PM or DM based on the 2017 EULAR/ACR classification criteria[34] and the web calculator located at:
https://www.niehs.nih.gov/research/resources/imacs/classificationcriteria/index.cfm
(Last accessed: 28 February 2019)

7.2.3. Medical History

Documentation of the patient's medical history should contain the patient's full medical history including past and concomitant illnesses/diseases, disease duration, prior medications, prior procedures, and social history (including tobacco use, drugs of abuse, and alcohol use).

7.2.4. Efficacy Assessments

Efficacy assessments will be performed for all patients, unless indicated otherwise, at the time points shown in the Schedule of Assessments (Table 2 and Table 4). As interrater reliability may result in increased variability of within-patient assessments, it is recommended that the same individual performs the assessments at all visits for an individual patient.

7.2.4.1. Total Improvement Score

The Myositis Response Criteria are recommended for use as primary endpoints in myositis therapeutic trials. The criteria use the 6 IMACS core set measures, combining the absolute percentage change in each with varying weights to obtain a TIS on a scale of 0-100. Different thresholds of improvement have been set for minimal, moderate, and major response. The TIS may be used as a continuous outcome measure or as a categorical outcome of improvement (minimal, moderate, or major improvement). The TIS can be calculated using the 2016 ACR/EULAR criteria[2] using the web calculator located at:
https://www.niehs.nih.gov/research/resources/imacs/response_criteria/adult.html

The User's Guide is located at:
https://www.niehs.nih.gov/research/resources/imacs/response_criteria/users_guide_for_the_a

dult_dermatomyositis_and_polymyositis_response_criteria_online_calculator_508.pdf
(Last accessed: 28 February 2019)

Investigators will not be required to make these calculations for the study.

7.2.4.2. Manual Muscle Testing-8 Muscle Groups (MMT-8)

This partially validated tool assesses muscle strength using manual muscle testing. A 0 to 10-point scale is proposed for use. An abbreviated group of 8 proximal, distal, and axial muscles (neck flexors, deltoids, biceps brachii, gluteus maximus, gluteus medius, quadriceps, wrist extensors, ankle dorsiflexors) performs similarly to a total of 24 muscle groups, and this abbreviated group is also proposed for use for research studies.[41,42] This is one of the IMACS disease CSAMs.

The MMT-8 should be completed by qualified personnel, and it is recommended that the same individual performs the assessment at all visits.

The MMT-8 can be found at:

https://www.niehs.nih.gov/research/resources/assets/docs/mmt8_grading_and_testing_procedures_for_the_abbreviated_8_muscle_groups_508.pdf
(Last accessed: 28 February 2019)

7.2.4.3. Myositis Disease Activity Assessment Tool (MDAAT)

This validated tool measures the degree of disease activity of extramuscular organ systems and muscle. This is a combined tool that includes the Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT), which is a series of physician's assessments of disease activity of various organ systems modified from the Vasculitis Activity Index,[50] and the Myositis Intention to Treat Activity Index (MITAX), which is modified from the British Isles Lupus Assessment Group approach to assess disease activity in SLE.[24] The MITAX is composed of a series of organ-specific questions relating to the presence or absence of the clinical feature and the degree of treatment needed for it (intention to treat).[42,47]

The MDAAT should be completed by qualified personnel, and it is recommended that the same individual performs the assessment at all visits. This is one of the IMACS disease CSAMs.

The MDAAT assessment tool and glossary, respectively, can be located at:

https://www.niehs.nih.gov/research/resources/assets/docs/myositis_disease_activity_assessment_tool_2009_pdf_format_508.pdf
(Last accessed: 28 February 2019)

https://www.niehs.nih.gov/research/resources/assets/docs/glossary_for_myositis_disease_activity_assessment_tool_0_4_version_2_2005_pdf_format_508.pdf
(Last accessed: 28 February 2019)

7.2.4.4. Physician Global Assessments of Disease Activity (MDGA)

This partially validated tool measures the global evaluation by the treating physician of the overall disease activity of the patient at the time of assessment using a 10 cm visual analog scale (VAS) and a 5-point Likert scale.[42] This is one of the IMACS disease CSAMs.

The MDGA is located at:

https://www.niehs.nih.gov/research/resources/assets/docs/physician_global_activity_pdf_format_508.pdf
(Last accessed: 28 February 2019)

The MDGA should be completed by qualified personnel, and it is recommended that the same individual performs the assessment at all visits.

7.2.4.5. Physician Global Impression of Change (MDGIC)

The MDGIC consists of 1 item taken from the Clinical Global Impressions scale (CGI), which was published in 1976 by the US National Institute of Mental Health. Answers are based on a 7-point Likert scale ranging from very much improved to very much worse, asking regarding the patient's overall status.[22]

The MDGIC should be completed by qualified personnel, and it is recommended that the same individual performs the assessment at all visits.

7.2.4.6. Functional Index-2 (FI-2)

The FI-2 is a functional outcome developed for patients with adult PM or DM assessing muscle endurance in 7 muscle groups. Each muscle group is scored as the number of correctly performed repetitions with 60 or 120 maximal number of repetitions depending on muscle group. The FI-2 is a further development of the original FI where redundant tasks were eliminated and the number of repetitions for each task were increased to avoid ceiling effects. It has been validated as to content and construct validity and intra- and interrater reliability. The FI-2 can be performed just on the dominant side, which takes approximately 21 minutes.[4,42]

This assessment tool is located at:

https://www.niehs.nih.gov/research/resources/assets/docs/functional_index2_training_guide_508.pdf
(Last accessed: 28 February 2019)

The FI-2 should be completed by qualified personnel, and it is recommended that the same individual performs the assessment at all visits.

7.2.4.7. Functional Index-3 (FI-3)

The FI-3 is an efficient and valid method for assessment of muscle endurance in DM and PM patients.[32] It comprises 3 assessments as follows:

- Sit-to-stand (STS): The score is the number of times that the patient rises to a full stand from the seated position with arms folded across the chest within 30 seconds[1]
- Timed up and go (TUG): The amount of time it takes the patient to stand from a seated position, walk 3 meters, turn, return to the chair, and then sit down.
- 6-minute walk distance (6MWD): Distance patient walks in 6 minutes.

The FI-3 should be completed by qualified personnel, and it is recommended that the same individual performs the assessment at all visits. The sit-to-stand test may be performed alone in place of the full FI-3 as per the Schedule of Assessments (Table 2 and Table 4).

