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# Efficacy and Safety of Subcutaneous Abatacept Plus Standard Treatment for Active Idiopathic Inflammatory Myopathy: Phase 3 Randomized Controlled Trial

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**Objective.** Our objective was to evaluate the efficacy and safety of subcutaneous (SC) abatacept and standard of care (SOC) for the treatment of idiopathic inflammatory myopathy (IIM) over 52 weeks.

**Methods.** In this randomized, double-blind, placebo-controlled phase III trial, patients with treatment-refractory IIM received SC abatacept (at 125 mg weekly) with SOC (abatacept group) or a placebo with SOC (placebo group). A 24-week double-blind period was followed by an open-label period to assess outcomes from continued therapy with abatacept and initiation with abatacept (placebo-to-abatacept switch group) from 24 to 52 weeks. The primary end point was International Myositis Assessment and Clinical Studies definition of improvement (IMACS DOI) at week 24. Secondary efficacy and safety end points were assessed.

**Results.** Overall, 148 (double-blind) and 133 (open-label) patients were treated. Baseline demographics were well-balanced between treatment groups and disease subtypes. At 24 weeks, improvement per IMACS DOI was 56.0% for the abatacept group and 42.5% for the placebo group ($P = 0.083$); at 52 weeks, improvement was 69.8% (continued abatacept) and 69.0% (placebo-to-abatacept switch). The IMACS DOI rate at 24 weeks was greater in the nondermatomyositis (non-DM) group (abatacept: 57.1%; placebo: 32.3%; $P = 0.040$) than the DM group (abatacept: 55.0%; placebo: 50.0%; $P = 0.679$). The observed safety profile was similar in both groups.

**Conclusion.** The proportion of patients who met improvement criteria after 24 weeks was similar between abatacept and placebo groups. However, analysis by IIM subtype suggested there may be a sustained benefit of SC abatacept for patients with non-DM subtypes.

## INTRODUCTION

Idiopathic inflammatory myopathy (IIM) comprises a group of chronic, systemic autoimmune inflammatory diseases of unknown etiology that primarily affect skeletal muscle with or without cutaneous involvement and clinically manifest as muscle weakness with or without characteristic rashes.[1,2] Other organs, such as the lungs, joints, vasculature, and gastrointestinal tract, are commonly involved.[3] Polymyositis (PM), dermatomyositis (DM), antisynthetase syndrome, and immune-mediated necrotizing myopathy (IMNM)

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are among the most common subtypes of IIM.[2,4,5] Disease-specific autoantibodies can be detected in approximately 60% of patients with IIM and are highly specific for subtypes, possibly even predicting clinical and histologic features of the disease.[6] The long-term effects of IIM can lead to significant physical disabilities, organ damage, and increased mortality.[7]

Treatment for most subtypes of IIM is anchored on the administration of systemic immunotherapies.[8–10] Glucocorticoid treatment is commonly used as first-line therapy; however, because of the requirement of high doses and long-term administration, it is associated with significant side effects.[11] Additional therapies include conventional synthetic disease-modifying antirheumatic drugs, such as methotrexate or azathioprine, and gamma globulin.[11] The administration of novel targeted therapies has been reported, but there have been very few large, prospective, randomized controlled trials in this field.[10] Given the paucity of available treatments, the toxicity of agents such as immunosuppressives, and the chronic, debilitating, and potentially life-threatening nature of the disease, there is a significant unmet need for safe and effective new therapies in IIM.

Up-regulation of multiple costimulatory molecules, such as CTLA-4 and CD28, have been identified in the muscle tissue of patients with IIM.[12,13] Along with the expression of major histocompatibility complex molecules, this aberrant expression appears to impact normal immunoregulation in muscle and is associated with dysregulated T cell activity. Abatacept is a recombinant fusion protein consisting of the extracellular domain of human CTLA-4 and a fragment of the Fc domain of human Ig G1. Native CTLA-4 is a naturally occurring regulatory molecule that acts as a selective T cell costimulation modulator by binding to CD80 and CD86 on antigen-presenting cells. The CTLA-4 domain of abatacept blocks CD28 engagement with T cells, thereby inhibiting full activation of T cells.[14] Abatacept has a well-established history of safety and efficacy in the treatment of autoimmune diseases, such as rheumatoid arthritis.[15,16]

Multiple case reports and a small open-label controlled trial have suggested that abatacept may be effective for the treatment of patients with refractory IIM.[17–22] The Abatacept Treatment in Polymyositis and Dermatomyositis study (ClinicalTrials.gov: NCT01315938) demonstrated efficacy of intravenous abatacept in patients with DM and PM IIM subtypes.[23] In this "delayed-start" study, at the three-month time point after study start, 5 of 10 patients treated with abatacept were responders, compared with 1 of 7 patients treated with conventional background immunotherapies only. The current study evaluated the efficacy and safety of subcutaneous (SC) abatacept (at 125 mg weekly) in combination with standard treatment compared to placebo with standard treatment in patients with active refractory IIM.

## PATIENTS AND METHODS

**Study design.** This was a randomized, double-blind, placebo-controlled phase III trial (ClinicalTrials.gov: NCT02971683) of SC abatacept for patients with active, treatment-refractory IIM (patients for whom standard immunosuppression did not work in the past). SC abatacept (at 125 mg once weekly) plus standard of care (SOC) was compared with SOC alone for patients with DM and non-DM IIM. The study was conducted from May 4, 2017, to February 8, 2021, at 58 clinical sites in 11 countries.

Here, we report data from the two main periods of the study (Figure S1). Candidate screening could last up to 28 days. The 24-week double-blind period began when patients were randomized (via automated interactive voice response system) in a 1:1 ratio to either abatacept (at 125 mg weekly) with SOC (abatacept group) or placebo with SOC (placebo group). Study drug administration was initiated at the time of randomization. At the discretion of the investigator, patients in either treatment group with worsening disease between weeks 12 and 24 were permitted to initiate rescue therapy if criteria for worsening disease were met. Worsening disease was defined as follows: (1) increase of ≥2 cm on visual analog scale (VAS) for physician global assessment of disease activity (PhGA), and either a ≥20% worsening in Manual Muscle Test-8 (MMT-8) score or an increase of ≥2 cm on VAS for extramuscular global activity assessed on the Myositis Disease Activity Assessment Tool (MDAAT) compared with baseline; or (2) any three of the six International Myositis Assessment and Clinical Studies (IMACS) core set measures worsening by ≥30% compared with baseline on two consecutive visits. IMACS definition of improvement (DOI) was based on six core measures (PhGA, patient global assessment of disease activity, MMT-8, Health Assessment Questionnaire-Disability Index [HAQ-DI], muscle enzyme levels, and extramuscular global disease activity as defined by MDAAT extramuscular global activity VAS).[24] Rescue therapy was given at the discretion of the clinician and included an increase in dose of current SOC therapy, addition of a new therapy or change in therapy. Rescue therapy was restricted to allowable concomitant medication per protocol: glucocorticoids alone, an immunosuppressant (methotrexate, azathioprine, mycophenolate, tacrolimus, or cyclosporine), or a combination of glucocorticoids and one of the listed immunosuppressants. Patients requiring rescue therapy remained anonymized to medication through week 24 and were able to enter the open-label period.

