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Dupilumab Treatment Produces Rapid and Sustained Improvements in FEV_1 in Patients With Uncontrolled, Moderate-to-Severe Asthma From the LIBERTY ASTHMA QUEST Study

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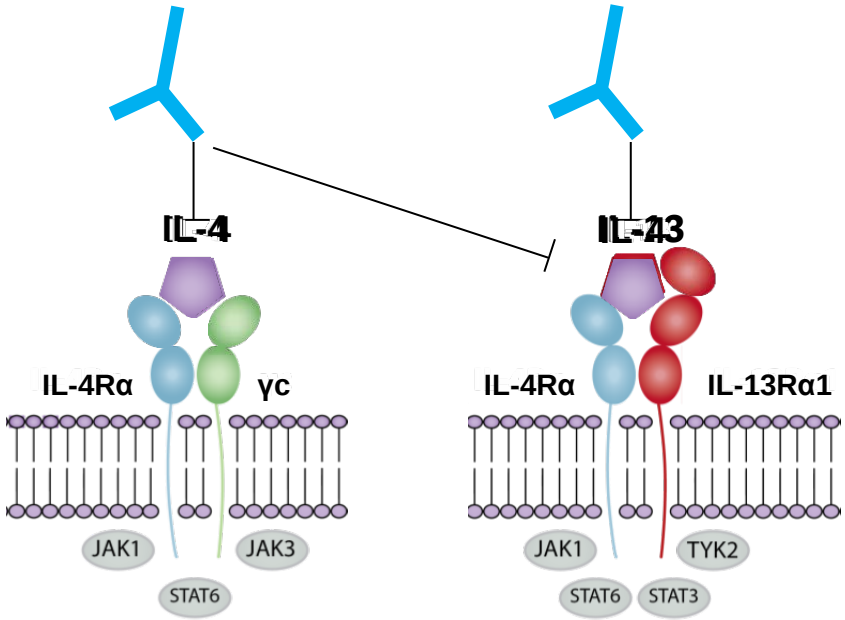
Disclosures

- Castro M: Sanofi – research support
- Busse W: Sanofi, Regeneron Pharmaceuticals, Inc. – consultant fees
- Zhang B, Rowe P, Pirozzi G, Teper A: Sanofi – employees, may hold stock and/or stock options in the company
- Maroni J, Amin N, Graham NMH: Regeneron Pharmaceuticals, Inc. – employees and shareholders

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,[1] and is approved for the treatment of adults with moderate-to-severe atopic dermatitis
- **Dupilumab** has also shown efficacy and an acceptable safety profile in patients with other Type 2 inflammatory diseases including nasal polyposis with chronic rhinosinusitis[2] and eosinophilic esophagitis[3]



Type I receptor

B cells, T cells, monocytes, eosinophils, fibroblasts

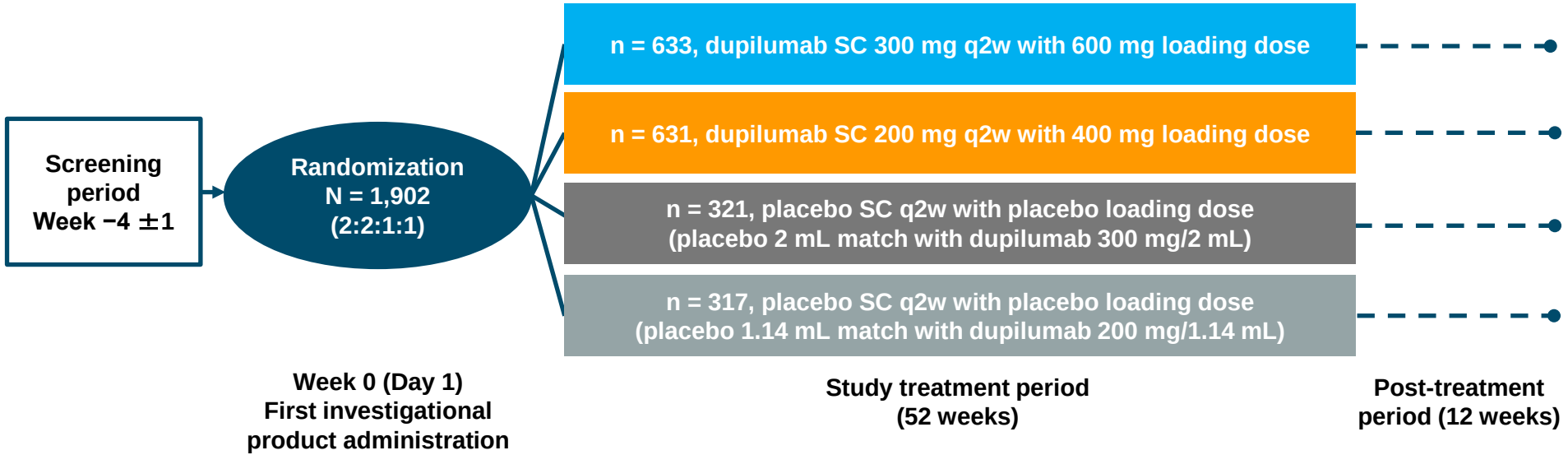
Type II receptor

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

IL-4Rα, interleukin-4 receptor alpha. 1. Gandhi NA, et al. Expert Rev Clin Immunol. 2017; 2. Bachert C, et al. JAMA. 2016; 3. Hirano I, et al. Presented at WCOG/ACG 2017.

Dupilumab asthma QUEST phase 3 trial

- The phase 3 LIBERTY ASTHMA QUEST study evaluated the efficacy and safety of dupilumab in patients with uncontrolled moderate-to-severe asthma



Patients were allowed to continue on to the open-label extension study (LTS12551) after completion of treatment

FEV_1, forced expiratory volume in 1 second; ITT, intent-to-treat; q2w, every 2 weeks; SC, subcutaneous. ClinicalTrials.gov Identifier: NCT02414854.

Patient main inclusion and exclusion criteria

Inclusion

- Age ≥ 12 years with physician-diagnosed persistent asthma for ≥ 12 months[1]
- Medium-to-high dose ICS plus up to 2 additional controllers
- FEV_1 ≤ 80% predicted normal (≤ 90% for adolescents)
- Bronchodilator reversibility ≥ 12% and 200 mL
- ACQ-5 score ≥ 1.5
- ≥ 1 asthma exacerbation in prior year
- No minimum requirements for baseline blood eosinophil count or any other Type 2 biomarker

Exclusion

- COPD or other lung diseases that might impair lung function
- Severe asthma exacerbation within 1 month of the enrollment visit or during screening period
- Current smoker, smoker who stopped within 6 months before screening or with a smoking history of > 10 pack-years
- Comorbid disease that might interfere with the evaluation of the study drug

ACQ-5, 5-item asthma control questionnaire; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids. 1. Global Initiative for Asthma (GINA). 2014.

Primary and secondary endpoints

- **Primary endpoints**
  - Change from baseline in pre-bronchodilator FEV_1 (L) at Week 12
  - Annualized rate of severe asthma exacerbations during the 52-week treatment period
- **Secondary endpoint**
  - Absolute change from baseline in pre-bronchodilator FEV_1 (L) over the 52-week treatment period
- **Endpoints assessed for the following subgroups**
  - ≥ 300 eosinophils cells/µL
  - FeNO ≥ 25 ppb

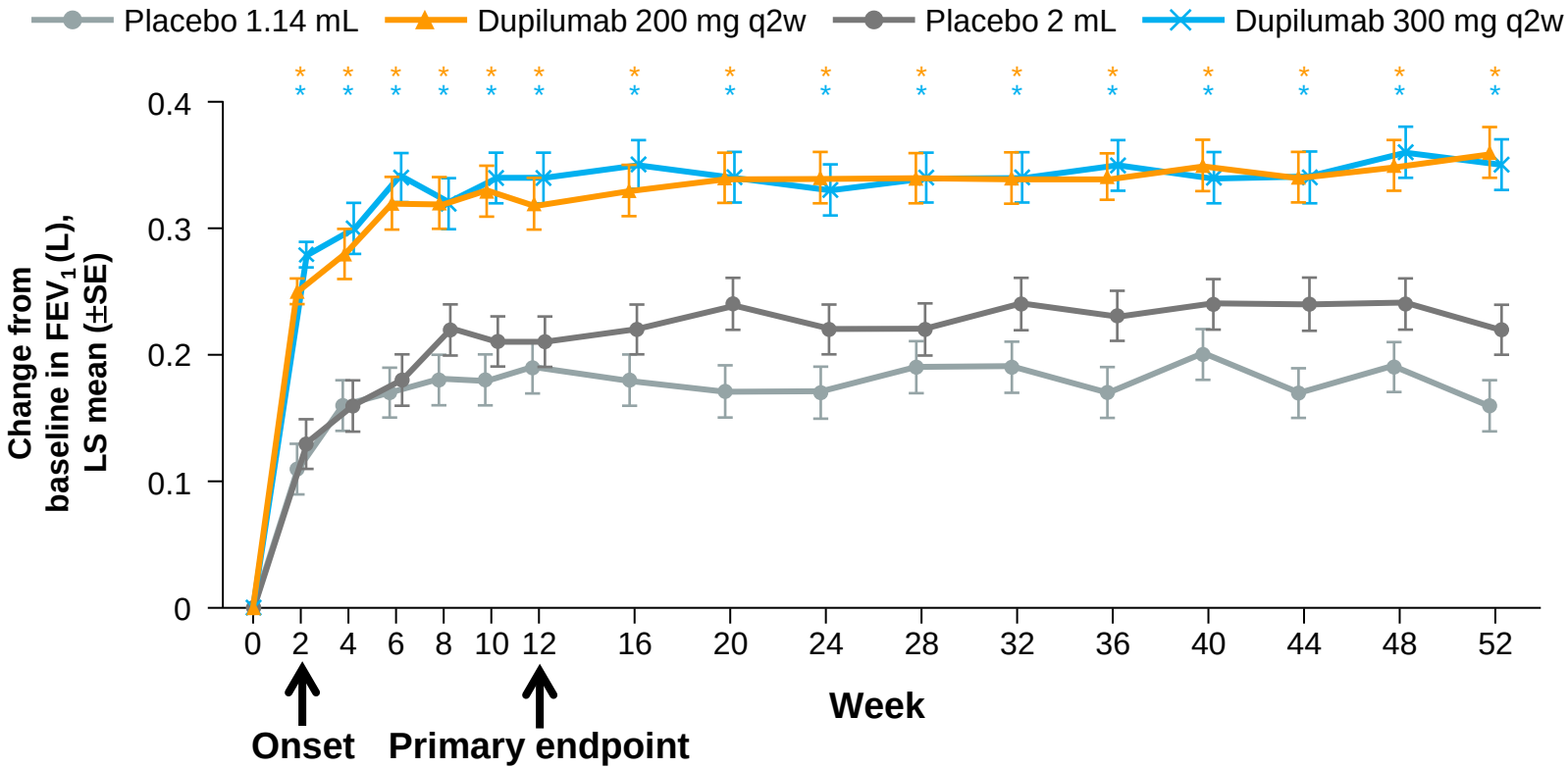
FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

