Dupilumab Provides Acceptable Long-Term Safety and Efficacy in Children Aged ≥ 6 to < 12 Years With Uncontrolled, Severe Atopic Dermatitis: Results From Patients Who Participated in an Open-Label Phase 2a Study and Then in a Subsequent Phase 3 Open-Label Extension Study

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INTRODUCTION

- Children with severe atopic dermatitis (AD) have limited treatment options with an acceptable benefit–risk profile[1–3]
  - Systemic corticosteroids are strongly discouraged in children[4]
  - Other systemic agents are used off-label and do not have an acceptable benefit–risk profile for children who use these therapies on a long-term basis[5]
- Dupilumab, a fully human monoclonal antibody,[6,7] blocks the shared receptor component for interleukin (IL)-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13, key cytokines involved in atopic diseases such as AD
- Adolescents with moderate-to-severe AD who received dupilumab in a phase 2a study and continued in an open-label extension (OLE) phase 3 study showed improvement in AD signs with an acceptable safety profile with over 52 weeks of total treatment[8]

OBJECTIVE

- **Here we report dupilumab pharmacokinetics (PK), safety, and efficacy in children aged ≥ 6 to < 12 years who participated in the phase 2a study, and then continued into the phase 3 OLE study**

METHODS

Study design

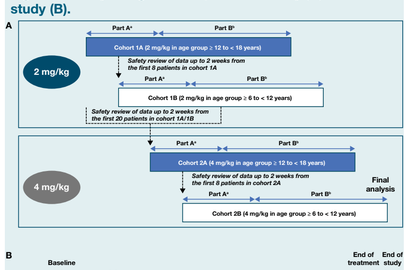
- The first study was a phase 2a, multicenter, open-label, ascending dose, sequential cohort study (NCT02407756)
  - The study had 2 treatment parts: in Part A, patients received a single dose of dupilumab (2mg/kg or 4mg/kg), followed by an 8-week follow-up sampling period for systemic drug concentration without treatment; this was followed by Part B, where patients received 4 weekly (qw) doses, followed by an 8-week safety follow-up period (**Figure 1A**)
  - An initial cohort of adolescents (aged ≥ 12 to < 18 years) with moderate-to-severe AD was enrolled; upon safety review of part A, a cohort of children (aged ≥ 6 to < 12 years) was enrolled for the corresponding dose group (**Figure 1A**)
- The second study is an ongoing, phase 3, OLE study (NCT02612454) enrolling pediatric patients who participated in previous dupilumab AD trials (**Figure 1B**)
  - Patients with a serious treatment-emergent adverse event (TEAE) deemed related to the study drug or with a TEAE related to study drug which led to discontinuation were not eligible to enroll in the OLE study
  - Patients continued on their original assigned regimen (2 mg/kg or 4 mg/kg qw)
- Here we present data from the patient population consisting of children who continued from the phase 2a study and received their original assigned regimen (2 mg/kg qw or 4 mg/kg qw, up to a maximum of 300 mg) in the OLE study

Endpoints

- Primary endpoints
  - Concentration–time profile (phase 2a study) of dupilumab, including PK parameters such as the area under the concentration time curve from 0 to the last measurable concentration (AUC_{last}), maximal concentration (c_{max}), and time to c_{max} (t_{max})
  - Incidence and rate of adverse events (phase 3 OLE study)

METHODS (CONT.)

Figure 1. Study design for the phase 2a study (A) and OLE study (B).



[a]Part A: single dose followed by an 8-week follow-up period with semi-dense sampling for systemic drug concentration. [b]Part B: 4 weekly doses followed by an 8-week safety follow-up period. [c]On visits in which study drug administration was planned, patients had the option to come to the clinic to have study drug administered by site staff. [d]In-clinic visits occurred every 3 months.
D, day; W, week.

