A Randomized, Double-Blind, Placebo-Controlled Clinical Study on the Efficacy and Safety of Tocilizumab in the Treatment of Anti-MDA5 Antibody-Positive Adult Dermatomyositis

Clinical Trial Protocol

Primary Research Institution: Peking Union Medical College Hospital

Principal Investigator: Professor Wang Qian, Department of Rheumatology and Immunology, Peking Union Medical College Hospital

Date of Submission: December 4, 2025

Protocol Number: PROMIS-RCT-I

Version: 2.0

Version Date: December 4, 2025

Research Abstract

Study Title	A Randomized, Double-Blind, Placebo-Controlled Clinical Study on the Efficacy and Safety of Tocilizumab in the Treatment of Anti-MDA5 Antibody-Positive Adult Dermatomyositis
Study Drug	Tocilizumab Injection
Study Design	IIT
Study Design	A 16-week prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial

Treatment Regimen	**Experimental Group**: Standard of Care (SOC)* + Tocilizumab Injection (8 mg/kg, administered intravenously at Weeks 0, 2, 4, and 8 for a total of 4 doses) **Control Group**: SOC + placebo injection intravenous infusion **SOC: Prednisolone (<1 mg/kg/day) + one calcineurin inhibitor (Tacrolimus 1 mg bid or cyclosporine 3–5 mg/kg/day)*
Study Endpoints	**Primary Endpoints:** 01) Proportion of patients achieving minimal improvement in Total Improvement Score (TIS⩾20) at Week 16 of treatment; 02) Change in PaO2/FiO2 ratio from baseline at Week 16 (patients with concomitant ILD). **Secondary Endpoints:** 01) Proportion of patients achieving moderate (TIS ≥ 40) or major improvement (TIS ≥ 60) in TIS at Week 16; 02) Change in Cutaneous Dermatomyositis Area and Severity Index (CDASI) score from baseline at Week 16 of treatment; 03) Change from baseline in Manual Muscle Testing (MMT-8) and Myositis Disease Activity Assessment Tool (MDAAT) Myositis disease activity assessment visual analogue scale (MYOACT) scores at Week 16; 04) The area under the curve (AUC) of glucocorticoid dose normalization over 16 weeks; 05) Laboratory tests: Changes in serum ferritin and creatine phosphokinase (CK) at weeks 4, 8, and 16; 06) Proportion of patients who discontinued the study due to disease progression, investigator judgment requiring increased steroid dosage or immunosuppressant (dosage or type), or investigator judgment of ineffectiveness; 07) Safety indicators: Incidence of adverse events (AE) and serious adverse events (SAE), and proportion of patients who discontinued due to study drug-related adverse reactions.

	Exploratory study endpoints: 01) Changes in pulmonary function indices from baseline at Week 16: ΔFVC%, ΔFVC, ΔDLco%, ΔDLco; 02) Change in chest HRCT (High-Resolution Computed Tomography) score from baseline at Week 16; 03) Changes in oxygenation index (PaO2/FiO2) and peripheral oxygen saturation (SpO2) from baseline at Week 16; 04) Changes in lymphocyte count, ferritin, and pulmonary alveolar type II cell surface antigen-6 (KL-6) at Week 16.
Number of Subjects	A total of 110 subjects will be enrolled, with 55 in the experimental group and 55 in the control group
Study Procedure	1. Screening Period: Eligible subjects were screened according to inclusion and exclusion criteria. After signing the informed consent form, subjects undergo screening examinations within 14 days prior to the first dose and provide relevant information, including: demographic data, medical history/past medical history, medication history, height and weight, BMI, vital signs, physical examination, 12-lead electrocardiogram, clinical laboratory tests, myositis antibody panel, pulmonary function tests, and chest CT.
	2. Follow-up Period: Eligible subjects undergo randomization and receive study medication at Week 0, followed by protocol-based treatment. Center follow-up visits occur at Weeks 4, 8, and 16, with a telephone follow-up at Week 12. During treatment, subjects undergo scheduled assessments, clinical laboratory tests, and safety evaluations.
Inclusion Criteria	**All inclusion criteria must be met for eligibility:** 1. Age ≥ 18 years and < 65 years; no gender restriction; total body weight ≥ 45 kg; 2. Diagnostic Criteria for Anti-MDA5-DM: Refer to the "2023 Chinese Expert Consensus on Diagnosis and Treatment of Anti-Melanoma Differentiation-Related

	Gene 5 Antibody-Positive Dermatomyositis in China." Dermatomyositis patients exhibiting one of the following manifestations—Gottron's papules, Gottron's rash, or periorbital erythema—along with positive serum anti-MDA5 antibodies, may be diagnosed with anti-MDA5-DM; 3. If patients have concomitant ILD, the following conditions must be met: i) Pulse oxygen saturation (SpO_2) ≥ 90% or PaO_2 ≥ 60 mmHg; ii) Pulmonary function tests showing forced vital capacity percentage of predicted (FVC%) ≥ 60% and carbon monoxide diffusion capacity percentage of predicted (DLco%) ≥ 40%; iii) High-resolution chest CT demonstrating pulmonary interstitial lesions involving < 50% of lung fields; 4. Patients must have received oral prednisone (< 1 mg/kg/day, or equivalent dose of other glucocorticoids) for ≥ 4 weeks prior to randomization; 5. Patients must have received a stable dose of a calcineurin inhibitor (CNI, such as cyclosporine or tacrolimus) for ≥4 weeks prior to randomization; if immunosuppressive therapy was discontinued prior to the screening visit, a washout period of at least 4 weeks is required; 6. Patients must receive prophylactic treatment with trimethoprim-sulfamethoxazole (TMP-SMZ, 400mg trimethoprim/80mg sulfamethoxazole) 1-2 tablets daily during treatment; 7. Women of childbearing potential must have a negative pregnancy test at study entry. If sexually active, they must agree to use effective contraception throughout the study period and must not intend to become pregnant during the study. 8. Patients voluntarily participate in this study and sign an informed consent form.
Exclusion Criteria	**Subjects meeting any of the following criteria will be excluded from the trial:** 1. Polymyositis, anti-synthetase syndrome, immune-mediated necrotizing myositis, or overlap myositis with other connective tissue diseases;

