Efficacy of intravenous immunoglobulins (IVIg) in improving skin symptoms in patients with dermatomyositis: a post-hoc analysis of the ProDERM study

Victoria P. Werth,[a,*] Rohit Aggarwal,[b] Christina Charles-Schoeman,[c] Joachim Schessl,[d] Todd Levine,[e] Norbert Kopasz,[f] Margitta Worm,[g] and Zsuzsanna Bata-Csörgő[h]

[a]Corporal Michael J. Crescenz VAMC and the University of Pennsylvania, Philadelphia, PA, USA
[b]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[c]University of California, Los Angeles, CA, USA
[d]Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians University of Munich, Munich, Germany
[e]HonorHealth Neurology, Scottsdale, AZ, USA
[f]Octapharma AG, Lachen, Switzerland
[g]Clinic of Dermatology, Venerology and Allergology, Charité, Berlin, Germany
[h]Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary

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Summary

Background Dermatomyositis (DM) is a rare autoimmune disease characterized by skin involvement, with or without proximal muscle weakness. Recently, following the ProDERM study, intravenous immunoglobulin (IVIg) was approved for treatment of DM. Until ProDERM evidence from large, placebo-controlled studies supporting its use for dermatological symptoms, was lacking. Here we present efficacy data from ProDERM of IVIg versus placebo for treatment of the cutaneous aspect of DM.

Methods ProDERM was a double-blind, randomized, multicenter, Phase 3 study. In the First Period (Weeks 0–16), adults with active DM received 2.0 g/kg IVIg (Octagam 10%; Octapharma AG) or placebo every 4 weeks. In the open-label Extension Period (Weeks 16–40), all patients received IVIg for 6 additional cycles. Cutaneous disease was assessed using measures including modified cutaneous DM disease area and severity index activity (CDASI-A) and damage (CDASI-D) scores, and myositis disease activity assessment tool (MDAAT) including visual analogue scale (VAS). This trial is registered with ClinicalTrials.gov, NCT02728752.

Findings The study took place from February 2017 to November 2019. 95 patients received IVIg (N = 47) or placebo (N = 48) in the First Period. Together, 664 IVIg infusion cycles were administered (median dose, 2.0 g/kg). At Week 16, mean CDASI-A change from baseline was −9.36 (95% CI: −12.52, −6.19) in the IVIg group versus −1.16 (−3.32, 0.99) in placebo group ($p < 0.0001$). At the end of the Extension Period, mean changes from baseline were −10.44 (95% CI: −13.94, −6.94) and −10.03 (−13.12, −6.94), respectively. Similar changes were seen for CDASI-D and VAS of MDAAT. These observations were seen regardless of baseline disease severity.

Interpretation ProDERM is the first large prospective, randomized trial to demonstrate the efficacy of IVIg to improve the cutaneous manifestations of DM. IVIg treatment significantly improved dermatological symptoms in patients with DM, regardless of disease severity before treatment, suggesting that IVIg is effective for even the most severe cutaneous DM.

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Keywords: Assessment tool; Cutaneous symptom; Cutaneous dermatomyositis disease area and severity index; Dermatomyositis; Intravenous immunoglobulin; Skin

*Corresponding author. Department of Dermatology, Perelman Center for Advanced Medicine, University of Pennsylvania, Suite 1-330A, 3400 Civic Center Boulevard, Philadelphia, PA 19104, USA.
E-mail address: victoria.werth@pennmedicine.upenn.edu (V.P. Werth).

Research in context

Evidence before this study

PubMed was searched for articles published in any language from database conception until the present date (March 09, 2023), using the search terms "("dermatomyositis") AND ("intravenous immunoglobulin" OR "immune globulin") AND ("dermatological" OR "cutaneous") NOT ("editorial" OR "review" OR "survey")". A total of 25 articles were retrieved. The articles included one open label study, two retrospective studies and six case reports that studied the use of intravenous immunoglobulin (IVIg) to treat the cutaneous aspect of dermatomyositis (DM). Only one randomized, controlled trial was identified: the ProDERM study. This report focused on the efficacy of IVIg for treatment of muscle weakness, with cutaneous disease activity assessed as a secondary endpoint using the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI). No other large, prospective, randomized studies were identified that investigated the efficacy of IVIg for treatment of the cutaneous aspects of DM.

Added value of this study

This study is an in-depth analysis of data from the ProDERM study regarding the efficacy of IVIg in treating the cutaneous aspect of DM, assessed using multiple dermatological disease assessment tools. These results demonstrate that IVIg treatment significantly improved the cutaneous manifestations of DM. Moreover, when patients were analyzed according to cutaneous disease severity at baseline, IVIg treatment significantly improved cutaneous symptoms for patients with any disease severity prior to treatment. After Week 28, more than 70% of patients experienced improvement of cutaneous symptoms above a threshold that is associated with a meaningful change in quality of life.

Implications of all the available evidence

This is the first large, randomized study to demonstrate that IVIg is efficacious for treatment of the cutaneous aspect of DM. Other therapeutics currently used to treat the dermatological symptoms of DM are associated with significant side effects and the cutaneous symptoms of DM often do not respond well to therapy. ProDERM study provides evidence to support the use of IVIg for the cutaneous aspect of DM and will allow physicians and patients to make an informed decision regarding its use in this setting.

Introduction

Dermatomyositis (DM) is a rare chronic, systemic autoimmune disease characterized by skin involvement, with or without progressive symmetric, proximal muscle weakness.[1] Dermatological symptoms are characterized by heliotrope rash (an erythematous eruption of the periorbital region) and Gottron's sign (erythema over joints) or papules (raised erythematous papules over joints).[2] In addition, shawl sign, V neck, periungual changes, mechanic's hands, poikiloderma, and calcinosis are also common.[3]

Several therapeutics are currently available for treatment of the dermatological aspect of DM, including sun protection, topical glucocorticoids, topical calcineurin inhibitors, antimalarial agents, immunosuppressants such as methotrexate, azathioprine or mycophenolate mofetil, oral glucocorticoids, and Janus kinase inhibitors. However, these drugs are often associated with significant side effects[2] and the cutaneous symptoms of DM often do not respond as well to therapy as other symptoms.[4]

Intravenous immunoglobulin (IVIg) is a highly purified liquid immunoglobulin G concentrate prepared from human plasma that is widely used in the treatment of autoimmune and inflammatory disorders.[5,6] IVIg has been used off-label for more severe and refractory cutaneous manifestations of DM, with some studies[7,8] and guidelines[9,10] supporting its use. A double-blind, placebo-controlled study of 15 adult patients showed improvements in muscle strength and neuromuscular and cutaneous symptoms in patients with refractory dermatomyositis following high-dose intravenous immunoglobulin treatment.[7] However, good quality evidence from large, placebo-controlled studies to support the use of IVIg in DM, especially for dermatological symptoms, was lacking.