- Secondary endpoints (phase 2a and phase 3 OLE study)
  - Percent change from baseline in Eczema Area and Severity Index (EASI)
  - Percent change in Peak Pruritus Numerical Rating Scale (NRS)
  - Proportion of patients achieving an Investigator's Global Assessment (IGA) score of 0 or 1

Analysis

- PK, safety, and efficacy variables were summarized descriptively
  - The analysis set for all statistical analyses for both studies included all patients who received any study drug
  - Patients in the PK population had to have ≥ 1 non-missing functional dupilumab result following the first dose of the study drug; only observed data were used for PK analyses, and data were set to missing if PK drug concentrations were not available
- For phase 2a efficacy analyses, data after rescue treatment use during Part B were set to missing
  - Missing values during the first 4-week repeat-dose treatment period of Part B up to end-of-treatment visit were imputed by the last observation carried forward method; after the end of treatment in Part B, no imputation of missing data was made
- For the phase 3 OLE, an all-observed method was employed, regardless of whether rescue treatment was used or data were collected after withdrawal from study treatment; no missing values were imputed

RESULTS

- 37 children completed the phase 2a study (the safety analysis set), of whom 33 continued to the OLE
- Baseline demographic and disease characteristics are shown in **Table 1**

RESULTS (CONT.)

Table 1. Baseline demographics and disease characteristics.

	Phase 2a study		Phase 3 OLE study	
	Dupilumab 2 mg/kg (n = 18)	Dupilumab 4 mg/kg (n = 19)	Dupilumab 2 mg/kg (n = 17)	Dupilumab 4 mg/kg (n = 16)
Age, mean (SD), years	8 (2)	8 (2)	9 (2)	8 (2)
Male sex, n (%)	9 (50)	11 (58)	8 (47)	9 (56)
BMI, mean (SD), kg/m^2	17.5 (2.8)	16.8 (2.0)	16.9 (3.0)	17.0 (2.2)
Duration of AD, mean (SD), years	7 (2)	7 (2)	7 (3)	8 (2)
EASI, mean (SD)	33 (16)	39 (19)	21 (18)	32 (20)
IGA, n (%)				
IGA = 3	1 (6)[a]	0	9 (53)	7 (44)
IGA = 4	17 (94)	19 (100)	4 (24)	8 (50)
Peak Pruritus NRS, mean (SD)	6 (2)	7 (2)	6 (3)	6 (2)
Percent BSA affected, mean (SD)	59 (22)	62 (30)	37 (27)	50 (31)
Any previous non-corticosteroid immunosuppressants, n (%)	3 (17)	7 (37)	N/A	N/A
Patients with comorbid atopic allergic conditions, n (%)	14 (78)	17 (90)	N/A	N/A
Allergic rhinitis	9 (50)	10 (53)	N/A	N/A
Food allergy	10 (56)	14 (74)	N/A	N/A
Asthma	7 (39)	9 (47)	N/A	N/A
Allergic conjunctivitis	3 (17)	5 (26)	N/A	N/A
Chronic rhinosinusitis	0	1 (5)	N/A	N/A
Urticaria	1 (6)	0	N/A	N/A
Other allergies	12 (67)	12 (63)	N/A	N/A

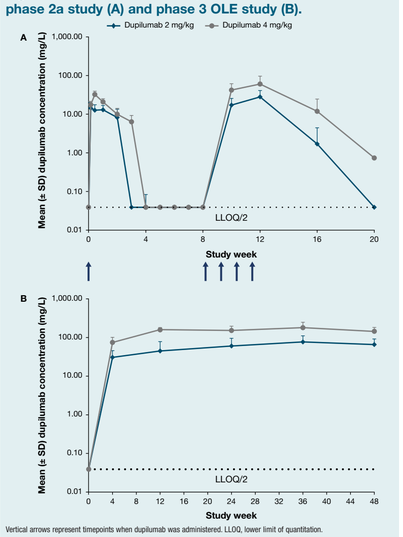
[a]1 patient from this age group enrolled in the study had a baseline disease severity of IGA = 3 but was still included in the analyses sets.
BMI, body mass index; BSA, body surface area; N/A, not applicable; SD, standard deviation.

