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ORIGINAL RESEARCH ARTICLE

Safety of Lebrikizumab in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis: An Integrated Analysis of Eight Clinical Trials

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Abstract

Background Lebrikizumab is a monoclonal antibody that binds with high affinity to interleukin (IL)-13, thereby blocking the downstream effects of IL-13 with high potency.

Objectives To report integrated safety of lebrikizumab in adults and adolescents with moderate-to-severe atopic dermatitis from phase 2 and 3 studies.

Methods Five double-blind, randomized placebo-controlled studies; one randomized open-label study; one adolescent open-label, single-arm study; and one long-term safety study were summarized in two datasets: (1) placebo-controlled week 0–16 (All-PC Week 0–16) in patients who received lebrikizumab 250 mg every 2 weeks (LEBQ2W) versus placebo and (2) patients who received any dose of lebrikizumab at any time during the studies (All-LEB). Exposure-adjusted incidence rates (IR)/100 patient-years (PY) are provided.

Results A total of 1720 patients received lebrikizumab (1637.0 PY exposure). In All-PC Week 0–16, the frequency of treatment-emergent adverse events (TEAEs) was similar between treatment groups; most events were nonserious and mild or moderate in severity. The most frequently reported TEAEs were atopic dermatitis (placebo) and conjunctivitis (LEBQ2W). Frequencies of conjunctivitis cluster were 2.5% (placebo) and 8.5% (LEBQ2W), and all events were mild or moderate (All-LEB 10.6%, IR, 12.2). Frequencies of injection site reactions were 1.5% (placebo) and 2.6% (LEBQ2W; All-LEB 3.1%, IR, 3.3). Frequencies of adverse events leading to treatment discontinuation were 1.4% (placebo) and 2.3% (LEBQ2W; All-LEB 4.2%, IR, 4.5).

Conclusion The safety profile for lebrikizumab consisted of TEAEs that were mostly nonserious, mild or moderate in severity, and did not lead to treatment discontinuation. The safety profile was similar in both adults and adolescents.

Clinicaltrials.gov NCT02465606, NCT02340234, NCT03443024, NCT04146363, NCT04178967, NCT04250337, NCT04250350, NCT04392154

Plain Language Summary

Atopic dermatitis (AD) is a common chronic (persistent) skin disease that occurs in up to 7% of adults and approximately 20% of children. Lebrikizumab is a monoclonal antibody that goes against interleukin-13, which is overexpressed in patients with AD. Lebrikizumab is given by injection and is being studied to treat AD. It has been tested in several studies in both adults and adolescents (patients age ≥ 12 – < 18 years). In some of those studies, patients used lebrikizumab by itself, and in other studies patients used lebrikizumab in combination with low-to-moderate strength topical (rubbed on the skin) corticosteroid medicines. We examined the safety of lebrikizumab by combining the data from eight of those studies and analyzing the data in two datasets. The first dataset compared the safety of lebrikizumab 250 mg injected every 2 weeks with placebo (no drug in the injection) in four 16-week studies in which neither patient nor physician knew whether lebrikizumab

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or placebo was being injected. The second dataset included four additional studies and examined the safety of lebrikizumab in all patients receiving at least 1 injection of lebrikizumab at any dose. A total of 1720 patients took lebrikizumab. In the first dataset the frequency of adverse events was similar between lebrikizumab and placebo, and most events that did occur were mild or moderate in severity and were not serious. The most common adverse event in patients treated with placebo was atopic dermatitis, and in patients treated with lebrikizumab it was conjunctivitis. Frequencies of adverse events in the conjunctivitis cluster, which included a search for the terms of conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, and giant papillary conjunctivitis, were 2.5% in placebo and 8.5% in lebrikizumab, and all events were mild or moderate. Frequencies of injection site reactions were 1.5% in placebo and 2.6% in lebrikizumab, and frequencies of adverse events that led to patients stopping treatment were 1.4% in placebo and 2.3% in lebrikizumab. In the second dataset, the rate of these adverse events did not increase with longer duration of lebrikizumab. The safety profile for lebrikizumab consisted of adverse events that were mostly nonserious, mild or moderate in severity, and did not lead to stopping treatment. The safety profile was similar in both adults and adolescents.

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Key Points

This integrated safety analysis of lebrikizumab for the treatment of moderate-to-severe atopic dermatitis is consistent with the safety profile of lebrikizumab previously described in individual studies.

During the placebo-controlled period, the frequency of treatment-emergent adverse events was similar between placebo-treated and lebrikizumab-treated patients. The frequency of conjunctivitis cluster events was 2.5% in the placebo group and 8.5% in the lebrikizumab group. All events were nonserious, and mild or moderate in severity, and most did not lead to treatment discontinuation.

In the All-LEB analysis set, the exposure-adjusted incidence rates of most treatment-emergent adverse events did not increase with longer duration of exposure to lebrikizumab.

1 Introduction

Atopic dermatitis (AD) is a chronic, relapsing, heterogeneous skin disease affecting up to 7% of the adult population [1–3] and approximately 20% of children [4] worldwide, with approximately 30% of adults and adolescents with AD having moderate-to-severe disease [5, 6]. It is characterized by eczematous skin lesions associated with a disrupted skin barrier and symptoms of intense itch, sleep disturbance, and skin pain that affects sleep and daily activities, necessitating long-term management [7–9]. Systemic therapy and/or phototherapy is recommended for patients with moderate-to-severe disease who have inadequate treatment response or are not candidates for topical therapy [10]. Recent treatments for moderate-to-severe AD include such biologic therapies as dupilumab and tralokinumab [11], and systemic Janus kinase (JAK) inhibitors in patients whose disease is not adequately controlled with other systemic treatments. Despite these recent advances in systemic treatment, an unmet medical need remains for long-term management of AD due to the chronic and heterogenous nature of the disease and concerns of side effects of current treatments.

Interleukin (IL)-13 is a pro-inflammatory Th2 cytokine and is implicated as the key cytokine in the pathogenesis of AD [12–14]. Lebrikizumab is a monoclonal antibody that binds with high affinity and slow off-rate to IL-13, thereby blocking the downstream effects of IL-13 with high potency [15]. In completed phase 2 and 3 clinical trials, lebrikizumab as monotherapy and in combination with topical corticosteroids (TCS) improved signs and symptoms of AD in adolescent and adult patients [16–18]. Here, we report integrated safety data of lebrikizumab in adolescent and adult patients with moderate-to-severe AD from eight clinical trials in the AD program.

