Pharmacokinetics, Safety, and Efficacy of Dupilumab in a Pediatric Population with Moderate-to-Severe Atopic Dermatitis: Results from an Open-Label Phase 2a Trial

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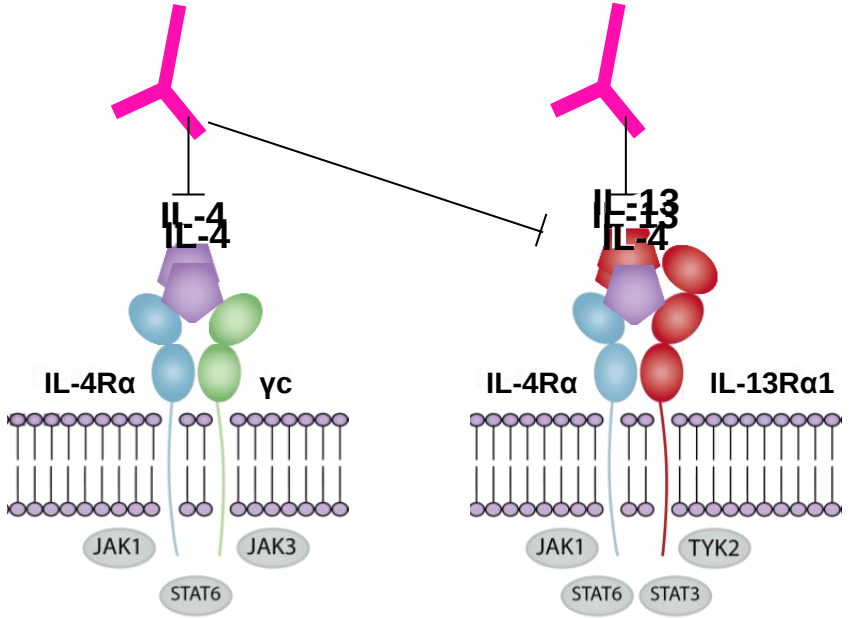
Dupilumab is not currently approved for labeling or advertising by the FDA

Dupilumab Mechanism of Action

- **Dupilumab is a potent blocker of IL-4 and IL-13 pathways**
- **IL-4 and IL-13 are type 2 (Th2) cytokines that mediate many features of AD as well as asthma and other atopic and allergic diseases**
- **AD is more Th2-driven in pediatric patients than in adults[1]**



Type I receptor

B cells, T cells, monocytes, eosinophils, fibroblasts

Type II receptor

Epithelial cells, smooth muscle cells, fibroblasts, monocytes, activated B cells

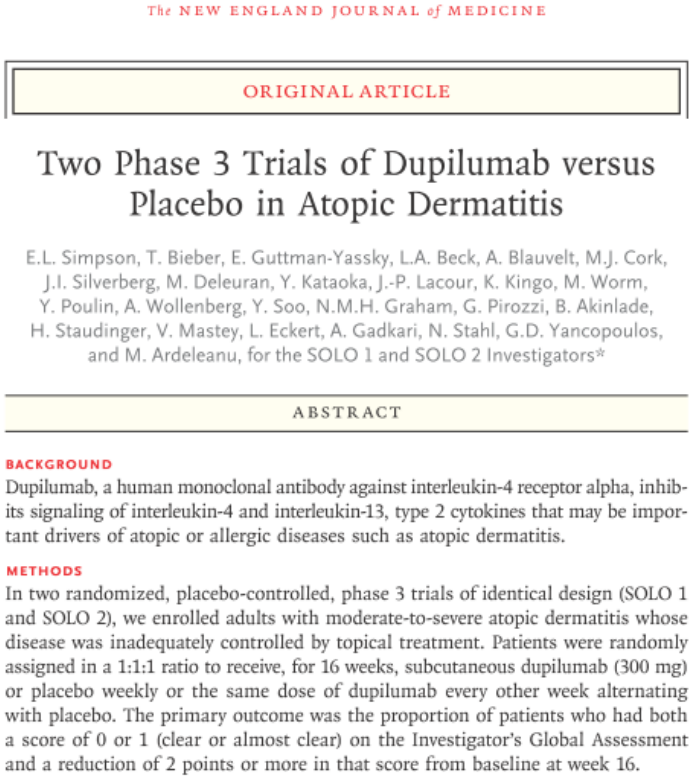
γc, common gamma chain; IL, interleukin; IL-4Rα, IL-4 receptor alpha; IL-13Rα, IL-13 receptor alpha; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TYK2, tyrosine kinase type 2.

