Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study of ustekinumab in Japanese patients with active polymyositis and dermatomyositis who have not adequately responded to one or more standard-of-care treatments

Kimito Kawahata,1 Tomonori Ishii,2 Takahisa Gono,3 Yumi Tsuchiya,4 Hiroki Ohashi,4 Katsunori Yoshizawa,4 Richuan Zheng,5 Maori Ayabe,6 Kazuko Nishikawa4

ABSTRACT
Objectives To evaluate the efficacy and safety of ustekinumab (UST) in a multicentre, randomised, double-blind, placebo-controlled trial in adult Japanese patients with active polymyositis (PM) and dermatomyositis (DM).
Methods Fifty-one Japanese adults diagnosed with active PM/DM who did not respond adequately to one or more standard-of-care treatments were randomised 1:1 to receive UST (n=25) or placebo (n=26). Participants received body weight-range based intravenous administration of UST (6 mg/kg) or placebo at week 0 followed by 90 mg subcutaneous (SC) administration of UST or placebo every 8 weeks from week 8 to week 24. At week 24, placebo group crossed over to receive body weight-range based intravenous administration of UST, and thereafter, all participants received/were to receive SC administration of UST 90 mg every 8 weeks (week 32 through to week 72). The primary efficacy endpoint was the proportion of participants who achieved minimal improvement (≥20) in the International Myositis Assessment and Clinical Studies Total Improvement Score (IMACS TIS) at week 24.
Results No statistically significant difference was seen in the proportion of participants who achieved minimal improvement (≥20) in IMACS TIS at week 24 between the treatment groups (UST 64.0% vs placebo 61.5%, p=0.94) based on the primary estimand of the primary endpoint analysis.
Conclusions UST was safe and well tolerated but did not meet the primary efficacy endpoint in adult Japanese participants with active PM/DM based on the primary analysis at week 24 in the study.
Trial registration number NCT03981744.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Existing therapies for idiopathic inflammatory myopathies (IIMs) including polymyositis (PM) and dermatomyositis (DM) are either cytotoxic or immunosuppressive and have notable safety risks.

WHAT THIS STUDY ADDS
⇒ Ustekinumab failed to demonstrate efficacy measured using the International Myositis Assessment and Clinical Studies Group Total Improvement Score in adult Japanese patients with active PM and DM at week 24.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ The findings of the present study add to the body of research in the treatment of IIMs and improve the understanding of the pathogenesis of disease. Furthermore, the information collected in this study may help optimise future clinical studies involving inflammatory myopathy treatments.

INTRODUCTION
Polymyositis (PM) and dermatomyositis (DM) are the major subsets of idiopathic inflammatory myopathies (IIMs), a heterogeneous disorder affecting skeletal muscle.1 The main clinical features of PM and DM include progressive symmetric, predominantly proximal muscle weakness along with a characteristic skin exanthema in DM. Manifestations also include other organs such as the heart, lungs, joints and the gastrointestinal tract.2 In view of unknown aetiology,
poor prognosis and lack of effective treatment, PM and DM have been designated as intractable diseases by the Ministry of Health, Labour and Welfare of Japan. Previous studies have reported that the estimated prevalence of PM/DM in Japan was 13.2/100 000 in 2010, and the incidence rate was estimated to be 10–13/1 000 000 person years to 2010. According to the updated information on epidemiology of the disease in Japan, there were 25 259 patients diagnosed with PM/DM in 2021 from the intractable disease registration database. Four main types of inflammatory myopathies are now widely recognised: DM, immune-mediated necrotising myopathy, sporadic inclusion-body myositis, overlap myositis (including antisynthetase syndrome) and PM. Recent studies suggested that the current IIM classification requires integration of clinicorheumatological approaches. Additional information along with transcriptomics, human leucocyte antigen haplotyping and potential biomarkers help tailoring categorisation that may have future diagnostic and therapeutic implications. IIMs are treated by immunosuppressive agents such as glucocorticoids (GCs) or synthetic or biological immunosuppressants. Although GCs are the first line treatment, systemic use of GCs induces various adverse effects on all body systems, and there is a study that reported 38% of patients on prednisolone had relapse. Immunosuppressive agents such as azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), tacrolimus (TAC) and cyclosporins have been found to be effective and introduced as steroid-sparing agents in different stages of the disease. While the combination of these agents reduces the risk of relapse during GC tapering, the effect is often limited and many patients fail to ameliorate muscle dysfunction as well as extramuscular symptoms. Intravenous immunoglobulin (IVIG) for refractory cases or rituximab for flare cases may be further options of treatment. DM despite treatment with one or more standard-care treatments. IL-12 could induce IL-21 producing T follicular helper (Thf) cell in a manner dependent on signal transducer and activator of transcription 4 (STAT4). It has been reported that IL-21 expression is upregulated in patients with PM/DM in both serum and muscle tissue. The number of Thf cells in patients with IIM was found to be increased compared with healthy control subjects. These findings indicate IL-12 blockade could reduce the inflammatory response related to Thf and IL-21. IL-12 and IL-23 secreted by dendritic cells help polarise Th1 and Th17 cells. The cytokines secreted by Th1 and Th17 cells, such as interferon-γ, play some role in development of myositis via upregulation of toll-like receptor 3 pathway.

