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BRIEF REPORT

Real-World Effectiveness of Dupilumab in Adult and Adolescent Patients with Atopic Dermatitis: 2-Year Interim Data from the PROSE Registry

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ABSTRACT

Introduction: There is a scarcity of data beyond 1 year for the use of dupilumab to treat atopic dermatitis (AD) in a real-world setting. This study aimed to evaluate the 2-year effectiveness of dupilumab among adult and pediatric patients with moderate-to-severe AD included in a real-world, longitudinal database study.
Methods: PROSE is an ongoing, prospective, observational, multi-center registry in the USA and Canada, designed to collect real-world data from patients aged ≥ 12 years with moderate-to-severe AD who initiate dupilumab in accordance with country-specific prescribing information. Assessments include body surface area affected by AD (BSA), Eczema Area and Severity Index (EASI), Dermatology Life Quality Index (DLQI), Pruritus Numerical Rating Scale (P-NRS), Patient-Oriented Eczema Measure (POEM), Patient Global Assessment of Disease (PGAD) questionnaire score, and occurrence of adverse events (AEs).
Results: Of 764 patients who enrolled in PROSE, 632 (83%) remained in the study at the time of this interim analysis. Improvements were observed at the first post-baseline clinic visit (approximately 3 months) in the clinician-assessed measures (mean BSA and EASI scores); improvements were sustained throughout the 2-year period covered in the present study. Consistent and sustained improvements were also observed over the 2-year period in the patient-reported measures of P-NRS, POEM, and DLQI, and in the proportion of patients reporting "very good/excellent" in answer to the question

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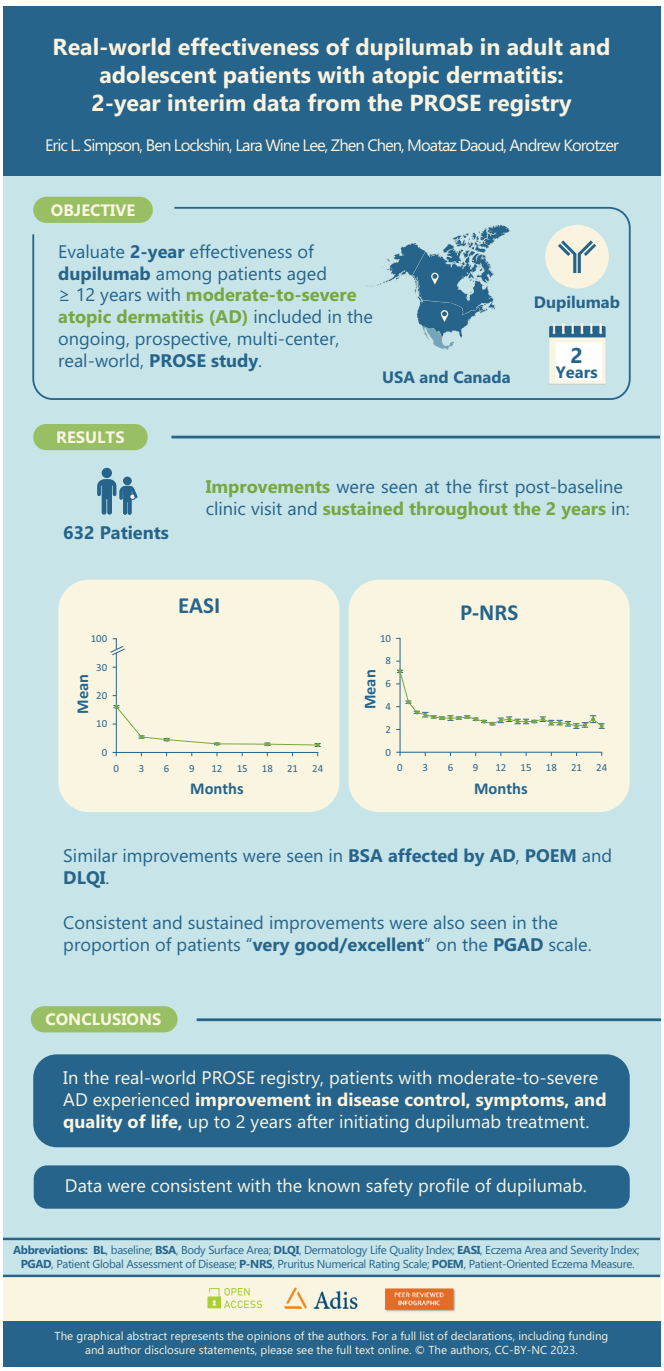
in the PGAD questionnaire: "Considering all the ways in which your eczema affects you, indicate how well you are doing". Dupilumab treatment was well tolerated, with safety findings consistent with those previously reported in studies of dupilumab for the treatment of AD.