The randomized, placebo controlled ProDERM study recently evaluated efficacy, safety and tolerability of IVIg in adult patients with DM.[11,12] The primary endpoint of the study was the proportion of responders in total improvement score (TIS),[13] a validated myositis response criteria for adult DM and polymyositis patients, in those who received IVIg versus placebo. The results of the ProDERM study led to approval of IVIg (Octagam® 10%) for treatment of DM in the United States, most European countries, and Canada.[14–16]

To effectively monitor, treat, and perform clinical trials focused on treating the dermatological aspects of DM, it is important to have standardized tools,[9] of which several are currently available. The modified cutaneous DM disease area and severity index (CDASI) comprises three activity measures: erythema, scale, and erosion/ulceration, plus two damage measures: poikiloderma and calcinosis, which are each assessed at 15 anatomical locations. In addition, Gottron's signs or papules, periungual changes, and alopecia are included in the CDASI activity (CDASI-A) and/or damage (CDASI-D) scores. Another tool, the myositis disease activity assessment tool (MDAAT) consists of a myositis disease activity (MYOACT) assessment visual analogue scale (VAS),

performed alongside a myositis intention-to-treat activity index (MITAX),[17] whereby individual activities are scored 0–4 for each assessment. The MDAAT assesses multiple organs, including the skin.

Objectives of this analysis were to determine the efficacy of IVIg versus placebo on the treatment of the dermatological aspect of DM. Here, we present data from the ProDERM study on cutaneous symptoms using multiple assessment tools, including CDASI and the cutaneous element of MDAAT.

Methods

Study design

Details of the ProDERM study (NCT02728752) protocol and design have been published previously.[11,12] In summary, the study was a multicenter, prospective, randomized, placebo-controlled, double-blind, parallel-group, Phase 3 study including patients with DM from 36 centers in Europe and North America. The study took place from February 2017 to November 2019. The study was conducted in accordance with the Declaration of Helsinki, in compliance with Good Clinical Practice guidelines, and was approved by the relevant Independent Ethics Committees or Institutional Review Boards. Each patient gave informed consent before study-related procedures were started.

Both the investigator and patients were blinded to the treatment received. In the blinded, placebo-controlled First Period (Weeks 0–16), patients were randomly assigned by the hospital pharmacist/designee in a 1:1 ratio to two groups. Randomization was performed via an interactive response technology system in blocks of 4 and was stratified according to disease-activity score before enrollment.[11] The first group received 2.0 g/kg IVIg (Octagam® 10%; Octapharma AG, Lachen, Switzerland) and the second group received placebo (sodium chloride 0.9% w/v solution) for 4 infusion cycles at Weeks 0, 4, 8, and 12. During this Period, patients meeting confirmed deterioration criteria were crossed over to the other treatment group while maintaining blinding. All patients except those on IVIg with confirmed deterioration could continue to the open-label Extension Period (Weeks 16–40), where all patients received 2.0 g/kg IVIg every 4 weeks for a further 6 infusion cycles.[11,12] From Week 28, the dose could be reduced to 1.0 g/kg IVIg if patients were stable, as assessed by the investigator. Patients entering the study were aged ≥18 to <80 years with a diagnosis of definite or probable active DM according to the Bohan and Peter criteria,[12,18,19] which included characteristic dermatological features of DM, such as Gottron's papules or heliotrope rash, reported either currently or previously. Currently active dermatological symptoms were not an inclusion criterion for the study. Full lists of inclusion and exclusion criteria were described previously.[12]

The primary endpoint of the study was the proportion of responders in TIS in the IVIg versus the placebo group at Week 16. Secondary endpoints included mean change in CDASI-A score from baseline to Week 16 for the IVIg versus placebo groups and mean change in CDASI-A score during the Extension Period (Weeks 16–40). The other remaining data reported here was analyses post-hoc.

Assessments of cutaneous disease severity

All assessments of cutaneous disease activity are described in detail in Supplementary Appendix 1. In brief, a modified version of the CDASI score was used, comprising three activity measures (erythema, scale, and erosion/ulceration) and two damage measures (poikiloderma and calcinosis).[20] Patients with any missing values were excluded from that analysis. CDASI-A ≤14 was used as the cut-off to define mild disease and >14 to define moderate/severe disease.[21,22] The MDAAT consists of a MITAX, with individual cutaneous activities rated 0–4 (where 0 defines "not present in the last 4 weeks" and 4 "new in the last 4 weeks") and a myositis disease activity assessment VAS, where 0 cm represents no disease activity and 10 cm represents extreme activity.[17] The TIS consists of six core set measures, with responders defined as patients with a score of ≥20 points without confirmed deterioration.[11]

Statistical methods

This study was powered with respect to the primary endpoint, the proportion of responders in TIS, as described previously.[12] The full analysis set (FAS) was defined according to the intention-to-treat principle and consisted of all randomized patients. All endpoints were analyzed and presented by means of descriptive statistics and inferential analyses as appropriate for the FAS. Analysis of covariance (ANCOVA) was used to analyze changes from baseline to Week 16. For patients who were switched to the alternate treatment before Week 16, the last value prior to switch was carried forward to Week 16 and used to calculate change from baseline to Week 16. Least square means were derived with two-sided 95% confidence intervals by treatment group, as well as the two-sided 95% confidence intervals for the difference in least square means between. The standardized mean difference (SMD; Cohen's d) was calculated as (new treatment improvement – placebo improvement)/pooled standard deviation.[23] Spearman rank correlation was used to analyze the correlation between scores for cutaneous disease assessment tools.

This trial is registered with ClinicalTrials.gov, NCT02728752.

Role of the funding source

The trial was sponsored, designed and conducted by Octapharma Pharmazeutika with the authors of this

publication. The sponsor monitored trial conduct, collected data, and performed statistical analyses. The sponsor could not delay/interdict publication of the manuscript. The authors had access to the data, were responsible for content and editorial decisions, and approved the final version of the manuscript.

Results

Patient demographics and baseline characteristics

The study was conducted from first patient screening in February, 2017 until last patient visit in November, 2019. A total of 126 patients were screened, of whom 95 were enrolled into the study and comprised the FAS. Of these, 47 patients were randomized to receive IVIg in the First Period and 48 to receive placebo. During the First Period, five patients in the placebo group crossed over to IVIg while no patients on IVIg crossed over to placebo. Of the FAS, 45 patients (95.7%) in the IVIg group and 46 patients (95.8%) in the placebo group continued to the Extension Period, and 69 (72.6%) patients completed the study. Patient flow is shown in Fig. 1 (see Aggarwal et al.[11] for further details).