Ustekinumab (UST) is a fully human IgG1 kappa monoclonal antibody (IgG1k) that binds with high affinity to the p40 subunit, common to both IL-12 and IL-23. This blocks the binding of IL-12 or IL-23 to the IL-12R receptor on the surface of natural killer cells and CD4+ T cells, inhibiting IL-12 and IL-23-specific intracellular signalling and their subsequent activation and cytokine production. Abnormal regulation of IL-12 and IL-23 has been associated with multiple inflammatory immunemediated diseases. UST has been approved for the treatment of plaque psoriasis, psoriatic arthritis, Crohn’s disease and ulcerative colitis. Though clinical usage of UST for PM/DM is limited, there is a case report of amyopathic dermatomyositis (ADM). As per this case report, a 20-year-old man had a history of ADM which was refractory to multiple immunosuppressors, developed psoriasis and responded well to treatment with UST. In addition, there was a report of successful treatment for refractory mechanic’s hand’s with UST in a patient with the antisynthetase syndrome.

The present study was planned to evaluate the efficacy of UST in Japanese participants with active PM/DM despite treatment with one or more standard-of-care treatments.

**METHODS**

**Study population and study design**

This was a phase 3, randomised, double-blind, placebo-controlled, parallel group multicentre intervention study. The study was conducted between 26 July 2019 and 12 July 2022, at 32 sites in Japan. We used the Consolidated Standards of Reporting Trials checklist to prepare our manuscript.

Participants or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

There were three amendments to the protocol. The details of each amendment are included in the protocol.

**Study population**

The study included Japanese men and women between the ages of 18 and 75 with active PM/DM who had not responded adequately to one or more standard-of-care
treatments; GC or immunomodulatory drugs (MMF, AZA, oral MTX, oral TAC or oral cyclosporine A) at the time of enrolment. Diagnoses of PM/DM had been made or confirmed by physicians experienced in PM/DM treatment, and the participants had a documented medical history that met the diagnostic criteria for probable or definite IIM based on the classification criteria of 2017 EULAR/American College of Rheumatology for adult and juvenile IIM. Participants were to exhibit muscle weakness at both the screening and week 0 as measured by Manual Muscle Testing (MMT)-8 with a score of ≤135 units. Furthermore, disease activity at the time of screening was confirmed by two or more of the following criteria:

1. Physician Global Assessment (PhGA) ≥1.5 cm.
2. One or more muscle enzymes (creatine kinase (CK) and aldolase) >1.4× the upper limit of normal.
3. Myositis Disease Activity Assessment Tool (MDAAT)-Extramuscular Global Assessment ≥1.5 cm.

Participants who had myositis other than PM/DM, other inflammatory diseases that might confound the evaluations of efficacy, severe respiratory muscle weakness, severe muscle damage by Myositis Damage Index-Visual Analogue Scale (VAS) >7 cm or GC-induced myopathy, positive test result for anti-MDA5 antibodies and previously received IVIG therapy were excluded from the study.

**Study intervention**

Participants received UST or placebo according to the randomisation scheme. At week 0, participants assigned to the active treatment group received an initial body weight-range based intravenous dose of UST at approximately 6 mg/kg (260 mg for weight ≤55 kg; 390 mg for weight >55 kg and ≤85 kg; 520 mg for weight >85 kg), while the placebo group received a single intravenous dose of placebo. Starting at week 8, participants received subcutaneous (SC) dosing of placebo or UST 90 mg every 8 weeks through week 24. At week 24, participants who received placebo crossed over and received body weight-range based intravenous administration of UST. Starting at week 32, all participants received SC dose of UST 90 mg every 8 weeks through week 72 (figure 1).