The open-label period consisted of an additional 28 weeks (weeks 24–52; Figure S1). At completion of the last double-blind visit, all patients in the placebo group were eligible to switch to SC abatacept (at 125 mg weekly) treatment in combination with SOC for the open-label period. The results summarized here for the open-label period are presented based on patients' original treatment group assignments during the double-blind period (abatacept or placebo).

This study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki. The study received appropriate approval by a central institutional review board (IRB)/independent ethics committee before initiation. Additionally, full board approval was obtained from the respective

governing IRBs and documentation of approval was submitted to the sponsor before initiating any study procedures. All patients or their legal representative provided written informed consent.

Consideration was given to the potential impact of the COVID-19 pandemic to study analyses and interpretations. Although the pandemic impacted key study visits for some participants, no adjustment to the analyses was considered necessary.

**Study population.** Patients with IIM including DM, PM, IMNM, juvenile myositis (JM), or overlap myositis subtypes were eligible for enrollment. Diagnosis was based on the Bohan and Peter classification criteria.[25] A diagnosis of DM required a confirmed characteristic rash. PM, IMNM, JM, or overlap myositis diagnoses had to be confirmed by previous muscle biopsy or a positive test for ≥1 myositis-specific autoantibody, available from either previous testing or testing at screening. Inclusion criteria were age ≥18 years, active treatment-refractory disease with muscle weakness, and taking background SOC (see Supplementary Methods).

Active IIM was determined by one of two approaches. Patient clinical history, clinical evaluation and testing (laboratories and studies) were reviewed by an independent expert adjudication committee who were asked to ascertain whether the patient had clearly active disease. Candidates could meet activity criteria without committee review if they met any one of these criteria: currently active myositis-associated rash, recent (within three months) muscle biopsy, magnetic resonance imaging, or electromyogram demonstrating active disease or creatine kinase more than five times the upper limit of normal (ULN) at screening. Patients were required to present with muscle weakness defined as an MMT-8 score ≤135 units at the time of screening. Additionally, eligibility required three of the six IMACS core set measures to be abnormal according to the following thresholds: MMT-8 ≤125 units; PhGA, or patient global assessment VAS ≥2; HAQ-DI ≥0.5; one or more muscle enzyme ≥1.3 times the ULN; or MDAAT extramuscular global activity VAS ≥2. Overall eligibility of patients including diagnosis and disease activity was determined by an adjudication committee composed of IIM experts who evaluated patient medical records and adjudication forms submitted by study sites.

Patients were required to be started on SOC for IIM, defined as treatment with glucocorticoids and/or one of the following immunosuppressants: methotrexate, azathioprine, mycophenolate, tacrolimus, or cyclosporine. Dosages up to 30 mg/day of prednisone (or the equivalent) were allowed as SOC. Combinations of nonglucocorticoid immunosuppressants were not permitted during the double-blind period. Patients must have been taking the same medication(s) for IIM for 12 weeks before randomization (including a stable dosage for at least four weeks before randomization). Patients receiving azathioprine must have started at least 24 weeks before randomization (stable dosage for 12 weeks before randomization). SOC changes were not allowed in the double-blind phase (except those required for toxicity or intolerance) but could be adjusted during the open-label period. Exclusion criteria are summarized in the Supplementary Methods; notably, patients with inclusion body myositis, severe muscle damage, severe pulmonary disease, and administration of rituximab and Ig within past six and three months, respectively, were excluded.

**Patient and public involvement.** Before completing the protocol, the research team engaged with both patients and patient advocacy groups for their input on the trial design using Bristol Myers Squibb's patient engagement group resources. Additionally, communications with patient advocacy groups occurred throughout the study regarding enrollment status. There was no patient or public involvement in the analysis or reporting of this study.

**Study measures.** *Efficacy.* The primary efficacy end point was achieving IMACS DOI, based on the six aforementioned core measures, at week 24 in patients who did not require rescue therapy. Achievement of IMACS DOI was defined as meeting the following criteria: (1) improvement of ≥20% in any three IMACS core measures, (2) ≤2 IMACS core measure scores worsening by ≥25%, and (3) MMT-8 score worsening by <25%. All patients who discontinued study medication before week 24 and/or received rescue medication at any time during the 24-week double-blind period (defined as nonresponders) were considered as not achieving IMACS DOI for the primary analysis.

Secondary end points were mean changes at week 24 in Myositis Functional Index-2 using three proximal muscle groups (FI-3, calculated from FI-2 testing), HAQ-DI, extramuscular global disease activity, and Myositis Response Criteria (MRC) (with Total Improvement Score [TIS] of ≥20 as minimal improvement).[26–28] TIS ranged from 0 to 100, and MRC categories were based on TIS and categorized per TIS thresholds for minimal, moderate, and major improvement (≥20, ≥40, and ≥60 points, respectively).

Exploratory end points included IMACS DOI, MRC TIS, mean changes in FI-3, HAQ-DI, and extramuscular global activity at week 52. The proportion of patients with minimal, moderate, and major improvement in disease by MRC score; mean changes in MMT-8, individual PhGA, and patient global assessment scores; and Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity and damage scores were assessed at weeks 24 and 52.[29]

*Safety.* Adverse events (AEs), serious AEs (SAEs), and deaths were recorded. The safety analyses specified for the week 24 analysis were to be performed for the open-label period.

**Statistical analyses.** A sample size of 150 patients was planned based on the primary comparison of the proportion of patients with IMACS DOI at week 24 between the SC abatacept and the SC placebo groups on background SOC. With a 1:1

randomization, this would yield a power of approximately 90% to detect a treatment difference of 27% in the rate of IMACS DOI between the treatment groups based on a continuity corrected chi-square test. Analysis of the primary end point by IIM subtype (DM vs non-DM) was prespecified.