7.2.4.8. Myositis Damage Index (MDI)

This validated tool assesses the degree of disease damage of all organ systems. It is composed of a series of organ-specific questions relating to the presence or absence of a given sign or symptom or problem to measure the extent of damage, and an overall rating of the disease damage of each system using a 10 cm VAS to measure the severity of damage.[42,48]

The MDI is located at:

https://www.niehs.nih.gov/research/resources/assets/docs/myositis_damage_index_pdf_format_508.pdf
(Last accessed: 28 February 2019)

The MDI should be completed by qualified personnel, and it is recommended that the same individual performs the assessment at all visits.

7.2.4.9. Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)

The CDASI will be performed only for those patients with DM.

The CDASI is a clinician-scored single-page instrument that separately measures activity and damage in the skin of DM patients for use in clinical practice or clinical/therapeutic studies. The modified CDASI (Version 2) is the one in current use. The modified CDASI has 3 activity measures (erythema, scale, and erosion/ulceration) and 2 damage measures (poikiloderma and calcinosis) which are assessed over 15 body areas. In addition, Gottron's papules on the hands are evaluated both for activity and damage. Lastly, the activity of periungual changes and alopecia is assessed.[42,52]

The CDASI is located at:

https://www.niehs.nih.gov/research/resources/imacs/othertools/cdasi_training_slide_set_508.pdf
(Last accessed: 28 February 2019)

The CDASI should be completed by qualified personnel, and it is recommended that the same individual performs the assessment at all visits.

7.2.4.10. Muscle Enzymes

Muscle enzymes (aldolase, ALT, AST, CK, and LDH) will be measured to evaluate disease activity via laboratory testing per Section 7.2.6.10. Muscle enzyme measurements are one of the IMACS disease CSAMs.

7.2.5. Patient Reported Outcome Assessments

Several PROMs will be used in this study, including the PtGADA, HAQ-DI, PGIC, PROMIS-29, EQ-5D-5L, HRU, PtGADD, Peak Pruritus NRS (DM patients only), and TSQM. It is recommended that PROMs be completed before any other assessments or procedures are performed, at each visit where they are to be performed.

7.2.5.1. Patient Global Assessment of Disease Activity (PtGADA)

This partially validated tool measures the global evaluation of the patient's overall disease activity at the time of assessment using a 10 cm VAS.[42] The PtGADA is a PROM and is one of the IMACS disease CSAMs. It is recommended that, at each visit where it is to be performed that PROMs are completed before any other assessments or procedures are performed.

The PtGADA is located at:

https://www.niehs.nih.gov/research/resources/assets/docs/patientparent_global_activity_pdf_format_508.pdf
(Last accessed: 28 February 2019)

7.2.5.2. Health Assessment Questionnaire-Disability Index (HAQ-DI)

The HAQ-DI is a partially validated tool to assess physical function in myositis.[42] The HAQ-DI is a PROM and is one of the IMACS disease CSAMs. It is recommended that, at each visit where they are to be performed, that PROMs are completed before any other assessments or procedures are performed.

The HAQ-DI is located at:

https://www.niehs.nih.gov/research/resources/assets/docs/haq_instructions_508.pdf
(Last accessed: 28 February 2019)

7.2.5.3. Patient Global Impression of Change (PGIC)

The PGIC is the PROM counterpart to the CGI, which was published in 1976 by the US National Institute of Mental Health. It consists of one item taken from the CGI and adapted to the patient. Answers are based on a 7-point Likert scale ranging from very much improved to very much worse, asking regarding the patient's overall status.[22]

It is recommended that, at each visit where they are to be performed, that PROMs are completed before any other assessments or procedures are performed.

7.2.5.4. Patient Reported Outcomes Measurement Information System 29-item Short Form Profile Version 2.1 (PROMIS-29)

The Patient Reported Outcomes Measurement Information System® (PROMIS) is a flexible set of tools designed to measure self-reported physical, mental, and social health and wellbeing. The PROMIS has been constructed and validated rigorously, with more than 50 research protocols and over 60,000 people contributing data. Development included a comprehensive literature review, focus group and psychometric testing, cognitive interviews, and expert review. The PROMIS-29 is a generic health related quality of life survey containing 4 items for the following 7 domains: depression; anxiety; physical function; pain interference; fatigue; sleep disturbance; and ability to participate in social roles and activities. The 7 domains cover the most relevant areas of self-reported health for the greatest majority of people with chronic illness. The questions are ranked on a 5-point Likert Scale. There is also one 11-point rating scale for pain intensity. More information is available at:
http://www.healthmeasures.net/explore-measurement-systems/promis.
(Last accessed: 28 February 2019)
An overview of the PROMIS-29 is available at:
https://www.aci.health.nsw.gov.au/__data/assets/pdf_file/0003/402087/Overview-of-the-PROMIS-29_EH-140817.pdf
(Last accessed: 28 February 2019)

The PROMIS-29 is a PROM. It is recommended that, at each visit where they are to be performed, that PROMs are completed before any other assessments or procedures are performed.

7.2.5.5. EuroQoL 5-dimension 5-level (EQ-5D-5L)

The EQ-5D is a standardized instrument developed by the EuroQoL Group as a measure of health related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D consists of a descriptive system and the EQ-VAS.

The descriptive system comprises 5 levels of severity for each of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-VAS records the patient's self-rated health on a vertical VAS. This can be used as a quantitative measure of health outcome that reflects the patient's own judgment. The scores on these 5 dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles.

The EQ-5D-5L is located at:

https://euroqol.org/eq-5d-instruments/
(Last accessed: 28 February 2019)

The EQ-5D-5L is a PROM. It is recommended that, at each visit where they are to be performed, that PROMs are completed before any other assessments or procedures are performed.

7.2.5.6. Healthcare Resource Utilization (HRU)

The HRU questionnaire to be used in this study has been modified from one created for osteoarthritis.[33,40] It covers aspects of work productivity as well as hospitalizations, specialist and nonspecialist care, ancillary health care, use of community services, and out of pocket costs. Self-reported questionnaires on resource utilization have been shown to have good agreement with administrative data, although visits to general practitioners, outpatient days, and nurse visits had poorer agreement.

Data entered by the patient on the HRU form should be reviewed by the Investigator or designee for the potential occurrence of AEs or SAEs to be reported.

The HRU is a PROM. It is recommended that, at each visit where they are to be performed, that PROMs are completed before any other assessments or procedures are performed.

