doi:10.36849/JDD.2020.5095

Demographics and Baseline Disease Characteristics of Early Responders to Crisaborole for Atopic Dermatitis

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ABSTRACT

Introduction: Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate atopic dermatitis (AD). This post hoc, pooled analysis identified demographic characteristics associated with early response to crisaborole.

Methods: Early response was defined as day 8 Investigator's Static Global Assessment (ISGA) success (clear [0] or almost clear [1] with ≥2-grade improvement), ISGA clear/almost clear, or Severity of Pruritus Scale (SPS) response (≥1-point improvement). Correlations between early response and day-29 response were calculated.

Results: Patients were more likely to be early ISGA success responders if they were aged <12 years (P=0.0023), were white (P=0.0316), had moderate baseline disease by ISGA (P=0.0003), had not received prior AD treatment (P=0.0213), had disease duration shorter than or equal to the median (≤6.45 years; P=0.0349), or did not concurrently use antihistamines (P=0.0148). Similar early response results were observed for patients achieving ISGA clear or almost clear; however, they were more likely to have mild baseline disease by ISGA (P<0.0001) or mild percentage of treatable body surface area involvement (5 to <16; P<0.0001). Patients aged <12 years (P=0.0001) or with moderate baseline disease (P=0.0475) were more likely to be early responders based on SPS criteria. By all 3 definitions, patients who achieved early response at day 8 were more likely to be responders at day 29 (P<0.0001).

Conclusion: Based on this analysis, patients aged <12 years were more likely to be early responders to crisaborole per all 3 definitions. Early response to crisaborole was a predictor of response at day 29.

Clinical Trial Registration: ClinicalTrials.gov, NCT02118766 and NCT02118792

J Drugs Dermatol. 2020;19(6):619-624. doi:10.36849/JDD.2020.5095

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by eczematous lesions and pruritus that occurs in approximately 15%-30% of children and 2%-10% of adults worldwide.[1,2] AD causes psychological, social, quality-of-life, and financial burden to patients and their families, often related to intense pruritus.[3] Despite the impact of the disease, adherence to AD treatment may be poor, related to a lack of patient understanding of the disease, improper topical medication application that can lead to reduced effectiveness, and fear of topical corticosteroids, among other reasons.[4]

Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD. In 2 large, randomized, double-blind, vehicle-controlled phase 3 clinical studies (AD-301: NCT02118766; AD-302: NCT02118792), a greater proportion of crisaborole-treated patients than vehicle-treated patients had improvement in global disease severity, as measured by Investigator's Static Global Assessment (ISGA) success (defined as ISGA of clear [0] or almost clear [1] with ≥2-grade improvement) at day 29.[5] In both studies, differences in ISGA success rates were observed between crisaborole and vehicle as early as day 8 of treatment, which was the first day of postbaseline clinical assessment.[5] Crisaborole-treated patients also achieved improvement in pruritus earlier than vehicle-treated patients, and the improvement was sustained until day 29.[6]

Patients with AD may become frustrated if improvement is not observed early in the course of treatment and may discontinue treatment prematurely if the signs and symptoms of the disease do not seem to improve.[7] Suboptimal management of AD can lead to flares[1] and, potentially, an increased risk for comorbidities, such as allergies, infections, depression, and autoimmune disease.[8] Therefore, it may be valuable to identify factors that predict early treatment response with crisaborole.

This post hoc, pooled analysis was designed to identify patient baseline characteristics that could predict early response to crisaborole therapy, as defined by ISGA success at day 8 (after 1 week of therapy), ISGA of clear or almost clear at day 8, and ≥1-point improvement in Severity of Pruritus Scale (SPS) score based on the weekly average SPS score at day 8, using data from 2 phase 3 studies of patients aged ≥2 years with mild-to-moderate AD (AD-301 and AD-302).

METHODS

Study Design

Complete study design details and inclusion/exclusion criteria for the 2 phase 3 studies have been previously published.[4] Briefly, eligible patients were aged ≥2 years, with a clinical diagnosis of AD, baseline ISGA indicating mild (2) or moderate (3) disease, and percentage of treatable body surface area (%BSA) ≥5. Patients were randomly assigned 2:1 to receive treatment with crisaborole or vehicle applied twice daily to all treatable areas of the body, except the scalp, for 28 days. Patients were ineligible if they had previously used biologic therapy, systemic corticosteroids within 28 days of treatment initiation, or topical calcineurin inhibitors or topical corticosteroids within 14 days of treatment initiation. Patients on stable regimens of inhaled corticosteroids, antihistamines, or topical retinoids for non-AD treatment could continue these medications. Patients could also use acceptable bland emollients throughout the study to manage dry skin areas around, but not overlapping, the treatable AD-involved areas. Use of rescue medication was not permitted.

