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Dupilumab improves patient-reported symptoms and health-related quality of life in children aged 6–11 years with severe atopic dermatitis

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Dear Editor, Severe atopic dermatitis (AD) in children poses a high disease burden and requires long-term management, which in turn relies on monitoring symptoms and quality of life (QoL) over time. It is important that children and caregivers observe rapid improvement in signs, symptoms and QoL to ensure adherence to treatment. The Patient-Oriented Eczema Measure (POEM) is recommended as the main instrument for assessing patient-reported AD symptoms.[1,2] POEM assesses the frequency, during the previous week, of symptoms in seven domains: itch, sleep disturbance, bleeding, oozing of clear fluid, cracked skin, flaking skin, and dry/rough skin.[2] The effect of AD on QoL[3] is evaluated using the Children's Dermatology Life Quality Index (CDLQI).[4] CDLQI assesses 10 patient-reported items, during the previous week, in six domains that affect QoL: symptoms and feelings, leisure, school and holidays, personal relationships, sleep, and treatment burden.[4] In children aged 6–11 years, a six-point threshold has been established as the minimal clinically important difference (MCID) in both POEM and CDLQI.[5]

Dupilumab is the only systemic treatment approved for children aged 6–11 years with severe AD in Europe.[6] Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases, including AD.

LIBERTY AD PEDS (R668-AD-1652, NCT03345914) was a randomized, double-blind, placebo-controlled, phase III clinical trial investigating efficacy and safety of treatment with dupilumab plus topical corticosteroids (TCS) in 367 children aged 6–11 years with severe AD. In this 16-week trial, dupilumab + TCS significantly improved AD signs, symptoms and QoL compared with placebo + TCS, with an acceptable safety profile.[7] Here, we evaluated the effect of dupilumab + TCS on POEM and CDLQI scores, reporting on the change in total POEM scores and the frequency of the seven symptoms assessed by POEM, change in QoL assessed by total CDLQI score and its individual items, and proportions of patients achieving a clinically meaningful change in POEM and CDLQI.[5]

Details of the study design and primary efficacy and safety results have been reported previously.[7] This current post-hoc analysis included children treated with 300 mg dupilumab every 4 weeks (q4w) + TCS ($n = 122$) or children with baseline weight ≥ 30 kg treated with 200 mg dupilumab every 2 weeks (q2w) + TCS ($n = 59$) and two matched placebo + TCS groups. Patients with missing values or who received rescue treatment were categorized as 'nonresponders'. Statistical comparisons between dupilumab and placebo arms used nominal *P*-values with a 0.05 two-sided significance level derived using the Cochran–Mantel–Haenszel test stratified by region and baseline weight group.

At baseline, mean (SD) overall POEM score was 20.8 (5.5), corresponding to severe disease[2] and 59.5% of patients had a total CDLQI score indicating a 'very large' or 'extremely large' impact on life.[4] Mean total POEM scores were balanced across treatment groups [q4w dupilumab: 21.3 (5.5) vs. placebo: 20.7 (5.5); q2w dupilumab: 19.9 (5.3) vs. placebo: 20.4 (6.0)], as were mean CDLQI scores [q4w dupilumab: 16.2 (7.9) vs. placebo 14.6 (7.4); q2w dupilumab: 13.0 (6.2) vs. placebo 13.2 (7.7)]. Least-squares mean POEM scores were significantly lower in both dupilumab-treated arms vs. placebo from week 2 onwards to week 16 of the study ($P < 0.0001$) (Figure 1a). At week 16, significantly more patients treated with dupilumab vs. placebo achieved a POEM score of 0/1 ('clear skin'/'almost clear skin') (dupilumab q4w: 13.9% vs. 2.4%, $P = 0.001$; dupilumab q2w: 22.0% vs. 1.6%, $P = 0.0005$). Also, significantly more reported CDLQI scores of 0 or 1 ('no effect on life') (dupilumab q4w: 31.3% vs. 9.5%, $P = 0.0001$; dupilumab q2w: 35.1% vs. 10.2%, $P < 0.01$; Figure 1b).

At week 16 in the dupilumab q4w and q2w groups 81.7% and 79.3% of patients, respectively (vs. 31.1% and 32.0% placebo, respectively, $P < 0.0001$ for both) achieved a MCID (at least a six-point reduction) in POEM, and 77.3% and 80.8% (vs. 42.3% and 35.8% placebo, $P < 0.0001$ for both) in CDLQI.