	2. Patients with life-threatening complications, including but not limited to acute coronary syndrome (e.g., myocardial infarction, unstable angina) within 24 weeks prior to screening or any history of significant cerebrovascular disease; 3. Any of the following laboratory abnormalities at screening: white blood cell count $<3.0\times10^9$/L, neutrophil count $<1.0\times10^9$/L, lymphocyte count $<0.5\times10^9$/L, hemoglobin <90 g/L, platelet count $<50\times10^9$/L; severe hepatic impairment (ALT or AST ≥3 times ULN, total bilirubin ≥1.5 times ULN, excluding serum ALT or AST elevation due to dermatomyositis); severe renal impairment (creatinine clearance ≤45 mL/min); 4. Patients hospitalized for severe infection within 60 days prior to screening, or who received intravenous antibiotics (patients who used intravenous antibiotics must complete a five-half-life washout period and confirm absence of active infection before enrollment), but may receive empirical oral antibiotics or topical antibiotics; 5. Active tuberculosis infection that is untreated or inadequately treated; Latent tuberculosis infection (LTBI) requires at least 2 weeks of preventive antituberculosis therapy (including at least 2 antituberculosis drugs) prior to randomization, continuing through study completion. LTBI is defined as: Positive IGRA result (acceptable IGRA assays include: QFT-GIT, QFT-G, and T-spot® TB test); 6. Active viral hepatitis at screening: HBsAg-positive, HBeAg-positive, or HBV-DNA $>10^3$ copies/L (HBV-DNA testing required if HBcAb-positive); HCVAb-positive; 7. Documented HIV infection, evidenced by positive serological test results or positive HIV serological test results at screening; 8. If the patient develops ILD-related clinical manifestations or progressive radiographic worsening within 4 weeks, RP-ILD should be considered. RP-ILD is defined as the presence of any one of the following four conditions within 1 month after the onset of respiratory symptoms: ① Acute and progressive worsening of dyspnea requiring hospitalization or supplemental oxygen; ② Decline in pulmonary function, manifested as a decrease in FVC% >10% with or without a decrease in

	DLco% >15%; ③ Increased interstitial abnormalities on chest HRCT scan >20%; ④ Decrease in arterial blood gas or partial pressure of oxygen >10 mmHg, indicating respiratory failure; and $PaO_2/FiO_2 \geqslant 200$ mmHg. 9. Allergy to the active ingredient tocilizumab or any of its excipients; 10. Patients with sulfonamide allergy; 11. Patients unable to complete pulmonary function testing at baseline; 12. Patients receiving prednisone at a dose exceeding 2 mg/kg/day prior to screening; 13. Patients receiving intravenous immunoglobulin (IVIG) prior to screening must discontinue treatment for at least 30 days; 14. Patients who used one or more of the following medications within the specified time window prior to screening: a) Rituximab within 6 months prior to screening; b) JAK inhibitors within 2 weeks prior to screening; c) Use of other biologics (including but not limited to anakinra, adalimumab, infliximab) or other immunosuppressive agents (including but not limited to methotrexate, azathioprine, mycophenolate mofetil) within 4 weeks prior to screening; 15. Patients with prior use of the study drug, other IL-6 inhibitors, or analogues; 16. Pregnant or lactating women, or women planning to become pregnant or initiate lactation; 17. History of malignant tumors within the past 5 years (excluding adequately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or cervical carcinoma in situ with no evidence of recurrence within the preceding 5 years); 18. Other conditions deemed ineligible for study inclusion by the investigator.

A. Principal Investigator Information

Name	Wang Qian	**Gender**	Male	**Date of Birth**	November 1976
Education	Doctoral Candidate	**Degree**		Doctorate	
Professional Title	Chief Physician	**Position**		Deputy Director	
Email	zhengaqian@126.com	**Phone**		13681211155	

B. Research Background

Dermatomyositis (DM) is a chronic inflammatory autoimmune disease primarily affecting the skin and skeletal muscles. Anti-MDA5 antibody-positive dermatomyositis (anti-MDA5-DM) represents the most common and severe subtype of DM, characterized by ulcerative skin lesions and rapidly progressive interstitial lung disease (RP-ILD). The etiology and pathogenesis of anti-MDA5-DM remain incompletely understood. Existing research suggests that genetic factors, viral infections, abnormal activation of the type I interferon pathway, and dysregulation of immune cell subsets may collectively contribute to its development. The disease can occur at any age but predominantly affects individuals aged 40–50 years, with a higher prevalence in women. Epidemiological data on anti-MDA5-DM remains scarce in China. However, cohort studies indicate higher prevalence in Asian populations compared to Western populations, accounting for approximately 20%–50% of adult DM cases. In East Asia, approximately 60% to 80% of anti-MDA5-DM patients develop interstitial lung disease (ILD). Furthermore, recent studies have revealed a significant increase in anti-MDA5-DM incidence following the COVID-19 pandemic [1,2,3].