ISGA, a 5-point rating scale used to measure overall disease severity from clear (0) to severe (4),[5] was assessed at baseline and every 7 days (day 8 was the first postbaseline assessment) up to day 29. SPS, a 4-point rating scale of the severity of pruritus from none (0) to severe (3),[9] was recorded twice daily up to day 29 via electronic diary by patients or caregivers (for patients aged 2-7 years) before study drug was applied.

Study Outcomes

Early response outcomes

Early response at day 8 was defined using 3 different definitions: ISGA success (defined as ISGA of clear [0] or almost clear [1] with ≥2-grade improvement from baseline), ISGA of clear or almost clear, and SPS response (defined as ≥1-point improvement in SPS based on weekly average scores). The analyses were performed for crisaborole-treated patients, and comparisons were made between subgroups based on baseline characteristics. The subgroups included in the analyses were age (<12 years vs ≥12 years), sex (male vs female), race (white vs nonwhite), ethnicity (Hispanic vs non-Hispanic), baseline ISGA (mild [2] vs moderate [3]), %BSA involvement (mild [5 to <16] vs moderate/severe [≥16]),[10] prior AD treatment (prior vs no prior, defined as any prior use of systemic or topical corticosteroids or topical calcineurin inhibitors for the treatment of AD within 90 days before the first dose of study medication), median disease duration (≤6.45 years vs >6.45 years), history of asthma/allergic rhinitis (history vs no history), and concurrent antihistamine use (use vs no use).

Early response as predictor of day 29 response

Correlations between early response at day 8 and response at day 29 were calculated to investigate whether early response was a predictor of response at day 29. The analyses were performed for crisaborole-treated patients using ISGA success, ISGA of clear or almost clear, and SPS responses; comparisons were made between responders and nonresponders at day 8 and day 29.

Statistical Analysis

In the early response outcomes analysis, odds ratios (ORs), 95% CIs, and *P* values were calculated using a logistic model with response as the dependent variable and subgroup as the independent variable. *P* values were not adjusted for multiplicity. In the correlation of early response with day-29 response analysis, ORs, CIs, and *P* values in early response outcomes were calculated using a logistic model with response at day 29 (ISGA success, ISGA clear or almost clear, or SPS response) as the dependent variable and response at day 8 (ISGA success, ISGA clear or almost clear, or SPS response) as the independent variable. *P* values were not adjusted for multiplicity, with no imputation of missing data.

RESULTS

Patient Disposition

A total of 1522 patients were included in the combined phase 3 studies, and 1016 and 506 patients received crisaborole and vehicle, respectively (Table 1). The mean age in the crisaborole group was 12.3 years; the mean %BSA was 18.3. Greater proportions of patients were aged <12 years (61.7%), female (55.7%), white (60.7%), and non-Hispanic (80.3%); had moderate disease per ISGA (61.3%); had mild %BSA involvement (64.8%); and had not received prior AD treatment within 90 days before starting the study (59.0%). Most patients did not have a history of asthma/allergic rhinitis (65.7%) and/or did not concurrently use antihistamines (75.9%). The median disease duration was 6.45 years.

Early Responder Outcomes

Patients were more likely to be early (day 8) ISGA success responders if they were aged <12 years (<12 years vs ≥12 years, OR [95% CI], 1.83 [1.24-2.69]; *P*=0.0023), were white (white vs non-white, 1.51 [1.04-2.19]; *P*=0.0316), had moderate baseline disease by ISGA (mild vs moderate, 0.48 [0.32-0.72]; *P*=0.0003), had not received prior AD treatment (prior vs no prior, 0.65 [0.45-0.94]; *P*=0.0213), had disease duration ≤6.45 years (≤6.45 years vs >6.45 years, 1.46 [1.03-2.08]; *P*=0.0349), or did not concurrently use antihistamines (use vs no use, 0.56 [0.35-0.89]; *P*=0.0148; Figure 1).

TABLE 1.

