Dupilumab in Patients With Corticosteroid-Dependent Severe Asthma: Efficacy and Safety Results From the Randomized, Double-Blind, Placebo-Controlled Phase 3 LIBERTY ASTHMA VENTURE Study

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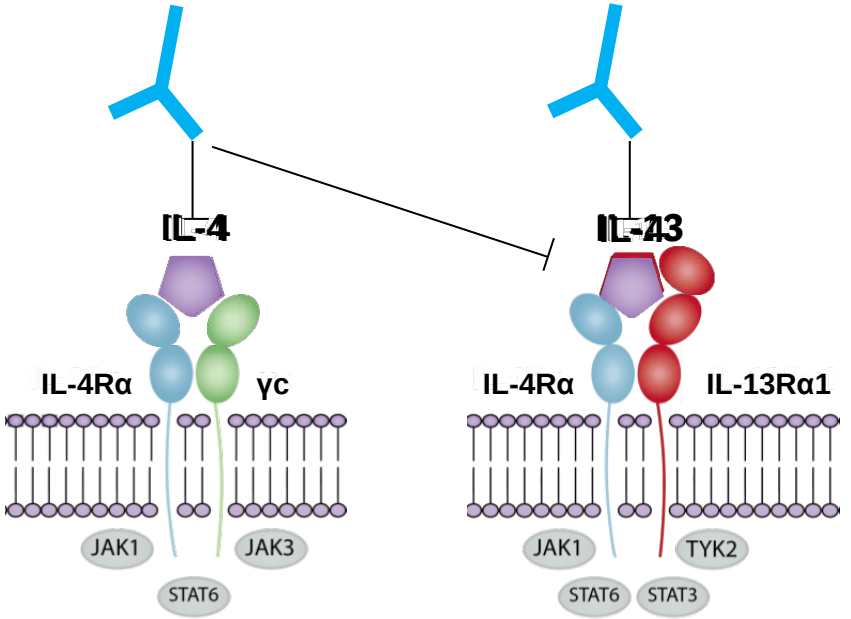
Background

- An estimated 45% of patients with severe asthma require systemic corticosteroids to control their disease
- Systemic corticosteroids are associated with significant toxicities across multiple organ systems
- There is a need for additional targeted therapies that optimize asthma control and minimize or eliminate systemic corticosteroid use

Dupilumab Mechanism of Action

- **Dupilumab** is a fully human VelocImmune®-derived IL-4Rα monoclonal antibody inhibiting **IL-4** and **IL-13** signaling pathways, key drivers of Type 2 inflammation, and is approved for the treatment of adults with moderate-to-severe atopic dermatitis
- **Dupilumab** has also shown efficacy in patients with other Type 2 inflammatory diseases, including nasal polyposis with chronic rhinosinusitis and eosinophilic esophagitis



Type I receptor

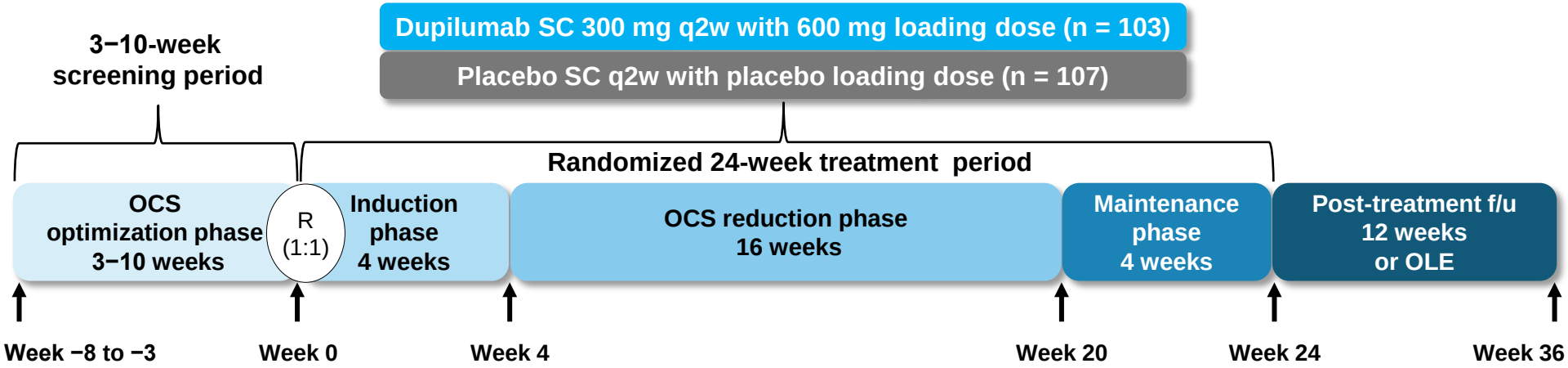
B cells, T cells, monocytes, eosinophils, fibroblasts

Type II receptor

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

Dupilumab Asthma VENTURE Phase 3 Trial

- The phase 3 LIBERTY ASTHMA VENTURE study evaluated whether dupilumab could reduce oral corticosteroid (OCS) use in severe asthma patients while maintaining asthma control



ClinicalTrials.gov number: NCT02528214.

Main Inclusion and Exclusion Criteria

Inclusion

- Age ≥ 12 years with physician-diagnosed persistent asthma for ≥ 12 months
- Chronic daily systemic steroids in the previous 6 months (5−35 mg/day of prednisone/prednisolone/ equivalent) during the 4 weeks prior to screening
- High-dose ICS in combination with up to two controllers for ≥ 3 months
- Pre-bronchodilator FEV_1 (L) ≤ 80% predicted (≤ 90% for adolescents) at screening and baseline
- FEV_1 reversibility ≥ 12% and 200 mL, or hyper-responsiveness documented in the 12 months prior to screening
- No minimum requirement for baseline blood eosinophil count or any other Type 2 biomarkers (e.g. FeNO, serum total IgE)

Exclusion

- Lung diseases other than asthma
- Deterioration of asthma requiring emergency treatment or hospitalization within 4 weeks of Visit 1
- Current smokers or smokers who had stopped within 6 months before screening or who had a smoking history of > 10 pack-years

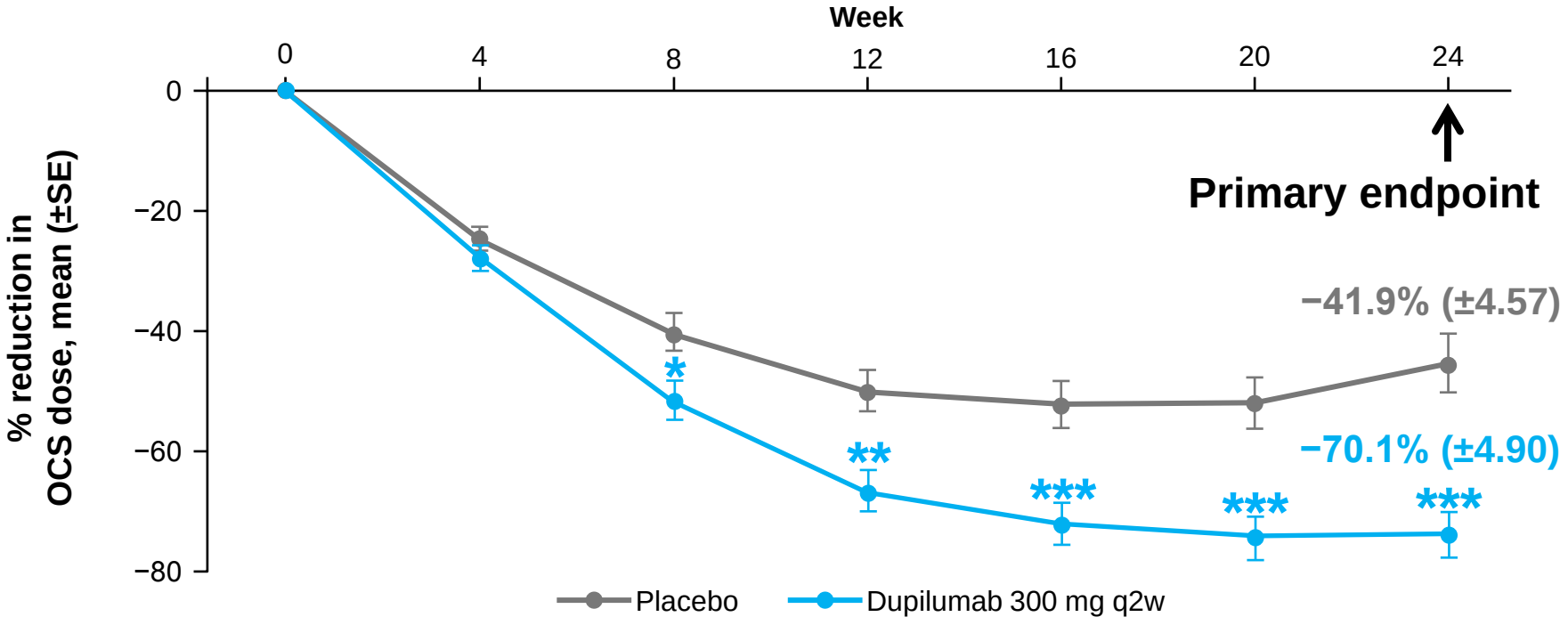
Primary, Secondary, and Other Endpoints

- **Primary endpoint**
  - Percentage reduction in OCS dose from baseline to Week 24
- **Key secondary endpoints**
  - Proportion of patients achieving ≥ 50% reduction from baseline in OCS dose at Week 24
  - Proportion of patients achieving a reduction in OCS dose to < 5 mg/day at Week 24
- **Other secondary endpoint**
  - Proportion of patients no longer requiring OCS at Week 24
- **Other efficacy endpoints**
  - Rate of severe exacerbations during the 24-week treatment period
  - FEV_1 during the 24-week treatment period