UST for intravenous administration was provided as a single-use, sterile solution in 30 mL vials with a single dose strength of 130 mg in a nominal volume of 26 mL. The solution also contained 10 mM L-histidine, 8.5% (w/v) sucrose, 0.04% (w/v) polysorbate 80, 0.4 mg/mL L-methionine and 20 µg/mL EDTA disodium salt dihydrate at pH 6.0 without preservatives. The matching placebo was also provided as a single use sterile solution in 30 mL vials with a nominal volume of 26 mL. It contained the same ingredients as the UST solution, except UST.

UST for SC administration was provided as a single-use prefilled syringe (PFS). Each PFS contained 90 mg of UST in a nominal volume of 1 mL. The UST solution in PFS contained nominal excipient concentrations of 6.7 mM L-histidine, 7.6% (w/v) sucrose, and 0.004% (w/v) polysorbate 80, at pH 6.0, without preservatives. The matching placebo had the same appearance as the UST PFS. Each PFS of placebo consisted of 10 mM L-histidine, 8.5% (w/v) sucrose, and 0.004% (w/v) polysorbate 80, at pH 6.0, without preservatives.

**Randomisation and blinding**

Participants were randomly assigned to one of the two intervention groups according to a computer-generated central randomisation schedule prepared before the study. Randomisation was balanced using randomly permuted blocks and stratified by disease subset (PM/DM, juvenile IIM). Participants were randomly assigned to one of the two intervention groups according to a computer-generated central randomisation schedule prepared before the study. Randomisation was balanced using randomly permuted blocks and stratified by disease subset (PM/DM, juvenile IIM).
DM) and baseline treatment level (GC dose (≥0.5 mg/kg/day or <0.5 mg/kg/day of prednisolone or equivalent)). The study intervention and the allocation of the matching drug kit were carried out using an Interactive Web Response System (IWRS) with a unique intervention code. Neither the participants nor the investigators knew what treatment the participants were receiving. The investigators did not receive randomisation codes. The codes were maintained in the IWRS until the final database lock (DBL) of this study.

Efficacy evaluations
The primary efficacy endpoint was the proportion of participants who achieved the minimal improvement (≥20) in the International Myositis Assessment and Clinical Studies Group Total Improvement Score (IMACS TIS) at week 24. The IMACS response criteria are a set of standardised guidelines used to evaluate minimal, moderate (≥40) and major (≥60) clinical improvement in participants with adult PM/DM. The criteria use six core measures (PhGA, Patient Global Activity (PtGA), MMT-8, muscle enzyme levels, extra-muscular assessment using MDAAT and Health Assessment Questionnaire Disability Index (HAQ-DI)) to calculate a TIS on a scale of 0–100. The TIS is determined by combining the absolute percentage change in each of the core measures with different weights assigned to each measure. These criteria provide a standardised method for assessing the clinical response to treatment in participants with PM/DM.

Secondary efficacy endpoints were the mean change from baseline in Functional Index-2 (FI-2), selected key measures of the IMACS core set that included PhGA, MMT-8 and muscle enzymes (CK, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase and aldolase) and MDAAT at week 24 along with the proportion of participants who experienced disease worsening through week 24. The worsening of disease was defined as one of the following criteria based on internal consensus guidelines developed by IMACS: (1) worsening of the PhGA by ≥2 cm on a 10 cm VAS and worsening of MMT-8 findings by ≥20% from baseline, (2) worsening of MDAAT-global extramuscular organ disease activity (a composite of constitutional, cutaneous, skeletal, gastrointestinal, pulmonary and cardiac activity) by ≥2 cm on a 10 cm VAS from baseline and (3) worsening of any of three IMACS core set activity measures by ≥30% from baseline.

The tertiary efficacy endpoints of the study were improvement and changes of PM/DM disease activity over time, reduction in systemic GC use, time to disease worsening at week 24, and patient-reported outcomes including PtGA, 36-item Short Form and HAQ-DI.

Safety evaluations
All adverse events (AE), administration reactions, clinical laboratory tests, vital signs and physical findings, ECG, chest CT and X-ray, blood gas analysis, pulmonary function tests and tuberculosis (TB) tests were evaluated and summarised.

Pharmacokinetic evaluations
Serum UST concentrations were measured using the validated, specific and sensitive immunoassay (electrochemiluminescence immunoassay (ECLIA)) method on the Meso Scale Discovery (MSD) platform or under the supervision of the sponsor. Serum UST concentrations were summarised over time for all participants who received UST.

