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Dupilumab Improves Lung Function and Reduces Exacerbation Frequency and IgE Levels in Patients With Asthma and Allergic Bronchopulmonary Aspergillosis (Phase 2 LIBERTY ABPA AIRED Study)

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Background

- Allergic bronchopulmonary aspergillosis (ABPA) is a rare progressive lung disease that is characterized primarily by hypersensitivity to, and airway colonization with, *Aspergillus fumigatus* in patients with asthma and a robust type 2 inflammatory response, increased IgE levels, and elevated blood eosinophil counts[1–3]
- ABPA affects 2.5% of asthma patients globally[1]
- Standard treatment is SCS, plus adjunctive antifungals in patients with poor steroid response[2,4,5]
  - Many patients become steroid dependent, and long-term use is not recommended
  - Response to adjunctive antifungals is variable

1. Denning DW, et al. Med Mycol. 2013;51:361-70. 2. Agarwal R, et al. Clin Chest Med. 2022;43:99-125. 3. Agarwal R, et al. Eur Respir J. 2024;63:2400061.
4. Knutsen AP, Slavin RG. Clin Dev Immunol. 2011;2011:843763. 5. Agbetile J, et al. J Allergy Clin Immunol. 2014;134:33-9.
ABPA, allergic bronchopulmonary aspergillosis; IgE, immunoglobulin E; SCS, systemic corticosteroid(s).

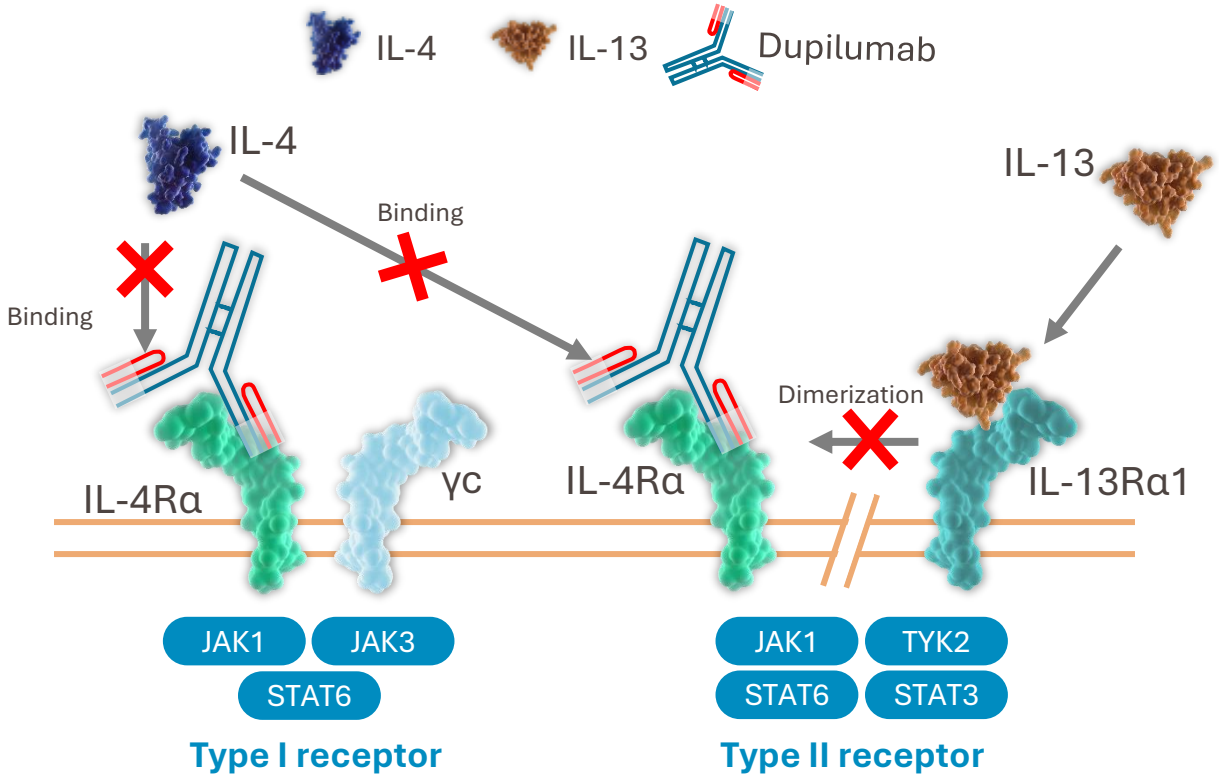
Background

- Clinically, patients with asthma and ABPA experience clinical outcomes of greater severity than those without ABPA, highlighting the need for treatments that address the immunological basis of ABPA
- Dupilumab is a fully human monoclonal antibody that blocks the shared receptor component for IL-4 and IL-13, key drivers of type 2 inflammation in multiple diseases[1–3]
- Dupilumab efficacy in diseases involving type 2 inflammation has been demonstrated in phase 3 clinical trials for AD,[4] CRSwNP,[5] EoE[6] , and asthma[7]
- Therefore, dupilumab may have the potential to treat ABPA, a disease driven by type 2 inflammation

1. Stevens DA, et al. N Engl J Med. 2000;342:756-62. 2. Global Initiative for Asthma (GINA) 2019 . www.ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf. Accessed June 2025. 3. Agarwal R, et al. Clin Exp Allergy. 2013;43:850-73. 4. Simpson EL, et al. N Engl J Med. 2016;375:2335-48. 5. Bachert C, et al. Lancet. 2019;394:1638-50. 6. Dellon ES, et al. N Engl J Med. 2022;387:2317-30. 7. Castro M, et al. N Engl J Med. 2018;378:2486-2496.
AD, atopic dermatitis; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic esophagitis; IL, interleukin.