Baseline Demographics and Clinical Characteristics

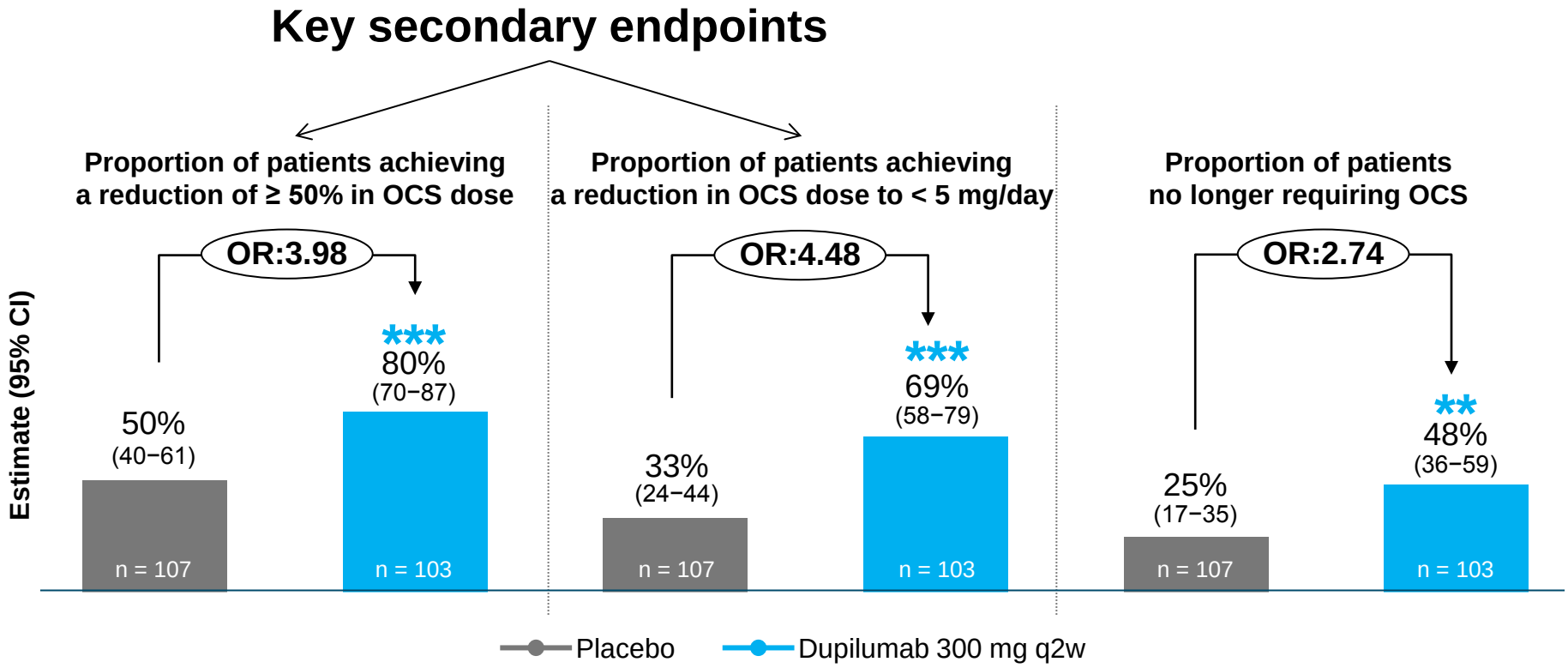
	Placebo (n = 107)	Dupilumab 300 mg q2w (n = 103)	All (N = 210)
Age, mean (SD) — yr	50.7 (12.8)	51.9 (12.5)	51.3 (12.6)
Male — no. (%)	42 (39.3)	41 (39.8)	83 (39.5)
Pre-bronchodilator FEV_1, mean (SD) — L	1.63 (0.61)	1.53 (0.53)	1.58 (0.57)
Pre-bronchodilator FEV_1, mean (SD) — % predicted	52.69 (15.14)	51.64 (15.28)	52.18 (15.18)
Daily OCS dose pre-optimization, mean (SD) — mg/day	11.83 (6.02)	11.79 (6.40)	11.81 (6.20)
Optimized OCS dose at baseline, mean (SD) — mg/day	11.75 (6.31)	10.75 (5.90)	11.26 (6.12)
ACQ-5 score, mean (SD) — scale 0−6	2.58 (1.09)	2.42 (1.24)	2.50 (1.16)
Arithmetic blood eosinophil count, mean (SD) — cells/µL	325 (298)	370 (316)	347 (307)
FeNO, mean (SD) — ppb	39.62 (34.12)	35.55 (28.34)	37.61 (31.38)

Primary Endpoint: Percentage Reduction in OCS Dose From Baseline to Week 24

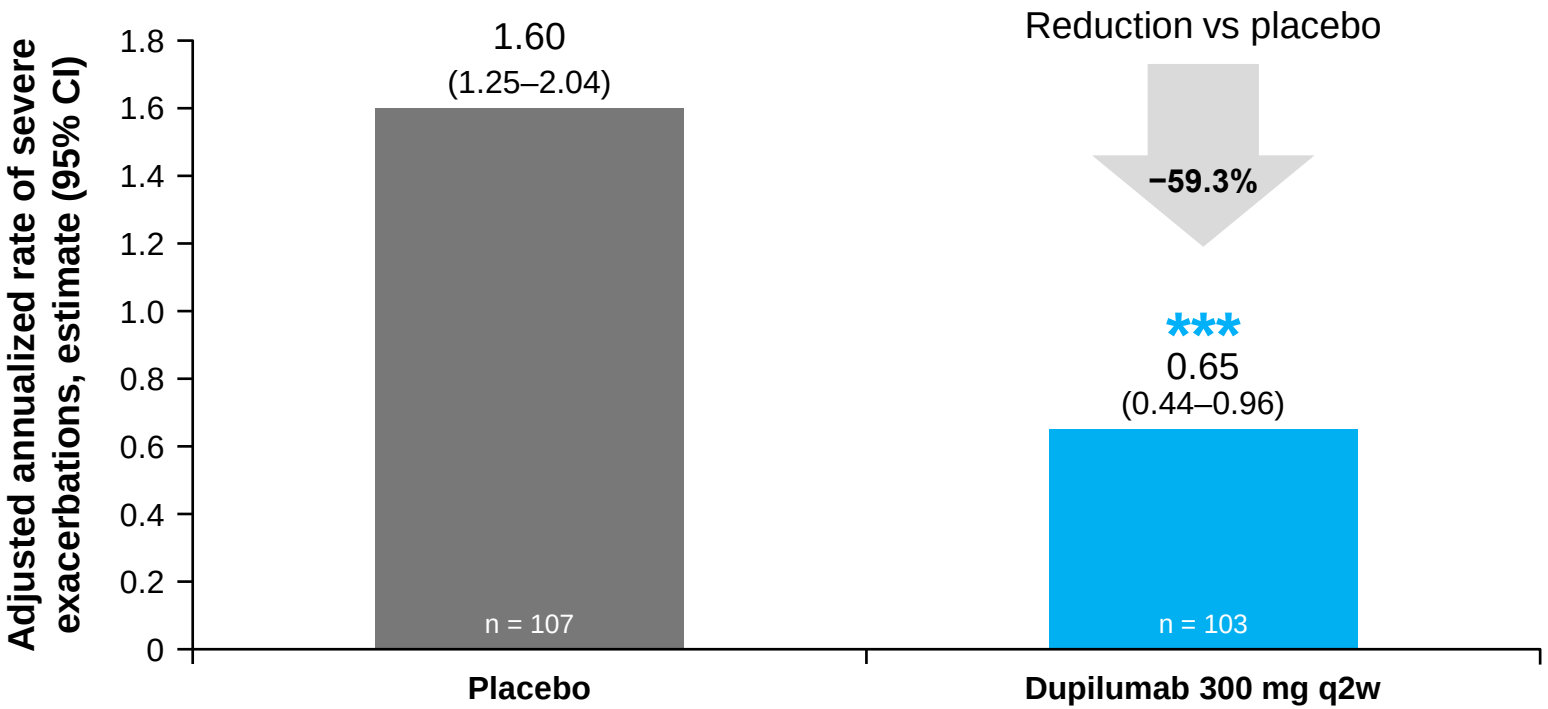


No. of patients							
Placebo	107	107	107	107	107	107	106
Dupilumab 300 mg q2w	103	103	102	101	101	101	101

