Lebrikizumab Provides Rapid Response in EASI Components and Itch in Moderate-to-Severe Atopic Dermatitis

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BACKGROUND

- Lebrikizumab is a novel monoclonal antibody that binds to IL-13 with high affinity and slow off-rate, thereby blocking the downstream effects of IL-13 with high potency[1]
- IL-13 is a critical cytokine in the pathophysiology of AD[2]
- Lebrikizumab has demonstrated efficacy and a positive benefit-risk profile:
  - As a monotherapy in patients with moderate-to-severe AD at the 16-week primary endpoint of the 2 Phase 3, randomized, double-blind, placebo-controlled trials (ADvocate1 [NCT04146363] and ADvocate2 [NCT04178967])[3,4]
  - In a TCS combination study in patients with moderate-to-severe AD at the 16-week endpoint in the Phase 3, randomized, double-blind, placebo-controlled ADhere study (NCT04250337)[5]

OBJECTIVE

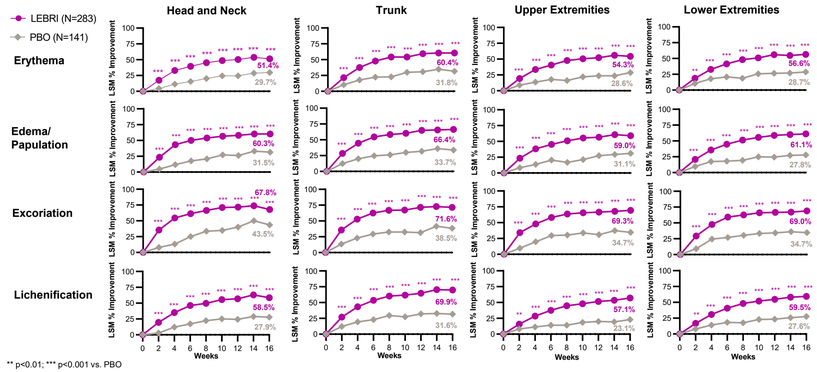
- To describe early changes with lebrikizumab treatment using EASI clinical signs by body region and itch data

Note: Statistical results of the primary and major secondary endpoints for ADvocate1, ADvocate2, and ADhere were confirmed through replicate statistical programming, validation, and quality reviews[3-5]

KEY RESULTS

EASI Clinical Sign Score Percent Improvement From Baseline Through Week 16

ADvocate1 (ITT)- Significant Improvement With Lebrikizumab First Seen by Week 2 in All Regions for All Clinical Signs



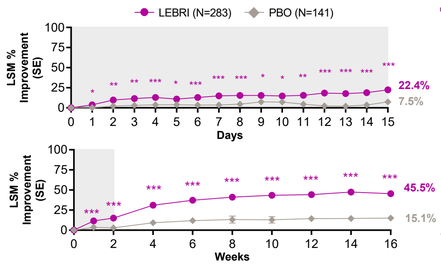
** p<0.01; *** p<0.001 vs. PBO

ADvocate2 and ADhere (mITT) (See Supplementary Data)

- For ADvocate2, significant improvement with lebrikizumab treatment was first seen:
  - For excoriation by Week 2 in all regions
  - For edema/papulation and lichenification by Week 2 in the head/neck, trunk, and upper extremities and by Week 4 in lower extremities
  - For erythema by Week 2 in the trunk and upper extremities and by Week 4 in head/neck and lower extremities
- For ADhere (lebrikizumab + TCS), significant improvement was first seen:
  - For excoriation by Week 2 in head/neck and by Week 4 in all other regions
  - For edema/papulation by Week 4 in all regions
  - For erythema by Week 4 in trunk and Week 6 in all other regions
  - For lichenification by Week 6 in head/neck and trunk, and by Week 8 in upper and lower extremities

Supplementary Data: ADvocate2 and ADhere Results

Rapid Improvement in Pruritus NRS: ADvocate1 (ITT)



- Patient-reported daily itch diaries showed rapid improvement by Day 1 in ADvocate1 (p<0.05) and Day 10 in ADvocate2 (p<0.01) (see Supplementary Data)
- Significant differences in LSM percent improvement from baseline in Pruritus NRS between lebrikizumab and placebo-treated groups were reported from Week 1 in ADvocate1 (p<0.001) and ADvocate2 (p<0.05), and Week 6 in ADhere (p<0.001)