Patient demographics and clinical characteristics at baseline were presented in detail previously,[11] with a summary of key demographic data shown in Table 1. During the study, 664 infusion cycles were administered with a median dose of 2.0 g/kg IVIg.

Baseline dermatological scores

Overall disease assessment scores for patients in the IVIg and placebo groups at baseline are shown in Table 1. Values for SMD indicate only a 'small' difference (i.e., SMD <0.2)[23] in diseases severity, as measured by CDASI-A, CDASI-D, MDAAT extra-muscular global assessment, and MDAAT cutaneous disease activity on VAS, between the IVIg and placebo groups at baseline.

At baseline, four patients (4.2%) had a total CDASI-A score of 0; 78 (82.1%) had a score >6 and 51 patients (53.7%) had a score >14.

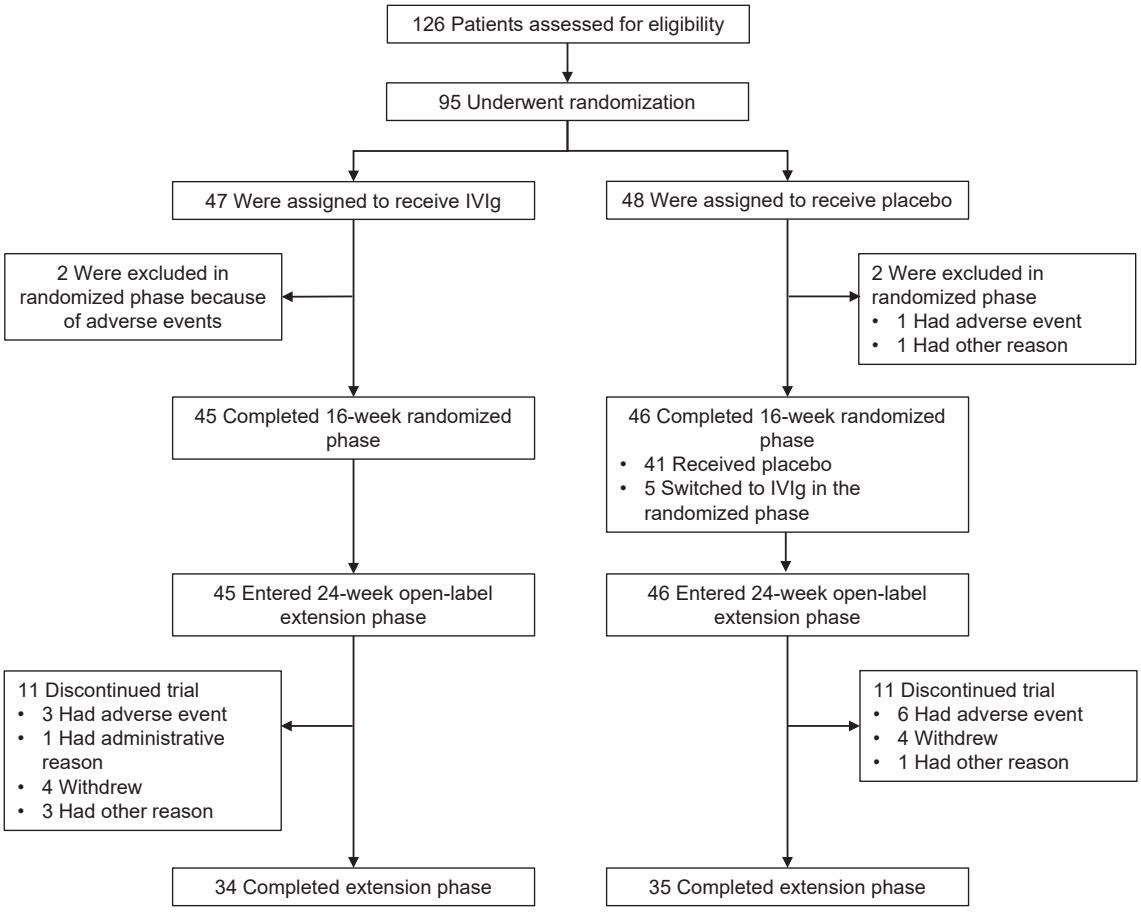

***Fig. 1:* Screening, randomization and follow-up.** IVIg, intravenous immunoglobulin. From *N Engl J Med*, Aggarwal R, Charles-Schoeman C, Schessl J, et al. Trial of Intravenous Immune Globulin in Dermatomyositis. Vol. 387, p. 1267. Copyright© 2022. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

	IVIg N = 47	Placebo N = 48	Total N = 95	Standardized mean difference (Cohen's d)
Demographics				
Sex, N (%)				–
Female	36 (76.6%)	35 (72.9%)	71 (74.7%)	
Male	11 (23.4%)	13 (27.1%)	24 (25.3%)	
Race, N (%)				–
Asian	1 (2.1%)	1 (2.1%)	2 (2.1%)	
Black or African American	2 (4.3%)	3 (6.3%)	5 (5.3%)	
White	44 (93.6%)	43 (89.6%)	87 (91.6%)	
Other	0 (0.0%)	1 (2.1%)	1 (1.1%)	
BMI, kg/m^2				–
Mean (SD)	26.87 (4.965)	27.57 (4.903)	27.22 (4.920)	
Median	26.70	26.70	26.70	
Min, max	16.5, 37.0	19.7, 39.4	16.5, 39.4	
Baseline disease assessment scores				
CDASI total activity score				0.020
Mean (SD)	19.04 (13.169)	18.77 (14.322)	18.91 (13.691)	
Median	16.00	16.00	16.00	
Min, max	0.0, 49.0	0.0, 67.0	0.0, 67.0	
CDASI total damage score				0.131
Mean (SD)	2.89 (3.421)	2.44 (3.548)	2.66 (3.475)	
Median	2.00	1.00	2.00	
Min, max	0.0, 15.0	0.0, 14.0	0.0, 15.0	
MDAAT extra-muscular global assessment				0.033
Mean (SD)	4.23 (1.744)	4.17 (2.187)	4.20 (1.970)	
Median	4.00	4.00	4.00	
Min, max	1.1, 9.1	1.1, 9.6	1.1, 9.6	
MDAAT cutaneous disease activity on VAS				0.099
Mean (SD)	4.43 (2.156)	4.20 (2.607)	4.31 (2.385)	
Median	4.50	4.35	4.50	
Min, max	0.0, 9.0	0.0, 10.0	0.0, 10.0	

BMI, body mass index; CDASI, cutaneous dermatomyositis disease area and severity index; IVIg, in vitro immunoglobulin; MDAAT, myositis disease activity assessment tool; SD, standard deviation; VAS, visual analogue scale.

