2021.04.09
제16회 대한결핵 및 호흡기학회 폐암심포지엄 만찬

Comprehensive Clinical Evidence of

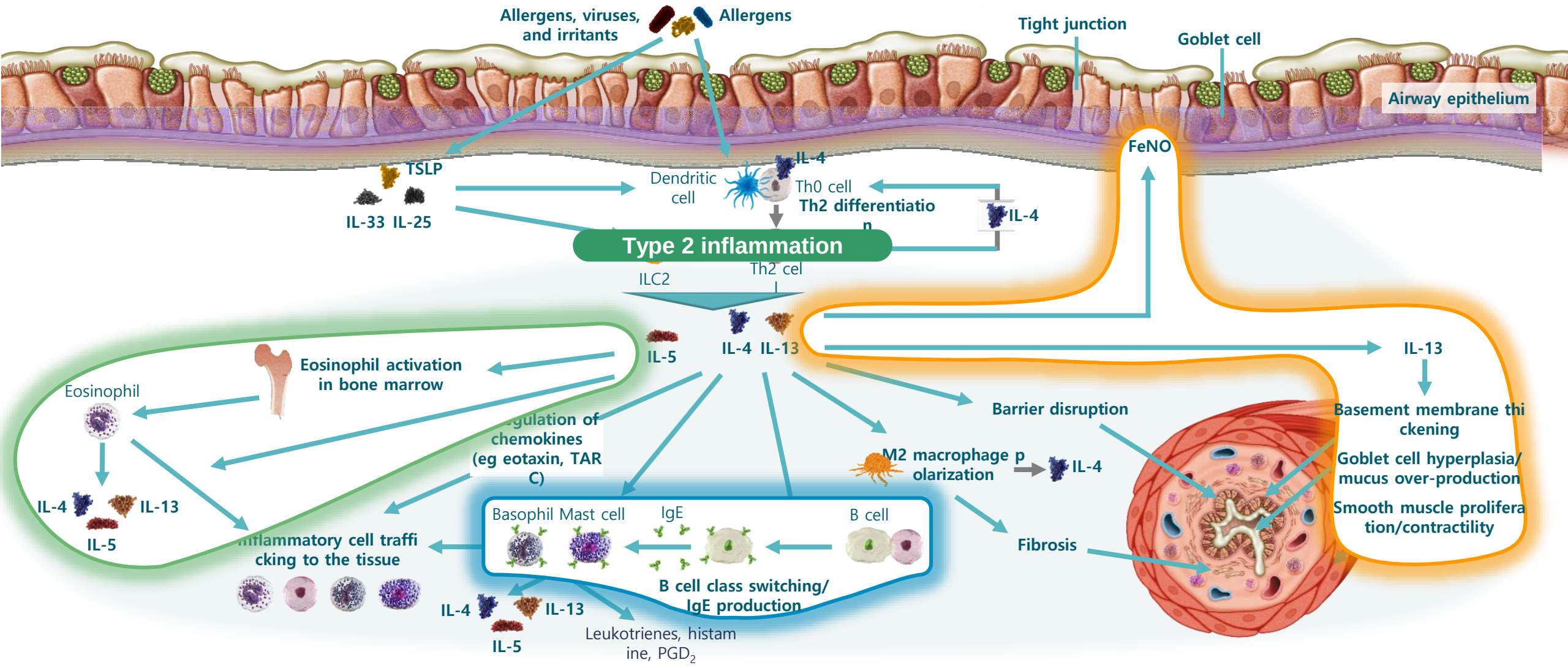
Dupilumab in Severe Asthma

문 지 용

한양대학교구리병원

Contents

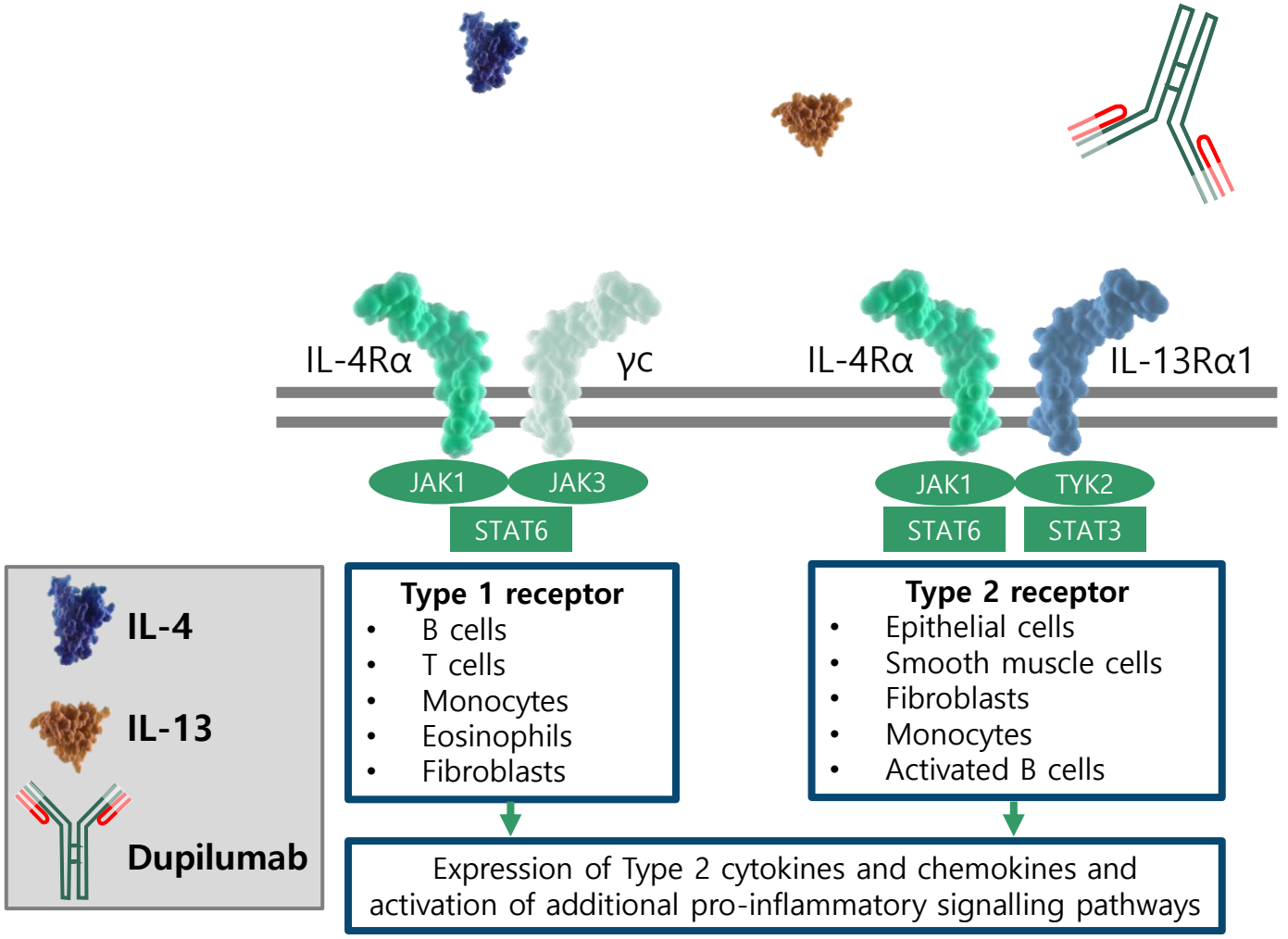
IL-4, IL-13, and IL-5 Are Key Cytokines in Asthma Pathophysiology[1–4]



1. Gandhi NA, et al. *Nat Rev Drug Discov.* 2016;15:35–50; 2. Fahy JV. *Nat Rev Immunol.* 2015;15:57–65;
3. Nonaka M, et al. *Int Arch Allergy Immunol.* 2010;152:327–341; 4. GINA. Global strategy for asthma management and prevention. 2019

Dupilumab Exerts its Mechanism of Action by Inhibiting IL-4 and IL-13 Pathways

1. IL-4 and IL-13 bind to a shared subunit, IL-4Rα
2. Dupilumab, a human monoclonal IgG4 antibody, binds to IL-4Rα, blocking both IL-4 and IL-13 signalling pathway



γc, gamma chain; IL-4Rα, interleukin-4 receptor alpha; IL-13Rα, interleukin-13 receptor alpha 1; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase

Gandhi NA, et al. *Nat Rev Drug Discov.* 2016;15(1):35–50

DUPIXENT® (dupilumab) in Korean Label

[효능.효과]

Atopic Dermatitis

성인 및 소아 (만6세이상) 국소 치료제로 적절히 조절되지 않거나 이들 치료제가 권장되지 않는 중등도에서 중증 **아토피 피부염**의 치료

Asthma

성인 및 청소년(만12세이상)에서 기존 치료에 적절하게 조절이 되지 않는 중증 천식으로 다음 중 하나에 해당하는 **제2형 염증성 천식**의 추가 유지 치료

1) 중증 **호산구성** 천식 (혈중 호산구 ≥ 150/㎕ 또는 호기산화질소 (FeNO) ≥25 ppb)
2) 경구 **코르티코스테로이드 의존성** 중증 천식

[용법.용량]

성인

환자 몸무게	초회 용량	유지 용량 (2주 간격)
모두	600mg (300mg 2회 투여)	**300mg**

청소년(만 6세 이상)

환자 몸무게	초회 용량	유지 용량 (2주 간격)
60kg 미만	400mg (200mg 2회 투여)	**200mg**
60kg 이상	600mg (300mg 2회 투여)	**300mg**

이 약은 단독으로 또는 국소 코르티코스테로이드와 병용으로 투여할 수 있다. 국소 칼시뉴린 저해제를 사용할 수 있으나, 얼굴, 목, 접힘 부위 및 생식기 부위 같은 문제가 되는 부위에만 사용하도록 한다.

이 약은 다음의 한 가지 방법으로 피하 투여한다.

1. 초회 용량 400mg (200mg 2회 투여), 유지 용량 200mg 2 주 간격 투여 또는
2. 초회 용량 600mg (300mg 2회 투여), 유지 용량 300mg 2주 간격 투여

- 경구 코르티코스테로이드 의존성이 있거나 중등도에서 중증 아토피 피부염을 동반하고 있는 경우 초회 용량으로 600 mg(300 mg을 다른 투여부위로 연속 2회 주입) 투여 후 유지 용량으로 300 mg을 2주 간격으로 투여

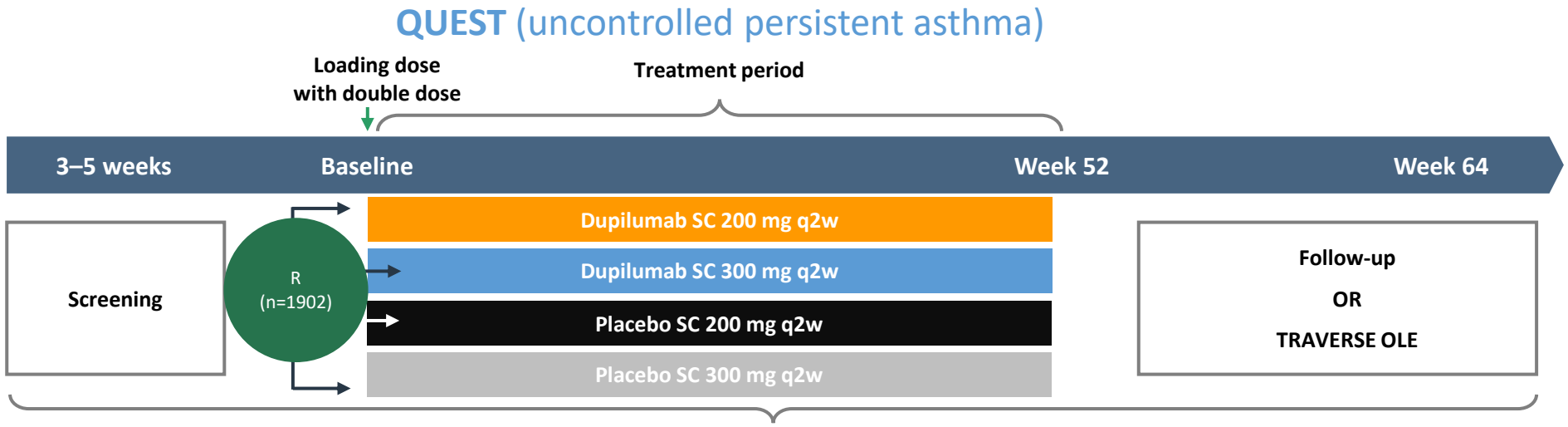
듀피젠트 제품설명서 (최종개정일: 2020.05.06)

Contents

1-1. Phase 3 LIBERTY Asthma QUEST[1]

Key eligibility criteria

- Treatment with medium- to high-dose ICS + up to two additional controllers
- Pre-BD FEV_1 ≤80% of predicted for adults (≤90% of predicted for adolescents)
- ACQ-5 ≥1.5
- FEV_1 reversibility ≥12%
- ≥1 SCS treatment, or a hospitalization/emergency care visit, for worsening asthma



Background therapy: Medium- to high-dose ICS + a second controller medication (eg LABA, LTRA, etc.); a third controller is allowed

Primary endpoint(s)

- Annualized **rate** of severe **exacerbation** events[a] over 52 weeks
- Δ in pre-BD **FEV_1** at **Week 12**

Key secondary endpoints

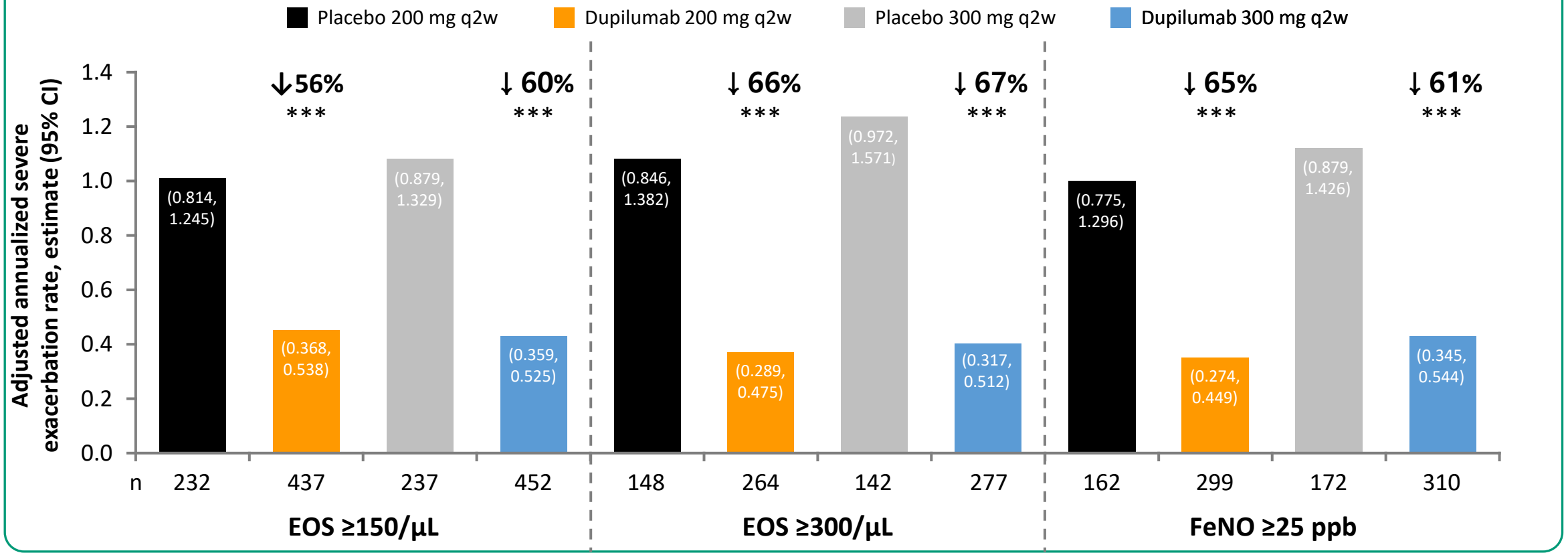
- Annualized rate of severe exacerbation events[a] over 52 weeks in patients with EOS ≥150 and ≥300 cells/μL
- Δ in pre-BD FEV_1 at Week 12 in patients with EOS ≥150 and ≥300 cells/μL
- Δ in ACQ-5, AQLQ(S) scores at Week 24
- Annualized rate of severe asthma exacerbations resulting in hospitalization or ER visit