2 Patients and Methods

2.1 Patients

This integrated analysis included adolescent (≥ 12 – < 18 years, weighing ≥ 40 kg) and adult patients with moderate-to-severe AD who had an Eczema Area and Severity Index

score of ≥ 16, Investigator's Global Assessment (IGA) score of ≥ 3, ≥ 10% of the total body surface area affected, and chronic AD for ≥ 1 year, and for whom topical treatment was inadequate or inadvisable. Key exclusion criteria included uncontrolled chronic disease that might require bursts of oral corticosteroids, an active endoparasitic infection or being at high risk of these infections, or a history of anaphylaxis as defined by the Sampson criteria [19]. Patients with a history of malignancy, including mycosis fungoides, within 5 years before the screening visit; severe concomitant illness(es); and any medical or psychological condition that would adversely affect their participation in the studies were also ineligible.

2.2 Study Design

Safety data are included from one randomized open-label phase 2 study (NCT02465606 [ARBAN]); five double-blinded, randomized, placebo-controlled clinical studies (phase 2: NCT03443024 [dose-ranging], NCT02340234 [TREBLE]; phase 3: NCT04146363 [Advocate 1], NCT04178967 [ADvocate 2], NCT04250337 [ADhere]); one phase 3 open-label adolescent single-arm study (NCT04250350 [ADore]); and one phase 3 long-term safety study (NCT04392154 [ADjoin]). Data cutoff in ongoing studies was 6 June 2022. Study designs are described in Supplemental Table 1 and Supplemental Figure. Studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by individual institutional review boards at each participating study center. All patients provided written informed consent.

2.3 Safety Assessments

Safety was assessed by monitoring treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs), deaths, and adverse events (AEs) leading to discontinuation of study drug. Adverse events are reported using preferred terms based on Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. Vital signs, growth assessments including height and weight, and laboratory testing were also monitored. For some AEs, cluster analyses grouped preferred terms that represented similar clinical disease. Event clusters and other AE definitions are described in Supplemental Table 2. For the phase 3 studies, an independent external data safety monitoring board (DSMB), comprised of members independent of the study sponsor and study investigators, monitored patient safety by conducting formal reviews of accumulated safety data that was unblinded by treatment group. The DSMB could request access to the treatment allocation code or any other data for the purpose of a risk-benefit assessment. The DSMB provided the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study.

2.4 Analysis Sets

This analysis examined 2 pooled datasets:

1. AD placebo-controlled week 0–16 dataset (All-PC Week 0–16): assessed the safety profile of placebo versus lebrikizumab 250 mg every 2 weeks (LEBQ2W) during the 16-week, placebo-controlled period for patients in the phase 2b dose-ranging study and three phase 3 studies (ADvocate1, ADvocate2, and ADhere). The placebo-controlled dataset for this analysis included both monotherapy and combination studies with TCS.
2. AD All-LEB dataset (All-LEB): evaluated the long-term safety profile of lebrikizumab and included data for all patients who received at least 1 dose (exposure to doses of 250 mg Q2W, 250 mg every 4 weeks [Q4W], 125 mg single dose, 125 mg Q4W, and 250 mg single dose) of lebrikizumab at any time from any of the eight AD clinical trials (ARBAN, TREBLE, one phase 2b dose-ranging study, ADvocate 1, ADvocate 2, ADhere, ADore, and ADjoin).

Safety populations are generally defined as all randomized patients who receive ≥ 1 dose of study treatment. The population for this analysis, however, is a modified safety population that included all patients receiving ≥ 1 dose of study drug excluding 38 patients in studies ADhere, ADvocate 2, and ADjoin (from a single study site) since some or all the study patients did not meet the eligibility criteria of having moderate-to-severe AD. Sensitivity analysis of the overall safety population was completed and showed the safety profile was consistent with observations from the modified safety analysis population.

2.5 Statistical Analysis

To provide appropriate direct comparisons between treatment groups for the placebo-controlled dataset, study-size adjusted percentages were calculated for AEs to avoid Simpson's paradox, where crude incidence from pooled data comprised of studies with different randomization ratios could give misleading results. Exposure-adjusted incidence rates (IRs) were calculated as the number of patients reporting an event per 100 patient-years at risk. These IRs can be viewed in context with the IRs from other analysis sets and/or literature. However, comparisons across analysis sets and/or literature are for context only, as direct comparisons between studies may not be possible.

Table 1 Baseline demographics and disease characteristics and disease activity

	All-PC Week 0–16		All-LEB[a] (*N* = 1720)
	Placebo (*N* = 404)	LEB 250 mg Q2W (*N* = 783)	
Age at baseline, years, mean (SD)	36.1 (17.3)	36.8 (17.8)	34.0 (17.8)
Patients aged ≥ 12 – < 18 years, *n* (%)	48 (11.9)	99 (12.6)	372 (21.6)
Patients aged ≥ 18 years, *n* (%)	356 (88.1)	684 (87.4)	1348 (78.4)
Female, *n* (%)	204 (50.5)	396 (50.6)	877 (51.0)
Body mass index, kg/m^2, mean (SD)	27.5 (7.1)	26.8 (6.4)	26.8 (6.6)
Race, *n* (%)			
White	244 (60.4)	493 (63.0)	1079 (62.7)
Asian	93 (23.0)	141 (18.0)	311 (18.1)
Black or African American	51 (12.6)	100 (12.8)	232 (13.5)
Multiple	6 (1.5)	18 (2.3)	40 (2.3)
American Indian or Alaska Native	4 (1.0)	16 (2.0)	26 (1.5)
Other	5 (1.2)	7 (0.9)	17 (1.0)
Native Hawaiian or other Pacific Islander	1 (0.2)	7 (0.9)	9 (0.5)
Geographic region, *n* (%)			
USA	222 (55.0)	413 (52.7)	945 (54.9)
Europe	94 (23.3)	196 (25.0)	428 (24.9)
Rest of the world	88 (21.8)	174 (22.2)	347 (20.2)
Prior AD therapy, *n* (%)			
Topical therapy (TCS/TCI)	395 (97.8)	768 (98.1)	1494 (97.3)
Immunosuppressive/immunomodulating drugs[b]	188 (46.5)	351 (44.8)	674 (43.9)
Dupilumab	13 (3.2)	25 (3.2)	67 (4.4)
Phototherapy	86 (21.3)	149 (19.0)	280 (18.2)
Other biologics	15 (3.7)	29 (3.7)	44 (2.9)
Medical history of conjunctivitis[c]	68 (19.3)	152 (21.5)	291 (22.2)
Disease characteristics			
IGA score of 3, *n* (%)	258 (63.9)	495 (63.2)	1123 (65.3)
IGA score of 4, *n* (%)	146 (36.1)	288 (36.8)	597 (34.7)
EASI score, mean (SD)	29.5 (11.7)	28.6 (11.5)	32.5 (21.3)
Percent body surface area affected, mean (SD)	45.3 (22.4)	44.1 (22.5)	44.7 (22.4)
Pruritus NRS, mean (SD)	7.2 (1.9)	7.2 (1.9)	7.0 (2.1)