Table 1: **Summary of baseline demographics and disease assessment scores (N = 95).**

The percentage of patients with CDASI-A scores ≥1 for each of the three activity measures (erythema, scale, erosion/ulceration), and two damage measures (poikiloderma and calcinosis) for each of the 15 body areas assessed for the CDASI score at baseline are shown in Table 2. The only body sites with scale scores ≥1 for fewer than 10% of patients were periorbital and abdomen.

For erythema, the most frequent anatomical sites affected at baseline were V area neck frontal, periorbital, malar area, rest of the face, posterior neck, and dorsum of the hands; all of which had a score ≥1 for erythema in >50% of patients (Table 2). The spread of CDASI scores for erythema at baseline for these sites is presented in Supplementary Figure S1. A total of 4.2% of patients had a highest CDASI erythema score of 0 (absent) for any body part at baseline; 18.9% had a highest score of 1 (pink; faint erythema); 46.3% had a highest score of 2 (red); and 30.5% had a highest score of 3 (dark red) at baseline.

Other assessments as part of the CDASI score included assessment of Gottron's signs and papules on the hands, and periungual changes. At baseline, Gottron's on the hands was reported in 71.6% of patients and periungual changes reported in 63.2% of patients (both excluding the dorsum of the hands), with Gottron's papules on the hands reported in 53.7% of patients (Table 2). Gottron's hand damage was reported in 25.3% and Gottron's hand ulcerations were reported in 4.2% of patients. Scores were similar between the IVIg and placebo groups.

Using the MDAAT, a total of 42.1% of patients were classed as MITAX cutaneous category A, 50.5% as category B, 1.1% as category C and 6.3% as category D/E. For the cutaneous VAS, the mean (±SD) score at baseline was 4.31 cm (±2.385), with a mean of 4.43 cm

	Activity measures			Damage measures	
	Erythema	Scale	Erosion/ulceration	Poikiloderma	Calcinosis
V area neck frontal	75.8	12.6	0.0	37.9	0.0
Periorbital/heliotrope rash	72.6	9.5	0.0	14.7	0.0
Malar area	63.2	13.7	0.0	20.0	0.0
Rest of the face	63.2	11.6	2.1	18.9	0.0
Posterior neck	60.0	12.6	0.0	21.1	0.0
Dorsum of hands	52.6	20.0	2.1	11.6	0.0
Arm	49.5	20.0	2.1	10.5	7.4
Scalp	47.4	21.1	2.1	12.6	0.0
Upper back and shoulders	46.3	11.6	1.1	14.7	2.1
Lateral upper thigh	45.3	14.7	2.1	9.5	0.0
Gottron's not on hands	43.2	16.8	0.0	5.3	0.0
Mechanic's hand	41.1	32.6	3.2	5.3	2.1
Rest of back and buttocks	36.5	11.6	3.2	16.8	3.2
Rest of legs and feet	29.5	11.6	1.1	8.4	1.1
Abdomen	18.9	6.3	1.1	5.3	3.2
	Erythema	–	Ulceration	Hand damage	–
Gottron's hands	71.6	–	4.2	25.3	–
	Present	–	–	–	–
Periungual changes	63.2	–	–	–	–
Alopecia	53.7	–	–	–	–

CDASI-A, cutaneous dermatomyositis disease area and severity index activity.

Table 2: **Percentage of patients with scores ≥1 for activity measures (erythema, scale, and erosion/ulceration) and damage measures (poikiloderma and calcinosis) on the CDASI score for 15 body areas at baseline (N = 95).**

(±2.156) for the IVIg group and 4.20 cm (±2.607) for the placebo group.

Overall, clinical baseline characteristics were similar in both arms.

Change in dermatological assessment scores with IVIg versus placebo

At Week 16, there was a mean change from baseline in CDASI-A of −9.36 (95% CI: −12.52, −6.19) in the IVIg group versus −1.16 (95% CI: −3.32, 0.99) in the placebo group. ANCOVA analysis of changes from baseline to Week 16 in CDASI-A for all patients revealed a statistically significant effect of treatment with IVIg ($p < 0.0001$). Least square means for the change from baseline to Week 16 in CDASI-A were −10.3 for the IVIg group versus −2.3 for the placebo group, with a statistically significant difference in the least square means of −8.0 (95% CI: −11.5, −4.6; $p < 0.0001$); i.e., a significantly greater improvement was seen in CDASI-A for the IVIg group. At the end of the open label Extension Period, in which all patients received IVIg, the mean scores for both groups were similar (7.91 [±SD, 10.092] for the IVIg group and 9.51 [±12.620] for patients on placebo).

Fig. 2a shows mean CDASI-A scores over the study. A total of four (4.2%) patients had a CDASI-A of zero at baseline, which remained at zero throughout the study. Since improvement could not be measured in these patients, they have been excluded from this figure. CDASI-A scores were available for all patients who remained in the study, except for one missing score at Week 8 for one (1.1%) patient, who was on IVIg.

Similar results were seen for the mean change in CDASI-D. At Week 16, there was a change from baseline in mean CDASI-D of −0.67 (95% CI: −1.23, −0.10) in the IVIg group versus −0.02 (95% CI: −0.26, 0.21) in the placebo group. ANCOVA analysis showed that treatment with IVIg had a statistically significant effect on CDASI-D ($p = 0.0304$). The corresponding least square means for the change in total damage score were −0.7 for the IVIg group and −0.1 for the placebo group, with a statistically significant difference in the least square means of −0.6 (95% CI: −1.1, −0.1; $p = 0.0304$). At the end of the open label Extension Period, mean CDASI-D was similar between the IVIg group and the placebo group who had switched to IVIg (2.38 [±SD, 3.490] and 1.77 [±2.723], respectively).

Fig. 2b shows mean CDASI-D scores over the study. A total of 37 (38.9%) patients had a CDASI-D of zero at baseline and since improvement could not be measured in these patients, they have been excluded from this figure. Of these patients, CDASI-D score remained at zero in 35 patients. The remaining two patients, who both received placebo, experienced transient increases to a score of 2.