ACQ, Asthma Control Questionnaire; AHR, airway hyperresponsiveness; BD, bronchodilator; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonist; SCS, systemic corticosteroids

1. Castro M, et al. *N Engl J Med*. 2018;378:2486–2496;

1-1. QUEST_Severe Exacerbations

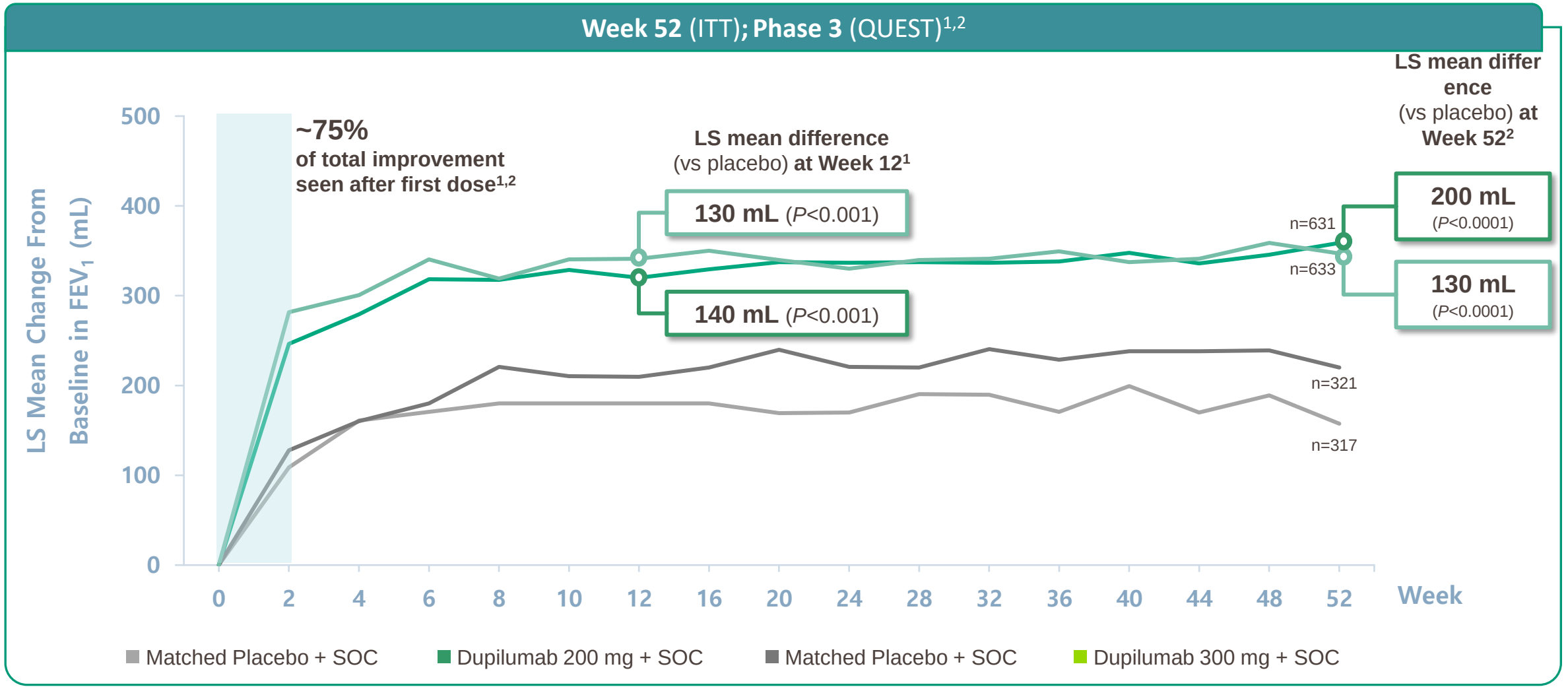
Severe asthma exacerbations over 52 weeks in patients with a range of elevated type 2 biomarkers at baseline[1–4]



***p<0.001 vs placebo

1. Castro M, et al. *N Engl J Med*. 2018;378:2486–2496; 2. Ford LB, et al. *EAACI*. 2018; 3. Wenzel S, et al. *ATS*. 2018; 4. Castro M, et al. *ATS*. 2018

1-1. QUEST_Pre-BD FEV_1

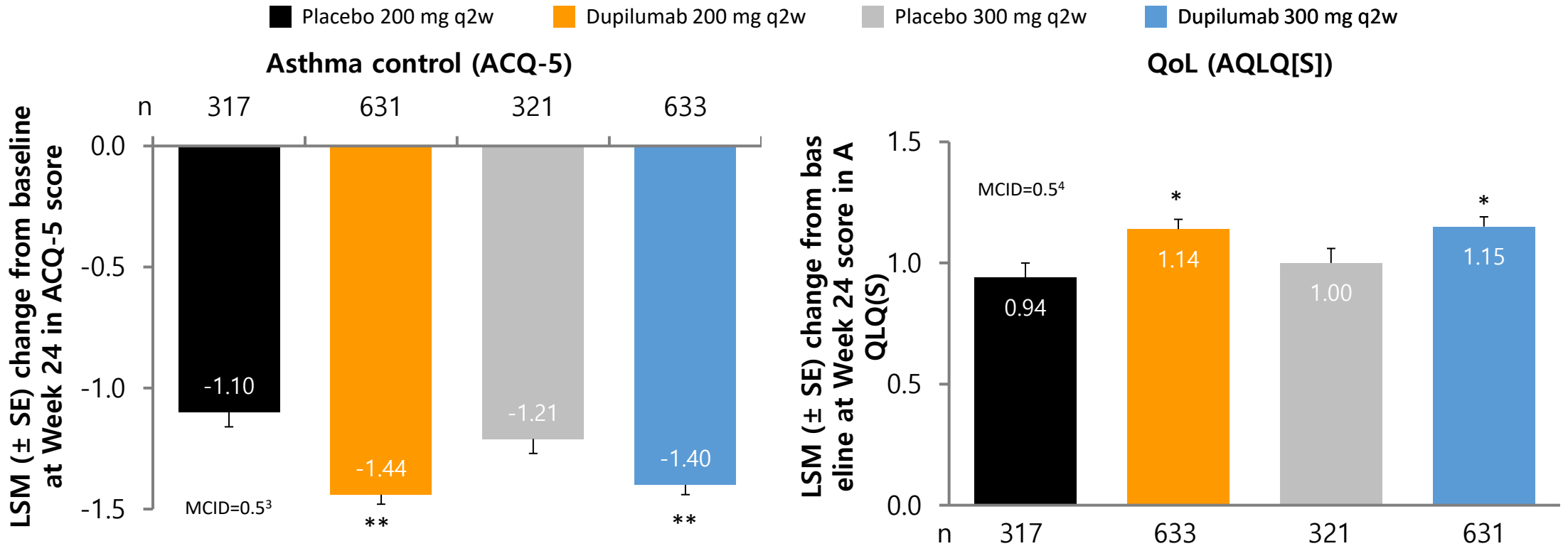


***p<0.001
NIH, National Institutes of Health

1. Castro M, et al. *N Engl J Med*. 2018;378:2486–2496; 2. Castro M, et al. *ATS*. 2018; 3. Tepper RS, et al. *J Allergy Clin Immunol*. 2012;129(3 suppl):S65–S87

1-1. QUEST_Asthma Control and Quality of Life

Change in PRO measures at Week 24 in the ITT population[1,2]



Improvements in ACQ-5 with dupilumab were rapid (by Week 2) and sustained to Week 52[1,2]

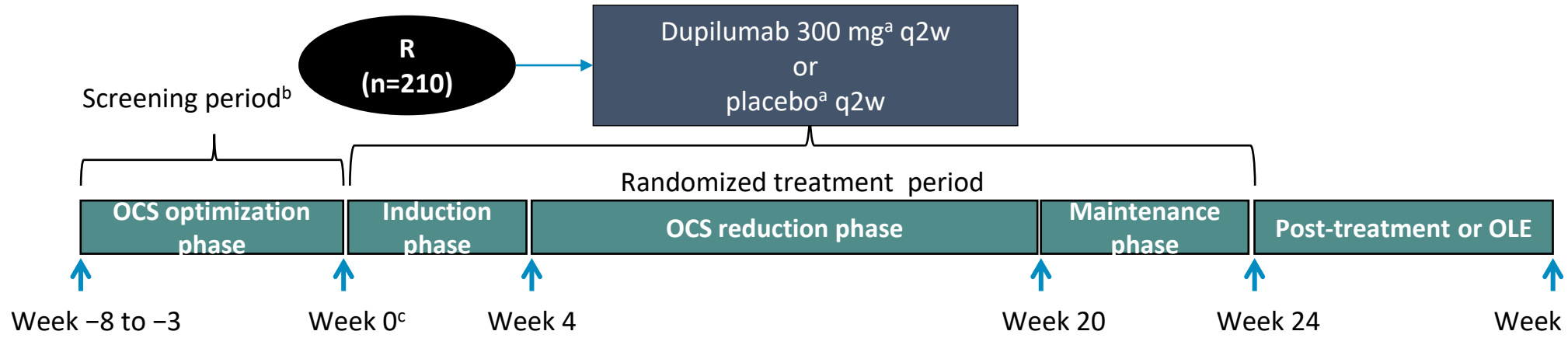
*p<0.05; **p<0.01 vs placebo

1. Castro M, et al. *N Engl J Med*. 2018;378:2486–2496; 2. Corren J, et al. *ATS*. 2018;
3. Juniper EF, et al. *Respir Med*. 2005;99:553–558; 4. Wilson SR, et al. *J Allergy Clin Immunol*. 2012;129:S88–S123

1-2. Phase 3 LIBERTY Asthma VENTURE[1]

Key eligibility criteria

- Treatment with **high-dose ICS + up to two additional controllers**
- **Pre-BD FEV_1 ≤80%** of predicted for adults (≤90% of predicted for adolescents)
- **OCS : 5-35 mg / day**



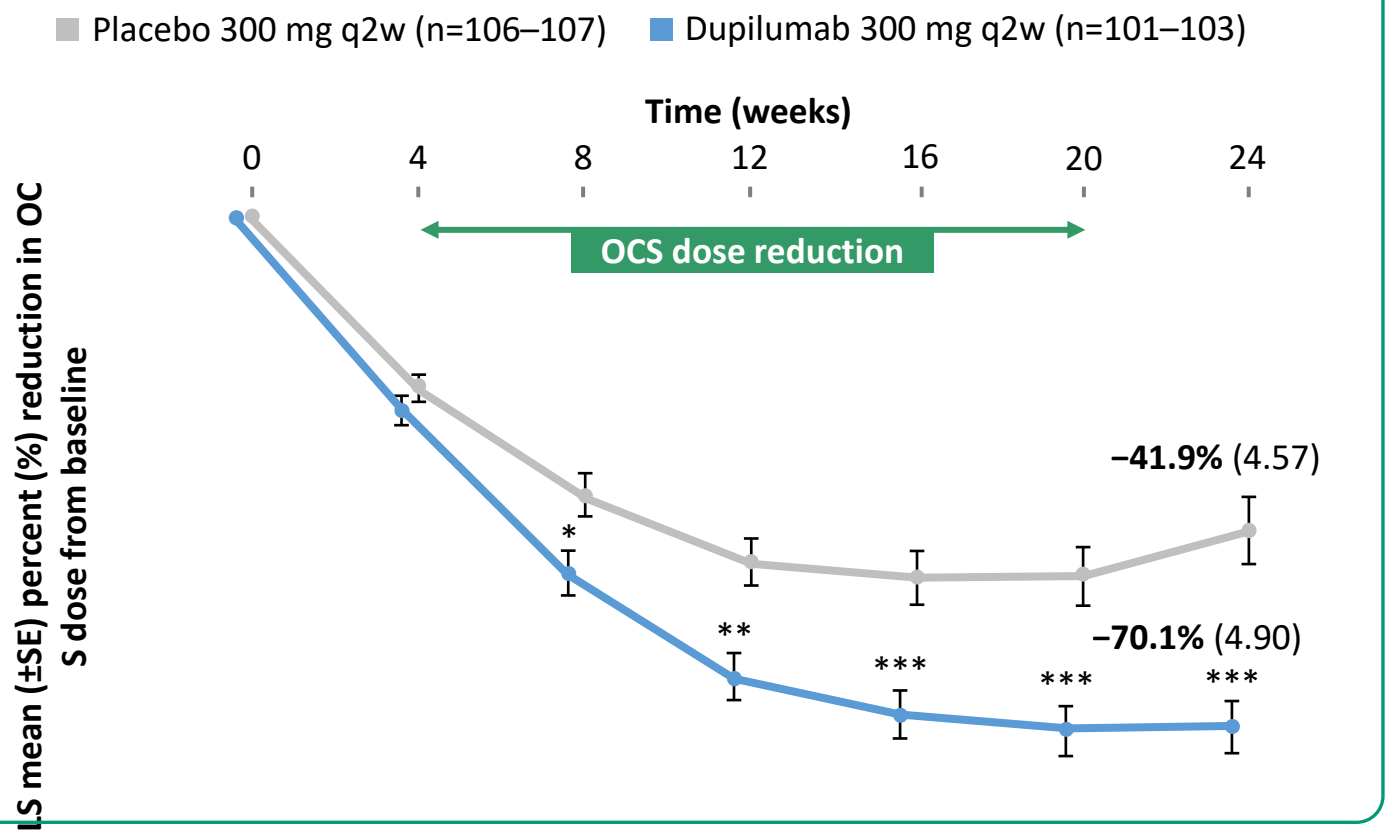
Primary endpoint(s)	Key secondary endpoints
▪ **Percentage reduction of the OCS** dose at Week 24	▪ Reduction of ≥50% in the OCS dose ▪ Reduction of OCS dose to <5 mg/day ▪ Achieving their maximum possible OCS reduction per protocol ▪ No longer requiring OCS ▪ Reduction in rate of annualized severe exacerbation ▪ Improvement in lung function (FEV1)

ACQ-5=5-item Asthma Control Questionnaire; EOS=eosinophil; FeNO=fractional exhaled nitric oxide; FEV_1=forced expiratory volume in 1 second; ICS=inhaled corticosteroid; IgE=immunoglobulin E; LABA=long-acting β-agonist; LTRA=leukotriene-receptor antagonist. *Based on GINA 2014 guidelines.

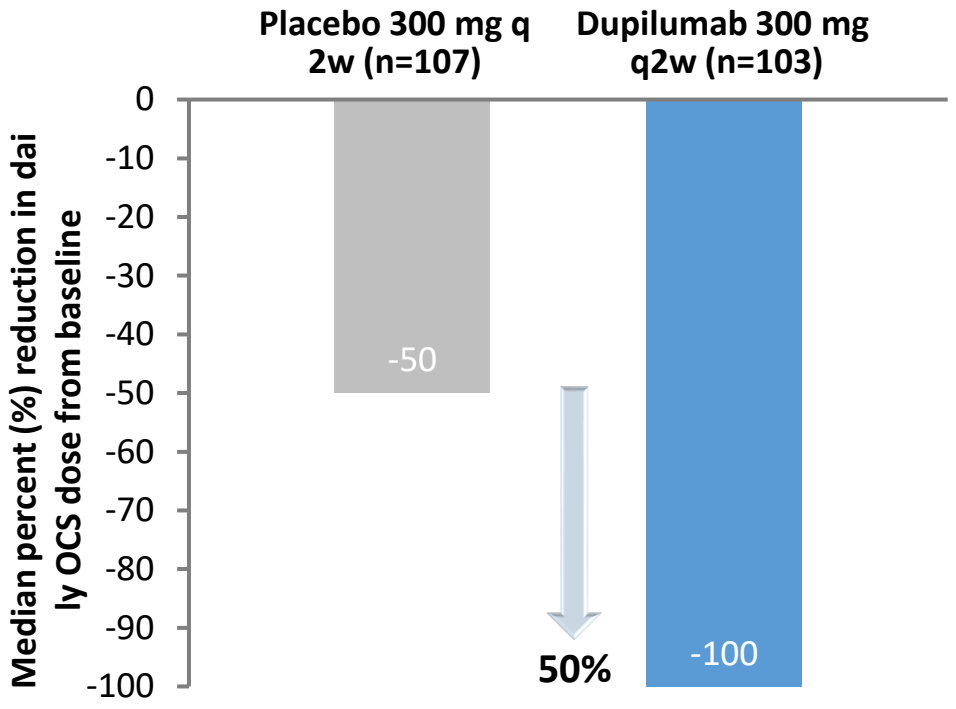
1. Rabe KF, et al. *N Engl J Med*. 2018;378(26):2475-2485. 2. Dupixent (dupilumab) [summary of product characteristics]. Paris, France: sanofi-aventis groupe; 2019.