1. Czarnowicki T et al., J Allergy Clin Immunol. 2015 Oct;136(4):941-951.e3

Dupilumab Efficacy and Safety in Adults

- In two pivotal phase 3 trials, dupilumab monotherapy reduced signs and symptoms in adults with AD and had a favorable safety profile[1]

- Dupilumab has also shown efficacy in patients with uncontrolled persistent asthma[2] and in patients with chronic sinusitis with nasal polyposis[3]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis

E.L. Simpson, T. Bieber, E. Guttman-Yassky, L.A. Beck, A. Blauvelt, M.J. Cork, J.I. Silverberg, M. Deleuran, Y. Kataoka, J.-P. Lacour, K. Kingo, M. Worm, Y. Poulin, A. Wollenberg, Y. Soo, N.M.H. Graham, G. Pirozzi, B. Akinlade, H. Staudinger, V. Mastey, L. Eckert, A. Gadkari, N. Stahl, G.D. Yancopoulos, and M. Ardeleanu, for the SOLO 1 and SOLO 2 Investigators*

ABSTRACT

BACKGROUND

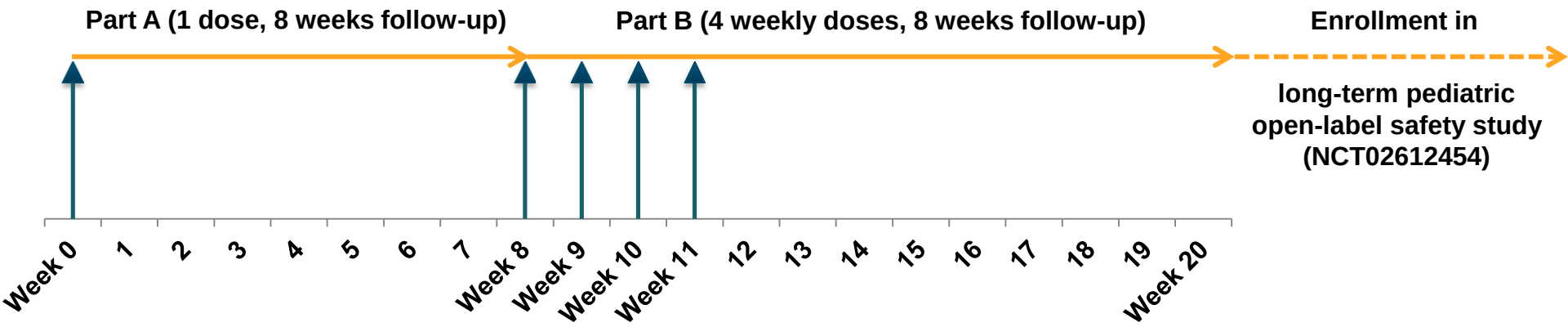
Dupilumab, a human monoclonal antibody against interleukin-4 receptor alpha, inhibits signaling of interleukin-4 and interleukin-13, type 2 cytokines that may be important drivers of atopic or allergic diseases such as atopic dermatitis.

METHODS

In two randomized, placebo-controlled, phase 3 trials of identical design (SOLO 1 and SOLO 2), we enrolled adults with moderate-to-severe atopic dermatitis whose disease was inadequately controlled by topical treatment. Patients were randomly assigned in a 1:1:1 ratio to receive, for 16 weeks, subcutaneous dupilumab (300 mg) or placebo weekly or the same dose of dupilumab every other week alternating with placebo. The primary outcome was the proportion of patients who had both a score of 0 or 1 (clear or almost clear) on the Investigator's Global Assessment and a reduction of 2 points or more in that score from baseline at week 16.

1. Simpson EL et al., N Engl J Med. 2016;375(24):2335-2348; 2. Wenzel S et al., Lancet 2016;388:31-44; 3. Bachert C et al., JAMA 2016;315:469-79

Study Design: Five Dupilumab Doses (NCT02407756)



Phase 2a, open-label, ascending-dose, sequential-cohort trial among AD patients failing TCS; 19.5% had failed non-steroid systemic medications

4 cohorts

- Two age groups: 6–11 years (IGA = 4) and 12–17 years (IGA = 3 or 4)
- Two dose levels in each age group: 2 mg/kg and 4 mg/kg