Conclusions: In the real-world PROSE registry, patients with moderate-to-severe AD experienced sustained improvement in disease control, symptoms, and quality of life up to 2 years after initiating dupilumab treatment. Safety data were consistent with the known safety profile of dupilumab.

Trial Registration: ClinicalTrials.gov identifier: NCT 03428646.

Infographic:



PLAIN LANGUAGE SUMMARY

Atopic dermatitis (AD) is a long-term disease that affects the skin of patients, causing rash, inflammation, and intense itching, all leading to profound negative effects on their quality of life. In short-term studies, dupilumab has been shown to improve the signs and symptoms of AD, and to improve patients' quality of life. However, there is currently little information about the effectiveness of dupilumab when patients use it over the long term in the real world. This study used data from the ongoing PROSE registry, which is collecting information on 764 adults and adolescents (aged ≥ 12 years) with moderate-to-severe AD who are using dupilumab in the real world; patients were allowed to use other AD treatments and could even stop using dupilumab. Most patients (83%) were evaluated after 2 years of treatment. The study looked at how physicians judged changes over time in the severity of patients' AD. Importantly, it also used measures to allow patients themselves to report how they felt treatment affected their AD, the amount of itch they experienced, and their quality of life. Improvements in the severity of AD were already seen at 3 months, and they were maintained over the 2-year period. Patients also reported consistent and sustained improvements in their AD symptoms and quality of life during the 2 years of treatment. This analysis shows that patients with AD who began dupilumab treatment can have sustained long-term improvements.

Keywords: Atopic dermatitis; Disease control; Dupilumab; Efficacy; Health-related quality of life; Patient-reported outcomes; Real-world study; Safety

Key Summary Points

Why carry out this study?

A 2-year analysis of the PROSE study, a longitudinal patient registry, was undertaken to better understand the long-term safety and effectiveness of dupilumab (administered according to local guidelines) in adolescents and adults with moderate-to-severe atopic dermatitis (AD) treated in a real-world setting.

The primary outcome of this interim analysis of the PROSE study was to examine clinician-assessed measures of AD disease severity, and patient-reported measures of symptoms and quality of life, after 2 years of treatment.

What was learned from the study?

Data from our registry analysis showed treatment with dupilumab resulted in rapid and sustained improvements in AD signs, symptoms, and quality of life, with an acceptable safety profile.

The results support the long-term use of dupilumab in adolescent and adult patients with moderate-to-severe AD.

DIGITAL FEATURES

This article is published with digital features, including a video abstract to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24361180.

INTRODUCTION

Atopic dermatitis (AD) is a chronic type 2 inflammatory disease that is characterized by eczematous skin lesions and intense itching [1]. Patients with moderate-to-severe AD experience a substantial disease burden dominated by itch,

which has been shown to have a profound impact on daily functioning and sleep quality, significantly impairing patient quality of life [2–4]. The pathophysiology of AD involves upregulation of type 2 immune responses, including expression of interleukin (IL)-4 and IL-13, two key drivers of type-2 mediated inflammation in AD and multiple other diseases [5, 6].