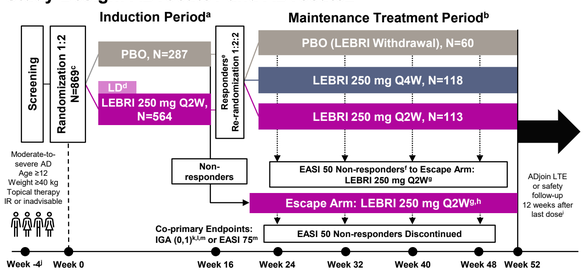
* p<0.05; ** p<0.01; *** p<0.001 vs. PBO

CONCLUSIONS

- After the first dose of lebrikizumab, patients with moderate-to-severe AD showed significant improvements in skin sign severity and itch
- EASI improvement was seen across all 4 body regions by Week 2, beginning with excoriation, followed by edema/papulation, lichenification, and erythema
- Rapid itch improvement was also seen as early as Day 1

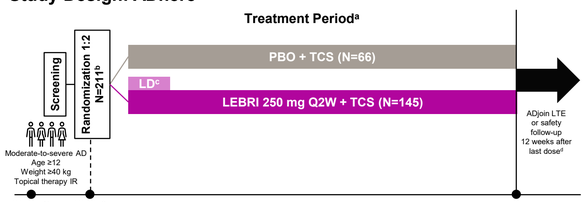
METHODS

Study Design: ADvocate1 and ADvocate2



[a] Use of topical/systemic treatments for AD prohibited; [b] Use of intermittent topical rescue medications for AD permitted. Responders who received PBO during induction and who were re-randomized to LEBRI received an LD of either 500 mg given at W16 or 500 mg given at W16 and W18; [c] 424 patients (ADvocate1) and 445 patients (ADvocate2) with moderate-to-severe AD; [d] 500 mg LD at W0 and W2; [e] Responders achieved EASI 75 or IGA (0,1) with ≥2-point improvement at W16 without rescue medication use; [f] Patients who did not maintain ≥EASI 50 were assigned to the Escape Arm; [g] Maintenance of response assessed by EASI 50 at W24, W32, W40, and W48, respectively. Patients receiving systemic rescue medication were required to washout for 5 half-lives prior to initiating treatment in the Escape Arm; [h] Participants who were eligible for the Escape Arm at W16 received blinded LD at W16 and W18, based on their prior treatment assignment; [i] Patients completing ADvocate1/2 were offered open-label treatment in ADjoin, otherwise patients participated in a safety follow-up 12 weeks after their last dose; [j] ≤30-day screening period; [k] IGA (0,1) with ≥2-point improvement from baseline; [l] FDA primary endpoint; [m] EMA co-primary endpoint

Study Design: ADhere



[a] Use of TCS required at baseline; may be tapered and stopped then resumed as needed; [b] A total of 228 patients with moderate-to-severe AD enrolled, including 53 adolescent patients; however, 17 patients were excluded from a single site; [c] 500 mg LD at W0 and W2; [d] Patients completing ADhere were offered open-label treatment in ADjoin, otherwise patients participated in a safety follow-up 12 weeks after their last dose; [e] ≤30-day screening period; [f] IGA (0,1) with ≥2-point improvement from baseline; [g] FDA primary endpoint; [h] EMA co-primary endpoint

Key Eligibility Criteria

- Adults or adolescents (≥12 to <18 years; weight ≥40 kg)
- Diagnosis of AD, as defined by the American Academy of Dermatology Consensus Criteria, for ≥1 year before screening
- Moderate-to-severe AD, defined as having all the following at the baseline visit:
  - EASI score ≥16
  - IGA score ≥3
  - BSA involvement ≥10%
- Candidate for systemic therapy

Outcomes

- Each of 4 body regions (head and neck, trunk, upper extremities, and lower extremities) assessed separately for the following 4 EASI clinical signs of AD on a scale of 0 (absent) to 3 (severe):
  - Erythema
  - Edema/papulation
  - Excoriation
  - Lichenification
- The Pruritus NRS was used by patients to rate their worst itch severity over the past 24 hours, with 0 indicating "no itch" and 10 indicating "worst itch imaginable"[6]
  - Patients rated their worst itch intensity over the previous 24 hours using an electronic daily diary
  - The baseline mean was the prorated average of the daily scores in the week prior to the first injection and was considered missing if a patient had <4 responses
  - Post-baseline daily Pruritus NRS scores are the scores for the past 24 hours
  - Post-baseline weekly Pruritus NRS scores were calculated by averaging the daily scores from the previous 7 days for patients with ≥1 non-missing values

Statistical Analysis

Analysis Populations

- Analyses were performed post hoc without multiplicity control by study in the ITT population in ADvocate1 and the mITT[a] population in ADvocate2 and ADhere