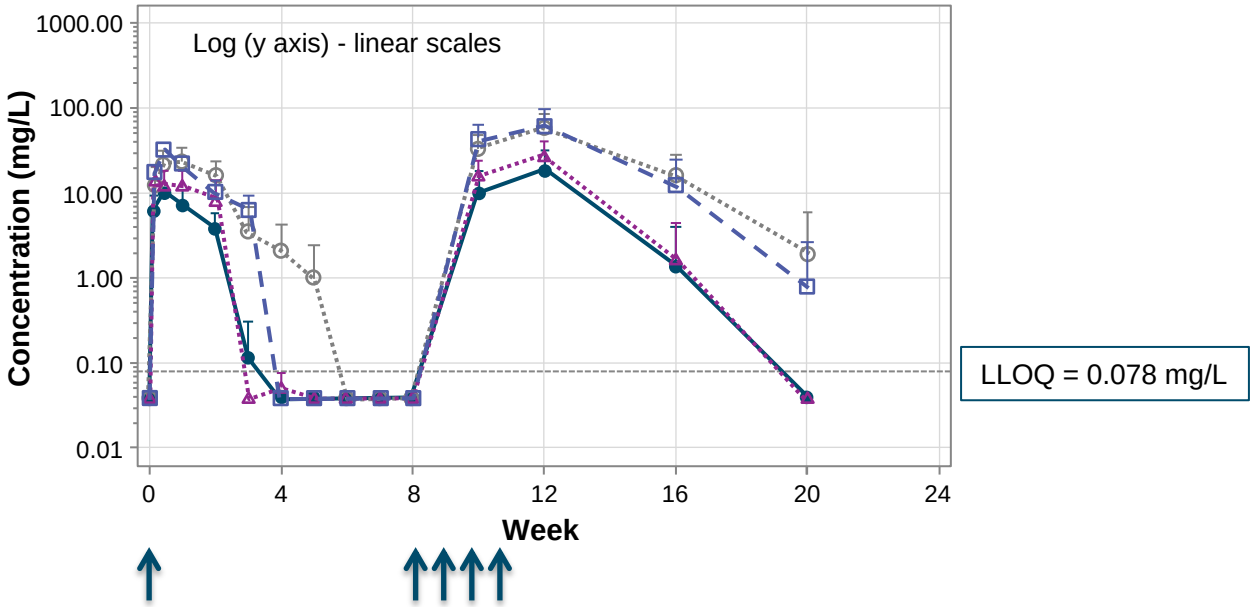
Note: Vertical arrows show the time points when the five dupilumab doses were administered.

Study Endpoints

- Primary endpoint
  - Characterization of the PK profile of dupilumab in pediatric patients with AD
- Key secondary endpoints
  - Incidence of AEs
  - Percent change from baseline in EASI score
  - Percent change from baseline in peak pruritus NRS score

EASI, Eczema Area and Severity Index; NRS, Numerical Rating Scale; PK, pharmacokinetics.