Dupilumab is a fully human monoclonal antibody that blocks the shared receptor component for IL-4 and IL-13, thus inhibiting the signaling of both cytokines [5, 6]. In randomized clinical trials in patients with moderate-to-severe AD, treatment with dupilumab, with or without topical corticosteroids, produced significant improvement versus placebo in AD signs and symptoms, including itch and health-related quality of life (HRQoL), with an acceptable safety profile [7–11]. In the USA and Canada, dupilumab is approved for the treatment of patients (aged > 6 months in the USA, aged ≥ 6 months in Canada) with moderate-to-severe AD that is not adequately controlled with topical prescription medications [12, 13]. Observational data originating from clinical registry studies provide information about the effectiveness of a drug from the real-world clinical practice perspective and can add important insights into treatment use and its impact on patients' quality of life (QoL). We analyzed objective clinician-assessed measures of AD disease severity, patient-reported measures of symptoms and QoL, and the safety of dupilumab for up to 2 years in patients with moderate-to-severe AD who initiated dupilumab in the PROSE registry (ClinicalTrials.gov identifier: NCT 03428646).

METHODS

The methodology of PROSE (NCT 03428646) has been reported previously [14]. Briefly, PROSE is an ongoing, prospective, observational, multicenter registry across the USA and Canada in which patients with AD are administered dupilumab in accordance with country-specific prescribing information (Dupixent prescribing information USA—Regeneron Pharmaceuticals, Tarrytown, NY, USA [12]; Dupixent product mongraph Canada—Sanofi Canada, Toronto, ON, Canada [13]). Eligible patients aged ≥ 12 years with moderate-to-severe AD received their first administration of dupilumab at their baseline visit. There were no further restrictions after the baseline dupilumab dose; any dosing changes or concomitant medications were allowed as deemed necessary by the treating physician. Patients were encouraged to remain in the registry even if dupilumab treatment was discontinued, although these patients were not allowed to restart dupilumab. The PROSE study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements, and received institutional review board/ethics committee approval. Patients provided informed consent, and data were anonymized in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of the USA.

Patients were assessed by clinicians at baseline, and at post-baseline clinic assessments that were analyzed by protocol-defined windows as follows: month 3 (± 1 month), month 6 (± 2 months), and every 6 months (± 2 months) thereafter until the final visit at year 5. Clinician-reported outcomes (CRO) of AD severity included the percentage of body surface area affected by AD (%BSA), Eczema Area and Severity Index (EASI), and Overall Disease Severity score (ODS). Patient-reported outcomes (PRO) were assessed outside of clinic visits and captured via diaries or call center interactions. Patient-Oriented Eczema Measure (POEM), Patient Global Assessment of Disease (PGAD), Pruritus Numerical Rating Scale (P-NRS), and sleep Disturbance Numerical Rating Scale (Sleep-NRS) were assessed approximately monthly, whereas the Dermatology Life Quality Index (DLQI) was completed quarterly along with other patient-reported global assessments of the impact of AD on daily life. Adolescents were assessed for AD-related QoL impact using the Children's Dermatology Life Quality Index; given the small number of adolescents, only DLQI data (i.e., in adults) are presented in this report. Full details of the CRO and PRO instruments used are presented in Electronic Supplementary Material Table 1. Adverse events (AEs) were recorded for the duration of the study and were coded using the Medical Dictionary for

Regulatory Activities (MedDRA) version 22.0 (https://admin.meddra.org/sites/default/files/guidance/file/intguide_22_0_english.pdf).

In this analysis we present observed data up to 2 years; all data presented are for the safety analysis set. The number of patients at each visit represents those who attended their clinic (with or without ongoing dupilumab treatment) at months 3, 6, 12, 15, 18, 21, and 24, at the time of database lock. All analyses of data are descriptive. For continuous variables, descriptive statistics include means and standard deviations (SDs) or medians with interquartile ranges; frequencies and percentages are used for categorical or ordinal data, such as the PGAD score. AEs are reported as number of events (nE), and number of events per 100 patient-years (nE/100 PY). Patients remained eligible and were encouraged to stay in the study if dupilumab was discontinued (permanently or temporarily). Patients who permanently discontinued from the study before the end of study visit at month 60 were asked to complete an Early Termination visit.