Anti-MDA5-DM is the subtype with the poorest prognosis in dermatomyositis, with acute respiratory failure due to RP-ILD being the primary cause of death. Current clinical management relies primarily on empirical regimens, lacking high-quality evidence-based medical support. Glucocorticoids serve as the cornerstone therapy, often combined with calcineurin inhibitors (e.g., cyclosporine, tacrolimus) for anti-MDA5-DM-related ILD [4,5]. However, even with intensive therapy

combining steroids and calcineurin inhibitors, approximately 50% of patients experience persistent ILD progression, with some requiring advanced life support [6,7]. Consequently, developing targeted therapies with proven efficacy represents an urgent clinical need.

Tocilizumab is a humanized monoclonal antibody targeting the IL-6 receptor, exerting therapeutic effects by specifically blocking the IL-6 signaling pathway [8]. Studies indicate that IL-6, as a key pro-inflammatory factor, plays a crucial role in the pathogenesis of anti-MDA5-DM, potentially directly mediating inflammatory responses and tissue damage processes [9]. Clinical observations reveal significantly elevated serum IL-6 levels in RP-ILD patients, with high IL-6 levels closely associated with poor patient outcomes [9]. Based on this, tocilizumab, by precisely inhibiting the IL-6 signaling pathway, can effectively control excessive inflammatory responses, improve clinical symptoms, and potentially delay disease progression, offering a new targeted therapeutic option for anti-MDA5-DM treatment.

Currently, approved indications for tocilizumab worldwide do not include anti-MDA5-DM. Therefore, its use in treating anti-MDA5-DM constitutes off-label use. Our research team was the first internationally to report the clinical efficacy of tocilizumab in treating anti-MDA5-DM. Among 6 patients with anti-MDA5-DM complicated by ILD who responded poorly to conventional corticosteroid plus immunosuppressive therapy, 5 (83.3%) demonstrated significant improvement in respiratory symptoms and pulmonary imaging findings after adding tocilizumab, confirming the treatment regimen's favorable efficacy and safety profile [10]. Subsequent case reports further validated these findings, providing crucial evidence for tocilizumab's application in anti-MDA5-DM therapy [11,12].

Currently, the potential efficacy of tocilizumab in anti-MDA5-DM treatment has garnered attention in multiple domestic and international expert consensus statements. These consensus documents suggest considering its inclusion in treatment regimens for dermatomyositis, particularly anti-MDA5-DM cases [2,5,13]. However, as existing studies are predominantly small-sample case reports or case series lacking evidence from rigorously designed randomized controlled trials (RCTs), these consensus documents maintain a cautious stance without issuing explicit recommendations. To confirm the clinical value of tocilizumab, large-scale, multicenter clinical studies are still needed to

systematically evaluate its precise efficacy and long-term safety, thereby providing more reliable evidence-based medical support for clinical practice. Therefore, this study proposes to conduct a prospective, multicenter, randomized, placebo-controlled clinical trial to further provide high-quality evidence on the efficacy and safety of tocilizumab in treating anti-MDA5-DM. This is expected to address the current lack of definitively effective treatments for this disease and offer a new therapeutic option for this rare but severely debilitating autoimmune disorder.

C. Study Objectives

Through a 16-week, multicenter, prospective, randomized, placebo-controlled clinical trial, this study aims to systematically evaluate the efficacy and safety of tocilizumab in treating Chinese adult patients with anti-MDA5-DM, thereby providing high-quality clinical evidence for its clinical application in this disease. If this study confirms the efficacy and safety of tocilizumab for anti-MDA5-DM, it will help address the current lack of therapeutic options for this disease. It holds promise as a new treatment choice for anti-MDA5-DM, potentially improving treatment standards, reducing patient mortality, enhancing quality of life, alleviating the burden on families and society, and saving healthcare costs.

D. Research Methods and Content

1. Study Design

This study will conduct a 16-week prospective, multicenter, randomized, placebo-controlled clinical trial. It aims to enroll 110 Chinese adult patients with anti-MDA5-DM. Patients will be stratified based on whether their PaO_2/FiO_2 ratio is less than 300 mmHg. Within each stratum, patients will be randomly assigned in a 1:1 ratio to either the treatment group or the control group. The specific medication regimens for each group are as follows:

Experimental Group: Standard treatment regimen combined with tocilizumab injection (8 mg/kg administered intravenously at weeks 0, 2, 4, and 8 for a total of 4 doses)

Control group: Standard treatment regimen combined with placebo intravenous infusion

The standard treatment regimen consists of prednisone (<1 mg/kg/day) combined with one calcineurin inhibitor (tacrolimus 1 mg bid or cyclosporine 3-5 mg/kg/day).

Permitted concomitant medications: During the study treatment period, necessary treatments may be provided by the investigator based on routine clinical practice for the benefit of the subject. The following medications/treatments may be used as appropriate: medications for hypertension, diabetes, etc. During concomitant use, the following must be recorded: drug name (generic and brand name), daily dosage, route of administration, start and end dates of use, and reason for use.

Criteria for discontinuation of study drug: Occurrence of a serious adverse event (SAE) related to the study drug, such as life-threatening or fatal events, severe infection, severe allergic reaction (e.g., anaphylaxis) or infusion reaction, clinically significant severe laboratory abnormalities, or any circumstance where the investigator deems the risk of continued treatment outweighs the benefit for the subject's safety.

The study will be conducted using a double-blind method, with neither the subjects nor the clinicians aware of the study group assignment. The randomization protocol will be generated via an electronic IWRS system, which will not disclose any information regarding treatment allocation to the investigators or any personnel responsible for conducting the study or analyzing the data. The results of randomization may only be reported to the hospital pharmacist or designated personnel in the specified manner; other trial personnel shall not have access to this information.