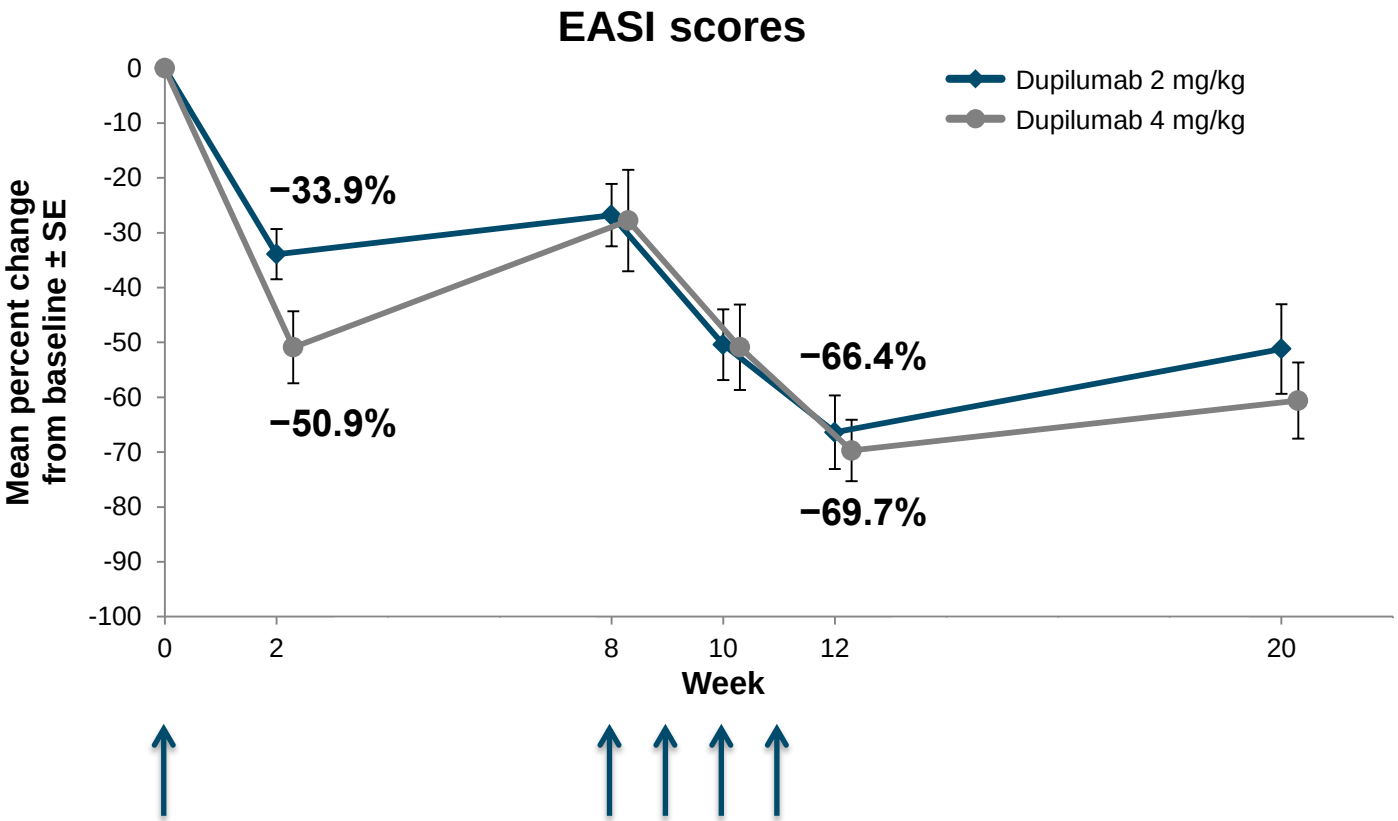
Pharmacokinetics of Functional Dupilumab in Pediatric Patients



	Adolescents (aged 12–17 years)		Children (aged 6–11 years)	
	2 mg/kg	4 mg/kg	2 mg/kg	4 mg/kg
AUC_{last} (day x mg/L)	104	362	160	330

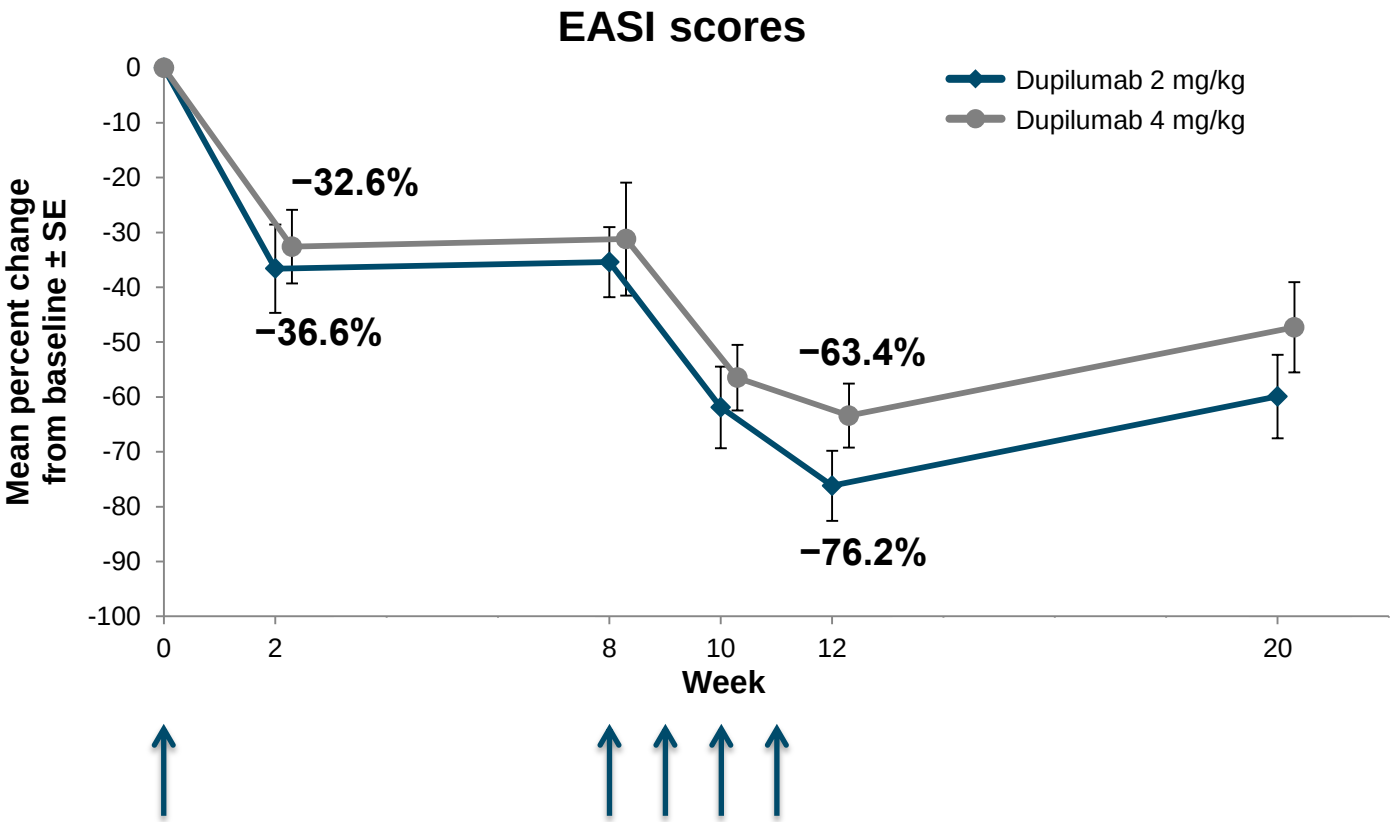
Note: Arrows show the time points when the five dupilumab doses were administered. LLOQ: lower limit of quantitation.