Immunogenicity evaluations
The detection and characterisation of anti-UST antibodies were performed using a validated ECLIA method on MSD platform. Serum samples were screened for antibodies binding to UST. Serum samples that were tested positive for antibodies to UST were further characterised to determine the neutralising antibodies (NAbs) to UST. The incidence of anti-UST antibodies and NAbs to UST were summarised.

Statistical methods
Sample size determination
The sample size calculation was based on the primary endpoint, the proportion of participants who achieved the IMACS TIS response at week 24. To determine the effect size vs placebo used to calculate the sample size, meta-analyses were performed to synthesise the evidence. Considering the primary endpoint evaluation at week 24 in Japanese patients, a dropout rate of 5% was used to calculate the sample size. In particular, focusing on the effect size of 40%, which was considered a reasonable estimate of the effect size, a sample size of 50 participants was projected to give 82.2% power to detect a significant difference in response rate compared with placebo (assuming 25% and 65% response rates in placebo and UST, respectively, with the dropout rate of 5% in 24 weeks, which translates to an absolute 40% increase over placebo or an OR of 5.57) with an alpha level of 0.05 (two sides).

An Independent Data Monitoring Committee (IDMC) reviewed the futility analysis data conducted after 20 participants had completed the visit at week 24. The IDMC recommended continuing this study without futility stopping at this interim analysis. On receiving the IDMC interim analysis recommendation, this study continued until week 24 DBL. However, the study was terminated due to lack of efficacy based on the primary analysis result at week 24. No safety concerns were raised during the termination of the study.

Statistical analysis
Descriptive statistics (eg, mean, median, SD, IQR, minimum and maximum) were used to summarise continuous variables. Numbers and percentages were used to summarise categorical variables. Median values are reported for the time-to-event variables. In addition, graphical data displays (eg, line plots) and subject lists were used to summarise and present the data.
The primary estimand of this study was defined as the IMACS TIS binary response at week 24, where a responder was defined as a participant who achieved the IMACS TIS response at week 24 and did not have a prohibited change in PM/DM medications. A participant who had a prohibited change in PM/DM medications or discontinued treatment for any reason including COVID-19 but excluding other COVID-19 reasons was considered as a non-responder. Logistic regression adjusting for two stratification factors was used to analyse the primary endpoint. The magnitude of the effect was estimated by the OR in IMACS TIS response rates between the UST and placebo groups, the associated 95% CI, and the statistical significance of the difference. The study would have been considered positive if the proportion of IMACS TIS responders in the UST group had been significantly different from placebo (two-sided p value < 0.05). In addition, multiple imputation procedure was used to impute intermediate (non-monotone) missing data for all the participants.

All statistical tests were performed at a two-sided significance level of α=0.05.

RESULTS

Study population

This study was conducted at 32 sites in Japan and included 51 participants. The final set of efficacy analysis included data from the 51 enrolled participants randomly assigned to UST (n=25) or placebo (n=26). All participants who received at least one dose of the study agent were included in all randomisation analysis set.

Following the preplanned DBL at week 24, the primary endpoint was not met, and the sponsor discontinued the study on 17 March 2022. Data for this report were collected from 26 July 2019 to 12 July 2022.

All participants were Asian (Japanese). The majority of the participants were women (36/51; 70.6%). The median age was 53.0 years (range: 30–75 years) with a median body mass index of 22 kg/m² (range: 15.8–37.4 kg/m²). The median duration of the disease was 4.38 years, with 41.2% of the participants diagnosed with PM, while 58.8% diagnosed with DM. Detailed demographic and baseline characteristics are described in Table 1.

The baseline demographics and disease characteristics were generally balanced between the treatment groups, with few exceptions. In the UST group, there were more women participants (80%) compared with the placebo group (61.5%). Median CK was higher in the placebo group (202.50 U/L) compared with the UST group (170.00 U/L). The mean extramuscular evaluation (MDAAT) was higher in the UST group (3.19 cm) compared with the placebo group (2.33 cm). The UST group also had a higher mean baseline dose of GC (14.32 mg/day vs 12.57 mg/day) and a higher proportion of participants who received a baseline dose of GC more than 15 mg/day (36% vs 26.9%) compared with placebo. The baseline values for the IMACS TIS core sets of PhGA, PtGA, MMT-8, HAQ-DI and non-biological immunomodulators were generally balanced between the UST and placebo groups.

