# KZR-616-003E

# AN OPEN-LABEL EXTENSION TO THE 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 AND DERMATOMYOSITIS


| | |
|---|---|
| Clinicaltrials.gov Identifier | *NCT04628936* |
| Date of protocol: | *13 September 2021* |

# CLINICAL STUDY PROTOCOL

| | |
|---|---|
| **Protocol Title:** | An Open-label Extension to the 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-616-003E |
| **Investigational Medicinal Product:** | KZR-616 |
| **Indications:** | Polymyositis (PM) and Dermatomyositis (DM) |
| **Development Phase:** | 2 |
| **US IND Number:** | [redacted] |
| **EudraCT Number:** | 2020-004382-39 |
| **Sponsor:** | Kezar Life Sciences, Inc.<br>4000 Shoreline Court, Suite 300<br>South San Francisco, CA 94080<br>Telephone: 650-822-5600 |
| **Original Protocol Date:** | 17 September 2020 |
| **Amendment 1** | 13 September 2021 |



**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 SIGNATURES

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

*See electronic signature*

[redacted]
Kezar Life Sciences, Inc.

Date

*See electronic signature*

[redacted]
Kezar Life Sciences, Inc.

Date

*See electronic signature*

[redacted]
Kezar Life Sciences, Inc.

Date

# STUDY PERSONNEL

## Kezar/Clinical Study Lead

| | |
|---|---|
| Name | [redacted] |
| Title | Clinical Research Associate |
| Address | 4000 Shoreline Court, Suite 300, South San Francisco, CA 94080 |
| Telephone No. | [redacted] |

## Serious Adverse Event Reporting Contact

[redacted] **Safety Lead**

| | |
|---|---|
| Name | [redacted] |
| Title | Associate Project Manager |
| Telephone No. | [redacted] |

## Serious Adverse Event Reporting Details (to be used for submitting SAE forms):

[redacted]

Central Safety Fax: [redacted]

* = country exit code

# 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 Name:

Name of Institution/Site:

Signature: _____

Date: _____

# PROTOCOL SYNOPSIS

**NAME OF INVESTIGATIONAL PRODUCT:**
KZR-616

**NAME OF ACTIVE INGREDIENT:**
KZR-616

**CLINICAL CONDITION(S)/INDICATION(S)**

- Polymyositis (PM)
- Dermatomyositis (DM)

**PROTOCOL NUMBER:** KZR-616-003E

**PROTOCOL TITLE:**

An Open-label Extension to the 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:** An Open-label Extension to Study KZR-616-003

**STUDY PHASE:** Phase 2

**STUDY OBJECTIVES:**

**Efficacy**: To evaluate the long-term efficacy of KZR-616 in patients with PM or DM.

**Safety:** To evaluate the long-term safety and tolerability of KZR-616 in patients with PM or DM.

**STUDY DESIGN:**

This is an open-label study to evaluate the long-term efficacy and safety of KZR-616 in patients with active PM or DM who completed the double-blind treatment period of Study KZR-616-003, up to and including the Week 32 Visit, prior to the first dose of open-label KZR-616.

Patients will be evaluated for eligibility according to the entry criteria at, or within 8 weeks after, the Week 32 Visit (ie, the End of Treatment [EOT] Visit [Visit 34]) of Study KZR-616-003. Informed consent may be signed prior to the Week 32 Visit of Study KZR-616-003, and must be signed prior to any study-related activity in KZR-616-003E. For patients who are eligible and willing to enroll in the open-label extension study, the KZR-616-003 Week 32 Visit may also serve as Visit 1 (Day 1) for the open-label extension study. Assessments at this visit performed as part of Study KZR-616-003 will be used as baseline values for the extension study; therefore, these assessments must be performed prior to the first dose of open-label KZR-616.

All patients will receive a subcutaneous (SC) injection of 30 mg KZR-616 at Visit 1 (Day 1), followed by weekly SC injections of 45 mg KZR-616 up to a maximum of 96 weeks. Study drug administration will end for all patients in Study KZR-616-003E when the last patient enrolled has completed 48 weeks of dosing. Patients will have a final follow-up visit 12 weeks after their last dose of KZR-616 (End of Study [EOS] Visit), for a maximum potential length of participation of 108 weeks.

On-site study visits will occur at Weeks 12, 24, 36, 48, 60, 72, 84, and 96 (EOT Visit), and the EOS Visit. At these visits, safety and efficacy assessments will be performed according to the Schedule of Assessments (Table 1). While these visits are mandatory, in recognition of constraints imposed by the SARS-CoV-2 pandemic, sites may elect to use a combination of telemedicine (as permitted by their institutions) and/or home health providers, including at-home administration of KZR-616. All other study visits may occur either at the site or at patients' homes via home health providers (Table 2). If necessary, samples for clinical laboratory assessments will be collected by home health providers and sent to the laboratory. For at-home KZR-616 administration, doses may be administered by home health providers or, for patients deemed appropriate by the Investigator, by the patient or caregiver following appropriate instruction (see Section 5.4).

**ENDPOINTS:**

**Efficacy Endpoints**:

- Mean change in TIS over time for all patients, for patients with DM only, for patients with PM only, and for patients with a myositis-associated antibody or myositis-specific antibody at the Screening Visit of Study KZR-616-003
- Proportion of patients by TIS response (minimal response = TIS ≥ 20, moderate response = TIS ≥ 40, major response = TIS ≥ 60)
- Proportion of patients meeting International Myositis Assessment and Clinical Studies Group (IMACS) definition of improvement (DOI) over time for patients with baseline core set measures as ascertained at the beginning of KZR-616-003
- Mean change and mean percentage change over time in the IMACS individual core set activity measures (CSAMs) and core set damage measures (CSDMs), stratified by all patients and patients with myositis-associated or myositis-specific antibody at the Screening Visit of Study KZR-616-003
- Mean change over time in the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) for all patients with DM, and for patients with DM who have active skin manifestations at baseline of Study KZR-616-003E
- Mean change over time in the Myositis Damage Index (MDI)
- Mean change over time in muscle enzymes
- Change in proportion and dose of corticosteroid and non-corticosteroid immunosuppressants during Study KZR-616-003E for all patients, and for patients taking corticosteroids or non-corticosteroid immunosuppressants at baseline of Study KZR-616-003E
- Percentage of patients requiring additional medication for myositis treatment during Study KZR-616-003E
- Mean change over time in the EuroQol 5-dimension 5-level (EQ-5D-5L)
- Additional exploratory endpoints (Physician Global Impression of Change [MDGIC], Functional Index-2 [FI-2], Patient Global Impression of Change [PGIC], and Peak Pruritis Numerical Rating Scale [NRS]) will be assessed at multiple time points

**Safety Endpoints:**

- Incidence, nature, and severity of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of AEs leading to KZR-616 discontinuation
- Changes in standard laboratory parameters and vital signs

**Exploratory Endpoints:**

- Relationships between clinical efficacy, clinical safety, and various biomarker endpoints including changes in circulating cytokine and whole blood gene expression
- Corticosteroid-free TIS response by visit (corticosteroid-free is defined as corticosteroid fully tapered off for ≥ 12 weeks [3 months] prior to a visit; minimal response = TIS ≥ 20, moderate response = TIS ≥ 40, major response = TIS ≥ 60)

**INVESTIGATIONAL PRODUCT(S), DOSE, AND MODE OF ADMINISTRATION:**

**Active Product:**

**Investigational Medicinal Product:** KZR-616 is supplied as a refrigerated lyophilized drug product in single-use borosilicate glass vials packaged in multi-vial cartons. For patients eligible for at-home administration by the patient or caregiver, a premeasured, pre-filled syringe (PFS) containing sterile water for injection (WFI), a needleless vial adaptor system, and additional clinical supplies needed for reconstitution will also be provided.

**Dose and Dose Frequency:** KZR-616 will be administered by SC injection once weekly. The first injection will be a 30-mg dose, and subsequent injections will be a 45-mg dose.

**Control/Comparator:**

This is an open-label study with no control or comparator.

**PATIENT SELECTION:**

**Targeted Number of Patients:** Up to 24 patients

**Planned Number of Sites:** Up to 24 sites

**Inclusion Criteria:**

1. Must have successfully completed Study KZR-616-003 through Week 32, including the Week 32 Visit assessments, be willing and able to provide written informed consent prior to any study-related procedures, and be willing and able to comply with study requirements.
2. Women of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test prior to the first dose of KZR-616 in Study KZR-616-003E, and must agree to continue to use a highly effective method of birth control until completion of the study (or 30 days following the last dose of KZR-616 in case of early withdrawal). Women of childbearing potential are defined as 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 or local laboratory and if patient is not on supplementary hormonal therapy) or surgically sterile (ie, tubal ligation, hysterectomy, bilateral salpingoophorectomy).
3. Male patients must continue to use an effective contraception method (eg, condom with spermicide) for 1 week following their last dose of KZR-616 or be congenitally or surgically sterile (eg, vasectomy with documented confirmation of post-surgical aspermia).

**Exclusion Criteria:**

1. Have clinical evidence of significant unstable or uncontrolled diseases other than the disease under study (eg, cardiac [including congestive heart failure, hypertension, angina, or myocardial infarction], pulmonary [including pulmonary hypertension or interstitial lung disease], hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurological, or infectious disease, any ongoing SAE(s), or AE(s) $\geq$ Grade 3 by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]) that, in the opinion of the Investigator or Sponsor/designee, could confound the results of the study, put the patient at undue risk, or interfere with protocol adherence.
2. Has participated in any clinical study other than KZR-616-003 between the Week 32 Visit of Study KZR-616-003 and the first study visit of KZR-616-003E, if they are not on the same calendar day.
3. Are females who are breastfeeding or who plan to become pregnant during the study, or who are actively trying to conceive at the time of signing of the informed consent form (ICF).
4. Have hypersensitivity to KZR-616 or any of its excipients.

**STATISTICAL ANALYSIS:**

This study is descriptive in nature, and no formal hypothesis testing will be performed. No formal statistical sample size estimation has been performed, since the number of patients in this study is determined by the number of patients who completed Study KZR-616-003 and enrolled in this study.

**Analysis Sets:**

Full Analysis Set (FAS): The FAS for summaries of efficacy endpoints will include all patients who receive KZR-616 in this study and have baseline and any post baseline data. All observed data will be included in the statistical summaries. No missing data will be imputed except as pre-defined in the statistical analysis plan (SAP).

Per Protocol (PP): A PP population may be used to analyze select efficacy endpoints, and will be based on KZR-616 exposure (time on treatment) and protocol deviations. The decision to summarize a PP population will be made prior to database lock.

Safety Population: The safety population will include all patients enrolled who received at least one dose of KZR-616, and will be the population used for the analysis of safety. Adverse event data will be coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA; Version 19.1 or later).

Further details of the statistical methodology, including methods for handling missing data and early withdrawals, will be provided in an SAP that will be finalized prior to database lock.

# TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

## LIST OF ABBREVIATIONS

| Abbreviation or Term | Definition |
|---|---|
| ACR | American College of Rheumatology |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| CD | Cluster of differentiation |
| CDASI | Cutaneous Dermatomyositis Disease Area and Severity Index |
| CFR | Code of Federal Regulations |
| CGI | Clinical Global Impressions scale |
| CIM | C-protein induced myositis |
| CK | Creatine kinase |
| C-L | Caspase-like |
| CT-L | Chymotrypsin-like |
| CRP | C-reactive protein |
| CSAM | Core set activity measures |
| CSDM | Core set damage measures |
| CYP | Cytochrome P450 |
| DDI | Drug-drug interaction |
| DM | Dermatomyositis |
| DMC | Data Monitoring Committee |
| DNA | Deoxyribonucleic acid |
| DOI | Definition of Improvement |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| ELISA | Enzyme-linked immunosorbent assay |
| EOS | End of Study |
| EOT | End of treatment |
| EQ-5D-5L | EuroQol 5-dimension 5-level |
| EQ-VAS | EuroQol visual analog scale |
| ETV | Early Termination Visit |
| EULAR | European League Against Rheumatism |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |

| Abbreviation or Term | Definition |
|---|---|
| FI-2 | Functional Index-2 |
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| HAQ-DI | Health Assessment Questionnaire-Disability Index |
| hCG | Beta-human chorionic gonadotropin |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| I/E | Inclusion/Exclusion |
| IEC | Independent Ethics Committee |
| IFU | Instructions for Use |
| IgG | Immunoglobulin G |
| IMACS | International Myositis Assessment and Clinical Studies Group |
| IV | Intravenous |
| IRB | Institutional Review Board |
| ISR | Injection site reaction |
| LDH | Lactate dehydrogenase |
| LMP | Low-molecular mass polypeptide |
| LN | Lupus nephritis |
| 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 |
| MITAX | Myositis Intention to Treat Activity Index |
| MMF | Mycophenolate mofetil |
| MMT-8 | Manual Muscle Testing-8 Muscle Groups |
| MYOACT | Myositis Disease Activity Assessment Visual Analogue Scales |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NRS | Numerical Rating Scale |
| PBMC | Peripheral blood mononuclear cell |
| PD | Pharmacodynamic |
| PFS | Pre-filled syringe |
| PGIC | Patient Global Impression of Change |

| Abbreviation or Term | Definition |
|---|---|
| P-gp | P-glycoprotein |
| PK | Pharmacokinetic |
| PM | Polymyositis |
| PP | Per protocol |
| PROM | Patient-reported outcome measure |
| PtGADA | Patient Global Assessments of Disease Activity |
| PtGADD | Patient Global Assessments of Disease Damage |
| RA | Rheumatoid arthritis |
| RNA | Ribonucleic acid |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SC | Subcutaneous |
| SD | Standard deviation |
| SLE | Systemic lupus erythematosus |
| STS | Sit-to-stand |
| SUSAR | Suspected unexpected serious adverse reaction |
| TEAE | Treatment-emergent adverse event |
| Th | T helper cell |
| T-L | Trypsin-like |
| TIS | Total Improvement Score |
| Treg | Regulatory T cell |
| US | United States |
| VAS | Visual analog scale |
| WFI | Water for injection |
| WHO | World Health Organization |
| WOCBP | Women of childbearing potential |

# 1. INTRODUCTION

Study KZR-616-003E is an open-label extension of the Phase 2 study KZR-616-003, which is a randomized, double-blind, placebo-controlled crossover study to evaluate the efficacy and safety of KZR-616 in the treatment of patients with active polymyositis (PM) or dermatomyositis (DM).

## 1.1. 26S Proteasome Background

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 (Ciechanover 2012; Coux 1996; Wilk 1983). Each proteasome contains a 20S core, containing 2 copies of 3 distinct proteolytic enzymes, and 2 regulatory caps forming a 26S complex.

The proteasome exists in 2 forms: the constitutive proteasome and the immunoproteasome. The constitutive proteasome is expressed ubiquitously throughout the body and is responsible for protein degradation in tissues such as the heart, kidney, and liver. In the constitutive proteasome, proteolytic activities are encoded in the β5, β1, and β2 subunits and are characterized based on substrate specificity as chymotrypsin-like (CT-L), caspase-like (C-L) and trypsin-like (T-L), respectively. The immunoproteasome is expressed primarily in hematopoietic cells (eg, lymphocytes and monocytes), and is induced in cytokine-exposed nonhematopoietic cells (Glynne 1991; Martinez 1991; Nandi 1996). In the immunoproteasome, low-molecular mass polypeptide (LMP) 7, LMP2, and multicatalytic endopeptidase complex-like 1 (MECL-1) replace the β5, β1, and β2 subunits of the constitutive proteasome, respectively. Low-molecular mass polypeptide 7 has a similar substrate preference as β5 and is thus referred to as the CT-L subunit of the immunoproteasome.

The proteasome has been validated as a therapeutic drug target through regulatory approval of 3 compounds, bortezomib (VELCADE®), carfilzomib (KYPROLIS®), and ixazomib (NINLARO®), for use in the treatment of the plasma cell neoplasm, multiple myeloma. These compounds all show equivalent potency for the β5 subunit of the constitutive proteasome and the LMP7 subunit of the immunoproteasome (Kirk 2012; Kisselev 2012). This dual-targeting nature is necessary for their ability to induce cytotoxicity in multiple myeloma cells and other cell types. Selective inhibitors of LMP7 or β5 alone have no cytotoxic potential (Parlati 2009).

## 1.2. Proteasome Inhibitors for the Treatment of Inflammatory Disorders

The proteasome has been posited as a target for drug development in chronic inflammatory conditions and autoimmune disorders (Elliott 2003). Bortezomib, a constitutive or dual-targeting proteasome inhibitor, blocks cytokine release from immune effector cells and has demonstrated anti-inflammatory activity in several animal models of autoimmune disorders including rheumatoid arthritis (RA) (Palombella 1998) and systemic lupus erythematosus (SLE) (Neubert 2008). More recently, bortezomib was shown to have rapid clinical activity in patients with refractory SLE and lupus nephritis (LN) who had failed standard immunosuppressive therapies (Alexander 2015; Zhang 2017; de Groot 2015). However, systemic toxicities associated with dual-targeting proteasome inhibition, such as anemia and thrombocytopenia, restrict chronic administration (Bross 2004). Further, bortezomib is associated with a

dose-limiting side effect of peripheral neuropathy, likely caused by off-target inhibition of the serine protease HtrA2 in neurons (Arastu-Kapur 2011). Peripheral neuropathy is not induced by peptide ketoepoxide proteasome inhibitors such as carfilzomib (Arastu-Kapur 2011; Dimopoulos 2016).

The discovery of PR-957 (now called ONX 0914), a selective immunoproteasome inhibitor, demonstrated that the immunomodulatory and anti-inflammatory effects of dual-targeting proteasome inhibitors are due to inhibition of immunoproteasome activity in immune effector cells and inflamed tissues (Ichikawa 2012; Muchamuel 2009). ONX 0914 is a tripeptide ketoepoxide analog of carfilzomib that selectively inhibits the immunoproteasome in vitro and upon administration to mice. ONX 0914 exposure inhibited cytokine production in immune effector cells, reduced the number and activity of inflammatory T cell subsets such as T helper (Th) cells 1 and Th17, increased the number of regulatory T cells (Treg), and blocked autoantibody formation (Ichikawa 2012; Muchamuel 2009; Kalim 2012). ONX 0914 was shown to be therapeutically active in mouse models of SLE, in which it demonstrated equivalent activity but better tolerability than bortezomib (Ichikawa 2012; Kalim 2012). In addition, treatment of mice with ONX 0914 did not reduce the number of splenic lymphocytes or impair viral clearance in multiple infection models (Muchamuel 2009; Mundt 2016).

## 1.3. KZR-616 Background

KZR-616 is a tripeptide ketoepoxide that is an analog of both ONX 0914 and the United States (US) Food and Drug Administration (FDA)-approved agent carfilzomib. KZR-616 was developed in a medicinal chemistry effort to optimize potency and selectivity for multiple immunoproteasome subunits. KZR-616 demonstrates potent and selective inhibition of the LMP7 subunit of the immunoproteasome and targets multiple subunits of the immunoproteasome at therapeutically relevant concentrations. KZR-616 has no apparent off-target activities, no significant signals in safety pharmacology studies, and no apparent genotoxic potential.

KZR-616 blocks cytokine production across multiple immune cell types, reduces the activity of inflammatory Th cell subsets, and blocks plasma cell formation and autoantibody production. In mouse models of SLE and LN, KZR-616 treatment improved renal function in diseased animals and dramatically reduced tissue damage and leukocyte infiltration in kidneys. In addition, combining KZR-616 with mycophenolate mofetil (MMF) improved the therapeutic response versus either treatment alone in the same mouse models. The pharmacokinetics (PK) and metabolic properties of KZR-616 in preclinical models indicate little risk for drug-drug interactions (DDIs) and are similar to carfilzomib, an agent which has been shown to have little to no DDI risk (Wang 2013). In both range-finding and Good Laboratory Practice (GLP)-compliant toxicity studies, KZR-616 was well tolerated at doses that resulted in selective and potent inhibition of the immunoproteasome.

The safety, PK, and proteasome inhibition level of KZR-616 has been studied in healthy volunteers in 2 Phase 1 trials, KZR-616-001 and KZR-616-004. Subcutaneous (SC) administration of KZR-616 was well tolerated at doses that resulted in potent and selective inhibition of the immunoproteasome, but not the constitutive proteasome. Adverse events (AEs) were generally mild and transient and were predominantly injection site reactions (ISRs) such as erythema, induration, and tenderness (pain). Treatment with KZR-616 for 4 weeks did not appear

to result in persistent laboratory abnormalities as commonly seen with the dual-targeting proteasome inhibitors (eg, thrombocytopenia, anemia, and neutropenia).

Subcutaneous administration of KZR-616 resulted in consistent, dose-proportional PK. At all dose levels tested, KZR-616 was rapidly absorbed and cleared with no accumulation following weekly repeat doses. Drug levels were below the limit of quantitation by 24 hours post dose. The pharmacology was consistent across subjects, with low inter-subject variability in both exposure and target inhibition, regardless of concomitant treatment with or without corticosteroids and antihistamines. Though KZR-616 is a weak time-dependent inhibitor of Cytochrome P450 (CYP) 3A4 and a substrate of P-glycoprotein (P-gp), the rapid clearance and extrahepatic metabolism of KZR-616 by epoxide hydrolases strongly suggest that there is minimal risk for a DDI.

Across a dose range from 7.5 to 75 mg, SC administration of KZR-616 resulted in selective and dose-dependent inhibition of peripheral blood mononuclear cell (PBMC) CT-L activity (predominantly immunoproteasome), with doses of ≥30 mg resulting in mean inhibition of PBMC CT-L activity >80% and mean inhibition of whole blood CT-L activity (predominantly constitutive proteasome) ≤36%. Data further showed that despite incomplete recovery of immunoproteasome activity on Day 7 (6 days after dosing), there was not an accumulation of proteasome inhibition. From a PK and pharmacodynamic (PD) perspective, weekly SC administration of KZR-616 appeared equivalent to serial episodic dosing.

## 1.4. Rationale for Use of KZR-616 in the Proposed Study Populations, and Rationale for the Study

Idiopathic inflammatory myopathies such as PM and DM are characterized by inflammatory infiltrates in the skeletal muscle. Innate and adaptive immune mechanisms (eg, macrophages, autoreactive lymphocytes, autoantibodies, pro-inflammatory cytokine production) and intrinsic defects in skeletal muscle contribute to muscle weakness and damage in myositis. For example, Treg are considered instrumental for healing via interactions with muscle stem cells, whereas accumulation of cluster of differentiation (CD)4+ and CD8+ T lymphocytes are associated with further immune-mediated injury, as occurs in inflammatory myositis and some muscular dystrophies (Sciorati 2016). The immunoproteasome has also been shown to be upregulated in the muscle of patients with PM and DM and the skin of patients with DM (Bhattarai 2016; Ghannan 2014). 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 creatine kinase (CK) and myoglobin levels (Egerer 2002).

In vitro, KZR-616 and other immunoproteasome inhibitors block cytokine production across multiple immune cell types, reduce the activity of inflammatory Th cell subsets, increase the number of Treg cells, and block plasma cell formation and autoantibody production (Ichikawa 2012; Kalim 2012; Muchamuel 2009). KZR-616 does not induce cytotoxicity in vitro, has demonstrated promising therapeutic activity in animal models of RA and SLE/LN. In particular, in a C-protein induced myositis (CIM) model, KZR-616 treatment improved grip strength in diseased mice, which correlated with reduced serum levels of CK and reduced tissue damage and lymphocytic infiltration of the triceps and gastrocnemius muscles. Of note, grip

strength in the diseased mice treated with KZR-616 was equivalent to age-matched control animals in which myositis had not been induced (data on file).

Because of the promising nonclinical characteristics of KZR-616, along with its favorable safety profile in healthy volunteers, 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, an unmet medical need remains for new therapies for the treatment of PM and DM.

This open-label study was designed to allow up to 96 weeks of additional treatment with KZR-616, which will allow for assessment of the durability of therapeutic response and evaluation of longer-term improvement in the symptoms of PM and DM.