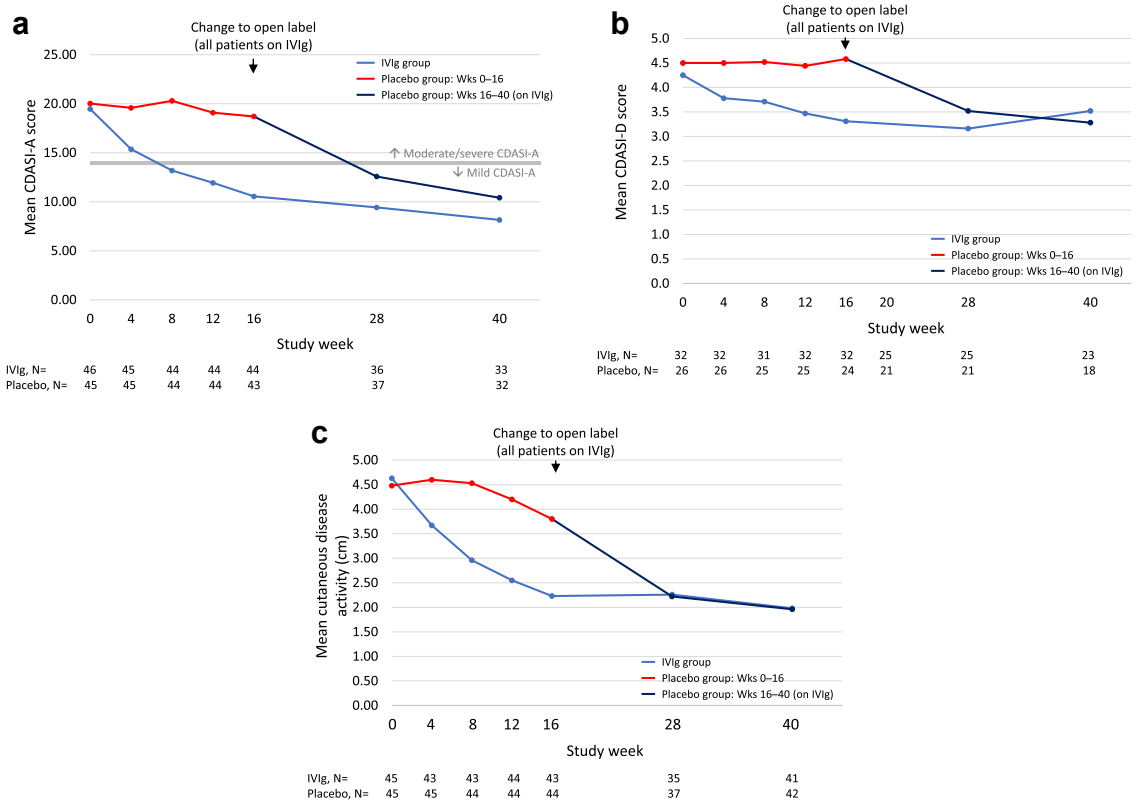

Fig. 2: **(a) Mean Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity (CDASI-A)*, (b) mean CDASI damage (CDASI-D), and (c) mean cutaneous disease activity from the visual analogue scale (VAS) of the myositis disease activity assessment tool (MDAAT).** *CDASI-A ≤14 was characterized as mild disease and >14 as moderate/severe disease.[21,22] IVIg, intravenous immunoglobulin. (a and b) The ProDERM study was not powered to test for statistical significance between these subgroups. Patients with a CDASI score of 0 at baseline were excluded from the corresponding CDASI-A and CDASI-D analysis. (c) Patients with a VAS score of <0.2 were excluded from the analysis.

A similar pattern was also seen for the cutaneous VAS of MDAAT (Fig. 2c). A total of 3 (6.3%) patients in the placebo group and 2 (4.3) patients in the IVIg group had a VAS of ≤0.2 at baseline and were excluded from the analysis. From baseline to Week 16 there was a change in mean cutaneous VAS of −2.44 (95% CI: −3.15, −1.73) in the IVIg group versus −0.66 (95% CI: −1.18, −0.13) in the placebo group, with the CI ranges indicating a difference between the mean changes. ANCOVA analysis showed that treatment with IVIg had a statistically significant effect on the VAS of the MDAAT ($p < 0.0001$). The corresponding least square means for the change in cutaneous VAS were −2.4 for the IVIg group and −0.7 for the placebo group, with a statistically significant difference in the least square means of −1.7 (95% CI: −2.4, −1.1; $p \leq 0.0001$). By the end of the open label Extension Period, mean scores were similar between groups (1.98 cm [±SD, 1.785] and 1.96 [±1.904], respectively).

Change in dermatological assessment scores stratified by disease severity

Patients were stratified by skin disease severity at baseline, by CDASI-A >0 to ≤6, >6 to ≤14, and >14. For patients with CDASI-A >0 to ≤6, there was a change in CDASI-A from baseline to Week 16 in the IVIg group of −2.00 (95% CI: −4.74, 0.74; n = 6) versus −0.60 (95% CI: −3.46, 2.26; n = 5) in the placebo group (Fig. 3a). For patients with CDASI-A >6 to ≤14, there was a change in CDASI-A from baseline to Week 16 in the IVIg group of −6.31 (95% CI: −8.41, −4.21; n = 13) versus −3.00 (95% CI: −6.63, 0.63; n = 13) in the placebo group, and in patients with CDASI-A >14 there was a change in the IVIg group of −13.08 (95% CI: −18.30, 7.86; n = 25) versus −1.50 (95% CI: −5.06, 2.06; n = 26) in the placebo group. For all three groups, patients on placebo who switched to IVIg attained similarly improved disease control at Week 40 at the end of the Extension Period as compared to those who had received IVIg throughout the study (Fig. 3a).