Baseline demographic and clinical characteristics: ITT population

	Placebo (n = 317)	Dupilumab 200 mg q2w (n = 631)	Placebo (n = 321)	Dupilumab 300 mg q2w (n = 633)	Overall population (N = 1,902)
Age, mean (SD) — years	48.2 (15.6)	47.9 (15.3)	48.2 (14.7)	47.7 (15.6)	47.9 (15.3)
Female sex — n (%)	198 (62.5)	387 (61.3)	218 (67.9)	394 (62.2)	1,197 (62.9)
Pre-bronchodilator FEV_1, mean (SD) — L	1.76 (0.61)	1.78 (0.62)	1.75 (0.57)	1.78 (0.60)	1.78 (0.60)
Pre-bronchodilator FEV_1, mean (SD) — % predicted	**58.43 (13.22)**	**58.38 (13.52)**	**58.35 (13.87)**	**58.51 (13.52)**	**58.43 (13.52)**
FEV_1 reversibility, mean (SD) — %	25.06 (18.76)	27.39 (22.79)	26.45 (17.65)	25.73 (23.79)	26.29 (21.73)
Number of exacerbations in past year — mean (SD)	**2.07 (1.58)**	**2.07 (2.66)**	**2.31 (2.07)**	**2.02 (1.86)**	**2.09 (2.15)**
High-dose inhaled corticosteroids use — n (%)	172 (54.3)	317 (50.2)	167 (52.0)	323 (51.0)	979 (51.5)
Atopic/allergic ongoing condition — n (%)	266 (83.9)	509 (80.7)	266 (82.9)	524 (82.8)	1,565 (82.3)
Nasal polyposis and/or chronic rhinosinusitis	73 (23.0)	141 (22.3)	80 (24.9)	145 (22.9)	439 (23.1)
ACQ-5 score — mean (SD)	**2.71 (0.73)**	**2.76 (0.80)**	**2.77 (0.77)**	**2.77 (0.76)**	**2.76 (0.77)**
Blood eosinophil count, mean (SD) — cells/μL	**370 (338)**	**349 (345)**	**391 (419)**	**351 (369)**	**360 (366)**
FeNO, mean (SD) — ppb	**34.47 (28.54)**	**34.45 (34.91)**	**38.39 (38.00)**	**34.01 (29.74)**	**34.97 (32.85)**

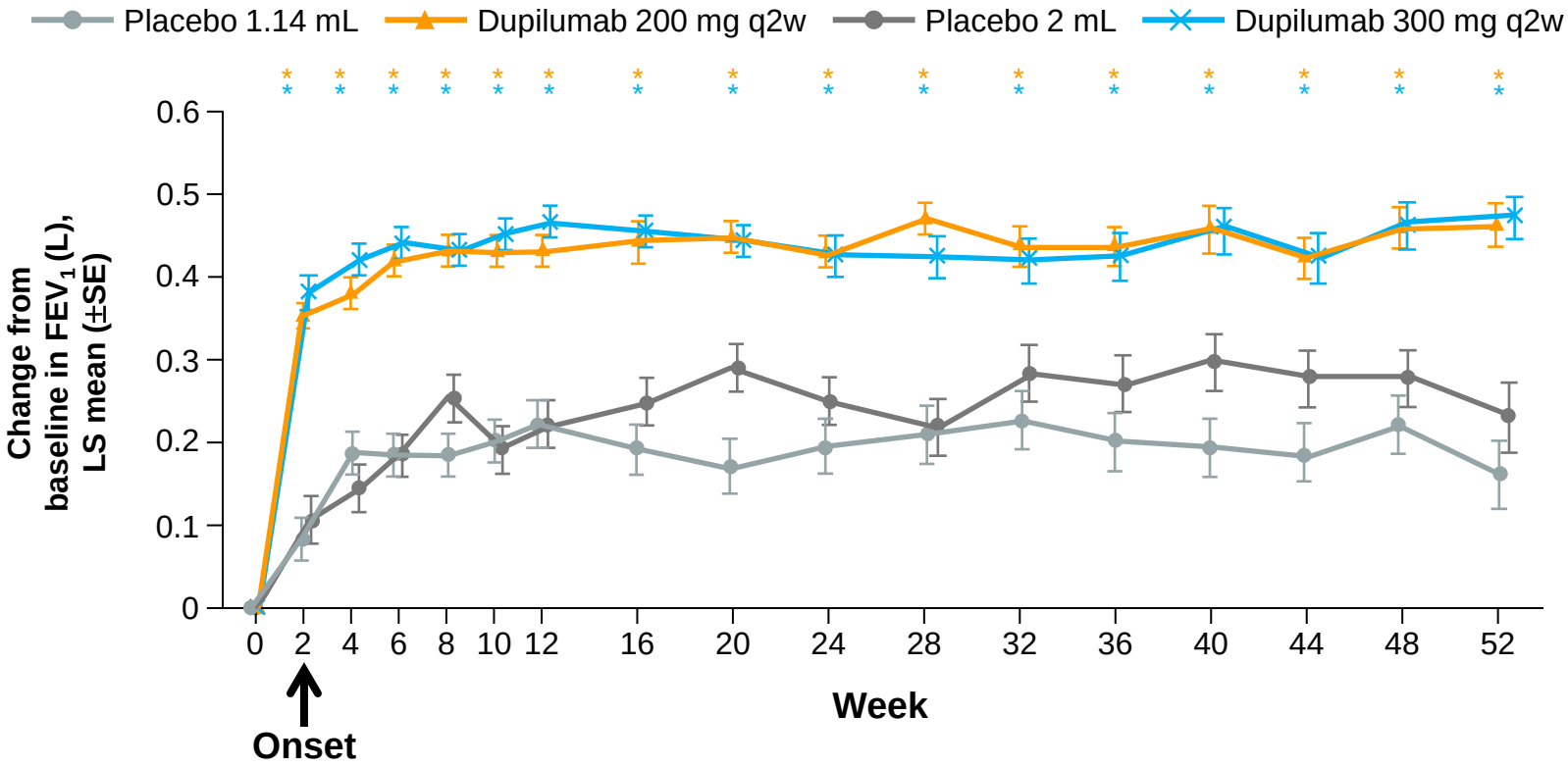
SD, standard deviation. ACQ-5 scored 0 to 6, higher scores indicate less control.

Dupilumab significantly improved FEV_1 by Week 2 and sustained through Week 52 in the ITT population