Study Procedure: 1) Screening Period: Eligible subjects are screened according to inclusion and exclusion criteria. After signing informed consent, subjects undergo screening examinations within 14 days prior to first dosing and provide relevant information, including: demographic data, medical history/past medical history, medication history, height/weight, BMI, vital signs, physical examination, 12-lead ECG, clinical laboratory tests, myositis antibody panel, pulmonary function tests, and chest CT. 2) Follow-up Period: Eligible subjects randomized at Week 0 to receive study drug and undergo protocol-defined treatment. Center follow-up visits occur at Weeks 4, 8, and 16, with a telephone follow-up at Week 12. During treatment, subjects undergo scheduled assessments, clinical laboratory tests, and safety evaluations.

Primary endpoints include: 1) Proportion of patients achieving TIS minimal improvement (TIS ≥ 20) at Week 16 (TIS: Total Improvement Score as defined by the International Myositis Assessment

and Clinical Study Group (IMACS); TIS minimal improvement defined as TIS score ⩾ 20); 2) Change in PaO_2/FiO_2 from baseline at Week 16 (patients with concomitant ILD). Secondary endpoints included: 1) Proportion of patients achieving moderate (TIS ≥ 40) or major improvement (TIS ≥ 60) at Week 16; 2) Change in the Cutaneous and Muscular Dermatomyositis Area and Severity Index (CDASI) score from baseline at Week 16; 3) Change in Manual Muscle Testing (MMT-8) and Muscle Disease Activity Assessment Tool (MDAAT) Myositis disease activity assessment visual analogue scale (MYOACT) scores from baseline at Week 16; 4) Glucocorticoid dose-normalized AUC over 16 weeks; 5) Laboratory tests: Changes in serum ferritin and creatine phosphokinase (CK) at weeks 4, 8, and 16; 6) Proportion of patients who discontinued the study due to disease progression, investigator judgment requiring increased glucocorticoid dose or immunosuppressant (dose or type), or investigator judgment of treatment failure; 7) Safety measures: incidence of adverse events (AE) and serious adverse events (SAE), and proportion of patients withdrawing due to study drug-related adverse reactions. Exploratory measures: 1) Changes in pulmonary function parameters at Week 16 compared to baseline: ΔFVC%, ΔFVC, ΔDLco%, ΔDLco; 2) Change in chest HRCT score at Week 16 compared to baseline; 3) Changes in oxygenation index (PaO_2/FiO_2) and oxygen saturation (SpO_2) at Week 16 compared to baseline; 4) Changes in lymphocyte count, ferritin, and pulmonary alveolar type II cell surface antigen-6 (KL-6) at Week 16.

2. Study Population

2.1 Inclusion Criteria (all criteria must be met):

1. Age ≥18 years and <65 years, male or female; total body weight ≥45 kg;
2. Anti-MDA5-DM Diagnostic Criteria: Refer to the "2023 Chinese Expert Consensus on Diagnosis and Treatment of Anti-Melanocyte Differentiation-Related Gene 5 Antibody-Positive Dermatomyositis in China." Dermatomyositis patients exhibiting one of the following manifestations—Gottron's papules, Gottron's rash, or erythema ab igne—along with positive serum anti-MDA5 antibodies, meet the criteria for anti-MDA5-DM diagnosis.
3. If the patient has concomitant ILD, the following conditions must also be met: i) Pulse oxygen saturation (SpO_2) ≥90% or PaO_2 ≥ 60 mmHg; ii) Pulmonary function tests showing

forced vital capacity percentage of predicted (FVC%) ≥ 60% and carbon monoxide diffusion capacity percentage of predicted (DLco%) ≥ 40%; iii) High-resolution chest CT demonstrating pulmonary interstitial lesions involving < 50% of lung fields;

4. Patients must have received oral prednisone (< 1 mg/kg/day, or equivalent dose of other glucocorticoids) for ≥ 4 weeks prior to randomization.
5. Patients must have received a stable dose of a calcineurin inhibitor (CNI, such as cyclosporine or tacrolimus) for ≥4 weeks prior to the randomization visit; If immunosuppressive drugs were discontinued prior to the screening visit, a washout period of at least 4 weeks is required (specifically, for immunosuppressive drugs such as methotrexate, azathioprine, or mycophenolate mofetil, a complete discontinuation period of at least 4 weeks must be observed between the last dose of the immunosuppressive drug and the randomization visit to ensure elimination of drug effects);
6. Patients must take co-trimoxazole (TMP-SMZ: trimethoprim 400mg/sulfamethoxazole 80mg) for infection prophylaxis during treatment, 1-2 tablets daily;
7. Women of childbearing potential must have a negative pregnancy test at study entry. If sexually active, they must agree to use effective contraception throughout the study period and must not intend to become pregnant during the study;
8. Patients voluntarily participate in this study and sign an informed consent form.

2.2 Exclusion Criteria (Subjects meeting any of the following criteria will be excluded from the trial):

1. Polymyositis, anti-synthetase syndrome, immune-mediated necrotizing myositis, or overlap myositis with other connective tissue diseases;
2. Patients with life-threatening complications, including but not limited to acute coronary syndrome (e.g., myocardial infarction, unstable angina) within 24 weeks prior to screening or any history of significant cerebrovascular disease;
3. Any of the following laboratory abnormalities at screening: white blood cell count <3.0 × 10^9/L, neutrophil count <1.0 × 10^9/L, lymphocyte count <0.5 × 10^9/L, hemoglobin <90 g/L,

platelet count <50 × 10^{9}/L; severe hepatic impairment (ALT or AST ≥3 times ULN, total bilirubin ≥1.5 times ULN, excluding serum ALT or AST elevation due to dermatomyositis); severe renal impairment (creatinine clearance ≤45 ml/min);