At week 16, dupilumab improved each individual POEM item in both q4w and q2w groups, with significantly more

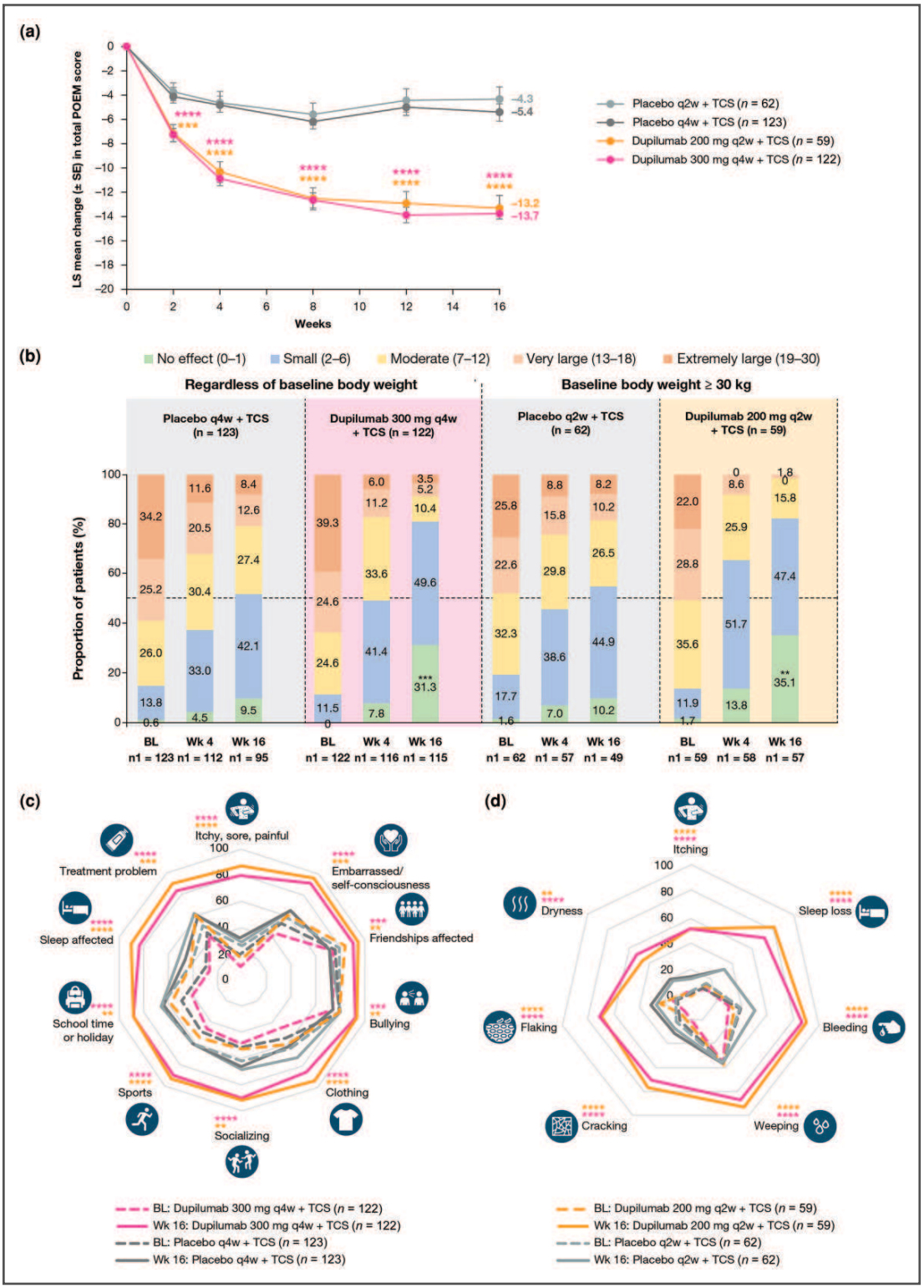

Figure 1 (a) LS mean change in total POEM score over time. (b) CDLQI total score at BL, Wk 4 and Wk 16. Percentages were calculated based on n1. *P*-values shown are for comparison of proportions of patients who achieved CDLQI scores of 0 or 1 (indicating no effect on their quality of life) at Wk 16 between dupilumab-treated and placebo-treated arms. (c) POEM item level at BL and outcomes at Wk 16: proportion of patients who reported 'no days'/'1–2 days'; patients treated with dupilumab with TCS or placebo with TCS. Percentages were calculated based on the number of responders at each respective visit and the total number of patients within each treatment arm. (d) CDLQI item level at baseline and outcomes at Wk 16: proportion of patients who reported 'not at all' or 'only a little'; patients treated with dupilumab + TCS or placebo + TCS. Percentages were calculated based on the number of responders at each respective visit and the total number of patients within each treatment arm. Continuous endpoints were analysed using a multiple imputation method with data set to missing after rescue treatment use. Categorical endpoints were analysed using a nonresponder imputation method with patients with missing values and patients who used rescue treatment considered as nonresponders.**$P<0.01$; ***$P<0.001$; ****$P<0.0001$. BL, baseline; CDLQI, Children's Dermatology Life Quality Index; LS, least-squares; *n*, number of patients within each treatment arm; n1, number of patients with non-missing CDLQI total score within treatment arm and visit; POEM, Patient-Oriented Eczema Measure; q2w, every 2 weeks; q4w, every 4 weeks; SE, standard error; TCS, topical corticosteroids; Wk, week.

