Dupilumab Treatment in Children with Moderate-to-Severe Atopic Dermatitis Increases Bone Alkaline Phosphatase, a Marker of Bone Mineralization

Alan D. Irvine[1], Amy S. Paller[2,3], Sara Hamon[4], Julie Horowitz[4], Annamaria Farrell[4], Sarah Hatsell[4], Ainara Rodríguez Marco[5], Ashish Bansal[4], Zhen Chen[4], Sonya L. Cyr[4]

[1]Trinity College Dublin, Dublin, Ireland; [2]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [3]Ann and Robert H. Lurie Children's Hospital, Chicago, IL, USA; [4]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [5]Sanofi, Madrid, Spain

BACKGROUND

- Children with atopic dermatitis (AD) are at risk of low bone mineral density (BMD), which is associated with increased prevalence of osteopenia, osteoporosis, and fracture risk[1,2]
- Factors such as restricted nutrition, vitamin D deficiency, poor sleep, chronic inflammation and corticosteroid use may contribute to lower levels of bone alkaline phosphatase (BALP), a marker of bone mineralization, seen in children with moderate-to-severe AD compared with healthy children[3]
- A major determinant for lifetime risk of fractures and osteoporosis is the magnitude of peak bone mass achieved during prepubescent years
- Low BALP and BMD in children with moderate-to-severe AD could contribute to a higher prevalence of osteopenia and osteoporosis

OBJECTIVE

- **To report the impact of dupilumab treatment on markers of bone mineralization in children aged 6 to 11 years with moderate-to-severe AD**

METHODS

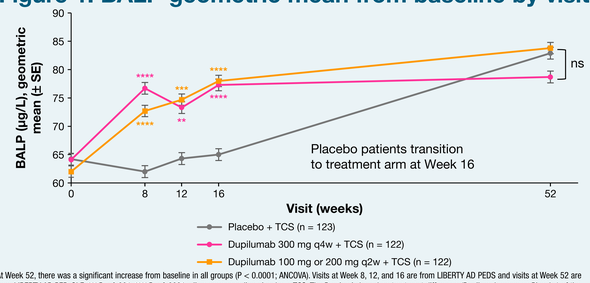
- The analysis was performed retrospectively on sera from participants in LIBERTY AD PEDS (NCT03345914) and LIBERTY AD PED-OLE (NCT02612454)
- In LIBERTY AD PEDS, a double-blind, 16-week, phase 3 trial, children aged 6 to 11 years were randomized 1:1:1 to 300 mg dupilumab every 4 weeks (q4w), a weight-based regimen of dupilumab every 2 weeks (100 mg q2w for patients with baseline weight < 30 kg, and 200 mg q2w for those with baseline weight ≥ 30 kg), or placebo; all patients received concomitant medium-potency topical corticosteroids (TCS)

METHODS (CONT.)

- After the initial 16-week trial, children aged 6 to 11 years who participated in the original trial were eligible to be enrolled in the open-label extension study LIBERTY AD PED-OLE; patients received dupilumab 300 mg q4w, which could be titrated up in case of inadequate clinical response at Week 16 (200 mg q2w for patients with baseline weight < 60 kg, and 300 mg q2w for those with baseline weight ≥ 60 kg); all patients received concomitant medium-potency TCS
- Bone biomarkers[4] including BALP, procollagen type 1 N-terminal propeptide (P1NP), C-terminal crosslinking telopeptide of type 1 collagen (β-CTX) and osteocalcin (OC), as well as insulin-like growth factor 1 (IGF-1) were analyzed at baseline, 8, 12, and 16 weeks, and BALP only at 52 weeks
- There is a limited number of data points for P1NP, β-CTX, OC and IGF-1 due to insufficient volumes of serum available for analysis

RESULTS

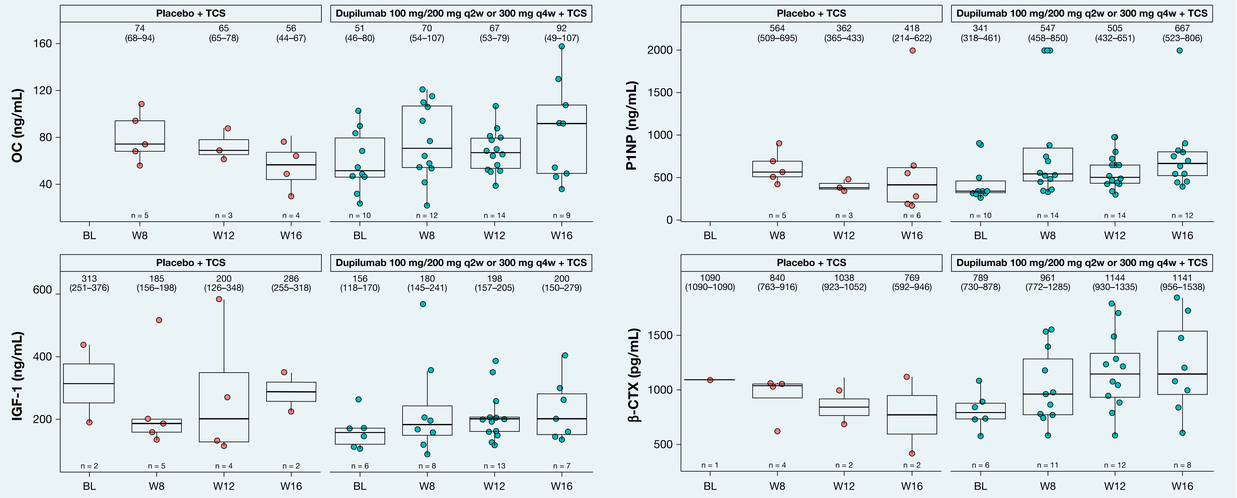
Figure 1. BALP geometric mean from baseline by visit.