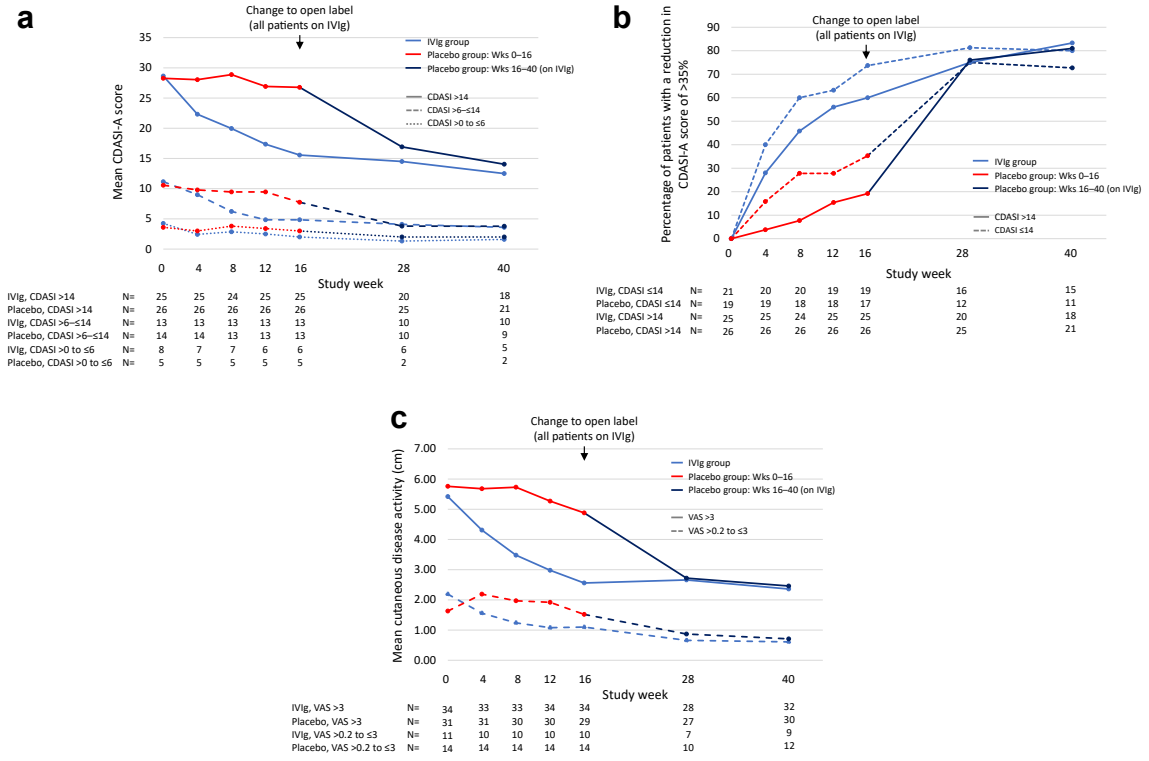

Fig. 3: **(a) Mean CDASI-A score in patients with (CDASI-A >0 to ≤6), (CDASI-A >6 to ≤14) and (CDASI >14) skin disease severity at baseline, (b) percentage of patients on IVIg and placebo with a reduction in CDASI-A score of >35%*, stratified by CDASI-A scores of ≤14 and >14 at baseline (N = 91[†]), and (c) mean cutaneous VAS in patients with baseline VAS ≥0.2 to ≤3 and >3.** *A 35% change in CDASI-A score was found to be associated with a meaningful change in quality of life.[21] [†]Patients with CDASI of 0 at baseline were excluded from this analysis. CDASI, cutaneous dermatomyositis disease area and severity index; CDASI-A, CDASI activity; IVIg, intravenous immunoglobulin; N, number of patients; VAS, visual analogue scale.

The percentage of patients with a reduction in CDASI-A of >35%, which was associated with a meaningful improvement in the Emotions subscale of the Skindex-29 tool in patients with moderate/severe DM,[21] is shown in Fig. 3b. At Week 16, a higher percentage of patients on IVIg (29/44, 65.9%) had a reduction in CDASI-A of >35% compared to those on placebo (11/43, 25.6%). By the end of the Extension Period at Week 40, when all patients had received IVIg, similar percentages of patients achieved a decrease in CDASI-A of at least 35%, regardless of having received IVIg or placebo in the First Period and having moderate/severe (CDASI-A >14) or mild (CDASI-A ≤14) disease severity at baseline. Patients were also stratified by cutaneous disease activity according to the MDAAT VAS at baseline, by VAS >0.2 to ≤3 and VAS >3. For patients with VAS >0.2 to ≤3, there was a change in cutaneous disease activity from baseline to Week 16 in the IVIg group of –1.01 (95% CI: –2.04, 0.02) versus –0.07 (95% CI: –0.78, 0.64) in the placebo group (Fig. 3c). For patients with VAS >3 there was a change in the IVIg group of –2.86 (95% CI: –3.70, –2.03) versus –0.94 (95% CI: –1.64, –0.24) in the placebo group. As was seen with CDASI-A, for each stratum of disease severity, patients on placebo who switched to IVIg attained similarly improved disease control at the end of the Extension Period versus those who had received IVIg throughout the study.

MDAAT and MITAX scores

At Week 16, a total of 47.7% patients in the IVIg group had improvement from baseline of at least one MDAAT-MITAX cutaneous category, compared with 25.6% in the placebo group. By week 40, 47.6% patients who had originally been in the IVIg group, versus 51.2% who started in the placebo group and switched to IVIG at week 16, had improvement from baseline of at least one MDAAT-MITAX cutaneous category.

As a sensitivity analysis, the change in CDASI-A from baseline was calculated for patients in the IVIg group stratified by TIS response (either minimal, moderate, and major) at Week 16 (Fig. 4a). In addition, the change in TIS was evaluated in patients with baseline CDASI-A of ≤6, 6 to ≤14, and >14 (not including patients who had a CDASI-A value of 0 at baseline; Fig. 4b). An improvement in TIS was seen in all CDASI-A groups over the 40 weeks of the study. Assessment of

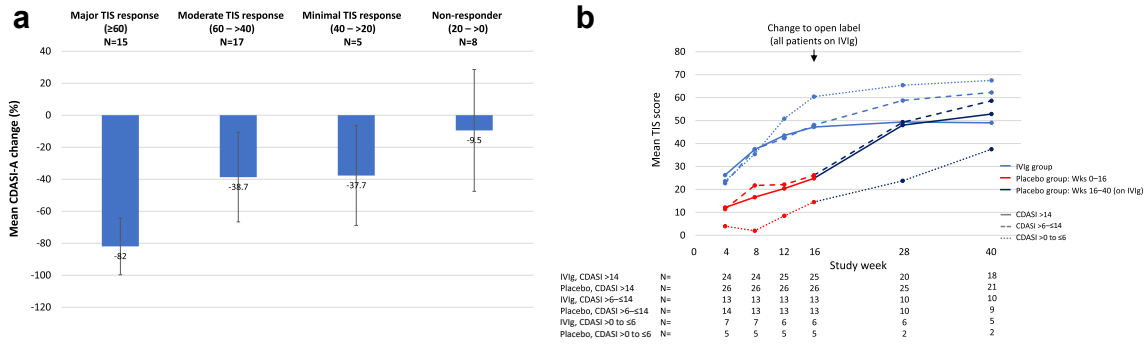

Fig. 4: **(a) Mean change in CDASI-A from baseline stratified by TIS response at Week 16 in patients in the IVIg arm (N = 45)* and (b) mean TIS over time in patients with CDASI-A ≤6, >6 to ≤14 and >14 on IVIg or placebo (N = 95).** *Only those patients were considered for the analysis who had both baseline and Week 16 CDASI-A measure. CDASI-A, cutaneous dermatomyositis disease area and severity index activity; IVIg, intravenous immunoglobulin; N, number of patients; TIS, total improvement score.