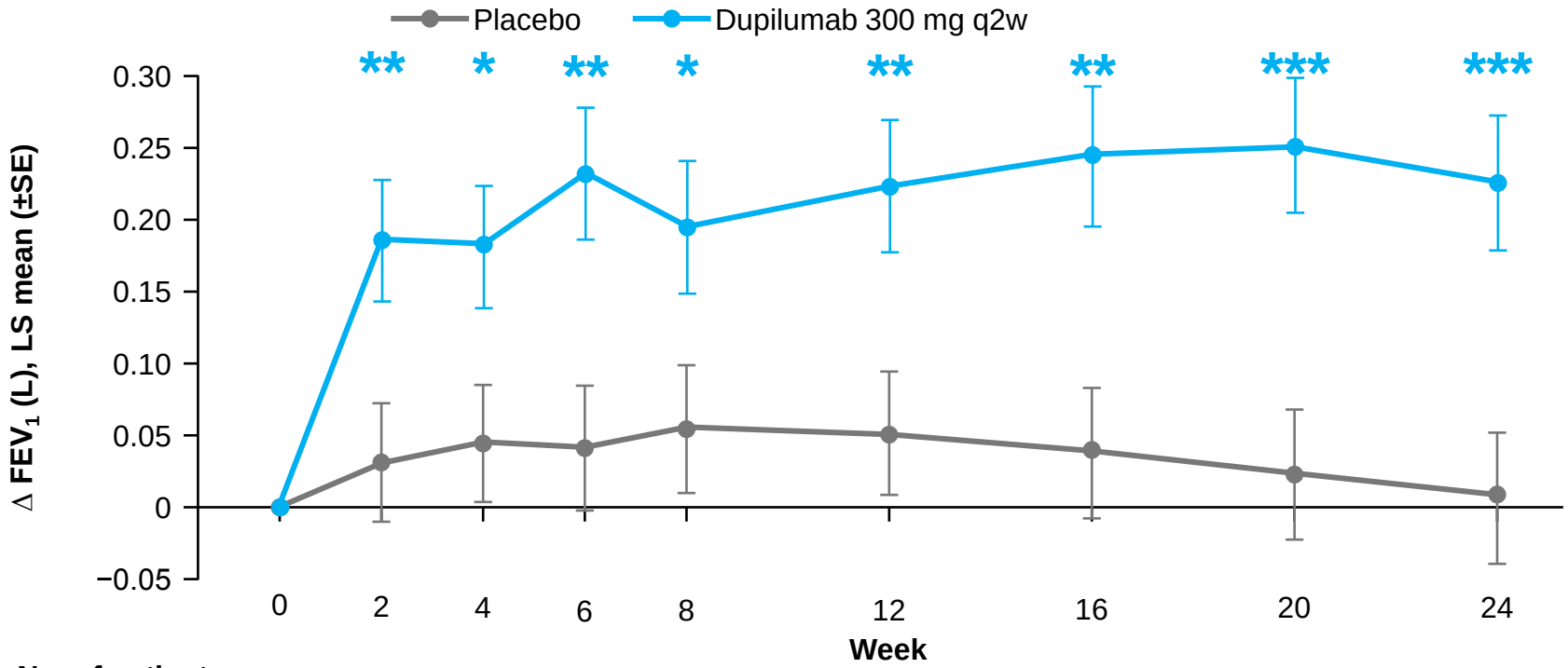
Effect of Dupilumab on Secondary OCS Endpoints



Rate of Severe Exacerbations During the 24-Week Treatment Period



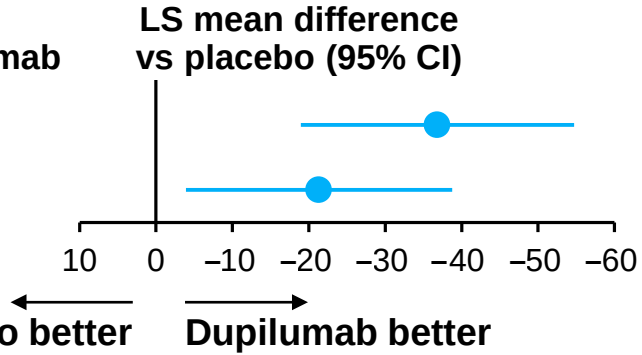
Change From Baseline in Pre-Bronchodilator FEV_1 During the 24-Week Treatment Period



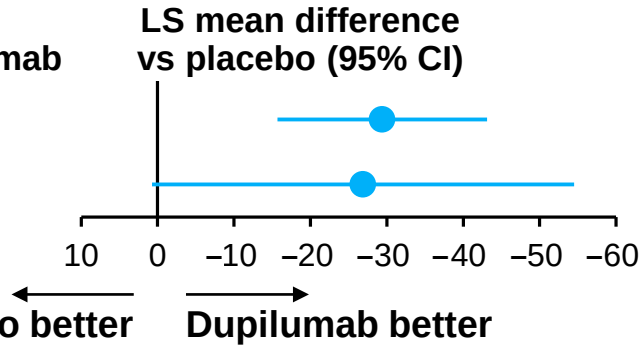
No. of patients									
Placebo	107	104	104	106	107	105	106	107	104
Dupilumab 300 mg q2w	103	101	98	101	100	99	98	100	97

Percentage Reduction in OCS Dose at Week 24 by Baseline Blood Eosinophil Subgroup

Subgroups	Placebo	Dupilumab
≥ 300 cells/μL	41	48
< 300 cells/μL	66	55

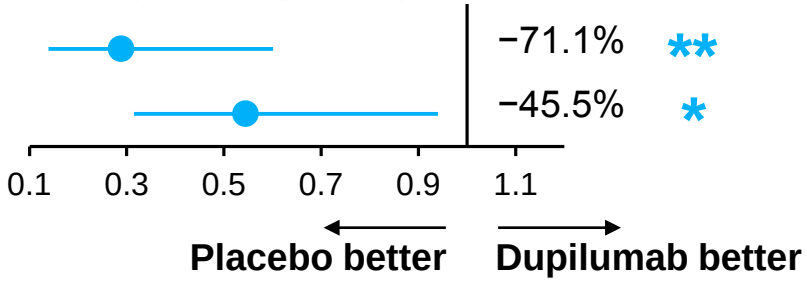


Subgroups	Placebo	Dupilumab
≥ 150 cells/μL	69	81
< 150 cells/μL	38	22

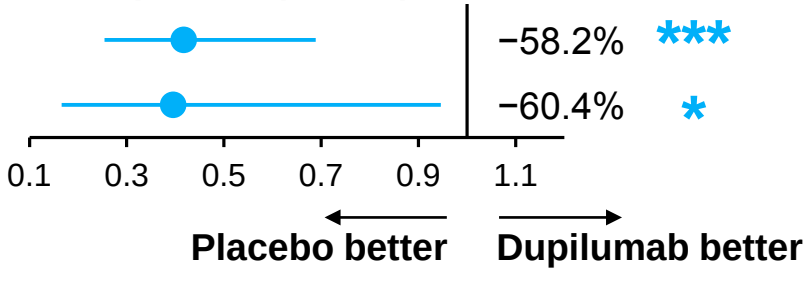


Severe Exacerbation Rates During the 24-Week Treatment Period by Baseline Blood Eosinophil Subgroup

Subgroups	Placebo	Dupilumab	Relative risk vs placebo (95% CI)	
≥ 300 cells/µL	41	48	−71.1%	**
< 300 cells/µL	66	55	−45.5%	*

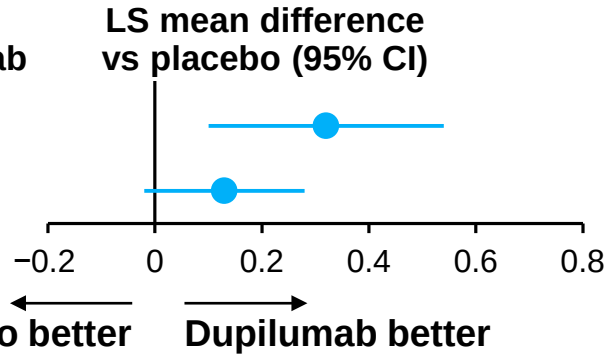


Subgroups	Placebo	Dupilumab	Relative risk vs placebo (95% CI)	
≥ 150 cells/µL	69	81	−58.2%	***
< 150 cells/µL	38	22	−60.4%	*



Change From Baseline in FEV_1 (L) at Week 24 by Baseline Blood Eosinophil Subgroup

Subgroups	Placebo	Dupilumab
≥ 300 cells/µL	39	45
< 300 cells/µL	65	52



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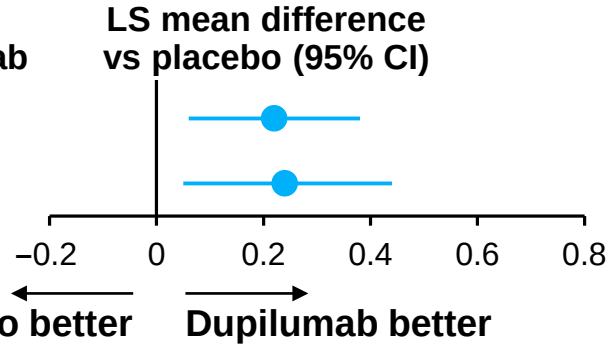
P = 0.086