Dupilumab is a dual inhibitor of IL-4 and IL-13 signaling pathways

1. IL-4 and IL-13 bind to receptors containing a shared subunit, IL-4Rα[1,2]
2. Dupilumab binds specifically to IL-4Rα, thus inhibiting the dual signaling pathways of both IL-4 and IL-13[1,2]
3. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor[1,2]
4. Dupilumab is approved for patients with type 2 inflammatory diseases, including AD, asthma, CRSwNP, and EoE



Expression of type 2 cytokines and chemokines and activation of additional pro-inflammatory signaling pathways

1. Gandhi NA, et al. Nat Rev Drug Discov. 2016;15:35-50. 2. Le Floc'h A, et al. Allergy. 2020;75:1188-204.
γc, common gamma chain; JAK, Janus kinase; Rα, receptor-alpha; STAT, signal transducer and activator of transcription; TYK2, tyrosine kinase type 2.

Objective

- The phase 2 LIBERTY ABPA AIRED study (NCT04442269) evaluated the efficacy and safety of dupilumab in patients with asthma and ABPA

Methods: Key inclusion criteria

- Patients with a physician diagnosis of asthma[1] meeting clinical criteria for ABPA[2]
- Elevated serum total IgE >1,000 IU/mL; ≤1,000 IU/mL acceptable if all three supportive criteria met:
  - For patients on OCS, blood eosinophil count >500 cells/μL; for patients not on OCS, ≥300 to ≤500 cells/μL acceptable with historical result >500 cells/μL within 12 months of screening
  - Serum precipitating or IgG antibodies to *A. fumigatus*
  - Documented radiological findings consistent with ABPA by historical chest x-ray or chest CT or MRI within the previous 18 months or at screening
- Age ≥12 years[a]
- On maintenance ICS and possibly LABA/LTRA/LAMA for at least 12 weeks prior to screening
- ≥1 severe respiratory exacerbation requiring treatment with SCS, or hospitalization, or emergency department /urgent care visit within the past 12 months, or receiving long-term low-dose OCS
- ACQ-5 score ≥1.5 at screening and at baseline visit

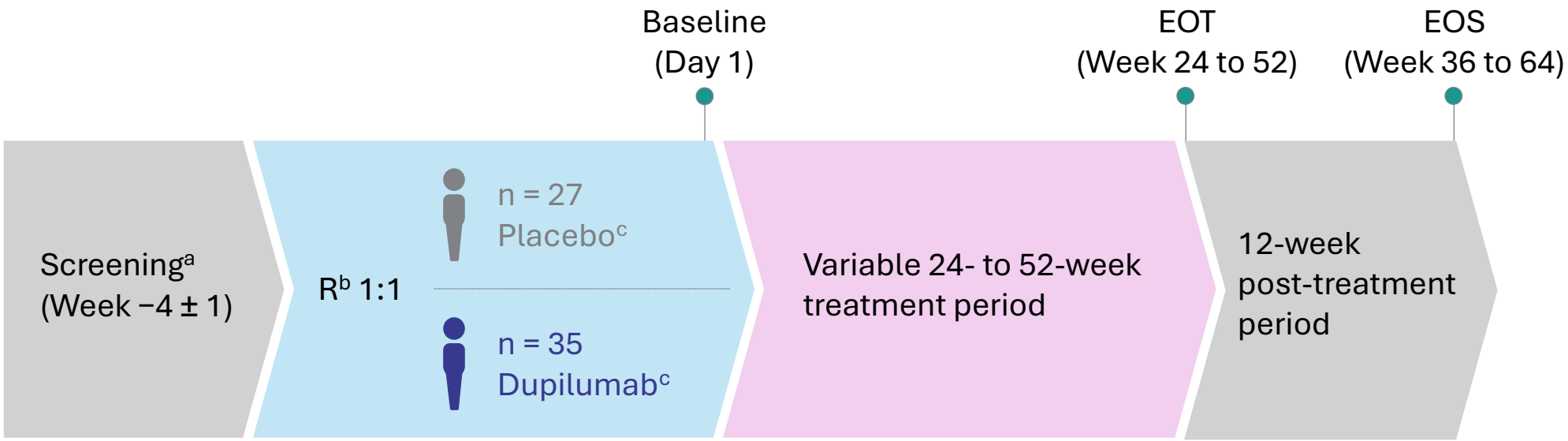
[a]No adolescents were enrolled in the trial.

1. Global Initiative for Asthma (GINA) 2019. www.ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf. Accessed June 2025.
2. Agarwal R, et al. Clin Exp Allergy. 2013;43:850-73.