patients treated with dupilumab than placebo reporting 'no days' or '1–2 days' for each item over the past week (Figure 1c). Additionally, in both the dupilumab q4w and q2w groups vs. placebo, a significantly greater proportion of patients reported 'not at all' or 'only a little' for each individual CDLQI item (Figure 1d). The long-term benefits of dupilumab in children with severe AD have been previously demonstrated in the open-label extension study, LIBERTY AD PED-OLE, with improvements in POEM and CDLQI sustained for up to 48 weeks of treatment.[8]

In conclusion, in children aged 6–11 years with severe AD, dupilumab with TCS compared with placebo with TCS resulted in rapid and clinically meaningful improvement in patients' assessment of frequency of AD lesions, itching, sleep impairment and QoL. This analysis highlights the benefits of dupilumab treatment from the patient's perspective.

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Conflicts of interest: See Appendix S1 for full Conflicts of Interest list.

Data availability: Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this research letter. Individual anonymized participant data will be considered for sharing once the product and indication has been approved by major health authorities (e.g. FDA, EMA, PMDA), if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Full Conflicts of Interest statement.

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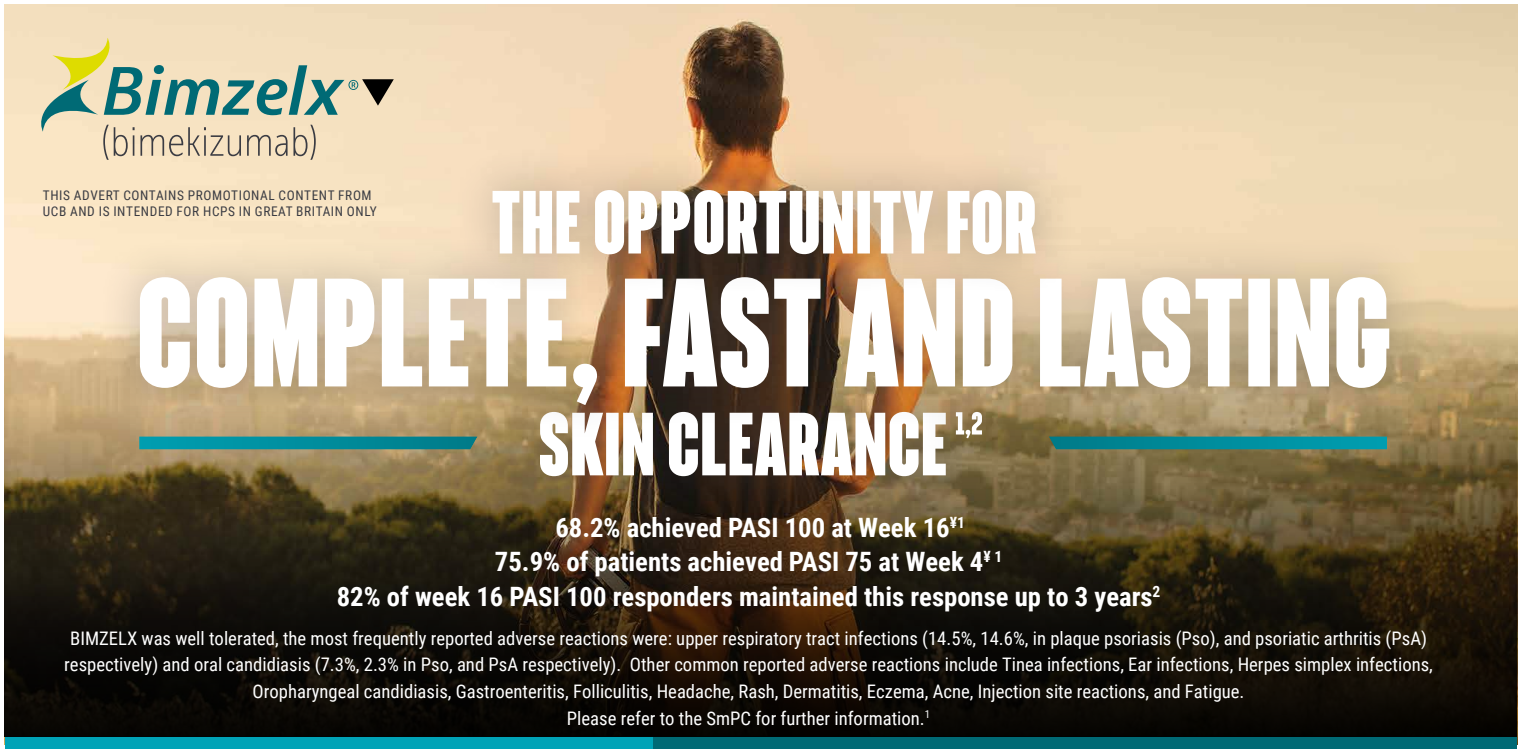