Subgroups	Placebo	Dupilumab
≥ 150 cells/µL	66	76
< 150 cells/µL	38	21



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Adverse Events in the Overall Study Population

	Placebo (n = 107)	Dupilumab 300 mg q2w (n = 103)
Any TEAE	69 (64.5)	64 (62.1)
Any treatment-emergent severe adverse event	6 (5.6)	9 (8.7)
Any TEAE leading to death	0	0
Any TEAE leading to permanent treatment discontinuation	4 (3.7)	1 (1.0)
TEAEs occurring in ≥ 5% of patients (MedDRA Preferred Term)		
Viral upper respiratory tract infection	19 (17.8)	9 (8.7)
Bronchitis	6 (5.6)	7 (6.8)
Sinusitis	4 (3.7)	7 (6.8)
Influenza	6 (5.6)	3 (2.9)
Eosinophilia	1 (0.9)	14 (13.6)
Injection-site reaction (MedDRA High-level Term)	4 (3.7)	9 (8.7)
≥ 1 measurement of blood eosinophils > 3,000 cells/µL	1 (0.9)	13 (12.6)

Conclusions

- Add-on dupilumab therapy significantly reduced OCS use while simultaneously reducing severe asthma exacerbations and improving FEV_1 in patients with OCS-dependent severe asthma
- Subgroup analyses support efficacy in patients with and without elevated baseline blood eosinophils or FeNO levels, with more robust results observed in those with high baseline blood eosinophils and FeNO levels
- Dupilumab was generally well tolerated
  - Eosinophilia was observed in 1 of 7 dupilumab-treated patients

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ORIGINAL ARTICLE

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

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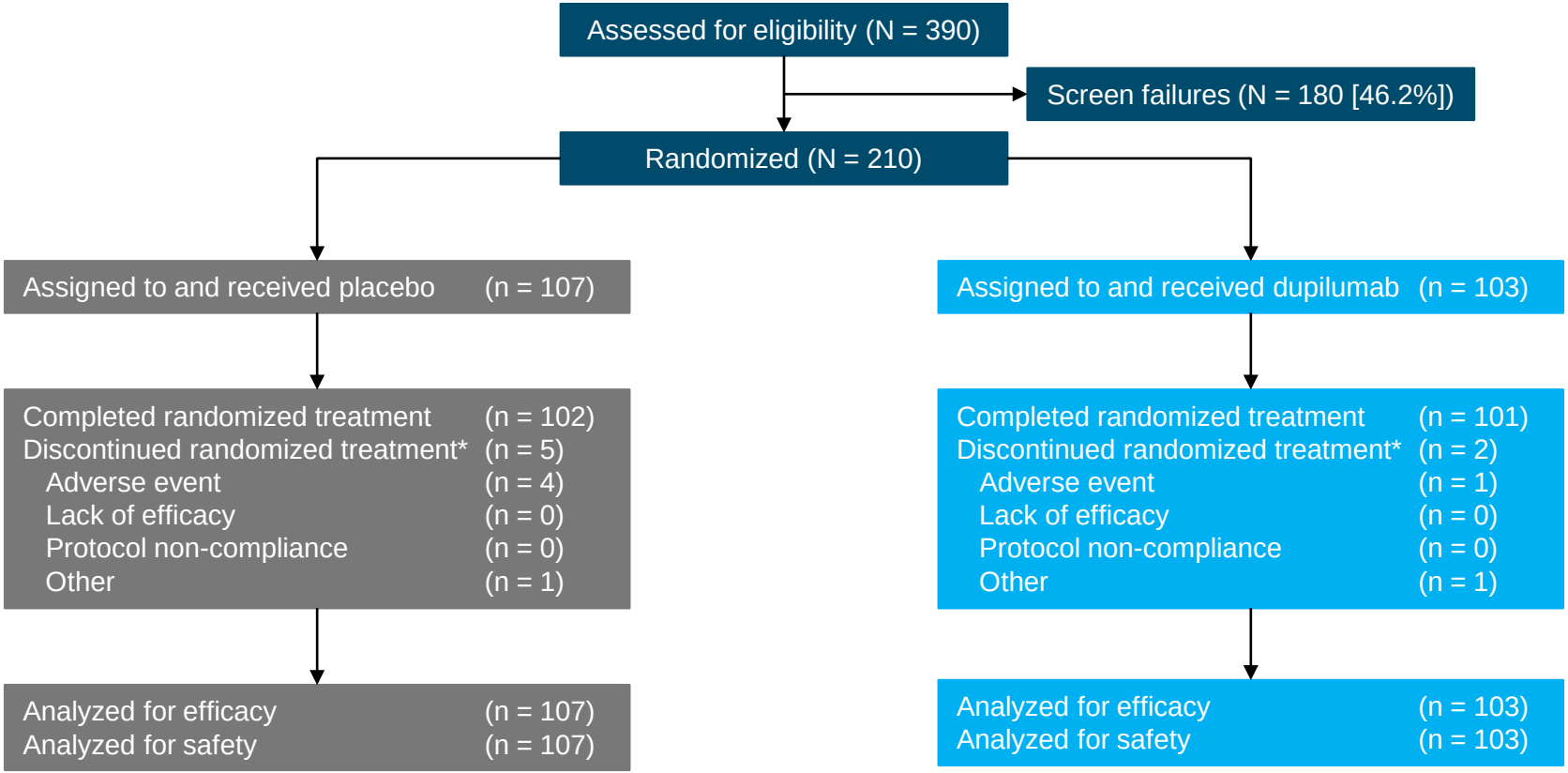
Back-up Slides

OCS Titration Schedule During the 16-week OCS Reduction Phase

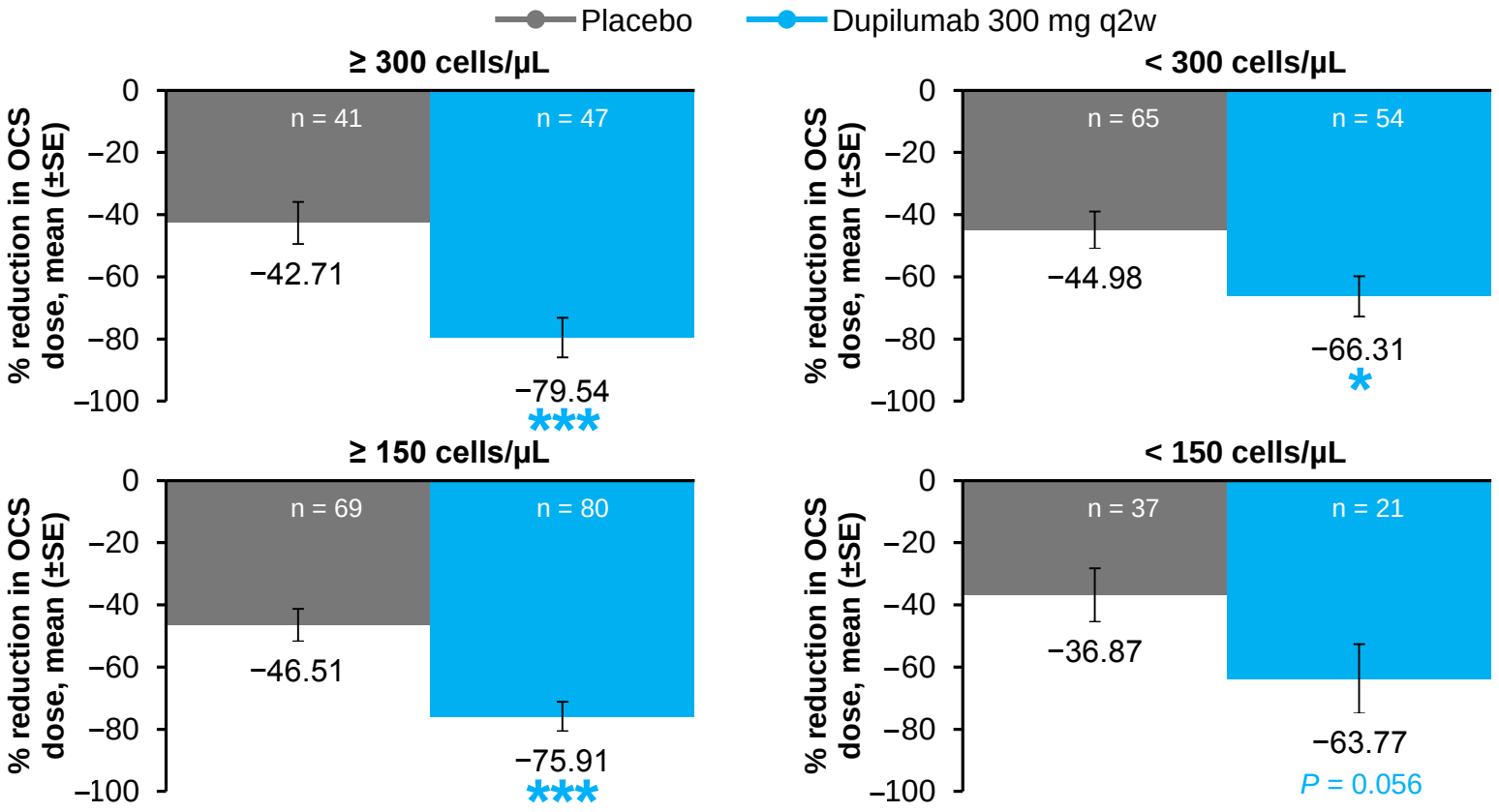
Time course	OCS dose (mg/day)								
Optimized OCS dose	35	30	25	20	15	12.5	10	7.5	5
First dose reduction	25	20	15	10	10	10	5	5	2.5
+4 week	15	10	10	5	5	5	2.5	2.5	0
+4 week	10	5	5	2.5	2.5	2.5	0	0	
+4 week	5	2.5	2.5	0	0	0			
+4 week	2.5	0	0						