Efficacy end points were assessed in the intent-to-treat (ITT) population, which consisted of all patients randomly assigned and treated (with at least one dose of abatacept or placebo) in the double-blind period. Efficacy end points were assessed in the open-label abatacept population, which comprised all patients treated with at least one dose of abatacept during the open-label period. Safety end points were assessed in the as-treated population, which comprised all patients randomly assigned and treated in the double-blind period or the previously defined open-label abatacept population. Prespecified analyses by IIM subtype were performed and reported as overall, DM, and non-DM (PM and IMNM).

*Double-blind period.* For the primary end point, the proportion of patients meeting IMACS DOI at week 24 and not requiring rescue therapy was compared between the abatacept and placebo groups using a logistic regression model. Point estimates of the adjusted odds ratios (ORs) of the likelihood of achieving DOI and not requiring rescue therapy in the abatacept group compared with the placebo group were calculated with corresponding 95% confidence intervals (CIs) and *P* values. Secondary end points were assessed using a longitudinal (repeated measures) model. Adjusted means, standard errors, and 95% CIs for the adjusted mean difference between treatment groups were calculated. Primary end point data for 11 active participants were not available for week 24. The COVID-19 pandemic impacted data collection for five patients who were unable to attend in-person site visits to complete study assessments because of pandemic-related restrictions; data were missing for other reasons for six additional patients. No adjustments to the prespecified analyses were considered necessary.

*Open-label period.* All patients who were treated during the open-label period were included in the open-label analysis, which was performed once all patients completed 52 weeks of study treatment. No formal statistical testing was conducted for any of the efficacy analyses. The open-label period analyses were based on the open-label–treated analysis population and are presented by patient treatment group during the double-blind period (abatacept or placebo). BMS policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

## RESULTS

**Patient disposition, demographics, and disease characteristics.** Overall, 202 patients were enrolled, 149 patients were randomly assigned (75 in the abatacept group and 73 in the placebo group; one patient was randomly assigned and not treated), and 134 patients (89.9%) completed the double-blind period and entered the open-label period (Figure 1). The overall rates of discontinuation were low: 6 patients (8.0%) and 8 patients (11.0%) in the double-blind period for the abatacept and placebo groups, respectively (Figure 1). Based on ITT analysis, these 14 patients were considered nonresponders for the primary end point. None of the enrolled patients

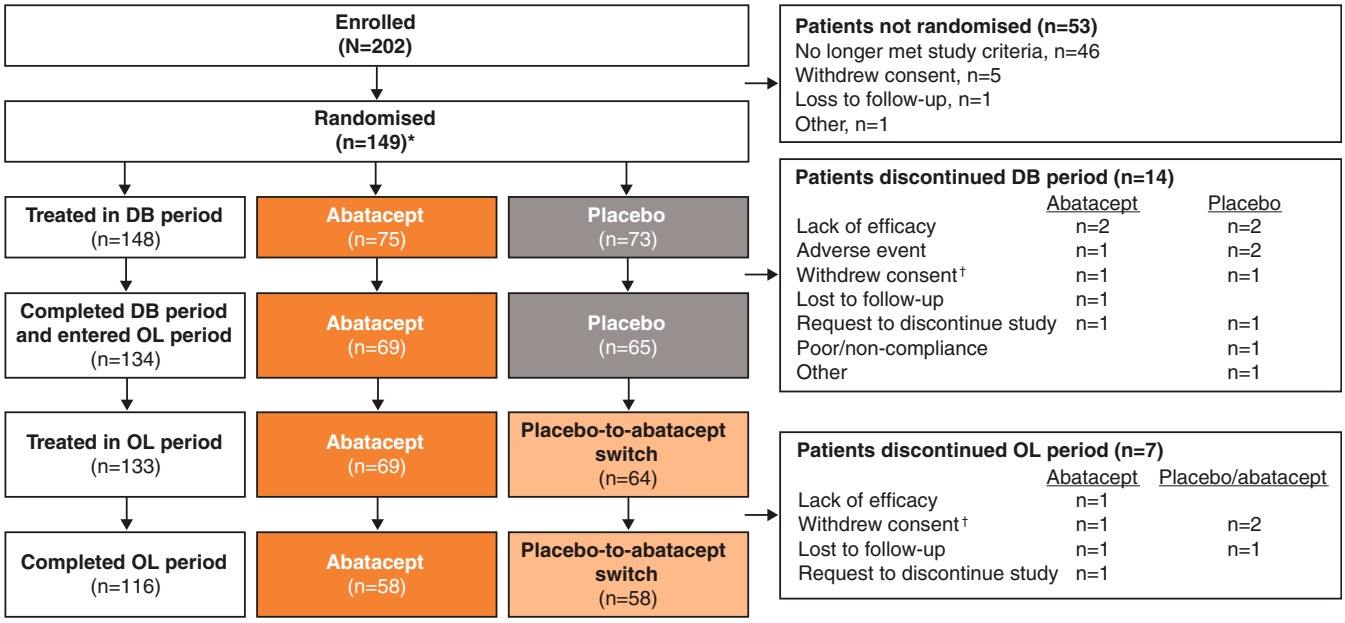



**Figure 1.** Patient disposition. *One patient was randomly assigned but not treated, leaving 148 randomly assigned and treated. †Includes patient request to discontinue treatment and patient withdrew consent. DB, double-blind; OL, open label. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.43066/abstract.

had JM or overlap myositis; therefore, the IIM population only comprised patients with DM, PM, and IMNM.

The proportions of patients across treatment groups from each country included in the analysis were similar (Table S1). Baseline demographics and disease characteristics were similar across treatment groups (Table 1) and disease subtypes (Table S2) and were typical for this patient population. Overall, the mean age of patients was 48.7 (SD ±14.2) years, and the majority of patients were female (71.6%) and White (56.8%) (Table 1). Previous and concomitant use of glucocorticoids and immunosuppressants was comparable between treatment groups; concomitant glucocorticoid and an immunosuppressant agent were the most common SOC (Table S3). Overall, 55.4% of patients in both treatment groups had DM (Table 1); patients with PM and IMNM comprised the remainder (abatacept: 25.3% and 21.3%; placebo: 34.2% and 8.2%, respectively). Patients had significant muscle weakness, with a mean MMT-8 score of 113.0 (SD ±18.1), and notable active disease indicated by a mean PhGA score of 5.4 (SD ±1.5). However, the mean extramuscular global activity VAS was low (2.6), and the skin disease activity score was moderate (mean CDASI activity score 15.5) for both groups. One patient in each treatment group met the criteria of worsening disease and received rescue therapy during the double-blind period; both patients were rescued with an increase in dose of current therapy and were considered as not achieving DOI for the primary objective analysis per the protocol.