Dupilumab Improved EASI Scores in Adolescents (Aged 12–17 Years)



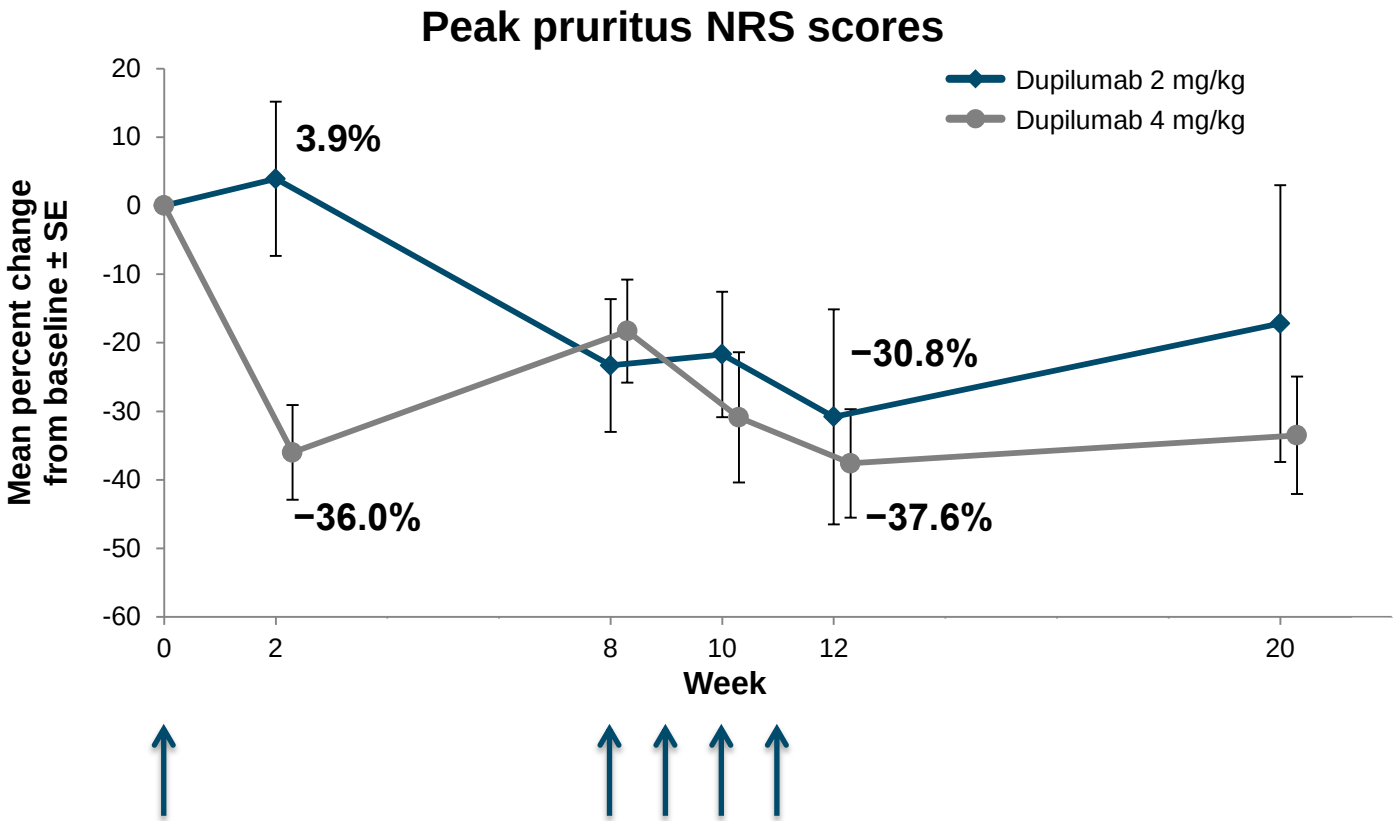
Note: Arrows show the time points when the five dupilumab doses were administered.