Patient Disposition



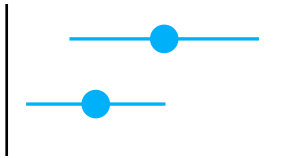
*During randomized treatment period.

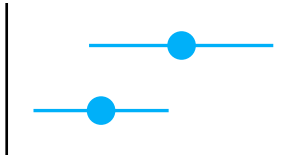
Percentage Reduction in OCS dose at Week 24 by Baseline Blood Eosinophil Subgroup

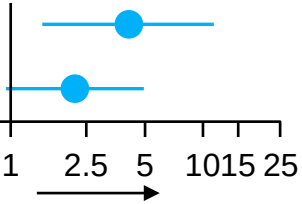


Reduction in OCS Dose at Week 24 by Baseline Blood Eosinophil Subgroups

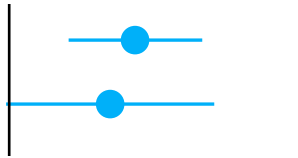
Subgroups	Placebo	Dupilumab	Odds ratio vs placebo (95% CI)
Proportion of patients achieving a reduction of ≥ 50% in OCS dose			
≥ 300 cells/µL	41	48	
< 300 cells/µL	66	55	
Proportion of patients achieving a reduction in OCS dose to < 5 mg/day			
≥ 300 cells/µL	41	48	
< 300 cells/µL	66	55	
Proportion of patients no longer requiring OCS			
≥ 300 cells/µL	40	48	
< 300 cells/µL	66	55	

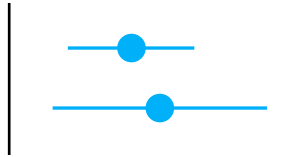


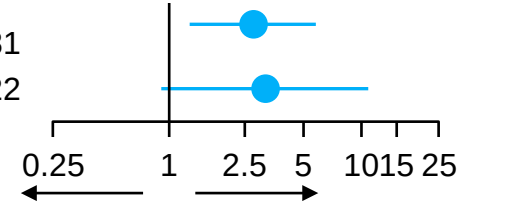




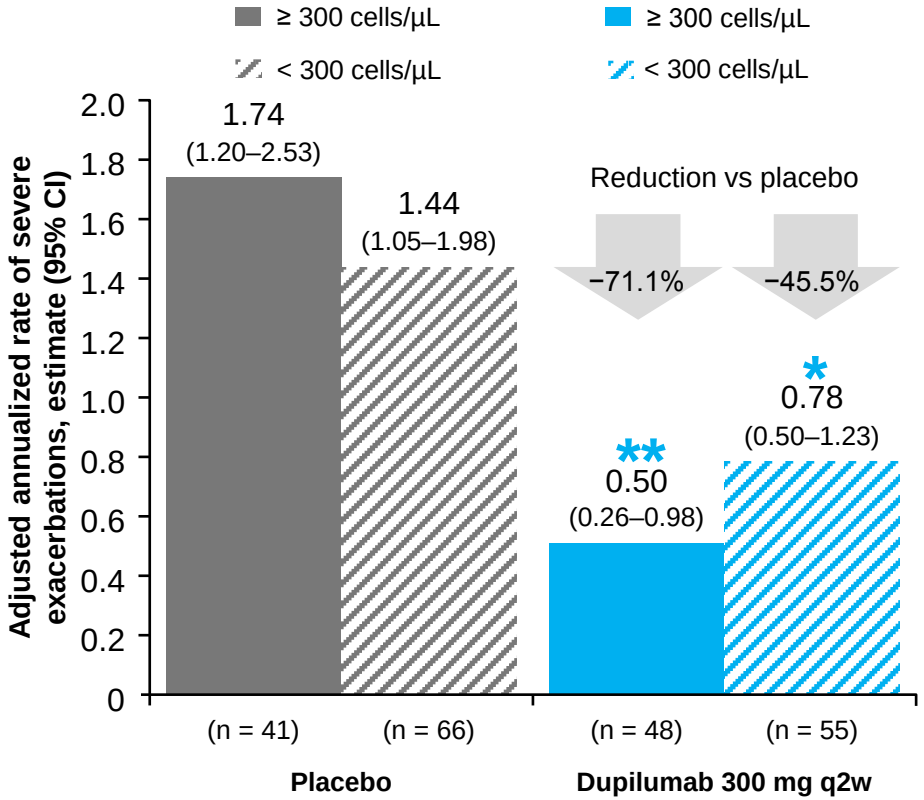
Subgroups	Placebo	Dupilumab	Odds ratio vs placebo (95% CI
≥ 150 cells/µL	69	81	
< 150 cells/µL	38	22	
≥ 150 cells/µL	69	81	
< 150 cells/µL	38	22	
≥ 150 cells/µL	68	81	
< 150 cells/µL	38	22	