*Open-label period.* A total of 133 patients were treated in the open-label period; 69 patients continued abatacept from the double-blind period, and 64 patients switched from a placebo to

**Table 1.** Baseline demographics and disease characteristics for patients with IIM during the double-blind period (week 24, intent-to-treat analysis population)*

| Characteristic | Abatacept (n = 75) | Placebo (n = 73) | Total (N = 148) |
|---|---|---|---|
| Patients completed treatment, n (%) | 69 (92.0) | 65 (89.0) | 134 (90.5) |
| Age, mean (SD), yr | 49.3 (14.4) | 48.1 (14.1) | 48.7 (14.2) |
| Female, n (%) | 52 (69.3) | 54 (74.0) | 106 (71.6) |
| Hispanic or Latino, n (%) | 7 (9.3) | 3 (4.1) | 10 (6.8) |
| Not Hispanic or Latino, n (%) | 19 (25.3) | 19 (26.0) | 38 (25.7) |
| Race, n (%) | | | |
| White | 42 (56.0) | 42 (57.5) | 84 (56.8) |
| Black or African American | 9 (12.0) | 8 (11.0) | 17 (11.5) |
| American Indian or Alaska Native | 3 (4.0) | 3 (4.1) | 6 (4.1) |
| Asian | 10 (13.3) | 6 (8.2) | 16 (10.8) |
| Japanese | 11 (14.7) | 10 (13.7) | 21 (14.2) |
| Other | 0 | 3 (4.1) | 3 (2.0) |
| Unknown | 0 | 1 (1.4) | 1 (0.7) |
| Geographic region, n (%) | | | |
| North America | 26 (34.7) | 22 (30.1) | 48 (32.4) |
| South America | 18 (24.0) | 26 (35.6) | 44 (29.7) |
| Asia | 20 (26.7) | 16 (21.9) | 36 (24.3) |
| Europe | 11 (14.7) | 9 (12.3) | 20 (13.5) |
| Others | 0 (0) | 0 (0) | 0 (0) |
| Disease duration, mean (SD), mo | 61.8 (60.2) | 58.3 (55.4) | 60.1 (57.7) |
| IIM type, n (%) | | | |
| DM | 40 (53.3) | 42 (57.5) | 82 (55.4) |
| PM | 19 (25.3) | 25 (34.2) | 44 (29.7) |
| IMNM | 16 (21.3) | 6 (8.2) | 22 (14.9) |
| Disease activity, mean (SD)[a] | | | |
| Physician global assessment of disease activity[b] | 5.4 (1.6) | 5.4 (1.5) | 5.4 (1.5) |
| Patient global assessment of disease activity[b] | 6.3 (2.1) | 6.2 (2.2) | 6.2 (2.2) |
| Extramuscular global activity[b] | 2.4 (2.2) | 2.7 (2.4) | 2.6 (2.3) |
| MMT-8 score, mean (SD)[a] | 115.1 (17.1) | 110.8 (18.9) | 113.0 (18.1) |
| HAQ-DI score, mean (SD)[a] | 1.5 (0.7) | 1.4 (0.7) | 1.5 (0.7) |
| CDASI score, mean (SD) | | | |
| Activity | 15.2 (15.1) | 15.8 (13.9) | 15.5 (14.4) |
| Damage | 1.8 (3.5) | 1.8 (2.9) | 1.8 (3.2) |
| Muscle enzyme, mean (SD), CK (U/L)[a] | 1,301.5 (1,844.0) | 1,111.0 (2,024.5) | 1,207.5 (1,930.9) |
| Concomitant medications of special interest, n (%) | | | |
| Systemic glucocorticoids | 66 (88.0) | 64 (87.7) | 130 (87.8) |
| Immunosuppressive agents | 56 (74.7) | 54 (74.0) | 110 (74.3) |

* CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; CK, creatinine kinase; DM, dermatomyositis; HAQ-DI, Health Assessment Questionnaire-Disability Index; IIM, idiopathic inflammatory myopathy; IMNM, immune-mediated necrotizing myopathy; MMT-8, Manual Muscle Test-8; PM, polymyositis.
[a] Core set measure.
[b] 100-mm visual analog scale.

**Table 2.** Primary, secondary, and exploratory end points by treatment group and disease comparisons for the double-blind period (24 weeks, intent-to-treat analysis population)*