1-2. VENTURE_OCS Dose Reduction[1,2]

Reduction in OCS dose from baseline through Week 24 (Primary Endpoint)



Reduction in median daily OCS dose; Week 24



Dupilumab significantly reduced OCS dose while maintaining asthma control vs placebo at Week 24 in the overall population[1]

1-2. VENTURE_OCS use elimination and lung function improvement

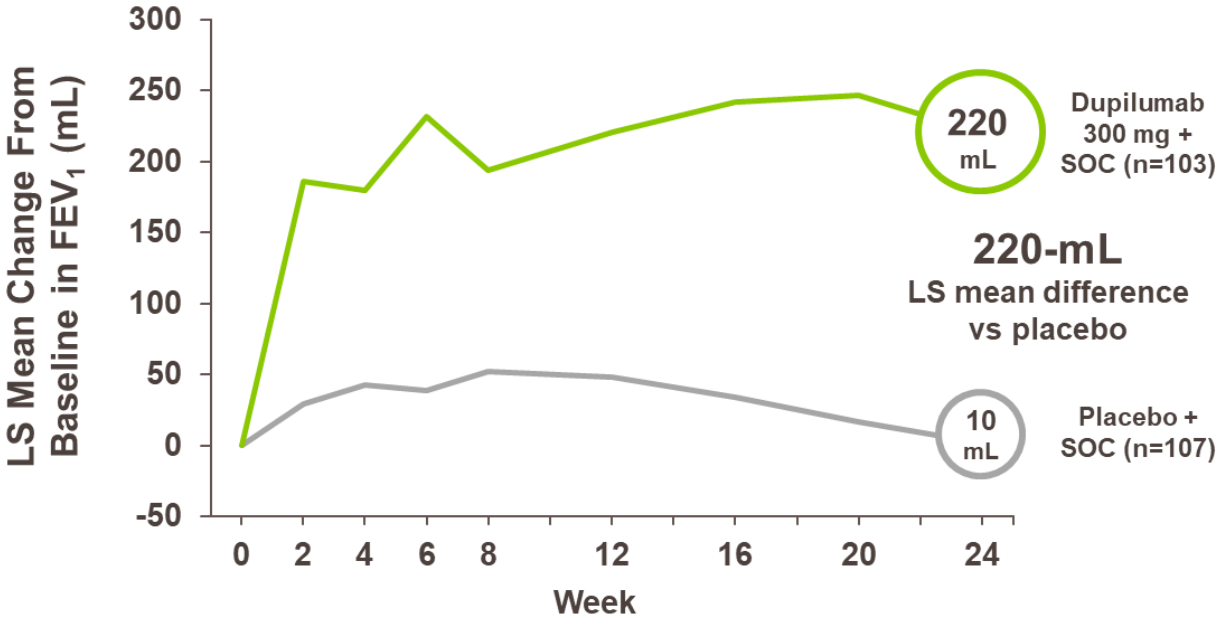
86% reduced or eliminated OCS use
versus 68% in placebo (*P*<0.0001[3])

80% achieved ≥50% OCS dose reduction
versus 50% in placebo (*P*<0.001)

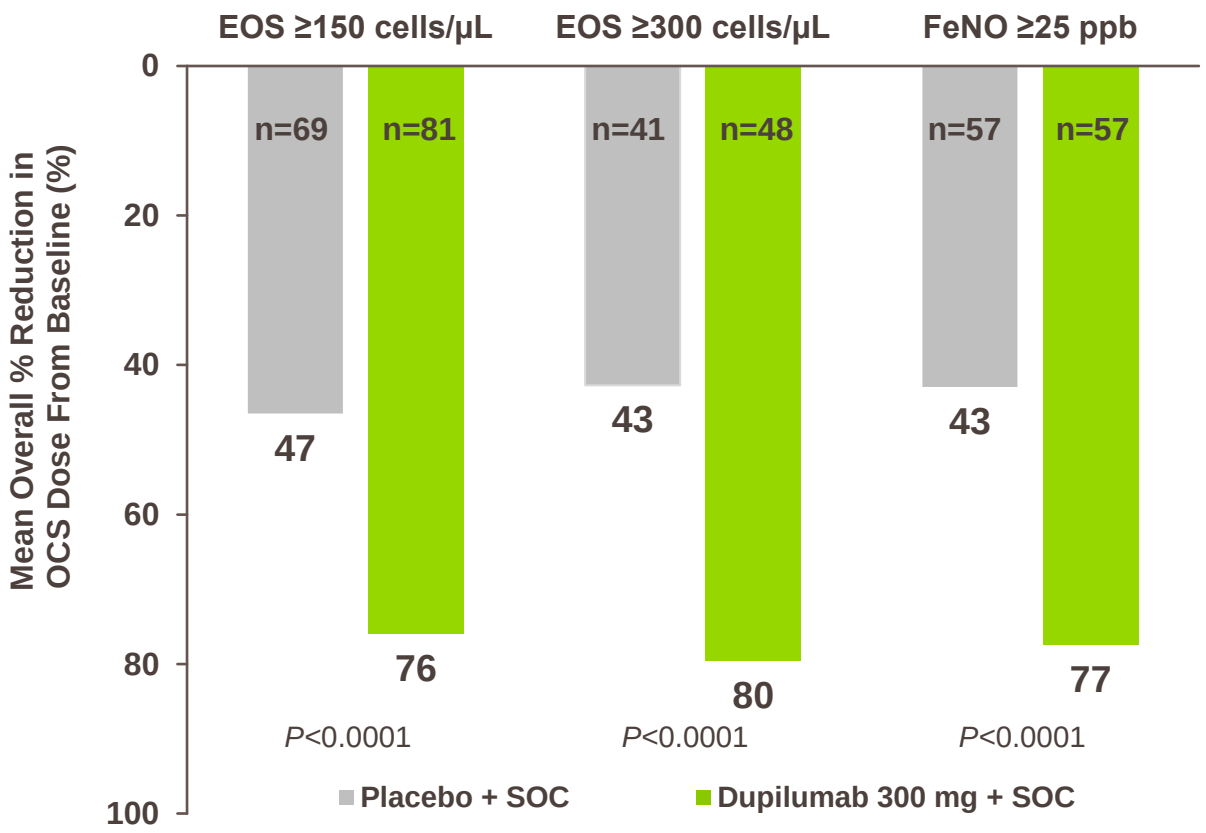
69% reduced OCS dose to <5 mg/day
versus 33% in placebo (*P*<0.001)

52% completely eliminated OCS use
versus 29% in placebo (*P*=0.002)

Improvement rate of lung function[1,2]



1-2. VENTURE_OCS Dose reduction in Type 2 patients



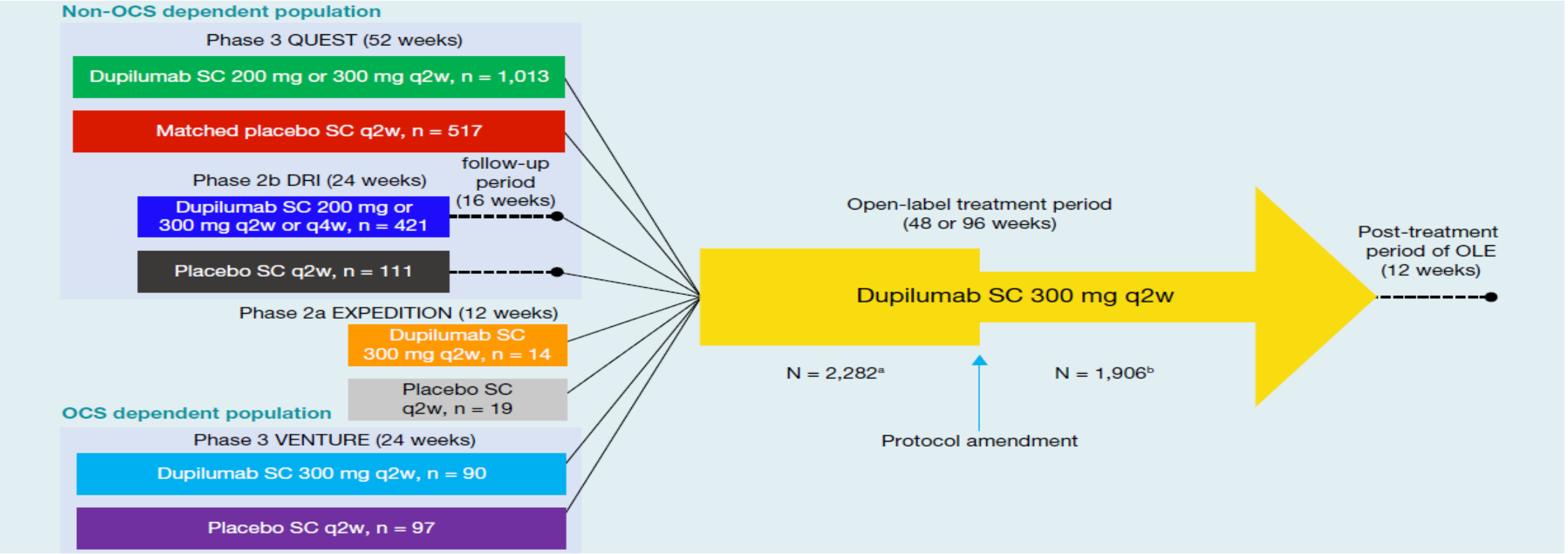
Reduction of OCS dose to <5 mg/day

- **77%** of patients with **EOS ≥150 cells/µL** versus 44% placebo (*P*=0.0001)
- **84%** of patients with **EOS ≥300 cells/µL** versus 40% placebo (*P*=0.0002)
- **79%** of patients with **FeNO ≥25 ppb** versus 34% placebo (*P*<0.0001)

EOS=eosinophil; FeNO=fractional exhaled nitric oxide; LD=loading dose; OCS=oral corticosteroid; SABA=short-acting β-agonist; SOC=standard of care.
Study participants were randomised 1:1 to receive dupilumab 300 mg (LD=600 mg) or matched placebo every 2 weeks. SOC therapy permitted during study included background asthma controllers at stable dose and SABA (as needed).[2] All patients were on OCS for ≥6 months prior to study initiation. The baseline mean OCS use was 11.75 mg in the placebo group and 10.75 mg in the dupilumab 300-mg group.[1,2]

1. Dupixent (dupilumab) [summary of product characteristics]. Paris, France: sanofi-aventis groupe; 2019. 2. Rabe KF, et al. *N Engl J Med*. 2018;378(26):2475-2485.

1-3. LIBERTY Asthma TRAVERSE

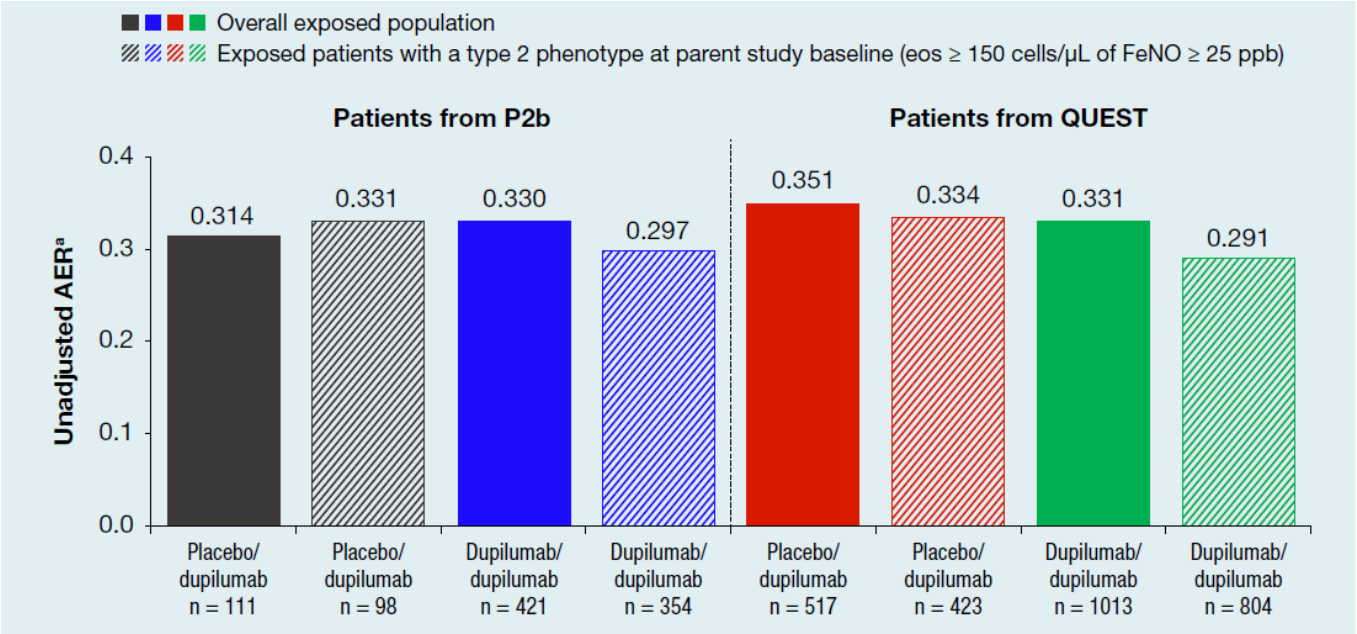


Primary endpoint(s)	Key secondary endpoints
▪ proportion of patients experiencing any Treatment-emergent adverse event (**TEAEs**) up to Week 96 of open-lable extension (**OLE**) in populations from P2b, QUEST, EXPEDITION or VENTURE	▪ assessed in populations from P2b, QUEST, EXPEDITION or VENTURE: ▪ AER up to Week 96 of OLE ▪ FEV1 to Week 96 of OLE ▪ Blood EOS and serum total IgE levels up to Week 96 of OLE

AER, annualized severe exacerbation rate; **OLE**, open-label extension.