Statistical Methods

- EASI clinical sign by body region scores and daily Pruritus NRS were set to missing after rescue or treatment discontinuation. All the missing values were handled by MMRM
  - Days 0-15 Pruritus NRS LSM percent improvement from baseline and p-values were from MMRM
  - LSM percent improvement from baseline for EASI clinical sign by body region was calculated as LSM improvement from baseline / overall mean at baseline × 100%. LSM improvement from baseline was fitted using MMRM with p-values reported
- For Pruritus NRS weekly score, data after rescue medication or treatment discontinuation due to lack of efficacy were set to their baseline value; data collected after treatment discontinuation due to other reasons were set to missing. MI was used for handling missing data
  - LSM percent improvement from baseline is reported using ANCOVA. Results were combined across all multiply imputed datasets
- Statistical results of the primary and major secondary endpoints for ADvocate1, ADvocate2, and ADhere were confirmed through replicate statistical programming, validation, and quality reviews[3-5]

RESULTS

Baseline Demographics and Disease Characteristics

Characteristics	ADvocate1		ADvocate2		ADhere	
	PBO (N=141)	LEBRI 250 mg Q2W (N=283)	PBO (N=146)	LEBRI 250 mg Q2W (N=281)	PBO + TCS (N=66)	LEBRI 250 mg Q2W + TCS (N=145)
Age, years	34.2 (16.4)	36.1 (17.8)	35.3 (17.2)	36.6 (16.8)	36.7 (17.9)	37.5 (19.9)
Adolescent (12 to <18 years), n (%)	18 (12.8)	37 (13.1)	17 (11.6)	30 (10.7)	14 (21.2)	32 (22.1)
Adult (≥18 years), n (%)	123 (87.2)	246 (86.9)	129 (88.4)	251 (89.3)	52 (78.8)	113 (77.9)
Female, n (%)	73 (51.8)	141 (49.8)	75 (51.4)	136 (48.4)	33 (50.0)	70 (48.3)
Region, n (%)						
US	62 (44.0)	128 (45.2)	60 (41.1)	107 (38.1)	48 (72.7)	103 (71.0)
Europe	46 (32.6)	92 (32.5)	38 (26.0)	76 (27.0)	10 (15.2)	28 (19.3)
Rest of the world	33 (23.4)	63 (22.3)	48 (32.9)	98 (34.9)	8 (12.1)	14 (9.7)
Race, n (%)						
White	93 (66.0)	196 (69.3)	85 (58.2)	168 (59.8)	40 (60.6)	90 (62.1)
Asian	31 (22.0)	39 (13.8)	44 (30.1)	78 (27.8)	13 (19.7)	18 (12.4)
Black	16 (11.3)	33 (11.7)	10 (6.8)	25 (8.9)	9 (13.6)	19 (13.1)
BMI, kg/m²	27.8 (7.2)	26.6 (5.8)	26.3 (6.3)	26.7 (6.6)	27.9 (7.5)	26.5 (7.2)
Prior systemic treatment, n (%)	85 (60.3)	144 (50.9)	81 (55.5)	156 (55.5)	34 (51.5)	66 (45.5)
IGA, n (%)						
3 (Moderate)	83 (58.9)	170 (60.1)	95 (65.1)	175 (62.3)	48 (72.7)	98 (67.6)
4 (Severe)	58 (41.1)	113 (39.9)	51 (34.9)	106 (37.7)	18 (27.3)	47 (32.4)
BSA % involvement	47.8 (23.9)	45.3 (22.5)	46.0 (21.1)	46.1 (22.6)	38.2 (20.8)	40.4 (21.9)
Pruritus NRS	7.3 (1.7)	7.3 (1.9)	7.2 (1.9)	7.1 (1.9)	6.8 (2.0)	7.3 (1.8)
≥4, n (%)	130 (95.6)	263 (94.9)	134 (93.7)	253 (94.1)	57 (90.5)	130 (93.5)
DLQI[a]	15.7 (7.2)[b]	15.3 (7.4)[c]	15.9 (7.6)[d]	15.4 (7.0)[e]	13.5 (7.5)[f]	14.9 (7.2)[g]

[a] DLQI was completed only for patients ≥16 years at baseline; patients <16 years used the Children's DLQI; Patients who answered DLQI at baseline: [b] n=121; [c] n=239; [d] n=118; [e] n=218; [f] n=51; [g] n=109

Data are mean (SD) unless stated otherwise

Baseline Mean EASI Score for Each Clinical Sign by Body Region and EASI Total Score