| Outcome and IIM types | Abatacept (n = 75) | Placebo (n = 73) | Nominal *P* value or adjusted mean difference from placebo (95% CI)[a] |
|---|---|---|---|
| Primary end point: IMACS DOI without requiring rescue, n/m (%) | | | |
| All | 42/75 (56.0) | 31/73 (42.5) | 0.083 |
| DM | 22/40 (55.0) | 21/42 (50.0) | 0.679 |
| Non-DM | 20/35 (57.1) | 10/31 (32.3) | 0.040 |
| MRC (mean TIS), adjusted mean change from baseline (SE) | | | |
| All | 40.8 (2.9), n = 62 | 37.2 (3.0), n = 58 | 3.6 (−2.9 to 10.1) |
| DM | 46.0 (3.2), n = 31 | 43.6 (3.1), n = 35 | 2.5 (−6.5 to 11.4) |
| Non-DM | 38.4 (3.2), n = 31 | 31.7 (3.6), n = 23 | 6.6 (−3.1 to 16.4) |
| Patients meeting MRC (TIS), n/m (%) | | | |
| All | | | |
| Moderate + major response | 36/62 (58.1) | 29/58 (50.0) | N/A |
| DM | | | |
| Moderate + major response | 19/31 (61.3) | 22/35 (62.9) | N/A |
| Non-DM | | | |
| Moderate + major response | 17/31 (54.8) | 7/23 (30.4) | N/A |
| FI-3, adjusted mean (SE) change from baseline | | | |
| All | 4.1 (1.3), n = 59 | 1.2 (1.4), n = 58 | 2.9 (0 to 5.8) |
| DM | 2.3 (1.6), n = 29 | 0.3 (1.4), n = 35 | 1.9 (−2.3 to 6.2) |
| Non-DM | 3.2 (1.4), n = 30 | −0.6 (1.5), n = 23 | 3.7 (−0.3 to 7.8) |
| HAQ-DI score,[b] adjusted mean (SE) change from baseline | | | |
| All | −0.3 (0.1), n = 66 | −0.2 (0.1), n = 62 | −0.1 (−0.3 to 0.0) |
| DM | −0.3 (0.1), n = 35 | −0.2 (0.1), n = 37 | −0.1 (−0.3 to 0.1) |
| Non-DM | −0.3 (0.1), n = 31 | −0.1 (0.1), n = 25 | −0.2 (−0.4 to 0.1) |
| Extramuscular global activity,[b] adjusted mean (SE) change from baseline | | | |
| All | −1.6 (0.2), n = 63 | −1.4 (0.2), n = 60 | −0.2 (−0.6 to 0.3) |
| DM | −1.9 (0.3), n = 32 | −1.9 (0.3), n = 36 | −0.1 (−0.8 to 0.7) |
| Non-DM | −1.1 (0.2), n = 31 | −0.9 (0.2), n = 24 | −0.2 (−0.8 to 0.3) |
| MMT-8 score,[b] adjusted mean (SE) change from baseline | | | |
| All | 12.9 (1.9), n = 64 | 11.0 (2.0), n = 59 | 1.8 (−2.7 to 6.4) |
| DM | 14.4 (2.2), n = 33 | 14.0 (2.1), n = 35 | 0.4 (−5.7 to 6.4) |
| Non-DM | 12.1 (2.5), n = 31 | 7.8 (2.7), n = 24 | 4.3 (−3.0 to 11.7) |
| Physician global assessment of disease activity,[b,c] adjusted mean (SE) change from baseline | | | |
| All | −2.9 (0.3), n = 65 | −2.7 (0.3), n = 62 | −0.2 (−0.9 to 0.5) |
| DM | −2.8 (0.3), n = 34 | −2.4 (0.3), n = 37 | −0.4 (−1.2 to 0.5) |
| Non-DM | −2.4 (0.4), n = 31 | −2.2 (0.5), n = 25 | −0.1 (−1.4 to 1.2) |
| Patient global assessment of disease activity,[b,c] adjusted mean (SE) change from baseline | | | |

(Continued)

**Table 2.** (*Cont'd*)

| Outcome and IIM types | Abatacept (n = 75) | Placebo (n = 73) | Nominal *P* value or adjusted mean difference from placebo (95% CI)[a] |
|---|---|---|---|
| All | −1.4 (0.3), n = 66 | −0.1 (0.3), n = 62 | −0.4 (−1.1 to 0.4) |
| DM | −1.4 (0.3), n = 35 | −1.4 (0.3), n = 37 | −0.0 (−0.9 to 0.9) |
| Non-DM | −1.2 (0.4), n = 31 | −0.3 (0.5), n = 25 | −0.9 (−2.1 to 0.3) |
| CDASI score, adjusted mean (SE) change from baseline | n = 32 | n = 34 | – |
| Activity | −3.9 (2.8) | −4.4 (2.8) | 0.5 (−2.7 to 3.7) |
| Damage | −0.2 (0.9) | −0.2 (0.9) | 0.0 (−1.0 to 0.9) |
| Muscle enzyme,[b] CK (U/L), adjusted mean (SE) change from baseline | | | |
| All | −390.1 (142.3), n = 67 | −63.1 (145.9), n = 61 | −327.1 (−684.2 to 30.0) |
| DM | −270.5 (61.1), n = 35 | −24.3 (59.4), n = 36 | −246.1 (−413.9 to 78.3) |
| Non-DM | −475.8 (239.7), n = 32 | −117.3 (264.9), n = 25 | −358.5 (−1,074.6 to 357.6) |

* CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; CI, confidence interval; CK, creatine kinase; DM, dermatomyositis; FI-3, Functional Index-2 using three proximal muscle groups; HAQ-DI, Health Assessment Questionnaire-Disability Index; IIM, idiopathic inflammatory myopathy; IMACS DOI, International Myositis Assessment and Clinical Studies definition of improvement; MMT-8, Manual Muscle Test-8; MRC, Myositis Response Criteria; N/A, not applicable; n/m, number of patients with response/number of patients in the analysis; TIS, Total Improvement Score.
[a] Abatacept vs placebo.
[b] Core set measure.
[c] 100-mm visual analog scale.

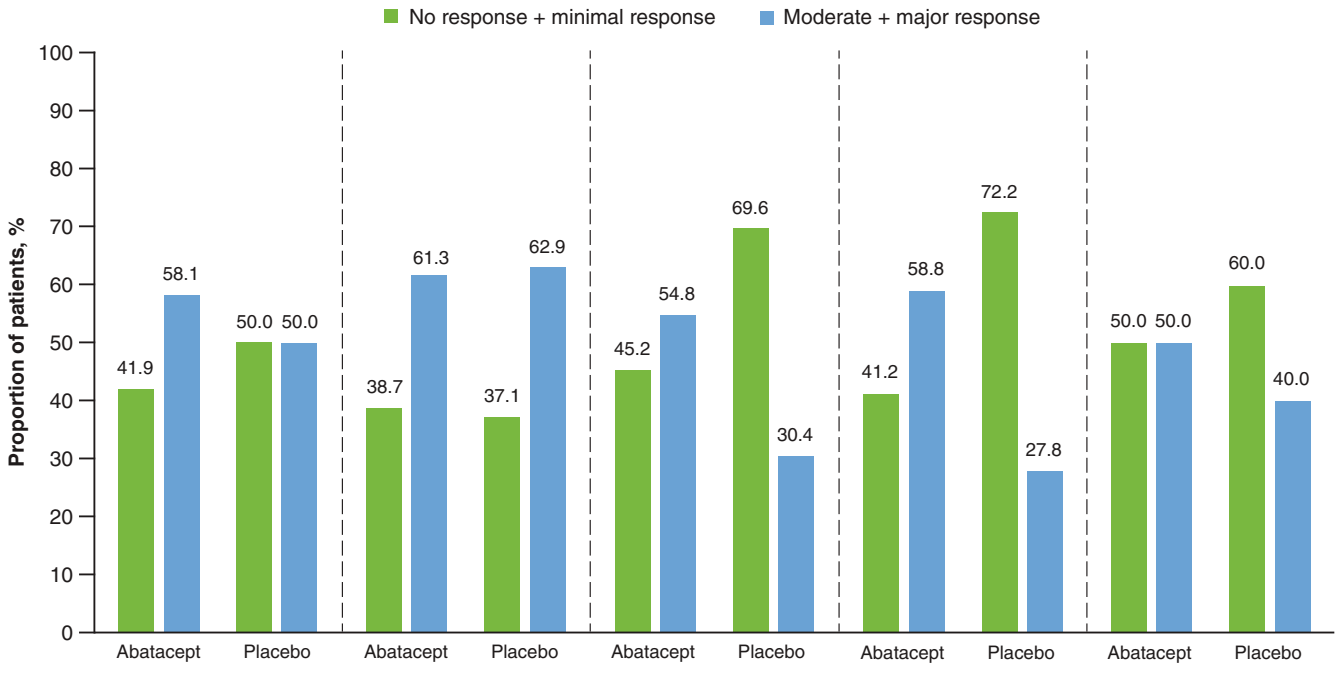
abatacept. Approximately 95% of patients (n = 126) completed the open-label period. The overall rates of discontinuation in the open-label period were low: four patients (5.8%) and three patients (4.7%) in the abatacept and placebo-to-abatacept switch groups, respectively. Among the seven patients who discontinued the open-label period, the most common reasons for discontinuing included lack of efficacy, consent withdrawal, and loss to follow-up. The abatacept and placebo-to-abatacept switch treatment groups were well-balanced for the proportion of patients with DM (52.2% vs 60.9%, respectively) and PM (27.5% vs 31.3%, respectively). The baseline disease characteristics for patients in the open-label period did not differ significantly from those of patients in the double-blind period.