- Mean pruritus scores showed moderate or severe pruritus at the baseline of the phase 2a study
- A significant proportion of patients received systemic non-steroidal immunosuppressants prior to the baseline of the phase 2a study
- Most patients had other concomitant allergic diseases, including asthma, allergic rhinitis, and food allergies

PK assessment

- Following a single subcutaneous dose of dupilumab on Day 1 of the phase 2a study, AUC_{last} calculated from the mean concentration–time profile in serum was 160 day·mg/L and 330 day·mg/L for the 2 and 4 mg/kg groups, respectively
  - In the 2 mg/kg group, t_{max} was observed at 2 days after dosing with a c_{max} (± SD) of 14.3 mg/L (5.9), while in the 4 mg/kg group, t_{max} was observed 4 days after dosing with a c_{max} (± SD) of 32.4 mg/L (7.0) (**Figure 2A**)
- In the OLE study, steady-state dupilumab trough mean (± SD) concentrations at Weeks 24–48 ranged from 61.3 mg/L (35.0) to 76.8 mg/L (35.8) in the 2 mg/kg qw group and 143 mg/L (40.3) to 181 mg/L (65.9) in the 4 mg/kg qw group (**Figure 2B**)
- The overall PK profile was comparable to that seen in adults and adolescents, and characterized by nonlinear, target-mediated kinetics

Figure 2. Concentration–time profiles of dupilumab in the phase 2a study (A) and phase 3 OLE study (B).



Vertical arrows represent timepoints when dupilumab was administered. LLOQ, lower limit of quantitation.

Safety

- Phase 2a study (**Table 2**)
  - The majority of reported TEAEs in the phase 2a study were of mild or moderate severity; 14% patients reported a severe TEAE
  - 2 (5%) patients experienced a serious TEAE, both in the 4 mg/kg dose group during Part A, with the serious adverse events deemed unrelated to dupilumab
  - There were no permanent treatment discontinuations due to TEAEs
  - The most frequent TEAEs were nasopharyngitis and AD exacerbation
- In the phase 3 OLE (**Table 2**)
  - 2 (12%) and 3 (19%) patients reported ≥ 1 serious TEAE in the 2 mg/kg and 4 mg/kg dose groups, respectively; none of these events were related to treatment, and none led to discontinuation of study drug
  - The most common TEAEs were nasopharyngitis and AD exacerbation
  - Conjunctivitis was reported in a total of 7 patients: 2 (12%) and 5 (31%) in the 2 mg/kg and 4 mg/kg groups, respectively
- Dupilumab treatment for up to 52 weeks was well tolerated with a acceptable safety profile consistent with the known dupilumab safety profile from studies in adolescents and adults with moderate-to-severe AD

Table 2. Safety assessment.

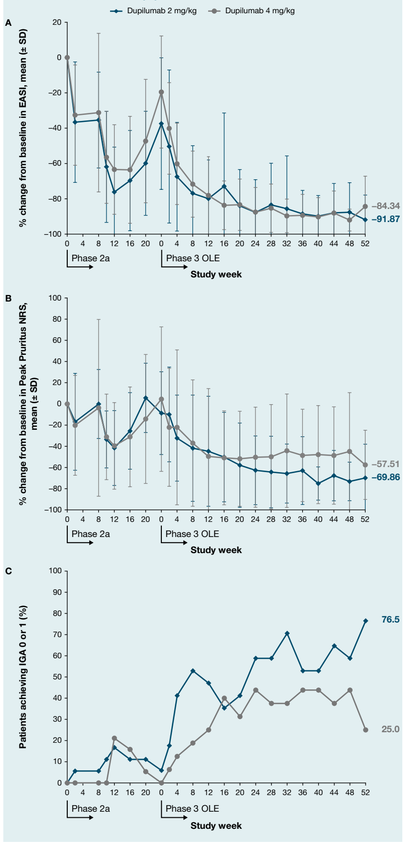
	Phase 2a study				Phase 3 OLE study			
	Dupilumab 2 mg/kg (n = 18)		Dupilumab 4 mg/kg (n = 19)		Dupilumab	Dupilumab	Dupilumab	Dupilumab
	Part A	Part B	Part A	Part B	2 mg/kg (n = 17)	4 mg/kg (n = 16)	2 mg/kg (n = 17)	4 mg/kg (n = 16)
Patients with TEAEs	n (%)				n (%)		nP/100 PY	
Any TEAE	9 (50)	10 (56)	16 (84)	17 (89)	16 (94)	16 (100)	266	471
Any serious TEAE	0	0	2 (11)	0	2 (12)	3 (19)	6	11
TEAEs related to treatment	0	1 (6)	3 (16)	3 (16)	4 (24)	2 (13)	13	7
TEAEs leading to discontinuation	0	0	0	0	0	0	0	0
Any infection (SOC)	6 (33)	8 (44)	10 (53)	12 (63)	12 (71)	15 (94)	98	209
Skin infection (HLT)	1 (6)	1 (6)	7 (37)	5 (26)	5 (29)	6 (38)	17	25
Non-herpetic skin infection (adjudicated)	1 (6)	1 (6)	6 (32)	5 (26)	4 (24)	3 (19)	12	11
Herpes viral infection (HLT)	1 (6)	0	1 (5)	0	2 (12)	4 (25)	6	15
Injection-site reaction (HLT)	0	0	1 (5)	1 (5)	2 (12)	1 (6)	5	3
Conjunctivitis[a]	0	0	1 (5)	2 (11)	2 (12)	5 (31)	5	21
Most common TEAEs (PT)[b]								
Nasopharyngitis	3 (17)	4 (22)	6 (32)	4 (21)	8 (47)	9 (56)	35	37
Dermatitis atopic	4 (22)	4 (22)	5 (26)	3 (16)	5 (29)	2 (13)	16	7
Cough	0	1 (6)	5 (26)	3 (16)	2 (12)	5 (31)	6	20
Dermatitis infected	1 (6)	0	3 (16)	2 (11)	2 (12)	0	5	0
Headache	0	1 (6)	2 (11)	1 (5)	4 (24)	2 (13)	13	7
Upper respiratory tract infection	0	1 (6)	0	1 (5)	2 (12)	4 (25)	6	16
Herpes simplex	0	0	0	0	0	4 (25)	0	15