RESULTS

The sociodemographic, treatment history, disease characteristics, and disease burden of the initial 315 patients included in the PROSE registry baseline analyses have been reported previously [14]. By the cut-off date for the present interim analysis, a total of 764 patients had been enrolled in PROSE and all were included in this analysis (males, 41.5%; adolescents aged ≥ 12 to < 18 years, 6.2%; mean [SD] age, 40.5 [17.9]; mean [SD] duration of AD, 17.5 [16.3] years). Mean (SD) scores for CRO and PRO measures of AD at baseline were: EASI total, 16.1 (12.4); P-NRS, 7.1 (2.3); POEM, 18.7 (6.5); DLQI, 13.3 (7.3). Mean (SD) %BSA affected by AD at baseline was 24.7 (21.8). Baseline CRO and PRO values were consistent with moderate-to-severe AD. At baseline, most patients were rated by physicians as having an ODS score that indicated either moderate (434 patients, 56.8%) or severe (245 patients, 32.1%) AD. Additionally, 58.6% of patients (n = 448) had ≥ 1 other "type 2-inflammatory" comorbid condition at baseline: 33.9% (n = 259) had allergic rhinitis; 31.9% (n = 240) had asthma; and 18.7% (n = 143) had allergic conjunctivitis. Overall, 57.2% (n = 437) of the patients had ≥ 1 current medication(s) that started before the first dupilumab dose and continued beyond or ended after the initial dupilumab dose, including 34.2% of patients (n = 261) using topical corticosteroids, 3.7% (n = 28) using emollients and protectives, 2.6% (n = 20) using systemic corticosteroids, and 2.9% (n = 22) using immunosuppressants.

The mean (SD) dupilumab treatment duration was 18.9 (11.6) months, with 632 patients still in the study at the time of data cut-off. While the maximum treatment duration for patients in the sample was 42 months, this analysis is limited to the first 2 years of patient experience in the PROSE study. The most common reasons for withdrawal from the PROSE study were loss-to-follow-up and patient withdrawal of consent (n = 60; 7.9%). Furthermore, 21 (2.7%) patients were documented as withdrawn as there was an end-date for dupilumab logged but these patients had not completed the end-of-treatment page; 18 (2.4%) withdrew due to the investigator/sponsor decision; ten (1.3%) were lost to follow-up; 9 (1.2%) patients withdrew documented as 'other' reasons; 7 (0.9%) patients were noncompliant with the protocol; 1 (0.1%) patient withdrew due to the COVID-19 pandemic; 3 (0.4%) patients withdrew due to AEs; and there were 3 (0.4%) deaths (1 case reported with the AE of congestive cardiac failure; 2 causes were not reported). Patients who withdrew from the study altogether before the final study visit (month 60) were asked to return to the clinic for early termination assessments.

Improvements in all clinician- and patient-reported AD signs and symptoms in patients who initiated dupilumab in PROSE were observed at the first clinic visit 3 months post-baseline, and these were sustained throughout 24 months of observation (Fig. 1). For example, mean EASI score was 16.1 at baseline, 5.5 at month 3, and 2.6 at month 24 (Fig. 1), with a mean (SD) absolute change from baseline to month 24 of –14.0 (13.7). Mean (SD) absolute change from baseline to month 24 in %BSA affected by AD was –22.0 (22.0). Similar consistent and sustained improvements were

observed in patient-reported measures of P-NRS, POEM, DLQI, and the proportion of patients reporting "very good/excellent" in the PGAD questionnaire over the 2-year period following treatment with dupilumab (Fig. 1).