**Primary and secondary efficacy end points.** *Double-blind period.* The primary end point of proportion of patients meeting IMACS DOI at week 24 and not requiring rescue therapy was achieved by 56.0% of the abatacept group and 42.5% of the placebo group (adjusted OR 1.8, 95% CI 0.9–3.5; $P = 0.083$) (Table 2). No significant between-treatment differences were observed for the primary end point for patients with DM, but the non-DM (PM and IMNM) subtypes showed higher IMACS DOI rates in the abatacept group compared with placebo (57.1% vs 32.3%; $P = 0.040$) (Table 2). Only one patient in each treatment arm required rescue in the double-blind phase after meeting the criteria of worsening disease. Rates of achieving secondary end points, IMACS core measures, and FI-3 were numerically higher in the abatacept group compared with the placebo group; these treatment benefits were more notable for the non-DM (PM and IMNM) than the DM subtypes (Table 2, Table S4).

Overall, MRC categories of minimal, moderate and major improvement were comparable between the abatacept and placebo groups (Table 2). It is worth noting that the total number of patients for mean TIS and TIS categories was reduced from 75 to 62 patients in the abatacept group and from 73 to 58 patients in the placebo group because some core set measures were missed for some patients due to isolation and social distancing measures during the COVID-19 pandemic. Post hoc analysis for the MRC mean TIS category at week 24 showed greater improvement with abatacept versus placebo in the non-DM subtype (adjusted mean difference from placebo 6.6, 95% CI –3.1 to 16.4), whereas the difference in the DM subtype was not as pronounced (2.5, 95% CI –6.5 to 11.4; Figure 2).

*Open-label period.* In the open-label–treated analysis population at week 52, the proportion of patients achieving IMACS DOI at week 52 demonstrated a sustained benefit in continuing abatacept and an improvement when switching from a placebo to abatacept (proportion of patients achieving IMACS DOI: 69.8% [abatacept], 69.0% [placebo-to-abatacept switch]; Table 3, Figure S2A).

Similarly, MRC TIS continued to improve in both groups in the open-label period (Figures S3 and S2B). The proportion of patients in IMACS DOI and the MRC TIS over time in the abatacept and placebo groups with non-DM subtype are shown in Figures S2C and S2D. The proportion of patients without DM showing moderate-to-major response to abatacept was 54.8% at week 24 and 67.9% at week 52. For the placebo non-DM subtype, the proportion of patients showing moderate-to-major response was only 30.4%, which increased to 55.6% after




| | All | | DM | | Non-DM | | PM | | IMNM | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Abatacept | Placebo | Abatacept | Placebo | Abatacept | Placebo | Abatacept | Placebo | Abatacept | Placebo |
| Adjusted mean MRC TIS | 41.5 (n=47) | 38.7 (n=45) | 46.0 (n=31) | 43.6 (n=35) | 38.4 (n=31) | 31.7 (n=23) | 39.5 (n=17) | 32.0 (n=18) | 36.9 (n=14) | 33.5 (n=5) |

**Figure 2.** MRC at week 24 by TIS category (intent-to-treat analysis population). DM, dermatomyositis; IMNM, immune-mediated necrotizing myopathy; MRC, Myositis Response Criteria; PM, polymyositis; TIS, Total Improvement Score.

switching to abatacept in the open-label period. Other study end points also showed continued improvement, with a mean improvement from the baseline of 5.0 and 4.6 for FI-3 and –6.7 and –8.1 for CDASI in abatacept and placebo-to-abatacept switch groups, respectively, as well as –0.4 for HAQ-DI for both groups (Table 3).

**Safety.** *Double-blind period.* During the double-blind period, the observed safety end points were similar between the abatacept and placebo groups (Table 4) and consistent with the known safety profile of abatacept. The overall frequencies of AEs, SAEs, and AEs leading to discontinuation were comparable between the abatacept and placebo groups; four patients experienced SAEs in each treatment group.

Infections were reported in 25.3% of patients in the abatacept group and 42.5% of patients in the placebo group. Most of the reported infections were mild or moderate in intensity (17 patients [22.7%] in the abatacept group; 31 patients [42.4%] in the placebo group). No malignancies were reported in the abatacept or placebo groups. One death in the placebo arm was due to an unexplained acute respiratory event. No new safety concerns were identified during the double-blind period.

*Open-label period.* During the open-label period, the observed safety profile was consistent with that of the double-blind period and the known safety profile of abatacept (Table 4). SAEs were reported in 10 patients (14.5%) receiving abatacept and 4 patients (6.3%) in the placebo-to-abatacept switch group; most were considered unrelated to treatment. A total of four serious infections were reported, all of which were resolved, and the study drug was continued. COVID-19 was reported in one patient receiving abatacept, which led to a brief hospitalization. AEs were reported in 45 abatacept patients (65.2%) and 37 placebo-to-abatacept switch patients (57.8%). Infections were reported in 23 patients (33.3%) in the abatacept group and 17 patients (26.6%) in the placebo-to-abatacept switch group.