1-3. TRAVERSE_Result 1. Exacerbation rate

AER up to Week 96 of OLE in the non-OCS dependent population and in the subgroup of non-OCS dependent patients with a type 2 phenotype

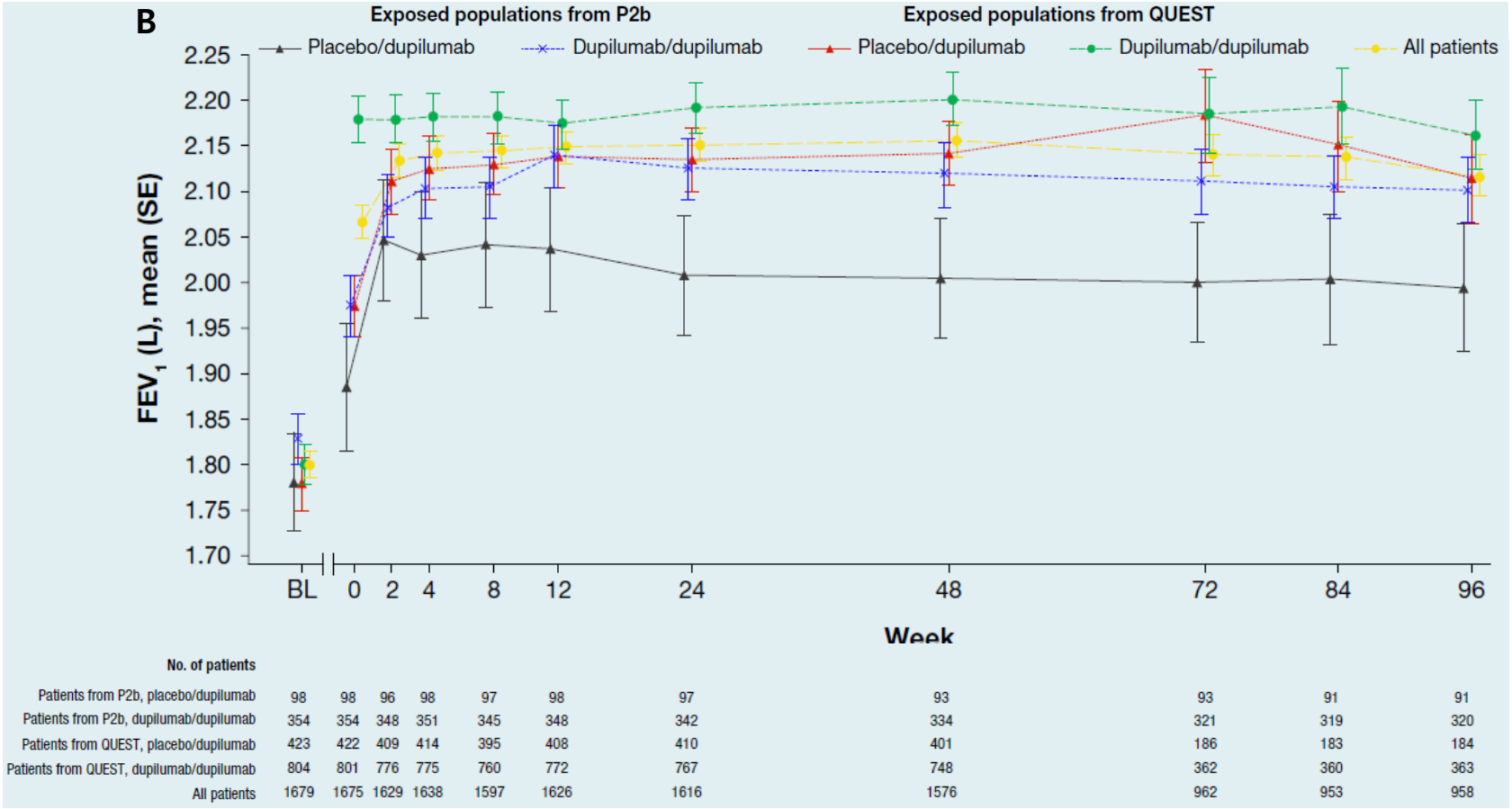


- At parent study **baseline** for P2b and QUEST, **mean no. of exacerbations** in the past year across treatment groups in the overall ITT popu lations were 1.85–2.37 and 2.02–2.31, respectively
- **At end of parent study** treatment **unadjusted AER** for placebo- and dupilumab treated patients were 1.07 and 0.31–0.69 for P2b, and 0. 98–1.09 and 0.48–0.56 for QUEST, respectively
- **During the OLE**, **unadjusted AER** ranged from 0.31–0.35 in the non-OCS dependent population and from 0.29–0.33 in the subgroup of n on-OCS dependent patients with a type 2 phenotype

- AER was assessed in the exposed population (observed cases).
- [a]The total number of events that occurred during the treatment period divided by the total number of patient-years followed in the treatment period.
- AER, annualized severe exacerbation rate; ITT, intent-to-treat; OCS, oral corticosteroid; **OLE**, open-label extension.

1-3. TRAVERSE_Result 2. FEV1

FEV1 from baseline of parent study to Week 96 of OLE in the subgroup of non-OCS dependent patients with a type 2 phenotype at parent study baseline

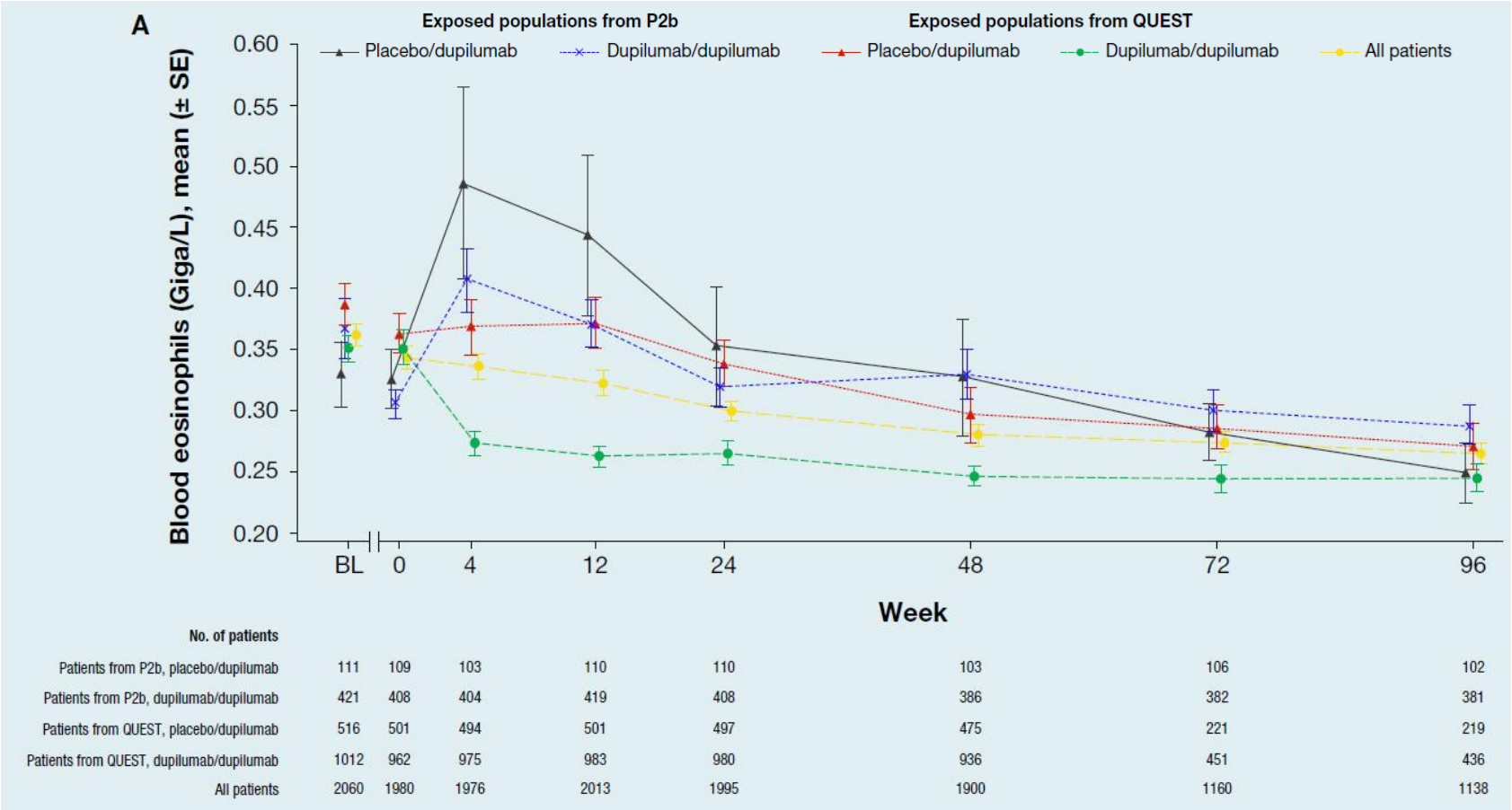


No. of patients											
Patients from P2b, placebo/dupilumab	98	98	96	98	97	98	97	93	93	91	91
Patients from P2b, dupilumab/dupilumab	354	354	348	351	345	348	342	334	321	319	320
Patients from QUEST, placebo/dupilumab	423	422	409	414	395	408	410	401	186	183	184
Patients from QUEST, dupilumab/dupilumab	804	801	776	775	760	772	767	748	362	360	363
All patients	1679	1675	1629	1638	1597	1626	1616	1576	962	953	958

- FEV_1 was assessed in the exposed population (observed cases) using descriptive statistics. BL represents the baseline of the parent study, Week 0 represents the start of the OLE and Weeks refer to the time in OLE without regard to any time in any parent study.
  BL, baseline; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroid; OLE, open-label extension; SE, standard error.

1-3. TRAVERSE_Result 3. EOS level

(A) Blood eosinophil levels from baseline of parent study to Week 96 of OLE in t he non-OCS dependent population

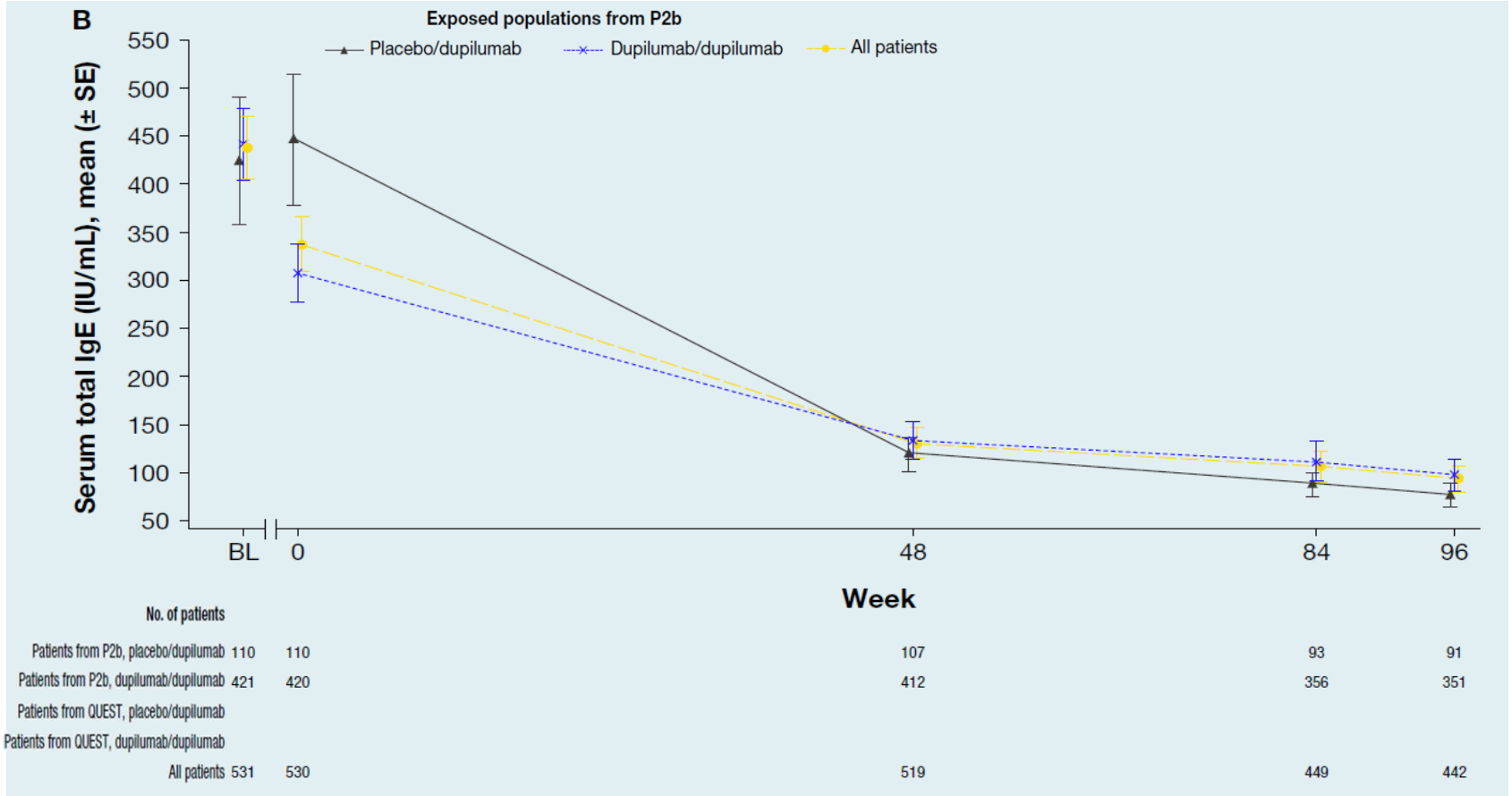


No. of patients								
Patients from P2b, placebo/dupilumab	111	109	103	110	110	103	106	102
Patients from P2b, dupilumab/dupilumab	421	408	404	419	408	386	382	381
Patients from QUEST, placebo/dupilumab	516	501	494	501	497	475	221	219
Patients from QUEST, dupilumab/dupilumab	1012	962	975	983	980	936	451	436
All patients	2060	1980	1976	2013	1995	1900	1160	1138

- BL represents the baseline of the parent study, Week 0 represents the start of the OLE and Weeks refer to the time in OLE without regard to any time in any parent study.
- BL, baseline; ITT, intent-to-treat; OCS, oral corticosteroid; OLE, open-label extension; SE, standard error.

1-3. TRAVERSE_Result 4. IgE level

(B) Total IgE from baseline of parent study to Week 96 of OLE in the exposed po pulation of patients from P2b



- BL represents the baseline of the parent study, Week 0 represents the start of the OLE and Weeks refer to the time in OLE without regard to any time in any parent study. Data presented for total IgE are for patients from the P2b study only and up to the end of collection in the OLE.
- BL, baseline; DPL, dupilumab; IgE, immunoglobulin E; OCS, oral corticosteroid; OLE, open-label extension; PBO, placebo; SE, standard error.

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- QUEST post-hoc : Effects of Co-Morbidities – CRSwNP
- QUEST post-hoc analysis_baseline FeNO

3. Meta-analyses

2-1. QUEST Korean subset analysis

Background

- In the LIBERTY ASTHMA **QUEST** (NCT02414854) study, dupilumab significantly decreased exacerbation compared with placebo in patients with severe asthma. However, little is known regarding the effect of dupilumab on Korean.

Objective

- To examine the efficacy of dupilumab in the subpopulation of Korean patients (n=**74**, **4%** of total patients) who participated in QUEST.

Assessment

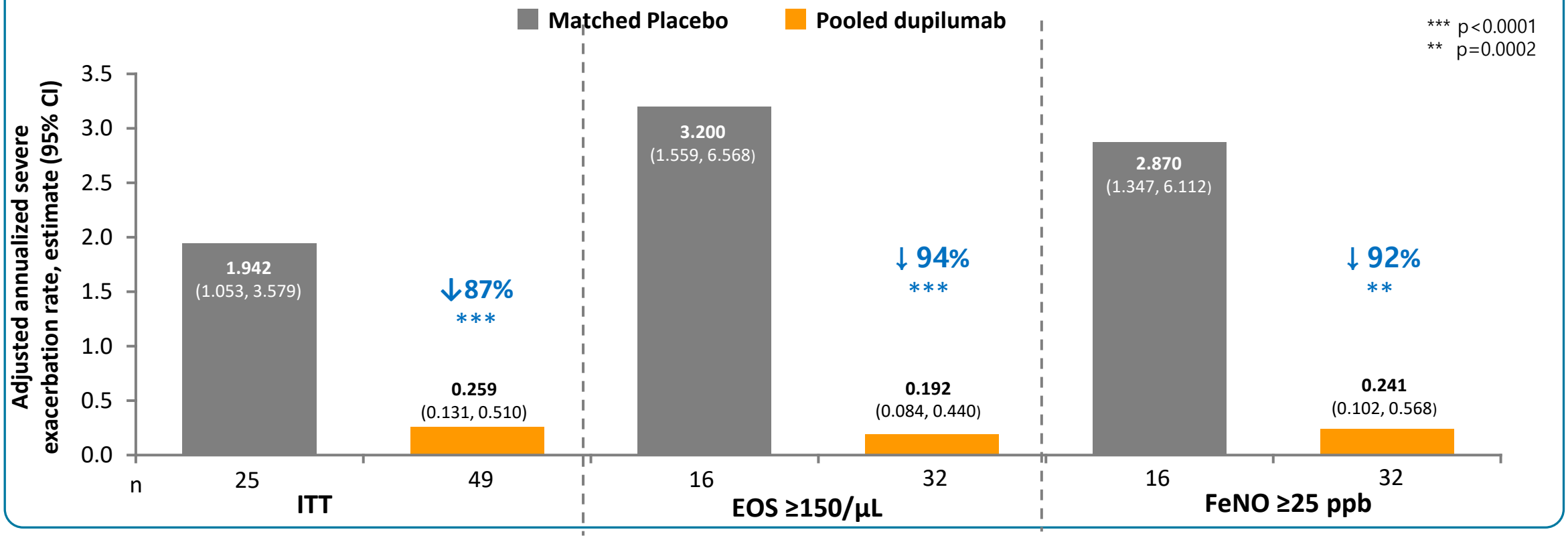
- Dupilumab 200mg and 300mg were combined (dupilumab group) in this post-hoc analysis.
- Outcomes assessed were effect of treatment over the 52-week treatment period on annualized rate of severe exacerbation, FEV_1, asthma control, asthma-related quality of life, and markers of type 2 inflammation.