AD atopic dermatitis, *EASI* Eczema Area and Severity Index, *n* number of patients in the specified category, *N* number of patients, *NRS* numeric rating scale, *IGA* Investigator's Global Assessment, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *TCS* topical corticosteroids, *TCI* topical calcineurin inhibitors

[a]All-LEB AD includes lebrikizumab exposure to doses of 250 mg Q2W, 250 mg Q4W, 125 mg single dose, 125 mg Q4W, and 250 mg single dose

[b]Includes dupilumab

[c]Prespecified medical history of conjunctivitis not collected in the TREBLE, ARBAN, phase 2 dose-ranging studies; therefore, these studies are not included in the numbers here

3 Results

At baseline, disease characteristics and history of prior AD therapies were similar between placebo and LEBQ2W and across both treatment datasets. Approximately 50% of patients were female, and mean age in All-LEB was 34.0 years, with the majority of patients (78.4%) being ≥ 18 years. In All-LEB, 22% of patients were aged ≥ 12 – < 18 years versus approximately 12% in All-PC Week 0–16, with this difference driven by the open-label phase 3 ADore trial that only enrolled adolescents and was not included in the placebo-controlled dataset. Across all groups, approximately 36% of patients presented with severe AD (IGA = 4; Table 1). In All-LEB, 1720 patients received ≥ 1 dose of lebrikizumab for 1637.0 patient years (PY), and 51.8% of patients had ≥ 1 year exposure to lebrikizumab (Table 2).

Table 2 Exposure of study drug

	All-PC Week 0–16		All-LEB[a] (*N* = 1720)
	Placebo (*N* = 404)	LEB 250 mg Q2W (*N* = 783)	
Total patient-years	113.8	233.3	1637.0
Patients with ≥ 52 weeks, *n* (%)	—	—	891 (51.8)
Patients with ≥ 78 weeks, *n* (%)	—	—	269 (15.6)
Patients with ≥ 104 weeks, *n* (%)	—	—	59 (3.4)
Weeks of exposure	–	—	
> 0–< 4 weeks	—	—	23 (1.3)
≥ 4–< 16 weeks	—	—	130 (7.6)
≥ 16–< 24 weeks	—	—	266 (15.5)
≥ 24–< 32 weeks	—	—	120 (7.0)
≥ 32–< 40 weeks	—	—	183 (10.6)
≥ 40–< 52 weeks	—	—	107 (6.2)
≥ 52–< 78 weeks	—	—	613 (35.6)
≥ 78–< 104 weeks	—	—	210 (12.2)
≥ 104 weeks	—	—	59 (3.4)
Median duration, days	112.0	112.0	365.0
Longest exposure, days	162	197	939

LEB lebrikizumab, *n* number of patients in the specified category, *PC* placebo-controlled, *Q2W* every two weeks

[a]All-LEB AD includes lebrikizumab exposure to doses of 250 mg Q2W, 250 mg Q4W, 125 mg single dose, 125 mg Q4W, and 250 mg single dose

3.1 Treatment-Emergent Adverse Events

In All-PC Week 0–16 the overall frequency of patients with ≥ 1 TEAE was similar in the placebo (53.1%) and LEBQ2W (49.2%) groups, and the majority of TEAEs were mild or moderate in severity (placebo, 91.6%; LEBQ2W, 95.3%; Table 3). Conjunctivitis and atopic dermatitis (single preferred terms) were the most frequently reported events, with atopic dermatitis reported more frequently in the placebo group (18.4% versus 6.0%) and conjunctivitis reported more frequently in LEBQ2W (6.5% versus 1.8%; Table 4). In addition to conjunctivitis, nasopharyngitis, headache, allergic conjunctivitis, dry eye, and allergic rhinitis were reported more frequently in LEBQ2W versus placebo (Table 4). No clinically relevant imbalance in TEAEs were found for sex, weight, race, and ethnicity. In All-LEB the most frequently reported TEAEs (single preferred terms, > 5.0%) were nasopharyngitis (9.1%), coronavirus disease 2019 (COVID-19; 7.7%), atopic dermatitis (7.4%), and conjunctivitis (6.5%; Table 4).

In All-PC Week 0–16 the frequency of patients reporting ≥ 1 SAE was similar in the placebo (1.9%) and LEBQ2W (1.3%) groups (Table 3), and no single preferred term was reported by more than 1 patient in each treatment group. In All-LEB the IR for SAEs (3.5) was similar to the IR reported in LEBQ2W (4.3) during the placebo-controlled period (Table 3); the single preferred terms of SAEs reported in more than 1 patient in All-LEB were atopic dermatitis (*n* = 4, IR 0.2), COVID-19 (*n* = 2, IR 0.1), and multiple injuries (*n* = 2, IR 0.1).