	ADvocate1		ADvocate2		ADhere	
	PBO (N=141)	LEBRI 250 mg Q2W (N=283)	PBO (N=146)	LEBRI 250 mg Q2W (N=281)	PBO + TCS (N=66)	LEBRI 250 mg Q2W + TCS (N=145)
Erythema						
Head and neck	2.2 (0.80)	2.1 (0.70)	2.1 (0.71)	2.1 (0.72)	1.9 (0.86)	2.1 (0.79)
Trunk	2.3 (0.59)	2.2 (0.61)	2.2 (0.56)	2.2 (0.56)	2.2 (0.58)	2.2 (0.62)
Upper extremities	2.5 (0.52)	2.4 (0.54)	2.4 (0.56)	2.3 (0.54)	2.5 (0.49)	2.5 (0.49)
Lower extremities	2.3 (0.61)	2.3 (0.63)	2.3 (0.50)	2.3 (0.56)	2.4 (0.61)	2.3 (0.74)
Edema/Papulation						
Head and neck	1.9 (0.77)	1.9 (0.69)	1.9 (0.71)	1.9 (0.74)	1.7 (0.87)	1.9 (0.77)
Trunk	2.1 (0.61)	2.1 (0.59)	2.1 (0.52)	2.1 (0.59)	2.0 (0.55)	2.1 (0.64)
Upper extremities	2.3 (0.55)	2.2 (0.51)	2.2 (0.53)	2.2 (0.55)	2.3 (0.55)	2.3 (0.51)
Lower extremities	2.2 (0.64)	2.1 (0.68)	2.2 (0.52)	2.2 (0.61)	2.2 (0.61)	2.2 (0.71)
Excoriation						
Head and neck	1.6 (0.89)	1.5 (0.82)	1.6 (0.80)	1.7 (0.80)	1.5 (0.91)	1.5 (0.92)
Trunk	1.9 (0.74)	1.9 (0.73)	1.9 (0.66)	2.0 (0.65)	2.0 (0.68)	1.8 (0.78)
Upper extremities	2.2 (0.62)	2.1 (0.65)	2.1 (0.65)	2.2 (0.63)	2.3 (0.50)	2.2 (0.59)
Lower extremities	2.1 (0.72)	2.0 (0.73)	2.1 (0.60)	2.2 (0.66)	2.3 (0.62)	2.1 (0.78)
Lichenification						
Head and neck	1.8 (0.84)	1.8 (0.76)	1.8 (0.81)	1.9 (0.82)	1.7 (0.96)	1.8 (0.90)
Trunk	2.0 (0.71)	1.9 (0.72)	1.9 (0.67)	2.0 (0.61)	1.9 (0.79)	1.9 (0.75)
Upper extremities	2.2 (0.63)	2.2 (0.61)	2.3 (0.59)	2.3 (0.58)	2.2 (0.75)	2.3 (0.67)
Lower extremities	2.1 (0.70)	2.1 (0.70)	2.1 (0.67)	2.2 (0.63)	2.2 (0.69)	2.1 (0.85)
EASI Total Score[a]	**31.0 (12.9)**	**28.8 (11.3)**	**29.6 (10.8)**	**29.7 (12.0)**	**26.4 (10.6)**	**27.7 (11.1)**

[a] EASI Total Score=0.1 × EASI head and neck + 0.3 × EASI trunk + 0.2 × EASI upper limbs + 0.4 × EASI lower limbs; EASI region = (erythema + edema/papulation + excoriation + lichenification) × (value from percent involvement), where erythema, edema/papulation, excoriation, and lichenification are evaluated on a scale of 0 to 3 and value from percent involvement is on a scale of 0 to 6

Data are mean (SD)

DISCLOSURES

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ABBREVIATIONS

AD=atopic dermatitis; ANCOVA=analysis of covariance; BMI=body mass index; BSA=body surface area; DLQI=Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; EASI 50/75=at least 50/75% improvement from baseline in EASI; EMA=European Medicines Agency; FDA=US Food and Drug Administration; IGA=Investigator's Global Assessment; IGA (0,1)=IGA response of clear or almost clear; IL=interleukin; IR=inadequate responder; ITT=Intent-to-Treat; LD=loading dose; LEBRI=lebrikizumab; LSM=least squares mean; LTE=long-term extension; MI=multiple imputation; mITT=modified Intent-to-Treat; MMRM=mixed-effects model of repeated measures; NRS=Numeric Rating Scale; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation; SE=standard error; TCS=topical corticosteroids; W=Week

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