At baseline, 98.0% of the participants received GC(s) and 84.3% received at least one non-biological immunomodulator (TAC: 51.0 %, MTX: 15.7%, Cyclosporine A: 11.8%, MMF: 7.8%, AZA: 5.9%) (Table 1). The prior and concomitant use of PM/DM medications was comparable between treatment groups except for the dose of corticosteroids.

All participants received study drugs according to their assigned treatment groups. Through week 24, 3 (12.0%) participants discontinued the study treatment, of whom 2 (8.0%) participants discontinued the study and 1 (4.0%) subject continued study assessments in the UST group. The reasons for discontinuation were withdrawal by the subject (8.0%) and the initiation of prohibited medication (4.0%). No participants discontinued the study drug in the placebo group (Figure 2).

Overall, four participants (15.4%) in the placebo group and three participants (12.0%) in the UST group had a prohibited change in PM/DM medications through week 24. They were considered non-responders in efficacy analysis based on the primary estimand.

Efficacy findings

Primary efficacy endpoint

No statistically significant difference was seen in the proportion of participants who achieved minimal improvement (≥20) in IMACS TIS at week 24 between the treatment groups (UST 64.0% vs placebo 61.5%, p=0.937) based on the primary estimand of the primary endpoint analysis (Figures 3 and 4). All sensitivity and additional analyses also had similar results.

In the DM subtype, numerically higher response rates were observed in the UST group compared with placebo (66.7% vs 46.7%). However, in the PM subtype, a higher proportion of participants in the placebo group (Figures 3 and 5) achieved improvement than in the UST group (81.8% vs 60.0%).

Secondary efficacy endpoint

Change in the Fl-2 from baseline at week 24

A significantly higher improvement was observed from baseline in shoulder abduction (least square (LS) mean difference (95% CI): 7.97 (0.98, 14.96); p value =0.026) for the UST group compared with the placebo group (online supplemental figure 1). No notable differences were observed between the UST group and the placebo group in other muscle groups.

Disease worsening over time through week 24

A numerically lower proportion of participants in the UST group (28.0%, p=0.489) experienced worsening of the disease at week 24 (online supplemental figures 2 and 3) than in the placebo group (38.5%).

No statistically significant differences were observed in MMT-8 between the UST group and placebo (p value...
=0.787) from baseline at week 24. A similar response was observed for PhGA (p value =0.877), MDAAT (p value =0.817) and muscle enzymes (p value =0.974) between the UST group and the placebo group at week 24 (online supplemental figures 4 and 5).

Other efficacy endpoints
At week 24, a numerically higher proportion of participants achieved moderate improvement (≥40) in IMACS TIS in the UST group (52.0%, p value =0.273) than in the placebo group (34.6%). No significant differences were observed between the two groups in terms of the number of participants who achieved a major improvement (IMACS TIS ≥60, p value =0.216) in IMACS TIS (figure 6 and online supplemental figure 6).

A numerically greater reduction in PtGA of the change in disease activity from baseline at week 24 was observed in the UST group (LS mean difference (95% CI): −1.08 (−2.27, 0.11); p value =0.073) compared with the placebo group.

No significant differences were observed between the UST group and the placebo group with regard to the following endpoints: (1) the number of participants who reduced the use of systemic GC from baseline at week 24 (p value =0.930), (2) time to disease worsening through week 24 (p value =0.508) and (3) change in HAQ-DI from baseline at week 24 (p value =0.498).

Pharmacokinetic findings
Participants assigned to the active treatment group (n=25) received an initial body weight-range based
The intravenous dose of UST at ~6 mg/kg (260 mg for <55 kg (n=12); 390 mg for >55 and ≤85 kg (n=11); 520 mg for >85 kg (n=2)). Starting at week 8, all participants received SC dosing of UST at 90 mg every 8 weeks through week 24. After a single intravenous dosing of weight-range based UST, the median serum UST concentrations at 1-hour postdose were 108.396 µg/mL (95.990 µg/mL; 112.360 µg/mL; 150.753 µg/mL, respectively) and those at week 8 (prior to the first SC dose) were 9.477 µg/mL (9.657 µg/mL; 8.966 µg/mL; 13.371 µg/mL, respectively). After SC dosing of UST 90 mg every 8 weeks, the median serum UST concentrations were 4.623 and 4.629 µg/mL at weeks 16 and 24, respectively. Following the intravenous dose of UST, the steady-state UST concentration was achieved at the beginning of the second SC dose (week 16).

### Immunogenicity findings

Through week 24, there were no participants who had anti-UST antibodies.