Table 3 Overview of treatment-emergent adverse events

	All-PC Week 0–16		All-LEB[a] (*N* = 1720)
	Placebo (*N* = 404)	LEB 250 mg Q2W (*N* = 783)	
Adverse events, *n* (adj %) [adj IR/100 PYR][b]			
Any TEAE	215 (53.1) [307.0]	384 (49.2) [247.3]	1106 (64.3) [137.9]
Mild	98 (24.2)	201 (25.7)	505 (29.4)
Moderate	99 (24.6)	165 (21.2)	510 (29.7)
Severe	18 (4.4)	18 (2.3)	91 (5.3)
SAE[c]	8 (1.9) [7.0]	10 (1.3) [4.3]	56 (3.3) [3.5]
AEs leading to treatment discontinuation[c]	6 (1.4) [5.1]	18 (2.3) [7.9]	73 (4.2) [4.5]
Death	1 (0.2) [0.9]	0	3 (0.2) [0.2]

adj adjusted, *AE* adverse event, *IR* incidence rate, *n* number of patients in the specified category, *N* number of patients in the analysis set, *NMSC* nonmelanoma skin cancer, *PYR* patient-years at risk, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event

[a]All-LEB AD includes lebrikizumab exposure to doses of 250 mg Q2W, 250 mg Q4W, 125 mg single dose, 125 mg Q4W, and 250 mg single dose

[b]Adjusted percentages are only shown for the placebo-controlled dataset; IRs in this analysis are exposure-adjusted IRs calculated as the number of patients reporting an event per 100 PYR or patient-years exposed

[c]Inclusive of death

Table 4 Common treatment-emergent adverse events reported in ≥ 1% of patients in All-LEB

	All-PC Week 0–16		All-LEB[a] (*N* = 1720) [PY = 1637.0]
	Placebo (*N* = 404) [PY = 113.8]	LEB 250 mg Q2W (*N* = 783) [PY = 233.3]	
TEAE by PT reported in ≥ 1.0% of patients in All-LEB, n (adj %) [adj IR][b]			
Nasopharyngitis	13 (3.2) [11.8]	34 (4.4) [15.2]	157 (9.1) [10.2]
COVID-19	5 (1.3) [4.4]	9 (1.1) [3.8]	133 (7.7) [8.4]
Atopic dermatitis	74 (18.4) [76.9]	47 (6.0) [21.2]	128 (7.4) [8.3]
Conjunctivitis	7 (1.8) [6.2]	51 (6.5) [22.8]	112 (6.5) [7.2]
Headache	12 (2.9) [10.5]	34 (4.4) [15.0]	81 (4.7) [5.1]
Conjunctivitis, allergic	3 (0.7) [2.6]	14 (1.8) [6.1]	70 (4.1) [4.4]
Upper respiratory tract infection	7 (1.7) [6.3]	3 (0.4) [1.3]	66 (3.8) [4.1]
Oral herpes	9 (2.3) [8.1]	15 (1.9) [6.5]	50 (2.9) [3.1]
Pruritus	7 (1.8) [6.4]	9 (1.2) [3.9]	33 (1.9) [2.0]
Urinary tract infection	2 (0.5) [1.7]	5 (0.6) [2.1]	32 (1.9) [2.0]
Hypertension	4 (1.0) [3.6]	9 (1.1) [3.8]	31 (1.8) [1.9]
Diarrhea	1 (0.2) [0.9]	4 (0.5) [1.7]	29 (1.7) [1.8]
Arthralgia	3 (0.7) [2.5]	6 (0.8) [2.6]	27 (1.6) [1.7]
Cough	1 (0.3) [0.9]	5 (0.7) [2.2]	27 (1.6) [1.7]
Acne	3 (0.7) [2.6]	2 (0.3) [0.8]	26 (1.5) [1.6]
Vaccination complication	0	3 (0.4) [1.3]	25 (1.5) [1.5]
Dry eye	4 (0.9) [3.4]	11 (1.4) [4.8]	25 (1.5) [1.5]
Fatigue	3 (0.7) [2.6]	5 (0.6) [2.2]	25 (1.5) [1.5]
Anxiety	3 (0.7) [2.6]	6 (0.8) [2.6]	23 (1.3) [1.4]
Nausea	2 (0.5) [1.8]	6 (0.8) [2.6]	21 (1.2) [1.3]
Folliculitis	5 (1.2) [4.3	5 (0.6) [2.2]	21 (1.2) [1.3]
Alanine aminotransferase increased	0	3 (0.4) [1.3]	21 (1.2) [1.3]
Injection site reaction	1 (0.30 [0.9]	5 (0.6) [2.1]	21 (1.2) [1.3]
Asthma	1 (0.3) [0.9]	5 (0.6) [2.1]	20 (1.2) [1.2]
Rhinitis, allergic	1 (0.2) [0.9]	8 (1.0) [3.5]	18 (1.0) [1.1]
Herpes dermatitis	2 (0.5) [1.7]	1 (0.1) [0.4]	18 (1.0) [1.1]
Abdominal pain	0	2 (0.3) [0.9]	17 (1.0) [1.0]
Impetigo	6 (1.5) [5.4]	6 (0.8) [2.6]	17 (1.0) [1.0]
Back pain	2 (0.5) [1.8]	2 (0.3) [0.9]	17 (1.0) [1.0]

[a]All-LEB AD includes lebrikizumab exposure to doses of 250 mg Q2W, 250 mg Q4W, 125 mg single dose, 125 mg Q4W, and 250 mg single dose

[b]Adjusted percentages and adjust IRs are only shown for the placebo-controlled dataset; IRs in this analysis are exposure-adjusted IRs calculated as the number of patients reporting an event per 100 PY at risk or patient-years exposed

adj adjusted, *IR* incidence rate, *n* number of patients in the specified category, *LEB* lebrikizumab, *N* number of patients in the analysis set, *PY* patient years, *PT* preferred term, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *TEAE* treatment-emergent adverse event

Four deaths were reported, none of which were assessed by the investigator as related to study drug. One death was reported in All-PC Week 0–16 in the placebo group due to myocardial infarction in a 56-year-old male. Three deaths were reported in the All-LEB group: 1 due to metastatic pancreatic cancer in a 74-year-old male that occurred during the maintenance escape period, 1 due to natural causes in a 56-year-old male with medical history of hypertension and a previous cardiac ablation during the long-term extension period, and 1 due to cardiac arrest assessed as related to COVID-19 in a 13-year-old male with medical history of congenital anomalies in the open-label period of ADore.

