FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

All authors declare no potential, perceived or real conflict of interest regarding the content of this manuscript.

DATA AVAILABILITY STATEMENT

Data are not available.

Erik Sören Halvard Hansen[1,2]
Hannah Kaiser[3]
Kristine Tronier Hansen[4]
Klaus Bønnelykke[5]
Bo Chawes[5]
Vibeke Backer[6]
Christian Torp-Pedersen[7]
Charlotte Suppli Ulrik[1]
Nicklas Brustad[5]

[1]*Respiratory Research Unit Hvidovre, Copenhagen University Hospital – Hvidovre, Hvidovre, Denmark*
[2]*Department of Respiratory Medicine, Slagelse Hospital, Slagelse, Denmark*
[3]*Department of Dermatology and Allergy, Herlev and Gentofte Hospital, Copenhagen, Denmark*
[4]*Department of Child and Adolescent Psychiatry, Roskilde, Denmark*
[5]*Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte University Hospital, Copenhagen, Denmark*
[6]*Department of Otorhinolaryngology Head & Neck Surgery and audiology, Rigshospitalet, Copenhagen University, Copenhagen, Denmark*
[7]*Department of Cardiology, North Zealand Hospital, Hillerød, Denmark*

Correspondence
Nicklas Brustad, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte University, Ledreborg Allé 34, 2820 Gentofte, Copenhagen, Denmark.
Email: nicklas.brustad@dbac.dk

ORCID

Bo Chawes https://orcid.org/0000-0001-6846-6243
Vibeke Backer https://orcid.org/0000-0002-7806-7219
Nicklas Brustad https://orcid.org/0000-0001-6383-8845

REFERENCES

1. Razaz N, Cnattingius S, Joseph KS. Association between Apgar scores of 7 to 9 and neonatal mortality and morbidity: population based cohort study of term infants in Sweden. *BMJ (Clinical Research Ed)*. 2019;365:l1656.
2. Razaz N, Boyce WT, Brownell M, et al. Five-minute Apgar score as a marker for developmental vulnerability at 5 years of age. *Arch Dis Child Fetal Neonatal Ed*. 2016;101:F114-F120.
3. Ekelund CK, Kopp TI, Tabor A, Petersen OB. The Danish fetal medicine database. *Clin Epidemiol*. 2016;8:479-483.
4. Bliddal M, Broe A, Pottegård A, Olsen J, Langhoff-Roos J. The Danish medical birth register. *Eur J Epidemiol*. 2018;33:27-36.
5. Pinot De Moira A, Pearce N, Pedersen M, Nybo Andersen A-M. The influence of early-life animal exposure on the risk of childhood atopic dermatitis, asthma and allergic rhinoconjunctivitis: findings from the Danish National Birth Cohort. *Int J Epidemiol*. 2023;52:1231-1242. doi:10.1093/ije/dyad040

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

DOI: 10.1111/all.16147

Clinical and molecular response to dupilumab treatment in pediatric atopic dermatitis: Results of the German TREATkids registry

To the Editor,

Dupilumab is a first-in-class biologic for moderate-to-severe atopic dermatitis (AD). Whereas multiple real-world studies confirmed its robust effectiveness and favorable safety in adults,[1] routine data on children and adolescents are still scarce. In an interim analysis on 61 pediatric patients of the Dutch BioDay registry dupilumab significantly improved disease severity, however, results were difficult to interprete, because a considerable proportion of patients were

in the wash-out or concomitantly treated with immunosuppressants at baseline.[2] TREATkids is a section of the TREATGermany registry and has been approved by the Medical Faculty of the Technical University of Dresden (No. EK 118032016) and by the respective ethics committees of the participating sites. It currently (data release May 2023) comprises 314 pediatric patients with moderate-to-severe AD (51.0% female, mean age 7.8). Their mean (±SD) baseline scores were Investigator Global Assessment [IGA, 3.2 (1.0)], Eczema Area and Severity Index [EASI, 13.4 (9.9)], peak pruritus numerical rating scale [PP-NRS, 5.5 (2.9)], and (Children's) Dermatology Life Quality Index [(c) DLQI, 9.5 (6.3)].

Systemic therapy was initiated in 99 of these 314 pediatric patients; most of them ($n=87$) received dupilumab. Fifty nine of those had at least one documented follow-up visit after 3 (±14 days) or 6 months (±28 days). Baseline mean EASI, PP-NRS and (C)DLQI scores were 18.1 (±9.5), 7.1 (±2.5) and 13.0 (±5.7).