4. Hospitalization for severe infection within 60 days prior to screening, or intravenous antibiotic administration (patients receiving IV antibiotics must complete a five-half-life washout period and confirm absence of active infection before enrollment); patients may receive empirical oral antibiotics or topical antibiotics;
5. Untreated or inadequately treated active tuberculosis infection; Latent tuberculosis infection (LTBI) requires at least 2 weeks of preventive antituberculosis therapy (including at least 2 antituberculosis drugs) prior to randomization, continuing through study completion. LTBI is defined as: Positive IGRA result (acceptable IGRA assays include: QFT-GIT, QFT-G, and T-spot® TB test);
6. Active viral hepatitis at screening: HBsAg-positive, HBeAg-positive, or HBV-DNA >10^{3}copies/L in serum; HBV-DNA testing required if HBcAb-positive; HCVAb-positive;
7. Documented HIV infection, evidenced by positive serology results or positive HIV serology at screening;
8. If a patient develops ILD-related clinical manifestations or progressive radiographic worsening within 4 weeks, RP-ILD should be considered. RP-ILD is defined as meeting any one of the following four criteria within 1 month after onset of respiratory symptoms: ① Acute and progressive worsening of dyspnea requiring hospitalization or supplemental oxygen; ② Decline in pulmonary function, manifested as a decrease in FVC% >10% with or without a decrease in DLco% >15%; ③ Increased interstitial abnormalities on chest HRCT scan >20%; ④ Decrease in arterial blood gas analysis or partial pressure of oxygen (PaO_2)>10 mmHg, indicating respiratory failure; and PaO_2/FiO_2 ≥200 mmHg;
9. Allergy to the active ingredient tocilizumab or any of its excipients;
10. Patients with sulfonamide allergy;
11. Patients unable to complete pulmonary function testing at baseline;
12. Patients receiving prednisone therapy at a dose exceeding 2 mg/kg/day prior to screening;

13. Patients who received intravenous immunoglobulin (IVIG) prior to screening must discontinue treatment for at least 30 days;
14. Patients who used one or more of the following medications within the specified time window prior to screening:
    a) Rituximab within 6 months prior to screening;
    b) JAK inhibitors within 2 weeks prior to screening;
    c) Other biologics (including but not limited to anakinra, adalimumab, infliximab) and other immunosuppressive agents (including but not limited to methotrexate, azathioprine, mycophenolate mofetil) within 4 weeks prior to screening;
15. Patients with prior exposure to the study drug, other IL-6 inhibitors, or analogues;
16. Pregnant or lactating women, or women planning pregnancy or initiating lactation;
17. History of malignant tumors within the past 5 years (excluding adequately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or cervical carcinoma in situ with no evidence of recurrence within the preceding 5 years);
18. Other conditions deemed ineligible for study inclusion by the investigator.

2.3 Withdrawal Criteria

During the study, participants may voluntarily withdraw from the trial at any time for any reason. Investigators may also decide to withdraw a participant from the trial if unacceptable risks or other circumstances arise. Specific reasons may include:

1. The subject requests withdrawal from the trial;
2. Pregnancy of the subject;
3. Progression of the subject's disease or occurrence of a serious adverse reaction;
4. Participation in another clinical trial during the study period;
5. Other circumstances where the investigator deems the subject unsuitable for continued participation in the study.

3. Sample Size Calculation

The primary endpoint of this study is the proportion of subjects achieving a minimum improvement in TIS (TIS ≥ 20). For the subgroup of patients with concomitant ILD, the primary endpoint is the change in PaO_2/FiO_2 from baseline. To control Type I error, the significance level for the TIS≥20 analysis is set at 0.025 (two-tailed), and the significance level for the PaO_2/FiO_2 analysis is also set at 0.025 (two-tailed). The study will be considered positive if either the TIS≥20 analysis or the PaO_2/FiO_2 analysis yields statistically significant results.

Sample size was calculated based on the proportion of subjects achieving the primary endpoint of minimal TIS improvement (TIS ≥ 20). Previous studies reported a range of 25%–30% for subjects achieving minimal TIS improvement with standard polymyositis therapy, and 66%–79% for subjects achieving minimal TIS improvement with biologics or JAK inhibitors combined with standard therapy. Considering clinical efficacy, this study hypothesizes that 25% of subjects in the placebo group will achieve the minimum TIS improvement at Week 12, and 65% in the TCZ treatment group (i.e., a 40% between-group difference), with a two-sided α level of 0.025 and 90% power. At least 74 subjects are required to demonstrate a significant difference in primary efficacy between the TCZ and placebo groups. Accounting for a 20% dropout rate, a total of 94 subjects must be enrolled, equating to 47 subjects per group.

[Comment: Update to 'Week 16' for consistency with trial duration.]

Sample size calculation based on the expected change in$PaO_{2/FiO_2}$from baseline. Clinical experience suggests that the change in PaO_2/FiO_2 after treatment can reach 100 mmHg, with one-third of this change considered a clinically significant difference. Assuming a between-group difference of 30 mmHg in the change in PaO_2/FiO_2 from baseline at Week 12, with a standard deviation of 25 mmHg, a two-sided α level of 0.025, and 90% power, at least 38 subjects are required to demonstrate a significant difference in primary efficacy between the TCZ and placebo groups. Accounting for a 20% dropout rate, a total of 48 subjects will ultimately be required, equating to 24 subjects per group.

This study plans to conduct one interim analysis and one final analysis. The interim analysis will occur after 55 patients are enrolled. The Haybittle-Peto method will be used to control Type I error at 0.025 (two-sided). If the interim analysis results for TIS ≥ 20 or PaO_2/FiO_2 reject the null hypothesis (two-sided p-values both < 0.001), the endpoint will be declared reached. If the interim analysis fails

to reject the null hypothesis, the final analysis will test TIS ≥ 20 and PaO_2/FiO_2 at a 0.025 (two-sided) significance level. Therefore, accounting for alpha expenditure from the interim analysis, the sample size is increased by 15% from the original plan, resulting in a final target enrollment of 110 subjects.