ACQ-5, 5-item Asthma Control Questionnaire; CT, computed tomography; ICS, inhaled corticosteroid(s); LABA, long-acting β_2-agonist(s); LAMA, long-acting muscarinic antagonist(s); LTRA, leukotriene receptor antagonist(s); MRI, magnetic resonance imaging; OCS, oral corticosteroid(s).

Methods

Design of the LIBERTY ABPA AIRED phase 2 study



Stable background therapy for ABPA & asthma (ICS and possibly LABA, LTRA, and/or LAMA)

[a]Approximately 37% of patients were on SCS at screening. [b]Randomization was stratified by region (Asia, Eastern Europe, Western countries), chronic SCS use at screening (yes, no), and oral antifungal use at screening (yes, no). [c]600-mg loading dose on Day 1 (2 injections of 300 mg), or placebo loading dose (2 injections).
EOS, end of study; EOT, end of treatment.

Methods

- **Primary endpoint:** change from baseline in pre-bronchodilator FEV_1 at Week 24, assessed through formal hypothesis testing
- **Select secondary endpoints:** annualized rate of severe respiratory exacerbations and change from baseline in SGRQ total score, assessed through within-group, descriptive statistics
  - Scores on the SGRQ range from 0 to 100, with lower scores indicating a better quality of life and a change of 4 points being the minimal clinically important difference

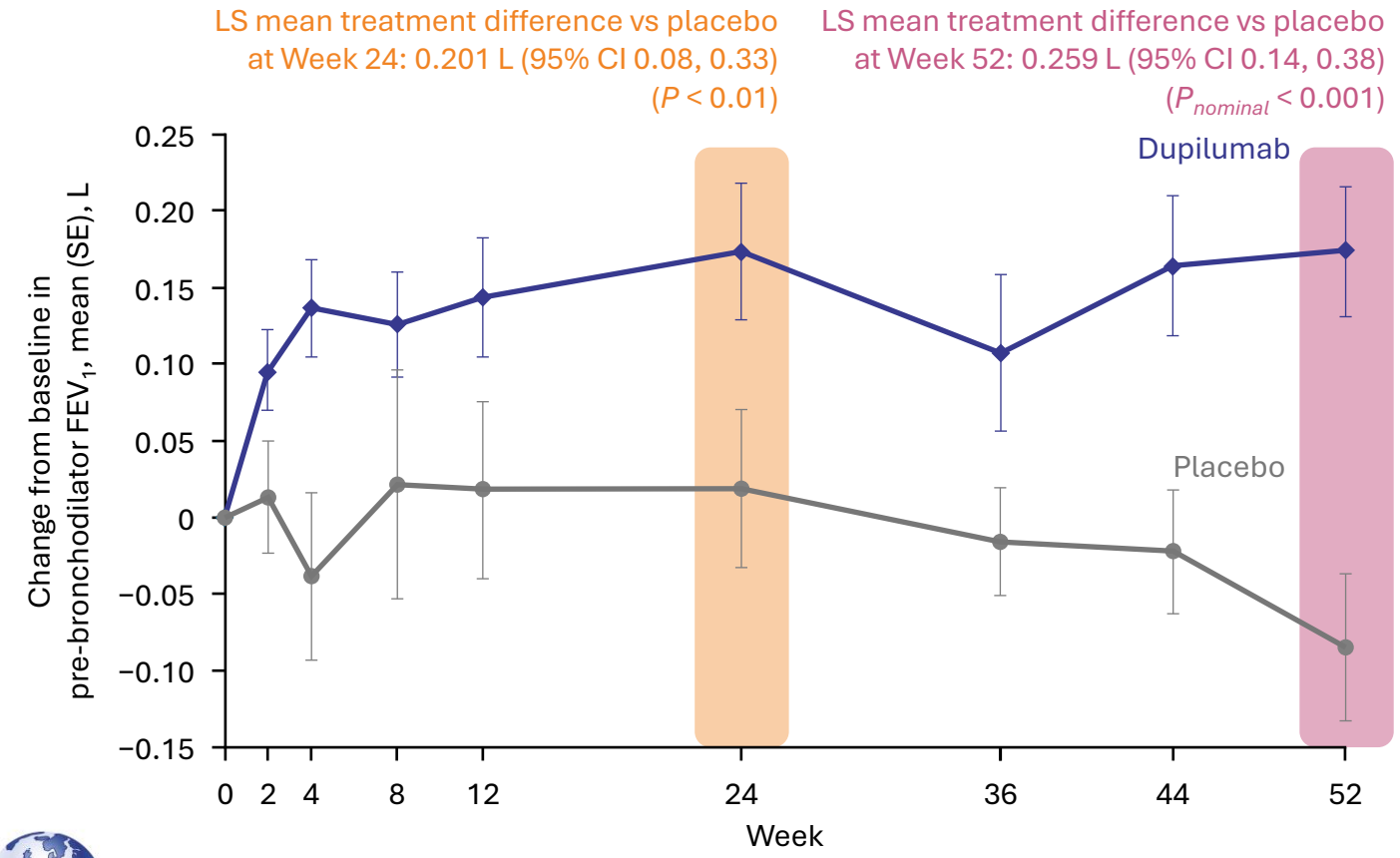
FEV_1, forced expiratory volume in 1 second; SGRQ, St. George's Respiratory Questionnaire.