Demographics and Baseline Disease Characteristics. %BSA = percentage of treatable body surface area; AD = atopic dermatitis; ISGA = Investigator's Static Global Assessment.

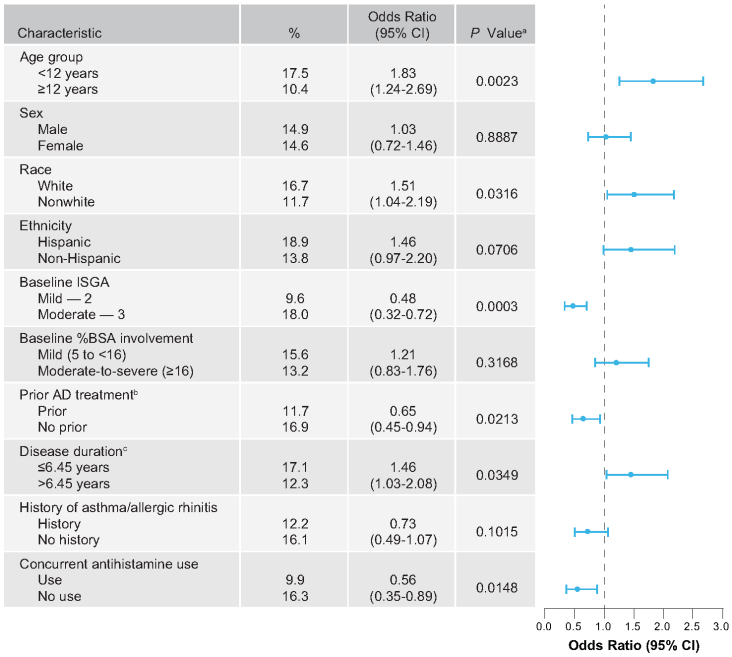
Characteristic, n (%)		Crisaborole-Treated Patients N=1016
Age group	<12 years	627 (61.7)
	≥12 years	389 (38.3)
Sex	Male	450 (44.3)
	Female	566 (55.7)
Race	White	617 (60.7)
	Nonwhite	399 (39.3)
Ethnicity	Hispanic	200 (19.7)
	Non-Hispanic	816 (80.3)
ISGA score	Mild – 2	393 (38.7)
	Moderate – 3	623 (61.3)
%BSA	Mild (5 to <16)	658 (64.8)
	Moderate-to-severe (≥16)	358 (35.2)
Prior AD treatment[a]	Yes	417 (41.0)
	No	599 (59.0)
Disease duration[b]	≤6.45 years	515 (50.7)
	>6.45 years	501 (49.3)
History of asthma/ allergic rhinitis	Yes	349 (34.4)
	No	667 (65.7)
Concurrent anti-histamine use	Yes	245 (24.1)
	No	771 (75.9)

[a]Defined as any prior use of systemic or topical corticosteroids or topical calcineurin inhibitors for the treatment of AD within 90 days before starting the study.
[b]6.45 years was the median disease duration at baseline.

In patients achieving ISGA clear or almost clear, patients were more likely to be early (day 8) responders if they were aged <12 years (<12 years vs ≥12 years, OR [95% CI], 1.47 [1.12-1.95]; *P*=0.0063), were white (white vs non-white, 1.57 [1.19-2.07]; *P*=0.0015), had mild baseline disease by ISGA (mild vs moderate, 5.63 [4.22-7.50]; *P*<0.0001), had mild %BSA involvement (mild vs moderate/severe, 1.95 [1.46-2.62]; *P*<0.0001), had not received prior AD treatment (prior vs no prior, 0.75 [0.57-0.98]; *P*=0.0338), had disease duration ≤6.45 years (≤6.45 years vs >6.45 years, 1.61 [1.24-2.11]; *P*=0.0005), or did not concurrently use antihistamines (use vs no use, 0.52 [0.37-0.72]; *P*=0.0001; Figure 2).

Early SPS responders were more likely to be aged <12 years (<12 years vs ≥12 years, OR [95% CI], 1.93 [1.38-2.70]; *P*=0.0001) or have moderate baseline disease severity by ISGA (mild vs moderate, 0.72 [0.52-1.00]; *P*=0.0475; Figure 3). No additional significant differences were observed between remaining subgroups for ISGA or SPS early response definitions.

FIGURE 1. Early (day 8) ISGA success responders among crisaborole-treated patients.