Dupilumab Improved EASI Scores in Children (Aged 6–11 Years)



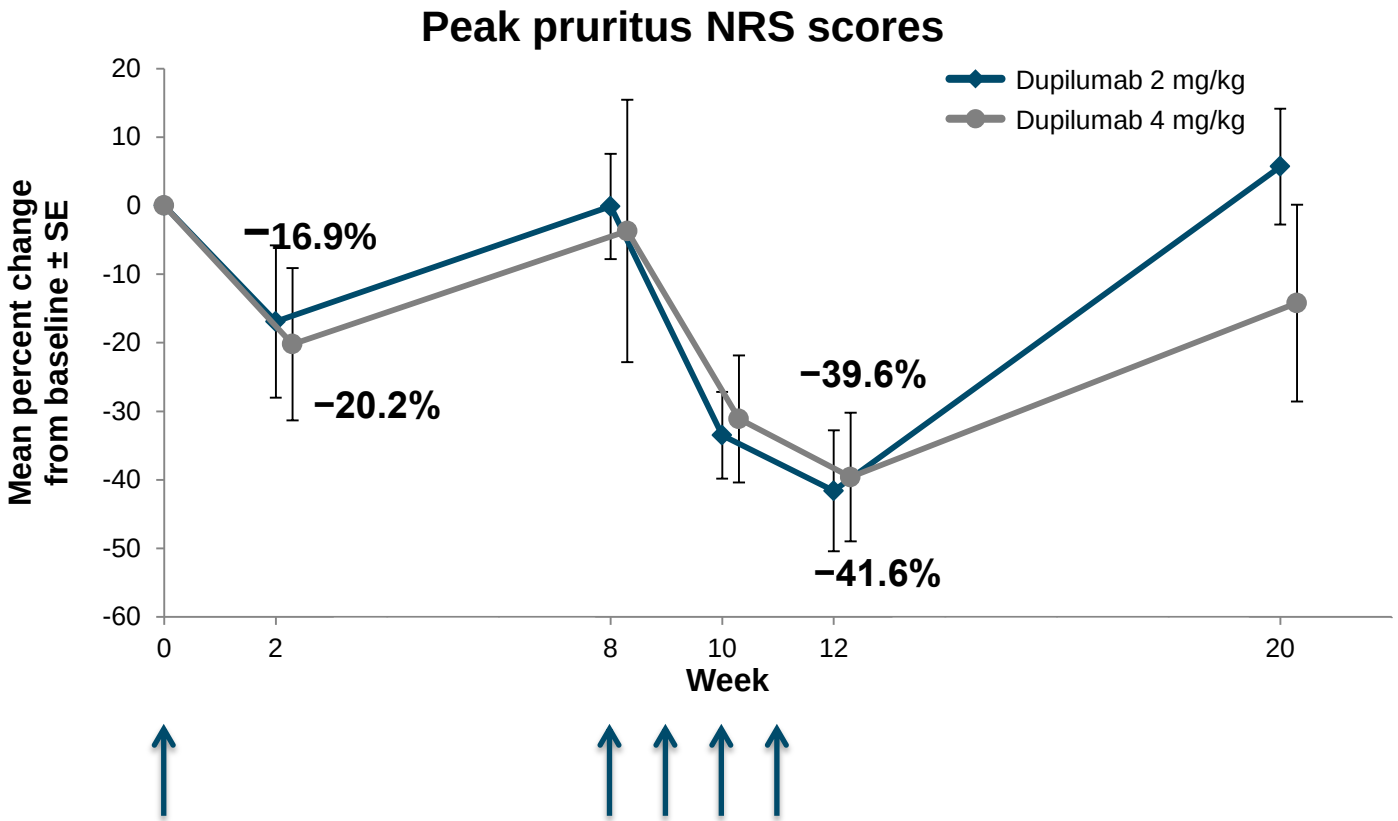
Note: Arrows show the time points when the five dupilumab doses were administered