Results: Select baseline characteristics

Characteristics	Placebo n = 27	Dupilumab n = 35	Total n = 62
Age, mean (SD), years	57.1 (14.38)	61.2 (8.62)	59.4 (11.56)
Female, n (%)	17 (63.0)	22 (62.9)	39 (62.9)
Pre-bronchodilator FEV_1, mean (SD), L	1.83 (0.58)	1.95 (0.68)	1.90 (0.63)
Pre-bronchodilator $ppFEV_1$, mean (SD), %	64.4 (18.5)	71.4 (25.7)	68.3 (22.9)
Severe respiratory exacerbations requiring SCS in the 12 months prior to screening, n (%)			
≤1	20 (74.1)	23 (65.7)	43 (69.4)
2	6 (22.2)	5 (14.3)	11 (17.7)
>2	1 (3.7)	7 (20.0)	8 (12.9)
SGRQ total score, mean (SD)	51.3 (17.2)	52.4 (15.3)	51.9 (16.0)
Biomarkers, median (Q1–Q3)			
Blood eosinophil count, cells/μL	600 (230–1,260)	560 (180–800)	575 (230–890)
Total IgE, IU/mL	2051 (693–4,206)	1969 (1005–3475)	2010 (1,005–3,475)
A. fumigatus-specific IgE, kU/L	52.5 (4.7–108.6)	39.9 (1.1–91.5)	44.4 (3.8–91.5)
FeNO, ppb	47.0 (18.0–63.0)	33.5 (19.0–54.0)	35.0 (18.5–60.0)
Medical history events			
Bronchiectasis, n (%)	3 (11.1)	3 (8.6)	6 (9.7)

FeNO, fractional exhaled nitric oxide; $ppFEV_1$, percent predicted FEV_1; Q, quartile; SD, standard deviation.

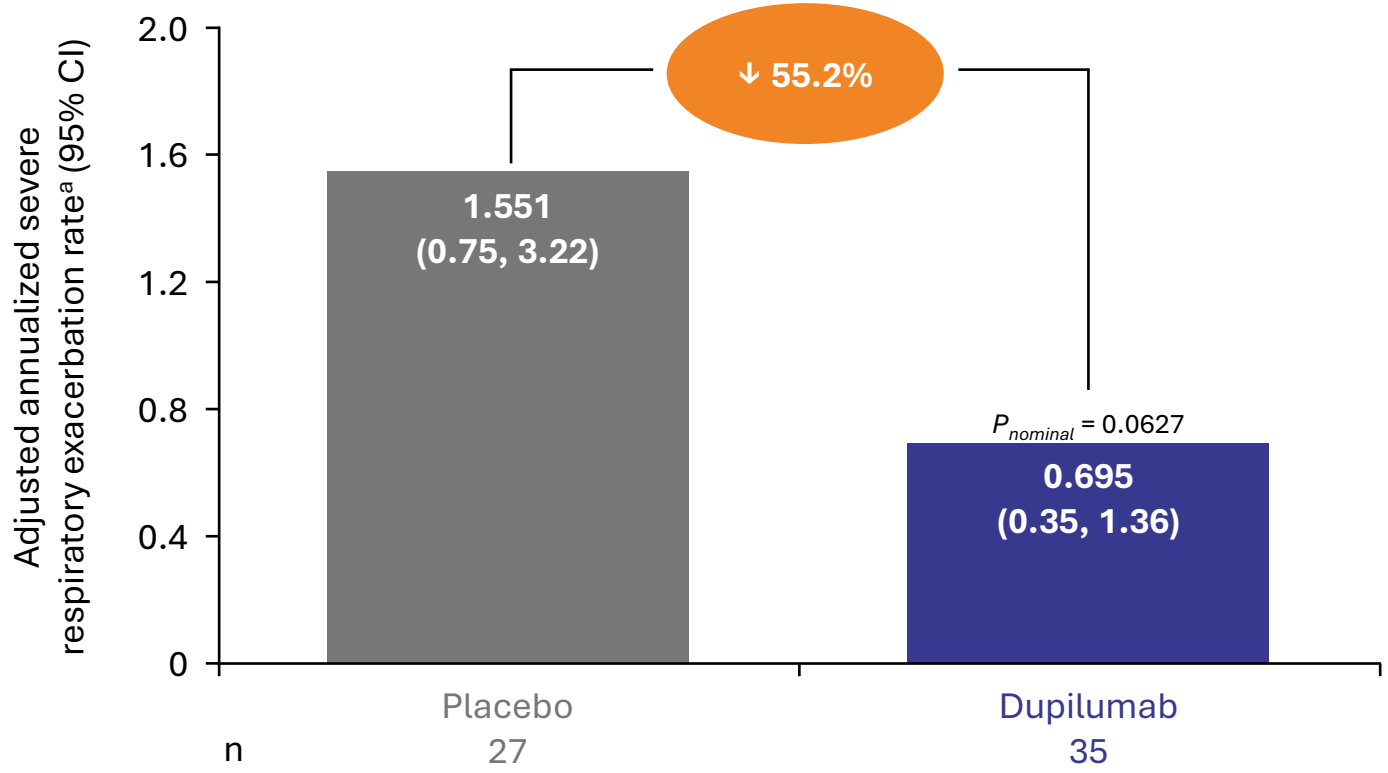
Results: Dupilumab vs placebo improved pre-bronchodilator FEV_1 over the 24- to 52-week treatment period