## 1.5. Rationale for Study Endpoints

The Myositis Response Criteria are recommended for use as primary endpoints in myositis therapeutic trials. The criteria use core set activity measures (CSAMs) from the International Myositis Assessment and Clinical Studies Group (IMACS). By combining the absolute percentage change in these 6 core set measures (each with varying weights), a Total Improvement Score (TIS), ranging from 0 to 100, is obtained. The IMACS CSAMs consist of:

- Manual Muscle Testing-8 Muscle Groups (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, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)
- Myositis Disease Activity Assessment Tool (MDAAT, 2005 version)

In addition, IMACS has defined the following core set damage measures (CSDMs):

- Myositis Damage Index (MDI)
- Patient Global Assessment of Disease Damage (PtGADD)

Mean change from start to end of KZR-616 treatment was the primary efficacy endpoint for Study KZR-616-003, and secondary and exploratory endpoints utilized the CSAMs and CSDMs, along with other measures of function and outcomes. To determine long-term efficacy in the same patient population, many of the endpoints used in Study KZR-616-003 will also be used in this study with consideration for treatment periods (see Section 10).

## 1.6. Summary of Potential Risks and Benefits

KZR-616 is a selective and irreversible inhibitor of the immunoproteasome, a key intracellular function in immune effector cells. Selective inhibition of the immunoproteasome is

immunomodulatory rather than immunosuppressive in preclinical models. KZR-616 is demonstrated to have marked ability to block the inflammatory response in multiple mouse models of autoimmune disease, including but not limited to, models of RA, the progression of nephritis in 2 mouse models of SLE, and in the CIM mouse model of myositis.

KZR-616 is an investigational agent. To date, 2 studies in healthy volunteers using doses ranging from 7.5 to 75 mg KZR-616 weekly have been completed. In addition, a Phase 2 study in patients with SLE with or without LN (KZR-616-002) and a study of patients with PM or DM (KZR-616-003) are ongoing. Adverse events most often associated with KZR-616 to date have been ISRs that are transient, generally mild, and do not appear to increase in severity or frequency with repeat dosing. Tolerability of KZR-616 is improved with an initial 30 mg SC dose of KZR-616, followed by subsequent higher target doses of 45 or 60 mg. It is anticipated that participants in KZR-616-003E will have already demonstrated tolerability to KZR-616 following participation in KZR-616-003. Nonetheless, initial high doses of KZR-616 have been associated with at least one of the following signs/symptoms: hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors and/or chills.

Based on nonclinical studies with KZR-616, including a mouse model of myositis, the safety of KZR-616 at 45 mg in healthy volunteers, the safety of KZR-616 to date in 46 patients with SLE, and the potential benefit from anti-inflammatory activity induced by immunoproteasome inhibition, the overall positive benefit-risk balance of KZR-616 supports its continued development in patients with PM and DM.

For additional information, please refer to the current version of the KZR-616 Investigator's Brochure.

# 2. STUDY OBJECTIVES AND ENDPOINTS

## 2.1. Study Objectives

The efficacy objective is to evaluate the long-term efficacy of KZR-616 in patients with PM or DM.

The safety objective is to evaluate the long-term safety and tolerability of KZR-616 in patients with PM or DM.

## 2.2. Study Endpoints

### 2.2.1. Efficacy Endpoints

- Mean change in TIS over time for all patients, for patients with DM only, for patients with PM only, and for patients with a myositis-associated antibody or myositis-specific antibody at the Screening Visit of Study KZR-616-003
- Proportion of patients by TIS response (minimal response = TIS $\geq$ 20, moderate response = TIS $\geq$ 40, major response = TIS $\geq$ 60)
- Proportion of patients meeting IMACS definition of improvement (DOI) over time for patients with baseline core set measures as ascertained at the beginning of KZR-616-003
- Mean change and mean percentage change over time in the IMACS individual CSAMs and CSDMs, stratified by all patients and patients with myositis-associated or myositis-specific antibody at the Screening Visit of Study KZR-616-003
- Mean change over time in the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) for all patients with DM, and for patients with DM who have active skin manifestations at baseline of Study KZR-616-003E
- Mean change over time in the MDI
- Mean change over time in muscle enzymes
- Change in proportion and dose of corticosteroid and non-corticosteroid immunosuppressants during Study KZR-616-003E for all patients, and for patients taking corticosteroids or non-corticosteroid immunosuppressants at baseline of Study KZR-616-003E
- Percentage of patients requiring additional medication for myositis treatment during Study KZR-616-003E
- Mean change over time in the EuroQol 5-dimension 5-level (EQ-5D-5L)
- Additional exploratory endpoints (Physician Global Impression of Change [MDGIC], Functional Index-2 [FI-2], Patient Global Impression of Change [PGIC], and Peak Pruritis Numerical Rating Scale [NRS]) will be assessed at multiple time points

As KZR-616-003E is an open-label extension study, additional exploratory endpoints may be conducted, and will be described in the final statistical analysis plan (SAP). Efficacy endpoints may include treatment periods that include data from Study KZR-616-003 based on treatment sequence in that study. See Section 10 for additional details of statistical analyses.

All endpoints, except where noted, will include analyses of all patients, those with DM only, and those with PM only.

### 2.2.2. Safety Endpoints

- Incidence, nature, and severity of AEs and serious adverse events (SAEs)
- Incidence of AEs leading to KZR-616 discontinuation
- Changes in standard laboratory parameters and vital signs

### 2.2.3. Exploratory Endpoints

- Relationships between clinical efficacy, clinical safety, and various biomarker endpoints including changes in circulating cytokine and whole blood gene expression
- Corticosteroid-free TIS response by visit (corticosteroid-free is defined as corticosteroid fully tapered off for ≥ 12 weeks [3 months] prior to a visit; minimal response = TIS ≥ 20, moderate response = TIS ≥ 40, major response = TIS ≥ 60)

# 3. STUDY DESIGN

## 3.1. Type and Design of Study

This is an open-label study to evaluate the long-term efficacy and safety of KZR-616 in patients with active PM or DM who completed the double-blind treatment period of Study KZR-616-003, up to and including the Week 32 Visit, prior to the first dose of open-label KZR-616.

The study design schema is presented in Figure 1.

Patients will be evaluated for eligibility according to the entry criteria (see Section 4) at, or within 8 weeks after, the Week 32 Visit (ie, the End of Treatment [EOT] Visit [Visit 34]) of Study KZR-616-003. Informed consent may be signed prior to the Week 32 Visit of Study KZR-616-003, and must be signed prior to any study-related activity in KZR-616-003E. For patients who are eligible and willing to enroll in the open-label extension study, the KZR-616-003 Week 32 Visit may also serve as Visit 1 (Day 1) for the open-label extension study. Assessments at this visit performed as part of Study KZR-616-003 will be used as baseline values for the extension study; therefore, these assessments must be performed prior to the first dose of open-label KZR-616 (see Figure 1).

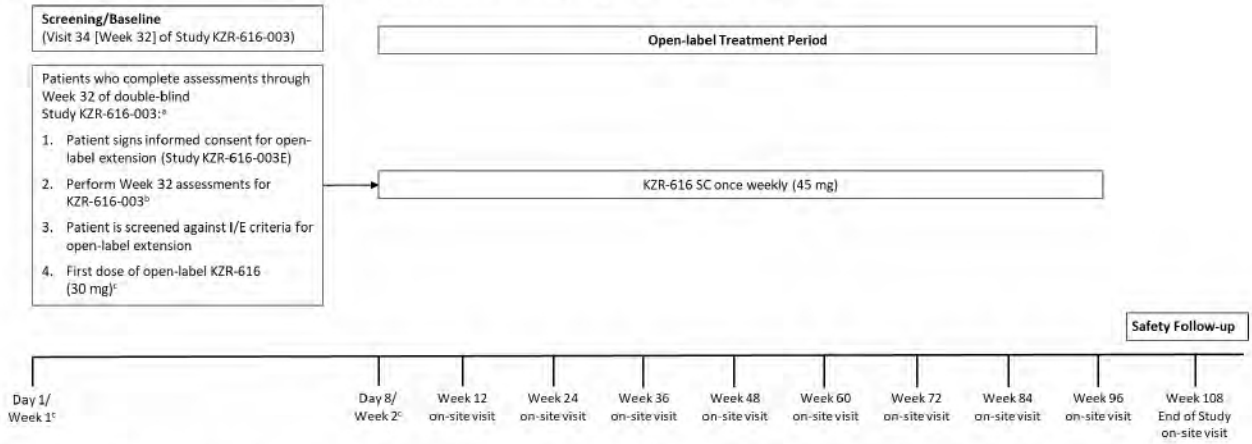
All patients will receive a SC injection of 30 mg KZR-616 at Visit 1 (Day 1), followed by weekly SC injections of 45 mg KZR-616 up to a maximum of 96 weeks. Study drug administration will end for all patients in Study KZR-616-003E when the last patient enrolled has completed 48 weeks of dosing. Patients will have a final follow-up visit 12 weeks after their last dose of KZR-616 (End of Study [EOS] Visit), for a maximum potential length of participation of 108 weeks.

On-site study visits will occur at Weeks 12, 24, 36, 48, 60, 72, 84, and 96 (EOT Visit), and the EOS Visit. At these visits, safety and efficacy assessments will be performed according to the Schedule of Assessments (Table 1). While these visits are mandatory, in recognition of constraints imposed by the SARS-CoV-2 pandemic, sites may elect to use a combination of telemedicine (as permitted by their institutions) and/or home health providers, including at-home administration of KZR-616. All other study visits may occur either at the site or at patients' homes via home health providers (Table 2). If necessary, samples for clinical laboratory assessments will be collected by home health providers and sent to the laboratory. For at-home KZR-616 administration, doses may be administered by home health providers or, for patients deemed appropriate by the Investigator, by the patient or caregiver following appropriate instruction (see Section 5.4).

Efficacy assessments will be performed for all patients, unless indicated otherwise; these assessments are discussed in Section 7.2.4.

Safety will be assessed throughout the study by monitoring of vital signs, clinical laboratory tests, and physical examinations, and by recording and analyzing all AEs and SAEs.

**Figure 1 Study KZR-616-003E Study Design Schema**




a Informed consent may be signed at any time relative to step 2; however, it must be signed prior to steps 3 and 4.
b Values used as baseline values for KZR-616-003E
c The first dose (Day 1) will be 30 mg KZR-616 SC; subsequent doses will be 45 mg KZR-616 SC.

Abbreviations: I/E=inclusion/exclusion; SC=subcutaneous

### 3.1.1. Study Design Rationale

This is an open-label, up to 108-week study to evaluate the long-term efficacy and safety of KZR-616 in patients with PM or DM who completed the double-blind treatment period of Study KZR-616-003 (ie, up to and including the Week 32 Visit prior to the first dose of open-label KZR-616).

## 3.2. Minimization of Bias

KZR-616-003E is an open-label study.

## 3.3. Number of Sites

Up to 24 sites are planned to participate in this study.

# 4. PATIENT SELECTION AND ENROLLMENT

## 4.1. Number of Patients

Up to 24 patients are planned for enrollment.

Patients will be evaluated for eligibility in the open-label extension study according to the eligibility criteria (see Section 4) at, or within 8 weeks after, the Week 32 Visit of Study KZR-616-003. The Investigator will ensure that the patient has provided written informed consent before administration of open-label KZR-616 as part of the open-label extension study KZR-616-003E.

Once informed consent is obtained, the evaluations may begin to assess study eligibility (inclusion/exclusion criteria). The patient identification number used in Study KZR-616-003 will continue to be used to identify the patient throughout study participation.

## 4.2. Inclusion Criteria

Only individuals who meet all of the following criteria may be enrolled in the study.