7.2.5.7. Patient Global Assessment of Disease Damage (PtGADD)

This partially validated tool measures the global evaluation of the patient's overall disease damage at the time of assessment using a 10 cm VAS. The PtGADD is a PROM. It is recommended that, at each visit where they are to be performed, that PROMs are completed before any other assessments or procedures are performed.

The PtGADD is located at:

https://www.niehs.nih.gov/research/resources/assets/docs/patientparent_global_assessment_of_disease_damage_pdf_format_508.pdf
(Last accessed: 28 February 2019)

7.2.5.8. Peak Pruritus Numeric Rating Scale

In a study of patients with DM, 50% reported moderate-to-severe itch, and itch was correlated with increased cutaneous severity.[29] The Peak Pruritus NRS, used to evaluate itch in atopic dermatitis, will be utilized to evaluate the severity of itch in patients with DM. It ranges from a score of 0 to 10, with 0 representing no itch and 10 representing the worst itch imaginable during the worst moment within a 24-hour recall period.

The Peak Pruritus NRS will be performed only in those patients with DM.

The Peak Pruritus NRS is a PROM. It is recommended that, at each visit where they are to be performed, that PROMs are completed before any other assessments or procedures are performed.

7.2.5.9. Treatment Satisfaction Questionnaire for Medication Version II (TSQM)

The TSQM is a generic measure of treatment satisfaction for medication. It was rigorously developed and has sound psychometric properties.[6] The TSQM assesses 4 key dimensions of treatment satisfaction: effectiveness (2 questions); side effects (3 questions); convenience (3 questions); and global satisfaction (2 questions). It comprises 11 questions, with possible responses ranging from yes/no to 5- to 7-point Likert-type scales. Higher scores indicated more satisfaction with the treatment.

The TSQM is located at:

https://www.iqvia.com/landing/treatment-satisfaction-questionnaire-for-medication-tsqm (Last accessed: 28 February 2019)

The TSQM is a PROM. It is recommended that, at each visit where they are to be performed, that PROMs are completed before any other assessments or procedures are performed.

7.2.6. Safety Assessments

Safety will be assessed throughout the study by monitoring of vital signs (blood pressure, pulse rate, temperature, and respiration rate), laboratory tests (hematology, chemistry, urinalysis, immunoglobulins), ECGs, and physical examinations; and by recording and analyzing all AEs and SAEs.

7.2.6.1. Tuberculosis

Evaluation of all patients by an interferon gamma release assay for TB will be performed by the central clinical laboratory or local laboratory at Screening. The following tests are permitted:

- QuantiFERON®-TB Gold
- QuantiFERON®-TB Gold Plus
- T-SPOT® TB.

History of active TB infection is excluded, regardless of treatment history.

If the screening test is negative and there is no known history of recent exposure to individuals with active TB, and chest radiograph shows no evidence of active TB, the patient may be enrolled and/or randomized. If the screening test is positive at Screening and/or the patient is diagnosed with latent TB, they must have documentation confirming completion of appropriate treatment prior to being permitted to enroll or being randomized.

A patient with an indeterminate or borderline TB test at Screening must have a repeat test performed at least 1 time by the central laboratory or local laboratory, and it must be repeated

as soon as possible. If the result remains indeterminate or borderline or is positive, the patient is not eligible for enrollment into the study or randomization.

7.2.6.2. Viral Serology

Viral serology tests for human immunodeficiency viruses 1 and 2, hepatitis B virus core antibody and surface antigen, and hepatitis C virus antibody will be performed at Screening. Patients with positive tests for any of these assessments will be excluded, regardless of treatment history.

7.2.6.3. Chest Radiograph

A chest radiograph should be obtained at Screening (posteroanterior view) if findings from a radiograph taken within 12 weeks before Screening are not available. The chest radiograph should be read by a radiologist or pulmonologist, and documented results should be reviewed by the Investigator or designee to exclude patients with active TB infection. If necessary, additional chest radiographs may be performed to confirm findings required for the MDAAT.

7.2.6.4. Follicle Stimulating Hormone and Pregnancy

Samples for FSH testing may be collected at Screening to confirm postmenopausal status in female patients.

For WOCBP, a serum pregnancy test will be performed at Screening and urine testing will be performed at all other time points shown in the Schedule of Assessments (Table 2 and Table 4).

7.2.6.5. Coagulation, Thyroid, and Antiphospholipid Antibodies

Samples for coagulation, thyroid, and antiphospholipid antibodies (APLA) will be collected and testing will be performed at the time points shown in the Schedule of Assessments (Table 2). Coagulation tests will include: prothrombin time, INR, aPTT, and lupus anticoagulant panel. Thyroid function tests will include: free T4, free T3, and thyroid stimulating hormone. The APLA testing will include: anti-β2 glycoprotein I and anticardiolipin (IgG and IgM for both).

7.2.6.6. Physical Examination

Complete physical examinations will be performed only at Screening, W16, the ETV, and the End of Study Visit. A complete physical examination should include at least assessments of these systems: general appearance, head, ears, eyes, nose and throat, neck, dermatological, respiratory, cardiovascular, abdomen, extremities, neurological, musculoskeletal.

At all other specified time points, a limited physical examination will be performed as directed by the patient complaints and the clinical judgment of the Investigator. Medically significant changes from physical examination will be recorded as AEs. Muscle evaluation findings captured in the muscle assessment instruments will not be recorded unless they are classifiable as SAEs, as per Section 9.4.

7.2.6.7. Vital Sign Measurements

Blood pressure, pulse rate, respiration rate, and temperature will be measured at the time points shown in the Schedule of Assessments (Table 2, Table 3, Table 4, and Table 5). Blood pressure and pulse rate should be collected after the patient has had at least 5 minutes of rest in the seated position. If the blood pressure is elevated on the first measurement at Screening and Baseline, it should be repeated after an additional 5 minutes of rest. It is recommended that blood pressure is measured using the same arm at each assessment. When the time of vital signs measurement coincides with a blood sample collection, the vital signs will be measured before blood sample collection.

7.2.6.8. Weight and Height

Body weight will be recorded at the time points shown in the Schedule of Assessments (Table 2 and Table 4). Body weight, with the patient wearing light clothing and the shoes and jacket or coat removed, will be measured and recorded in kilograms.

Body height will be measured and recorded, in centimeters, at Screening only.