In All-PC Week 0–16, frequencies of patients with ≥ 1 adverse event leading to permanent discontinuation of study drug were low in the placebo (1.4%) and LEBQ2W (2.3%) groups (Table 3). The most frequently reported events (single preferred terms) leading to discontinuation of study treatment were atopic dermatitis in the placebo group

($n = 4$, 0.9%) and conjunctivitis in the LEBQ2W group ($n = 2$, 0.3%). The IR for discontinuation from study drug did not increase with longer duration of exposure with All-LEB IR of 4.5 compared with the LEBQ2W IR of 7.9 during All-PC Week 0–16 (Table 3); conjunctivitis ($n = 11$, 0.6%; IR, 0.7) and atopic dermatitis ($n = 7$, 0.4%; IR, 0.4) were the most frequent events leading to discontinuation in All-LEB. Overall, the frequency of TEAEs were similar in adolescent and adult patients.

3.2 Special Safety Topics

3.2.1 Conjunctival Disorders

In patients from the phase 3 trials, approximately 22% had a medical history of conjunctivitis at baseline (Table 1). In All-PC Week 0–16, AEs within the conjunctivitis cluster (conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, and giant papillary conjunctivitis), keratitis cluster (keratitis, atopic keratoconjunctivitis, allergic keratitis, ulcerative keratitis, and vernal keratoconjunctivitis), and preferred term of blepharitis were reported more frequently in LEBQ2W compared with placebo (Table 5). All events were nonserious and mild or moderate in severity, with the exception of 1 severe event of blepharitis in LEBQ2W that did not lead to treatment discontinuation. In the placebo group, 1 event of conjunctivitis led to treatment discontinuation, while in LEBQ2W, 5 events led to treatment discontinuation: conjunctivitis ($n = 2$), bacterial conjunctivitis ($n = 1$), keratitis ($n = 1$), and atopic keratoconjunctivitis ($n = 1$). In All-LEB, the IRs for the conjunctivitis cluster (12.2) and keratitis cluster (0.6) did not increase with longer duration of exposure (IRs were 30.6 and 2.2 for conjunctivitis and keratitis clusters, respectively, in LEB2QW during All-PC Week 0–16; Table 5). In ALL LEB, all events were nonserious, and most (96.7%) were mild or moderate in severity; severe events included preferred terms of conjunctivitis ($n = 2$, 0.1%) and allergic conjunctivitis ($n = 4$, 0.2%). Most events (72.1%) were recovered or resolved.

3.2.2 Infections

In All-PC Week 0–16, the frequency of treatment-emergent infection was similar in the placebo (18.9%) and LEBQ2W (21.2%) groups (Table 5). Infections reported in ≥ 1% of LEBQ2W, excluding ocular-related disorders, were nasopharyngitis, oral herpes, and COVID-19. Nasopharyngitis and herpes zoster were reported at a higher frequency in LEBQ2W (4.4% and 0.6%, respectively) compared with the placebo group (3.2% and 0.0%, respectively). Most events (97.4% and 98.2% in the placebo and LEBQ2W groups, respectively) were mild or moderate in severity. During All-PC Week 0–16, 2 patients reported serious infections. One patient (0.2%) in the placebo group reported 2 serious events (cellulitis of the right extremity and sepsis), and 1 patient (0.1%) in LEBQ2W reported a serious event of severe infectious colitis due to prepackaged food. The IR of treatment-emergent infection did not increase with longer duration of exposure (All-LEB IR 50.2 versus 82.1 for LEBQ2W during the All-PC Week 0–16; Table 5), and most infections (97.6%) were mild or moderate in severity. In All-LEB, an additional 5 serious infections were reported in 4 patients: mild COVID-19 ($n = 2$), moderate pneumonia ($n = 1$), and moderate erysipelas and scabies in the same patient ($n = 1$). There were no reports of parasitic helminth infections in All-PC Week 0–16. In All-LEB there was 1 parasitic infection, a mild enterobiasis and ascariasis coinfection that did not lead to treatment discontinuation. There were no confirmed opportunistic infections according to the Winthrop criteria [20] in All-PC Week 0–16 or All-LEB.

In All-PC Week 0–16, similar proportions of patients in the placebo (3.7%) and LEBQ2W (2.9%) groups reported treatment-emergent herpes infection (MedDRA high-level term), and the most frequently reported herpes infection in both treatment groups was oral herpes (Table 5). A higher frequency of patients in LEBQ2W reported herpes zoster (0.6%) and herpes simplex (0.3%) infections compared with the placebo group, where no events of herpes zoster or herpes simplex were reported. No eczema herpeticum events were reported in LEBQ2W compared with 3 (0.7%) events in the placebo group. All herpes infection events were nonserious, most were mild or moderate in severity, and none led to treatment discontinuation. The IR for herpes infection (MedDRA high-level terms) did not increase with longer duration of exposure (5.5 for All-LEB IR versus 10.0 for LEBQ2W during the placebo-controlled period (Table 5).

3.2.3 Injection Site Reactions

In All-PC Week 0–16 the frequency of injection site reactions (MedDRA high-level term) was low in both groups (placebo, $n = 6$, 1.5%; LEBQ2W, $n = 20$, 2.6%). The most frequently reported injection-site-related AEs in LEBQ2W were: injection site pain, injection site erythema, and injection site reaction. Most events were mild or moderate in severity, none were serious, and 2 led to treatment discontinuation (both LEBQ2W: 1 injection site dermatitis and 1 injection site rash). The IR did not increase with longer duration of exposure, with 53 patients in All-LEB reporting a treatment-emergent injection site reaction (MedDRA high-level term) for an IR of 3.3 versus 9.0 for LEBQ2W during All-PC Week 0–16 (Table 5). A total of 5 patients in the All-LEB group discontinued treatment due to injection site reactions.