correlations between the different efficacy measures used in the study (Fig. 5) showed highest correlations between the TIS and manual muscle testing 8 (MMT-8) scores (r = 0.82), while the CDASI-A correlated well with both the cutaneous disease activity (r = 0.72) and extramuscular global assessment (r = 0.67). In addition, an increase in TIS correlated with a decrease (i.e., improvement) in both CDASI-A (r = –0.68) and

	TIS score	Change in MMT-8	Change in CDASI-A	Change in Extramuscular Global Assessment†	Change in Cutaneous Disease Activity†
TIS score	1.00				
Change in MMT-8	0.82	1.00			
Change in CDASI-A	–0.68	–0.53	1.00		
Change in Extramuscular Global Assessment†	–0.79	–0.56	0.67	1.00	
Change in Cutaneous Disease Activity†	–0.77	–0.60	0.72	0.79	1.00

Fig. 5: **Spearman correlations between different efficacy measures at Week 16 (N = 91)*.** *Darker = stronger correlation. †Part of the myositis disease activity assessment tool. CDASI-A, cutaneous dermatomyositis disease area and severity index activity; MMT-8, manual muscle testing 8; TIS, total improvement score. All p-values were <0.0001.

extramuscular global assessment (r = –0.79). An additional sensitivity analysis compared the categorical CDASI improvement versus TIS improvement at week 16 (Table 3).

Discussion

These results from the ProDERM study, the first large, prospective, randomized, placebo-controlled study to assess the long-term efficacy and safety of IVIg (Octagam® 10%) in patients with DM, demonstrated that IVIg was effective in improving dermatological assessment scores including CDASI-A, CDASI-D, cutaneous VAS, and MDAAT-MITAX, versus placebo. After switching from placebo to IVIg, patients attained similarly improved disease control at the end of the study as those who had received IVIg throughout the full study period. Most patients had >35% improvement in CDASI-A or one category improvement in MDAAT-MITAX, suggesting that patients had clinically meaningful improvement in dermatological symptoms. These observations were seen for all patients, regardless of disease severity at baseline, suggesting that IVIg is effective for even the most severe cutaneous DM.

	CDASI-A improvement[b]			
	None	Minimal	Moderate	Major
TIS[a] improvement				
None	21	4	0	3
Minimal	8	3	2	3
Moderate	4	6	5	9
Major	1	0	3	15
Fisher's exact test				
Table probability (P)			<0.0001	
Pr ≤ P			<0.0001	
Symmetry test				
Chi square			14.3333	
DF			6	
Pr > chi square			0.0261	
Simple kappa				
Estimate			0.3318	
Standard effort			0.0658	
95% CI			0.2029–0.4608	
Weighted kappa				
Estimate			0.5145	
Standard effort			0.0656	
95% CI			0.3860–0.6430	

CI, confidence interval; CDASI-A, cutaneous dermatomyositis disease area and severity index activity; TIS, total improvement score. [a]TIS >0–20 was defined as no improvement, >20–40 as minimal, >40–60 as moderate, and ≥60 as major improvement. [b]Change in CDASI-A of 0 to <20% was defined as no improvement, 20% to <35% was defined as minimal improvement, 35% to <50% as moderate improvement, and >50% as major improvement.

***Table 3*: Sensitivity analysis: categorial change in CDASI-A versus TIS at week 16 (N = 87).**

DM is classified as a rare idiopathic inflammatory myopathy, with a prevalence of 1/10,000–50,000.[24] IVIg is recommended for corticoresistant/corticodependent DM, but a limited number of studies have reported IVIg use for skin involvement related to DM. One study investigated the efficacy of rituximab for the cutaneous manifestations of adult and juvenile DM, and found that treatment led to significant improvements in cutaneous VAS in both adult (3.22–1.72; p = 0.0002) and juvenile (3.26–1.56; p < 0.0001) patients.[25] Findings also demonstrated that erythroderma (p < 0.001), erythematous rashes without secondary changes of ulceration or necrosis (p = 0.001), heliotrope rash (p < 0.001), and Gottron's sign and papules (p < 0.001) were the most significantly improved MDAAT variables between baseline and the last study visit at Week 44 (for adults and juveniles combined); however, there were no significant improvements in myositis damage index scores.

In a retrospective monocentric study of patients treated with IVIg (TEGELINE® or CLAIRYG®, LFB Biomedicaments, Les Ulis, France) for severe DM-related skin lesions (with no or minor muscle involvement) following failure of photoprotection, the majority of patients (19/27 [70%]) exhibited a major dermatological response to IVIg treatment; 4 patients (15%) exhibited a partial response and 4 patients (15%) exhibited no response.[26] In the same study, 10 patients (53%) relapsed in a median time of 6.2 months after the last course of IVIg, but six of these patients (60%) were successfully re-treated with an additional course of IVIg.[26] A second retrospective review of patients treated with any IVIg for refractory cutaneous DM showed similar results, with the majority of patients (35/42 [83%]) demonstrating cutaneous improvement following IVIg treatment.[8] This improvement occurred with a mean (±SD) of 1.82 (±1.38) cycles of IVIg (range, 1–6) and occurred regardless of DM subtype; however, most responders required more than one cycle of IVIg before improvement was seen.[8] These studies are limited by their retrospective nature and relatively small cohort sizes, as well as the latter study lacking an objective assessment for cutaneous DM activity. One double-blind, placebo-controlled trial of intravenous immunoglobulin has been carried out, in patients with treatment-resistant dermatomyositis, where patients showed marked improvements in cutaneous disease following treatment.[7] This study was also on a relatively small cohort of patients (n = 15), and could not use validated endpoints for cutaneous disease as these were not available at the time the study was carried out.

CDASI score, which was a secondary endpoint in ProDERM, was also used in a single-center, double-blind, randomized, placebo-controlled Phase 2 study of lenabasum, a non-immunosuppressive cannabinoid type 2 receptor (CB2R) agonist, in 22 adult patients with moderate DM skin activity (defined as CDASI-A ≥14). The study showed that treatment with lenabasum was

associated with a greater improvement in CDASI scores and multiple efficacy outcomes,[27] and there was a significant difference in improvement in CDASI scores from baseline in the lenabasum group versus the placebo group at the end of the study (Day 113, p = 0.0382).

The results seen in the ProDERM study are of clinical relevance, as after Week 28 more than 70% of patients experienced at least a 35% improvement in CDASI-A score, a threshold which is associated with a meaningful change in quality of life.[21] Dermatological scores had not plateaued by Week 40 and it is possible that further improvement may be seen after this timeframe. In addition, the sensitivity analysis performed here demonstrates good alignment between different efficacy measures. Of note, there is strong correlation at Week 16 between decrease in cutaneous disease activity score and improvement in extramuscular global assessment with TIS, demonstrating that both the myopathic and cutaneous aspects of DM improve similarly with IVIg therapy.