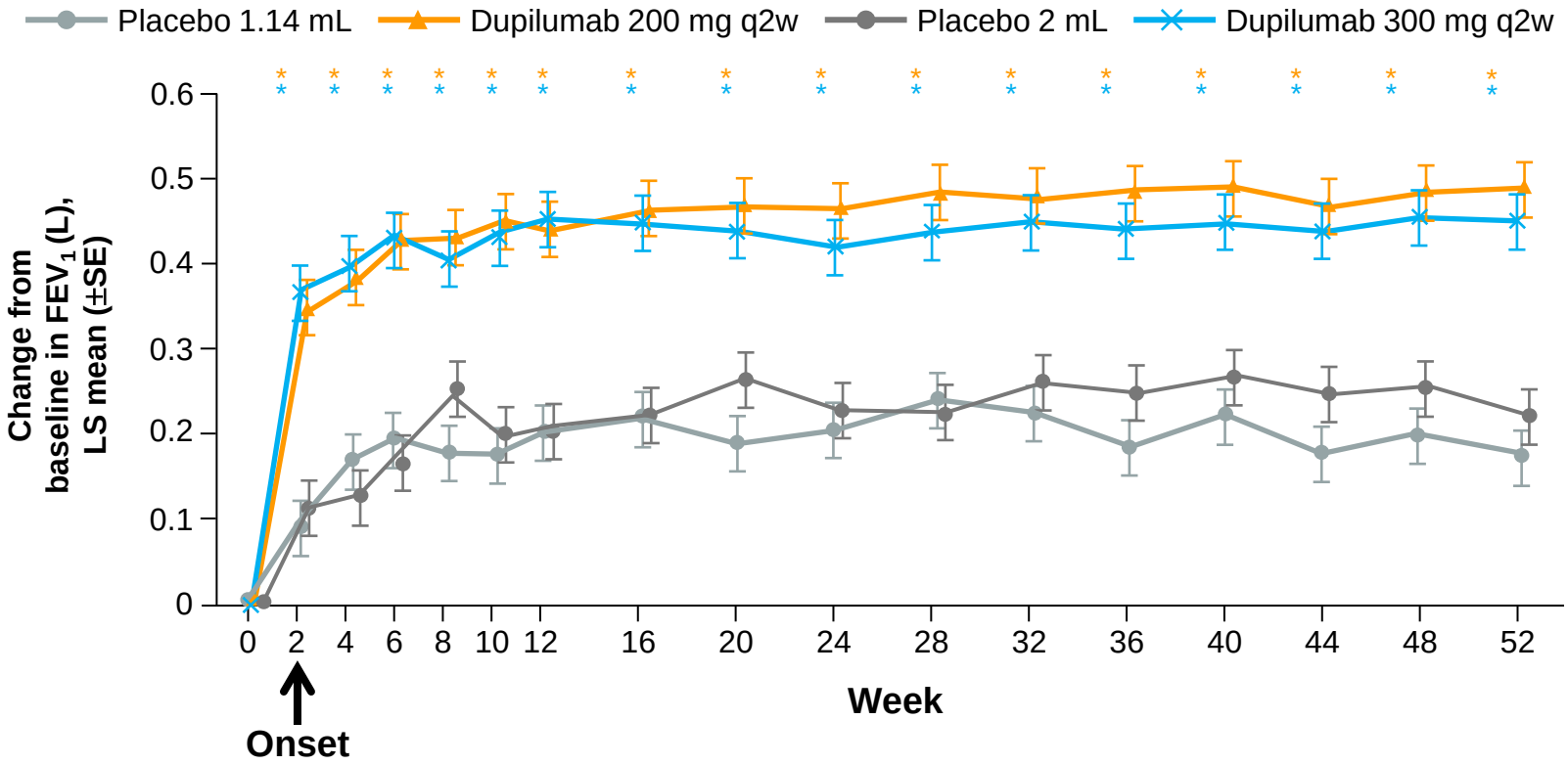
*P < 0.001 at Week 12, and nominal P < 0.001 at all other time points. LS, least squares; SE, standard error.

Dupilumab significantly improved FEV_1 by Week 2 and sustained through Week 52 in patients with eosinophils ≥ 300 cells/µL



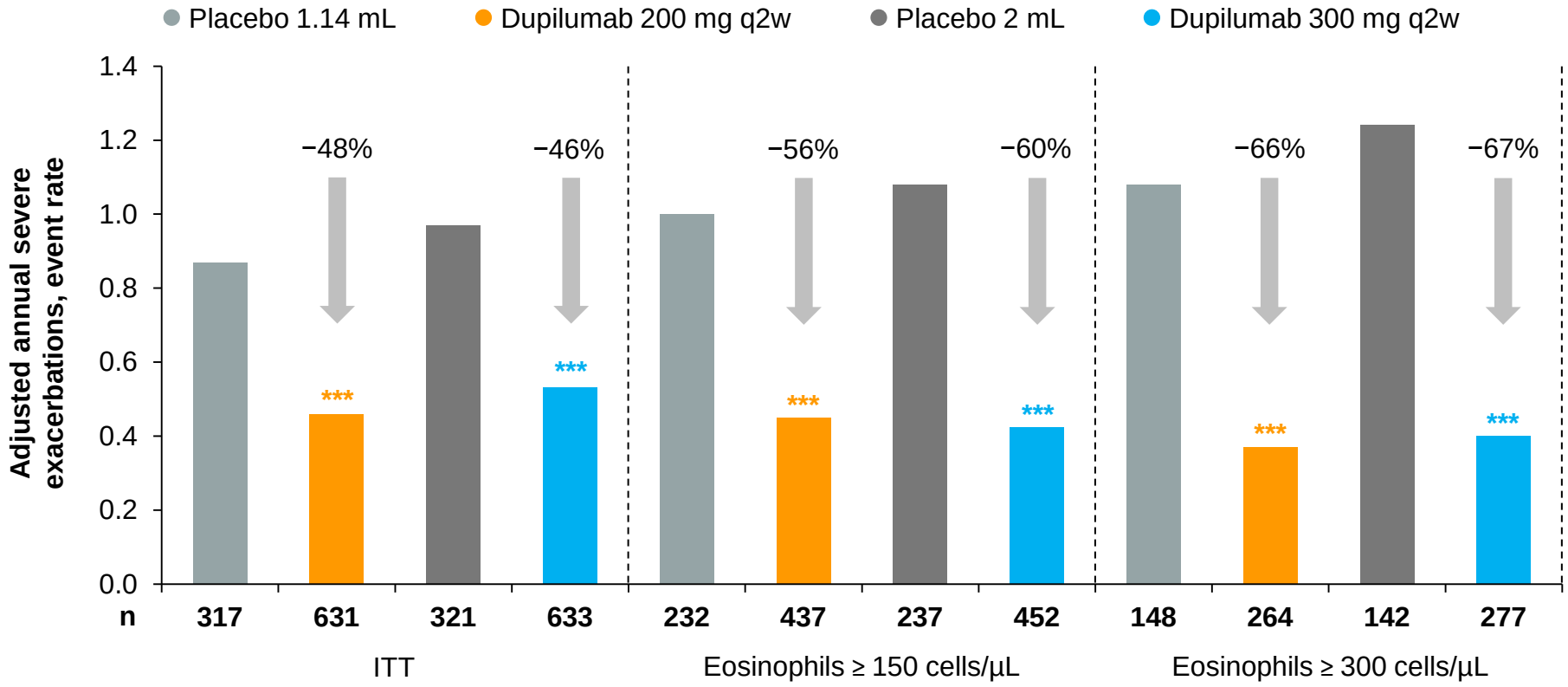
*P < 0.001 vs placebo (nominal for dupilumab 200 mg q2w due to hierarchy break and at all time points except Week 12).

Dupilumab significantly improved FEV_1 by Week 2 and sustained through Week 52 in patients with FeNO ≥ 25 ppb



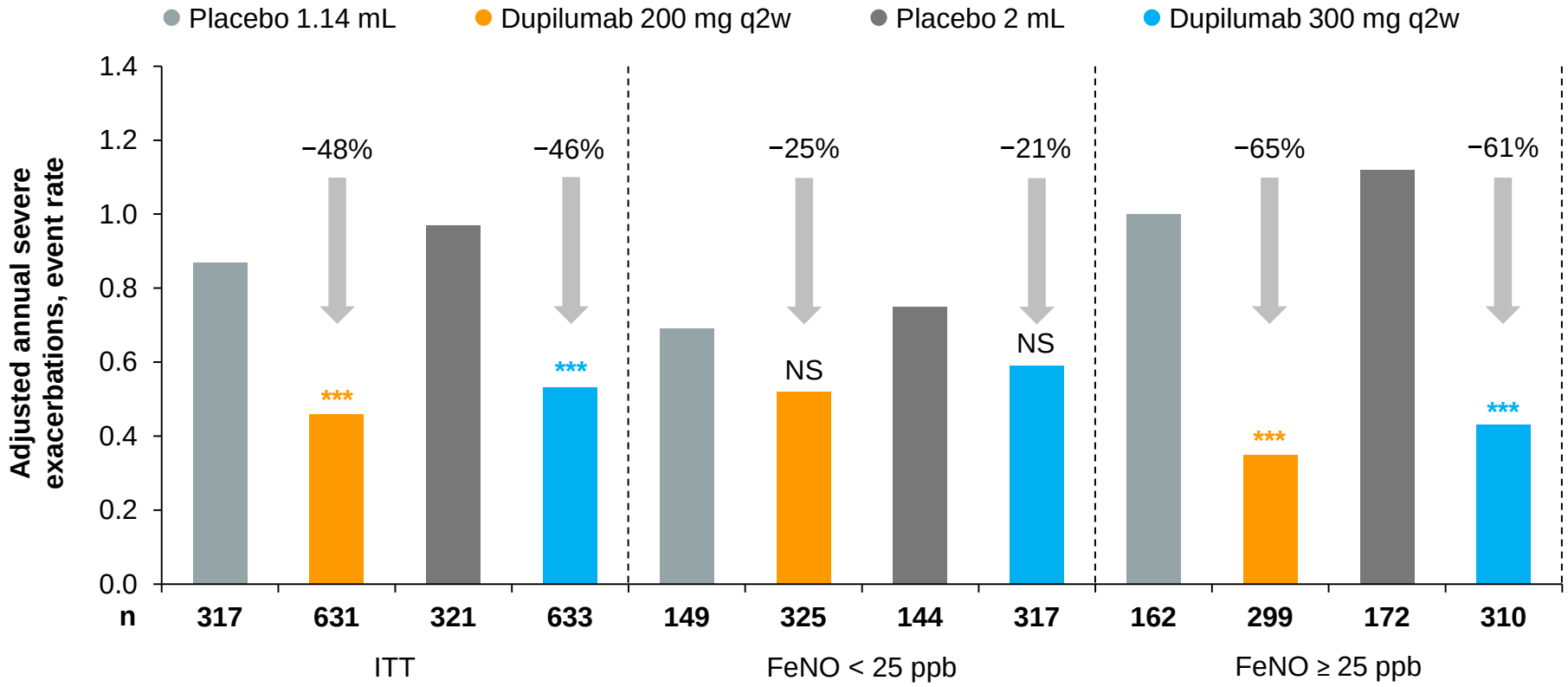
* Nominal *P* < 0.001 vs placebo.