Overall, 142/764 (19%) of patients reported ≥ 1 treatment-emergent AE (TEAE) during the 2-year follow-up period, with an estimated incidence rate (IR) of 31.2 events per 100 PY [31.2/100 PY]; Table 1). The most common AEs were conjunctivitis (2.4% of patients; IR: 1.9/100 PY) and AD (1.7%; IR: 1.3/100 PY). Serious AEs were reported by 16/764 (2.1%) patients (IR: 1.8/100 PY; Table 1) and included AD (n = 2 patients; IR: 0.2/100 PY), coronary artery disease (n = 2 patients; IR: 0.2/100 PY), congestive cardiac failure, acute myocardial infarction, anaphylactic reaction, cellulitis, death, diverticulitis, lymphadenectomy, mania, marginal zone lymphoma, metastatic squamous cell carcinoma, pneumonia, prostate cancer, pyelonephritis, squamous cell carcinoma, and uncoded TEAE (all n = 1; IR 0.1/100 PY). In total, 27 of the 764 (3.5%) patients experienced an AE that led to the discontinuation of dupilumab (IR: 5.6/100 PY), with the most common being AD, conjunctivitis, and nausea (all 3/764 [0.4%]; IR AD: 0.4/100 PY; IR conjunctivitis, nausea: 0.3; Table 1). Overall, there were 3 deaths, 1 of which was reported as congestive cardiac failure, while the causes of the other 2 deaths were not reported.

DISCUSSION

The baseline characteristics of patients from the USA and Canada in the observational, real-world PROSE registry indicate that patients with AD had a significant, multidimensional disease burden despite the previously reported use of standard topical therapies (39.0%) and systemic therapies (6.0%) [14]. Prior to starting dupilumab treatment, patients had moderate or severe AD disease that had a substantial effect on their HRQoL. Most of these patients also had other "type 2-inflammatory" comorbid conditions, such as allergic rhinitis and/or asthma. The high disease burden and relatively low proportion of patients who were well controlled using topical and/or systemic medications in this real-world patient cohort with moderate-to-severe AD suggest an important unmet need for effective and well-tolerated therapies that can be used over longer-term time periods.

Dupilumab treatment was associated with consistent improvements in clinician-assessed signs, patient-reported symptoms, and HRQoL in AD that were sustained through the 2-year period. It is noteworthy that mean EASI scores were reduced to approximately ≤ 5 beginning at least by month 3, and continued for the entire 2-year observational window. As indicated by data from Silverberg et al. [15] that looked at the relationship between EASI and Investigator Global Assessment (IGA) using pooled data from two phase III trials, this level of EASI score is consistent with an IGA score of 0 or 1 [15], a stringent response definition utilized in randomized controlled clinical trials. Moreover, dupilumab was well tolerated in this cohort of adolescents and adults with AD, with a safety profile consistent with previous observations and clinical trial data [4, 11]. These results are consistent with those reported in other real-world studies of dupilumab from several global populations, although, as reported in a recent systematic literature review, most of those studies did not follow patients beyond 1 year [16, 17].

Limitations

The findings in this study are limited by the real-world design of the PROSE registry, including the lack of a comparator or placebo group, and no a priori statistical hypothesis. The selection of sites that enrolled patients into PROSE, and the types of patients who chose to enroll in PROSE, may not be fully representative of the AD patient population in the USA and Canada. Because the registry only enrolls patients from North America, the generalizability of PROSE registry data worldwide may be further limited. It is also worth noting that as this is an observed analysis, the population may be biased towards better responses; however, the low drop-out rate likely minimized the impact of this effect. Finally, while all patients were required to initiate dupilumab treatment at baseline per approved