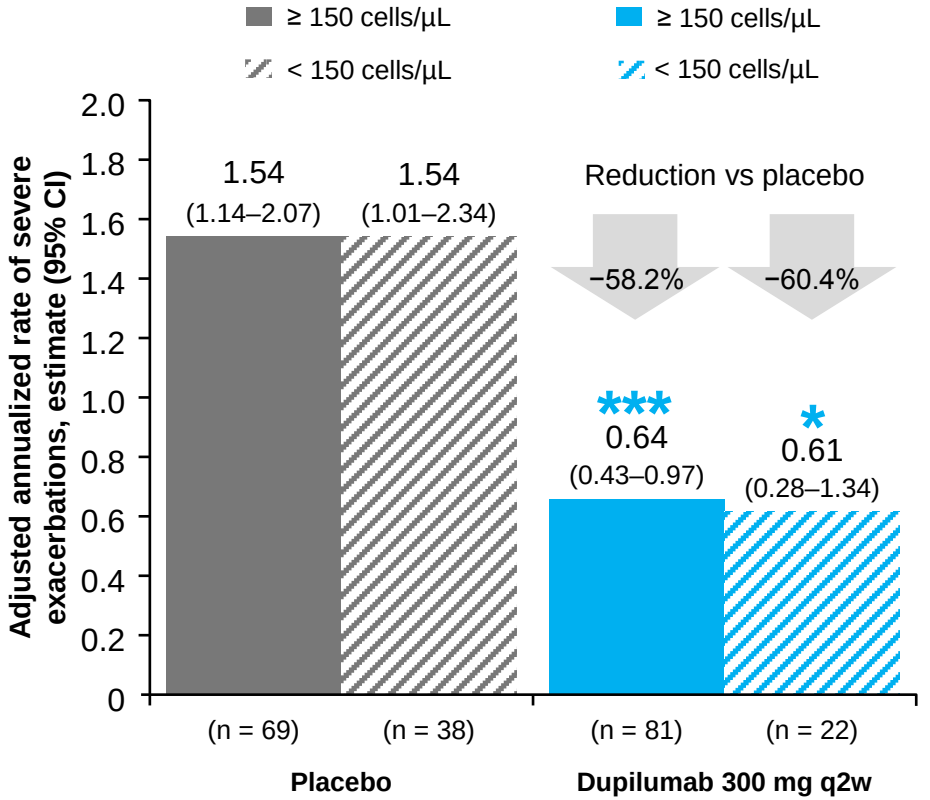




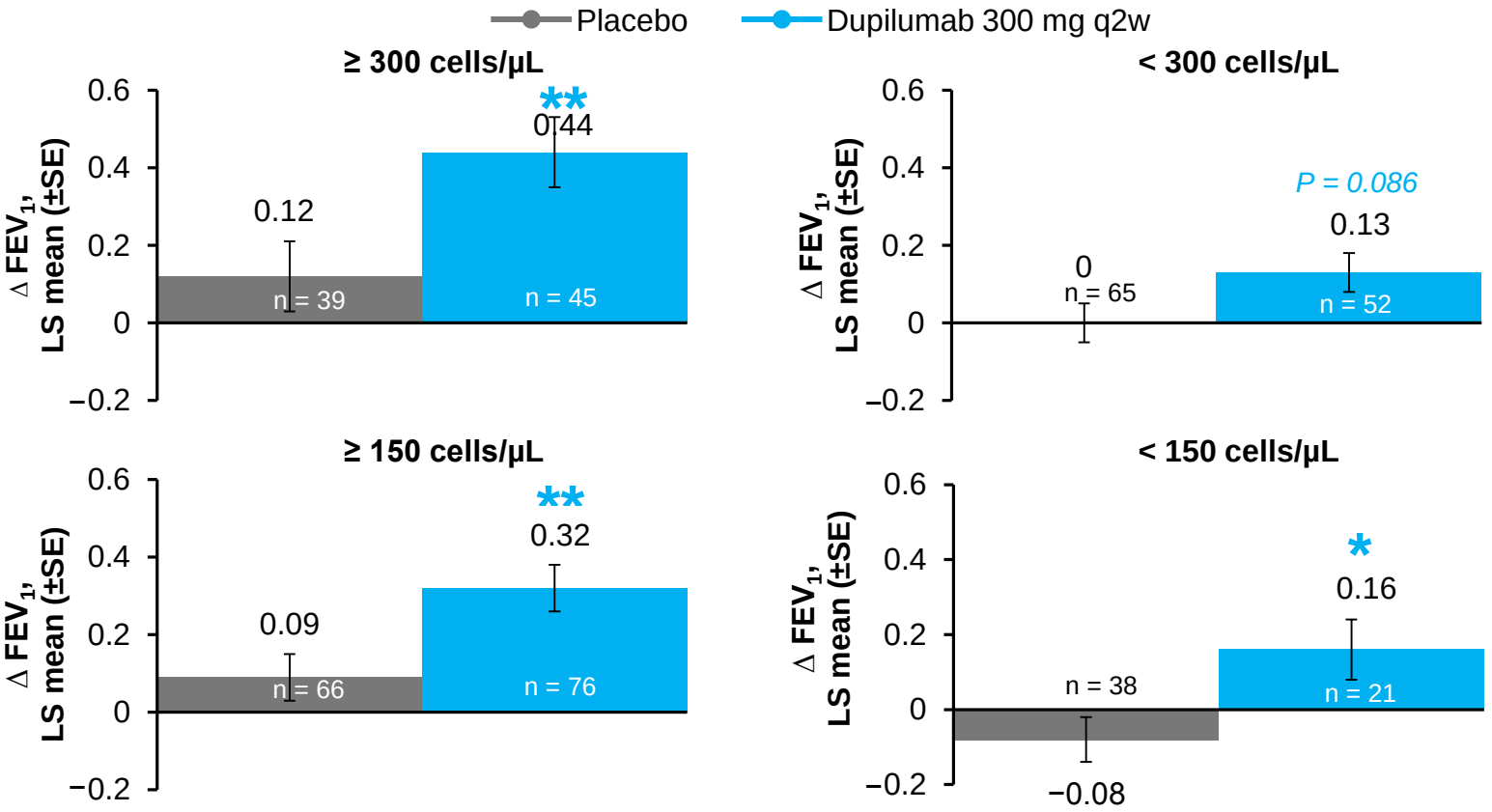


Rate of Severe Exacerbations During the 24-week Treatment Period by Baseline Blood Eosinophil Subgroup

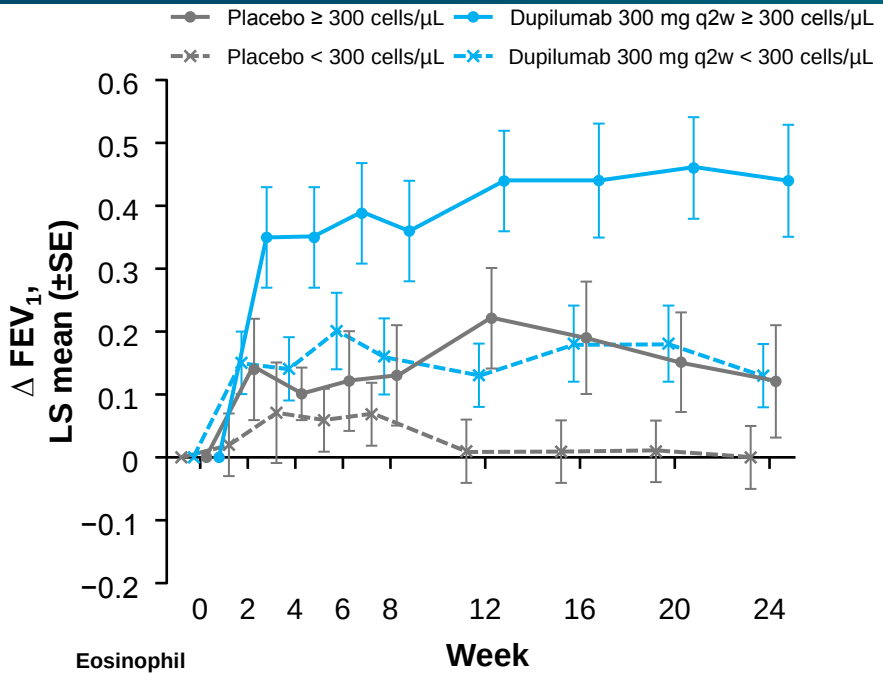




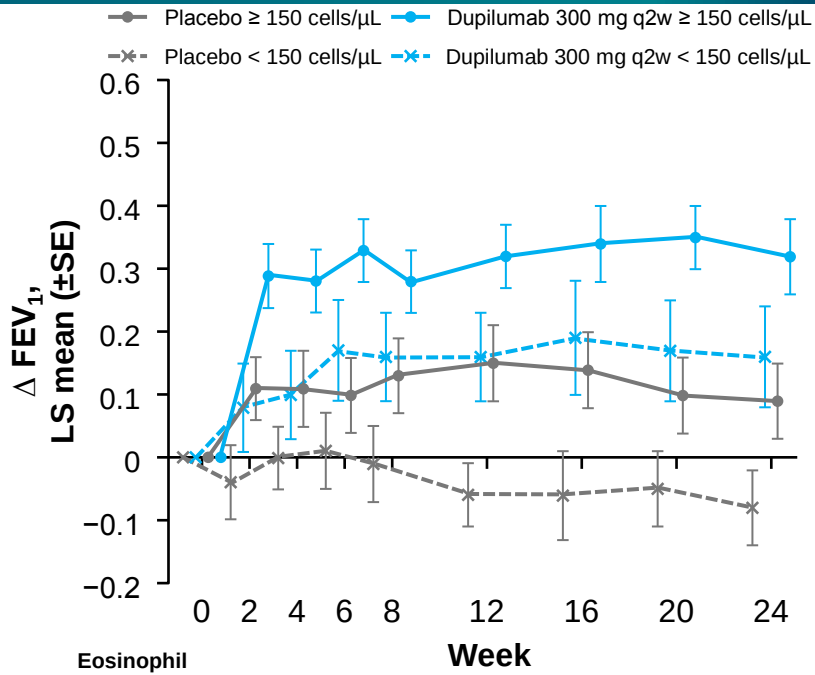
Change From Baseline in FEV_1 at Week 24 by Baseline Blood Eosinophil Subgroup



Change From Baseline in FEV_1 During the 24-Week Treatment Period by Baseline Blood Eosinophils