7.2.6.9. Electrocardiogram

A 12-lead ECG will be taken at the time points shown in the Schedule of Assessments (Table 2 and Table 4). The ECG should be performed after the patient has rested for at least 5 minutes in a supine position. When scheduled at the same time point as vital sign measurements or a blood sample collection, the ECG should be performed first.

The ECG measurements will include heart rate, PR interval, QT interval, RR interval, QRS complex, and rhythm. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. Corrections to QT interval should be done by both QTcF and QTcB, if possible.

The Investigator or qualified designee will review and indicate if the ECG is normal or abnormal, and whether clinically significant. Any medically significant changes from the screening ECG will be recorded as an AE.

7.2.6.10. Clinical Laboratory Tests

Clinical laboratory tests for safety (hematology, serum chemistries, urinalyses, coagulation tests, serum pregnancy) and other tests during scheduled visits will be performed at a central laboratory. Urine pregnancy tests and erythrocyte sedimentation rate (ESR) will be performed locally using an approved test; TB testing may be performed locally or centrally using a licensed test.

Clinical laboratory results the Investigator deems clinically significantly abnormal should be repeated ideally within 48 to 72 hours from when the result became available. Guidance for laboratory values that could be considered clinically significantly abnormal is provided in Appendix B. Certain clinically significantly abnormal laboratory values may also influence continued dosing as per Section 6.1.1.

Unscheduled or additional laboratory samples may be collected and analyzed by local laboratories if immediate results are necessary for management of TEAEs or dosing determination. Unless otherwise noted, when scheduled simultaneously with a dosing visit, samples for laboratory evaluations should be collected prior to administration of the study drug.

Detailed instructions for sample collection, processing, storage and shipment will be provided in the Laboratory Manual.

7.2.6.11. Hematology and Erythrocyte Sedimentation Rate

Samples for hematology and ESR will be collected, and testing will be performed at the time points shown in the Schedule of Assessments (Table 2 and Table 4). Hematology tests to be performed are presented in Table 6.

Table 6 Hematology Tests

Hematology Tests
• Hemoglobin
• Hematocrit
• WBC count (total and differential)
• Red blood cell (RBC) count
• Platelet count
• Mean corpuscular volume (MCV)
• Mean corpuscular hemoglobin (MCH)
• MCH concentration (MCHC)

The ESR will be measured by the local laboratory, and the value entered into the eCRF.

7.2.6.12. Clinical Chemistry, C-Reactive Protein, and Aldolase

Samples for clinical chemistry will be collected for patients in a nonfasting state, and testing will be performed at the time points shown in the Schedule of Assessments (Table 2 and Table 4). Clinical chemistry tests to be performed are presented in Table 7.

Table 7 Clinical Chemistry, Aldolase, and C-Reactive Protein Tests

Serum Chemistry Tests (Non-Fasting)	
• Creatinine	• Sodium
• Creatine kinase (CK)	• Potassium
• Urea (or blood urea nitrogen [BUN])	• Chloride
• Aspartate aminotransferase (AST)	• Glucose
• Alanine aminotransferase (ALT)	• Uric acid
• Gamma glutamyltransferase (GGT)	• Total cholesterol
• Alkaline phosphatase	• Magnesium (Mg)
• Lactate dehydrogenase (LDH)	• Calcium
• Total bilirubin	• Phosphorus
• Albumin	• C-reactive protein (CRP)
• Total protein	• Aldolase

Patients will have estimated glomerular filtration rate (eGFR) calculated based on CKD-EPI formula:

$$eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

Where:

- S_{cr} is serum creatinine in mg/dL
- κ is 0.7 for females and 0.9 for males
- α is -0.329 for females and -0.411 for males
- min indicates the minimum of S_{cr}/κ or 1
- max indicates the maximum of S_{cr}/κ or 1.

7.2.6.13. Urinalysis

Samples for urinalysis will be collected and testing will be performed at the time points shown in the Schedule of Assessments (Table 2 and Table 4). Urinalysis will include: color, appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite, leukocyte esterase with reflex testing for microscopic parameters.

7.2.6.14. Immunoglobulins

Samples for immunoglobulins will be collected and testing will be performed at the time points shown in the Schedule of Assessments (Table 2 and Table 4). Quantitative immunoglobulins measured will include IgG, IgM, and IgA.

7.2.6.15. CD19 Count

At Screening, a CD19 count is required to be performed only for those patients being evaluated for eligibility who had their last dose of rituximab ≥24 and <48 weeks before Screening.

7.2.7. Pharmacokinetic Assessments

Blood samples will be collected as outlined in the Schedule of Assessments (Table 2 and Table 4). All patients will have blood samples collected at predose and at 0.5 and 4 hours postdose. In addition, patients will be randomly assigned via RTSM to Cohort A (0.25 hour postdose PK sample), Cohort B (1 hour postdose PK sample), or Cohort C (2 hour postdose PK sample). Samples will be used to measure the plasma concentration of KZR-616 and its metabolite KZR-59587 (area under the time-concentration curve [AUC], maximum concentration [C_{max}], time to maximum plasma concentration [T_{max}]), and other PK calculations). At the visits and times specified, blood samples of approximately 4 mL will be collected. Additional information regarding sample collection and handling are outlined in the Laboratory Manual.

Samples collected to measure investigational product concentration and metabolism and/or protein binding will be retained for as long as legally permitted in the country of origin or until Sponsor decision to destroy.

7.2.8. Pharmacodynamic Assessments

The extent of proteasome activity in whole blood and isolated PBMCs will be assessed in blood samples collected as outlined in the Schedule of Assessments (Table 2 and Table 4). Proteasome CT-L peptidase activity will be measured by a cleavable fluorogenic substrate enzymatic activity assay. KZR-616 occupancy of individual subunits of the proteasome in whole blood and PBMCs will be measured by the proteasome constitutive/ immunoproteasome subunit enzyme-linked immunosorbent assay (ELISA) (ProCISE), a subunit-specific proteasome active site ELISA.

Additional information regarding sample collection and handling are outlined in the Laboratory Manual.

7.2.9. Exploratory Biomarkers

7.2.9.1. Cytokines, Proteomics, and Leukocyte Subsets

Blood samples will be collected at the times shown in the Schedule of Assessments (Table 2 and Table 4) for the measurement of cytokines by ELISA including IFNα, IFNβ, IFNγ, IL-2, IL-6, IL-12, IL-17A, IL-21, IL-23, CXCL10, BLyS, TNFα, TGFβ; and to profile immune cells by flow cytometry including B cell subgroups (naïve, activated, memory), plasma cell subgroups (long, short-lived), T cell subgroups (CD4 [Th1, Th17, all, naïve, activated], CD8 [memory], Treg). Immune cell profiling may also be performed by immune cell subset identification by deoxyribonucleic acid (DNA) methylation polymerase chain reaction methodology. Additional information regarding sample collection and handling are outlined in the Laboratory Manual.