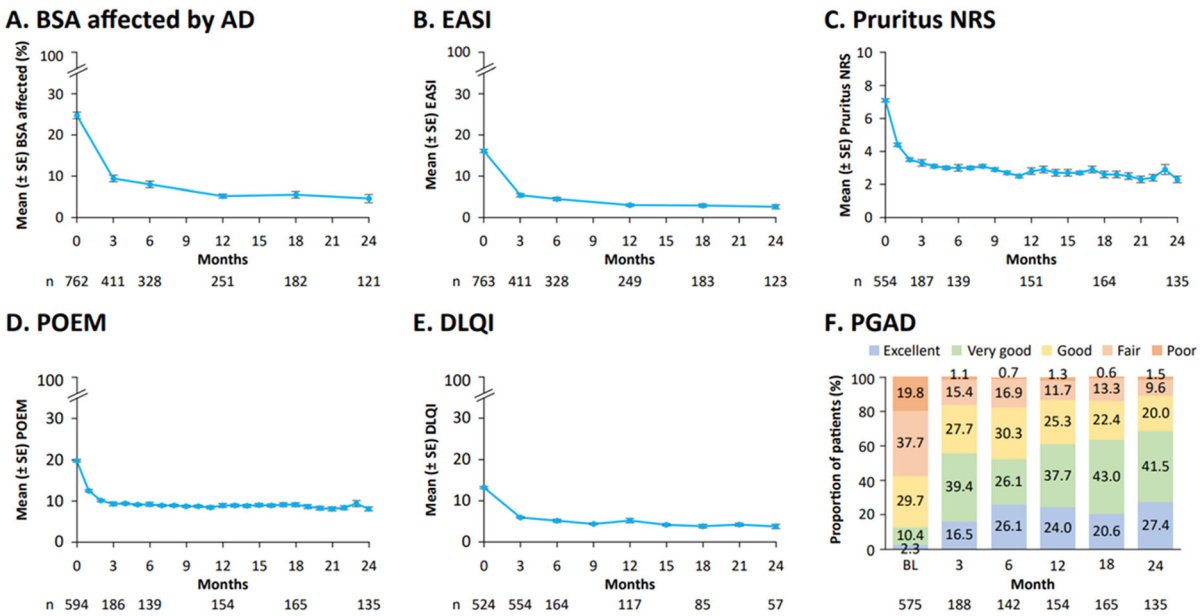


Fig. 1 Improvement in AD signs, symptoms, quality of life, and patients' perspective of disease from baseline. *AD* atopic dermatitis, *BL* baseline, *BSA* body surface area, *DLQI* dermatology life quality index, *EASI* eczema area and severity index, *NRS* numerical rating scale, *POEM* patient-oriented eczema measure, *PGAD* patient global assessment of disease, *SE* standard error

product labeling, there were no requirements or restrictions on subsequent dosing or usage of dupilumab or of the use of concomitant treatments for AD, as these patients were being treated per standard-of-care in a real-world setting. Therefore, it is not possible to entirely attribute the improvements noted in this patient sample to dupilumab treatment.

CONCLUSIONS

In conclusion, interim real-world data from the ongoing PROSE AD registry indicate that adolescent and adult patients with moderate-to-severe AD who initiated dupilumab experienced sustained improvement in disease control, symptom burden, and HRQoL; safety data were consistent with the known safety profile of dupilumab. These results support previous findings from the dupilumab clinical trial program in AD, showing dupilumab has a risk/benefit profile suitable for the treatment of patients with moderate-to-severe AD.

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Table 1 Summary of treatment-emergent adverse events for the PROSE registry at the 2-year follow-up

Treatment-emergent adverse events	Total patient cohort (N = 764)[a]	
	n **(%)**	**nE (nE/100 PY)[b]**
All-cause TEAEs		
≥ 1 TEAE	142 (18.6)	325 (31.2)
Severe AE	25 (3.3)	32 (3.1)
Serious AE[c]	16 (2.1)	19 (1.8)
≥ 1 AE leading to dupilumab discontinuation	27 (3.5)	58 (5.6)
Most common TEAEs (≥ 1% of patients)[d]		
Conjunctivitis	18 (2.4)	20 (1.9)
Atopic dermatitis	13 (1.7)	14 (1.3)
Dry eye	9 (1.2)	9 (0.9)
Noninfective conjunctivitis	8 (1.0)	8 (0.8)
TEAEs leading to dupilumab discontinuation in ≥ 2 patients[d,e]		
Atopic dermatitis	3 (0.4)	4 (0.4)
Conjunctivitis	3 (0.4)	3 (0.3)
Nausea	3 (0.4)	3 (0.3)
Nasopharyngitis	2 (0.3)	3 (0.3)
Dyspnea	2 (0.3)	2 (0.2)
Pregnancy	2 (0.3)	2 (0.2)
Deaths	3 (0.4)	0
Death associated with known TEAEs[f]	2 (0.3)	2 (0.2)

Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 (https://admin.meddra.org/sites/default/files/guidance/file/intguide_22_0_english.pdf)

AE adverse event, *IR* incident rate, *nE* number of events, *PY* patient-years, *TEAE* treatment-emergent adverse event

[a]Of the 764 patients enrolled, 111 (14.5%) withdrew from the study at the time of the data cut-off. Mean duration of treatment with dupilumab was 18.9 (standard deviation 11.6) months, and cumulative total AE observation period was 1041.5 years

[b]Summary IRs are based on time at risk of first event

[c]A total of 19 serious AEs occurred in a total of 16 patients

[d]Presented by MedDRA Preferred Term

[e]2 events were uncoded

[f]2 deaths were reported in association with TEAEs: preferred terms congestive cardiac failure (n = 1) and death (n = 1)

Data Availability. Qualified researchers may request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of the trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

Declarations

Ethical Approval. The PROSE study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements, and received institutional review board/ethics committee approval. All patients provided informed consent, and data were anonymized in compliance with the Health Insurance Portability and Accountability Act (HIPAA) inserted by journal.

Conflict of Interest. Eric Simpson receives/has received grants/research support from AbbVie, Acrotech Biopharma Inc., Amgen, Arcutis Biotherapeutics, Aslan Pharmaceuticals, Castle Biosciences, CorEvitas, Dermavant Sciences, Dermira, Eli Lilly and Company, Incyte, Kymab, Kyowa Kirin, National Jewish Health, LEO Pharma, Pfizer, Regeneron Pharmaceuticals, Sanofi, and Target RWE; and is/has been a consultant for Advances in Cosmetic and Medical Dermatology Hawaii LLC, AbbVie, Amgen, AOBiome LLC, Arcutis Biotherapeutics, Arena Pharmaceuticals, Aslan Pharmaceuticals, Boehringer Ingelheim USA, Inc., Boston Consulting Group, Bristol Myers Squibb, Collective Acumen LLC (CA), CorEvitas, Dermira, Eli Lilly and Company, Evelo Biosciences, Evidera, Excerpta Medica, FIDE, Forte Biosciences, Galderma, GlaxoSmithKline, Incyte, Janssen, Johnson & Johnson, Kyowa Kirin Pharmaceutical Development, LEO Pharma, Medscape LLC, Merck, MauiDerm, MLG Operating, MJH Holdings, Pfizer, Physicians World LLC, PRImE, Regeneron Pharmaceuticals, Revolutionizing Atopic Dermatitis Inc., Roivant, Sanofi-Genzyme, Trevi Therapeutics, Valeant Pharmaceuticals, Vindico Medical Education, and WebMD. Ben Lockshin has received investigator and speaker fees from Eli Lilly and Regeneron Pharmaceuticals Inc.; investigator fees from Anacor Pharmaceuticals, Dermira, Franklin Bioscience, and LEO Pharma; and investigator/speaker/consultant fees from AbbVie. Lara Wine Lee is on the Advisory Board of Castle Creek, Eli Lilly, Pfizer, Regeneron Pharmaceuticals Inc., and Verrica; is a consultant for AbbVie, Amryt, Krystal Biotech, Novartis, and Kimberly Clark; is/has been an investigator for AbbVie, Amgen, Amryt, Arcutis, Castle Creek, Celgene, Eli Lilly, Galderma, Incyte Corp, Mayne Pharmaceuticals, Moonlake Pharmaceuticals, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi, Target Pharma, Timber Pharmaceuticals, Trevi Therapeutics, and UCB; and has received speaker fees from Amryt and Krytsal Biotech. Moataz Daoud is a Sanofi employee and may hold stock and/or stock options in the company. Zhen Chen and Andrew Korotzer are employees and shareholders of Regeneron Pharmaceuticals Inc.

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