2-1. QUEST Korea_Baseline characteristics

Demographic	200mg q2w		300mg q2w		Combined	
	Placebo (n=12)	Dupilumab (n=24)	Placebo (n=13)	Dupilumab (n=25)	Placebo (n=25)	Dupilumab (n=49)
Mean age, years (SD)	59.8 (7.8)	46.8 (11.3)	51.6(8.3)	53.3(13.0)	55.5(8.9)	50.1(12.5)
Female, n (%)	8 (67)	15 (63)	9 (69)	15 (60)	17 (68)	30 (61)
BMI kg/m^2 (SD)	25.61 (3.61)	25.05 (3.34)	25.50 (3.42)	26.33 (4.42)	25.55 (3.44)	25.70 (3.94)
Mean EOS/μL (SD)	508 (0.512)	650 (0.817)	501 (0.523)	410 (0.446)	504 (0.507)	527 (0.659)
Mean IgE, IU/mL (SD)	230.9 (290.7)	464.0 (717.7)	384.7 (383.0)	474.0 (552.5)	310.9 (343.9)	469.1 (632.0)
Mean FeNO, ppb (SD)	47.67 (53.33)	54.63 (62.77)	59.58 (38.18)	45.72 (36.75)	53.63 (45.76)	50.08 (50.83)
Mean age at asthma onset, years (SD)	45.4 (10.2)	35.0 (11.5)	37.1 (14.9)	42.9 (13.0)	41.1 (13.3))	39.0 (12.8)
With ongoing atopic medic al condition (YES, n (%))	8 (67)	20 (83)	12 (92)	21 (84)	20 (80)	41 (84)
Mean no. of severe exacerb ations in past year, n (SD)	1.83 (0.72)	2.33 (1.66)	2.62 (1.56)	2.12 (1.01)	2.24 (1.27)	2.22 (1.36)
Mean baseline pre-BD FEV1 L (SD)	1.46 (0.42)	1.59 (0.51)	1.30 (0.28)	1.56 (0.48)	1.38 (0.36)	1.57 (0.49)
Mean baseline pre-BD FEV percent predicted % (SD)	63.83 (9.07)	58.98 (12.99)	54.77 (15.17)	62.56 (9.77)	59.12 (13.20)	60.80 (11.49)

2-1. QUEST Korea_ Result 1. Annualized Severe Exacerbations

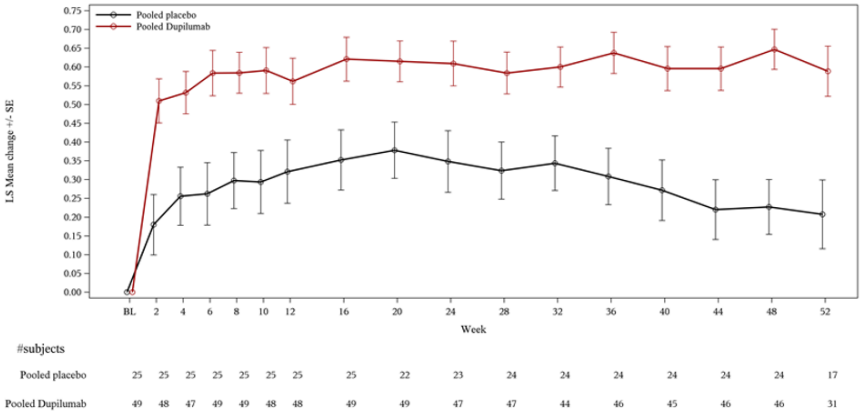
Severe asthma exacerbations over 52 weeks in patients with a range of elevated type 2 biomarkers at baseline[1–4]



- the Adjusted annualized rate of severe exacerbation was 0.259 in the dupilumab (total n=49, n=24 (200mg) and n=25 (300mg)) and 1.942 in placebo (n=25), for 86.6% lower rate with the dupilumab compared with placebo (P < 0.0001).
- In patients with blood eosinophils ≧ 150 cells/µL, severe exacerbation was reduced by 94% compared with placebo (P < 0.0001). In patients with FeNO ≧ 25 ppb, reduced by 92% (P = 0.0002)

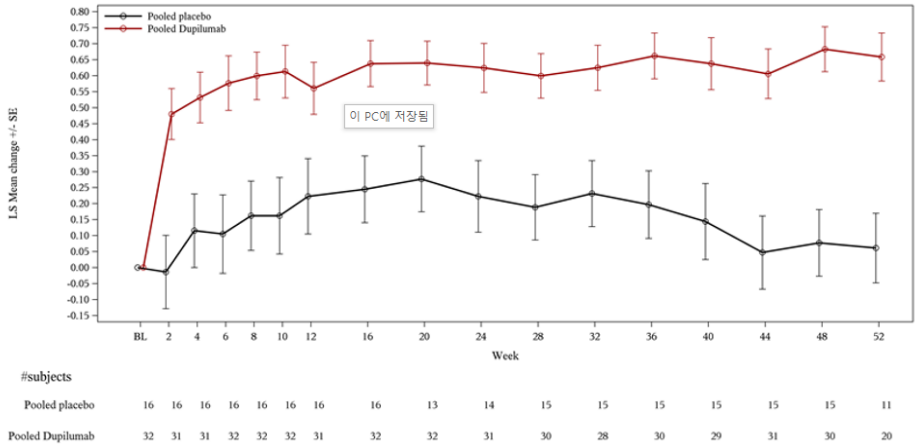
2-1. QUEST Korea_Result 2. Pre-BD FEV1 up to week 52

(A) FEV1 from baseline in pre-BD over week 52 in ITT population



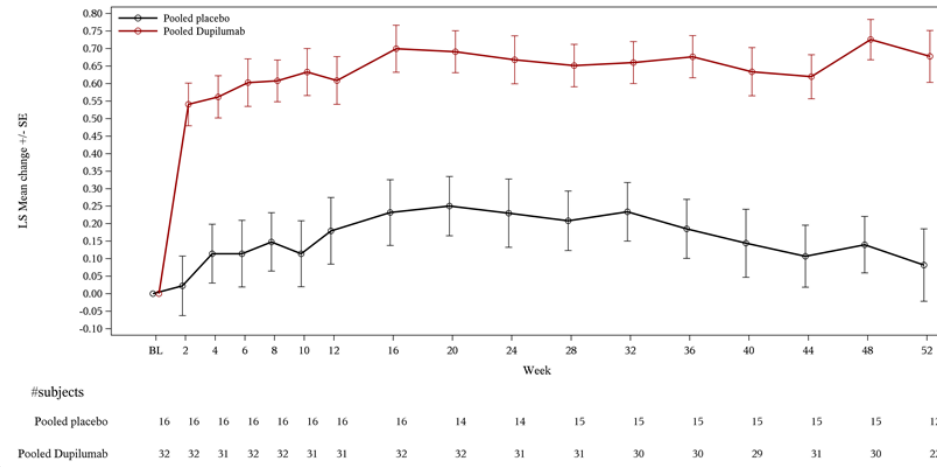
- The FEV1 at week 12 increased by **0.56 liters in dupilumab** (difference vs. placebo, 0.24 liters; P = 0.021).
- FEV1 was improved rapidly (by week 2) and sustained throughout treatment by **0.59 liters at week 52 in dupilumab** (difference vs. placebo, 0.38 liters; P = 0.001).

(B) FEV1 from baseline in pre-BD over week 52 in EOS ≥150/μL population



- The FEV1 at week 12 increased by **0.56 liters in dupilumab** (difference vs. placebo, 0.34 liters; P = 0.0166).
- FEV1 at week 52 invreased by **0.66 liters in dupilumab** and 0.06 in placebo (difference vs. placebo, 0.60 liters; P < 0.001).

(C) FEV1 from baseline in pre-BD over week 52 in FeNO ≥ 25 ppb population



- The FEV1 at week 12 increased by **0.61 liters in dupilumab** (difference vs. placebo, 0.43 liters; P = 0.0006).
- FEV1 at week 52 invreased by **0.68 liters in dupilumab** and 0.08 in placebo (difference vs. placebo, 0.60 liters; P < 0.001).

2-1. QUEST Korea_Safety Summary

n (%)	Placebo (n=25)	Dupilumab (n=49)
Any TEAE	22 (88.0%)	44 (89.8%)
Any treatment-emergent SAE	3 (12.0%)	5 (10.2%)
Any TEAE leading to death	0	0
Any AE leading to permanent treatment discontinuation	0	4 (8.2%)

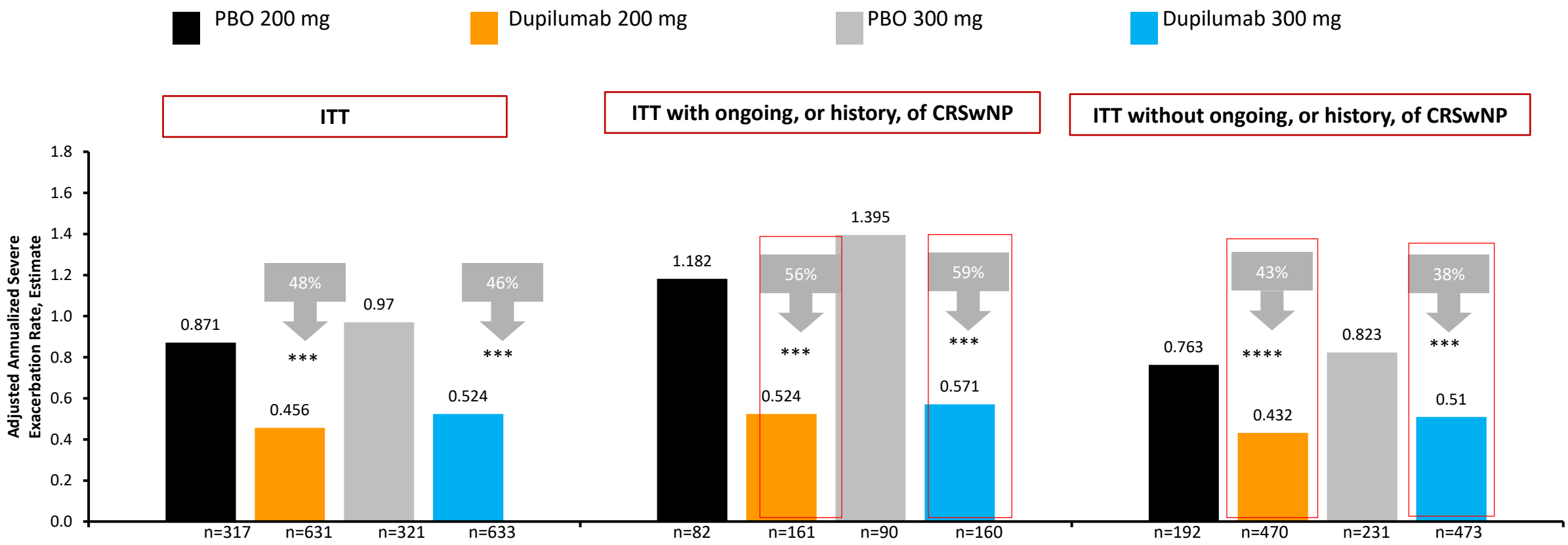
2-2. QUEST post-hoc : Effects of Co-Morbidities – CRSwNP

: 26% with ongoing or history of comorbid CRSwNP in QUEST

	+ ongoing, or history, of CRSwNP		- ongoing, or history, of CRSwNP	
	Placebo combined (n=172)	Dupilumab combined (n=321)	Placebo Combined (n=466)	Dupilumab Combined (n=943)
Mean age, years (SD)	50.7 (12.2)	51.5 (12.5)	47.2 (16.0)	46.5 (16.1)
Female, n (%)	114 (66)	186 (58)	302 (65)	595 (63)
BMI ≥30 kg/m^2, n (%)	67 (39)	126 (39)	194 (42)	364 (37)
Mean EOS/µL (SD)	520 (440)	450 (390)	330 (340)	320 (340)
Mean IgE, IU/mL (SD)	362 (578)	369 (559)	443 (761)	461 (819)
Mean FeNO, ppb (SD)	44.54 (40.24)	40.85 (36.75)	33.46 (30.41)	31.94 (30.46)
Mean age at asthma onset, years (SD)	31.8 (18.8)	30.5 (18.1)	25.7 (18.6)	25.6 (19.5)
Former smoker, n (%)	39 (23)	66 (21)	87 (19)	176 (19)

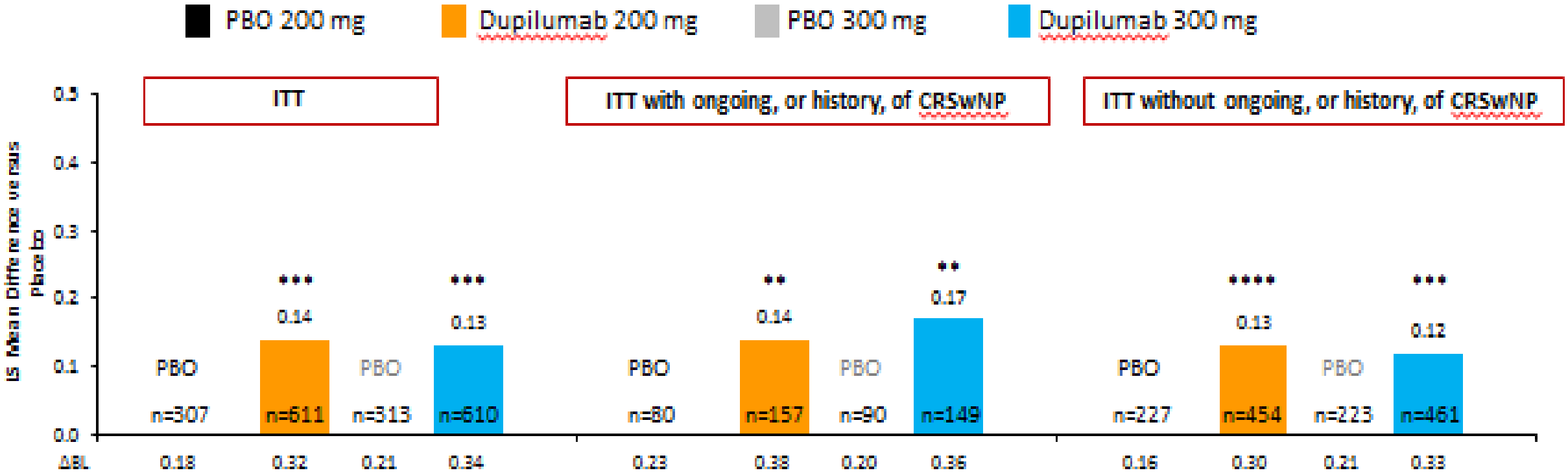
2-2. QUEST post-hoc : Effects of Co-Morbidities – CRSwNP

Adjusted Annual Severe Exacerbations



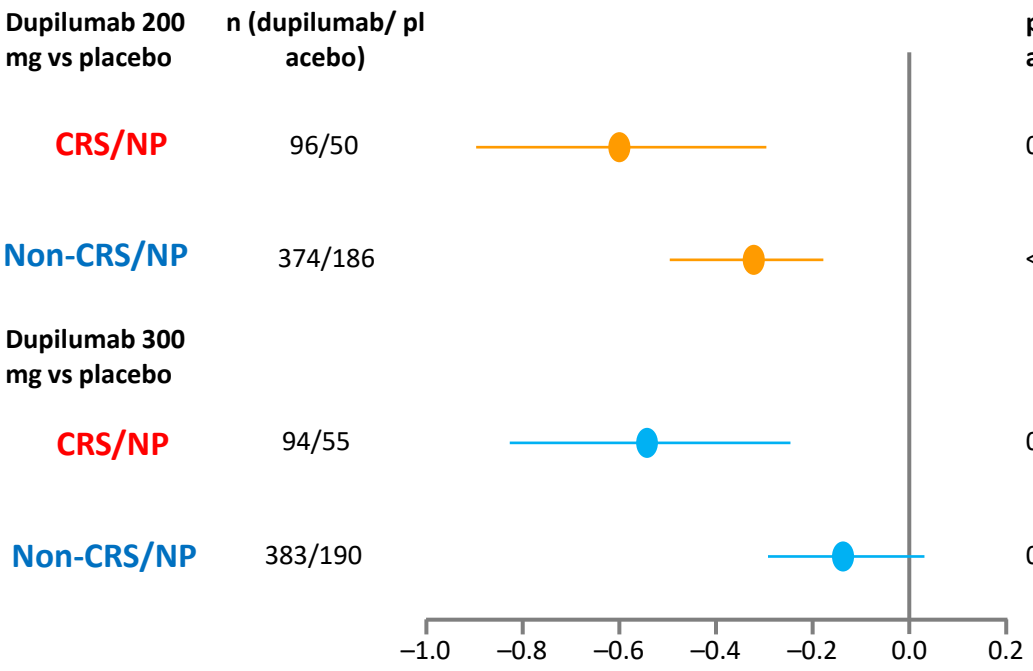
2-2. QUEST post-hoc : Effects of Co-Morbidities – CRSwNP