### Safety findings

UST was well tolerated by all participants during the 24-week placebo-controlled period. Through week 24, 23/25 (92.0%) participants on UST and 18/26 (69.2%) participants on placebo had at least one treatment emergent adverse event (TEAE).

At least one serious AE (SAE) was reported in 5/25 (20.0%) participants in the UST group compared with 1/26 (3.8%) participant in the placebo group. The most common (reported in ≥2 participants in any treatment group) SAEs were herpes zoster; 1/26 (3.8%) participant in the placebo group and 2/25 (8.0%) participants in the UST group (table 2). There was one event each for diverticulitis, osteonecrosis and respiratory failure in UST group. Of these events, osteonecrosis was considered not related to the study drug. Although the causality for the remaining events were not completely excluded, predisposing risk factors such as interstitial lung disease (ILD) associated with the underlying disease as well as the use of high dose corticosteroids and immunomodulators

![Figure 2](http://rmdopen.bmj.com/)

**Figure 2** Consort diagram.

![Figure 3](http://rmdopen.bmj.com/)

**Figure 3** Primary endpoint: proportion of subjects who achieved minimal improvement (≥20) in IMACS TIS at week 24 and subgroup analysis: proportion of subjects who achieved minimal improvement (≥20) in IMACS TIS at week 24 by disease type.
confounded the assessment of the relationship with the study drug. None of the participants discontinued the study due to a TEAE through week 24. No deaths were reported before week 24 in the present study (table 2).

At least one infection was observed in 8/25 (32.0%) participants in the UST group compared with 11/26 (42.3%) participants in the placebo group. Serious infections were reported in 3/25 (12.0%) participants in the UST group (herpes zoster in 2/25 (8%) participants and diverticulitis in 1/25 (4%) participant) and 1/26 (3.8%) participant in the placebo group (herpes zoster) through week 24. As described above for SAEs, there were two events of herpes zoster (mild and moderate) and one event of diverticulitis (moderate) in the UST group, one event of herpes zoster in placebo group.

Through week 24, no participants in this study had infusion reactions, ILD, malignancy or active TB. Possible opportunistic infections of oesophageal candidiasis and injection site reaction were observed in each 1/26 (3.8%) participant in the placebo group compared with none in the UST group. No COVID-19 related AE was reported until week 24 in the present study.

The most common TEAEs by system organ class observed during the study were musculoskeletal and connective tissue disorders in the UST treatment group (32.0%) compared with the placebo group (19.2%). Of which, the most common AE reported was worsening of PM (16.0%) compared with the placebo group (3.8%) while trying to reduce corticosteroids.

**DISCUSSION**

The present study assessed the efficacy of UST in Japanese participants with active PM/DM despite treatment with one or more standard-of-care treatments. Although GC is the first line of therapy for PM/DM, monotherapy with GC has been reported to be associated with relapse following dose tapering. In order to overcome this, it is recommended to combine GC with immunosuppressive agents. The current treatment strategy for PM/DM is to help improve the patient’s ability to perform daily activities by strengthening muscles and avoiding flares and extramuscular disease in the vital organs. Despite previous reports suggesting that IL-12 and IL-23 signalling could be a therapeutic target in autoimmune myositis including some case reports, the present study did not achieve the primary efficacy endpoint as no significant differences were observed in terms of the proportion of participants who achieved minimal improvement (≥20) in IMACS TIS at week 24 between participants in the UST-treated group and placebo group.

One of the key difficulties in interpreting the results is the higher placebo rate, which made the assessment of the key study objectives impossible. This higher
several factors may have contributed to the insufficient agents such as UST and tocilizumab in clinical trials. The broadly targeted study population such PM/DM categories with potentially different disease characteristics, the variability between assessors and the effort of the participants. The availability of more objective quantitative measures based on mechanical measurements of muscle strength and mobility would allow a more accurate assessment of changes in disease activities of the participants with PM/DM in future studies.

In the present study, it was found that participants with a GC dose $\geq 15$ mg/day had a better IMACS TIS response regardless of the treatment group (online supplemental table 1). We hypothesised that a prestudy GC stabilisation period of 2 weeks may be too short to evaluate efficacy avoiding the background carry-over effect of GC even with the protocol defined GC tapering scheme during the study, especially when participants are on GC dose $>13$ mg/day at baseline. Furthermore, this study protocol allowed for the increase in GC dose up to the baseline dose only once through week 16 and for the continuation of the same dose only once for less than six consecutive weeks. There may be possibility that these rescue rules impacted the background effect of GC.