4. Statistical Analysis

The statistical analysis plan will be initiated prior to study completion and finalized before database lock. The plan will detail all statistical analyses to be performed, including definitions of datasets and algorithms for data derivation, as well as descriptive and analytical methods for various outcomes. Statistical analyses will be conducted using IBM SPSS software (version 25.0 or higher). Quantitative data will be described using mean, median, standard deviation, maximum, and minimum values. Categorical or ordinal data will be presented as case counts and percentages. (1) Case Analysis: Describe trial completion status, with statistical descriptions for each excluded or withdrawn case. (2) Demographic and Baseline Analysis: Describe demographic characteristics and other baseline indicators of enrolled patients. Baseline data include gender, age, etc. (3) Endpoint analysis: Conduct efficacy outcome analysis based on both the FAS and PPS datasets. (4) Safety analysis: List the number of cases and occurrences of AEs and SAEs (NCICTCAE v5.0), calculate incidence rates, and report the proportion of patients who discontinued due to study drug-related adverse reactions.

5. Follow-up Schedule

Time / Item	Screening Period	Observation Period				
	-14 to 0 days	Randomization	Visit 1 4 weeks ± 3 days	Visit 2 8 weeks ± 3 days	Visit 3 (Telephone) 12 weeks ± 3 days	Visit 4 16 weeks ± 3 days
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
General Information and Medical History Collection [A]	X					

Vital Signs [B]	X	X	X	X		X
Physical Examination [C]	X	X	X	X		X
Complete Blood Count [D]	X	X	X	X		X
Liver and Kidney Function [E]	X	X	X	X		X
C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)		X	X	X		X
Serum ferritin		X	X	X		X
Creatine Kinase (CK)		X	X	X		X
Arterial Blood Gas Analysis		X				X
Prednisone Dosage		X	X	X	X	X
MYOACT, TIS Score [F]		X	X	X		X
Skin CDASI Score [G]		X	X	X		X
Pulmonary Function Tests: FVC%, FVC, DLco%, DLco	X					X
Chest HRCT	X					X
Oxygenation Index (PaO_2/FiO_2), Blood Oxygen Saturation (SpO_2)	X		X	X		X
Alveolar Type II Cell Surface Antigen-6 (KL-6)		X				X
12-lead electrocardiogram [ECG]	X		X	X		X
Research drug use [I]		X	X	X	X	X
Combination Therapy	X	X	X	X	X	X
AE/SAE		X	X	X	X	X
Safety Assessment		X	X	X	X	X
Adverse Event Correlation Assessment		X	X	X	X	X

A. General information includes name, age, gender, ethnicity, height, weight, BMI, etc.; medical history includes: current medical history, past medical history, medication history, allergy history, medication history, etc.

B. Vital signs include temperature, pulse, respiration, and blood pressure, with specific details determined by the investigator's comprehensive assessment.

C. Physical examination includes skin, mucous membranes, lymph nodes, head, neck, chest, abdomen, spine/extremities, and other areas.

D. Complete blood count includes lymphocytes, white blood cells, red blood cells, hemoglobin, neutrophils, platelets, etc.

E. Liver and kidney function: including alanine aminotransferase, aspartate aminotransferase, total protein, creatinine clearance, and urine protein.

F. TIS Score: Total Improvement Score of the ACR/EULAR Criteria for Myositis Response.

G. CDASI Score: Cutaneous Dermatomyositis Area and Severity Index Score.

H. 12-lead electrocardiogram including heart rate (P), P-R interval, QRS interval, Q-T interval, etc.

I. During medication administration, closely monitor for drug reactions.

6. Study Termination

Study termination refers to the premature cessation of an entire clinical trial before all subjects have been evaluated according to the protocol. The entire trial or a specific study site may be terminated early if any of the following conditions occur:

1. New, conclusive evidence indicating an unfavorable risk-benefit assessment of the investigational drug, such as unacceptable safety concerns;
2. Slow subject enrollment at a study site, preventing completion within an acceptable timeframe;
3. The investigator deems continuation of the trial inappropriate for medical, ethical, or other reasons;
4. The ethics committee terminates the trial for any reason.
5. If interim analysis results yield definitive conclusions regarding efficacy and safety, and continuation of the study would not alter the final conclusions, the investigator will terminate the study early.

E. Risk/Benefit Assessment

1. Known Potential Risks

All studies carry known and unknown risks. Tocilizumab is approved for treating rheumatoid arthritis, systemic juvenile idiopathic arthritis, and cytokine release syndrome, with its safety and

efficacy fully validated in these patient populations. Major adverse reactions reported in clinical studies include: risk of viral and bacterial infections, allergic rash, elevated liver enzymes and bilirubin, and granulocytopenia.

Anti-MDA5-DM therapy carries a risk of rapid progressive interstitial lung disease (RP-ILD), which may lead to respiratory failure or even be life-threatening. While this risk exists for some patients in this study, it is inherent to the disease progression and has been widely documented. This study will implement rigorous follow-up monitoring to detect and address this risk as early as possible. Should signs of respiratory failure emerge, investigators may terminate the study at any time and provide active treatment based on clinical need. An interim analysis is planned to assess related risks and determine whether to terminate the study early.