Dupilumab Improved Peak Pruritus NRS in Adolescents (Aged 12–17 Years)



Note: Arrows show the time points when the five dupilumab doses were administered.

Dupilumab Improved Peak Pruritus NRS in Children (Aged 6–11 Years)



Note: Arrows show the time points when the five dupilumab doses were administered.

Key Safety Parameters – Adolescents (Aged 12–17 Years)

	2 mg/kg n = 20		4 mg/kg n = 20	
	Part A period	Part B period	Part A period	Part B period
Total AEs, n	19	16	40	31
Total SAEs, n	1	1	1	1
Total AEs related to treatment, n	0	2	6	5
Total AEs related to permanent treatment discontinuation, n	0	1	0	0
Patients with, n (%)				
Any AE	10 (50)	8 (40)	13 (65)	11 (55)
Any SAE	1 (5)	1 (5)	1 (5)	1 (5)
AEs related to treatment	0	0	2 (10)	3 (15)
AEs leading to discontinuation	0	1 (5)	0	0
Any infection (SOC)	3 (15)	3 (15)	8 (40)	8 (40)
Skin infection (adjudicated)	0	1 (5)	3 (15)	3 (15)
Nasopharyngitis (PT)	1 (5)	2 (10)	6 (30)	4 (20)
Dermatitis atopic (PT)	2 (10)	0 (0)	3 (15)	1 (5)
Injection-site reactions (HLT)	0	1 (5)	1 (5)	0
Conjunctivitis (PT)	0	0	0	0

AE, adverse event; HLT, MedDRA high-level term; PT, MedDRA preferred term; SAE, serious adverse event; SOC, MedDRA system organ class.

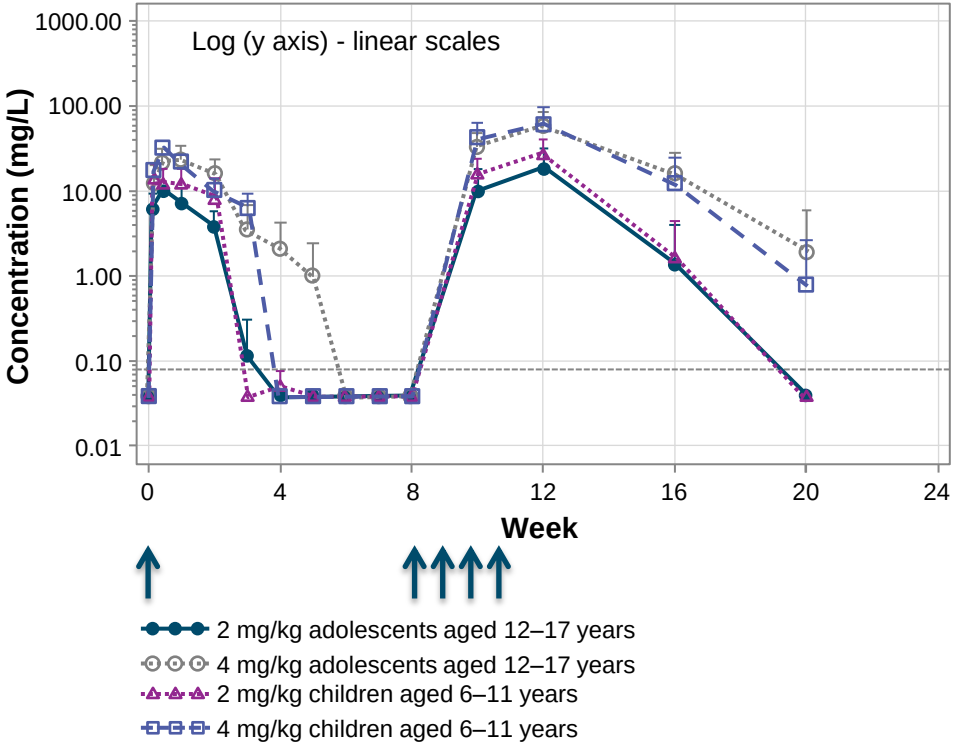
Key Safety Parameters – Children (Aged 6–11 Years)