7.2.9.2. Autoantibodies

Blood samples will be collected at the times shown in the Schedule of Assessments (Table 2 and Table 4) for the measurement of autoantibodies. Autoantibodies that may be assessed

include the following: myositis autoantibodies: anti-Jo-1, anti-PL-7, anti-PL12, anti-EJ, anti-OJ, anti-SRP, anti-Mi-2α, anti-Mi-2β, anti-MDA-5, anti-TIF-1γ, anti-NXP-2, anti-HMGCR; other autoantibodies: anti-PM-Scl, anti-U1RNP, anti-SSA, anti-SSB, anti-Ku, anti-SAE, anticentromere, and antinuclear.

Additional information regarding sample collection and handling are outlined in the Laboratory Manual.

7.2.9.3. Pharmacogenomics/Gene Expression

Gene expression (ribonucleic acid [RNA]) profiling and DNA genotyping and methylation status may be assessed in blood samples. A whole blood sample will be collected for pharmacogenomic analysis for storage and analysis at a later date as specified in the Schedule of Assessments (Table 2 and Table 4) and to the extent permitted by the national and/or local laws and regulations.

Samples will be used to conduct retrospective disease or population genetic research as a separate analysis not included in this study. Samples may be used to investigate variable response to KZR-616 and to investigate genetic or epigenetic variants thought to play a role in the diseases under investigation in this study. Assessment of variable response may include evaluation of AEs or differences in efficacy. The results may be reported in the separate report.

Additional information regarding sample collection and handling are outlined in the Laboratory Manual.

7.2.9.4. Biopsy

Biopsies will be collected from a subset of enrolled patients; skin biopsies will be performed only for selected patients with DM, and muscle biopsies will be performed for selected patients with PM or DM. For selected patients, biopsies will be collected from skin and/or muscle at the time points shown in the Schedule of Assessments (Table 2 and Table 4). The tissue samples may be used for exploratory investigations of treatment-related changes and regulation of inflammatory pathways.

Additional information regarding sample collection and handling are outlined in the Laboratory Manual.

8. STUDY DISCONTINUATION

The Investigator must make every reasonable effort to keep each patient on study for the whole duration of the study, including through the SFU, lost to follow-up, consent withdrawal, or End of Study, whichever occurs first.

8.1. Individual and Study Stopping Rules for Safety

8.1.1. Study Stopping Rules

If any of the following events occur, the accumulated safety data will be reviewed by the DMC.

- Death in any patient, unless the cause of death is due to obvious alternative etiology
- Any unexpected or life-threatening SAE, unless due to obvious alternative etiology
- Any event of TMA, thrombotic thrombocytopenic purpura (TTP), or hemolytic uremic syndrome (HUS)
- Three or more of the same Grade 3 or higher AE (judged by the Investigator, Medical Monitor, or Sponsor's representative), including ISRs, unless due to obvious alternative etiology
- Any event which, in the opinion of the Investigator, Medical Monitor, DMC, or Sponsor, contraindicates further dosing of additional patients.

Based on the review, the DMC will have the ability to recommend the study be continued as is, continued with modification, or discontinued. Modifications could include eg, implementation of additional monitoring measures or a dose reduction of KZR-616.

8.1.2. Individual Patient Stopping Rules

If any of the following events occur in an individual patient, administration of study drug to the patient should be interrupted until a review of the accumulated safety data is undertaken by the DMC.

- Any event that fulfills criteria for a Study Stopping Rule (per Section 8.1.1), unless due to obvious alternative etiology
- Any event that, in the opinion of the Investigator, Medical Monitor, DMC, or Sponsor, contraindicates further dosing

After such a review, the DMC may recommend the patient resume dosing, including consideration for any prophylactic interventions (eg, as per Section 6.1.3); reduce their dose (as per Section 6.1.4.1), or discontinue dosing.

8.2. Early Withdrawal of Patients from the Study

In accordance with applicable regulations, a patient has the right to withdraw from the study, at any time and for any reason, without prejudice to future medical care.

Patients may be withdrawn from the study for the occurrence of any of the following reasons:

- Patient request/informed consent withdrawn due to an AE
- Patient request/informed consent withdrawn due to reasons other than an AE
- Patient becomes pregnant
- Adverse event (whether or not related to the study drug) that precludes further participation in the study in the judgment of the Investigator and/or Sponsor
- Protocol noncompliance in the judgment of the Investigator and/or Sponsor
- Lost to follow-up
- The Investigator or Sponsor considers that it is in the patient's best interest for the patient not to continue participation in the study
- Administrative decision by the Investigator or Sponsor.

Patients who withdraw from the study will not be replaced.

Patients are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the eCRF. If a patient withdraws consent, all samples obtained will be retained for analysis unless the patient confirms that he or she wishes the samples to be discarded.

Patients who withdraw from the study prior to W32 will be requested to undergo the ETV procedures within 7 days of the withdrawal, and all patients who withdraw from the study prematurely will be requested to return for the SFU Visit 9 weeks (to perform W40 visit procedures) after receipt of their last dose of the study drug as per Table 4. Patients withdrawing from the study treatment will be encouraged to complete the same final evaluations as patients completing the study according to this protocol, particularly safety evaluations. The primary reason for withdrawal will be identified and recorded on the appropriate eCRF, along with the date of withdrawal.

Reasonable efforts will be made to contact patients who are lost to follow-up. These efforts must be documented in the patient's file.

8.3. Termination or Suspension of the Study

The Sponsor has the right to terminate the study at any time if judged necessary for safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). In this event, the Investigator(s) will be informed of the reason for study termination. Should this occur, all data available will also be recorded in the eCRFs. The Investigator should notify the relevant Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) in writing of the study's completion or early discontinuation.

9. ADVERSE EVENTS

9.1. Adverse Event Reporting

9.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a clinical study patient administered a medicinal product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the Investigator to document all AEs that occur during the study. Adverse events will be elicited by asking the patient a nonleading question, for example, "Have you experienced any new or changed symptoms since we last asked/since your last visit?" Adverse events should be reported on the appropriate page of the eCRF.