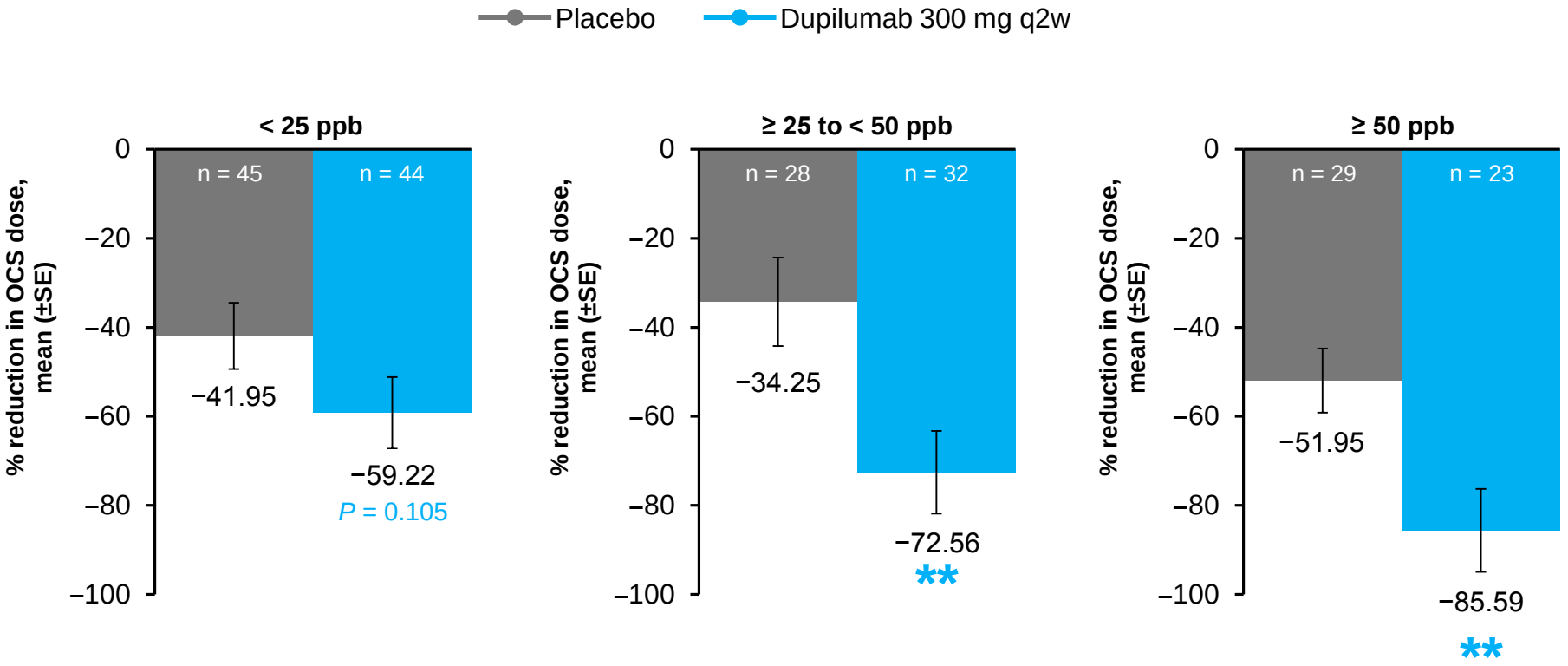


Eosinophil subgroup (cells/µL)		No. of patients								
Placebo	≥ 300	41	41	40	41	41	40	41	41	39
Dupilumab 300 mg q2w	≥ 300	48	46	44	47	45	47	45	47	45
Placebo	< 300	66	63	64	65	66	65	65	66	65
Dupilumab 300 mg q2w	< 300	55	55	54	54	55	52	53	53	52

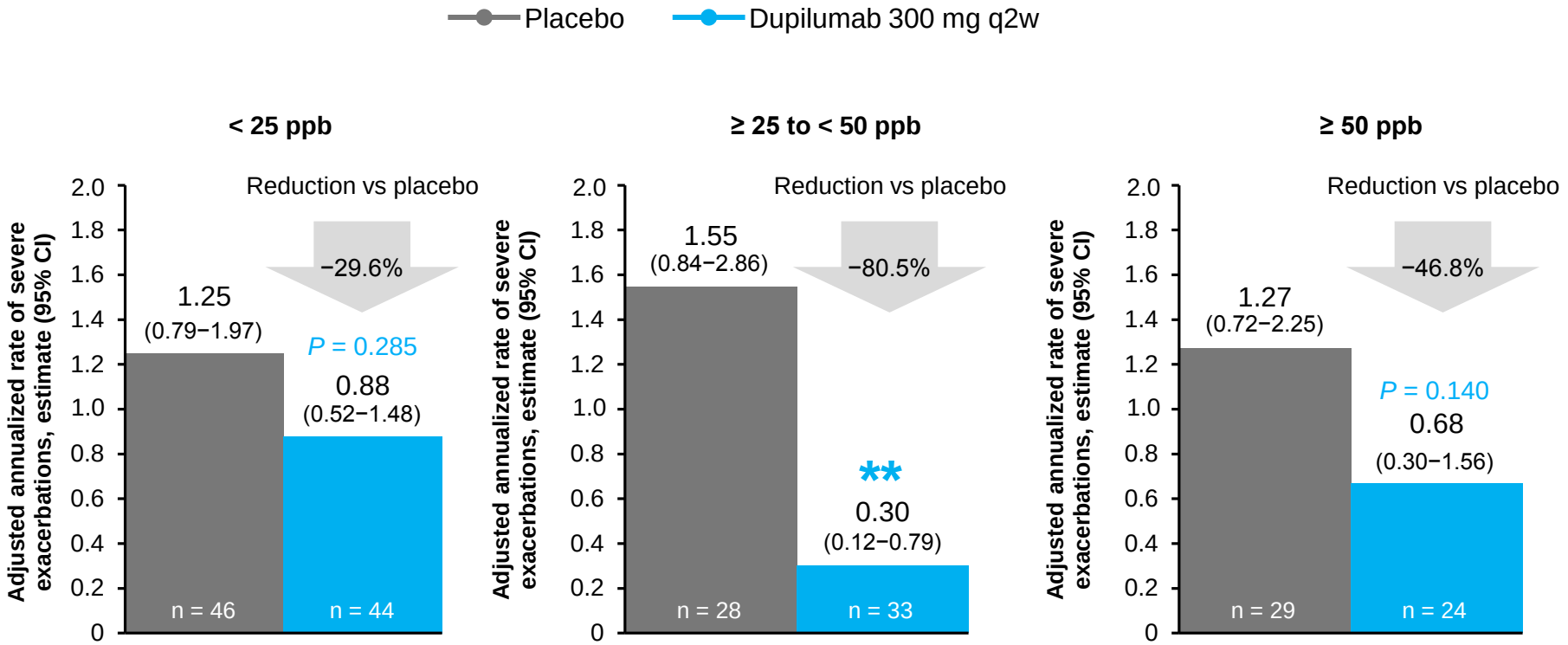


Eosinophil subgroup (cells/µL)		No. of patients								
Placebo	≥ 150	69	67	67	69	69	67	69	69	66
Dupilumab 300 mg q2w	≥ 150	81	79	77	80	78	79	77	79	76
Placebo	< 150	38	37	37	37	38	38	37	38	38
Dupilumab 300 mg q2w	< 150	22	22	21	21	22	20	21	21	21

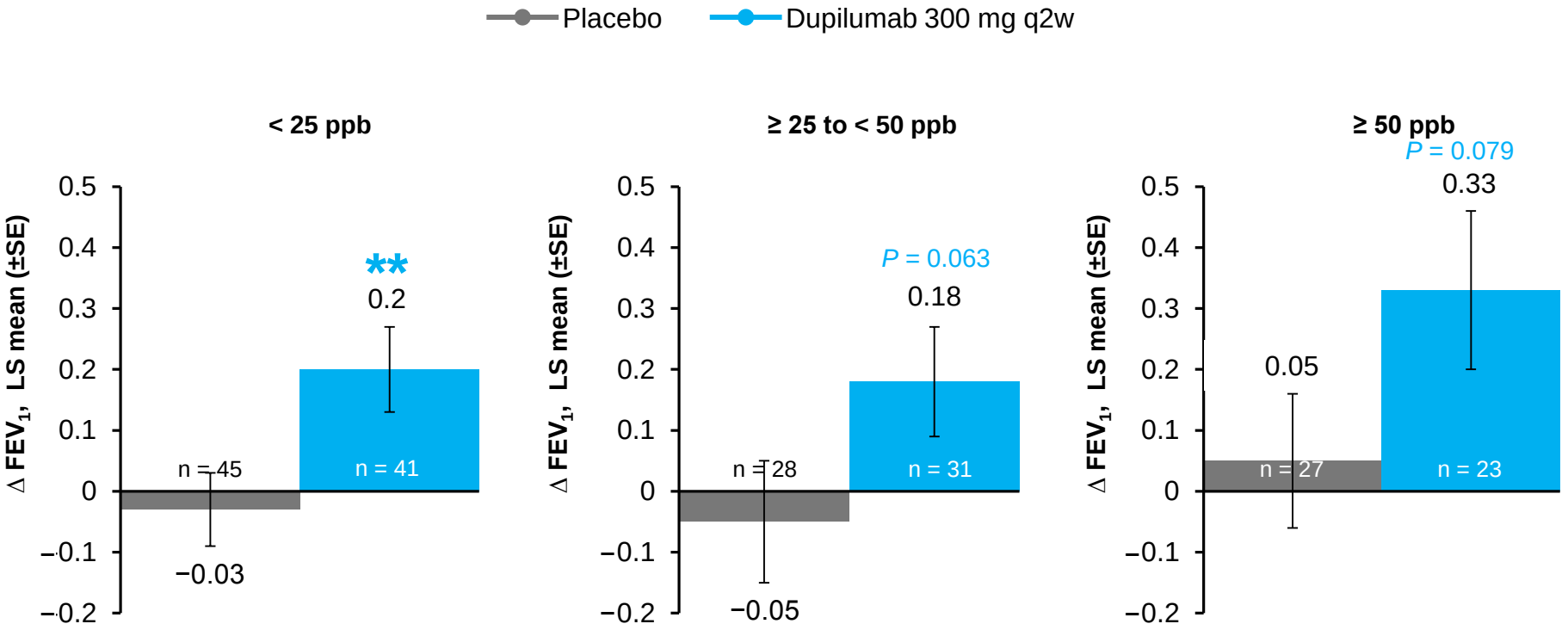
Percentage Reduction in OCS Dose at Week 24 by Baseline FeNO Subgroup