2. Known Potential Benefits

Tocilizumab injection is an approved recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody with established efficacy and safety. By precisely inhibiting the IL-6 signaling pathway, tocilizumab effectively controls excessive inflammatory responses and improves clinical symptoms, offering a promising new targeted therapeutic option for anti-MDA5-DM treatment. In our team's prior clinical practice, among 6 anti-MDA5-DM patients with ILD who responded poorly to conventional corticosteroid plus immunosuppressive therapy, 5 (83.3%) demonstrated significant improvement in respiratory symptoms and pulmonary imaging findings after adding tocilizumab. Subsequent case reports from multiple domestic and international sources further validated this finding, providing crucial evidence for the potential benefits of tocilizumab in anti-MDA5-DM therapy. Through rigorous trial design, this study offers patients follow-up monitoring at a higher frequency than standard clinical practice, along with more standardized and detailed assessment protocols and access pathways. This facilitates close monitoring of patient conditions and timely intervention.

3. Assessment of Potential Risks and Benefits

Tocilizumab has demonstrated overall controllable risks and clear clinical benefits within its approved indications. For the specific population receiving anti-MDA5-DM therapy, while known drug-related adverse reaction risks exist, these risks are largely predictable, monitorable, preventable,

and manageable. The study protocol established strict inclusion/exclusion criteria for major risks (particularly infections), excluding high-risk patients such as those with active infections or severe hepatic/renal impairment, alongside a comprehensive monitoring plan (including regular vital signs, CBC, hepatic/renal function, and AE assessments). Concurrently, existing mechanisms and clinical evidence strongly suggest that tocilizumab offers significant potential benefits in this population, particularly in improving pulmonary lesions and clinical symptoms. This is crucial for enhancing the prognosis of patients at high risk of mortality. Given the severity and rapid progression of anti-MDA5-DM disease itself, along with the limited treatment options for patients unresponsive to conventional therapies, the potential clinical benefits of using tocilizumab under close monitoring and management are expected to significantly outweigh its known and controllable risks. This randomized controlled trial design will provide higher-level evidence-based medical evidence, ultimately quantifying the risk-benefit ratio in this specific population to guide future clinical practice and enable patients to receive more scientifically effective treatment.

[Comment: Simplify to 'This randomized controlled trial will provide high-level evidence.']

Therefore, the benefits of this study outweigh the risks.

F. Expected Outcomes

Through a rigorous clinical study design, this research will systematically evaluate the efficacy and safety of tocilizumab in treating patients with mild-to-moderate anti-MDA5 antibody-positive dermatomyositis. It aims to provide high-quality evidence-based medical evidence, offering new therapeutic options for clinical practice. The findings are expected to be published in internationally renowned academic journals and translated into clinical applications, thereby improving patients' quality of life, reducing disease burden, and yielding significant social and economic benefits.

G. Data Retention and Confidentiality

Confidentiality of subject information is strictly enforced by the principal investigator, participating researchers, the sponsor, and its agents. Confidentiality extends beyond clinical

information to include biological samples. Consequently, the study protocol, documentation, data, and all other information generated will be kept strictly confidential. No research or data information may be disclosed to any unauthorized third party without the sponsor's prior written approval. Other authorized representatives of the sponsor, the Ethics Committee, and regulatory authorities may inspect all documents and records required to be maintained by the investigator, including but not limited to medical records and subject medication records. The study site shall permit access to these records. Subject contact information will be securely stored at each study site and used solely for internal purposes during the study. Upon study completion, all records will continue to be stored securely for the duration specified by the local Ethics Committee and applicable regulations. Research data collected from subjects for statistical analysis and scientific reporting will be uploaded and stored at the research center. This data shall not include subject contact information or personally identifiable information. Instead, subjects and their research data will be assigned unique study identification numbers. The research data entry and management systems used by investigators at each clinical research center are confidential and password-protected. At the conclusion of the study, all identifying information from the research databases will be removed and archived at the research center.

H. Informed Consent

Each subject (or their legal representative) must provide written consent after fully understanding the purpose and content of the study. This written consent must be signed (with signature and date) before any trial-related procedures are performed. The informed consent form should comply with the Declaration of Helsinki, current GCP guidelines, and applicable regulations.

Prior to potential subject enrollment, the investigator or authorized personnel shall explain the study's purpose, methods, potential benefits, possible risks, and any anticipated discomfort. Subjects shall be informed that participation is voluntary and may be withdrawn at any time. If a subject declines to participate, alternative treatments remain available, and the decision to participate shall not affect their disease management. Finally, subjects should understand that the investigator will maintain their identity records for long-term follow-up as needed. These records may be reviewed by regulatory authorities and the sponsor within the scope permitted by relevant laws and regulations. Subject

privacy will be protected. By signing the informed consent form, the subject authorizes the aforementioned actions.

The subject (or their legal representative) shall be given sufficient time to read the informed consent form and ask questions. After the investigator's explanation and prior to the subject's enrollment, the subject (or their legal representative) shall sign their name and date on the informed consent form for the record. Following the signing of the informed consent form, the subject shall receive a copy of the form.

If the subject (or their legal representative) cannot read or write, an impartial witness should participate in the entire informed consent process (including reading and explaining all written information) and personally sign their name and date after the subject (or their legal representative) gives verbal consent.

Subjects who cannot understand the content of the informed consent form may only participate in the trial after their legal representative has provided informed consent.

I. Research Quality Control

1. Data Quality Assurance

A Data Management Plan (DMP) shall be developed prior to data collection, detailing procedures for data collection, cleaning, and consistency checks. Data management processes shall follow the Data Management Company's Standard Operating Procedures (SOPs). Electronic Data Capture (EDC) systems will be used for data collection. Adverse events (AEs) will be medically coded using the MedDRA regulatory medical vocabulary. The database will be locked when all data has been cleaned, queries resolved, medical coding completed, protocol deviations and any issues identified during data list review addressed, and the investigator has completed electronic signatures on the eCRF.