Overall, dupilumab treatment led to significant reductions of all severity scores (Figure S1). The proportion of patients with an EASI50, 75 and 90 response were 92.2%, 58.8% and 25.5% at month 3, and 91.4%, 62.9%, and 48.6% at month 6, that is, slightly higher than observed in trials.[3] An EASI ≤7 reflecting mild disease was achieved by 78.4% and 82.9% at month 3 and 6. PP-NRS was reduced by 55.3% and 57.6% until month 3 and 6 ($p=2.72e-06$, $p=7.52e-05$), and mean (C)DLQI improved by 59.7% and 62.3% (p=7.41e-08). At month 3, 84.4% had experienced a 4-point reduction of the (C)DLQI (Table 1). Dupilumab was well tolerated with adverse events reported in only four patients. Three children experienced conjunctivitis and one child developed blepharitis, which led to discontinuation. Facial eczema was reported in one patient.

A sensitivity analysis on patients with data on both month 3 and 6 indicated that while baseline characteristics did not differ significantly between children ($n=14$) and adolescents ($n=14$), the latter showed slightly more pronounced improvements with a median EASI reduction at month 3 of 88.2% versus 77.5%, and EASI75 response rates of 78.6% versus 57.1% (Table S1). We additionally analyzed 21 AD candidate biomarkers in tape strips from 14 patients using a Luminex assay (Bio-techne, Minneapolis, USA). Fifteen markers moderately correlated with disease severity measured by the EASI (Table S2). Eighteen proteins showed differential expression in lesional versus non-lesional skin at baseline. At month 3, 15 of these had decreased significantly (Table S3) and no longer showed significant differences to non-lesional skin. In the absence of data on healthy individuals, it is unclear whether they reached levels of non-AD skin. The most pronounced reductions were observed for fibronectin (log2FC-4.63), IL-8 (log2FC-3.52), and S100A9 (log-2FC-2.13) (Figure 1). Fibronectin is central for adhesion and internalization of *S. aureus*.[4] IL-8 has pleiotropic effects, including attraction and activation of neutrophils, which contribute to *S. aureus* colonization by release of neutrophil extracellular traps.[5] S100A9 was reported to correlate with AD severity.[6]

The results from our analysis demonstrate that dupilumab treatment is safe and leads to clinical and molecular improvements in the majority of pediatric AD patients. Larger-size and longer-term routine data along with analysis of extended biomarker panels will be

TABLE 1 Severity scores and predefined endpoints over time.

		Month 3		Month 6	
	Baseline		*p* value		*p* value
Severity scores, mean (±SD)					
EASI	18.3±9.8	4.5±4.0	7.5495e-15	4.1±4.7	4.7468e-10
oSCORAD	44.3±11.0	21.1±11.0	3.7303e-14	18.1±11.3	2.4145e-10
IGA	3.6±0.8	2.0±0.9	2.7204e-11	1.8±1.0	6.4748e-07
PGA	3.9±0.8	2.2±1.0	6.3848e-11	2.1±1.0	1.4483e-06
POEM	20.0±5.5	8.5±6.5	2.7480e-11	8.9±5.7	2.1118e-08
(C)DLQI	12.9±5.7	5.2±4.8	7.9429e-10	4.3±4.7	8.9659e-08
Peak itch	7.2±2.4	3.2±2.5	2.5421e-06	2.9±2.4	1.6520e-04
Predefined endpoints, %					
EASI50 %		92.0%		90.9%	
EASI75 %		58.0%		60.6%	
EASI90 %		26.0%		45.5%	
EASI ≤7	7.0%	78.0%		81.8%	
IGA ≤1	0.0%	29.4%		42.4%	
PGA ≤1	0.0%	25.5%		27.3%	
4-point reduction peak itch		63.6%		75.9%	
4-point reduction (C) DLQI		84.4%		80.0%	