9.1.2. Assessment of Severity

Severity of AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. If there is a change in severity of an AE, it must be recorded as a separate event.

9.1.3. Assessment of Causality

Adverse events will be deemed related to study medication unless clearly unrelated to study medication.

The Investigator will assess the causal relationship between KZR-616 (or placebo) and AE. One of the following categories should be selected based on medical judgment, considering the definitions below and all contributing factors.

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

a Dechallenge: Upon discontinuation of a drug suspected of causing an AE, the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation, (positive dechallenge), or the symptoms continue despite withdrawal of the drug (negative dechallenge). Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

b Rechallenge: Upon re-administration of a drug suspected of causing an AE in a specific patient in the past, the AE recurs upon exposure (positive rechallenge), or the AE does not recur, (negative rechallenge).

9.1.4. Action Taken

The Investigator will describe the action taken with study drug in the appropriate section of the eCRF, as follows:

- None
- Study drug stopped
- Study drug temporarily interrupted
- Study drug dose reduced (only permissible with Medical Monitor confirmation in writing)
- Other, specify.

9.1.5. Follow-up on Adverse Events

Adverse events are intended to be collected according to the procedures outlined above from the time of informed consent and to continue for 30 days following the last dose, or the End of Study Visit, whichever occurs later.

All Investigators should follow up with patients with AEs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

9.1.6. Documentation and Reporting of Adverse Events

Adverse events (including SAEs) should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Diagnosed or description of the symptom if diagnosis is not established
- Classification of ‘serious’ or ‘not serious’

- Classification as AESI (yes or no)
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken with study drug
- Causal relationship with study drug
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported]).

9.2. Serious Adverse Events

9.2.1. Serious Adverse Event Definition

An SAE is any untoward medical occurrence or affect that, at any dose,

- Results in death
- Is life-threatening (an AE is life-threatening if the patient was at immediate risk of death from the event as it occurred, ie, it does not include a reaction that might have caused death if it had occurred in a more serious form)
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing nonworsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF)
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions)
- Results in a congenital anomaly/birth defect.

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the Investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the patient or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

9.2.2. Serious Adverse Event Reporting and Documentation Requirements

Any SAE must be reported (see Section 9.1.6) by the Investigator if it occurs from the time of signed consent through 30 days after the last dose of study drug (KZR-616 or placebo) if the patient is withdrawn from the study early or at the SFU, whether or not the SAE is considered to be related to the investigational product. After the reporting period, SAEs should be reported if the Investigator assesses the event to be related to study drug. An SAE report consists of the SAE form, provided separately, along with requested additional source documentation as considered necessary.

Serious adverse events that occur during the reporting period must be reported by the Investigator via entry of data into the eCRF within 24 hours from the point in time when the

Investigator becomes aware of the SAE. This will trigger an email notification to the Serious Adverse Event Reporting e-mail address (see below) that an SAE has occurred. If the EDC system is down or unavailable, a copy of the SAE form should be completed and emailed or faxed by the Investigator to the Serious Adverse Event Reporting e-mail address or dedicated fax (see below) within 24 hours from the point in time when the Investigator becomes aware of the SAE. Once the EDC system is available, the SAE should be entered in the eCRF. The Investigator should not wait for additional information to fully document the SAE before reporting it, though additional information may be requested. Requested source documentation (ie, relevant laboratory results, hospital case records, or autopsy reports) that is considered necessary should be provided separately to the Serious Adverse Event Reporting e-mail address using a cover sheet.

Contact Information:

Serious Adverse Event Reporting E-mail: [redacted]

Fax: [redacted]

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the Investigator at any time after cessation of study drug administration and linked by the Investigator to this study, should be reported to the study monitor.

The Sponsor and/or designee will promptly notify all relevant Investigators and the regulatory authorities of findings that could adversely affect the safety of patients, impact on the conduct of the study, or alter the DMC/IRB/IEC approval/favorable opinion of the study. In addition, the Sponsor or designee, will expedite the reporting of all adverse reactions that are both serious and unexpected to all concerned Investigators, to the DMC/IRBs/IECs where required, and to the regulatory authorities.

9.3. Pregnancy Reporting

Pregnancy occurring during a clinical investigation must be reported to safety within 24 hours and entered into the EDC. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse. Infants should be followed for a minimum of 8 weeks and all findings should be reported to the Sponsor. Study drug is to be discontinued immediately upon Investigator knowledge of the pregnancy and reported as per Section 8.2.

If the outcome of the pregnancy meets a criterion for immediate classification as an SAE—spontaneous abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly—the Investigator should repeat the procedures for expedited reporting of SAEs as outlined above.

Full details will be recorded on the withdrawal page of the eCRF, or an SAE report will be completed if the patient has completed the study.

9.4. New or Worsening Disease Manifestations

New or worsening manifestation(s) of DM or PM should not be recorded as AEs unless they are assessed as serious.

9.5. Adverse Events of Special Interest

Adverse events of special interest should be reported within 24 hours using the AE eCRF as per Section 9.1.6. No additional reporting will be required unless they become SAEs.

9.5.1. Systemic Injection Reactions

Systemic injection reactions have been observed with KZR-616 and other proteasome inhibitors and are considered AESIs.

Systemic injection reactions have included a number of signs and symptoms including fever, chills, myalgia, facial swelling or flushing, vomiting, weakness, hypotension, chest tightness, and shortness of breath, as well as abnormalities in laboratory values (eg, creatinine, transaminases). The relative roles of the immunoproteasome versus constitutive proteasomes to these specific events are not known. Therefore, terms such as eg, the NCI-CTCAE or Medical Dictionary for Regulatory Activities (MedDRA) terms of 'injection related reaction,' 'cytokine release syndrome,' 'systemic immune activation,' 'drug hypersensitivity,' 'hypersensitivity reaction,' or 'allergic reaction' should not be used. Instead, each sign or symptom should be recorded as an individual AE with its own level of severity, even if multiple signs or symptoms occur.

Management of systemic injection reactions is described in Section 6.1.3.