Effect on adjusted severe exacerbations: relative reduction versus placebo according to baseline eosinophil levels



***P < 0.001 (nominal for dupilumab 200 mg q2w in eosinophils ≥150 and ≥300µL subgroups due to hierarchy break).

Effect on adjusted severe exacerbations: relative reduction versus placebo according to baseline FeNO levels



***P < 0.001 for ITT population and nominal P < 0.001 in FeNO subgroups; NS, non-significant.

Dupilumab was generally well tolerated

n (%)	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined	
	Placebo (n = 313)	Dupilumab (n = 631)	Placebo (n = 321)	Dupilumab (n = 632)	Placebo (n = 634)	Dupilumab (n = 1263)
Any TEAE	257 (82.1)	508 (80.5)	270 (84.1)	515 (81.5)	527 (83.1)	1023 (81.0)
Any serious TEAE	26 (8.3)	49 (7.8)	27 (8.4)	55 (8.7)	53 (8.4)	104 (8.2)
Any TEAE leading to death[a]	3 (1.0)	1 (0.2)	0	4 (0.6)	3 (0.5)	5 (0.4)
TEAEs occurring in ≥ 10% of patients (MedDRA PT)						
Viral upper respiratory tract infection	60 (19.2)	119 (18.9)	64 (19.9)	111 (17.6)	124 (19.6)	230 (18.2)
Upper respiratory tract infection	37 (11.8)	69 (10.9)	49 (15.3)	77 (12.2)	86 (13.6)	146 (11.6)
Bronchitis	47 (15.0)	73 (11.6)	42 (13.1)	71 (11.2)	89 (14.0)	144 (11.4)
Injection site erythema	13 (4.2)	76 (12.0)	22 (6.9)	98 (15.5)	35 (5.5)	174 (13.8)
Injection-site reactions (MedDRA HLT)	17 (5.4)	96 (15.2)	33 (10.3)	116 (18.4)	50 (7.9)	212 (16.8)

[a]All deaths were considered unrelated to study medication. HLT, High-Level Term; MedDRA PT, Medical Dictionary for Regulatory Activities Preferred Term; TEAE, treatment-emergent adverse event.

Conclusions

- Dupilumab added to ICS plus up to 2 additional controllers significantly improved FEV_1 and reduced annualized severe exacerbation rates in the overall population of patients with uncontrolled moderate-to-severe asthma
- Significant improvements in FEV_1 were observed as early as Week 2 and were maintained up to Week 52
- Treatment effects were higher in subgroups with higher baseline blood eosinophil counts and FeNO levels
- Dupilumab was generally well tolerated

Acknowledgments

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Back-up Slides

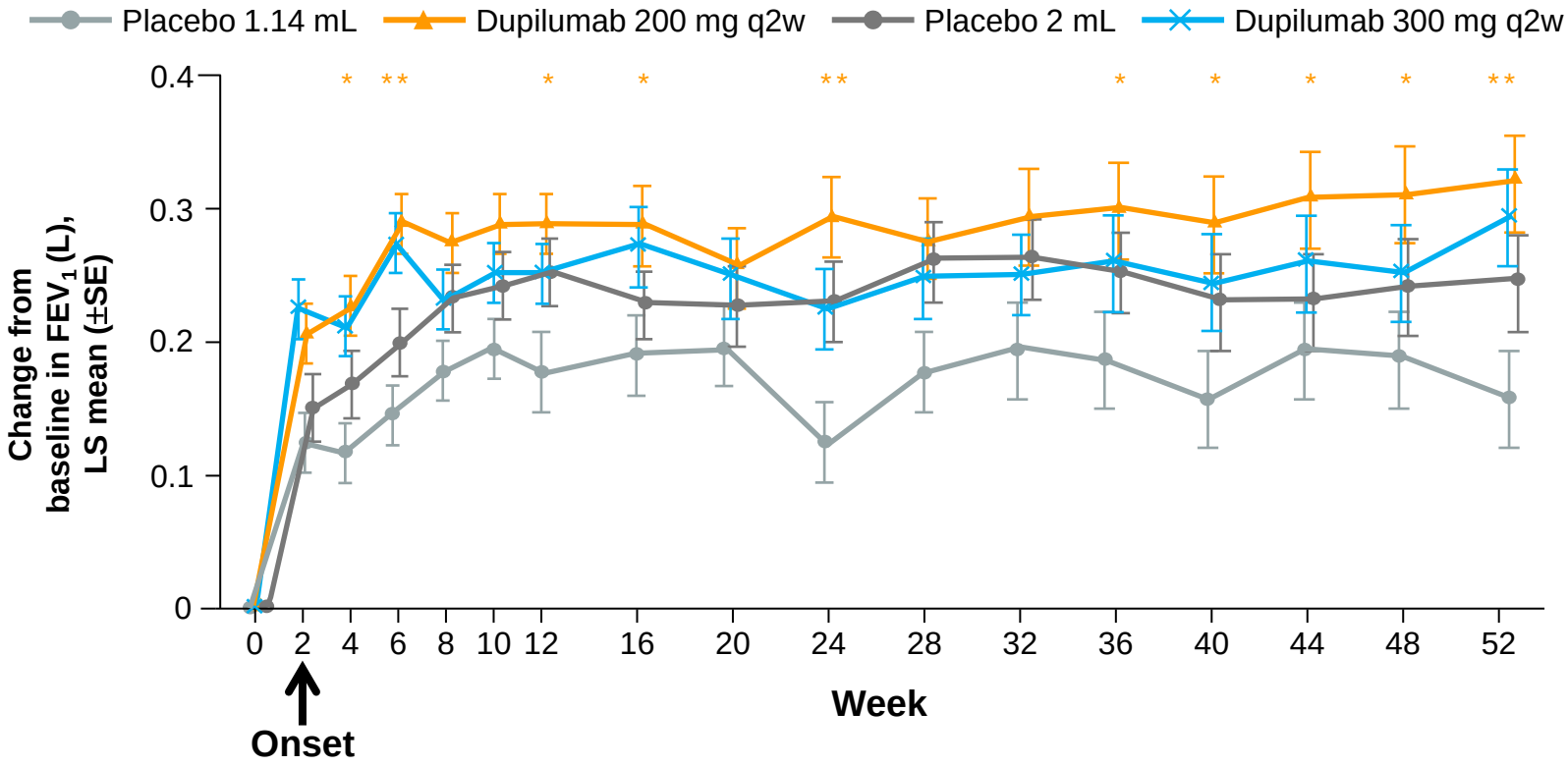
Patient disposition

Disposition, n (%)	Placebo 1.14 mL (n = 317)	Dupilumab 200 mg q2w (n = 631)	Placebo 2.0 mL (n = 321)	Dupilumab 300 mg q2w (n = 633)
Randomized and treated	315 (99.4)	629 (99.7)	321 (100)	632 (99.8)
Completed the 52-week treatment period	230 (72.6)	487 (77.2)	248 (77.3)	469 (74.1)
Discontinued randomized treatment during randomization treatment period	38 (12.0)	70 (11.1)	35 (10.9)	85 (13.4)
Reason for treatment discontinuation				
Adverse event	19 (6.0)	21 (3.3)	10 (3.1)	46 (7.3)
Lack of efficacy	3 (0.9)	4 (0.6)	5 (1.6)	3 (0.5)
Protocol non-compliance	4 (1.3)	3 (0.5)	3 (0.9)	1 (0.2)
Other reason	12 (3.8)	42 (6.7)	17 (5.3)	35 (5.5)