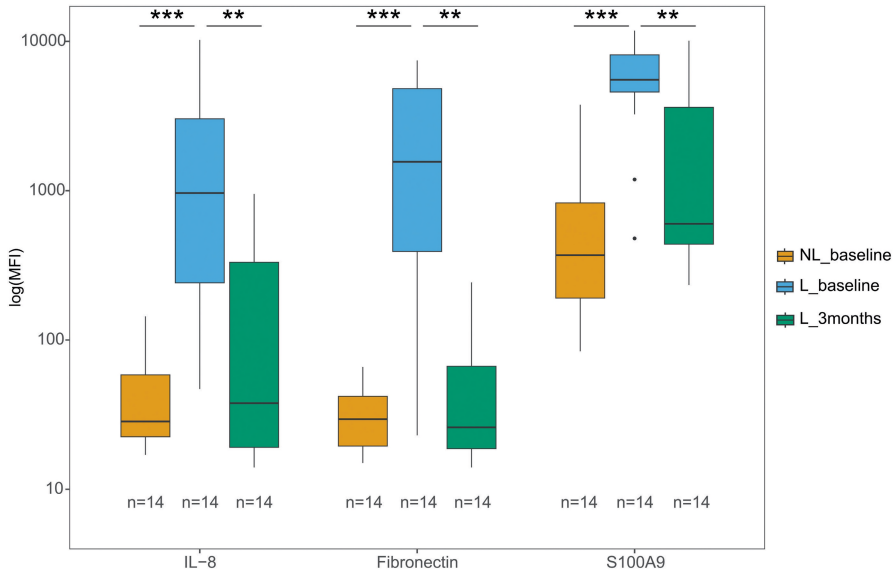

FIGURE 1 Treatment with dupilumab reduces levels of AD-associated stratum corneum biomarkers. Changes of protein marker levels (values in median florescence intensity (MFI)) in stratum corneum samples of non-lesional skin at baseline and lesional skin at baseline and 3 months after dupilumab treatment. Comparisons between time points were made using the Wilcoxon signed-rank test. $^{**}p < .01$, $^{***}p < .001$, (Benjamini–Hochberg corrected).

key to more comprehensively evaluate effects of systemic therapies in pediatric AD.

AUTHOR CONTRIBUTIONS

Dora Stölzl and Stephan Weidinger designed the study; Inken Harder and Melina Fonfara performed biomarker measurements; Dora Stölzl, Nicole Sander and Doreen Siegels contributed to methodology and analyzed and visualized the data; Jochen Schmitt, Thomas Werfel and Stephan Weidinger supervised the analysis; Dora Stölzl, Nicole Sanders and Stephan Weidinger wrote the manuscript draft; all authors reviewed and edited the manuscript.

ACKNOWLEDGMENTS

The authors thank the participating patients and caregivers, physcians and clinical staff, the TREATGermany and TREATkids study group, and the supporters of the registry. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

TREATkids is the children and adolesent section of TREATgermany, which is an academic, investigator-initiated clinical disease registry that is financially supported by AbbVie Deutschland GmbH & Co. KG, Almirall Hermal GmbH, Galderma S.A., LEO Pharma GmbH, Lilly Deutschland GmbH, Pfizer Inc. and Sanofi.

CONFLICT OF INTEREST STATEMENT

Dora Stölzl has received lecture fees from Novartis and Sanofi. Susanne Abraham has received lecture and/or consultancy fees from Novartis, LEO Pharma, Amgen, Lilly, Sanofi, Beiersdorf, Janssen, UCB and AbbVie. Sascha Gerdes has been an advisor and/or received speakers' honoraria and/or received grants and/or participated in clinical trials of the following companies: AbbVie, Acelyrin, Affibody AB, Akari Therapeutics Plc, Almirall, Amgen, Anaptys Bio, Argenx BV, Biogen Idec, Bristol-Myers Squibb, Boehringer-Ingelheim, Celgene, Dermira, Eli Lilly, Galderma, Hexal AG, Incyte Inc., Janssen-Cilag, Johnson & Johnson, Klinge Pharma, Kymab, Leo Pharma, Medac, MSD, Neubourg Skin Care GmbH, Novartis, Pfizer, Principia Biopharma, Regeneron, Sandoz, Sanofi, UCB Pharma. Katja Nemat has received lecture and/or consultancy fees from Sanofi, Stallergenes, Berlin-Chemie and HAL. Susanne Lau has received grants from Novartis, DBV, Infectopharm and honoraria from ALK, Allergopharma, Boehringer, GSK, LEO Pharma, Nutricia, Lilly, Viatris, GSK, and Sanofi-Aventis. Annice Heratizadeh reports personal fees from AbbVie, Almirall, ALK, LEO Pharma, Novartis, Pierre Fabre, Klinge Pharma, Sanofi, Beiersdorf, Hans Karrer, Nutricia, Meda, and Lilly; and grants from Janssen and Pfizer. Andreas Wollenberg has received institutional research grants, consulting fees and/or study support from Abbvie, Aileens, Almirall, Beiersdorf, Galapagos, Galderma, Glenmark, GSK, Janssen, LEO Pharma, Eli Lilly, L'Oreal, MedImmune, MSD, Novartis, Pfizer, Pierre Fabre, Regeneron, Sanofi and UCB. Jochen Schmitt reports institutional grants for investigator-initiated research from the German Federal Joint Committee, German Ministry of Health, German Ministry of Research, European Union, German Federal State of Saxony, Novartis, Sanofi, ALK, and Pfizer. He participated in advisory board meetings as a paid consultant for Sanofi, Lilly, and ALK. Prof. Schmitt serves the German Ministry of Health as a member of the German National Council for Health and Care. Thomas Werfel has received institutional grants from LEO Pharma and Novartis, has performed consultancies for Abbvie, Almirall, Janssen, Galderma, LEO, Lilly, Novartis, Pfizer and Sanofi-Regeneron and has lectured at events sponsored by Abbvie, Janssen, Celgene, Galderma, LEO Pharma, Lilly, Sanofi and Novartis. Stephan Weidinger has received institutional research grants from LEO, Pfizer and Sanofi; has been an advisor and/or received speakers' honoraria from AbbVie, Almirall, Boehringer, Eli Lilly, Galderma, LEO Pharma, Pfizer, Sanofi, and Regeneron; has participated in clinical trials of AbbVie, Almirall, Anaptys Bio, Boehringer-Ingelheim, Eli Lilly, Galderma, GSK, Incyte Inc., Janssen-Cilag, Kymab, Leo Pharma, Pfizer, Regeneron, Sanofi, UCB. All of the other authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