[a]*P* values are for the comparison of the top category with the bottom category and were not adjusted for multiplicity. [b]Defined as any prior use of systemic or topical corticosteroids or topical calcineurin inhibitors for the treatment of AD within 90 days before starting the study. [c]6.45 years was the median disease duration at baseline. %BSA = percentage of treatable body surface area; AD = atopic dermatitis; ISGA = Investigator's Static Global Assessment.

Early Response as Predictor of Day 29 Response

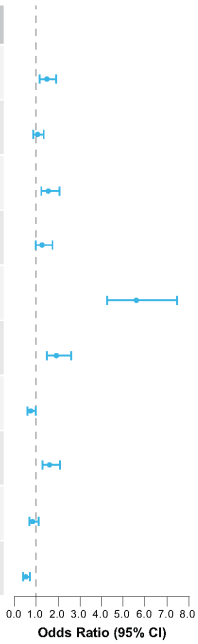
Patients who were early (day 8) ISGA success responders were more likely than those who were not day-8 responders to achieve day-29 ISGA success response (OR [95% CI], 4.32 [2.98-6.26]; *P*<0.0001; Figure 4A). Similarly, patients who were early (day 8) ISGA clear or almost clear responders were more likely than those who were not day-8 responders to achieve day-29 ISGA clear or almost clear response (5.50 [4.04-7.47]; *P*<0.0001; Figure 4B). Finally, patients who were early (day 8) SPS responders were more likely than those who were not day-8 responders to achieve SPS response at day 29 (10.71 [7.27-15.79]; *P*<0.0001; Figure 4C).

DISCUSSION

Based on this post hoc pooled analysis, patients who were aged <12 years versus patients aged ≥12 years were more likely to be early responders to crisaborole treatment according to all 3 early response criteria: ISGA success, ISGA clear or almost clear, and SPS response. In terms of ISGA success and ISGA clear or almost clear criteria, white patients, patients who had not received prior AD treatment, had disease duration ≤6.45 years, and/or did not concurrently use antihistamines were more likely to be early responders. The factors associated with early response were consistent between the 2 definitions of ISGA response, except for disease severity at baseline, which

FIGURE 2. Early (day 8) ISGA clear/almost clear response among crisaborole-treated patients.

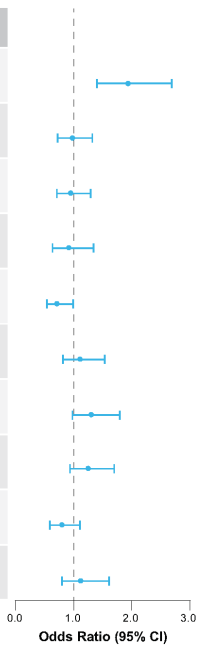
Characteristic	%	Odds Ratio (95% CI)	*P* Value[a]
Age group			
<12 years	35.6	1.47 (1.12-1.95)	0.0063
≥12 years	27.3		
Sex			
Male	33.0	1.05 (0.81-1.37)	0.7053
Female	31.9		
Race			
White	36.2	1.57 (1.19-2.07)	0.0015
Nonwhite	26.5		
Ethnicity			
Hispanic	36.7	1.27 (0.92-1.76)	0.1491
Non-Hispanic	31.4		
Baseline ISGA			
Mild — 2	55.3	5.63 (4.22-7.50)	<0.0001
Moderate — 3	18.0		
Baseline %BSA involvement			
Mild (5 to <16)	37.3	1.95 (1.46-2.62)	<0.0001
Moderate-to-severe (≥16)	23.4		
Prior AD treatment[b]			
Prior	28.6	0.75 (0.57-0.98)	0.0338
No prior	35.0		
Disease duration[c]			
≤6.45 years	37.5	1.61 (1.24-2.11)	0.0005
>6.45 years	27.1		
History of asthma/allergic rhinitis			
History	30.2	0.86 (0.65-1.14)	0.2889
No history	33.5		
Concurrent antihistamine use			
Use	22.2	0.52 (0.37-0.72)	0.0001
No use	35.7		



[a]*P* values are for the comparison of the top category with the bottom category and were not adjusted for multiplicity. [b]Defined as any prior use of systemic or topical corticosteroids or topical calcineurin inhibitors for the treatment of AD within 90 days before starting the study. [c]6.45 years was the median disease duration at baseline. %BSA = percentage of treatable body surface area; AD = atopic dermatitis; ISGA = Investigator's Static Global Assessment.