9.5.2. Thrombotic Microangiopathy

Cases of TMA, including TTP and HUS have been described with the nonspecific proteasome inhibitors, bortezomib, carfilzomib, and ixazomib, and are considered AESIs. One SAE of TMA has also been reported in a patient with SLE receiving KZR-616. While SLE itself is a risk factor for TMA, the contribution of KZR-616 to the event could not be ruled out. The clinical presentation of TMA typically includes fever, microangiopathic hemolytic anemia (with schistocytes on blood smear), thrombocytopenia, renal failure, purpura, and neurological manifestations. Patients should be monitored for signs and symptoms of TTP/HUS. If the diagnosis is suspected, interrupt treatment with study drug and evaluate (refer to Section 8.1.2). Missed doses should be addressed as per Section 6.1.4.2. If the diagnosis of TTP/HUS is excluded, study drug may be resumed. If the diagnosis is confirmed, study drug must be permanently discontinued (refer to Section 8.2).

9.6. Unexpected Adverse Reactions

9.6.1. Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable

product information (eg, IB for an unauthorized investigational medicinal product or prescribing information for an authorized product).

All suspected unexpected serious adverse reactions (SUSARs) will be subject to expedited reporting. The Sponsor or designee shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IRB/IEC within 7 days after knowledge by the Sponsor of such a case and that relevant follow-up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IRB/IEC within 15 days after knowledge by the Sponsor of such a case. All Investigators should follow up SUSARs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Post study SUSARs that occur after the patient has completed the clinical study must be reported by the Investigator to the Sponsor.

9.7. Data Monitoring Committee

To enhance the safety and integrity of the study data, a study-specific DMC will be established for interim safety monitoring. The specific responsibilities and composition of the DMC are outlined in a separate DMC Charter. In addition, the details of outputs provided for the meetings will be referenced in the separate document.

10. STATISTICAL ANALYSES

A detailed Statistical Analysis Plan (SAP) will be prepared for approval by the Sponsor prior to performing any unblinded analysis for presentation to personnel designated as being blinded to the randomization.

10.1. Sample Size Calculation

Prior summary statistics on change from Baseline in TIS score are not available. Hence, statistical power is quantified via standardized effect size (mean difference divided by pooled standard deviation [SD]). A sample size of 24 patients has 80% power to yield a statistically significant (α=0.05 2-sided) improvement from Baseline if the true underlying effect size is 0.6 (90% power if true effect size is 0.7). The minimum observed effect size that would yield statistical significance is 0.42. This level of statistical precision is thought to be adequate for this initial trial of KZR-616 in PM and DM.

10.2. Analysis Populations

The Safety Analysis Set consists of all patients who receive at least 1 dose of the study drug.

The Full Analysis Set (FAS) consists of all patients who receive at least 1 dose of the study drug and who have a Baseline and post-Baseline observation. This is the primary efficacy analysis set for the study.

The Per Protocol Analysis Set consists of all patients in the FAS, excluding those identified as having relevant protocol deviations.

The PK Analysis Set consists of all patients who received at least 1 dose of KZR-616 and for whom the PK data are considered sufficient. Since this is a Phase 2 trial, all analyses and summaries will be based on the actual test treatment the respective patients received.

10.3. Efficacy Analysis

The primary endpoint is mean change from start to end of KZR-616 treatment in TIS.[2]. For the continuous efficacy parameters, within-patient changes will be analyzed as follows:

- (1: primary) by comparing the Baseline and post Baseline observations within patients for the KZR-616 treatment periods combined, ie, W16 versus W0 for patients allocated to the randomized treatment sequence KZR-616 followed by placebo and W32 versus W16 for patients allocated to the randomized treatment sequence placebo followed by KZR-616, combined;
- (2: secondary) by comparing the change from Baseline in Treatment Period 1 between treatments, ie, change from W0 to W16 for patients allocated to the randomized treatment sequence KZR-616 followed by placebo versus change from W0 to W16 for patients allocated to the randomized treatment sequence placebo followed by KZR-616; and
- (3: exploratory) by comparing the last response on test treatment between treatments via a crossover design analysis, ie, W16 for patients allocated to the randomized treatment sequence KZR-616 followed by placebo and W32 for patients allocated to the

randomized treatment sequence placebo followed by KZR-616, combined, versus W16 for patients allocated to the randomized treatment sequence placebo followed by KZR-616 and W32 for patients allocated to the randomized treatment sequence KZR-616 followed by placebo, combined.

The rationale for this priority order is as follows. The usual crossover analysis for this design is prespecified as exploratory since it is unknown whether that analysis would be confounded by carryover effect. In order to maximize the precision for assessment of KZR-616 effect, it is assessed primarily via all patients' Baseline versus post-Baseline KZR-616 assessment and secondarily by the Treatment Period 1 between-treatment comparison. Summary statistics, including 95% confidence intervals, will be provided for each treatment for each of the 3 types of analysis. Within-patient changes will be analyzed via paired t-tests and corroborated by signed rank tests. Between-patient differences will be analyzed via analysis of covariance, with Baseline as a covariate. The crossover analysis will be via a mixed-model repeated-measures analysis. Normality will be assessed graphically and via the Shapiro-Wilk statistic. If substantial departure from normality is observed, transformations, eg, natural log and rank, will be explored. P values will be 2-sided with at the type 1 error level 0.05.

Binary endpoints will be summarized by counts and percent and 95% confidence intervals via Clopper-Pearson method. Additional analyses will be specified in the SAP.

10.4. Safety Analysis

The safety analysis set will be used for all presentations of safety endpoints. No statistical testing will be used to compare treatment groups for different safety endpoints. Safety data will be summarized descriptively for each test treatment. All AEs will be coded using the current version of the MedDRA. Treatment emergent AEs will be presented within summary presentations, by MedDRA system organ class, preferred term, and treatment group.

Additional analyses will be specified in the SAP.

10.5. Pharmacokinetic and Pharmacodynamic Analyses

Blood samples for assay of KZR-616 plasma concentrations will be collected periodically. The plasma KZR-616 and its metabolite KZR-59587 concentrations and PK parameters will be listed and summarized by appropriate summary statistics (eg, geometric means, natural log-scale SD, medians, quartiles). Further details of the analysis of PK data will be described in a PK analysis plan, if appropriate.

Whole blood samples for determination of proteasome activity will be collected periodically and processed to washed whole blood and isolated PBMC pellets. Chymotrypsin-like activity and proteasome subunit active site occupancy in each compartment will be assessed and presented as absolute and predose-normalized values. Individual proteasome activity and PBMC data will be listed for each patient and summarized by nominal sampling time point and treatment group with descriptive statistics (sample size [N], arithmetic mean, SD, median, minimum, and maximum). A summary of change from Baseline at each protocol specified time point by treatment group will also be presented. Individual and summary (by treatment group) parameter values over time will also be presented graphically.