## DISCUSSION

This was a large, multicenter, global, randomized controlled trial of 149 patients with IIM. The study failed to meet the primary objective of having an increase in the proportion of patients who met the improvement criteria (IMACS DOI) after 24 weeks of treatment with SC abatacept plus SOC compared with patients treated with placebo plus SOC. The observed responder rate in the treatment arm (56.0%) was very close to the rate expected

**Table 3.** Primary and secondary end points by treatment group and disease category in the open-label period (week 52, open-label–treated analysis population)*

| End point and IIM type | Abatacept (n = 69) | Placebo-to-abatacept switch (n = 64) | Adjusted mean difference between groups (95% CI) |
|---|---|---|---|
| Patients with IMACS DOI without rescue medication, n/m (%) | | | |
| All | 44/63 (69.8) | 40/58 (69.0) | N/A |
| DM | 25/35 (71.4) | 27/39 (69.2) | N/A |
| Non-DM | 19/28 (67.9) | 13/19 (68.4) | N/A |
| Patients meeting MRC (TIS), n/m (%) | | | |
| All | | | |
| Moderate + major response | 45/61 (73.8) | 37/56 (66.1) | N/A |
| DM | | | |
| Moderate + major response | 26/33 (78.8) | 27/38 (71.1) | N/A |
| Non-DM | | | |
| Moderate + major response | 19/28 (67.9) | 10/18 (55.6) | N/A |
| FI-3, adjusted mean (SE) change from baseline | | | |
| All | 5.0 (1.7), n = 55 | 4.6 (1.7), n = 56 | 0.4 (−3.7 to 4.5) |
| DM | 3.3 (2.3), n = 30 | 4.9 (2.0), n = 38 | −1.6 (−7.7 to 4.4) |
| Non-DM | 4.3 (1.8), n = 25 | 2.1 (2.0), n = 18 | 2.2 (−3.2 to 7.6) |
| HAQ-DI score,[a] adjusted mean (SE) change from baseline | | | |
| All | −0.4 (0.1), n = 64 | −0.4 (0.1), n = 59 | −0.1 (−0.3 to 0.1) |
| DM | −0.4 (0.1), n = 35 | −0.4 (0.1), n = 39 | −0.1 (−0.3 to 0.1) |
| Non-DM | −0.4 (0.1), n = 29 | −0.3 (0.1), n = 20 | −0.1 (−0.4 to 0.2) |
| Extramuscular global activity,[a] adjusted mean (SE) change from baseline | | | |
| All | −1.7 (0.2), n = 62 | −1.5 (0.2), n = 56 | −0.2 (−0.7 to 0.3) |
| DM | −2.0 (0.3), n = 33 | −1.9 (0.3), n = 38 | −0.1 (−0.9 to 0.7) |
| Non-DM | −1.3 (0.2), n = 29 | −1.0 (0.3), n = 18 | −0.2 (−0.9 to 0.4) |
| MMT-8 score,[a] adjusted mean (SE) change from baseline | | | |
| All | 14.1 (3.1), n = 63 | 15.8 (3.2), n = 58 | −1.6 (−9.9 to 6.6) |
| DM | 13.9 (4.5), n = 35 | 18.6 (4.3), n = 39 | −4.7 (−17.2 to 7.8) |
| Non-DM | 14.9 (2.6), n = 28 | 12.1 (3.1), n = 19 | 2.8 (−5.4 to 11.0) |
| Physician global assessment of disease activity,[a,b] adjusted mean (SE) change from baseline | | | |
| All | −3.7 (0.3), n = 64 | −2.9 (0.3), n = 58 | −0.7 (−1.4 to 0.0) |
| DM | −3.3 (0.3), n = 35 | −2.7 (0.3), n = 39 | −0.7 (−1.5 to 0.3) |
| Non-DM | −3.3 (0.4), n = 29 | −2.4 (0.5), n = 19 | −1.0 (−2.2 to 0.2) |
| Patient global assessment of disease activity,[a,b] adjusted mean (SE) change from baseline | | | |
| All | −2.2 (0.3), n = 64 | −1.2 (0.3), n = 59 | −1.0 (−1.8 to −0.2) |
| DM | −2.5 (0.4), n = 35 | −1.5 (0.4), n = 39 | −1.0 (−2.0 to 0.0) |
| Non-DM | −1.8 (0.4), n = 29 | −0.9 (0.5), n = 20 | −0.9 (−2.2 to 0.5) |
| CDASI overall score, adjusted mean (SE) change from baseline | n = 33 | n = 36 | |
| Activity | −6.7 (2.6) | −8.1 (2.5) | 1.4 (−1.8 to 4.6) |
| Damage | 0.5 (1.0) | −0.8 (1.0) | 1.2 (0.0 to 2.4) |
| Muscle enzyme,[a] CK, adjusted mean (SE) change from baseline | | | |
| All | −566.3 (110.4), n = 63 | −435.9 (114.7), n = 56 | −130.3 (−415.2 to 154.5) |
| DM | −314.9 (59.3), n = 35 | −174.6 (56.7), n = 38 | −140.2 (−303.9 to 23.4) |
| Non-DM | −823.6 (215.6), n = 28 | −636.9 (249.0), n = 18 | −186.8 (−850.1 to 476.6) |

* CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; CI, confidence interval; CK, creatine kinase; DM, dermatomyositis; FI-3, Functional Index-2 using three proximal muscle groups; HAQ-DI, Health Assessment Questionnaire-Disability Index; IIM, idiopathic inflammatory myopathy; IMACS DOI, International Myositis Assessment and Clinical Studies definition of improvement; MMT-8, Manual Muscle Test-8; MRC, Myositis Response Criteria; N/A, not applicable; n/m, number of patients meeting IMACS DOI/number of patients in the analysis; TIS, Total Improvement Score.
[a] Core set measure.
[b] 100-mm visual analog scale.

based on previous data. The response rate for the placebo group (42.5%), however, was higher than expected. Prespecified analysis by IIM subtype showed that the observed differences between the abatacept and placebo arms were due to the patients with PM and IMNM. Patients who continued into the open-label period demonstrated continued benefit up to week 52 regardless of