Outcomes frequently observed in clinical studies of different types of rheumatic diseases include a marked placebo effect, and a similar trend of improvement was observed in participants on placebo in this study, with nearly 60% of these participants achieving IMACS TIS with minimal improvement at week 24, which may have blunted the ability to assess the efficacy of UST. The finding that the placebo group performs in a similar fashion to that of UST-treated participants is consistent with the findings of a recent trial that reported the effect of tocilizumab in adult participants with refractory PM/DM. Participants with GC dose $\leq 15$ mg/day at baseline had a tendency to suppress the placebo response and it was more remarkable using IMACS TIS with moderate threshold in this study. To overcome the placebo effect, future studies may need to enrol participants with substantial activity of myositis disease despite stable treatments with titrated corticosteroids so that any effect of treatment is clearly visible.

It is also possible that the results of the present study were affected by the efficacy evaluation system, which included subjective and quantitative measures that could have been affected by the variability between assessors and the effort of the participants. The availability of more objective quantitative measures based on mechanical measurements of muscle strength and mobility would allow a more accurate assessment of changes in disease activities of the participants with PM/DM in future studies.

Consistent with the ProDERM trial that led to the approval of IVIG usage in DM, the present study also used IMACS TIS to assess the efficacy of UST treatment in participants with PM and DM. As the recent IIM research is moving toward more subdivided disease categories with potentially different disease characteristics, the broadly targeted study population such PM/DM may not be adequate when assessing targeted therapeutic agents such as UST and tocilizumab in clinical trials.

Upon review of the study data, we considered that several factors may have contributed to the insufficient presentation of the efficacy of UST in the treatment of PM/DM in this study.

In the present study, it was found that participants with a GC dose $>15$ mg/day had a better IMACS TIS response regardless of the treatment group (online supplemental table 1). We hypothesised that a prestudy GC stabilisation period of 2 weeks may be too short to evaluate efficacy avoiding the background carry-over effect of GC even with the protocol defined GC tapering scheme during the study, especially when participants are on GC dose $>13$ mg/day at baseline. Furthermore, this study protocol allowed for the increase in GC dose up to the baseline dose only once through week 16 and for the continuation of the same dose only once for less than six consecutive weeks. There may be possibility that these rescue rules impacted the background effect of GC.

Outcomes frequently observed in clinical studies of different types of rheumatic diseases include a marked placebo effect, and a similar trend of improvement was observed in participants on placebo in this study, with nearly 60% of these participants achieving IMACS TIS with minimal improvement at week 24, which may have blunted the ability to assess the efficacy of UST. The finding that the placebo group performs in a similar fashion to that of UST-treated participants is consistent with the findings of a recent trial that reported the effect of tocilizumab in adult participants with refractory PM/DM. Participants with GC dose $\leq 15$ mg/day at baseline had a tendency to suppress the placebo response and it was more remarkable using IMACS TIS with moderate threshold in this study. To overcome the placebo effect, future studies may need to enrol participants with substantial activity of myositis disease despite stable treatments with titrated corticosteroids so that any effect of treatment is clearly visible.

It is also possible that the results of the present study were affected by the efficacy evaluation system, which included subjective and quantitative measures that could have been affected by the variability between assessors and the effort of the participants. The availability of more objective quantitative measures based on mechanical measurements of muscle strength and mobility would allow a more accurate assessment of changes in disease activities of the participants with PM/DM in future studies.

Consistent with the ProDERM trial that led to the approval of IVIG usage in DM, the present study also used IMACS TIS to assess the efficacy of UST treatment in participants with PM and DM. As the recent IIM research is moving toward more subdivided disease categories with potentially different disease characteristics, the broadly targeted study population such PM/DM may not be adequate when assessing targeted therapeutic agents such as UST and tocilizumab in clinical trials.

Upon review of the study data, we considered that several factors may have contributed to the insufficient place of the efficacy of UST in the treatment of PM/DM in this study.
improvement threshold of ≥40 in those with baseline GC dose ≤15 mg/day. Interestingly, the UST response using the moderate threshold was 37.5% (n=6/16) and generally favorable against the placebo response of 10.5% (n=2/19) in participants with baseline GC dose ≤15 mg/day (online supplemental table 1). In addition, IMACS-TIS which was mainly established and validated through collaborative efforts in the USA and EU countries, might not be useful for the current study.31

Another factor related to the insufficient efficacy of UST in this study may be associated with the IIM subtype. In the DM subtype, numerically higher response rates were observed in the UST group compared with the placebo group (figure 3), although there were no statistically significant differences between the two groups. It may be worth re-evaluating the efficacy of UST in higher number of participants with the DM subtype. Further analysis for the disease subtypes including presence/absence of myositis specific autoantibodies could not be done due to the small sample size in the individual strata.