1. Must have successfully completed Study KZR-616-003 through Week 32, including the Week 32 Visit assessments, be willing and able to provide written informed consent prior to any study-related procedures, and be willing and able to comply with study requirements.
2. Women of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test prior to the first dose of KZR-616 in KZR-616-003E, and must agree to continue to use a highly effective method of birth control until completion of the study (or 30 days following the last dose of KZR-616 in case of early withdrawal). Women of childbearing potential are defined as 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 or local laboratory and if patient is not on supplementary hormonal therapy) or surgically sterile (ie, tubal ligation, hysterectomy, bilateral salpingoophorectomy). See Section 7.2.8 for detailed requirements for WOCBP.
3. Male patients must continue to use an effective contraception method (eg, condom with spermicide) for 1 week following their last dose of KZR-616 or be congenitally or surgically sterile (eg, vasectomy with documented confirmation of post-surgical aspermia).

## 4.3. Exclusion Criteria

Only individuals who do not meet any of the following criteria may be enrolled in the study.

1. Have clinical evidence of significant unstable or uncontrolled diseases other than the disease under study (eg, cardiac [including congestive heart failure, hypertension, angina,

or myocardial infarction], pulmonary [including pulmonary hypertension or interstitial lung disease], hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurological, or infectious disease, any ongoing SAE(s), or AE(s) ≥Grade 3 by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]) that, in the opinion of the Investigator or Sponsor/designee, could confound the results of the study, put the patient at undue risk, or interfere with protocol adherence.

2. Has participated in any clinical study other than KZR-616-003 between the Week 32 Visit of Study KZR-616-003 and the first study visit of KZR-616-003E, if they are not on the same calendar day.
3. Are females who are breastfeeding or who plan to become pregnant during the study, or who are actively trying to conceive at the time of signing of the informed consent form (ICF).
4. Have hypersensitivity to KZR-616 or any of its excipients.

# 5. STUDY TREATMENT INFORMATION

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

## 5.1. Physical Description of KZR-616

KZR-616 is supplied as a refrigerated lyophilized drug product in single use borosilicate glass vials. Each vial is reconstituted with sterile water for injection prior to administration.

## 5.2. Packaging and Labeling

The lyophilized drug product will be supplied in single-use vials packaged in multi-vial cartons. For patients eligible for at-home administration by the patient or caregiver, a premeasured, pre-filled syringe (PFS) containing sterile water for injection (WFI), a needleless vial adaptor system, and additional clinical supplies needed for reconstitution will also be provided. All KZR-616 vials and pre-filled syringes will be labeled according to appropriate regulatory guidelines. 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 KZR-616 Accountability

Refer to the Investigator's Brochure and Pharmacy Manual for storage conditions for KZR-616.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all KZR-616 received and any discrepancies are reported and resolved before use of the KZR-616.

Only participants enrolled in the study may receive KZR-616. All investigational products should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions. Access to investigational product must be limited to the Investigator and authorized site staff.

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).

Upon receipt of the KZR-616, the Investigator (or designee) will conduct an inventory of the supplies and verify that KZR-616 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.

It is the responsibility of the Study Monitor to ensure that the Investigator (or designee) has correctly documented the amount of the KZR-616 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 KZR-616 at the closeout visit to the study center. All discrepancies must be accounted for and documented.

## 5.4. At-Home Administration of KZR-616 by Patient or Caregiver

KZR-616 for at-home administration by the patient or caregiver may be dispensed as described in the Pharmacy Manual.

The site will assess patients' willingness and ability to undergo at-home administration of KZR-616. Patients considered for at-home administration must:

- be willing to self-administer (including administration by caregiver) KZR-616, and
- have been assessed as appropriate for at-home administration by the Investigator (eg, demonstrated tolerability to KZR-616, physically and mentally able).

Patients or caregivers may administer KZR-616 SC after appropriate instruction.

Patients and caregivers will be provided specific Instructions for Use (IFU) to ensure proper handling, storing, reconstitution, administration, and disposal of KZR-616. The IFU will be accompanied by an instructional video demonstrating each step involved.

Patients will document details of dates, times, and volumes of each administered dose in a patient diary. Patients will be instructed to return all used vials of drug product to the investigational site.

Patients who do not wish to administer KZR-616 at home will have the option of having KZR-616 administered at the site or by a home health provider.

# 6. DOSAGE AND KZR-616 ADMINISTRATION

## 6.1. KZR-616 Administration

KZR-616 will be administered by SC injection once weekly. The first injection will be a 30-mg dose, administered at the study site, and subsequent injections will be a 45-mg dose. Ideally, the first dose will be given on the same calendar day as the Week 32 Visit of Study KZR-616-003, but must be given no later than 8 weeks after the Week 32 Visit of Study KZR-616-003.

After the first dose, KZR-616 will be administered by study personnel at the site or by a home health provider at the patient's home. At-home administration of KZR-616 by the patient or caregiver may also be available as an option, as appropriate (see Section 5.4). Doses will be administered according to the Schedules of Assessments (Table 1 and Table 2).

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

### 6.1.1. Administration Site

Subcutaneous 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 anatomic site, if possible.

### 6.1.2. Suggested Measures to Improve KZR-616 Tolerance

Initial SC doses of 60 mg KZR-616 are associated with at least one of the following signs/symptoms: hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors and/or chills. These signs/symptoms typically begin within 8 to 24 hours after dosing, and usually resolve within 48 hours after dosing.

Although the numbers are small, the percentage of patient reporting treatment-emergent AEs (TEAEs) of the above signs/symptoms appears to be lower in patients who received KZR-616 as step-up doses and/or with pre-/post-dose prophylaxis, suggesting that these methods are effective at tolerizing patients to higher doses of KZR-616.

Step-up Dosing

It is unknown whether patients who start, stop, and then resume treatment with KZR-616 will experience tolerability issues (eg, patients randomized to Arm A of Study KZR-616-003). Thus, to maintain the blind for Study KZR-616-003, all patients enrolling in Study KZR-616-003E will receive an initial dose of 30 mg KZR-616, to be followed weekly by the target dose of 45 mg.

Pre/Post Dose Prophylaxis

Prophylactic measures may be considered if any of the signs and/or symptoms listed above develop, and may be used as treatment, either while the patient is at the study site or after leaving the study site. Measures that have been demonstrated to reduce the incidence and severity of infusion-related reactions with other proteasome inhibitors include the following:

- Fluid hydration, eg, 250-500 mL oral (or intravenous [IV] if necessary) of an electrolyte solution up to 48 hours prior to dosing, or up to 24 hours after dosing if symptoms are present

- Antiemetics, non-sedating antihistamines, and/or acetaminophen (if fever is present)

If additional guidance for improving initial tolerability symptoms is required, the Medical Monitor should be consulted. Home health providers do not provide or administer any of the fluids or medications listed above.

### 6.1.3. Dose Modification Guidelines

#### 6.1.3.1. Dose Reduction

Patients who experience a KZR-616-related AE at the 45 mg dose are permitted to undergo dose reduction to 30 mg KZR-616 for subsequent doses at the discretion of the Investigator, in consultation with the Medical Monitor. Written approval from the Medical Monitor should be obtained in advance of implementing dose reduction, when possible. After dose reduction is implemented, patients should remain on 30 mg KZR-616 for at least 2 doses, after which the dose may be re-escalated to 45 mg. If the 45-mg dose is not tolerated after re-escalation, the 30-mg dose may be continued for the remainder of the study, or re-escalation to 45 mg may be re-attempted after written approval from the Medical Monitor. Any dose modifications should be documented in the electronic case report form (eCRF) as per Section 9.1.4.

#### 6.1.3.2. Missed Doses

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

Patients who meet individual patient stopping rules (Section 8.1.2) may resume dosing after discussion between the Investigator and Medical Monitor. Upon resumption of dosing, subsequent doses should be timed according to the original dosing schedule based on Day 1. Missed doses should be documented in the eCRF as per Section 9.1.4. Patients who are discontinued for missed doses should have their discontinuation recorded in the eCRF based on the reason the doses were missed, eg, AE, protocol noncompliance (see Section 8.2).

If KZR-616 is permanently discontinued due to an AE, the planned assessments (see Schedule of Assessments in Table 1) should continue for the protocol-specified time period. If the patient cannot continue with the planned assessments, the Early Termination Visit (ETV) should be accomplished at a minimum (see Section 8.2).

## 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, physical therapy, surgery, or medication. A concomitant medication is any prescription or over-the-counter preparation, including vitamins and supplements. Concomitant medication use will be recorded 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.

### 6.2.1. Permitted Concomitant Medications

#### 6.2.1.1. Myositis Disease-related Concomitant Medications

Immunosuppressant and corticosteroid dose and frequency may be reduced at the Investigator's discretion (see Section 6.2.1.1.1 regarding optional tapering of oral corticosteroids). If a concomitant treatment for myositis is decreased or discontinued, the reason must be documented in the eCRF.

If an Investigator determines that a patient needs additional medication for treatment of myositis, the Medical Monitor should be informed; if possible, a discussion should occur between the Investigator and Medical Monitor prior to implementation of the additional medication. If a concomitant treatment for myositis is added, the reason must be documented in the eCRF.

##### *6.2.1.1.1. Optional Tapering of Oral Corticosteroids*

Tapers of concomitant oral corticosteroids are optional and may be initiated at the Investigator's discretion. Patients with well-controlled disease, in the Investigator's opinion, may be considered for tapers (eg, those with no, minimal, or stable active disease based on overall evaluation of activity such as weakness, myalgia, rash, CK and other assessments). There is no protocol-defined, mandatory tapering schedule. Possible schedules for gradual tapering of prednisone or prednisone equivalents in the setting of myositis include:

- Taper current dose by 5 mg/day every 12 weeks until 10 mg/day, then by 2.5 mg/day every 12 weeks until discontinued or worsening of disease requires an increase, in the Investigator's opinion.
- *For a slower taper from 5 mg/day until discontinuation or worsening of disease*: From 5 mg/day dose, taper by 1-2.5 mg/day every 12 weeks until discontinued or worsening of disease requires an increase, in the Investigator's opinion.

#### 6.2.1.2. Other Concomitant Therapies

Other concomitant therapies for comorbid conditions (eg, antihypertensives or lipid lowering agents) are permitted; these therapies should be recorded in the eCRF. Details regarding physical therapy, occupational therapy, or exercise should also be recorded in the eCRF.

#### 6.2.1.3. Potential Drug-Drug Interactions

KZR-616 should be administered at least 6 hours before, or 4 hours after, drugs that are known inhibitors of P-gp (eg, cyclosporine [not permitted during the study], atorvastatin, azithromycin, colchicine, omeprazole).

#### 6.2.1.4. Vaccinations

It is strongly recommended that patients be up to date on immunizations per current 2015 American College of Rheumatology (ACR) guidelines (Singh 2016). Vaccinations received at any time during the study should be recorded in the eCRF. Live vaccinations are not permitted during the study. If vaccination against herpes zoster is required during the study, Shingrix or

other non-live vaccine (if available) is preferred over live vaccines. Similarly, vaccination against influenza virus with inactivated vaccine is preferred.

### 6.2.2. Other Restrictions and Prohibitions

For patients requiring surgery, or for any planned surgery during the study, the Medical Monitor should be consulted to discuss KZR-616 dosing.

# 7. STUDY EVALUATIONS

## 7.1. Schedule of Assessments

The Schedule of Assessments is presented in Table 1, and the Schedule of KZR-616 Administration (with vital signs and pregnancy testing) is presented in Table 2.

On-site study visits will occur at Weeks 12, 24, 36, 48, 60, 72, 84, and 96, and the EOS Visit. At these visits, safety and efficacy assessments will be performed and KZR-616 will be administered according to the Schedule of Assessments (Table 1). All other study visits may occur either at the site or at patients' homes via home health providers (Table 2).

### 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 other reasons, as warranted. During an unscheduled visit, information regarding concomitant medications and AEs (at a minimum) will be collected. Any of the other procedures listed for the Week 24 visit may also be performed at the Investigator's discretion.

### 7.1.2. Telehealth Visits

While the study visits in Table 1 are mandatory, in recognition of constraints imposed by the SARS-CoV-2 pandemic, sites may elect to use a combination of telemedicine (as permitted by their institutions) and/or home health providers to conduct these visits. All other visits, including weekly KZR-616 injections, may occur at the site or at patients' homes via home health providers.