FIGURE 3. Early (day 8) SPS response[a] among crisaborole-treated patients.

Characteristic	%	Odds Ratio (95% CI)	*P* Value[b]
Age group			
<12 years	35.1	1.93 (1.38-2.70)	0.0001
≥12 years	21.9		
Sex			
Male	29.7	0.97 (0.71-1.33)	0.8639
Female	30.3		
Race			
White	29.6	0.95 (0.69-1.30)	0.7258
Nonwhite	30.8		
Ethnicity			
Hispanic	28.6	0.92 (0.62-1.35)	0.6537
Non-Hispanic	30.4		
Baseline ISGA			
Mild — 2	25.9	0.72 (0.52-1.00)	0.0475
Moderate — 3	32.7		
Baseline %BSA involvement			
Mild (5 to <16)	30.8	1.12 (0.80-1.55)	0.5138
Moderate-to-severe (≥16)	28.6		
Prior AD treatment[c]			
Prior	33.4	1.31 (0.96-1.80)	0.0881
No prior	27.7		
Disease duration[d]			
≤6.45 years	32.4	1.26 (0.92-1.71)	0.1509
>6.45 years	27.6		
History of asthma/allergic rhinitis			
History	27.2	0.80 (0.58-1.12)	0.1919
No history	31.7		
Concurrent antihistamine use			
Use	32.0	1.13 (0.78-1.62)	0.5222
No use	29.5		



[a]≥1-point improvement in SPS response based on weekly averages. [b]*P* values are for the comparison of the top category with the bottom category and were not adjusted for multiplicity. [c]Defined as any prior use of systemic or topical corticosteroids or topical calcineurin inhibitors for the treatment of AD within 90 days before starting the study. [d]6.45 years was the median disease duration at baseline. %BSA = percentage of treatable body surface area; AD = atopic dermatitis; ISGA = Investigator's Static Global Assessment; SPS = Severity of Pruritus Scale.

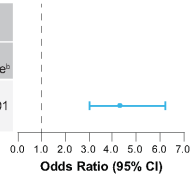
was dependent on whether a ≥2-grade improvement from baseline in ISGA severity was included in the definition. In terms of SPS response, only patients aged <12 years and patients with moderate disease were likely to be early responders, with no other baseline characteristics predicting early response. Patients treated with crisaborole who achieved early (day 8) ISGA success, ISGA clear or almost clear, or SPS response were more likely to achieve sustained response at day 29, suggesting that early treatment response may be an important prognostic factor for ongoing treatment response.

In the current analysis, 2 ISGA early response definitions were included: ISGA success and ISGA clear or almost clear. The primary definition of treatment success for registration studies has focused on achieving ISGA success due to regulatory guidance; however, ISGA success excludes many patients with mild AD at baseline since in order to attain ≥2-grade improvement from baseline, patients with mild ISGA [2] at baseline must achieve clear ISGA [0], which is 100% improvement and can be difficult to achieve in 8 days. Yet, patients with moderate ISGA [3] at baseline must achieve almost clear ISGA [1], which is ≥67% improvement and more attainable in 8 days. The ISGA clear or almost clear definition does not require ≥2-grade improvement from baseline, allowing smaller but still clinically relevant improvements experienced by patients with mild AD to be

FIGURE 4. Analysis of correlation between patients achieving early (day 8) response versus patients achieving response at day 29 among crisaborole-treated patients for (A) ISGA success (B) ISGA clear or almost clear, and (C) ≥1-point improvement in SPS.[a]

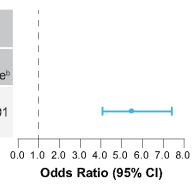
A

Patients who achieved ISGA success at day 8	Patients who achieved ISGA success at day 29			
	Achieved, %	Did not achieve, %	Odds Ratio (95% CI)	*P* Value[b]
Achieved	62.2	37.8	4.32 (2.98-6.26)	<0.0001
Did not achieve	27.6	72.4		



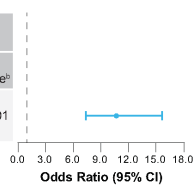
B

Patients who achieved ISGA clear or almost clear at day 8	Patients who achieved ISGA clear or almost clear at day 29			
	Achieved, %	Did not achieve, %	Odds Ratio (95% CI)	*P* Value[b]
Achieved	77.2	22.8	5.50 (4.04-7.47)	<0.0001
Did not achieve	38.1	61.9		



