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Post-hoc analyses of lebrikizumab phase III trials (LAVOLTA I and II): enhanced efficacy in patients with prior exacerbations and elevated baseline FE_{NO} or blood eosinophilia

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LAVOLTA I and II (LI&II) were duplicate placebo-controlled phase III trials of lebrikizumab (LEB) in moderate-to-severe asthma that enrolled patients irrespective of asthma exacerbation history, baseline blood eosinophilia or FE_{NO}. Two dose groups were studied: 125 mg and 37·5 mg Q4W. Primary endpoint was adjusted exacerbation rate ratio (AERR) in 'type 2 (T2) biomarker-positive' patients (defined as periostin ≥50 ng mL^{-1} or blood eosinophils ≥300 cells μL^{-1}). LI&II failed to show consistently significant results in AERR or a dose response. Recent studies in moderate-to-severe asthma have demonstrated that exacerbation history, baseline eosinophilia and/or FE_{NO} impact AERR in the placebo group of randomized controlled trials and on the magnitude of reduction in AERR upon treatment with anti-T2 cytokine antibodies. Post-hoc analysis determined AERR for LEB vs. placebo from LI&II in subpopulations with ≥1 exacerbation in the prior 12 months by baseline FE_{NO} (≤ 25, ≥ 25 to <50, ≥ 50 ppb) or eosinophilia (eos < 150, ≥ 150 to <300, ≥ 300 cells μL^{-1}) groups. A Poisson regression model was used. LEB reduced AERR vs. placebo in combined LI&II: $FE_{NO} \leq 25$ [125 mg: 0·79, 95% confidence interval (CI) 0·62–1·01; 37·5 mg: 0·75, 95% CI 0·58–0·96]; $FE_{NO} \geq 25$ to <50 (125 mg: 0·83, 95% CI 0·63–1·07; 37·5 mg: 0·70, 95% CI 0·53–0·92); $FE_{NO} \geq 50$ (125 mg: 0·55, 95% CI 0·41–0·72; 37·5 mg: 0·53, 95% CI 0·40–0·69); eos < 150 (125 mg: 0·94, 95% CI 0·68–1·29; 37·5 mg: 0·57, 95% CI 0·40–0·82); eos ≥150 to <300 (125 mg: 0·75, 95% CI 0·56–0·99; 37·5 mg: 0·76, 95% CI 0·57–1·02); and eos ≥300 (125 mg: 0·62, 95% CI 0·50–0·76; 37·5 mg: 0·59, 95% CI 0·48–0·73). Analyses demonstrate that LAVOLTA participants with a history of asthma exacerbations in the prior year and elevated T2 biomarkers had a significant reduction in asthma exacerbations. In future studies, optimal targeting of lebrikizumab to patients with exacerbation-prone T2 inflammation is warranted.

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Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: results from two phase III, randomized, double-blinded, placebo-controlled trials

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Lebrikizumab, a high-affinity IgG-4 monoclonal antibody targeting interleukin (IL)-13, selectively prevents the formation of the IL-13Rα1/IL-4Rα heterodimer receptor signalling complex. Lebrikizumab demonstrated rapid, dose-dependent efficacy and an acceptable safety profile in patients with moderate-to-severe atopic dermatitis (AD) in a phase IIb trial (NCT03443024). Here, we report 16-week efficacy and safety outcomes of lebrikizumab monotherapy in patients with AD from two ongoing 52-week, randomized, double-blinded, placebo-controlled phase III trials – ADvocate1 (NCT04146363) and ADvocate2 (NCT04178967). Eligible patients with moderate-to-severe AD [adults and adolescents (12–17 years of age, weighing ≥40 kg)] were randomized 2:1 to subcutaneous lebrikizumab 250 mg or placebo every 2 weeks. Efficacy analyses included proportions of patients achieving Investigator's Global Assessment (IGA) 0/1, Eczema Area and Severity Index (EASI)-75 and Pruritus Numerical Rating Scale (NRS) ≥ 4-point improvement from baseline (P ≥ 4) at week 16. Nonefficacy-related missing data were imputed by multiple imputation. In ADvocate1, proportions of patients treated with lebrikizumab 250 mg (n = 283) and placebo (n = 141) achieving IGA 0/1 at week 16 were 43·0% and 12·8% (P < 0·001); EASI-75 responses were 59·3% and 16·4% (P < 0·001); P ≥ 4 proportions were 46·3% and 12·7% (P < 0·001), respectively. In ADvocate2 (lebrikizumab, n = 281; placebo, n = 146), corresponding proportions for IGA 0/1 were 33·1% and 10·9% (P < 0·001); EASI-75 responses were 50·8% and 18·2% (P < 0·001); P ≥ 4 proportions were 38·3% and 11·3% (P < 0·001), respectively. The percentage of patients reporting ≥1 TEAE was comparable in ADvocate1 (lebrikizumab, 45·4%; placebo, 51·1%) and ADvocate2 (lebrikizumab 53·0%; placebo 66·2%). Data from two ongoing pivotal phase III trials suggest that lebrikizumab 250 mg Q2W provides an efficacious treatment option with an