	2 mg/kg n = 18		4 mg/kg n = 19	
	Part A period	Part B period	Part A period	Part B period
Total AEs, n	18	23	47	47
Total SAEs, n	0	0	3	0
Total AEs related to treatment, n	0	1	4	4
Total AEs related to permanent treatment discontinuation, n	0	0	0	0
Patients with, n (%)				
Any AE	9 (50.0)	10 (55.6)	16 (84.2)	17 (89.5)
Any SAE	0	0	2 (10.5)	0
AEs related to treatment	0	1 (5.6)	3 (15.8)	3 (15.8)
AEs leading to discontinuation	0	0	0	0
Any infection (SOC)	6 (33.3)	6 (33.3)	10 (52.6)	8 (40)
Skin infection (adjudicated)	1 (5.6)	1 (5.6)	7 (36.8)	4 (21.1)
Nasopharyngitis (PT)	3 (16.7)	4 (22.2)	6 (31.6)	3 (15.8)
Dermatitis atopic (PT)	4 (22.2)	4 (22.2)	5 (26.3)	1 (5.3)
Injection-site reactions (HLT)	0	0	1 (5.3)	1 (5.3)
Conjunctivitis (PT)	0	0	0	2 (10.6)

AE, adverse event; HLT, MedDRA high-level term; PT, MedDRA preferred term; SAE, serious adverse event; SOC, MedDRA system organ class.

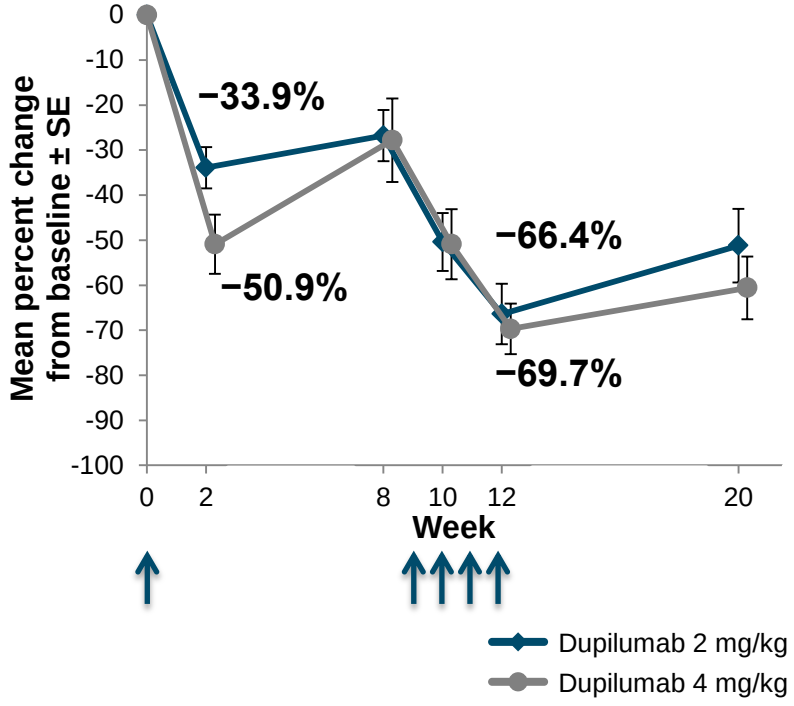
Summary: Dupilumab PK Exposure is Reflected in Improvements in Clinical Endpoints

Pharmacokinetics of functional dupilumab



Note: Arrows show the time points when the five dupilumab doses were administered.

EASI scores in adolescents (12-17 years)



Conclusions

- These are the first available data from use of dupilumab as repeated doses in pediatric patients aged ≥6 to <18 years
- Dupilumab administered both as single dose or as multiple weekly doses appeared safe and demonstrated preliminary efficacy in this open-label study
- Overall the PK profile of dupilumab in these pediatric patients with AD is generally consistent with that observed in adults with moderate-to-severe AD; exposure was comparable between the two age groups studied at the same dose levels
- The 2 mg/kg and 4 mg/kg dose regimens showed similar improvements in efficacy endpoints; while the 4 mg/kg dose was associated with more AEs, it did not lead to an increase in permanent discontinuations
- These data are very promising and support further development of dupilumab for use in adolescents and children ≥6 to <12 years of age
- Further characterization of the therapeutic profile of dupilumab in pediatric populations will be conducted in future phase 3 trials