Pre-bronchodilator FEV_1 (L), mean (SD)	Placebo n = 27	Dupilumab n = 35
Baseline	1.83 (0.58)	1.95 (0.68)
Week 24	1.88 (0.63)	2.15 (0.67)
Week 52	1.79 (0.69)	2.14 (0.69)

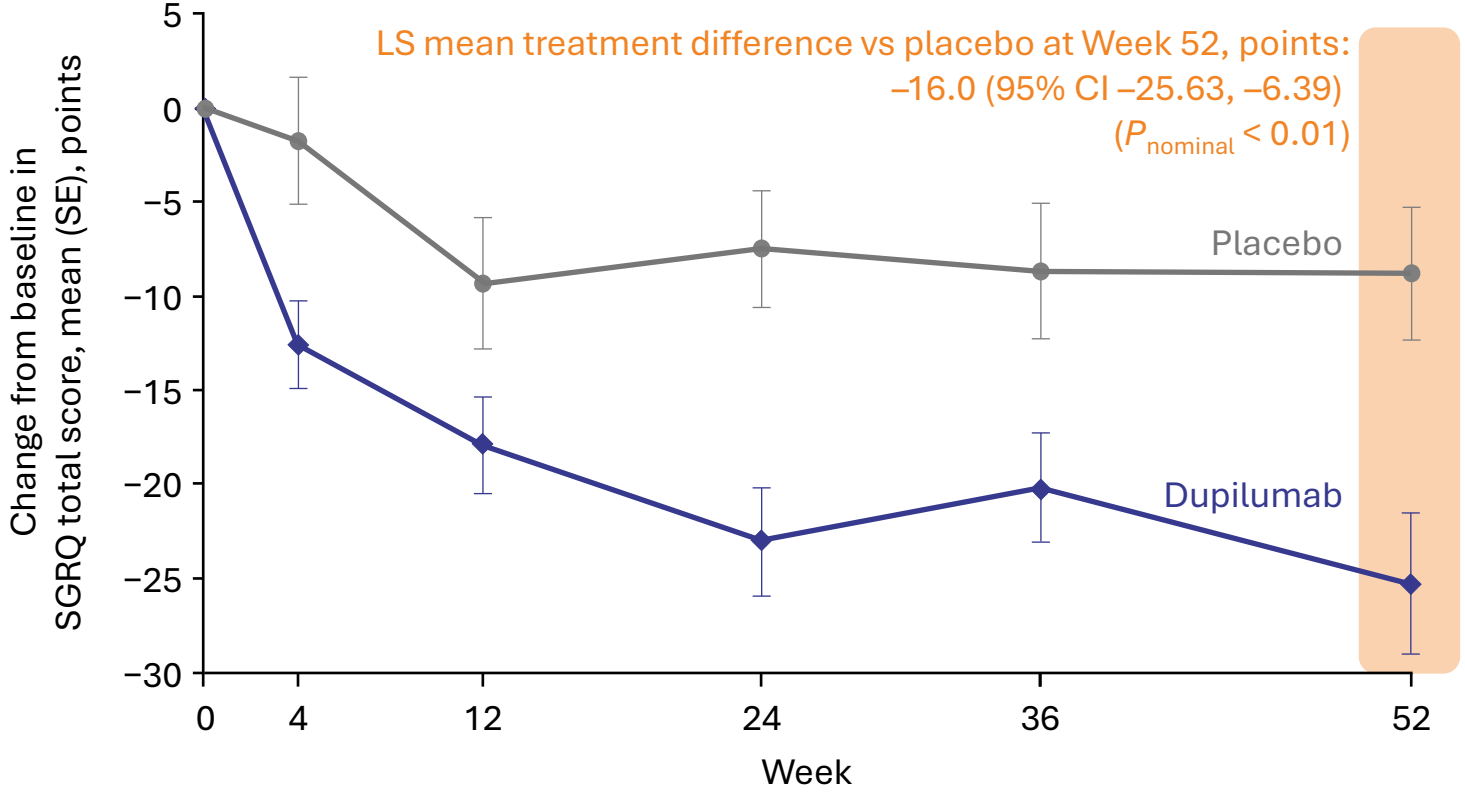
LS, least squares; SD, standard deviation; SE, standard error.

Results: Treatment with dupilumab vs placebo reduced the annualized rate of severe respiratory exacerbations



[a]Severe respiratory exacerbations are defined as new-onset symptoms or clinical worsening that requires SCS treatment for ≥3 consecutive days, and, for patients who are on maintenance SCS, at least double the dose of maintenance SCS for ≥3 consecutive days plus antibiotic therapy if indicated.