Statistical analysis

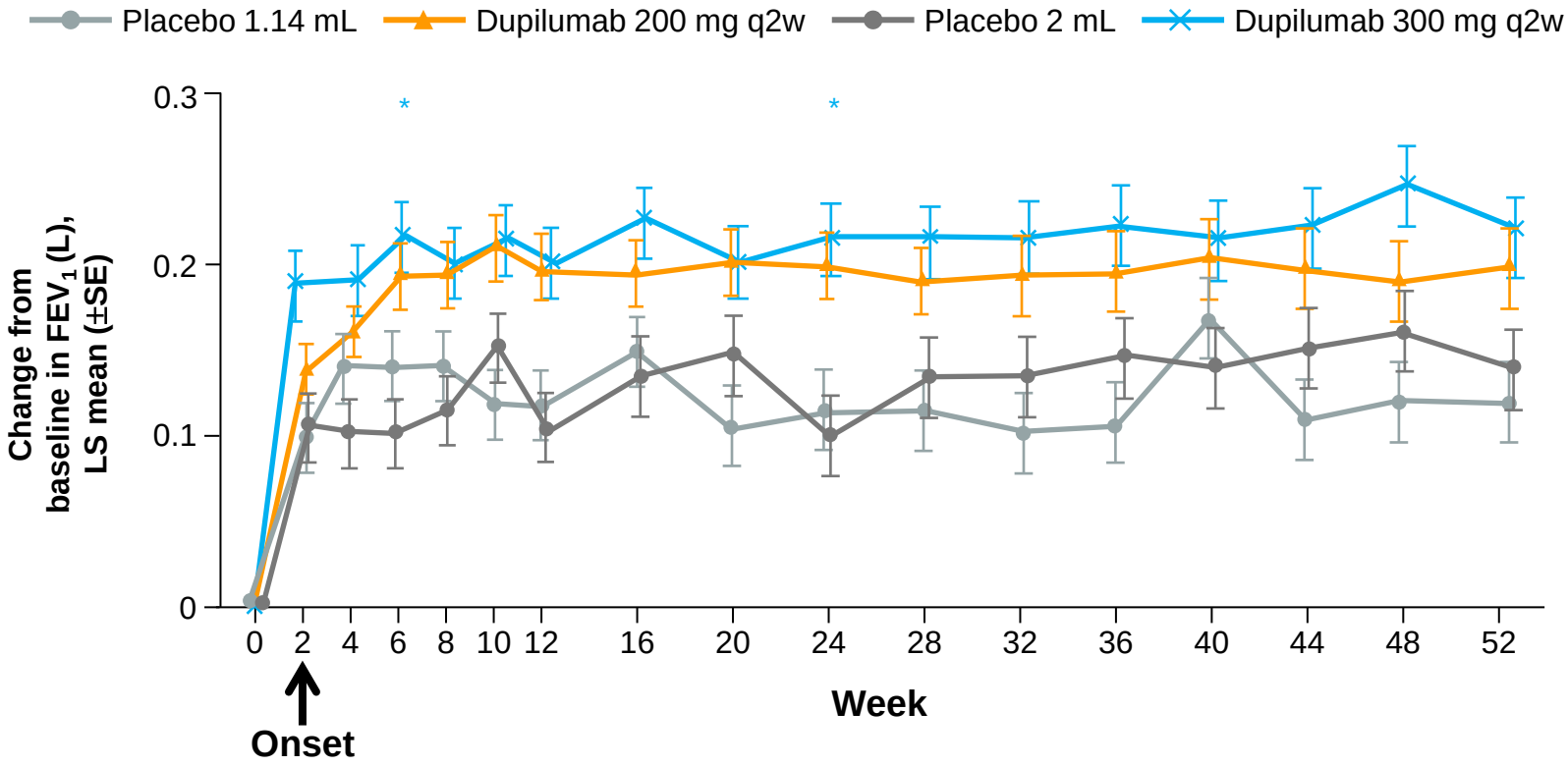
- Efficacy analyses were performed on the ITT population, defined as all randomized patients by allocated treatment whether or not treatment was received
- The annualized rate of severe asthma exacerbations during the 52-week treatment period was analyzed using a negative binomial regression model
- Change from baseline in FEV_1 at various time points during the 52-week treatment period was analyzed using a mixed-effects model with repeated measures
- The primary endpoints, severe asthma exacerbation rates and FEV_1, were also analyzed in a subgroup of patients defined by baseline blood eosinophil counts (≥ 300, ≥ 150 to < 300, and < 150 cells/μL) and FeNO levels (≥ 25 and < 25 ppb)
- The safety population included all patients who received ≥ 1 dose or part of a dose of the investigational treatment, analyzed according to the treatment received

Dupilumab significantly improved FEV_1 by Week 2 and sustained through Week 52 in patients with eosinophils ≥ 150 to < 300 cells/µL



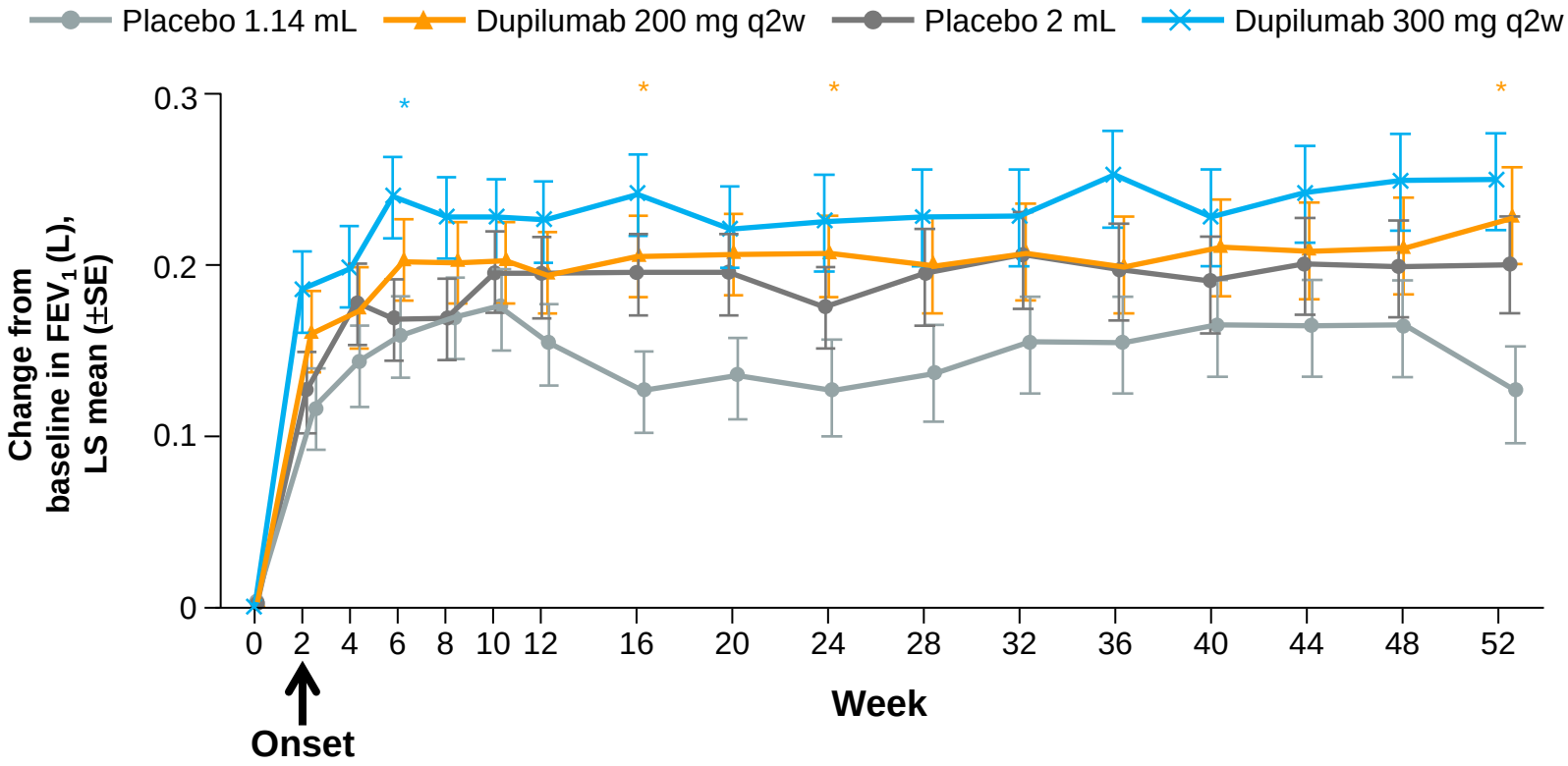
**Nominal *P* < 0.01; *Nominal *P* < 0.05 vs placebo.

Effect of dupilumab on FEV_1 during 52-weeks treatment period in patients with eosinophils < 150 cells/µL



*Nominal *P* < 0.05 vs placebo.

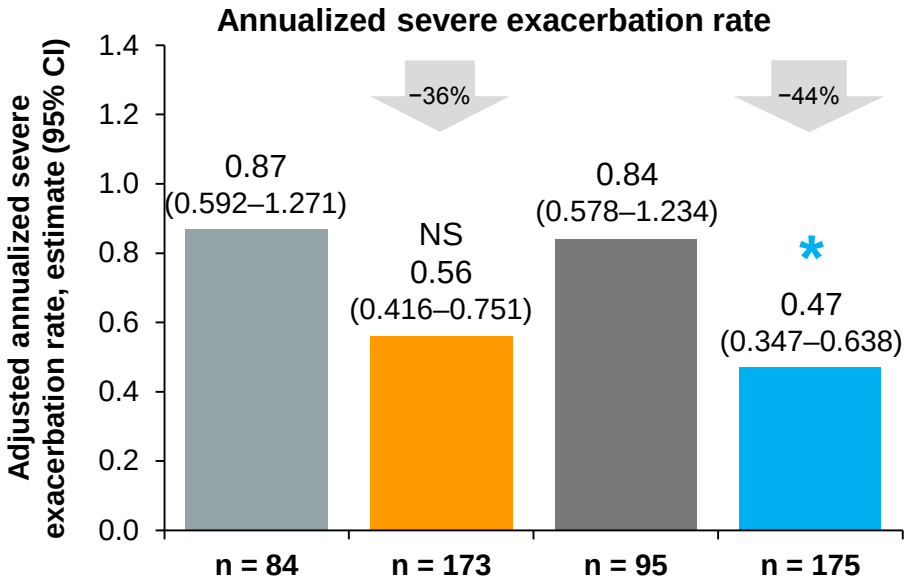
Effect of dupilumab on FEV_1 during 52-weeks treatment period in patients with FeNO < 25 ppb