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Adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy. **Dosage and Administration:** Should be initiated and supervised by a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated. **Recommended dose:** Plaque Psoriasis: 320 mg (given as two subcutaneous injections of 160 mg each) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter. Psoriatic arthritis: 160 mg (given as 1 subcutaneous injection of 160 mg) every 4 weeks. For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, the recommended dose is the same as for plaque psoriasis. After 16 weeks, regular assessment of efficacy is recommended and if a sufficient clinical response in joints cannot be maintained, a switch to 160 mg every 4 weeks can be considered. Axial spondyloarthritis (nr-axSpA and AS): 160 mg (given as 1 subcutaneous injection) every 4 weeks. For patients with plaque psoriasis (including psoriatic arthritis with coexistent moderate to severe psoriasis) and a body weight ≥ 120 kg who did not achieve complete skin clearance at week 16, 320 mg every 4 weeks after week 16 may further improve treatment response. Consider discontinuing if no improvement by 16 weeks of treatment. Renal or hepatic impairment: No dose adjustment needed. Elderly: No dose adjustment needed. Administer by subcutaneous injection to thigh, abdomen or upper arm. Rotate injection sites and do not inject into psoriatic plaques or skin that is tender, bruised, erythematous or indurated. Do not shake pre-filled syringe or pre-filled pen. Patients may be trained to self-inject. **Contraindications:** Hypersensitivity to bimekizumab or any excipient; Clinically important active infections (e.g. active tuberculosis). **Warnings and Precautions:** Record name and batch number of administered product. *Infection:* Bimekizumab may increase the risk of infections e.g. upper respiratory tract infections, oral candidiasis. Caution when considering use in patients with a chronic infection or a history of recurrent infection. Must not be initiated if any clinically important active infection until infection resolves or is adequately treated. Advise patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops an infection, the patient should be carefully monitored. If the infection becomes serious or is not responding to standard therapy do not administer bimekizumab until infection resolves. *TB:* Evaluate for TB infection prior to initiating bimekizumab – do not give if active TB. While on bimekizumab, monitor for signs and symptoms of active TB. Consider anti-TB therapy prior to bimekizumab initiation if past history of latent or active TB in whom adequate treatment course cannot be confirmed. *Inflammatory bowel disease:* Bimekizumab is not recommended in patients with inflammatory bowel disease. Cases of new or exacerbations of inflammatory bowel disease have been reported. If inflammatory bowel disease signs/symptoms develop or patient experiences exacerbation of pre-existing inflammatory bowel disease, discontinue bimekizumab and initiate medical management. *Hypersensitivity:* Serious hypersensitivity reactions including anaphylactic reactions have been observed with IL-17 inhibitors. If a serious hypersensitivity reaction occurs, discontinue immediately and treat. *Vaccinations:* Complete all age appropriate immunisations prior to bimekizumab initiation. Do not give live vaccines to bimekizumab patients. Patients may receive inactivated or non-live vaccinations. **Interactions:** A clinically relevant effect on CYP450 substrates with a narrow therapeutic index in which the dose is individually adjusted e.g. warfarin, cannot be excluded. Therapeutic monitoring should be considered. **Fertility, pregnancy and lactation:** Women of child-bearing potential should use an effective method of contraception during treatment and for at least 17 weeks after treatment. Avoid use of bimekizumab during pregnancy. It is unknown whether bimekizumab is excreted in human milk, hence a risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Bimzelx therapy. No data available on human fertility. **Driving and use of machines:** No or negligible influence on ability to drive and use machines. **Adverse Effects:** Refer to SmPC for full information. Very Common *(≥ 1/10):* upper respiratory tract infection; Common *(≥ 1/100 to < 1/10):* oral candidiasis, tinea infections, ear infections, herpes simplex infections, oropharyngeal candidiasis, gastroenteritis, folliculitis; headache, rash, dermatitis and eczema, acne, injection site reactions, fatigue; Uncommon *(≥ 1/1,000 to < 1/100):* mucosal and cutaneous candidiasis (including oesophageal candidiasis), conjunctivitis, neutropenia, inflammatory bowel disease. Storage precautions: Store in a refrigerator (2°C – 8°C), do not freeze. Keep in outer carton to protect from light. Bimzelx can be kept at up to 25°C for a single period of maximum 25 days with protection from light. Product should be discarded after this period or by the expiry date, whichever occurs first.

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