EASI 90 response sustained up to 38 weeks after lebrikizumab withdrawal despite negligible serum concentrations

Jonathan I. Silverberg¹, Thomas Bieber², Kilian Eyerich³, April W. Armstrong⁴, Brian J Nickoloff⁵, Chitra R Natalie⁶, Gaia Gallo⁶, Angela Okragly⁶, Chenjia Xu⁶, Brian Moser⁶, Maria Jose Rueda⁶, Hany Elmaraghy⁶, Ozge Uluckan⁷, Johann E. Gudjonsson⁸

¹George Washington University School of Medicine and Health Sciences, Washington, DC, USA; ²Kühne-Foundation Medicine Campus Davos, Switzerland; ³Department of Dermatology, Medical Center, University of Freiburg, Germany; ⁴Department of Dermatology, University of California Los Angeles, Los Angeles, CA, USA; ⁵Net2Source Inc, Somerset, NJ USA; ⁶Eli Lilly and Company, Indianapolis, IN, USA; ⁷Almirall, S.A., Barcelona, Spain; ⁸Depts. of Dermatology and Internal Medicine, University of Michigan, Ann Arbor, MI, 48109, USA

Introduction/Background:
Lebrikizumab demonstrated robust efficacy as monotherapy for moderate-to-severe atopic dermatitis (AD) in two Phase 3, randomized, double-blind, placebo-controlled, 52-week trials, ADvocate1 (NCT04146363) and ADvocate2 (NCT04178967) (Silverberg, et al. N Engl J Med 2023;388:1080-91; Blauvelt, et al. Br J Dermatol 2023; 188:740–748). Among lebrikizumab responders at the end of the 16-Week induction period, EASI 75 was maintained in 82% of patients treated with continuous lebrikizumab every 4 weeks (Q4W) and by 66% of the patients in the lebrikizumab withdrawal arm at Week 52.

Objectives:
To better understand the relationship between lebrikizumab serum concentration levels and sustained clinical response after treatment cessation in a subpopulation of lebrikizumab responders who discontinue treatment.

Methods:
In ADvocate1 and ADvocate2, patients received 500-mg loading doses at Week 0 and Week 2, followed by 250-mg doses every two weeks (Q2W) from Week 4 to Week 14 of the induction period. At Week 16, lebrikizumab responders were re-randomized 2:2:1 to receive lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W or placebo Q2W (lebrikizumab withdrawal). Patients in the current analysis included lebrikizumab responders who were withdrawn from treatment and maintained EASI 90 for 80% of the
visits during the withdrawal period, achieved EASI 90 at the Week-52 visit, and did not use rescue medication with data pooled from ADvocate1 and ADvocate2. From Weeks 16 to 52, EASI was assessed every 4 weeks. Lebrikizumab serum concentration levels were measured at Weeks 16, 32, and 52. We evaluated the mean serum concentrations over time; the reduction in the lebrikizumab concentrations; and the number of half-lives during the withdrawal period, as calculated by a population pharmacokinetic (popPK) model-estimated half-life.

**Results:**

17 patients (28%) of the 60 lebrikizumab responders who were withdrawn from treatment maintained EASI 90 for 80% of the visits during the 38-week withdrawal period, achieved EASI 90 at Week 52, and did not use rescue medication. Withdrawal-period pharmacokinetic data were available from 16 of these 17 patients. At Week 16, the mean (SD) serum lebrikizumab concentration was 92.4 (29.9) μg/mL. The mean (SD) serum concentrations decreased to 7.3 (14.0) μg/mL at Week 32 and 0.15 (0.20) μg/mL at Week 52, representing 92% and >99% reductions, respectively. At Week 52, 12 of the 16 patients had serum concentrations below the lower level of quantification (LLOQ: 0.09 μg/mL) for the clinical assay. In the popPK analysis, the mean elimination half-life for lebrikizumab was approximately 24.5 days. Lebrikizumab, therefore, had undergone approximately 5 half-lives at Week 32 and 10.9 half-lives at Week 52; it should be noted 5 to 7 half-lives for a biologic are often considered for a washout period (Evans. J Exp Stroke Transl Med 2010; 9:8-18).

**Conclusions:**

In this analysis from ADvocate1 and ADvocate2, a subset of patients who were randomly withdrawn from lebrikizumab maintained a stable EASI 90 response up to Week 52 with negligible remaining lebrikizumab serum concentrations. This is the first analysis that could provide additional insights into
lebrikizumab therapy-free remission. Further studies are needed to identify and characterize this subpopulation of AD patients and lebrikizumab’s potential disease-modifying properties.

EASI percent change from baseline and mean lebrikizumab serum concentrations for 17 patients who sustained EASI 90 response for 80% of the visits during the 38-week withdrawal period and achieved EASI 90 at Week 52

Keywords:
Atopic dermatitis, disease remission, drug levels, lebrikizumab, pharmacokinetics

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YUHAN. He is founder and chairman of the board of the non-profit biotech “Davos Biosciences AG” within the international Kühne-Foundation and founder of the consulting firm “Bieber Dermatology Consulting.”

K.E. is speaker and/or advisory board member for AbbVie, Almirall S.A., Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Incyte, Janssen, LEO Pharma, Pfizer, Sanofi, and UCB Pharma and holds shares of Dermagnostix and Dermagnostix R&D

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