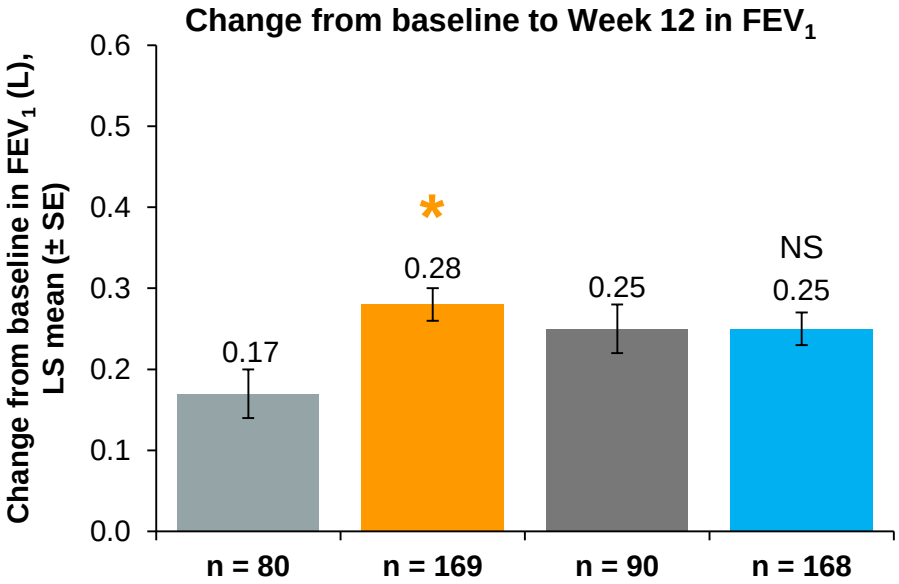


*Nominal *P* < 0.05 vs placebo.

Effect of dupilumab on annualized severe exacerbation rate during 52-weeks treatment period and FEV_1 at Week 12 in patients with eosinophils ≥ 150 to < 300 cells/μL

Placebo 1.14 mL Dupilumab 200 mg q2w Placebo 2 mL Dupilumab 300 mg q2w

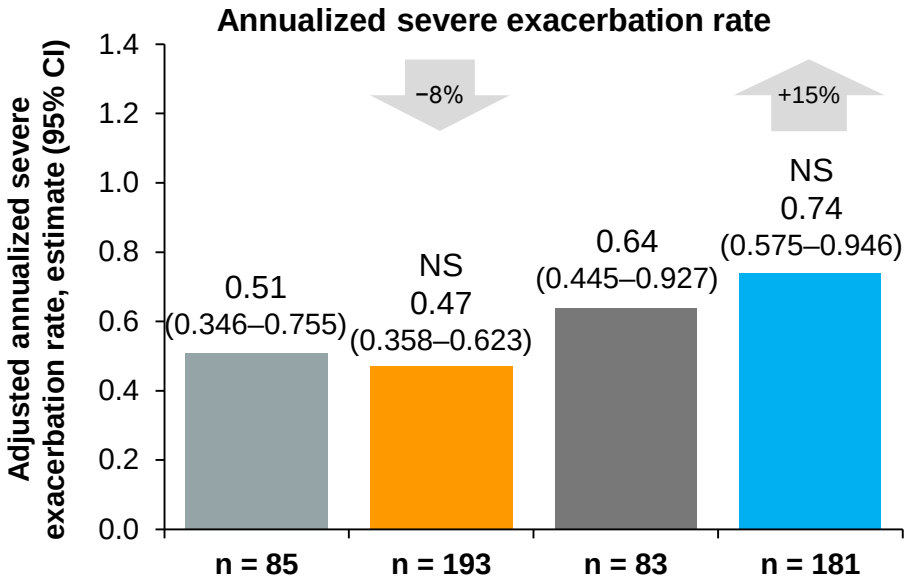


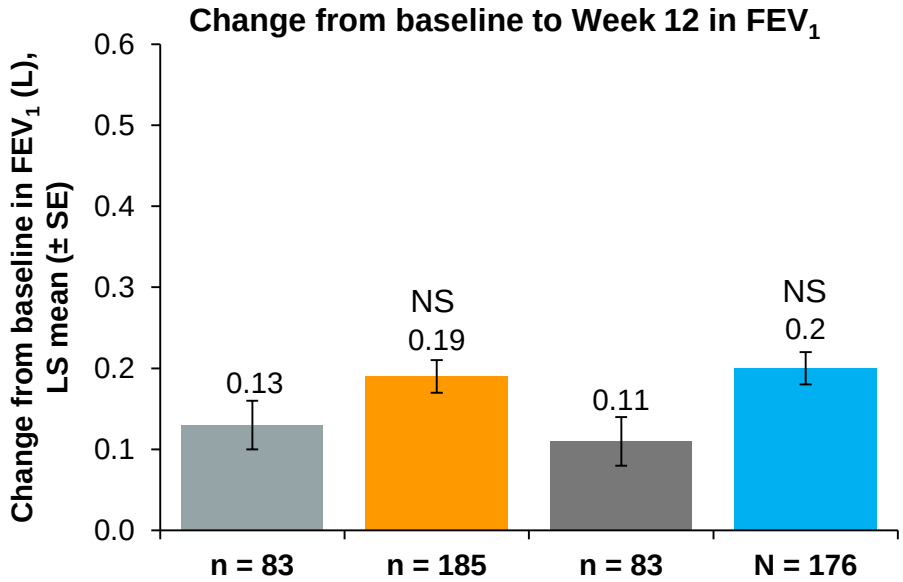


*Nominal *P* < 0.05 vs placebo.

Effect of dupilumab on annualized severe exacerbation rate during 52-weeks treatment period and FEV_1 at Week 12 in patients with eosinophils < 150 cells/µL

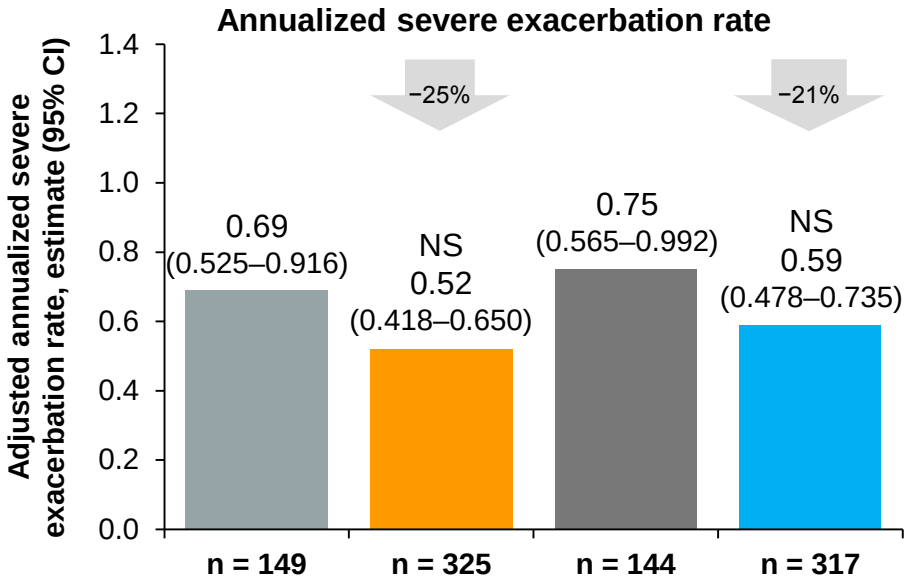
Placebo 1.14 mL · Dupilumab 200 mg q2w · Placebo 2 mL · Dupilumab 300 mg q2w