acceptable safety profile for patients with moderate-to-severe AD.

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Dupilumab treatment significantly improves skin barrier function in adult and adolescent patients with moderate-to-severe atopic dermatitis

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Atopic dermatitis (AD) is characterized by abnormal skin lipid and filaggrin (FLG) content. The role of dupilumab therapy in the regulation of skin barrier has not been fully evaluated. Transepidermal water loss (TEWL), and skin tape strip (STS) samples were collected from AD lesions (n = 26) and healthy controls (n = 26) over a 16-week course of dupilumab treatment [age 12–63 years; BALISTAD study (NCT04447417)]. Quantitative lipidomic and FLG breakdown product analysis of STS samples collected at days 1, 15, 29, 56 and 85 and at week16 was performed by liquid chromatography tandem mass spectrometry. Mean TEWL in AD lesions was significantly reduced from day 1 (47·2 g m^{-2} × h) to wk16 (23·6 g m^{-2} × h) representing a 52% reduction ($P < 0{\cdot}001$). STS samples from AD lesions had reduced levels of FLG breakdown products [urocanic (UCA) and pyroglutamic acids (PCA)] at baseline vs. healthy controls ($P < 0{\cdot}05$). Significantly increased levels of non-hydroxy fatty acid sphingosine ceramides (NS-CER) and decreased levels of esterified omega-hydroxy fatty acid sphingosine ceramides (EOS-CER) were found in AD lesions at baseline vs. healthy controls ($P < 0{\cdot}05$). With dupilumab treatment, significant increases in UCA and PCA were found in AD skin ($P < 0{\cdot}05$). Additionally, a significant decrease in NS-CER and increase in EOS-CER were found in AD ($P < 0{\cdot}05$), resulting in normalization of the NS-CER/EOS CER ratio following treatment. Partial changes for these parameters were already observed after 2 weeks, with a maximal response achieved after 8 weeks of dupilumab treatment. Dupilumab treatment significantly improves TEWL, lipid composition and FLG in AD lesions, providing normalization of epidermal barrier function.

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Improvement in disease severity and quality of life in patients with atopic dermatitis treated with dupilumab for up to 18 months: real-world data from the PROSE registry

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Atopic dermatitis (AD) is a chronic immune-mediated type 2 inflammatory disease. Dupilumab provides rapid and sustained long-term efficacy with an acceptable safety profile in patients with moderate-to-severe AD in clinical trials. Here, we report improvement of AD through objective assessments of disease signs, and patient-reported measures of symptoms and quality of life for up to 18 months after initiating dupilumab treatment, using real-world data from the PROSE registry. PROSE (NCT03428646) is an ongoing, multicentre, longitudinal, prospective, observational registry in the USA and Canada enrolling patients aged ≥12 years with moderate-to-severe AD, initiating real-world dupilumab treatment for AD per approved prescribing information. Data are presented as observed, and included all patients with available values at each scheduled visit (i.e. baseline and months 3, 6, 12 and 18). No formal statistical hypothesis testing was performed. This analysis included 563 patients (42·5% male, 95% aged ≥18 years; data cutoff October 2020). Of the 563 patients

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