FEV1 change (mean diff. vs placebo)

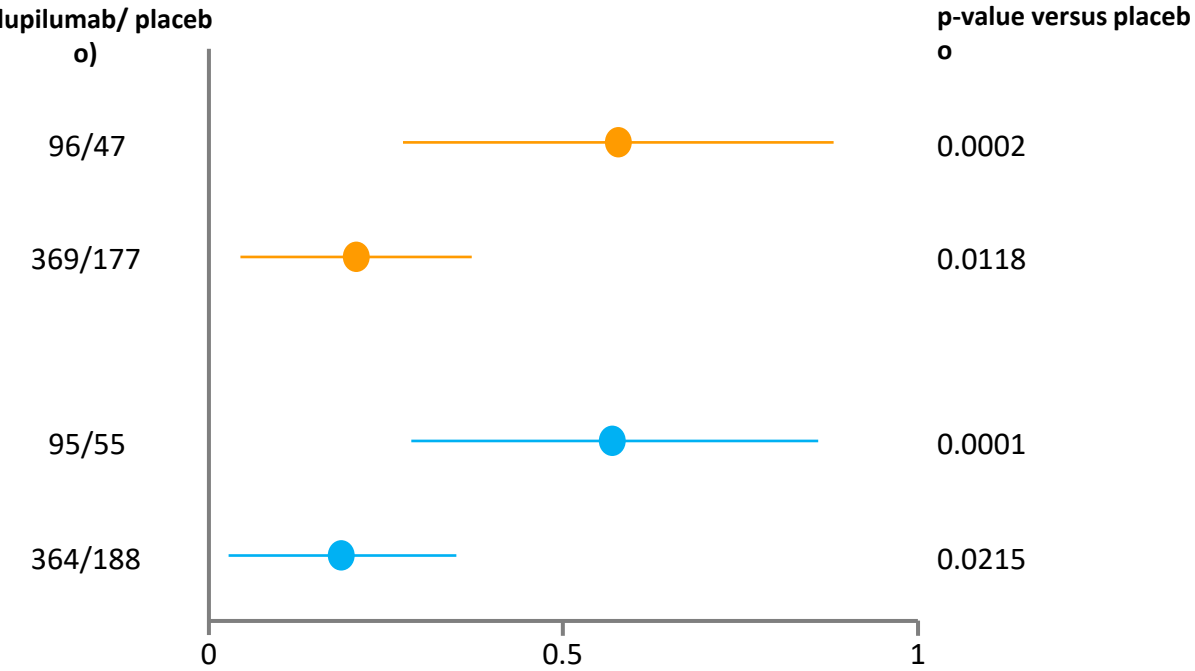


2-2. QUEST post-hoc : Effects of Co-Morbidities – CRSwNP

Improvement in ACQ-5 Scores

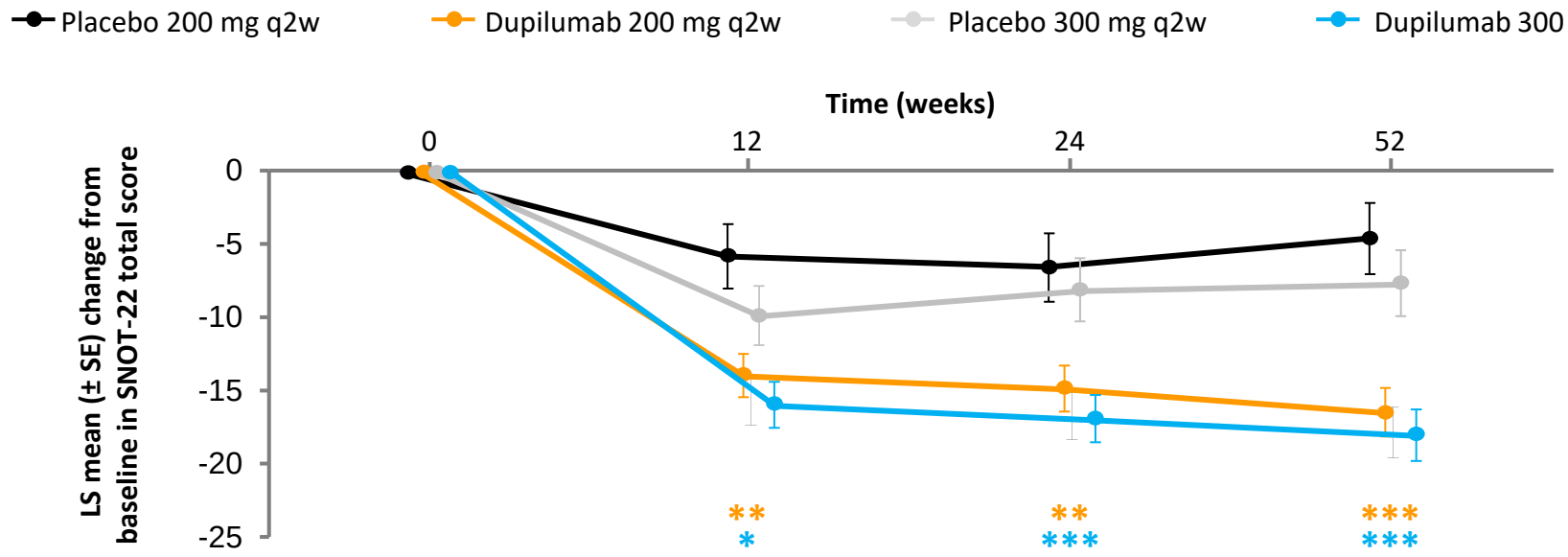


Improvement in AQLQ(S) Scores



2-2. QUEST post-hoc : Effects of Co-Morbidities – CRSwNP

Change from Baseline in SNOT-22 Scores



Number of patients			
Placebo 200 mg q2w, n	51	52	42
Dupilumab 200 mg q2w, n	113	111	89
Placebo 300 mg q2w, n	61	58	49
Dupilumab 300 mg q2w, n	102	102	85

- The magnitude of change in SNOT-22 scores from baseline to Weeks 12, 24, and 52 in the dupilumab-treated patients exceeded differences regarded as clinically meaningful (≥8.9)

"Dupilumab improved SNOT-22 scores in asthma patients with chronic rhinosinusitis with or without nasal polyposis in the LIBERTY ASTHMA QUEST study"
Prespecified analysis of the Phase 3 LIBERTY ASTHMA QUEST study

2-3. QUEST post-hoc analysis_baseline FeNO

Background

- FeNO is a clinically useful biomarker of IL-4/IL-13-mediated airway inflammation. In QUEST study, dupilumab 200/300mg vs placebo reduced severe asthma exacerbations, improved pre-bronchodilator FEV1 and was generally well tolerated.

Objective

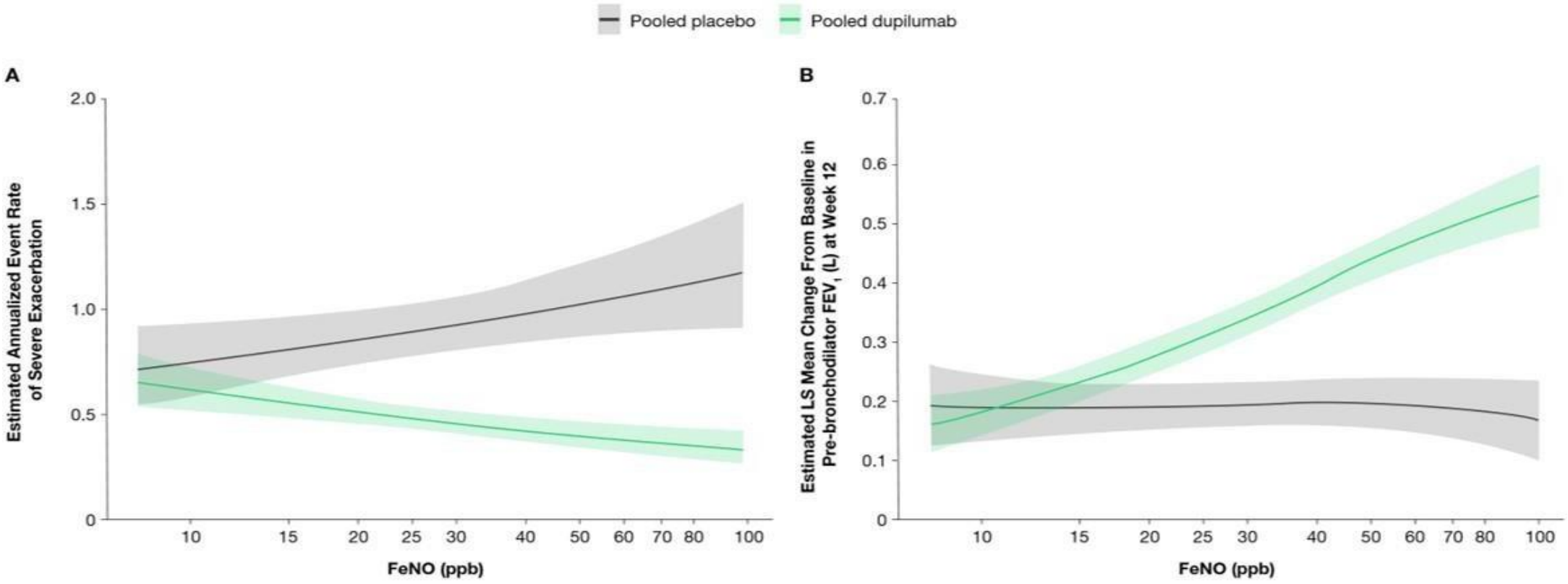
- To access baseline **FeNO** levels as **predictor** of response to dupilumab.

Assessment

- Annualized exacerbation rates (AER) during the 52-week treatment period and change from baseline in pre-bronchodilator FEV1 at Week 12 were analyzed by **FeNO levels** in the overall population (penalized negative binomial regression spline models), **accounting** for potential differences in baseline blood **eosinophils** (Eos) and other **clinical characteristics**.
- Efficacy outcomes were also analyzed by FeNO </≥25ppb and Eos ≥150cells/μL subgroups.

ACAAI 2020 abstract # 8099

2-3. QUEST post-hoc analysis_baseline FeNO



In patients with **Eos≥150cells/μL**, AER were significantly reduced in dupilumab vs placebo by 40.3/66.7% (*P*<0.001) in patients with **FeNO </≥25ppb**, respectively, whereas pre-bronchodilator FEV1 at Wk12 was significantly improved in patients with FeNO ≥25ppb (0.26L;*P*<0.0001**); significant differences in patients with FeNO <25ppb were not observed** (0.03L;*P*=0.3248).

ACAAI 2020 abstract # 8099

Contents

1. Randomized Controlled Trials

2. Post-hoc Data from RCTs

3. Meta-analyses

- An indirect treatment comparison (ITC) of dupilumab versus each of the anti-IL-5 and anti-IgE therapies
- Effect of Anti-IL5, Anti-IL5R, Anti-IL13 Therapy on Asthma Exacerbations

3-1. Indirect Treatment Comparison (ITC) of Dupilumab

Background

- Currently, five biologic treatment options are available for use in patients with uncontrolled persistent asthma: three interleukin (IL)-5 antagonists (**mepolizumab**, **reslizumab**) or to the IL-5 receptor (**benralizumab**); one anti-IgE therapy (**omalizumab**); and one anti-IL-4/IL-13 therapy (**dupilumab**).
- To date, no comparative data from head-to-head clinical trials are available for these biologics.

Objective

- To compare indirectly each of the anti-IL-5(R) and anti-IgE therapies vs dupilumab using the endpoints of annualized severe asthma **exacerbation** rates and change in **pre-BD FEV1**.

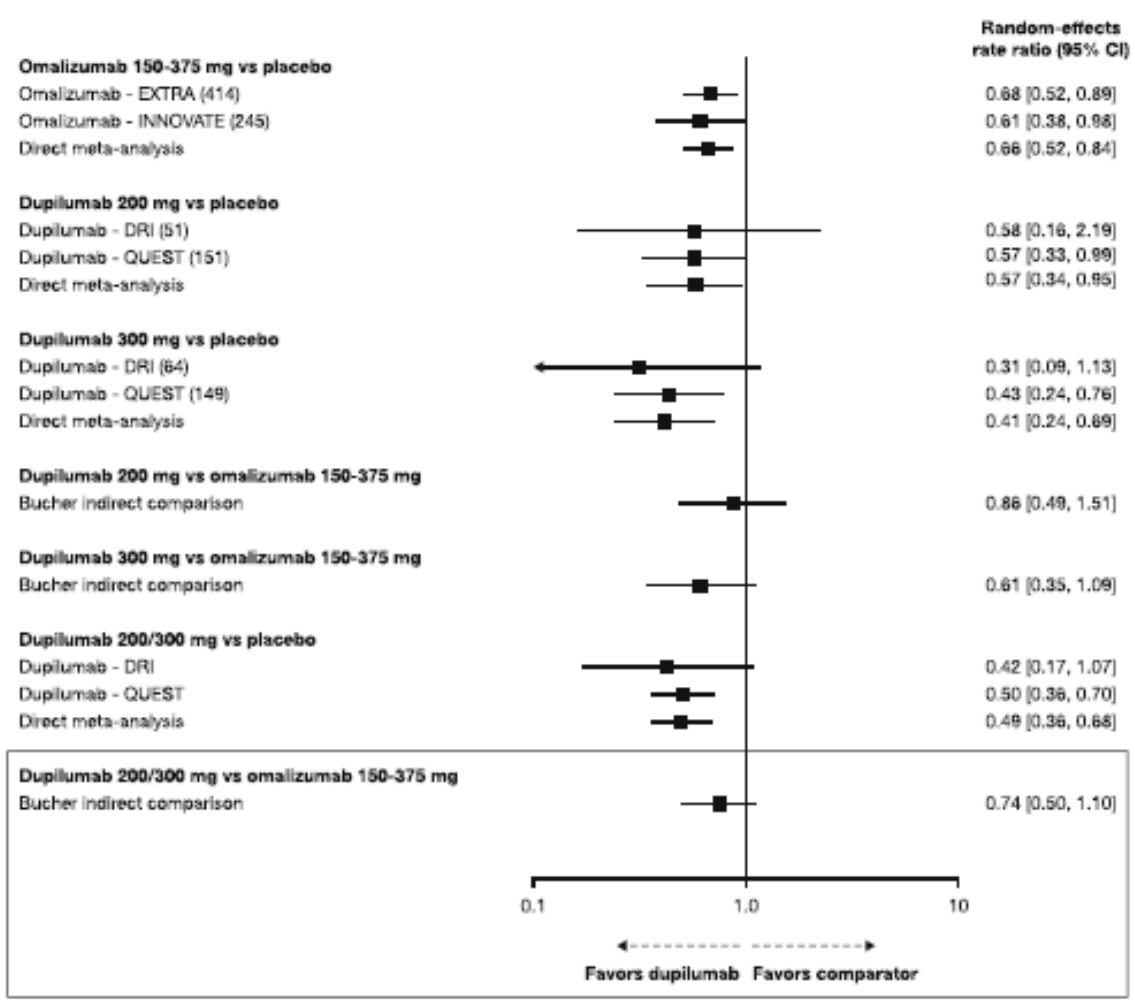
Method

- Embase®, MEDLINE®, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for studies published between January 1, 1980 and March 25, 2019. Eligible articles included randomized controlled trials in **patients aged ≧ 12 years** with persistent/uncontrolled asthma using at least **medium-to-high dose ICS plus LABA** with add-on biologic therapy. Bucher ITCs were performed to compare subgroups of dupilumab patients with the anti-IL-5s and anti-IgE trial populations .