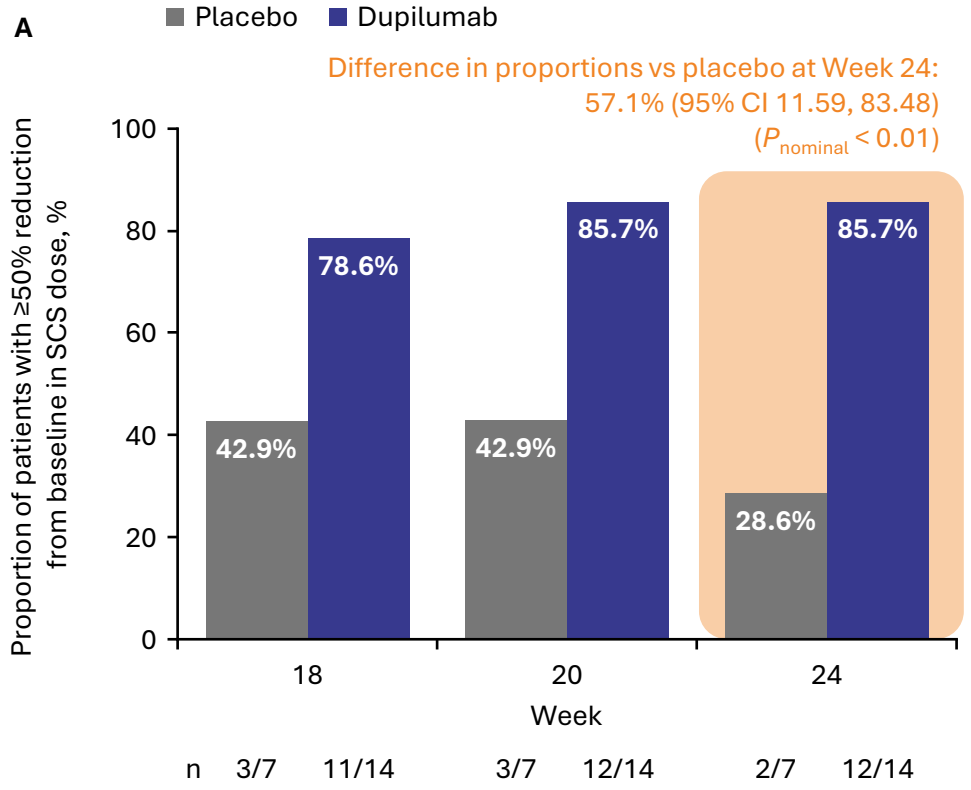
Results: Dupilumab vs placebo improved patient quality of life (SGRQ total score) during the 24- to 52-week treatment period

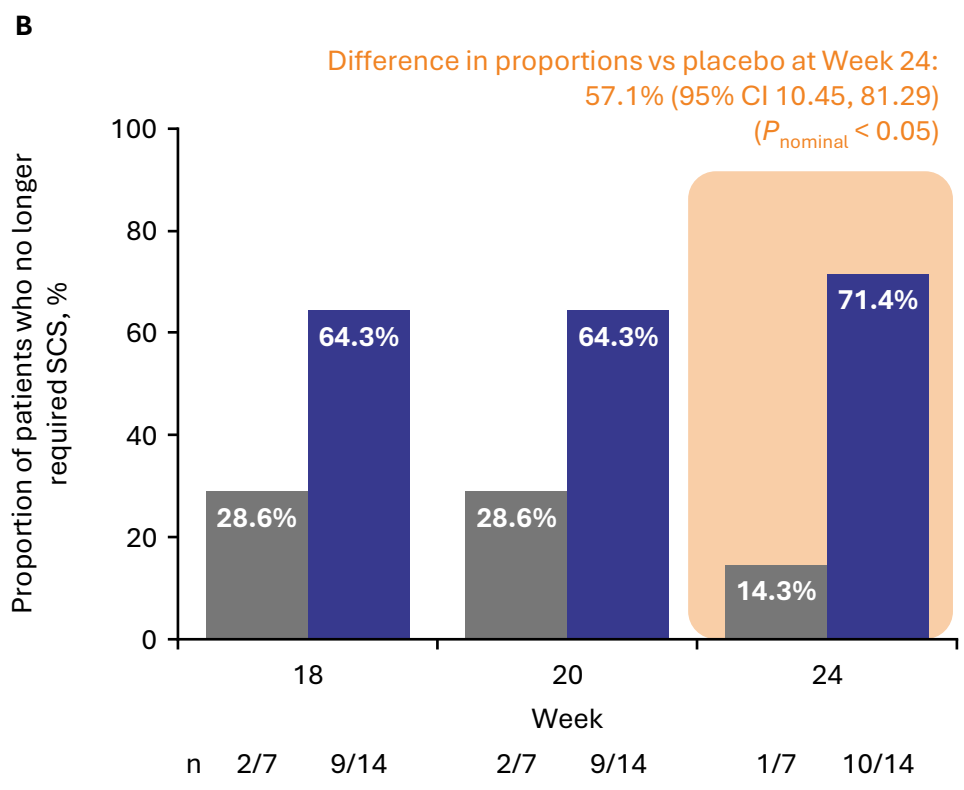


SGRQ total score, mean (SD)	Placebo n = 27	Dupilumab n = 35
Baseline	51.3 (17.2)	52.4 (15.3)
Week 24	43.3 (19.3)	29.3 (19.6)
Week 52	41.2 (19.5)	27.0 (20.5)

Lower scores indicate better quality of life, and a change of 4 points is the minimal clinically important difference.