At Week 52, there was a significant increase from baseline in all groups ($P < 0.0001$; ANCOVA). Visits at Week 8, 12, and 16 are from LIBERTY AD PEDS and visits at Week 52 are from LIBERTY AD PED-OLE. ***$P < 0.001$, ****$P < 0.0001$, all vs corresponding placebo + TCS. The P-value is based on treatment difference (Dupilumab group vs Placebo) of the exponentiated LS mean of log(value)-log(baseline) using ANCOVA model with log of baseline measurement as covariate and the treatment, region and baseline weight strata as fixed factors. ns, not significant; SE, standard error.

RESULTS (CONT.)

Figure 2. Bone biomarkers median and interquartile range from baseline by visit.



Visits at Week 8, 12, and 16 are from LIBERTY AD PEDS. BL, baseline. W, week.

CONCLUSIONS

- **Dupilumab treatment is associated with a rapid and significant increase in BALP in children aged 6 to 11 years with moderate-to-severe AD; a trend towards increased levels was observed for other bone turnover biomarkers, although data were limited**
- **Mean (BALP) or median (others) biomarker levels measured in dupilumab-treated children improved from below to within reference intervals levels for OC, P1NP and β-CTX and from low to near-mean reference interval levels for BALP and IGF-1, for this age group[4,5]**
- **Overall results suggest an increase in bone mineralization in pediatric patients with moderate-to-severe AD following dupilumab treatment**

References: 1. Wu D, Wu XD, Zhou X, et al. Ann Transl Med. 2021;9:40. 2. Lowe KE, Mansfield KE, Delmestri A, et al. J Allergy Clin Immunol. 2020;145:563-71.e8. 3. Silverberg JI. Pediatr Allergy Immunol. 2015;26:54-61. 4. Diemar SS, Lylloff L, Rønne MS, et al. Bone. 2021;146:115879. 5. https://www.mayocliniclabs.com/api/sitecore/TestCatalog/DownloadTestCatalog?testId=62750.

Acknowledgments and funding sources: Data first presented at the Revolutionizing Atopic Dermatitis (RAD 2022) Virtual Conference; December 11, 2022. Research sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. ClinicalTrials.gov Identifiers: NCT03345914 and NCT02612454. Medical writing/editorial assistance was provided by Mark C. Howell Jr, PhD, of Excerpta Medica, and was funded by Sanofi and Regeneron Pharmaceuticals, Inc., according to the Good Publication Practice guideline.

Disclosures: Alan D. Irvine: Almirall, Eli Lilly, LEO Pharma, Regeneron Pharmaceuticals, Inc., Sanofi – speaker, honoraria, consultant/advisory board member. **Amy S. Paller:** AbbVie, AnaptysBio, Eli Lilly, Incyte, Janssen, Krystal Biotech, Regeneron Pharmaceuticals, Inc., UCB – investigator; AbbVie, Acrotech, Almirall, Amgen, Amryt Pharma, Arcutis Biotherapeutics, Arena Pharmaceuticals, Azitra, BioCryst, BiomX, BMS, Boehringer Ingelheim, Botanix Pharmaceuticals, BridgeBio, Castle Creek Biosciences, Catawba Research, Eli Lilly, Exicure, Gilead, Incyte, Janssen, Kamari Pharma, LEO Pharma, Novartis, Pfizer, Pierre Fabre, RAPT Therapeutics, Regeneron Pharmaceuticals, Inc., Sanofi, Seanergy, UCB, UNION therapeutics– consultant with honorarium; AbbVie, Abeona Therapeutics, Bausch Health, Galderma, Inmed, Novan – data and safety monitoring board. **Sara Hamon, Julie Horowitz, Annamaria Farrell, Sarah Hatsell, Ashish Bansal, Zhen Chen, Sonya L. Cyr:** Regeneron Pharmaceuticals, Inc. – employees and shareholders. **Ainara Rodríguez Marco:** Sanofi – employee, may hold stock and/or stock options in the company.

Presented at the South Beach Symposium (SBS 2023); Miami Beach, Florida, USA; February 9 - 12, 2023.