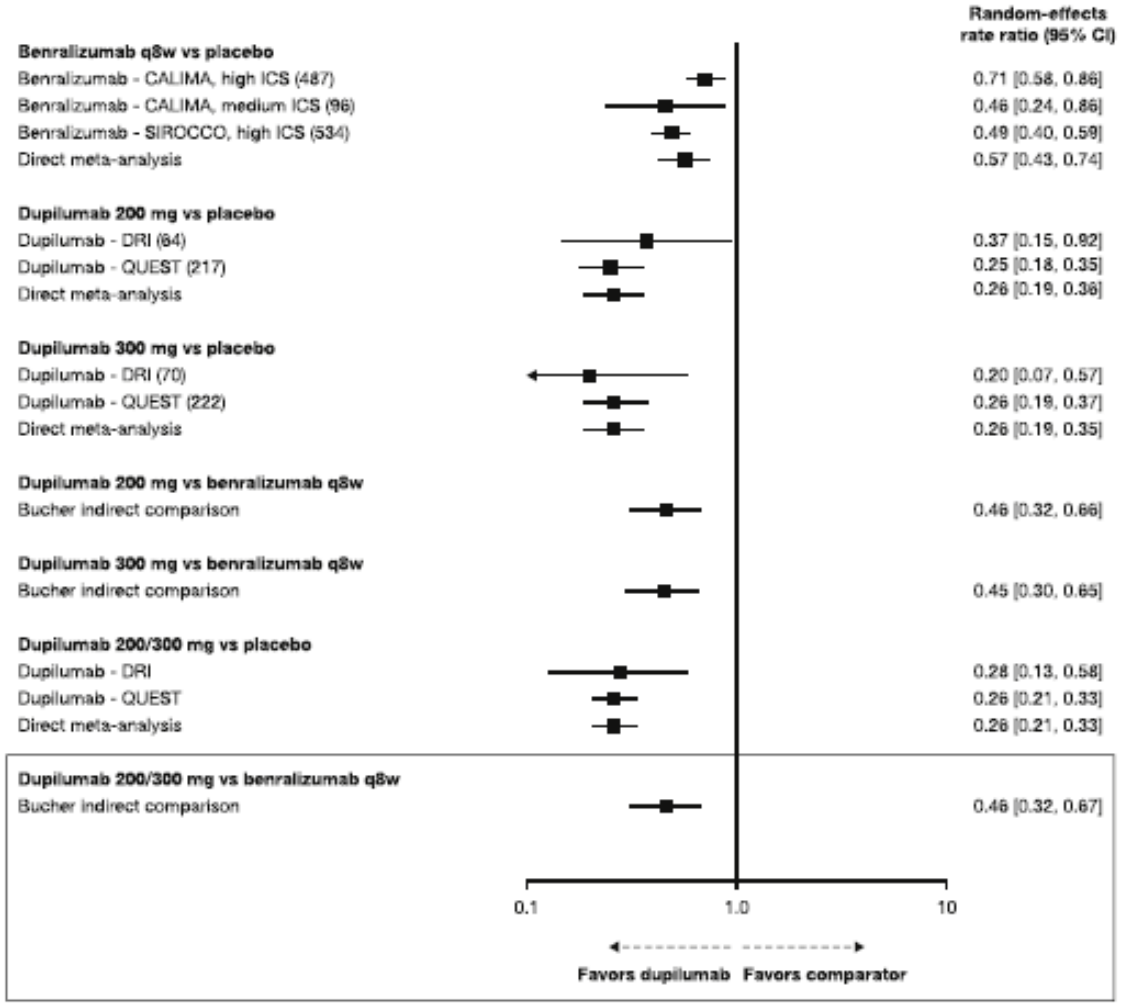
E.D. Bateman, et al., Pairwise indirect treatment comparison of dupilumab versus other biologics in patients with uncontrolled persistent asthma, Respir. Med. (2020). https://doi.org/10.1016/j.rmed.2020.105991.

3-1. ITC of dupilumab_Result 1. Severe Exacerbation Rate

Omalizumab vs dupilumab



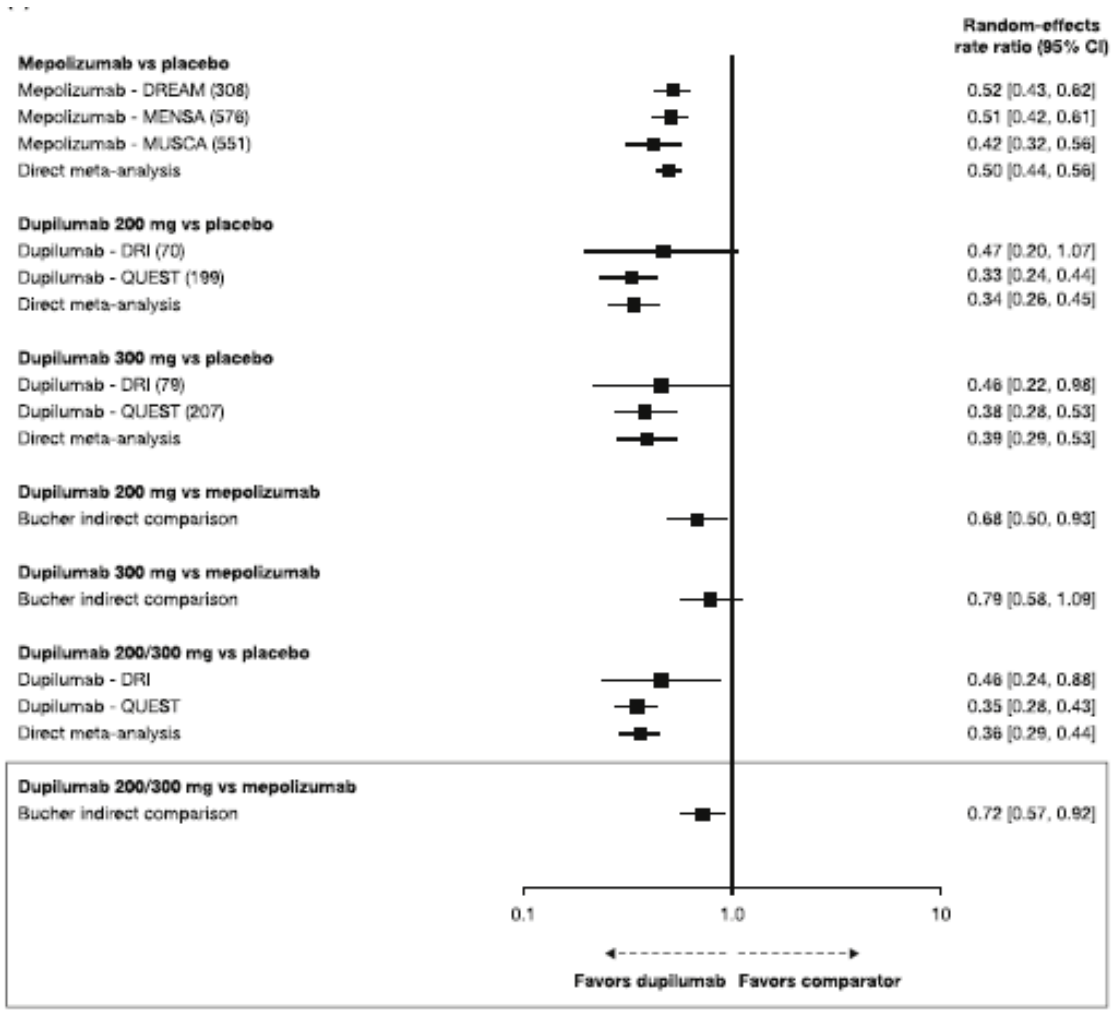
Benralizumab vs dupilumab



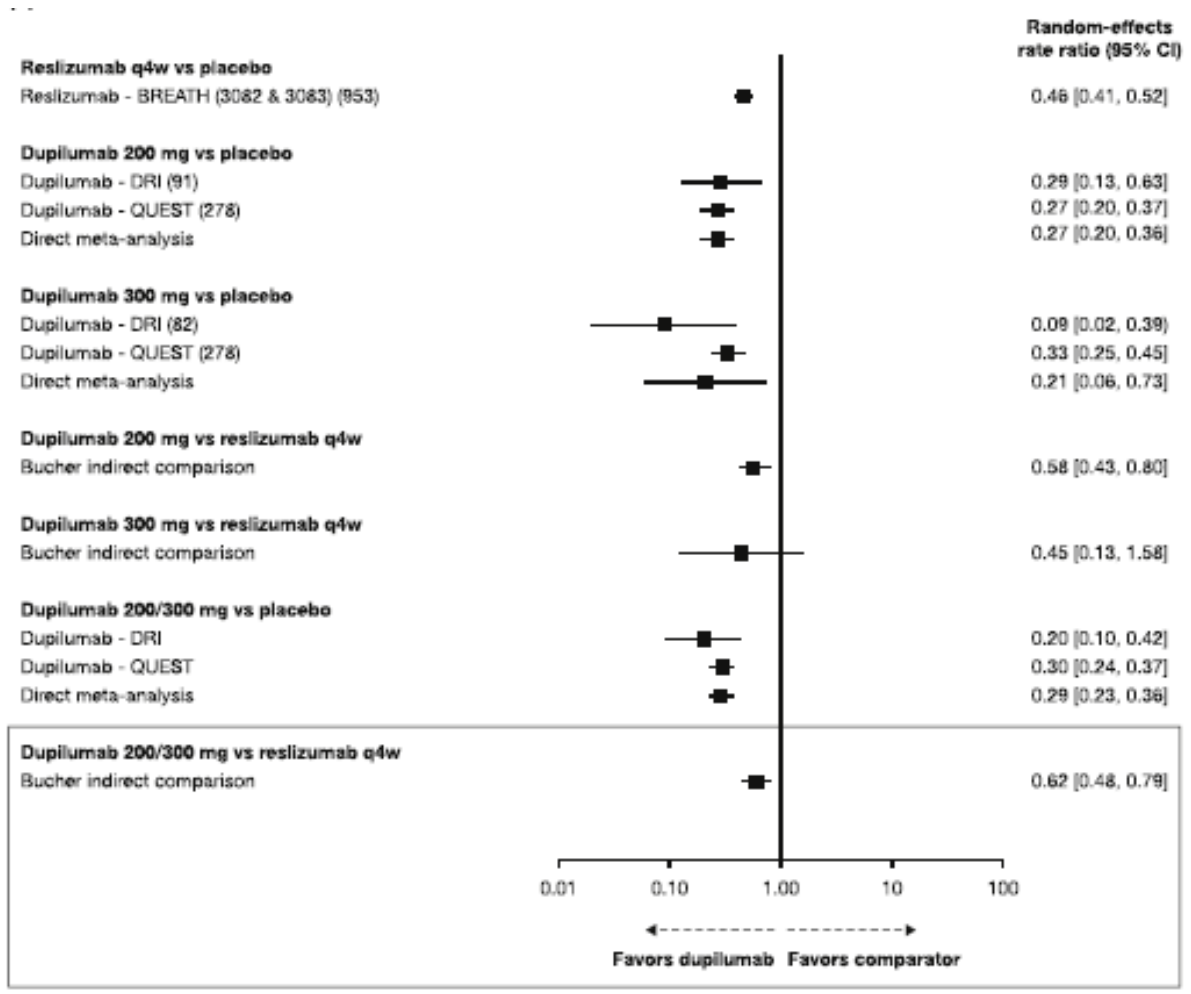
E.D. Bateman, et al., Pairwise indirect treatment comparison of dupilumab versus other biologics in patients with uncontrolled persistent asthma, Respir. Med. (2020). https://doi.org/10.1016/j.rmed.2020.105991.