For telehealth visits, a limited physical examination will be performed and the MMT-8 will not be assessed. All other assessments should be performed, if feasible. Samples for clinical laboratory assessments will be collected by home health providers and sent to the central laboratory.

Please refer to Sections 7.2.4, 7.2.6.1, 7.2.6.2, and 7.2.6.3 for additional information regarding assessments performed at telehealth visits.

**Table 1 Schedule of Assessments**

| **Study Period** | **Screening/ Baseline[a]** | **Open-Label Treatment** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **12** | **24** | **36** | **48** | **60** | **72** | **84** | **96/EOT /ETV** | **97/EOS** |
| **Start of Week** | **1** | **12** | **24** | **36** | **48** | **60** | **72** | **84** | **96** | **108** |
| **Day ± Window (Days)** | **1** | **78±14** | **162±14** | **246±14** | **330±14** | **414±14** | **498±14** | **582±14** | **666±14** | **750±14** |
| Informed consent[a] | X | | | | | | | | | |
| Informed consent for genotyping[b] | X | | | | | | | | | |
| Inclusion/exclusion criteria[c] | X | | | | | | | | | |
| Demographic data[d] | X | | | | | | | | | |
| Medical history (including procedures, prior therapy, social history) [d] | X | | | | | | | | | |
| Concomitant therapy | X | ← | | | | | | | | → |
| Pregnancy test[e] | X[f] | X | X | X | X | X | X | X | X | X |
| Physical examination | X[f] | X | X | X | X | X | X | X | X | X |
| Vital signs[g] | X[f] | X | X | X | X | X | X | X | X | X |
| Weight | X[f] | | X | | X | | X | | X | X |
| 12-lead ECG[h] | X[f] | | | | | | | | | |
| MMT-8[i] | X[f] | X | X | X | X | X | X | X | X | X |
| MDAAT, MDGIC[i] | X[f] | X | X | X | X | X | X | X | X | X |
| FI-2 (dominant side only)[i] | X[f] | | X | | X | | X | | X | X |
| Sit-to-stand test [i] | | X | X | X | X | X | X | X | X | X |
| MDI[i] | | | | | X | | | | X | |
| CDASI[i,j] | X[f] | X | X | X | X | X | X | X | X | X |
| PtGADA, HAQ-DI, PGIC[k] | X[f] | X | X | X | X | X | X | X | X | X |
| EQ-5D-5L[k] | X[f] | X | X | X | X | X | X | X | X | X |
| PtGADD[k] | X[f] | X | X | X | X | X | X | X | X | X |
| Peak Pruritus NRS[j,k] | X[f] | X | X | X | X | X | X | X | X | X |

| Study Period | Screening/ Baseline[a] | Open-Label Treatment | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **12** | **24** | **36** | **48** | **60** | **72** | **84** | **96/EOT /ETV** | **97/EOS** |
| **Start of Week** | **1** | **12** | **24** | **36** | **48** | **60** | **72** | **84** | **96** | **108** |
| **Day ± Window (Days)** | **1** | **78±14** | **162±14** | **246±14** | **330±14** | **414±14** | **498±14** | **582±14** | **666±14** | **750±14** |
| Hematology, chemistry, CRP, and aldolase[l] | X[f] | X | X | X | X | X | X | X | X | X |
| Total IgG | | | X | | | | | | X[m] | X |
| Cytokines/proteomics[n] | X[f] | X | X | X | X | X | X | X | X | X |
| Gene expression (RNA)[o] | X[f] | X | X | X | X | X | X | X | X | X |
| KZR-616 administration[p] | X[q] | X | X | X | X | X | X | X | X[r] | |
| Adverse events | ← | | | | | | | | | → |

Abbreviations: CDASI=Cutaneous Dermatomyositis Disease Area and Severity Index; CRP=C-reactive protein; DM=dermatomyositis; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=End of Study; EOT=End of Treatment; EQ-5D-5L=EuroQoL 5-dimension 5-level; ETV=Early Termination Visit; FI-2=Functional Index-2; HAQ-DI=Health Assessment Questionnaire-Disability Index; hCG=beta-human chorionic gonadotropin; IgG=immunoglobulin G; MDAAT=Myositis Disease Activity Assessment Tool; MDI=Myositis Damage Index; MDGIC=Physician Global Impression of Change; MMT-8=Manual Muscle Testing-8 Muscle Groups; NRS=numerical rating scale; PD=pharmacodynamics; PROM=patient-reported outcome measure; PtGADA=Patient Global Assessment of Disease Activity; PtGADD=Patient Global Assessment of Disease Damage; PGIC=Patient Global Impression of Change; RNA=ribonucleic acid

a Patients will be evaluated for eligibility at, or within 8 weeks after, the Week 32 Visit of Study KZR-616-003. Informed consent must be signed prior to any study-related activity in KZR-616-003E. The KZR-616-003 Week 32 Visit may also serve as Visit 1 (Day 1) for the open-label extension study. Assessments at this visit performed as part of Study KZR-616-003 will be used as baseline values for the extension study; therefore, these assessments must be performed prior to the first dose of open-label KZR-616.

b Patients who provide additional informed consent will undergo blood sampling for genetic analysis.

c Eligibility criteria for this study should be assessed only after the Week 32 assessments for Study KZR-616-003 have been completed and informed consent for Study KZR-616-003E has been signed. All data except central laboratory results from samples drawn at that visit should be used to confirm patient eligibility.

d Data from Study KZR-616-003 will be used.

e Women of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum hCG test.

f Assessments done as part of the Week 32 Visit of Study KZR-616-003.

g Vital signs will be collected prior to dosing. Blood pressure and pulse rate should be collected after the patient has been resting for at least 5 minutes in the seated position. If the blood pressure is elevated on the first measurement at Screening/Baseline, it should be repeated after at least an additional 5 minutes of rest. It is recommended that blood pressure be measured using the same arm at each assessment.

h 12-lead ECG should be performed after the patient has been resting for at least 5 minutes in the supine position.

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

j Should be performed only in patients with DM.

k It is recommended that PROMs are completed first at each visit where performed (ie, prior to any other procedures or assessments other than signing of informed consent).

l See Section 7.2.6.4 for assessments.

m Only for the ETV.

n Blood sampling for cytokines and proteomics will be performed prior to dosing.

o Samples will be collected prior to dosing in patients who have provided the proper informed consent for genetic analyses.

p Patients will receive study drug weekly according to Table 1 and Table 2. At-home administration by the patient or caregiver may be an option for patients deemed appropriate by the Investigator (see Section 5.4). Home health providers will be arranged for patients who choose not to return to the site or administer study drug at home.

q The Week 32 assessments from Study KZR-616-003 must be performed, and informed consent for this open-label extension study signed prior to the first dose of open-label KZR-616.

r Does not apply to the ETV.

**Table 2 Schedule of KZR-616 Administration and Assessments**

| Visit No. | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|
| Start of Week | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| Day ± Window (Days) | 8±1 | 15±1 | 22±1 | 29±1 | 36±1 | 43±1 | 50±1 | 57±1 | 64±1 | 71±1 |
| Vital signs[a] | | | X | | | | X | | | |
| Urine pregnancy testing[b] | | | X | | | | X | | | |
| KZR-616 administration | X | X | X | X | X | X | X | X | X | X |

| Visit No. | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Start of Week | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 |
| Day ± Window (Days) | 85±1 | 92±1 | 99±1 | 106±1 | 113±1 | 120±1 | 127±1 | 134±1 | 141±1 | 148±1 | 155±1 |
| Vital signs[a] | | | | X | | | | X | | | |
| Urine pregnancy testing[b] | | | | X | | | | X | | | |
| KZR-616 administration | X | X | X | X | X | X | X | X | X | X | X |

| Visit No. | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Start of Week | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 |
| Day ± Window (Days) | 169±1 | 176±1 | 183±1 | 190±1 | 197±1 | 204±1 | 211±1 | 218±1 | 225±1 | 232±1 | 239±1 |
| Vital signs[a] | | | | X | | | | X | | | |
| Urine pregnancy testing[b] | | | | X | | | | X | | | |
| KZR-616 administration | X | X | X | X | X | X | X | X | X | X | X |

| Visit No. | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Start of Week | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 |
| Day ± Window (Days) | 253±1 | 260±1 | 267±1 | 274±1 | 281±1 | 288±1 | 295±1 | 302±1 | 309±1 | 316±1 | 323±1 |
| Vital signs[a] | | | | X | | | | X | | | |
| Urine pregnancy testing[b] | | | | X | | | | X | | | |
| KZR-616 administration | X | X | X | X | X | X | X | X | X | X | X |

| Visit No. | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Start of Week | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 |
| Day ± Window (Days) | 337±1 | 344±1 | 351±1 | 358±1 | 365±1 | 372±1 | 379±1 | 386±1 | 393±1 | 400±1 | 407±1 |
| Vital signs[a] | | | | X | | | | X | | | |
| Urine pregnancy testing[b] | | | | X | | | | X | | | |
| KZR-616 administration | X | X | X | X | X | X | X | X | X | X | X |

| Visit No. | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Start of Week | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 |
| Day ± Window (Days) | 421±1 | 428±1 | 435±1 | 442±1 | 449±1 | 456±1 | 463±1 | 470±1 | 477±1 | 484±1 | 491±1 |
| Vital signs[a] | | | | X | | | | X | | | |
| Urine pregnancy testing[b] | | | | X | | | | X | | | |
| KZR-616 administration | X | X | X | X | X | X | X | X | X | X | X |

| Visit No. | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Start of Week | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 |
| Day ± Window (Days) | 505±1 | 512±1 | 519±1 | 526±1 | 533±1 | 540±1 | 547±1 | 554±1 | 561±1 | 568±1 | 575±1 |
| Vital signs[a] | | | | X | | | | X | | | |
| Urine pregnancy testing[b] | | | | X | | | | X | | | |
| KZR-616 administration | X | X | X | X | X | X | X | X | X | X | X |

| Visit No. | 85 | 86 | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Start of Week | 85 | 86 | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 |
| Day ± Window (Days) | 589±1 | 596±1 | 603±1 | 610±1 | 617±1 | 624±1 | 631±1 | 638±1 | 645±1 | 652±1 | 659±1 |
| Vital signs[a] | | | | X | | | | X | | | |
| Urine pregnancy testing[b] | | | | X | | | | X | | | |
| KZR-616 administration | X | X | X | X | X | X | X | X | X | X | X |

Abbreviations: hCG=beta-human chorionic gonadotropin

NOTE: Patients will receive study drug weekly according to Table 1 and Table 2. At-home administration by the patient or caregiver may be an option for patients deemed appropriate by the Investigator (see Section 5.4). Home health providers will be arranged for patients who choose not to return to the site or administer study drug at home.

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

b Women of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum hCG test.

## 7.2. Study Procedures and Assessments

All patients must be provided a consent form describing the study with sufficient information for them to make an informed decision regarding their participation as per Section 11.3. Informed consent must be signed prior to any procedures for the open-label extension. All study procedures and assessments should be performed according to the schedules presented in Table 1 and Table 2.

If a patient is not able to come to the study site for an on-site visit as per the Schedule of Assessments (Table 1), a telehealth visit should occur. Please refer to Sections 7.2.4, 7.2.6.1, 7.2.6.2, and 7.2.6.3 for additional information regarding assessments performed at telehealth visits.

### 7.2.1. Demographic Data

Demographic data collected in KZR-616-003 will be used for this study.

### 7.2.2. Polymyositis/Dermatomyositis Classification

Patient classification of PM or DM based on the 2017 ACR/European League Against Rheumatism (EULAR) classification criteria (Lundberg 2016) from KZR-616-003 will be used for this study.

### 7.2.3. Medical History

Medical history data collected in KZR-616-003 will be used for this study, with the potential to update.

### 7.2.4. Efficacy Assessments

Efficacy assessments will be performed for all patients, unless indicated otherwise, at the visits shown in the Schedule of Assessments (Table 1). 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. All personnel performing the assessments must be qualified to perform them.

Websites for the individual assessments (where available) are provided in Section 13.2 (Appendix B).