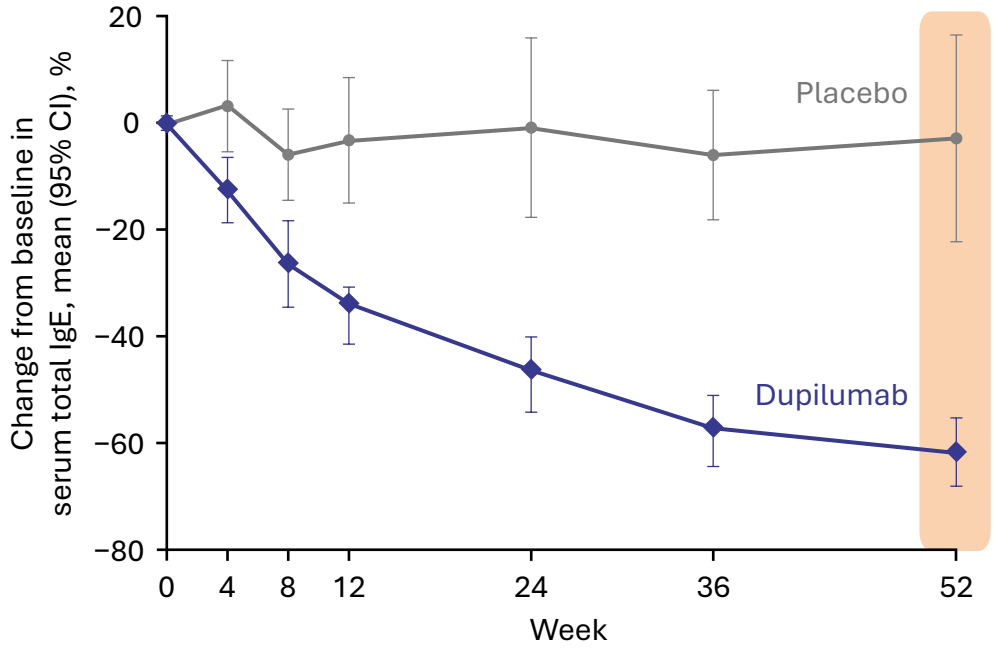
Results: Dupilumab vs placebo was associated with a higher proportion of patients with (A) SCS dose reduction by ≥ 50% and/or (B) complete cessation of SCS





Results: Dupilumab vs placebo led to a greater decrease in total IgE

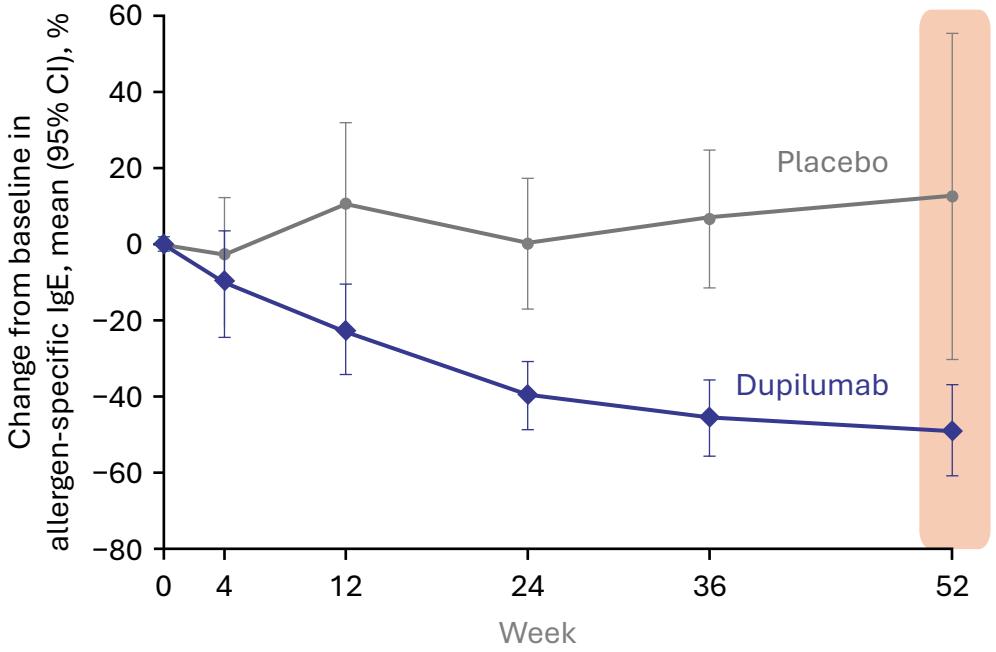
LS mean treatment difference vs placebo at Week 52:
–61.31% (95% CI –77.57, –45.06)
($P_{nominal}$ < 0.0001)