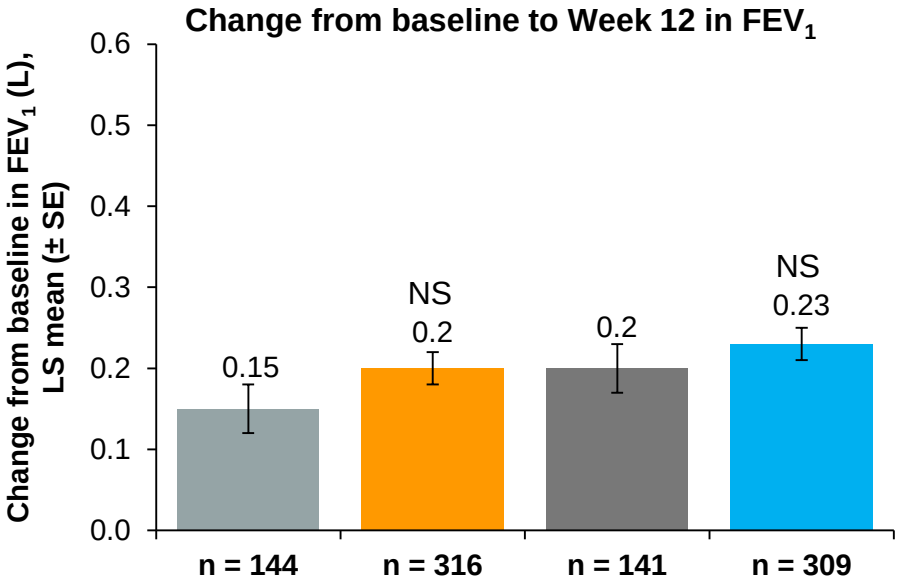




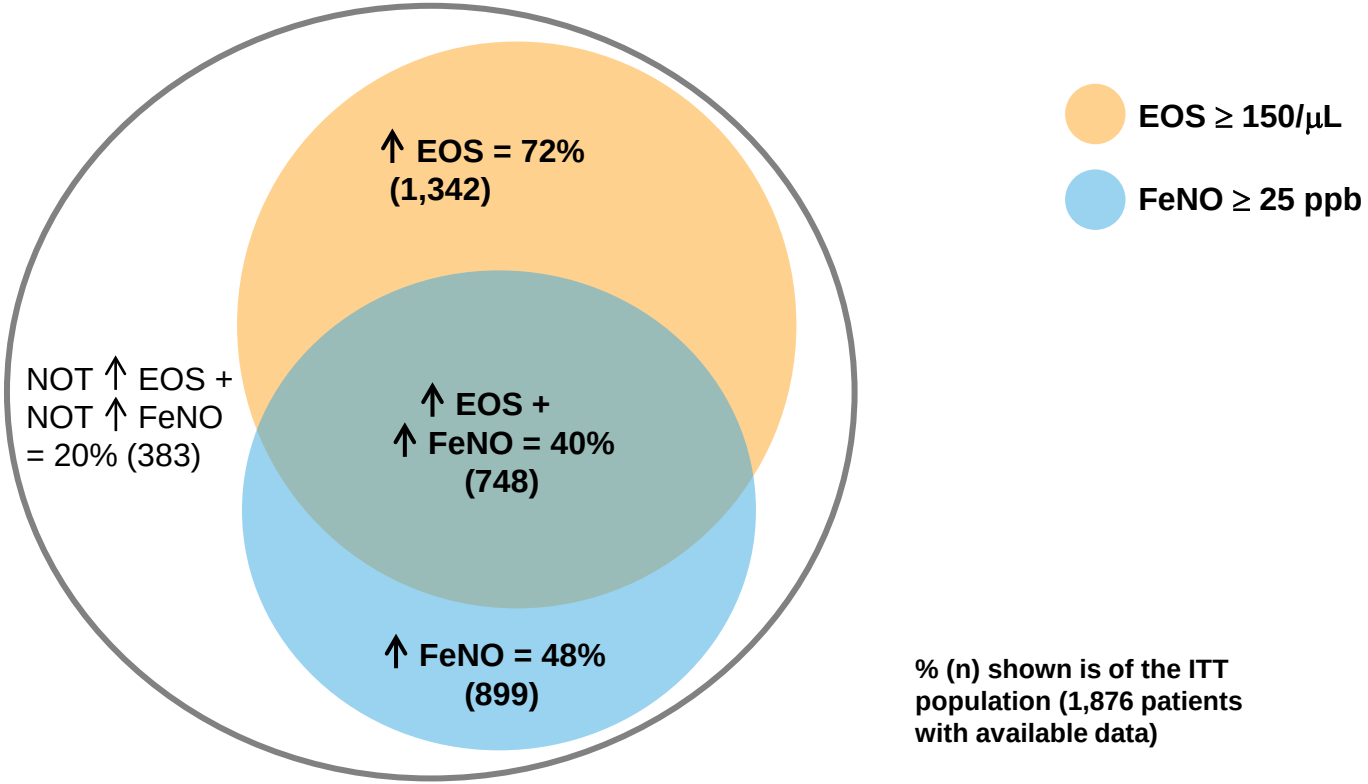
Effect of dupilumab on annualized severe exacerbation rate during 52-weeks treatment period and FEV_1 at Week 12 in patients with FeNO < 25 ppb

Placebo 1.14 mL Dupilumab 200 mg q2w Placebo 2 mL Dupilumab 300 mg q2w



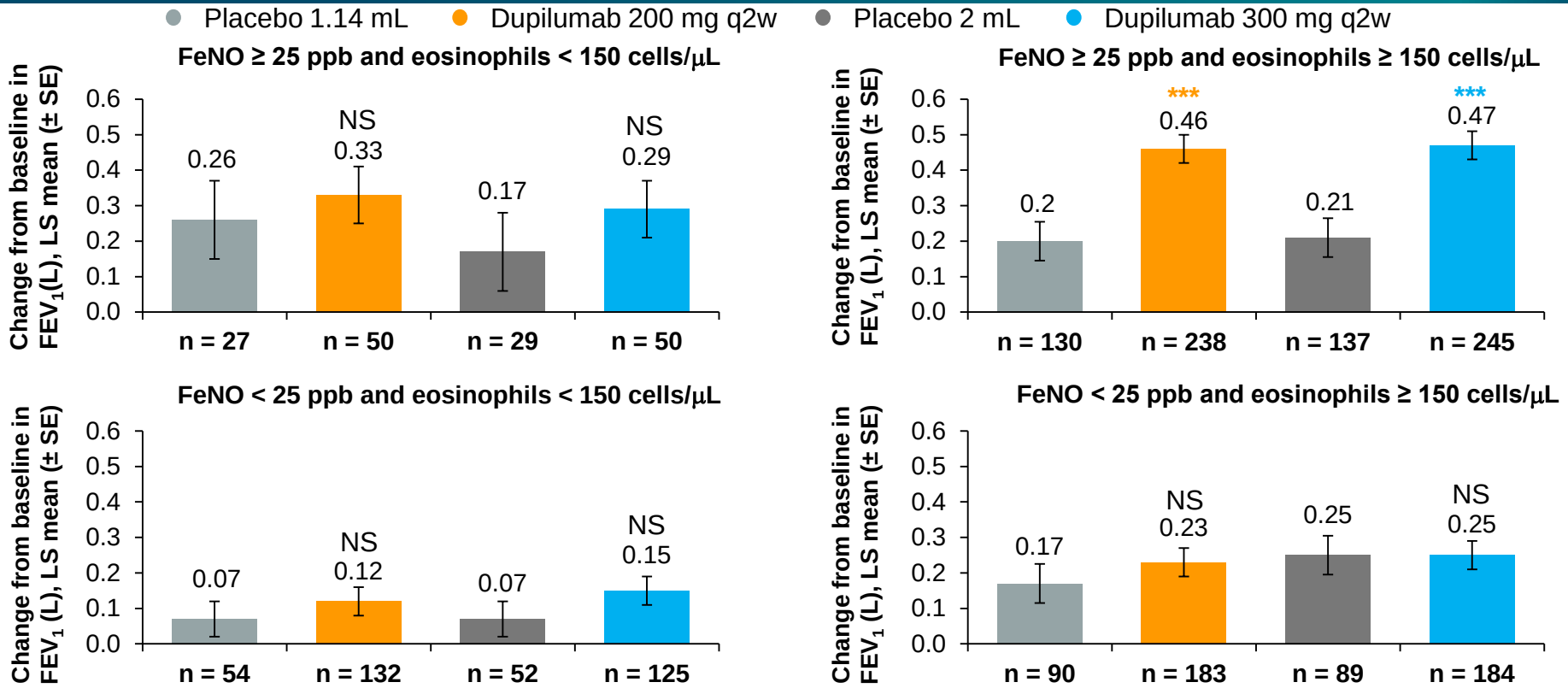


Proportion of overlapping patients with elevated eosinophils (≥ 150/µL) and/or elevated FeNO (≥ 25 ppb) at baseline in the QUEST ITT population



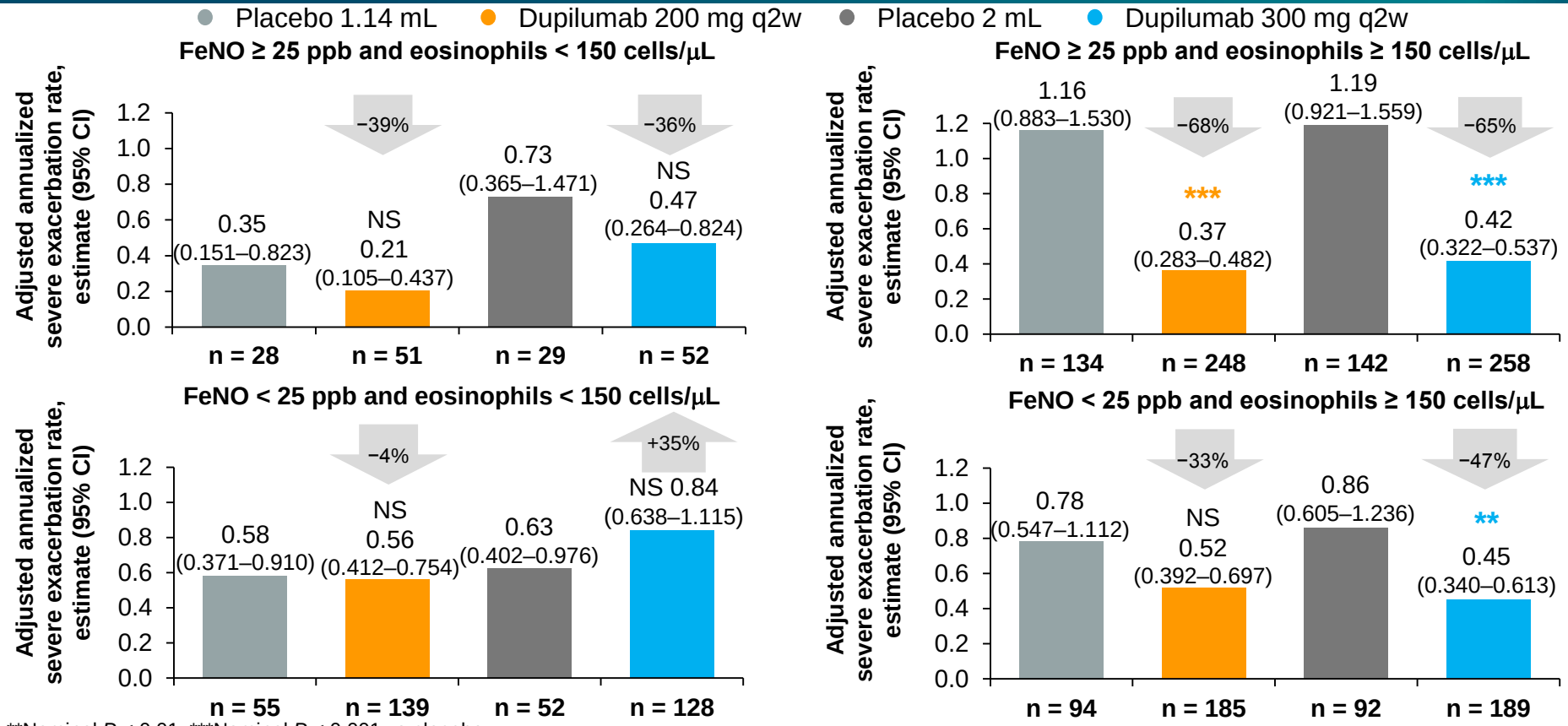
% (n) shown is of the ITT population (1,876 patients with available data)