#### 7.2.4.1. Total Improvement Score (TIS)

The TIS uses 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. Thresholds of improvement have been set for minimal, moderate, and major response. The TIS is the primary outcome measure for this study, and will not be calculated by sites.

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

This 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 (Rider 2010; Rider 2011).

#### 7.2.4.3. Myositis Disease Activity Assessment Tool (MDAAT)

This 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, (Whiting-O'Keefe 1999) 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 (Hay 1993). 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) (Rider 2011; Sultan 2008).

#### 7.2.4.4. Physician Global Assessment of Disease Activity (MDGA)

This 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 (Rider 2011).

#### 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 (Guy 1976).

#### 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 on just the dominant side, which takes approximately 21 minutes. (Alexanderson 2006; Rider 2011)

#### 7.2.4.7. Functional Assessment: Sit-to-Stand Test (STS)

The STS test 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 (Agarwal 2006). The STS test will be used as a functional assessment for this study.

#### 7.2.4.8. Myositis Damage Index (MDI)

The MDI is a tool that 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 (Rider 2011; Sultan 2011).

#### 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 (Rider 2011; Yassaee 2010).

### 7.2.5. Patient Reported Outcome Measures

The patient-reported outcome measures (PROMs) outlined in the sections that follow will be assessed in this study. For visits at which PROMs are performed, it is recommended that they be completed prior to any other assessments or procedures. All PROMs will be completed by the patient or a designee on a tablet, mobile phone, or other electronic device, with the exception of the EQ-5D-5L, which is a paper-based assessment.

Websites for the individual assessments (where available) are provided in Section 13.2 (Appendix B).

#### 7.2.5.1. Patient Global Assessment of Disease Activity (PtGADA)

The PtGADA is a tool that measures the global evaluation of the patient's overall disease activity at the time of assessment using a 10 cm VAS (Rider 2011).

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

The HAQ-DI is a tool to assess physical function in myositis (Rider 2011).

#### 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 (Guy 1976).

#### 7.2.5.4. EuroQoL 5-dimension 5-level (EQ-5D-5L)

EQ-5D-5L 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-5L consists of a descriptive system and the EuroQol visual analog scale (EQ-VAS).

The descriptive system comprises 5 levels of severity for each of 5 dimensions (ie, 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 converted to a single summary index number (utility) reflecting preferability compared to other health profiles.

#### 7.2.5.5. Patient Global Assessment of Disease Damage (PtGADD)

The PtGADD is a tool that measures the global evaluation of the patient's overall disease damage at the time of assessment using a 10 cm VAS.

#### 7.2.5.6. Peak Pruritus Numerical Rating Scale (NRS)

In a study of patients with DM, 50% reported moderate-to-severe itch, which was correlated with increased cutaneous severity (Kim 2018). The Peak Pruritus NRS, used to evaluate itch in atopic dermatitis, will be utilized to evaluate the severity of itch in patients with DM. The Peak Pruritus NRS ranges from 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.

### 7.2.6. Safety Assessments

Safety will be assessed throughout the study by monitoring of vital signs, physical examinations, and laboratory tests; and by recording and analyzing all AEs and SAEs.

#### 7.2.6.1. Vital Sign Measurements

Blood pressure, pulse rate, and temperature will be measured at the visits shown in the Schedules of Assessments (Table 1 and Table 2). 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 at least 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.

#### 7.2.6.2. Weight

When possible, body weight will be recorded at the on-site visits shown in the Schedule of Assessments (Table 1). Body weight, with the patient wearing light clothing and the shoes and jacket or coat removed, will be measured and recorded in kilograms.

For telehealth visits, weight will not be measured; a weight from any source other than the study site should not be recorded.

#### 7.2.6.3. Physical Examination

Complete physical examinations will be performed at the on-site visits specified on the Schedule of Assessments (Table 1). A complete physical examination should include assessments of at least the following systems: general appearance, head, ears, eyes, nose and throat, neck, dermatological, respiratory, cardiovascular, abdomen, extremities, neurological, musculoskeletal.

At other visits (including other on-site visits and unscheduled visits), a limited physical examination may 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 9.2.1.

Limited physical examinations will be performed at telehealth visits.

#### 7.2.6.4. Clinical Laboratory Assessments

Clinical laboratory tests for safety, including hematology, clinical chemistry, immunoglobulins, and clinical laboratory assessments for efficacy measures will be performed at a central laboratory at the visits shown on the Schedules of Assessment (Table 1).

Hematology: complete blood count with differential.

Clinical chemistry: chemistry panel including electrolytes, AST, ALT, and total bilirubin; aldolase, LDH, CK, and C-reactive protein (CRP).

Additional blood will be sent for biomarker studies as per Section 7.2.7.

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. Urine pregnancy tests will be performed locally.

Unless otherwise noted, when scheduled simultaneously with a dosing visit, samples for laboratory evaluations should be collected prior to administration of KZR-616.

Clinical laboratory results the Investigator deems clinically significantly abnormal should be repeated within 48 to 72 hours from when the result became available, when possible.

#### 7.2.6.5. Muscle Enzymes

Muscle enzymes (aldolase, ALT, AST, CK, and LDH) will be measured as per Section 7.2.6.4.

### 7.2.7. Exploratory Biomarkers

Additional blood and serum will be sent for biomarker studies. Detailed instructions for sample collection, processing, storage and shipment will be provided in the Laboratory Manual.

#### 7.2.7.1. Cytokines and Proteomics

Blood samples will be collected at the times shown in the Schedule of Assessments (Table 1) for the measurement of cytokines by enzyme-linked immunosorbent assay (ELISA). Additional information regarding sample collection and handling are outlined in the Laboratory Manual.

#### 7.2.7.2. Gene Expression

Gene expression (ribonucleic acid [RNA]) profiling may be assessed in blood samples. A whole blood sample will be collected for gene expression analysis for storage and analysis at a later date as specified in the Schedule of Assessments (Table 1) 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.

### 7.2.8. Contraception Requirements and Pregnancy Testing

Women of childbearing potential must have a negative urine pregnancy test before doses of KZR-616 outlined in Table 1 and Table 2, and must agree to use highly effective and medically acceptable methods of contraception to prevent pregnancy during the study and for 4 weeks after administration of the last dose of KZR-616. For the purposes of this study, WOCBP are defined as 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 FSH level in the postmenopausal range, as documented historically or measured by the central or local laboratory and if patient is not on supplementary hormonal therapy) or surgically sterile (ie, tubal ligation, hysterectomy, bilateral salpingoophorectomy).

Highly effective contraception is defined as the use of an intrauterine device or hormonal contraceptives (eg, implant or oral) or having a vasectomized partner. In regions where it is considered highly effective contraception, 2 barrier methods (eg, female diaphragm and male condom OR 1 barrier method with spermicide) may be used.

If using a hormonal form of contraception, use must have been stable for at least 4 weeks prior to the Week 1 Day 1 Visit, and if using concomitant mycophenolate, the patient must use another highly effective nonhormonal form of 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.

For WOCBP, urine pregnancy testing will be performed at the time points shown in Table 1 and Table 2. KZR-616 should not be administered prior to confirmation of a negative test at visits at which pregnancy tests are performed. Positive urine pregnancy tests should be confirmed by a serum pregnancy test.

Samples for FSH testing may be collected at any time during the study to confirm postmenopausal status in female patients whose childbearing potential status has changed since the Screening Visit of Study KZR-616-003. Only after confirmation of postmenopausal status is pregnancy testing not required.

Male patients must continue to use an effective contraception method (eg, condom with spermicide) for 1 week following the last dose of KZR-616 or be congenitally or surgically sterile (eg, vasectomy with documented confirmation of post-surgical aspermia). The decrease in male contraception use from 12 weeks in prior KZR-616 protocols to 1 week in Study KZR-616-003E is supported by the short half-life of KZR-616 (<2 hours), full recovery of immunoproteasome inhibition within 3 days of dosing, lack of mutagenic potential as determined in vitro and in vivo nonclinical studies, and lack of reproductive organ findings in the 6- and 9-month rodent and monkey repeat-dose toxicity studies. Additionally, no teratogenic effects were found in the definitive embryofetal toxicity studies in rats and rabbits. As per International Council for Harmonisation (ICH) M3 guidance, lack of reproductive and teratogenic findings in general toxicity and embryofetal toxicity studies is sufficient to support the treatment of male patients in Phase 1 and 2 trials prior to conducting fertility studies.

# 8. STUDY DISCONTINUATION

The Investigator must make every reasonable effort to keep each patient on study for the duration of the study, including through the safety follow-up, lost to follow-up, consent withdrawal, or end of study, whichever occurs first (see Section 8.2 for additional details).

## 8.1. Study and Individual Patient Stopping Rules

### 8.1.1. Study Stopping Rules

If any of the following events occur, administration of KZR-616 will be temporarily discontinued until a thorough review of the accumulated safety data is undertaken by the Data Monitoring Committee (DMC) (or appropriate alternative):

- Death in any patient, unless the cause of death is due to obvious alternative etiology
- Unexpected life-threatening event in any patient, unless due to obvious alternative etiology
- Three or more of the same Grade 3 or higher AE (judged by the Investigator, Medical Monitor, or Sponsor's representative), occurring in 20% or more individuals, unless due to obvious alternative etiology
- Any event of thrombotic microangiopathy, thrombocytopenic purpura, or hemolytic uremic syndrome
- Any event that, in the opinion of the Medical Monitor, DMC (or appropriate alternative), or Sponsor, contraindicates further dosing of additional patients

### 8.1.2. Individual Patient Stopping Rules

If any of the following events occur, administration of KZR-616 to an individual patient should be discontinued until a review of the accumulated safety data is undertaken by the DMC (or appropriate alternative):

- Any event that fulfills criteria for a study stopping rule, unless due to an obvious alternative etiology (see Section 8.1.1)
- Any event that, in the opinion of the Investigator, Medical Monitor, DMC (or appropriate alternative), or Sponsor, contraindicates further dosing

After such a review, resumption of dosing may be considered at the same or lower dose including consideration for any prophylactic interventions (eg, as per Section 6.1.2)

## 8.2. Early Withdrawal of Patients from the Study

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

- Patient request/informed consent withdrawn due to an AE
- Patient request/informed consent withdrawn for any reason other than an AE
- Patient becomes pregnant
- AE (whether or not related to KZR-616) that precludes further participation in the study, in the judgment of the Investigator and/or Sponsor
- Any event of thrombotic microangiopathy, thrombocytopenic purpura, or hemolytic uremic syndrome

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

- Protocol non-compliance, 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 not to continue participation in the study
- Administrative decision by the Investigator or Sponsor

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 withdrawing from study treatment will be encouraged to complete the ETV within 14 days and return for an EOS Visit approximately 12 weeks after receipt of their last dose of KZR-616 to complete the final evaluations according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for patients who complete the study.

## 8.3. Lost to Follow-Up

The Investigator must make reasonable efforts to contact patients who fail to return for scheduled visits so that they will not be declared "lost to follow-up." Patients will be considered "lost to follow-up" only after reasonable, documented attempts to reach the patient prove unsuccessful. These attempts include, but are not limited to, the following:

1. Attempt contact at all telephone numbers for the patient and his/her listed contacts (to be collected in the source documents at the patient's entry into the study), as applicable.
2. Contact the patient's primary care physician, referring specialist, or other healthcare professional, as applicable.
3. Send emails and texts, and certified letters through the postal service to all the patient's addresses and contacts, as applicable.

4. Review available medical records/notes for details of hospitalizations, clinic visits, or other procedures that may indicate the status of the patient, as applicable.
5. Perform an internet search for additional contact information, as applicable.
6. Check local, regional, and national public records to locate the patient or search for mortality status as allowed by law, as applicable.

The information and dates of attempted contact must be recorded in the patient's records and the patient's final status recorded in the appropriate eCRF. Once all attempts to contact the patient have been exhausted and documented, the Sponsor or Sponsor's designee should be contacted for additional guidance.

## 8.4. Early Termination Visit

If possible, the ETV should take place within 14 days after withdrawal. Procedures listed on the Schedule of Assessments (Table 1) should be performed at the ETV.