Table 5 Overview of special safety topics

	All-PC Week 0–16		All-LEB[a] (*N* = 1720)
	Placebo (*N* = 404)	LEB 250 mg Q2W (*N* = 783)	
Conjunctivitis, n (adj %) [adj IR/100 PYR][b]			
Conjunctivitis cluster[c]	10 (2.5) [8.9]	67 (8.5) [30.6]	183 (10.6) [12.2]
Conjunctivitis	7 (1.8) [6.2]	51 (6.5) [22.8]	112 (6.5) [7.2]
Conjunctivitis, allergic	3 (0.7) [2.6]	14 (1.8) [6.1]	70 (4.1) [4.4]
Conjunctivitis, bacterial	0	3 (0.4) [1.3]	11 (0.6) [0.7]
Conjunctivitis, viral	0	0	2 (0.1) [0.1]
Keratitis cluster	1 (0.3) [0.9]	5 (0.6) [2.2]	9 (0.5) [0.6]
Keratitis	1 (0.3) [0.9]	1 (0.1) [0.4]	3 (0.2) [0.2]
Vernal keratoconjunctivitis	0	2 (0.2) [0.8]	3 (0.2) [0.2]
Atopic keratoconjunctivitis	0	2 (0.3) [0.9]	3 (0.2) [0.2]
Blepharitis	1 (0.2) [0.9]	6 (0.8) [2.6]	11 (0.6) [0.7]
Infections, n (adj %) [adj IR/100 PYR][b]			
Treatment-emergent infections	77 (18.9) [76.6]	166 (21.2) [82.1]	615 (35.8) [50.2]
Herpes infection	15 (3.7) [13.4]	23 (2.9) [10.0]	87 (5.1) [5.5]
Oral herpes	9 (2.3) [8.1]	15 (1.9) [6.5]	50 (2.9) [3.1]
Herpes zoster	0	5 (0.6) [2.1]	14 (0.8) [0.9]
Herpes simplex	0	2 (0.3) [0.9]	13 (0.8) [0.8]
Eczema herpeticum	3 (0.7) [2.6]	0	1 (0.1) [0.1]
Skin infections[d]	24 (5.9) [21.8]	17 (2.2) [7.5]	63 (3.7) [3.9]
Parasitic helminth infections	0	0	1 (0.1) [0.1]
Confirmed opportunistic infections	0	0	0
Injection site reactions[e]	6 (1.5) [5.4]	20 (2.6) [9.0]	53 (3.1) [3.3]
Malignancy, n (adj %) [adj IR/100 PYR][b]			
Malignancy excluding NMSC	0	0	8 (0.5) [0.5]
Prostate cancer	0	0	1 (0.1) [0.1]
Cutaneous T-cell lymphoma	0	0	2 (0.1) [0.4]
Endometrial adenocarcinoma	0	0	1 (0.1) [0.1]
Invasive breast cancer	0	0	1 (0.1) [0.1]
Ovarian germ cell teratoma[f]	0	0	1 (0.1) [0.1]
Neuroendocrine tumor	0	0	1 (0.1) [0.1]
Pancreatic carcinoma metastatic	0	0	1 (0.1) [0.1]
Metastases to bone[g]	0	0	1 (0.1) [0.1]
Metastases to liver[g]	0	0	1 (0.1) [0.1]
NMSC	2 (0.5) [1.7]	2 (0.3) [0.8]	5 (0.3) [0.3]
Squamous cell carcinoma	1 (0.2) [0.9]	1 (0.1) [0.4]	1 (0.1) [0.1]
Keratoacanthoma	0	1 (0.1) [0.4]	1 (0.1) [0.1]
Bowen's disease	1 (0.2) [0.9]	0	1 (0.1) [0.1]
Squamous cell carcinoma of skin	0	0	1 (0.1) [0.1]
Basal cell carcinoma	0	0	1 (0.1) [0.1]
Penile squamous cell carcinoma[h]	0	0	1 (0.1) [0.1]
Eosinophilia[i], *n* (adj %) [adj IR/100 PYR][b]	3 (0.8) [2.7]	5 (0.6) [2.1]	27 (1.6) [1.7]
Eosinophil-related disorders[j], *n* (adj %) [adj IR/100 PYR][b]	0	0	0

adj adjusted, *AE* adverse event, *IR* incidence rate, *n* number of patients in the specified category, *N* number of patients in the analysis set, *NMSC* nonmelanoma skin cancer, *PYR* patient-years at risk, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event

[a]All-LEB AD includes lebrikizumab exposure to doses of 250 mg Q2W, 250 mg Q4W, 125 mg single dose, 125 mg Q4W, and 250 mg single dose

[b]Adjusted percentages are only shown for the placebo-controlled dataset; IRs in this analysis are exposure-adjusted IRs calculated as the number of patients reporting an event per 100 PYR or patient-years exposed

Table 5 (continued)

[c]The conjunctivitis cluster includes the preferred terms of conjunctivitis; conjunctivitis, allergic; conjunctivitis, bacterial; conjunctivitis, viral; and giant papillary conjunctivitis

[d]Skin infections were defined using the MedDRA high-level term of 'Skin structures and soft tissue infections' and included the following preferred terms: cellulitis, eczema impetiginous, folliculitis, staphylococcal skin infection, cellulitis staphylococcal, furuncle, erysipelas, fungal skin infection

[e]Injection site reactions were defined using MedDRA high-level term of injection site reactions excluding joint-related preferred terms

[f]After database lock, pathology showed that the ovarian germ cell teratoma was benign

[g]The metastases to the bone and liver were in the same patient with pancreatic carcinoma

[h]Denominator adjusted for gender-specific events for males, All-LEB: $N = 843$ and PYE = 798.4

[i]Eosinophilia is defined as two preferred terms of eosinophilia and allergic eosinophilia and the following preferred terms under the high-level term of white blood cell analysis: eosinophil count abnormal, eosinophil count increased, and eosinophil percentage increased

[j]Eosinophil-related disorder is defined as all preferred terms under the high-level term of eosinophil disorders except the following: eosinophilia and allergic eosinophilia

3.2.4 Hypersensitivity Reactions

No anaphylactic reactions or systemic hypersensitivity reactions related to lebrikizumab were reported.