Data management is performed by the Data Management Company. The Data Management Plan (DMP) is authored by the Data Manager (DM) as the guiding document for the entire data management process. All data management procedures shall be conducted according to the timelines, content, and methods defined therein. The DMP is a dynamic document subject to revision and updates during the trial based on actual circumstances.

This study employs an Electronic Data Capture (EDC) system for data collection and

management. Data managers design data capture forms according to protocol requirements, including study visits, form names, and data items collected. They configure data validation programs (DVP) based on the DVP plan, test these programs, and release them for use after investigator approval. The investigator or their authorized clinical research coordinator (CRC) accesses the data management system via a separate account. They accurately, timely, completely, and consistently complete the electronic case report form (eCRF) based on source documentation and eCRF completion guidelines. The investigator or their authorized personnel are responsible for performing 100% source data verification (SDV) of the information entered into the database. After data entry is completed and SDV is performed, the investigator confirms with an electronic signature. Any revisions to signed data require re-signature. After confirming the completeness and accuracy of database entries, the database is locked by the data management personnel following joint approval from the investigator, data management personnel, and statistical analysts.

2. Investigator Training

Investigators participating in this study must possess professional qualifications and capabilities, pass qualification reviews, and remain consistent throughout the study. Prior to study initiation, the principal investigator will conduct regular in-person and online training sessions for investigators at all participating sites in this multicenter study. This ensures investigators fully understand the study protocol and procedures, guaranteeing consistency in study-related assessment operations.

3. Preservation of Original Data

Essential clinical trial documents refer to records that evaluate the conduct and data quality of a clinical trial, serving as evidence that the investigator complied with relevant laws and regulations governing drug clinical trials throughout the study.

Both the investigators and clinical trial sites confirm they have suitable facilities and conditions for storing essential clinical trial documents. Storage equipment must prevent direct light exposure, water damage, and fire hazards to facilitate long-term preservation. In accordance with protocol requirements, stored documents must be readily identifiable, retrievable, accessible, and archivable. Storage media for clinical trial materials must ensure the integrity and readability of original data or certified copies throughout the retention period. Regular testing or verification of data recovery capability must be conducted to prevent intentional or unintentional alteration or loss.

Certain documents generated during clinical trial implementation, if not listed in the clinical trial essential document management directory, may also be included in the respective essential document archives of the investigator and clinical trial site based on necessity and relevance.

At the start of the clinical trial, the investigator must establish a critical document file management system. At the conclusion of the trial, critical documents are reviewed and confirmed, and these documents are properly preserved.

J. References

1. LU X, PENG Q, WANG G. Anti-MDA5 antibody-positive dermatomyositis: pathogenesis and clinical progress [J]. Nat Rev Rheumatol, 2024, 20(1): 48-62.
2. Lu Xin, Peng Qinglin, Shu Xiaoming, et al. Chinese Expert Consensus on Diagnosis and Treatment of Anti-MDA5 Antibody-Positive Dermatomyositis (2023 Edition) [M]. 2024. Chinese Journal of Rheumatology, 2024, 28(01): 5-14.
3. MCPHERSON M, ECONOMIDOU S, LIAMPAS A, et al. Management of MDA-5 antibody positive clinically amyopathic dermatomyositis associated interstitial lung disease: A systematic review [J]. Semin Arthritis Rheum, 2022, 53: 151959.
4. FUJISAWA T, HOZUMI H, KAMIYA Y, et al. Prednisolone and tacrolimus versus prednisolone and cyclosporin A to treat polymyositis/dermatomyositis-associated ILD: A randomized, open-label trial [J]. Respirology, 2021, 26(4): 370-7.
5. ROMERO-BUENO F, DIAZ DEL CAMPO P, TRALLERO-ARAGUÁS E, et al. Recommendations for the treatment of anti-melanoma differentiation-associated gene 5-positive dermatomyositis-associated rapidly progressive interstitial lung disease [J]. Semin Arthritis Rheum, 2020, 50(4): 776-90.
6. CHEN Z, WANG X, YE S. Tofacitinib in Amyopathic Dermatomyositis-Associated Interstitial Lung Disease [J]. N Engl J Med, 2019, 381(3): 291-3.
7. HE W, CUI B, CHU Z, et al. Radiomics based on HRCT can predict RP-ILD and mortality in anti-MDA5^{+} dermatomyositis patients: a multi-center retrospective study [J]. Respir Res, 2024, 25(1): 252.
8. SCOTT L J. Tocilizumab: A Review in Rheumatoid Arthritis [J]. Drugs, 2017, 77(17): 1865-79.
9. NARA M, KOMATSUDA A, OMOKAWA A, et al. Serum interleukin 6 levels as a useful prognostic predictor of clinically amyopathic dermatomyositis with rapidly progressive interstitial lung disease [J]. Modern Rheumatology, 2014, 24(4): 633-6.
10. ZHANG X, ZHOU S, WU C, et al. Tocilizumab for refractory rapidly progressive interstitial lung disease related to anti-MDA5-positive dermatomyositis [J]. Rheumatology (Oxford), 2021, 60(7): e227-e8.
11. WANG Q H, CHEN L H. Treatment of refractory anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis complicated by rapidly progressing interstitial pulmonary disease: Two case reports [J]. World J Clin Cases, 2023, 11(22): 5351-7.
12. SU C F, LIAO H T, TSAI C Y. Tocilizumab and rituximab for anti-MDA-5 positive amyopathic dermatomyositis complicated with macrophage activation syndrome and progressive fibrosing interstitial lung disease [J]. Scand J Rheumatol, 2022, 51(2): 166-8.
13. Chinese Expert Consensus on Diagnosis and Treatment of Adult Dermatomyositis (2022) [J]. Chinese

Journal of Dermatology, 2022, 55(11): 939-948.