[a]Includes MedDRA conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis, conjunctivitis viral, atopic keratoconjunctivitis. [b]Includes all MedDRA PTs reported in ≥ 15% or ≥ 20% of patients in any treatment group of the phase 2a study or OLE, respectively.
HLT, MedDRA High Level Term; MedDRA, Medical Dictionary for Regulatory Activities; nP/100 PY, number of patients with ≥ 1 event per 100 patient-years; PT, MedDRA Preferred Term; SOC, MedDRA System Organ Class.

Efficacy

- Mean EASI improved at Week 2 of the phase 2a, after a single dupilumab dose, and continued to improve through to Week 52 of OLE (**Figure 3A**)
- Mean NRS improved at Week 2 (phase 2a with improvements seen through Week 52 of OLE (**Figure 3B**)
- By Week 12 of the phase 2a study, 17% and 21% patients in the 2 and 4 mg/kg groups, respectively, achieved IGA 0/1, with proportions further increasing to 76% and 25%, respectively, at Week 52 of OLE (**Figure 3C**)
- Some loss of efficacy is observed between Weeks 48 and 52 due to 3 patients in the 4 mg/kg group temporarily discontinuing dupilumab
- AD signs and symptoms, including pruritus, showed rapid improvements with single-dose dupilumab in the phase IIa study. Improvements in clinical scores (EASI, SCORAD) and Peak Pruritus NRS were observed as early as week 2, with further improvement on continued treatment up to week 52 in the OLE

Figure 3. Efficacy assessment. Mean percent change from baseline in EASI (A); mean percent change from baseline in Peak Pruritus NRS (B); and proportion of patients achieving IGA scores of 0 or 1 (C).



CONCLUSION

- **Safety and efficacy results support the use of dupilumab as a continuous long-term treatment for children aged ≥ 6 to < 12 years with severe AD**

References: 1. Wollenberg A, et al. J Eur Acad Dermatol Venereol 2016;30:729–47. 2. Sidbury R, et al. J Am Acad Dermatol 2014;71:327–49. 3. Ring J, et al. J Eur Acad Dermatol Venereol. 2012;26:1176-93. 4. Drucker AM, et al. Br J Dermatol. 2018; 178:768-75. 5. Totri CR, et al. J Am Acad Dermatol. 2017; 76:281-5. 6. Macdonald LE, et al. Proc Natl Acad Sci U S A. 2014;111:5147-52. 7. Murphy AJ, et al. Proc Natl Acad Sci U S A. 2014;111:5153-8. 8. Cork MJ, et al. Br J Dermatol. 2020;182:85-96.

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