Limitations of this study include that the current analysis was post-hoc and therefore, the study was not prospectively powered to test for statistical differences in secondary endpoints or between subgroups stratified by efficacy or baseline disease severity score. Skin quality-of-life or itch was not measured in the study. All p-values reported are to be understood in the exploratory sense, and no adjustments for multiple comparison are used. As most patients completed the First Period of the study, in which IVIg and placebo were compared, and the number of dropouts was the same for the two groups, any bias from dropouts was considered to be minimal. Strengths include that this study was a prospective, double-blind trial using validated scores for prespecified secondary endpoints (such as CDASI).

In conclusion, the ProDERM study is the first large-scale international, randomized, placebo-controlled trial demonstrating the efficacy of IVIg treatment to significantly improve the cutaneous manifestations of DM, regardless of disease severity at baseline.

Contributors

VPW contributed to methodology, supervision, validation, and writing-reviewing and editing the manuscript. RA contributed to conceptualization, methodology, validation, supervision, and writing-reviewing and editing the manuscript. CC-S contributed to conceptualization, and writing-reviewing and editing the manuscript. JS contributed to conceptualization, and writing-reviewing and editing the manuscript. TL contributed to conceptualization, investigation, and writing-reviewing and editing the manuscript. NK contributed to formal analysis, methodology, validation, visualization, and writing-reviewing and editing the manuscript. MW contributed to investigation, and writing-reviewing and editing the manuscript. ZB-C contributed to investigation, methodology, and writing-reviewing and editing the manuscript.

Portland Medical Communications Ltd., assisted with writing and formatting the manuscript.

Data sharing statement

Access to the data underlying this paper is tightly governed by various legislative and regulatory frameworks. De-identified clinical and laboratory data and response to treatment data for the study cohort included in this study can only be made available to legitimate researchers and clinicians from medical and academic institutions, for academic and clinical research on request to Octapharma Pharmazeutika Produktionsges m.b.H. A proposal with a detailed description of study objectives and a statistical analysis plan will be requested. The proposal will be evaluated based on European and international data protection regulations and regulations about secondary use of patient data. After approval of a proposal, de-identified data will be shared through a secure online platform upon signing a data processing agreement. The study protocol, statistical analysis plan, and main results are available at: https://clinicaltrials.gov/ct2/show/NCT02728752.

Declaration of interests

VW has received grants from Celgene, Janssen, Pfizer, Biogen, Gilead, Corbus Pharmaceuticals, Genentech, AstraZeneca, Viela, Syntimmune, Amgen, Regeneron, Argenx, CSL Behring, Ventus, q32 Bio, BMS, Horizon, Rome Pharmaceuticals and Priovant; royalties for licenses from the University of Pennsylvania; consulting fees from Celgene, Genentech, Janssen, Lilly, Pfizer, Biogen, BMS, Gilead, Amgen, Medscape, Nektar, Incyte, EMD Sorona, CSL Behring, Principia, Crisalis, Viela Bio, Argenx, Kwoya Kirin, Regeneron, Principia, AstraZeneca, Abbvie, Octapharma, GSK, Astra-Zeneca, Cugene, UCB, Corcept, Beacon Bioscience, Rome Pharmaceuticals, Horizon, Gilead, Merck, Kezar, Sanofi, Bayer, Akari, Calyx and Cabaletta Bio; and has participated in a Data Safety Monitoring Board or Advisory Board for Astra Zeneca. RA has received grants or contracts from Mallinckrodt, Pfizer, Bristol Myers-Squibb, Boehringer Ingelheim, Q32, EMD Serono and Janssen; and consulting fees from Mallinckrodt, Octapharma, CSL Behring, Bristol Myers-Squibb, Alexion, Boehringer Ingelheim, Janssen, Roivant, Galapagos, Abbvie, Horizontal Therapeutics, Biogen, ANI Pharmaceutical, Capella, Ililli, Medicxi, EMD Serono, Kezar, Pfizer, Astra Zeneca, Argenx, Corbus, Kyverna, Merck, Actigraph, Scipher, Teva, Beigene, Nuvig, Cabaletta Bio and Sanofi. CC-S has received grants or contracts from Pfizer, Bristol Myers Squibb, Abbvie, CSL Behring, Alexion and Priovant; consulting fees from Pfizer, Bristol Myers Squibb, Abbvie, Octapharma, Priovant, Galapagos, Recludix and Boehringer Ingelheim Pharmaceuticals; and participated on a Data Safety Monitoring Board or Advisory Board for Bristol Myers Squibb. JS has received support for the current manuscript and consultancy fees from Octapharma; and honoraria for presentations, from Pfizer. TL is a consultant for FFF Enterprises. MW has received consulting fees from Novartis Pharma GmbH, Sanofi-Aventis Deutschland GmbH, DBV Technologies S.A., Aimmune Therapeutics UK Limited, Regeneron Pharmaceuticals, Inc., Leo Pharma GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, ALK-Abelló Arzneimittel GmbH, Lilly Deutschland GmbH, Kymab Limited, Amgen GmbH, Abbvie Deutschland GmbH & Co. KG, Pfizer Pharma GmbH, Mylan Germany GmbH (A Viatris Company), AstraZeneca GmbH and GlaxoSmithKline GmbH & Co. KG; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Novartis Pharma GmbH, Sanofi-Aventis Deutschland GmbH, DBV Technologies S.A., Aimmune Therapeutics UK Limited, Regeneron Pharmaceuticals, Inc., Leo Pharma GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, ALK-Abelló Arzneimittel GmbH, Lilly Deutschland GmbH, Kymab Limited, Amgen GmbH, Abbvie Deutschland GmbH & Co. KG, Pfizer Pharma GmbH, Mylan Germany GmbH (A Viatris Company), AstraZeneca GmbH and GlaxoSmithKline GmbH & Co. KG; and participated on a Data Safety Monitoring Board or Advisory Board for Novartis Pharma GmbH, Sanofi-Aventis Deutschland GmbH, DBV Technologies S.A., Aimmune Therapeutics UK Limited, Regeneron Pharmaceuticals, Inc., Leo Pharma GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, ALK-Abelló Arzneimittel GmbH, Lilly Deutschland GmbH, Kymab Limited, Amgen GmbH, Abbvie Deutschland GmbH & Co. KG, Pfizer Pharma GmbH, Mylan Germany GmbH (A Viatris Company), AstraZeneca GmbH and GlaxoSmithKline GmbH & Co. KG. ZB-C has received payment or honoraria for lectures from Sanofi, Berlin-Chemie and Abbvie; support for attending meetings from Sanofi and Biotest AG; and unpaid board membership in the Hungarian Dermatology and Immunology and Allergy Societies. NK has no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102234.

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