Post hoc analysis of FEV_1 in patients with FeNO levels ≥ 25 or < 25 ppb and eosinophils ≥ 150 or < 150 cells/μL



***Nominal *P* < 0.001 vs placebo.

Post hoc analysis of severe asthma exacerbations in patients with FeNO levels ≥ 25 or < 25 ppb and eosinophils ≥ 150 or < 150 cells/µL



**Nominal $P < 0.01$; ***Nominal $P < 0.001$ vs placebo.

Adverse events

- Eosinophilia was reported as a TEAE in 52 (4.1%) of dupilumab-treated vs 4 (0.6%) of placebo-treated patients
  - In 0.2% of the total patient population, these TEAEs were accompanied by clinical symptoms
- Increased blood eosinophil levels were associated with symptoms in 4 dupilumab-treated patients
  - 2 of these events were reported as serious adverse events (worsening of hypereosinophilia and chronic eosinophilic pneumonia)
- 8 cases of these eosinophilia TEAEs (7 dupilumab and 1 placebo) resulted in permanent treatment discontinuation

Eosinophilia cases associated with symptoms

Patient 1

- Male, aged 50 years with asthma for approximately 3 years, randomized to dupilumab 300 mg q2w
- Ongoing history of chronic rhinosinusitis and nasal polyps
- History of hypereosinophilia, elevated eosinophil count at screening (1140 cells/µL) resolved by the baseline visit (570 cells/µL), other blood cell counts within normal ranges
- 3 asthma exacerbations in the year prior to enrollment including 1 requiring hospitalization
- Few hours after second dose of investigational product (Day 16) patients developed injection site erythema, severe chills with fever, myalgia, arthralgia, and slight worsening of the asthma symptoms – vital signs and ECG were normal
- No lymphadenopathy and no sign of upper respiratory infection were reported to suggest an alternate cause of fever or myalgia. No prior history of myalgia or arthralgia that was not associated with viral infection
- Hydrocortisone butyrate was administered SC; myalgia and arthralgias persisted (Day 22): respiratory symptoms worsened, and patient was treated with oral paracetamol and oral thiocolchicoside
- On Day 30, eosinophil count of 10,280 cells/µL, with WBC count of 20,000 cells/µL and neutrophil 29.1%. Blood eosinophil count decreased to 670 cells/µL on Day 40
- The patient's other symptoms also resolved in this time frame
- The Investigator reported "worsening of hypereosinophilia" as an SAE with seriousness criteria of "other medically important event," and considered at this point that the previously reported events of fever, myalgia, and arthralgia were also due to hypereosinophilia
- The investigational product was permanently discontinued due to this event of hypereosinophilia

Eosinophilia cases associated with symptoms

Patient 2

- Male, aged 56 years with history of asthma for approximately 6 years, randomized to dupilumab 300 mg q2w
- 5 asthma exacerbations in the year prior to enrollment, none requiring hospitalization
- Eosinophil count was 660 cells/µL at baseline, 1,840 cells/µL on Day 30, and 2,080 cells/µL on Day 113
- On Day 118, the patient experienced fever requiring hospitalization: a SAE determined by the investigator to be “chronic eosinophilic pneumonia” was reported
- On Day 132, the patient was hospitalized for the same adverse event: the patient had persistent fever and increase of peripheral eosinophilia, but denied coughing, dyspnea, lack of energy, weight loss, or night sweats. Spirometry was within normal ranges. No symptoms or signs of neuropathies. Chest X-ray showed widespread parenchymal thickening bilaterally, no pleural effusion, cardiothoracic contour within normal limits
- Laboratory results (blood drawn on Day 133) revealed WBC count 10,360 cells/µL, eosinophils 26.2% and eosinophils count 2,710 cells/µL
- The investigational product was discontinued after the last dose on Day 127; the patient was treated with oral levofloxacin and parenteral piperacillin/tazobactum and oral prednisone
- On Day 140, patient had bronchoscopy with bronchoalveolar lavage, BAL fluid showed no eosinophils but was characteristic of neutrophilic pneumonitis
- On Day 170, needle biopsy showed inflammatory infiltrates rich in eosinophil granulocytes. The transbronchial biopsies did not reveal any necrotizing or granulomatous vasculitis, and the diagnosis of chronic eosinophils pneumonia of severe intensity was made
- The patient was treated with oral corticosteroids with resolution of chest X-ray findings and eosinophilia

Eosinophilia cases associated with symptoms

Patient 3

- Female, aged 28 years with a history of thyroiditis, chronic gastritis, duodenitis, and mitral valve prolapse, randomized to dupilumab 300 mg q2w group
- 3 asthma exacerbations in the year prior to enrollment, 1 requiring hospitalization or urgent medical care
- The patient experienced an AE of mild intensity, reported as eosinophilia on Day 114
- The patient was diagnosed with asthma approximately 6 years earlier
- Eosinophil count at screening was 690 cells/µL and at baseline 45 cells/µL
- The patient exerienced a TEAE of lymphadenitis of moderate intensity and unknown etiology at Day 105 which was resolved within 4 days
- The eosinophil count started to increase after the first dupilumab dose and remained elevated: on Day 114 the eosinophil count was 3,220 cells/µL, WBC count 16,100 cells/µL, neutrophils were 8,710 cells/µL and platelets were 48,4000 cells/µL
- On Day 170, the patient experienced radiculopathy of unknown etiology requiring treatment with NSAIDs that recovered in 2 weeks
- The patient experienced four asthma exacerbations requiring systemic steroid treatment during the study. No reduction of the eosinophil count was observed during steroids administration
- FEV_1 fluctuated over the course of the study, overall no improvement in FEV_1 was observed
- The TEAE of hypereosinophilia was reported as recovered on Day 367, with an eosinophil count of 2,310 cells/µL
- The investigational product treatment was continued with no interruption

Eosinophilia cases associated with symptoms

Patient 4

- Female, aged 52 years, with ongoing medical history of hives and history of two asthma exacerbations within the year preceding inclusion in the study, randomized to dupilumab 300 mg q2w group
- Eosinophil count at screening was 1770 cells/µL and at baseline 1,210 cells/µL
- The patient eperienced a TEAE of moderate intensity, reported as eosinophil count increased to 3,040 cells/µL, on Day 105
- On Day 127, the patient developed pneumonitis of moderate intensity attributed to the increased eosinophils. X-ray of the chest showed infiltrates in both lungs
- On Day 131, eosinophil count reached a peak of 4,920 cells/µL
- The investigational product was permanently discontinued due to the AE with the last dose administered on Day 120 Prednisone was given as corrective treatment
- The patient recovered from pneumonitis on Day 145 and from the eosinophilia on Day 215, with an eosinophil count of 940 cells/µL

Adjudicated MACE

	1.14 mL/200 mg q2w		2.0 mL/300 mg q2w		Combined	
No. of patients (%)	**Placebo (n = 313)**	**Dupilumab (n = 631)**	**Placebo (n = 321)**	**Dupilumab (n = 632)**	**Placebo (n = 634)**	**Dupilumab (n = 1263)**
MACE	2 (0.6)	1 (0.2)	0	4 (0.6)	2 (0.3)	5 (0.4)
MACE + hospitalization for unstable angina	2 (0.6)	1 (0.2)	0	5 (0.8)	2 (0.3)	6 (0.5)
Cardiovascular death	1 (0.3)	0	0	3 (0.5)	1 (0.2)	3 (0.2)
Non-fatal cardiovascular event						
Arrhythmia not associated with ischemia	0	0	0	2 (0.3)	0	2 (0.2)
Other[a]	1 (0.3)	2 (0.3)	1 (0.3)	2 (0.3)	2 (0.3)	4 (0.3)
Non-fatal myocardial infarction	0	1 (0.2)	0	1 (0.2)	0	2 (0.2)
Unstable angina	0	0	0	1 (0.2)	0	1 (< 0.1)
Venous thromboembolic event	0	0	0	1 (0.2)	0	1 (< 0.1)
Stroke	1 (0.3)	0	0	0	1 (0.2)	0

[a]These cases were all adjudicated syncope except for 1 case of coronary artery bypass graft in the dupilumab 200 mg q2w group.
MACE, major adverse cardiac event.