## 8.5. Termination or Suspension of the Study

The Sponsor has the right to terminate the study at any time in case of SAEs or circumstances concerning KZR-616 or the company, that makes further treatment of patients impossible. In this event, Investigators will be informed of the reason for study termination.

# 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.

It is the responsibility of the Investigator to document all AEs that occur during the study. AEs will be elicited by asking the patient a nonleading question such as, "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 the 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 KZR-616 unless clearly unrelated to KZR-616.

The Investigator will assess the causal relationship between KZR-616 and the AE. One of the categories in Table 3 should be selected based on medical judgment, considering the definitions and all contributing factors.

**Table 3 Causality Categories**

| | |
|---|---|
| Related | A clinical event, including laboratory test abnormality, that occurs in a plausible time relationship to treatment administration, and that 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 to treatment administration. May have negative dechallenge[a] and rechallenge[b] information. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals). |

Abbreviations: AE=adverse event

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 (eg, 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 with Regard to KZR-616

The Investigator will describe the action taken with KZR-616 in the appropriate section of the eCRF, as follows:

- None
- KZR-616 stopped
- KZR-616 temporarily interrupted
- KZR-616 dose reduced (with written confirmation from Medical Monitor)
- Other (specify)

### 9.1.5. Follow-up of Adverse Events

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

All Investigators should follow up patient 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.

- Diagnosis, or description of the symptoms if a diagnosis is not established
- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken with regard to KZR-616
- Outcome of the event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

## 9.2. Serious Adverse Events

### 9.2.1. Definition of a Serious Adverse Event

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 considered SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening 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 KZR-616.

### 9.2.2. Serious Adverse Event Reporting and Documentation Requirements

An 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 KZR-616, whether or not the SAE is considered to be related to KZR-616. After the reporting period, SAEs should be reported if the Investigator assesses the event to be related to KZR-616. 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 time the Investigator becomes aware of the SAE. This entry will trigger an email notification to the Serious Adverse Event Reporting e-mail address (see Study Personnel page) that an SAE has occurred. If the electronic data capture (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 Study Personnel page) within 24 hours from the time 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 (see Study Personnel page) using a cover sheet.

Instances of death, congenital abnormality, or an event 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 KZR-616 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 the conduct of the study, or alter the DMC (or appropriate alternative)/Institutional Review Board (IRB)/Independent Ethics Committee (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 (or appropriate alternative)/IRBs/IECs where required, and to relevant regulatory authorities.

For SAEs that have been reported in the KZR-616 development program, please refer to the most current KZR-616 Investigator's Brochure.

## 9.3. Pregnancy Reporting

Pregnancy occurring in female patients or female partners of male patients participating in the study or during a clinical investigation must be reported to the [redacted] (see Study Personnel page) within 24 hours and entered into the EDC. The outcome of a pregnancy should be followed up carefully, and any abnormal outcome for the mother or the child should be

reported. Infants should be followed for a minimum of 8 weeks, and all findings should be reported to the Sponsor. KZR-616 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 (ie, spontaneous abortion [for which any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for expedited reporting of SAEs as outlined in Section 9.2.2.

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 PM or DM should not be recorded as AEs unless they are assessed as serious.

## 9.5. Injection Site Reactions

In study participants who have received KZR-616 SC, ISRs, including bruising, discoloration, discomfort, erythema, induration, pain, pruritus and/or swelling, have been described in the majority of participants in KZR-616 studies to date; these events have been predominantly mild. No interventions have been formally studied to prevent or treat these reactions; however, local therapy such as topical antihistamines or corticosteroids may be helpful, and/or systemic antihistamines, anti-inflammatory drugs, and/or corticosteroids may be appropriate in more severe cases.

### 9.5.1. Adverse Events of Special Interest

An AE of special interest (AESI) is one that is of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a product or compound. A complex of tolerability symptoms (formerly referred to as systemic injection reaction; see Section 9.5.1.1) and thrombotic microangiopathy have been identified as AESIs, and should be reported within 24 hours using the AE eCRF.

#### 9.5.1.1. Tolerability Symptom Complex

Initial SC doses of 60 mg KZR-616 are associated with a complex of tolerability symptoms, with at least one of the following signs or symptoms: hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors, and/or chills. These symptoms typically begin within 8 to 24 hours after dosing, and usually resolve within 48 hours of dosing. These signs and symptoms can occur with any dose, though they are more likely to occur with initial doses of 60 mg or higher. When seen, they tend to be more common with the first dose than with subsequent doses.

The complex of tolerability symptoms seen with initial high doses of KZR-616 are similar to those seen with infusion reactions reported for carfilzomib (KYPROLIS 2018), as well as with systemic inflammatory response syndrome, a clinical syndrome that is a subset of cytokine

release syndrome manifested by at least 2 of the following findings: tachycardia (>90 beats per minute), leukocytosis (>12 × $10^9$/L or <4 × $10^9$/L, or >10% immature [band] forms), tachypnea (respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension [PaCO2] of less than 32 mmHg), and fever (temperature of more than 38°C [100.4°F] or less than 36°C [96.8°F]) (Bone 1992). The relative roles of the immunoproteasome versus constitutive proteasomes to these specific events are not known.

In reporting TEAEs related to KZR-616 tolerability, terms such as the NCI-CTCAE terms of 'infusion-related reaction,' 'cytokine release syndrome,' 'acute infusion reaction,' or 'allergic or hypersensitivity reaction' should not be used. Instead, each sign or symptom should be recorded as an individual TEAE. If multiple signs or symptoms occur with a given systemic injection-related event, each sign or symptom should be recorded separately with its own level of severity.

Management of these symptoms is described in Section 6.1.2.

#### 9.5.1.2. Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombocytopenic purpura and hemolytic uremic syndrome, have been described with the nonspecific proteasome inhibitors, bortezomib, carfilzomib, and ixazomib. The clinical presentation of thrombotic microangiopathy 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 thrombocytopenic purpura/hemolytic uremic syndrome. If the diagnosis is suspected, interrupt treatment with KZR-616 and evaluate (refer to Section 8.1.2). Missed doses should be addressed as per Section 6.1.3.2. If the diagnosis of thrombocytopenic purpura/hemolytic uremic syndrome is excluded, KZR-616 may be resumed. If the diagnosis is confirmed, KZR-616 must be permanently discontinued (refer to Section 8.2).

## 9.6. Unexpected Adverse Reactions

### 9.6.1. Definition of an Unexpected Adverse Reaction

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of KZR-616 at any dose that is not consistent with the applicable product information (eg, the Reference Safety information of the KZR-616 Investigator's Brochure).

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 bereported 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

A study-specific DMC or other appropriate review committee may be used to enhance the safety and integrity of the study data for interim safety monitoring. If such a committee is used, the specific responsibilities and composition will be outlined in a separate DMC Charter.

# 10. STATISTICAL ANALYSES

This study is descriptive in nature, and no formal hypothesis testing will be performed. No formal statistical sample size estimation has been performed, since the number of patients in this study is determined by the number of patients who completed Study KZR-616-003 and enrolled in this study. Descriptive statistics, including the numbers and percentages for categorical variables; and the numbers, means, standard deviations (SD), medians, minimums and maximums for continuous variables will be provided by treatment group, by indication (DM, PM), and overall.

The number and percentage of patients who experience TEAEs, SAEs/death, AEs leading to treatment/study discontinuation, and treatment modification/delay due to AE(s) will be summarized by treatment group and overall. The number and percentage of patients experiencing any TEAE(s), overall, and by system organ class (SOC) and preferred term and by grade will be tabulated.

Continuous measures in laboratory, vital sign, ECG, and efficacy data will be summarized descriptively (mean, median, SD, and minimum and maximum values) by treatment group and overall and will be summarized by protocol-specified time point along with a summary of change from baseline at each time point. Changes in physical examinations will be listed for each patient and described. In addition, 95% confidence intervals may be provided to describe some continuous efficacy data.

Patient listings will be provided to support these summaries.

PK analyses will include determination of plasma levels of KZR-616 including $C_{max}$, $T_{max}$, and AUC.

Full Analysis Set (FAS): The FAS for summaries of efficacy endpoints will include all patients who receive KZR-616 in this study and have baseline and any post-baseline data. All observed data will be included in the statistical summaries. No missing data will be imputed except as pre-defined in the SAP.

Per Protocol (PP): A PP population may be used to analyze select efficacy endpoints, and will be based on KZR-616 exposure (time on treatment) and protocol deviations. The decision to summarize a PP population will be made prior to database lock.

Safety Population: The safety population will include all patients enrolled who received at least one dose of KZR-616, and will be the population used for the analysis of safety. Adverse event data will be coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA; Version 19.1 or later).

Data will be summarized for the following groups of patients based on the sequence of treatments received in Study KZR-616-003:

Group 1: Arm A (KZR-616:Placebo) from Study KZR-616-003 beginning on Day 1 (first dose of KZR-616) through the end of Study KZR-616-003E

Group 2: Arm B (Placebo:KZR-616) from Study KZR-616-003 beginning on Week 16 (first dose of KZR-616) through the end of Study KZR-616-003E

Groups 1 and 2 combined: from the first dose of KZR-616 in KZR-616-003 through the end of KZR-616-003E

Group 3: Arm B2: Patients receiving KZR-616 from Weeks 16-32 in KZR-616-003 followed by KZR-616 in OLE throughout KZR-616-003E, to evaluate patients who continuously received KZR-616 from KZR-616-003 through KZR-616-003E

Groups 1 and 2 are being assessed for any differences due to the intervening placebo treatment period in Group 1. The rationale for combining Group 1 and Group 2 is to encompass all KZR-616 treatment, and the rationale for assessing Group 3 is to encompass all continuous KZR-616 treatment.

Further details of the statistical methodology, including methods for handling missing data and early withdrawals, will be provided in an SAP that will be finalized prior to database lock. As KZR-616-003E is an open-label extension study, endpoints in addition to those described in Section 2.2 may be conducted as described in the final 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, ICH guidelines for current Good Clinical Practice (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

Prior to initiation of the study at each study center, the protocol, 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, and before KZR-616 can be 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 documented in the study files.

The Investigator will promptly report any new information that may adversely affect the safety of the patients or the conduct of the study to the IRB/IEC. The Investigator will submit written summaries of the study status to the IRB/IEC as required, and will inform them when 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.

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 consent will be re-obtained.

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

The Sponsor or its representatives may periodically check a sample of 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 may 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 biological sample material will be stored off-site at Biostorage, 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, other authorized agents of the Sponsor and/or its designee, the IRB(s)/IEC(s) approving this study, the US FDA, and any other applicable agency(ies) will be granted direct access to the 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.

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 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. The Study Monitor will carry out source document verification in accordance with current GCP and ICH guidelines 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 into the EDC system by completing the eCRF via a secure internet connection. Data transcribed 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 (eSource concept). Any changes to the data entered into the EDC system will be recorded in the audit trail and will be compliant with FDA Code of Federal Regulations (CFR) 21 Part 11.

An essential element of the eSource concept is that the clinical assessment data and other source data is entered during the clinical visit in an eSource EDC system. When designing the system there are some fundamental aspects to be respected:

- The ability of the physician to record clinical information in the patient medical record should not be limited or constrained
- Information should be recorded in line with the current practice at the study site
- The integrity of the medical records should not be compromised
- The Sponsor should have access only to pseudonymized information mandated by the protocol

This guidance does not include direct data input from tablets, mobile phones, or other electronic devices.

Medical coding will use MedDRA for concomitant diseases and AEs, and will use the 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 after the discontinuation of clinical development of KZR-616. It is the Sponsor's responsibility 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.

# 12. REFERENCES

Agarwal S, Kiely PD. Two simple, reliable and valid tests of proximal muscle function, and their application to the management of idiopathic inflammatory myositis. Rheumatology (Oxford). 2006;45(7):874-9.

Alexander T, Sarfert R, Klotsche J, Kühl AA, Rubbert-Roth A, Lorenz HM, et al. The proteasome inhibitor bortezomib depletes plasma cells and ameliorates clinical manifestations of refractory systemic lupus erythematosus. Ann Rheum Dis. 2015;74(7):1474-8.