**Table 4.** Safety summary of patients with idiopathic inflammatory myopathy during the double-blind (24 weeks, as-treated analysis population) and open-label periods (52 weeks, as-treated analysis population)*

| | Double-blind period | | Open-label period | |
|---|---|---|---|---|
| End point | Abatacept (n = 75) | Placebo (n = 73) | Abatacept (n = 69) | Placebo-to-abatacept switch (n = 64) |
| Deaths | 0 (0) | 1 (1.4) | 0 (0) | 0 (0) |
| Serious AEs | 4 (5.3) | 4 (5.5) | 10 (14.5) | 4 (6.3) |
| Related serious AEs | 2 (2.7) | 0 (0) | 2 (2.9) | 1 (1.6) |
| Discontinued due to serious AEs | 0 (0) | 2 (2.7) | 0 (0) | 0 (0) |
| AEs | 52 (69.3) | 56 (76.7) | 45 (65.2) | 37 (57.8) |
| Related AEs | 15 (20.0) | 18 (24.7) | 9 (13.0) | 4 (6.3) |
| Discontinued due to AEs | 1 (1.3) | 2 (2.7) | 0 (0) | 0 (0) |
| Infections and infestations | 20 (26.7) | 32 (43.8) | 23 (33.3) | 17 (26.6) |
| Upper respiratory tract infection | 3 (4.0) | 3 (4.1) | 2 (2.9) | 1 (1.6) |
| Urinary tract infection | 4 (5.3) | 1 (1.4) | 2 (2.9) | 1 (1.6) |
| Herpes zoster | 1 (1.3) | 3 (4.1) | 3 (4.3) | 0 (0) |

* Values are the number (%). Serious AEs in the abatacept group: cellulitis, gastroenteritis, urinary tract infection, and renal failure; serious AEs in the placebo group: herpes zoster, vomiting, polymyositis, and acute respiratory failure. AE, adverse event.

original treatment group or IIM subtype. This was significant, given the patient population was notably weak with moderate-to-severe disease activity and did not respond to first-line therapy. Secondary efficacy end points showed a similar pattern.

Abatacept was generally well-tolerated and was relatively safe when added to concomitant background immunosuppressive drugs. No new safety concerns were identified. Comparable safety end points were observed between the abatacept and placebo groups during the double-blind and open-label periods.

This study enrolled patients with three types of IIM: DM, PM, and IMNM. PM is characterized by cellular infiltrate consisting of activated $CD8^+$ T lymphocytes and macrophages found in the endomysium and in the perimysium.[8] PM is often a diagnosis of exclusion and many patients previously diagnosed with PM are now considered to have antisynthetase syndrome or IMNM; patients with antisynthetase syndrome were not excluded in this study.[30] The more recently recognized IMNM is histologically characterized by myofiber necrosis with little or no inflammatory infiltrate.[30] IMNM is associated with antibodies against signal recognition particle and 3-hydroxy-3-methylglutaryl-coenzyme A reductase. Despite the clinical and histopathologic differences between subtypes of IIM, there is little evidence to guide the use of specific therapies in any given subtype, and treatment approaches are historically similar across subtypes.

The treatment of IIM subtypes has relied on the utilization of traditional immunosuppressants or immunomodulatory strategies.[10] Therapeutic trials have not always been successful but have helped to improve study design and outcome measures.[31–33] There is a significant unmet need for alternative, steroid-sparing therapies that are efficient, well-tolerated, and subtype specific. The recent successful study of intravenous immune globulin (Progress in Dermatomyositis [ProDERM] study) in patients with DM supports this argument.[34] Our study suggests that PM and IMNM subtypes may be more responsive to treatment with abatacept than DM. In addition to monitoring other exploratory outcomes of physical activity, an additional analysis of biomarker samples, including myositis-specific and myositis-associated autoantibodies, may provide further insights.

The 2016 American College of Rheumatology/EULAR criteria have progressed study end points for clinical trials with the provision of a continuous TIS measure within MRC.[35,36] This study design incorporated an escape protocol to identify patients whose symptoms worsened significantly during the double-blind period. Only two patients met the escape criteria and required rescue, suggesting future trial designs may be simplified. More specialized centers capable of identifying suitable patients and conducting these studies are needed. This will improve study recruitment and the reliability of study end points, including the predicted placebo response rate. Interventions that manage therapeutic expectations and improve patient ability to accurately report symptom severity have shown the most promise in reducing placebo response. It is worth assessing expectations of therapeutic benefit in clinical trials using these as covariables.[37]

Studies of patients with IIM are challenging, as evidenced in this trial. High response rates of placebo patients meeting the improvement criteria continue to be an issue in IIM trials; possible explanations for this include concomitant background immunosuppressive therapy (especially relatively high doses of steroids), the subjective nature of various core set measures, and lack of expert centers and investigators required for a large clinical trial. The present study had a higher-than-expected placebo response rate seen in the DM, but not the non-DM, subtype. Moreover, our study suggests that the protocol for stabilizing background therapy before study entry, particularly surrounding the administration of systemic glucocorticoids, may have differential effects based on IIM subtype. As adjustments in concomitant background immunosuppressive therapy during the double-blind period only occurred in one patient in each treatment arm, this did not

contribute to differences seen between treatment arms and IIM subtypes. Studies that include multiple subtypes are conducted with the expectation that the novel therapy may help all subtypes based on preliminary data and to improve study feasibility. Because of the possibility that response rate may differ between subtypes, statistical plans should allow for prespecified analyses by subtype, as was done in this study.

This study had a few limitations. First, the patients described here had limited extramuscular disease at baseline, limiting the utility of this study to address improvement in nonmuscle organ systems. In the setting of such clinical variability, more significant disease manifestations, such as with interstitial lung disease, may not be suitable for study in this type of trial. Second, disturbances associated with the COVID-19 pandemic resulted in some missed core set measures for five patients because of isolation and social distancing measures, but data for 68 other patients were missing for other reasons. In addition, there were 14 patients who discontinued before 24 weeks in the double-blind period and were considered nonresponders for the primary end point. Although the missing data due to the pandemic alone are unlikely to have impacted interpretation of study results, the combined missing data for ~8% of study patients may have impacted the findings of this study.

This study failed to meet the primary end point, but analysis by IIM subtype suggested benefit of SC abatacept that was sustained up to one year of treatment when it was added to background therapy in patients with PM and IMNM. Therapy was well-tolerated with no new safety concerns identified in this IIM population.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Aggarwal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Aggarwal, Lundberg, Werth, Maldonado.

**Acquisition of data.** Aggarwal, Lundberg, Song, Shaibani, Werth, Maldonado.

**Analysis and interpretation of data.** Aggarwal, Lundberg, Song, Shaibani, Werth, Maldonado.

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