Additional analyses will be specified in the SAP.

11. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

11.1. Compliance Statement

The Investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, International Conference on Harmonisation (ICH) guidelines for current GCP, and the applicable national and local laws and regulatory requirements.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/regional/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2. Institutional Review Board or Independent Ethics Committee

Before initiation of the study at each study center, the protocol, the informed consent form (ICF), other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate IRB/IEC. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the Investigator. Any necessary extensions or renewals of IRB/IEC approval must be obtained for changes to the study (ie, amendments to the protocol, the ICF, or other study documentation). The written approval of the IRB/IEC together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB/IEC as required. On completion of the study, the IRB/IEC will be notified that the study has ended.

11.3. Informed Consent and Human Patient Protection

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to current GCP.

Patients will provide written informed consent before any study-related procedures are performed.

The Investigator is responsible for ensuring that no patient undergoes any study-related examination or activity before that patient has given written informed consent to participate in the study.

The Investigator or designated personnel will inform the patient of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The patient should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the patient will be given ample time to consider the study. Patients will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the

Investigator's study file. A signed and dated copy of the patient ICF will be provided to the patient or their authorized representative.

It should be emphasized that the patient may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the patient is otherwise entitled. Patients who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the patient's willingness to continue participation in the study, a new ICF will be approved by the IRB(s)/IEC(s) (and regulatory authorities, if required). The study patients will be informed about this new information and reconsent will be obtained.

11.4. Direct Access to Source Data, Source Documents, and Study Reports

The Sponsor or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by the Sponsor, designee, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The Investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable review boards with direct access to the original source documents.

11.5. Data Collection and Handling

An EDC system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the EDC system.

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of patient personal information collected will be provided in a written document to the patient by the Sponsor or designee.

Remaining sample material will be stored off-site at [redacted], and will be accessible to only the Sponsor for up to 2 years after the completion of the study, or until the sample material is entirely used up.

11.6. Confidentiality

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IRB(s)/IEC(s) approving this research, and the Food and Drug Administration (FDA), as well as that of any other applicable agency(ies), will be granted direct access to the study patients' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the patients to the extent permitted by the law and regulations.

In any presentations of the results of this study or in publications, the patients' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act and national, regional and/or local laws and regulations on personal data protection.

11.7. Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between the Sponsor and designee.

11.8. Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

11.9. Monitoring

Data for each patient will be recorded on an eCRF. Data collection must be completed for each patient who signs an ICF.

In accordance with current GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The Investigator must permit the monitor, the IRB/IEC, the Sponsor's internal auditors, and representatives from regulatory authorities' direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

11.10. Data Management and Coding

The Sponsor or designee will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of Sponsor or designee.

Study centers will enter data directly into an EDC system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant.

Medical coding will use MedDRA for concomitant diseases and AEs and will use World Health Organization (WHO) drug classifications for medications.

Missing or inconsistent data will be queried in writing to the Investigator for clarification. Subsequent modifications to the database will be documented.

11.11. Reporting and Publication, Including Archiving

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (End of Study defined as the date of the last visit of the last patient), all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. This file will be available for inspection by the Sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the Sponsor to inform the study center when these documents no longer need to be retained. The Investigator must contact the Sponsor before destroying any study-related documentation. In addition, all patient medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The Sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the Investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

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13. APPENDICES

Appendix A: Recommended Cancer Screenings

Recommended Cancer Screenings (adapted from American Cancer Society guidelines, available at https://www.cancer.org/health-care-professionals/american-cancer-society-prevention-early-detection-guidelines.html (Last accessed 28 February 2019)

Breast Cancer

Ages 40-54: mammography annually

Age ≥55: mammography every 1 to 2 years

Enhanced detection methods should be considered (eg, magnetic resonance imaging, tomography, or ultrasound).

Colon and Rectal Cancer and Polyps

Ages 45-85: fecal immunochemical test or high sensitivity, guaiac-based fecal occult blood test annually or multitarget stool deoxyribonucleic acid (DNA) test every 3 years
AND
flexible sigmoidoscopy or computed tomography (CT) colonography every 5 years or colonoscopy every 10 years

Age ≥85: testing no longer recommended unless recent (less than 3 years) diagnosis of myositis; then the above should be performed

Cervical Cancer

For all women with a cervix (eg, no total hysterectomy), and regardless of human papilloma virus (HPV) vaccination status:

Ages 21-29: Papanicolaou (Pap) test every 3 years with HPV testing only if result abnormal

Ages 30-65: Pap test with HPV test every 5 years or Pap test only every 3 years

Ages ≥65: continued testing with Pap test with HPV test every 5 years or Pap test only every 3 years only if test in the prior 10 years has been abnormal or if recent diagnosis (less than 3 years) of myositis

Lung Cancer

Ages 55-74 and currently smoke or have quit smoking in the past 15 years, and have a 30 pack-year smoking history: low-dose CT scan yearly

Prostate Cancer

Ages ≥50: prostate-specific antigen blood test with rectal exam annually (ages ≥45 if African American or have a father or brother who had prostate cancer before age 65)

Appendix B: Potentially Clinically Significantly Abnormal Laboratory Values

Laboratory Parameter	Abnormal Value
Hematology	
Absolute neutrophil count	$<1.0 \times 10^9$/L
Hemoglobin	<8.0 g/dL or >16.5 g/dL
Leukocytes (total white blood cell)	$<1.5 \times 10^9$/L
Platelets	<50,000/mm^3 or >1,000,000/mm^3
Clinical Chemistry	
Bicarbonate (CO_2)	≤10 mEq/dL
Magnesium	<0.9 mg/dL or >3.0 mg/dL
Potassium	<3.0 mmol/L or >6.0 mmol/L
Sodium	<130 mmol/L or >155 mmol/L
Liver Function Tests	
Alanine aminotransferase	>3 × ULN (unless due to muscle origin)
Alkaline phosphatase	>5 × ULN
Aspartate aminotransferase	>3 × ULN (unless due to muscle origin)
Total bilirubin	>2 × ULN
Renal Function Tests	
Creatinine	>3.0 mg/dL
Other Chemistry	
Albumin	<2 g/dL
Calcium	<7.0 mg/dL or >12.5 mg/dL
Glucose	<40 mg/dL or >250 mg/dL

Abbreviations: dL=deciliter; L=liter; mg=milligram; mm^3=cubic millimeter; mmol=millimole; ULN=upper limit of the laboratory reference (normal) range.