Alexanderson H, Broman L, Tollbäck A, Josefson A, Lundberg IE, Stenström CH. Functional Index-2: validity and reliability of a disease-specific measure of impairment in patients with polymyositis and dermatomyositis. Arthritis Rheum. 2006;55(1):114-22.

Arastu-Kapur S, Anderl JL, Kraus M, Parlati F, Shenk KD, Lee SJ, et al. Nonproteasomal targets of the proteasome inhibitors bortezomib and carfilzomib: a link to clinical adverse events. Clin Cancer Res. 2011;17(9):2734-43.

Bhattarai S, Ghannam K, Krause S, Benveniste O, Marg A, de Bruin G, et al. The immunoproteasomes are key to regulate myokines and MHC class I expression in idiopathic inflammatory myopathies. J Autoimmun. 2016;75:118-29.

Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101(6):1644-55.

Bross PF, Kane R, Farrell AT, Abraham S, Benson K, Brower ME, et al. Approval summary for bortezomib for injection in the treatment of multiple myeloma. Clin Cancer Res. 2004;10(12):3954-64.

Ciechanover A. Intracellular protein degradation: from a vague idea through the lysosome and ubiquitin-proteasome system and onto human diseases and drug targeting. Neurodegener Dis. 2012;10(1-4):7-22.

Coux O, Tanaka K, Goldberg AL. Structure and functions of the 20S and 26S proteasomes. Ann Rev Biochem. 1996;65(1):801-47.

de Groot KA, Tsang ASM, Niewerth D, Cloos J, Blank JL, Niessen HW, et al. Pharmacodynamic monitoring of (immuno)proteasome inhibition during bortezomib treatment of a critically ill patient with lupus nephritis and myocarditis. Lupus Sci Med. 2015;2(1):e000121.

Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hájek R, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016;17(1):27-38.

Egerer K, Kuckelkorn U, Rudolph PE, Rückert JC, Dörner T, Burmester GR, et al. Circulating proteasomes are markers of cell damage and immunologic activity in autoimmune diseases. J Rheumatol. 2002;29(10):2045-52.

Elliott PJ, Zollner TM, Boehncke WH. Proteasome inhibition: a new anti-inflammatory strategy. J Mol Med (Berl). 2003;81(4):235-45.

Ghannan K, Martinez-Gamboa L, Spengler L, Krause S, Smiljanovic B, Bonin M, et al. Upregulation of immunoproteasome subunits in myositis indicates active inflammation with involvement of antigen presenting cells, CD8 T-cells and IFNγ. PLoS One. 2014;9(8):e104048.

Glynne R, Powis SH, Beck S, Kelly A, Kerr LA, Trowsdale J. A proteasome-related gene between the two ABC transporter loci in the class II region of the human MHC. Nature. 1991;353(6342):357-60.

Guy W (ed). ECDEU assessment manual for psychopharmacology. Rockville, MD U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976.

Hay EM, Bacon PA, Gordon C, Isenberg DA, Maddison P, Snaith ML, et al. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. QJ Medicine. 1993;86:447-58.

Ichikawa HT, Conley T, Muchamuel T, Jiang J, Lee S, Owen T, et al. Beneficial effect of novel proteasome inhibitors in murine lupus via dual inhibition of type I interferon and autoantibody-secreting cells. Arthritis Rheum. 2012;64(2):493-503.

Kalim KW, Basler M, Kirk CJ, Groettrup M. Immunoproteasome subunit LMP7 deficiency and inhibition suppresses Th1 and Th17 but enhances regulatory T cell differentiation. J Immunol. 2012;189(8):4182-93.

Kim HJ, Zeidi M, Bonciani D, Pena SM, Tiao J, Sahu S, et al. Itch in dermatomyositis: the role of increased skin interleukin-31. Br J Dermatol. 2018;179(3):669-78.

Kirk CJ. Discovery and development of second-generation proteasome inhibitors. Semin Hematol. 2012;49(3):207-14.

Kisselev AF, van der Linden WA, Overkleeft HS. Proteasome inhibitors: an expanding army attacking a unique target. Chem Biol. 2012;19(1):99-115.

KYPROLIS (carfilzomib) [prescribing information]. Thousand Oaks, CA: AMGEN; 2018.

Lundberg IE, Miller FW, Tjarnlund A, Bottai M. Diagnosis and classification of idiopathic inflammatory myopathies. J Intern Med. 2016;280(1):39-51.

Martinez CK, Monaco JJ. Homology of proteasome subunits to a major histocompatibility complex-linked LMP gene. Nature. 1991;353(6345):664-7.

Muchamuel T, Basler M, Aujay MA, Suzuki E, Kalim KW, Lauer C, et al. A selective inhibitor of the immunoproteasome subunit LMP7 blocks cytokine production and attenuates progression of experimental arthritis. Nat Med. 2009;15(7):781-7.

Mundt S, Engelhardt B, Kirk CJ, Groettrup M, Basler M. Inhibition and deficiency of the immunoproteasome subunit LMP7 attenuates LCMV-induced meningitis. Eur J Immunol. 2016;46(1):104-13.

Nandi D, Jiang H, Monaco JJ. Identification of MECL-1 (LMP-10) as the third IFN-gamma-inducible proteasome subunit. J Immunol. 1996;156(7):2361-4.

Neubert K, Meister S, Moser K, Weisel F, Maseda D, Amann K, et al. The proteasome inhibitor bortezomib depletes plasma cells and protects mice with lupus-like disease from nephritis. Nat Med. 2008;14(7):748-55.

Palombella VJ, Conner EM, Fuseler JW, Destree A, Davis JM, Laroux FS, et al. Role of the proteasome and NF-kappaB in streptococcal cell wall-induced polyarthritis. Proc Natl Acad Sci USA. 1998;95(26):15671-6.

Parlati F, Lee SJ, Aujay M, Suzuki E, Levitsky K, Lorens JB, et al. Carfilzomib can induce tumor cell death through selective inhibition of the chymotrypsin-like activity of the proteasome. Blood. 2009;114(16):3439-47.

Rider LG, Koziol D, Giannini EH, Jain MS, Smith MR, Whitney-Mahoney K, et al. Validation of manual muscle testing and a subset of eight muscles for adult and juvenile idiopathic inflammatory myopathies. Arthritis Care Res. 2010;62(4):465-72.

Rider LG, Werth VP, Huber AM, Alexanderson H, Rao AP, Ruperto N, et al. Measures of adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis: Physician and Patient/parent Global Activity, Manual Muscle Testing (MMT), Health Assessment Questionnaire (HAQ)/Childhood Health Assessment Questionnaire (C-HAQ), Childhood Myositis Assessment Scale (CMAS), Myositis Disease Activity Assessment Tool (MDAAT), Disease Activity Score (DAS), Short Form 36 (SF-36), Child Health Questionnaire (CHQ), physician global damage, Myositis Damage Index (MDI), Quantitative Muscle Testing (QMT), Myositis Functional Index-2 (FI- 2), Myositis Activities Profile (MAP), Inclusion Body Myositis Functional Rating Scale (IBMFRS), Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Cutaneous Assessment Tool (CAT), Dermatomyositis Skin Severity Index (DSSI), Skindex, and Dermatology Life Quality Index (DLQI). Arthritis Care Res. 2011;63(Suppl 11):S118-57.

Sciorati C, Rigamonti E, Manfredi AA, Rovere-Querini P. Cell death, clearance and immunity in the skeletal muscle. Cell Death Differ. 2016;23(6):927-37.

Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheum. 2016;68(1):01-26.

Sultan SM, Allen E, Cooper RG, Agarwal S, Kiely P, Oddis CV, et al. Interrater reliability and aspects of validity of the myositis damage index. Ann Rheum Dis. 2011;70(7):1272-6.

Sultan SM, Allen E, Oddis CV, Kiely P, Cooper RG, Lundberg IE, et al. Reliability and validity of the myositis disease activity assessment tool. Arthritis Rheum. 2008; 58(11):3593-9.

Wang Z, Yang J, Kirk C, Fang Y, Alsina M, Badros A, et al. Clinical pharmacokinetics, metabolism, and drug-drug interaction of carfilzomib. Drug Metab Dispos. 2013;41(1):230-7.

Whiting-O'Keefe QE, Stone JH, Hellmann DB. Validity of a vasculitis activity index for systemic necrotizing vasculitis. Arthritis Rheum. 1999;42(11):2365-71.

Wilk S, Orlowski M. Evidence that pituitary cation-sensitive neutral endopeptidase is a multicatalytic protease complex. J Neurochem. 1983;40(3):842-9.

Yassaee M, Fiorentino D, Okawa L, Taylor L, Coley C, Troxel AB, et al. Modification of the cutaneous dermatomyositis disease area and severity index, an outcome instrument. Br J Dermatol. 2010;162:669-73.

Zhang H, Liu Z, Huang L, Hou J, Zhou M, Huang X, et al. The short-term efficacy of bortezomib combined with glucocorticoids for the treatment of refractory lupus nephritis. Lupus. 2017;26(9):952-8.

# 13. APPENDICES

## 13.1. Appendix A: Protocol History

| Protocol Version | Date Issued | Rationale for Update |
|---|---|---|
| Original Protocol | 17 September 2020 | N/A |
| Amendment 1 | 13 September 2021 | Protocol amended to extend weekly KZR-616 administration until the last patient enrolled has completed 48 weeks of dosing, and to support optional at-home KZR-616 administration by patients and caregivers. |

## 13.2. Appendix B: Websites for Patient-Reported Outcomes Assessments

| Assessment | Website |
|---|---|
| TIS | Score calculator:<br>https://www.niehs.nih.gov/research/resources/imacs/response_criteria/adult.html<br>User's guide:<br>https://www.niehs.nih.gov/research/resources/imacs/response_criteria/users_guide_for_the_adult_dermatomyositis_and_polymyositis_response_criteria_online_calculator_508.pdf |
| MMT-8 | https://www.niehs.nih.gov/research/resources/assets/docs/mmt8_grading_and_testing_procedures_for_the_abbreviated_8_muscle_groups_508.pdf |
| MDAAT | Assessment tool:<br>https://www.niehs.nih.gov/research/resources/assets/docs/myositis_disease_activity_assessment_tool_2009_pdf_format_508.pdf<br>Glossary:<br>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 |
| MDGIC | https://www.psywellness.com.sg/docs/CGI.pdf |
| FI-2 | Training guide:<br>https://www.niehs.nih.gov/research/resources/assets/docs/functional_index2_training_guide_508.pdf<br>Scoring sheet and instructions:<br>https://www.niehs.nih.gov/research/resources/assets/docs/functional_index2_scoring_sheet_and_instructions_508.pdf |
| MDI | https://www.niehs.nih.gov/research/resources/assets/docs/myositis_damage_index_pdf_format_508.pdf |
| PtGADA | https://www.niehs.nih.gov/research/resources/assets/docs/patientparent_global_activity_pdf_format_508.pdf |
| HAQ-DI | https://www.niehs.nih.gov/research/resources/assets/docs/haq_instructions_508.pdf |
| EQ-5D-5L | https://euroqol.org/eq-5d-instruments/ |
| PtGADD | https://www.niehs.nih.gov/research/resources/assets/docs/patientparent_global_assessment_of_disease_damage_pdf_format_508.pdf |

Abbreviations: EQ-5D-5L=EuroQoL 5-dimension 5-level; FI-2=Functional Index-2; HAQ-DI=Health Assessment Questionnaire-Disability Index; MDAAT=Myositis Disease Activity Assessment Tool; MDI=Myositis Damage Index; MDGIC=Physician Global Impression of Change; MMT-8=Manual Muscle Testing-8 Muscle Groups; PtGADA=Patient Global Assessment of Disease Activity; PtGADD=Patient Global Assessment of Disease Damage; TIS=Total Improvement Score

Signature Page for VV-CLIN-000244 v1.0

| | |
|---|---|
| Approval Task | [redacted]2021 14:56:25 GMT+0000 |
| Approval Task | [redacted]-2021 19:57:48 GMT+0000 |
| Approval Task | [redacted]21 21:03:17 GMT+0000 |

Signature Page for VV-CLIN-000244 v1.0