3.2.5 Malignancies

There were no malignancies excluding nonmelanoma skin cancer (NMSC) in All-PC Week 0–16. In All-LEB 8 patients reported malignancies other than NMSC: 1 patient with pancreatic carcinoma with metastasis to the bone and liver; 2 patients with cutaneous T-cell lymphoma; and 1 patient each reporting prostate cancer, endometrial adenocarcinoma, ovarian germ cell teratoma, invasive breast cancer, and neuroendocrine tumor. After database lock, pathology showed the ovarian germ cell teratoma was benign. These events excluding cutaneous T-cell lymphoma started from 241 to 644 (median 310.0) days after first dose of lebrikizumab, while the cutaneous T-cell lymphomas started 39 and 85 days after first dose of lebrikizumab; all events were assessed by investigators as not related to the study drug. No patients reporting malignancies other than NMSC had a history of taking immunosuppressants.

In All-PC Week 0–16, the frequency of NMSC in LEBQ2W (0.3%) was lower than the placebo group (0.5%; Table 5); all NMSC events were nonserious, and none led to treatment discontinuation. The IR did not increase with longer duration of exposure with an IR of 0.3 for All-LEB versus 0.8 for LEBQ2W in All-PC Week 0–16. All NMSC events in All-LEB were nonserious and mild or moderate in severity, and none led to treatment discontinuation.

3.2.6 Eosinophilia

In All-PC Week 0–16 the proportion of patients with eosinophilia TEAEs was similar in the placebo (0.8%) and LEBQ2W (0.6%) groups (Table 5). All events were nonserious, were mild or moderate in severity, and did not lead to treatment discontinuation. Of the 5 TEAEs reported in LEBQ2W, the corresponding lab shifts were mild or moderate. There were no reported events of eosinophil-related disorders. The frequency of patients with increased blood eosinophils at any timepoint postbaseline was higher in LEBQ2W (20.3%) compared with the placebo group (11.7%). Most shifts were in the normal (< 500 per microliter) to mild (500–< 1500 per microliter) categories (Supplemental Table 3). No patients in the placebo and 3 patients in LEBQ2W group had an increase in blood eosinophils to severe category (> 5000 per microliter) (Supplemental Table 3), all transient elevations. In All-LEB, the proportion of patients who had increased blood eosinophils at any time postbaseline was 23.7%, similar to that of LEBQ2W during All-PC Week 0–16 (20.3%).

3.2.7 Laboratory and Vital Signs, Including Growth Evaluations

In All-PC Week 0–16, with the exception of blood eosinophils as described above, laboratory evaluations did not show clinically meaningful differences between the placebo and LEBQ2W groups. While elevated blood eosinophils were observed more frequently in LEBQ2W, this did not lead to eosinophil-related AEs. Lebrikizumab was not associated with clinically meaningful changes over time for blood pressure, and there was no impact on pulse and no association between lebrikizumab and weight changes. Growth assessments of adolescent patients showed no meaningful differences between the placebo and lebrikizumab groups, and patients maintained a growth velocity consistent with their baseline height, weight, or body mass index percentile in All-PC Week 0–16. In All-LEB, the average growth percentile, compared with age- and sex-matched peers, was maintained from baseline to week 52. Treatment

with lebrikizumab did not have a clinically meaningful impact on growth.

4 Discussion

This analysis of integrated data from lebrikizumab clinical trials showed a safety profile consistent with past studies [16–18]. In the placebo-controlled period, the majority of TEAEs were nonserious, mild, or moderate in severity, and did not lead to treatment discontinuation. The most common TEAE in the placebo group was atopic dermatitis, and in lebrikizumab-treated patients it was conjunctivitis. The safety profile of lebrikizumab was consistent across trials with or without TCS use and in adults and adolescents. Review of intrinsic factors including age, sex, and race revealed no differences in safety outcomes. While patients receiving doses other than LEBQ2W were included in the All-LEB data set, comparisons between doses was not part of this study. However, the safety profile of LEBQ2W in the current analysis is generally consistent with responders in the Advocate 1 and 2 studies who, during the weeks 16–52 maintenance period, were rerandomized to LEBQ4W [21]. Overall, the frequency of patients that reported TEAEs was similar across treatment groups. Few individual AE terms were reported more frequently with Q4W dosing in those trials compared with LEBQ2W in the current analysis. These were mainly COVID-19-related, and were nonserious, mild, or moderate in severity, and did not lead to treatment discontinuation.

Ocular complications, including conjunctivitis and keratitis, have been reported in over a third of patients with AD, ranging from 31 to 56%, [22] with more recent studies reporting up to 90% of adult patients with moderate-to-severe AD having ocular surface disorders [23]. In the current analysis approximately 22% of patients from the phase 3 studies presented with a medical history of conjunctivitis. These complications can be related to either the underlying disease or therapeutic interventions [24], and the increased risk of developing conjunctivitis in adults with AD has been found to be significant and disease-severity-dependent [23, 25, 26]. An association between AD and conjunctivitis [24] is known and is observed in patients treated with other biologics, including dupilumab. For these reasons, conjunctivitis is an AE of special interest for lebrikizumab. In this integrated analysis the frequency of conjunctivitis during the placebo-controlled period was higher in lebrikizumab-treated patients compared with placebo, but most events were mild or moderate in severity, and few led to treatment discontinuation. The IR of conjunctivitis did not increase with increased duration of exposure (IR of 30.6 in LEBQ2W and 12.2 in All-LEB), and most events recovered or resolved during the study.

Conjunctivitis is also observed at a higher incidence in other biologics used for the treatment of AD, including dupilumab [27] and tralokinumab [28], though it can be difficult to compare frequencies between lebrikizumab and other AD treatments due to different definitions used across study programs for conjunctivitis clusters and varied patient populations. Several theories have been proposed for the pathogenesis of conjunctivitis in patients with AD treated with IL-13- and IL-4-targeting biologic treatments, but the mechanism remains unclear. One theory proposes that inhibiting IL-13 and IL- 4 signaling may decrease conjunctival goblet cells that are essential for maintaining conjunctival mucosal surface homeostasis and may result in ocular AEs [29].