C

Patients who achieved ≥1-point improvement in SPS at day 8	Patients who achieved ≥1-point improvement in SPS at day 29			
	Achieved, %	Did not achieve, %	Odds Ratio (95% CI)	*P* Value[b]
Achieved	81.1	18.9	10.71 (7.27-15.79)	<0.0001
Did not achieve	28.6	71.4		



[a]≥1-point improvement in SPS response based on weekly averages. [b]*P* values are for the comparison of the top category with the bottom category and were not adjusted for multiplicity. ISGA = Investigator's Static Global Assessment; SPS = Severity of Pruritus Scale.

included. The ISGA success endpoint also does not address itch, characterize the extent of AD skin involvement, or characterize other relevant patient-reported AD symptoms.[11] SPS addresses itch, which is considered a hallmark symptom of AD.[12] This analysis included ISGA and SPS responses, resulting in a more in-depth characterization of the effect of crisaborole on patients with AD.

The results of this post hoc analysis showed that early response to crisaborole can be a prognostic factor for ongoing response to treatment, highlighting the importance of early treatment adherence to improve treatment outcomes. AD is a chronic condition necessitating prolonged periods of treatment,[13,14] which may impact treatment adherence. Adherence to treatment, especially topical medications, is poor in chronic diseases.[4] Differences in patient adherence could be a factor mediating differences in the response to topical crisaborole; however, >97% of patients in both phase 3 studies reported applying ≥95% of expected doses. Hence, treatment adherence was not an independent factor evaluated in this study. The early efficacy of crisaborole might have encouraged patients to adhere to treatment and might have improved patient accountability in treatment application,[15] explaining why patients experienced continued improvement in AD severity and pruritus. Patient education focused on the association of early response to continued response can be used to highlight the importance of using crisaborole as indicated.

This was a post hoc analysis and therefore not specifically powered to show differences between groups. The analyses may be limited by unequal sample sizes between groups; however, there were trends in the data. Additionally, responder analyses in general are limited because the response cutoff may not be a consensus-defined threshold and the dichotomizing results into binary responses tend to result in statistical power loss in comparison with the original continuous variable analysis,[16] which obscures smaller changes and continued improvement over time. However, this analysis used the common dichotomized endpoints of ISGA success and ISGA clear or almost clear. Additionally, this analysis defined SPS success as ≥1-point improvement, which is higher than the clinically important difference of 0.20.[9] Finally, the results of the analysis were robust, even using binary responses. However, the results should be interpreted with caution because additional prospective studies are necessary confirm these results.

CONCLUSION

The results of this post hoc analysis suggest that patients aged <12 years who were white, had not received prior AD treatment, had disease duration ≤6.45 years, or did not concurrently use antihistamines were more likely to be early ISGA success and ISGA clear or almost clear responders. Patients who had moderate baseline disease by ISGA were more likely to be early ISGA success responders, whereas patients with mild baseline disease by ISGA and mild %BSA were more likely to be early ISGA clear or almost clear responders. Patients aged <12 years or who had moderate baseline disease by ISGA were more likely to be early responders based on SPS criteria. Additionally, patients who achieved ISGA success, ISGA clear or almost clear, or ≥1-point improvement in SPS early response at day 8 with crisaborole treatment were more likely to achieve continued response at day 29.

DISCLOSURES

LFSG has been an investigator, consultant, or advisor for Pfizer Inc., AbbVie, Dermavant, Galderma, Incyte, LEO Pharma, Regeneron, and Sanofi. LT and CZ are employees and stockholders of Pfizer Inc. PS is an employee of Pfizer R&D UK Ltd., and stockholder of Pfizer Inc. SRF has received grant and consulting honoraria from Pfizer Inc., and is a consultant for and has received grants from Regeneron and Sanofi.

ACKNOWLEDGMENT

Editorial/medical writing support under the guidance of authors was provided by Juan Sanchez-Cortes, PhD, at ApotheCom, San Francisco, CA, USA, and was funded by Pfizer Inc., New York, NY, USA, in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med.* 2015;163:461-464).
This analysis was funded by Pfizer Inc.

Data Sharing Statement: Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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