D. Stölzl[1]
N. Sander[1]
D. Siegels[2]
I. Harder[1]
B. Kind[2]
M. Fonfara[1]
L. Heinrich[2]
Hagen Ott[3]
S. Abraham[4]
I. Neustädter[5]
A. Kleinheinz[6]
S. Gerdes[1]
A. Wollenberg[7,8]
S. Lau[9]
K. Nemat[10]
A. Heratizadeh[11]
I. Gellhaus[12]
T. Werfel[11]
J. Schmitt[2]
S. Weidinger[1]
the TREATgermany study group

[1]*Department of Dermatology and Allergy, University Hospital Schleswig-Holstein, Campus Kiel, Germany*
[2]*Center for Evidence-Based Healthcare, University Hospital Carl Gustav Carus, Technical University, Dresden, Germany*
[3]*Department of Pediatric Dermatology, Children's Hospital Auf Der Bult, Academic Hospital, Hannover, Germany*
[4]*Department of Dermatology, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany*
[5]*Cnopfsche Children's Hospital/Neonatology, Pediatrics, DIAKONEO KdöR, Nuremberg, Germany*
[6]*Clinics for Dermatology, Elbe Klinikum Buxtehude, Buxtehude, Germany*
[7]*Clinics and Outpatient Clinics for Dermatology and Allergy, LMU Munich, Munich, Germany*
[8]*Department of Dermatology and Allergy, University Hospital Augsburg, Augsburg, Germany*
[9]*Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany*
[10]*Praxis für Kinderpneumologie/Allergologie, Kinderzentrum Dresden-Friedrichstadt, Dresden, Germany*
[11]*Division of Immunodermatology and Allergy Research, Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany*
[12]*Rehaforschung Nord e.V, Sylt, Germany*

Correspondence
S. Weidinger, Department of Dermatology and Allergy, University Hospital Schleswig-Holstein, Campus Kiel, Germany.
Email: sweidinger@dermatology.uni-kiel.de

D. Stölzl, N. Sander, and D. Siegels equally contributing first authors.
T. Werfel, J. Schmitt, and S. Weidinger equally contributing senior authors.

ORCID

D. Stölzl https://orcid.org/0000-0001-7321-7305
N. Sander https://orcid.org/0000-0001-9084-7069
D. Siegels https://orcid.org/0000-0002-4049-9120
I. Harder https://orcid.org/0000-0002-3079-0440
B. Kind https://orcid.org/0009-0002-5254-6411
M. Fonfara https://orcid.org/0009-0000-9729-0494
L. Heinrich https://orcid.org/0009-0002-2878-2019
S. Lau https://orcid.org/0000-0002-5189-4265
T. Werfel https://orcid.org/0000-0001-6830-7672
J. Schmitt https://orcid.org/0000-0003-0264-0960
S. Weidinger https://orcid.org/0000-0003-3944-252X

REFERENCES

1. Stölzl D, Sander N, Heratizadeh A, et al. Real-world data on the effectiveness, safety and drug survival of dupilumab: an analysis from the TREATgermany registry. *Br J Dermatol*. 2022;187:1022-1024.
2. Kamphuis E, Boesjes CM, Loman L, et al. Dupilumab in daily practice for the treatment of pediatric atopic dermatitis: 28-week clinical and biomarker results from the BioDay registry. *Pediatr Allergy Immunol*. 2022;33:33. doi:10.1111/PAI.13887
3. Xu Y, Guo L, Li Z, Wu S, Jiang X. Efficacy and safety profile of dupilumab for the treatment of atopic dermatitis in children and adolescents: a systematic review and meta-analysis. *Pediatr Dermatol*. 2023;40:841-850.
4. Josse J, Laurent F, Diot A. Staphylococcal adhesion and host cell invasion: fibronectin-binding and other mechanisms. *Front Microbiol*. 2017;8:8. doi:10.3389/FMICB.2017.02433
5. Cambier S, Gouwy M, Proost P. The chemokines CXCL8 and CXCL12: molecular and functional properties, role in disease and efforts towards pharmacological intervention. *Cell Mol Immunol*. 2023;20:217-251.
6. Yu L, Li L. Potential biomarkers of atopic dermatitis. *Front Med (Lausanne)*. 2022;9:9. doi:10.3389/FMED.2022.1028694

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.