Patients with AD have an increased risk of bacterial and viral infections, both cutaneous and noncutaneous, due to defective skin barrier and immunologic dysregulation [30]. These cutaneous infections include an increased risk of herpes simplex virus infections or reactivation [31, 32]. Overall infections were reported with a similar frequency in the placebo and lebrikizumab groups with no confirmed opportunistic infections, and most were nonserious, mild, or moderate in severity, with few leading to treatment discontinuation. There was a lower frequency of skin infections in lebrikizumab-treated patients compared with patients in the placebo group, similar to findings with other treatments for AD, including dupilumab [33] and tralokinumab [34], and could potentially be attributable to the restoration of cutaneous barrier function in patients with AD. Herpes zoster events were reported in the lebrikizumab group and were uncommon and lower than reported in patients treated with JAK inhibitors [35, 36]. The occurrence of COVID-19 during this study, which occurred at similar frequencies in the placebo and lebrikizumab groups during the placebo-controlled period, is due to patient recruitment during the middle of the pandemic.

Overall, a low frequency of injection site reactions was reported, with a higher proportion in lebrikizumab compared with placebo. Higher rates of injection site reactions have been reported with other biologics for the treatment of AD [27, 34]. The most frequently reported preferred terms in lebrikizumab-treated participants were injection site pain, injection site erythema, and injection site reaction.

In our study during the placebo-controlled period, TEAEs of eosinophilia were infrequent and reported at a similar frequency in the lebrikizumab group compared with placebo. Increased blood eosinophil counts may be caused by IL-13 blockade leading to reduced chemotaxis and eosinophil trafficking from the skin, resulting in eosinophil accumulation in the peripheral blood [37–39]. Although increased postbaseline blood eosinophils (greater than the upper level of normal) were observed at a higher frequency in lebrikizumab-treated patients compared with placebo, the

eosinophilia was transient, resulted in few TEAEs, and did not result in treatment discontinuation. Eosinophils play a critical role in skin lesions of patients with AD [40]. Therefore, it is difficult to differentiate etiology of blood eosinophilia from underlying AD disease activity or lebrikizumab, as participants with AD have elevated eosinophil count due to concomitant atopic diseases.

Limitations in this study include a short placebo-controlled period that reduces the assessment of AEs with lebrikizumab versus the underlying disease, especially for uncommon or rare events. Limitations of the open-label and long-term safety studies include lack of a control arm and a relatively small number of PYs to date. Comparisons of IRs from this study with the current literature are for context only, as inferences cannot be made because study and treatment are confounded and risk over time can change for reasons other than treatment exposure. Long-term data are required to better evaluate risks for uncommon or rare events or events with long latency, such as malignancy.

5 Conclusion

This integrated safety analysis in adolescent and adult patients with moderate-to-severe AD is consistent with the previously published safety profile of lebrikizumab. The incidence of most TEAEs did not increase with longer duration of exposure. The safety profile in adults and adolescents was consistent with or without TCS use. Combining the integrated safety analysis in this study with previously reported efficacy data of lebrikizumab [16–18] shows a positive benefit/risk profile.

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Declarations

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Competing Interests Linda Stein Gold has been an investigator, speaker, and/or advisory board member for: AbbVie, Amgen, AnaptysBio, Arcutis, Arena, Aslan, Bausch Health, Boehringer Ingelheim, BMS, Celgene, Coherus, Dermira, Dermavant, Eli Lilly, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharmaceuticals, and UCB. Diamant Thaçi has been a consultant, investigator, speaker, and participant in scientific advisory boards for AbbVie, Almirall, Amgen, Bristol Myers Squibb, BMS, Janssen-Cilag, Galderma, Galapagos, LEO Pharma, Eli Lilly and Company, New-Bridge, Novartis, Pfizer, Regeneron, Samsung, Sanofi, SunPharma, and UCB. Jacob P Thyssen has been a consultant for and/or has received grant/research/honorarium support from: Regeneron, Sanofi-Genzyme, LEO Pharma, AbbVie, Eli Lilly and Company, and Pfizer. Melinda Gooderham has been a speaker, investigator, or advisory board member for: AbbVie, Amgen, Akros, AnaptysBio, Arcutis, Arena, Aslan, Bausch Health, Boehringer Ingelheim, BMS, Celgene, Coherus, Dermira, Dermavant, Eli Lilly and Company, Galderma, GSK, Incyte, Janssen, Kyowa Kirin, LEO Pharma, Medimmune, Merck, Moonlake, Nimbus, Novartis, Pfizer, Regeneron, Reistone, Sanofi Genzyme, Sun Pharmaceuticals, Tarsus, UCB, and Ventyx. Vivian Laquer conducts research for Abbvie, Acelyrin, Acrotech, Biofrontera, Amgen, Argenx, Arcutis, Aslan, Bristol Meyers Squibb, Cara, Dermavant, Eli Lilly, Galderma, Horizon Therapeutics, Incyte, Janssen, Leo, Novartis, Padagis, Pfizer, Q32, Rapt, Sun, UCB, and Ventyx. Angela Moore has received study funds or honoraria from Abbvie, Aclaris, Acrotech, Almirall, Arcutis, Bayer, Bristol Myer Squibb, Cara Therapeutics, Dermavant, Eli Lilly and Company, Galderma, Incyte, Janssen, Pfizer, Regeneron, and UCB. Chitra R. Natalie, Fangyi Zhao, Eric Meskimen, Hany Elmaraghy, Sonia Montmayeur, and Gaia Gallo are employees and stockholders of Eli Lilly and Company. Gemma Jimenez is an employee of Almirall. M. De Bruin-Weller has been a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Amgen, Aslan, Eli Lilly and Company, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron, and Sanofi-Genzyme.

Ethics approval and compliance with ethical standards Studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by individual institutional review boards at each participating study center. Studies are registered on ClinicalTrials.gov (NCT02465606, NCT02340234, NCT03443024, NCT04146363, NCT04178967, NCT04250337, NCT04250350, NCT04392154).

Consent to participate/publish All patients provided written informed consent.

Data Availability Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and European Union, and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

Code availability Not applicable.

Authors' contributions Natalie, Zhao, Meskimen, Elmaraghy, Montmayeur, and Gallo have contributed to study conception, design, analysis, and data interpretation. Zhao has contributed to study analysis and interpretation. de Bruin-Weller and Thyssen contributed to data interpretation. Jimenez contributed to data analysis and interpretation. Gooderham and Laquer contributed to the acquisition of data. Moore and Stein Gold contributed to the acquisition and interpretation of data. Thaçi contributed to the design, acquisition, and interpretation of data. All authors contributed to the drafting or critical revision of the manuscript and give final approval of the manuscript.

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