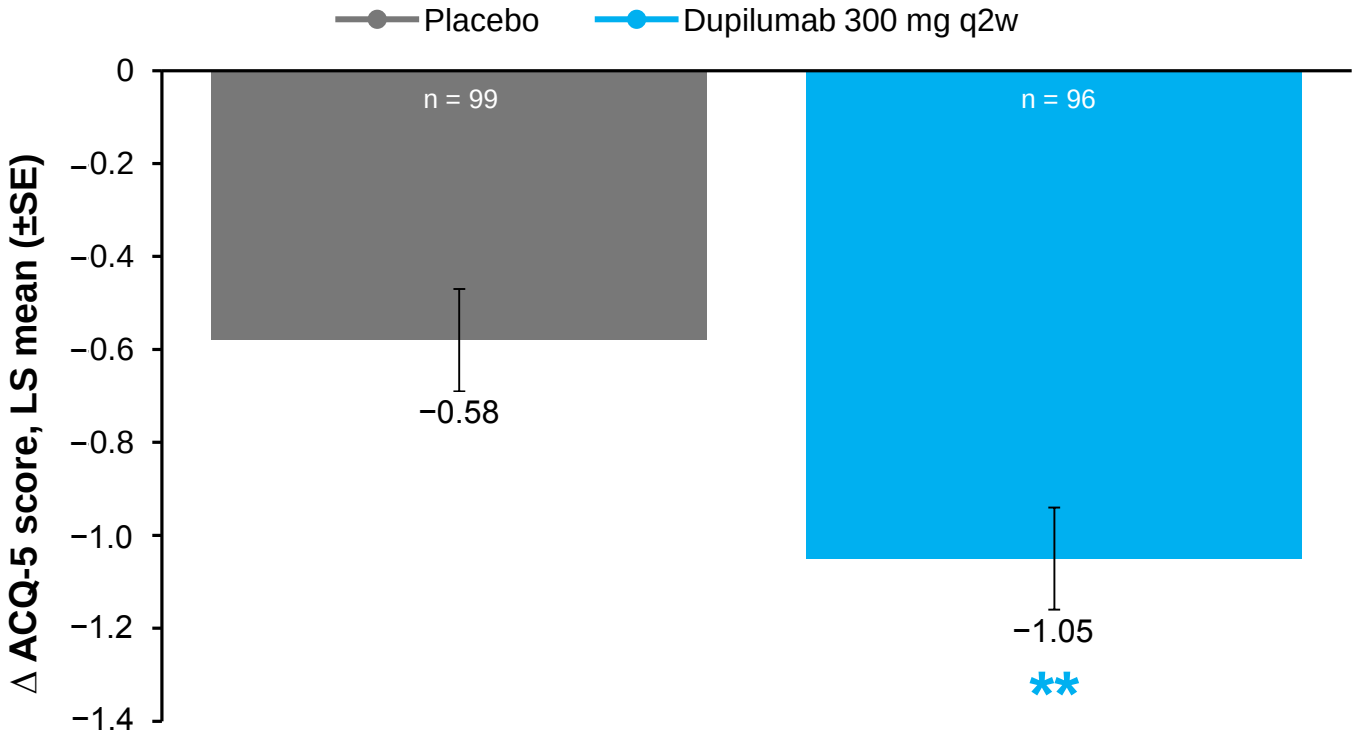
Rate of Severe Exacerbations During the 24-Week Treatment Period by Baseline FeNO Subgroups



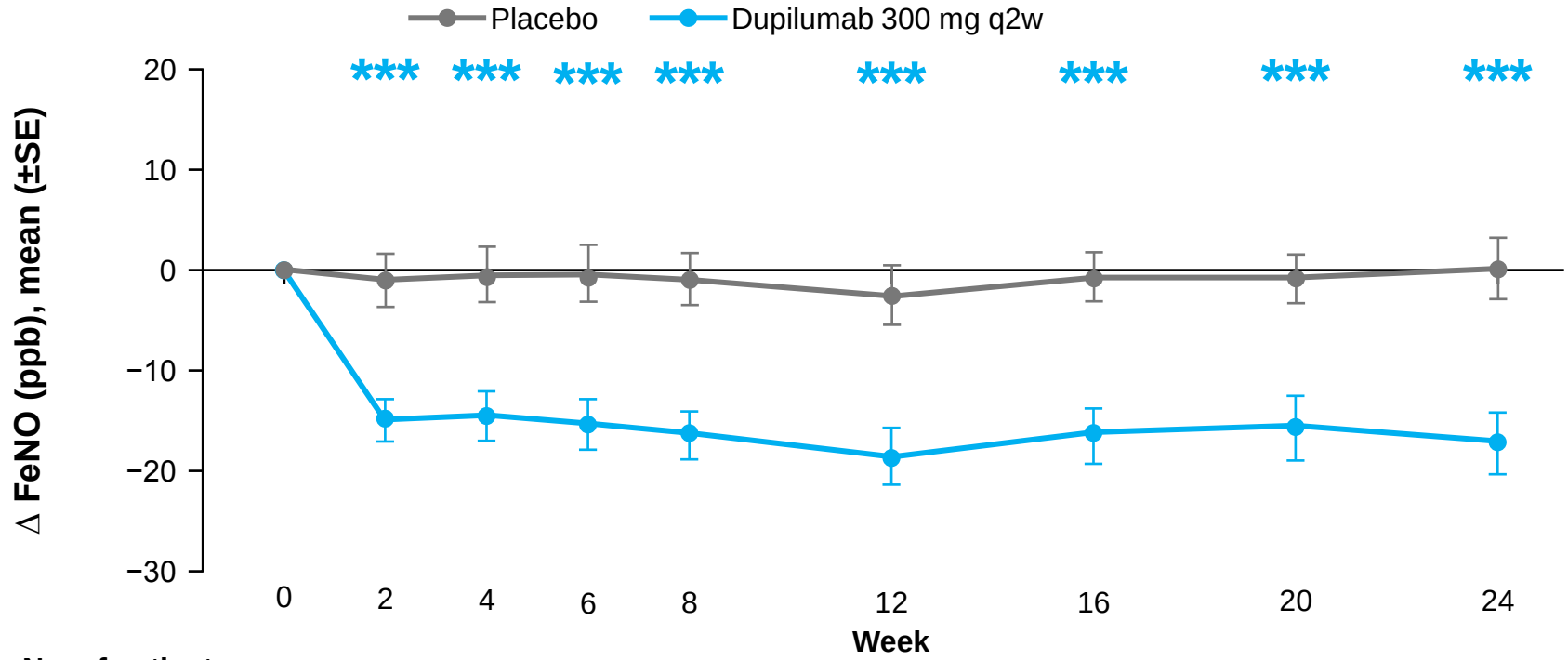
Change From Baseline in FEV_1 at Week 24 by Baseline FeNO Subgroup



Change From Baseline in ACQ-5 Score at Week 24



Effect of Dupilumab on FeNO During the 24-Week Treatment Period



No. of patients									
Placebo	103	90	95	98	95	93	92	93	89
Dupilumab 300 mg q2w	101	90	90	92	93	83	91	86	88

Dupilumab Efficacy in Patients With Baseline Blood Eosinophils ≥ 150 cells/μL Combined With FeNO ≥ 25 ppb at Week 24

	Placebo (n = 43)	Dupilumab 300 mg q2w (n = 49)
Percentage reduction in OCS dose at Week 24, n	43	48
LS mean (SE)	46.30 (6.28)	81.05 (5.83)
LS mean difference versus placebo (95% CI)		34.75 (18.20 to 51.30)
Annualized event rate of severe exacerbation during the 24-week treatment period, n	43	49
Estimate (95% CI)	1.819 (1.282−2.580)	0.440 (0.234 to 0.828)
Relative risk versus placebo (95% CI)		0.242 (0.121 to 0.485)
Change from baseline in pre-bronchodilator FEV_1 (L) at Week 24, n	41	47
LS mean (SE)	0.15 (0.09)	0.36 (0.08)
LS mean difference versus placebo (95% CI)		0.21 (−0.02 to 0.43)

Statistical Analyses

- The primary endpoint was analyzed using an analysis of covariance (ANCOVA) model
- The key secondary and other binary secondary endpoints were analyzed using logistic regression models
- The annualized rate of severe exacerbation events during the 24-week treatment period was analyzed using a negative binomial regression model
- A mixed-effect models with repeated measures approach was used to analyze pre-bronchodilator FEV_1 changes from baseline at various time points during the 24-week treatment period and ACQ-5 change from baseline at Week 24
- Efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all randomized patients analyzed according to treatment allocated, regardless of treatment received

Disclosures

- **Rabe KF:** AstraZeneca, Boehringer Ingelheim, Novartis, Sanofi, Teva – consultant, speaker fees.
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- **Zhu H, Staudinger H, Pirozzi G, Antoni C, Khan A, Teper A:** Sanofi – employees, may hold stock and/or stock options in the company.
- **Amin N, Graham NMH, Ruddy M, Akinlade B, Chao J:** Regeneron Pharmaceuticals, Inc. – employees and shareholders.