In this study, no new safety signals were identified and the overall safety results were consistent with the known safety profile of UST. Infections were the most commonly reported type of AEs. PK of UST was evaluated in participants with active systemic lupus erythematosus (SLE) at the same dose regimen as this study.37 Serum UST concentrations in the participants with active PM/DM were similar to the serum concentration observed in the participants with active SLE.

Limitations of the study

The present study was terminated early since the primary study end point at week 24 was not met.

CONCLUSIONS

Although UST was safe and well tolerated in the present study involving Japanese patients with active PM/DM with no new safety signals in addition to the profiles established with long-standing clinical use in other indications. The superiority of UST was not observed with respect to IMACS TIS with minimal improvement compared with placebo at week 24 under the present study settings. There is a possibility that these study results do not adequately evaluate whether UST is one of treatment options for PM/DM primarily due to the higher placebo response driven by various factors.

Author affiliations

1Department of Rheumatology and Allergology, St Marianna University School of Medicine, Kawasaki, Kanagawa, Japan
2Department of Hematology and Rheumatology, Tohoku University Hospital, Sendai, Miyagi, Japan
3Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan
4Research and Development, Janssen Pharmaceutical KK, Tokyo, Japan
5Statistics and Decision Sciences, Janssen Pharmaceutical KK, Tokyo, Japan
6Clinical Pharmacology and Pharmacometrics, Janssen Pharmaceutical KK, Tokyo, Japan

Acknowledgements

The authors appreciate the study participants in this trial, the staff members and all investigators at the clinical sites and the members of the independent data monitoring committee; the CNT012750MY3001 study team (Rieko Ishii, Maiko Kamei, Takeshi Mikami, Mayumi Mukai of Research and Development, Janssen Pharmaceutical K.K., Takayuki Kimura, formerly of Research and Development, Janssen Pharmaceutical K.K.). The writing support for the manuscript was provided by Pavithran Purushothaman of Syneos Health.

Contributors

Substantial intellectual contribution to conception and design: KK, YT, HO, YK, RZ, MA, KN. Acquisition of data or analysis and interpretation of data: KK, TI, TG, YT, HO, YK, RZ, MA, KN. Drafting the article or critically revising it for important intellectual content: KK, TI, TG, YT, HO, YK, RZ, MA, KN. Final approval of the version to be published: KK, TI, TG, YT, HO, YK, RZ, MA, KN. KN is the guarantor.

Funding

The study was funded by Janssen Pharmaceutical K.K. and Janssen Research and Development, LLC.

Competing interests

KK has received consulting fee as medical advisor, honoraria/speaking fees and support for conducting clinical studies (paid to the hospital) from Janssen. TI has received honoraria/speaking fees from Asahi Kasei, Astellas, Boehringer Ingelheim, Janssen, and Ono Pharmaceuticals and support for conducting clinical studies (paid to the hospital) from Janssen. TG has received honoraria/speaking fee from Asahi Kasei, Astellas, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Eisai, Janssen, MBL, Nippon Shinyaku, Pfizer, and Ono Pharmaceuticals and support for conducting clinical studies (paid to the hospital) from Janssen. YT, HO, RZ, MA and KN are employees of Janssen Pharmaceuticals. HO and KY are Janssen Pharmaceuticals employees and shareholders of Johnson & Johnson.

Patient consent for publication

Not applicable.

Ethics approval

This study involves human participants and this is a Japan local phase 3 study. The study was conducted according to the principles defined in the Declaration of Helsinki, the International Conference on Harmonization Guidelines (Good Clinical Practices) and local regulatory guidelines. All participants gave their informed written consent in writing prior to enrolling in the study. The investigatory review board at each study site approved the study protocol.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data may be obtained from a third party and are not publicly available. The Janssen Pharmaceutical Companies of Johnson & Johnson data sharing policy is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access [YODA] Project site at http://yoda.yale.edu.

Supplemental material

This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs

Kimito Kawahata http://orcid.org/0000-0002-4359-9897
Tomonori Ishii http://orcid.org/0000-0001-5361-5824
Takahisa Gono http://orcid.org/0000-0002-2593-1771
Yumi Tsuchiya http://orcid.org/0000-0008-9161-4708

REFERENCES