Total IgE, IU/mL median (Q1–Q3)	Placebo n = 27	Dupilumab n = 35
Baseline	2,051 (693–4,206)	1,969 (1,005–3,475)
Week 24	2,187 (912–4,861)	929 (486–1,800)
Week 52	1,844 (856–5,000)	766 (373–1,251)

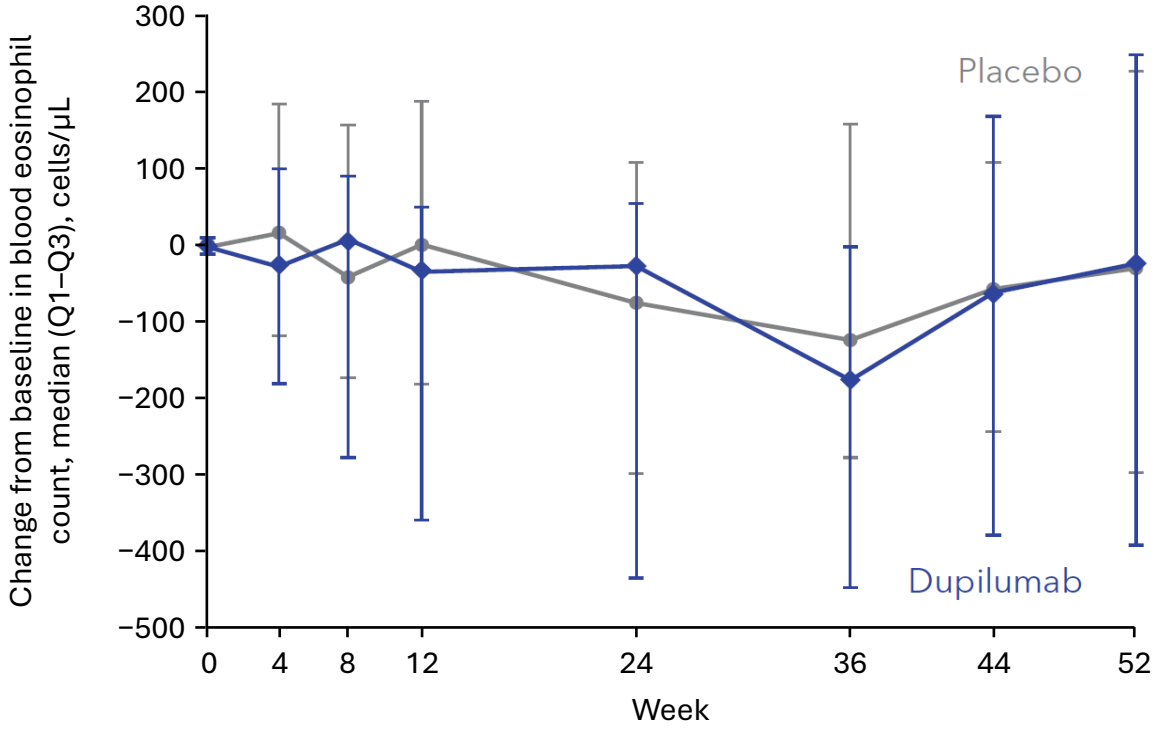
Results: Dupilumab vs placebo led to a greater decrease in *A. fumigatus*-specific IgE

LS mean treatment difference vs placebo at Week 52:
–67.33% (95% CI –102.94, –31.72)
($P_{nominal}$ < 0.001)



A. fumigatus-specific IgE, median (Q1–Q3)	Placebo n = 27	Dupilumab n = 35
Baseline	52.5 (4.7–108.6)	39.9 (1.1–91.5)
Week 24	41.7 (3.0–97.2)	15.7 (0.5–58.2)
Week 52	51.3 (10.3–100.5)	9.7 (0.3–32.4)

Results: Blood eosinophil counts were generally similar in the dupilumab and placebo groups at all timepoints



Safety

Safety	Placebo n = 27	Dupilumab n = 35
Any TEAE, n (%)	22 (81.5)	30 (85.7)
Any drug-related TEAE, n (%)	5 (18.5)	13 (37.1)
Any TEAE leading to discontinuation of study drug, n (%)	3 (11.1)	1 (2.9)
Maximum severity for any TEAE, n (%)		
Mild	8 (29.6)	11 (31.4)
Moderate	8 (29.6)	12 (34.3)
Severe	6 (22.2)	7 (20.0)
Any TESAE, n (%)	2 (7.4)	3 (8.6)
Any drug-related TESAE, n (%)	0	0
Any TESAE leading to discontinuation of study drug, n (%)	1 (3.7)	0
Any TEAE leading to death, n (%)	0	1 (2.9)

There was 1 death (due to Preferred Terms: pneumonia bacterial, respiratory disorder, hemoptysis, influenza, and nephrotic syndrome) in the dupilumab group considered unrelated to the study drug.
TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Conclusions

- Dupilumab treatment vs placebo significantly improved lung function and substantially reduced severe respiratory exacerbations while improving quality of life in patients with asthma and ABPA during the 24–52-week treatment period
- To our knowledge, this is the first evidence from a randomized placebo-controlled trial that demonstrates dupilumab benefit in patients with asthma and ABPA
- Safety was consistent with the known dupilumab safety profile