3-1. ITC of dupilumab_Result 1. Severe Exacerbation Rate

Mepolizumab vs dupilumab



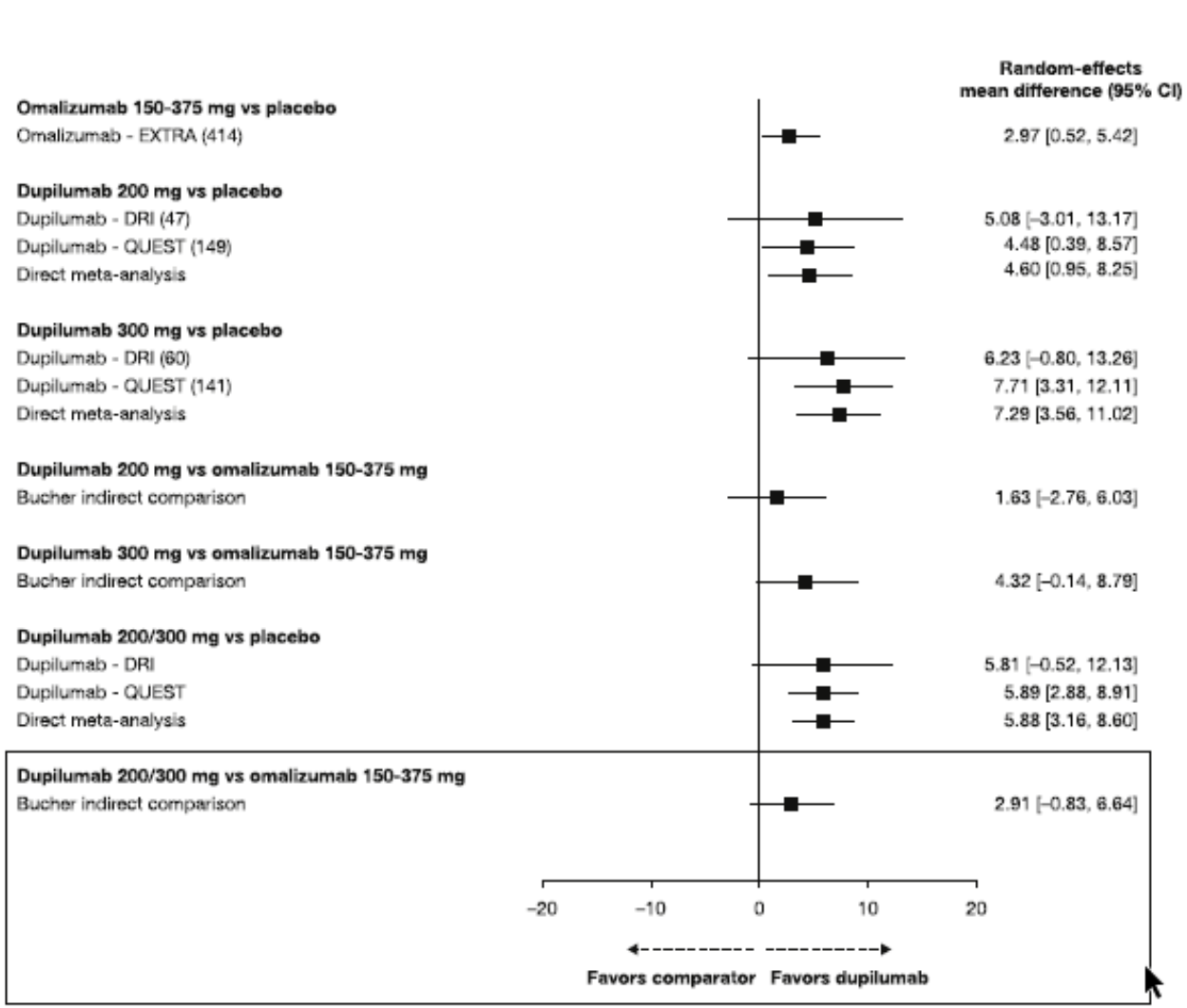
Reslizumab vs dupilumab



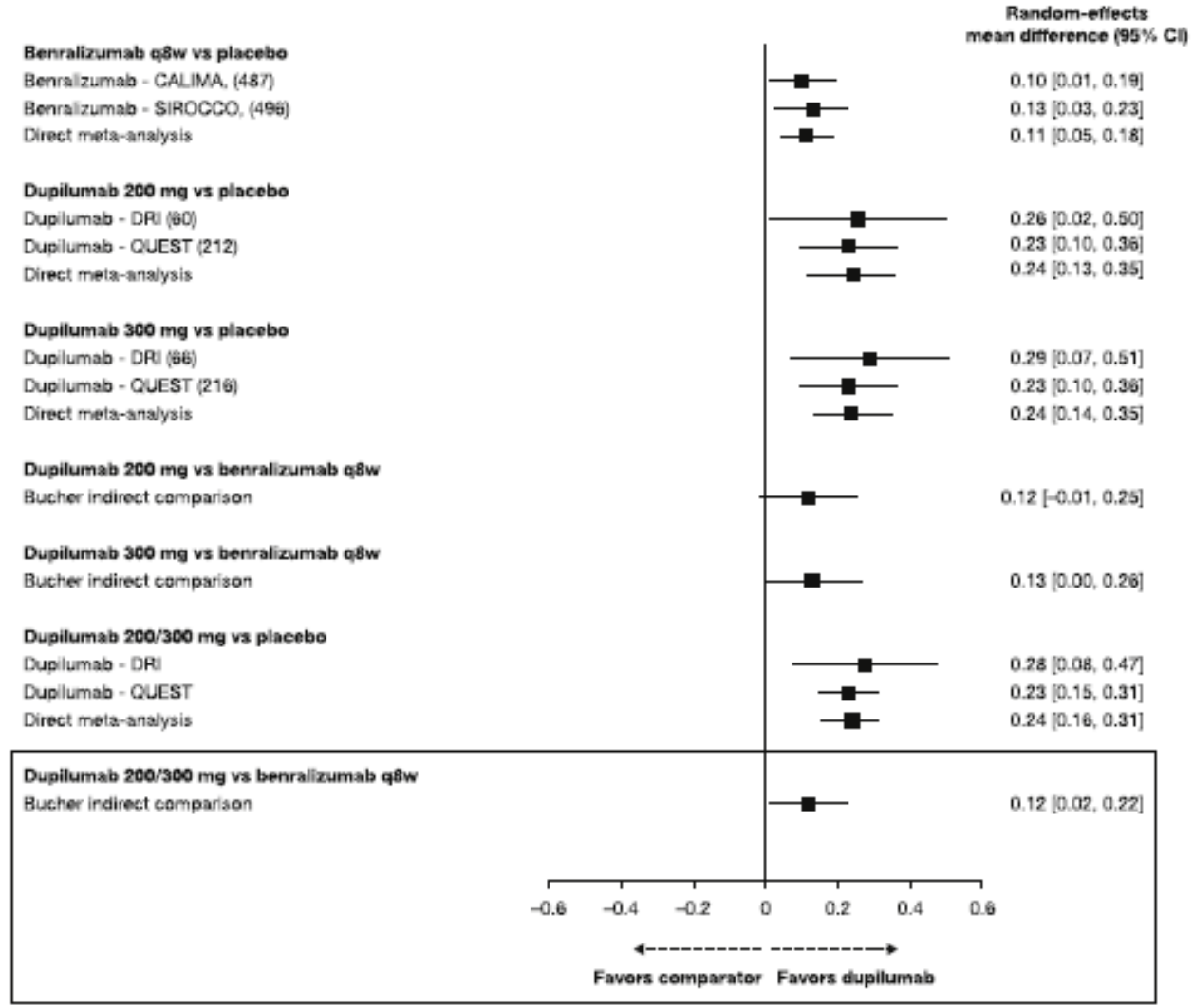
E.D. Bateman, et al., Pairwise indirect treatment comparison of dupilumab versus other biologics in patients with uncontrolled persistent asthma, Respir. Med. (2020). https://doi.org/10.1016/j.rmed.2020.105991.

3-1. ITC of dupilumab_Result 2. FEV1 (at week 12)

Omalizumab vs dupilumab



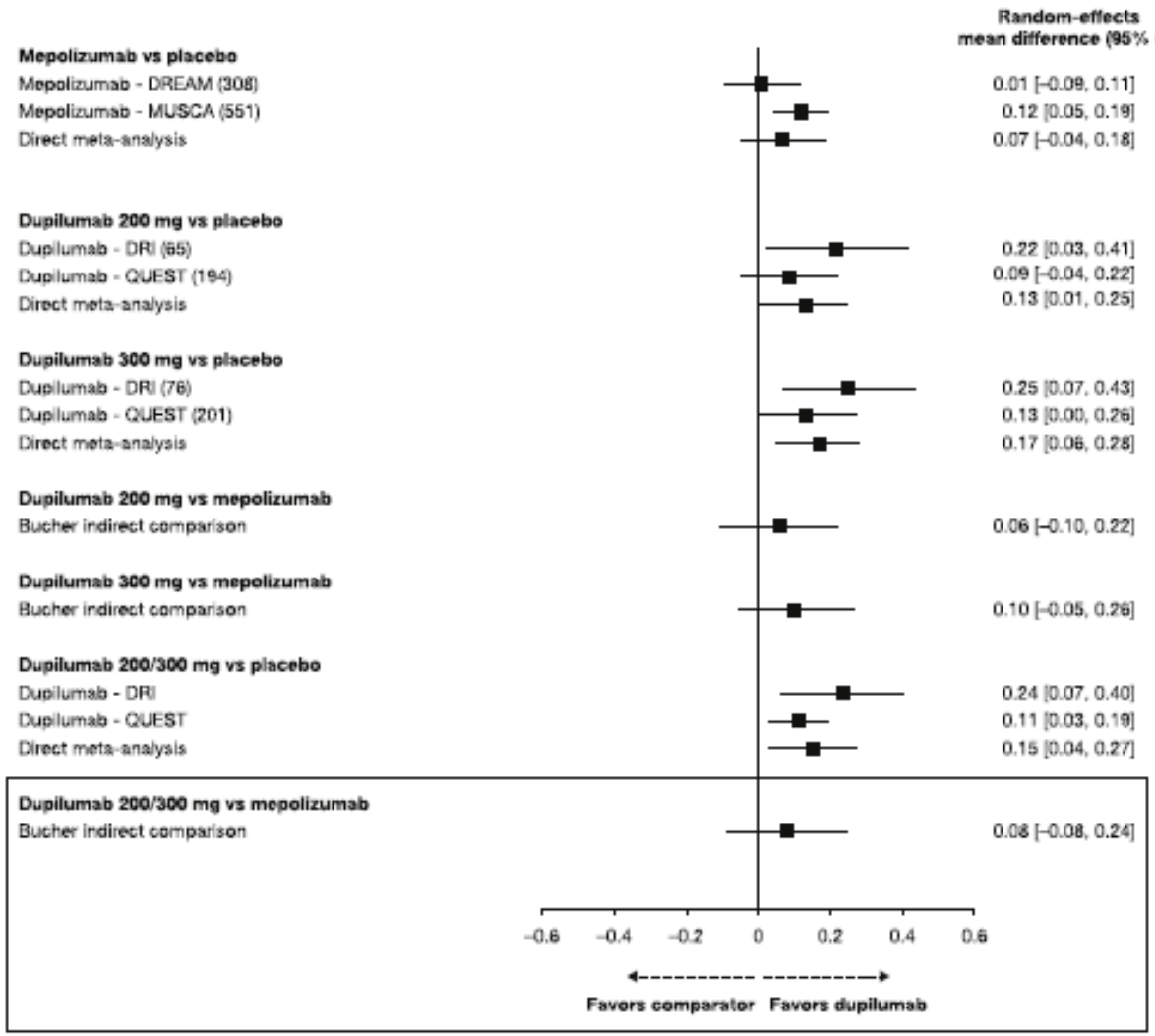
Benralizumab vs dupilumab



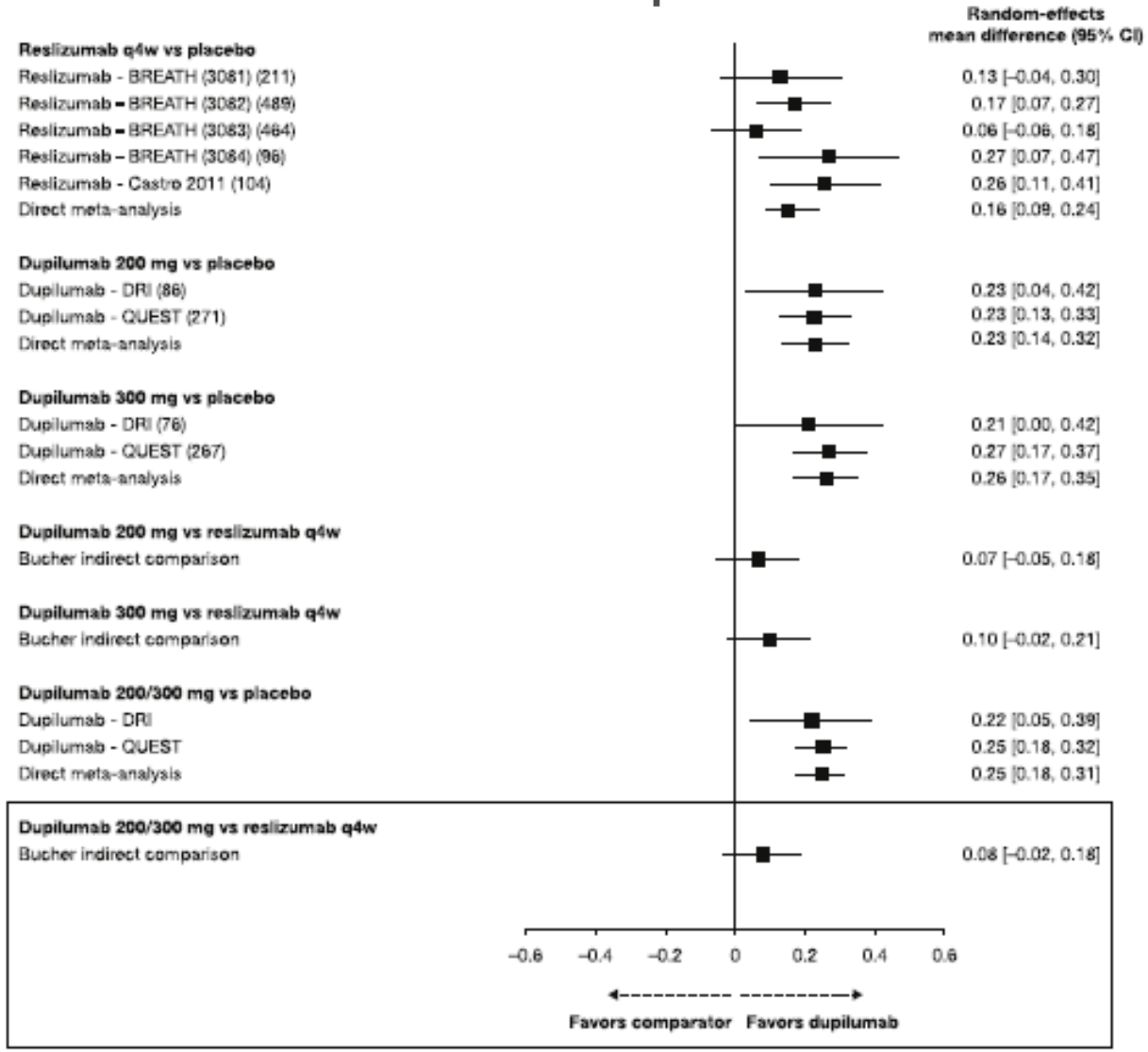
E.D. Bateman, et al., Pairwise indirect treatment comparison of dupilumab versus other biologics in patients with uncontrolled persistent asthma, Respir. Med. (2020). https://doi.org/10.1016/j.rmed.2020.105991.

3-1. ITC of dupilumab_Result 2. FEV1 (at week 12)

Mepolizumab vs dupilumab



Reslizumab vs dupilumab



E.D. Bateman, et al., Pairwise indirect treatment comparison of dupilumab versus other biologics in patients with uncontrolled persistent asthma, Respir. Med. (2020). https://doi.org/10.1016/j.rmed.2020.105991.

3-2. Effect of Anti-IL5, Anti-IL5R, Anti-IL13 Therapy on Asthma Exacerbations

Background

- Several new treatments for severe asthma have become available in the last decade; yet, little data exist to guide their use in **specific patient populations**.

Objective

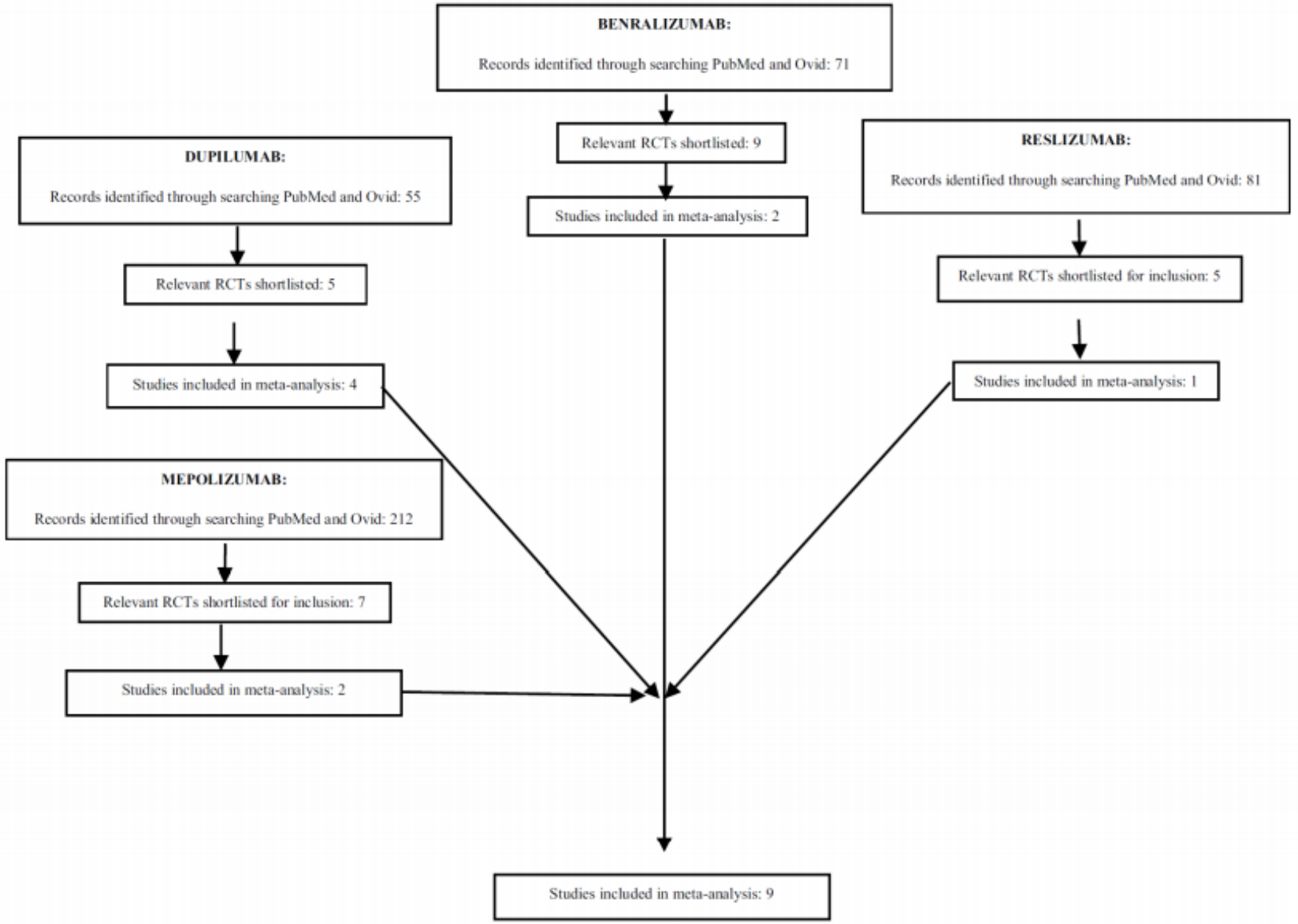
- A network meta-analysis was conducted comparing the efficacy of FDA-approved monoclonal antibody therapies in preventing **exacerbations** in patients with severe **eosinophilic** asthma.

Method

- PubMed and Ovid were searched from inception until July 2019 for randomized controlled trials that studied the efficacy of benralizumab, dupilumab, mepolizumab, and reslizumab, in preventing acute exacerbations of asthma. Studies were included if they reported data for patients with severe eosinophilic asthma (defined in this meta-analysis as **absolute eosinophil count ≥ 250** cells/μL). **Annualized rate ratios for asthma exacerbations** (during treatment) were calculated and converted to log rate ratios. **Direct and indirect treatment estimates** (for inter-drug differences) were analyzed using frequentist network meta-analysis methodology in R and treatments were **ranked based on P-scores.**

Ramonell RP. Lung 2020; 198: 95-103.

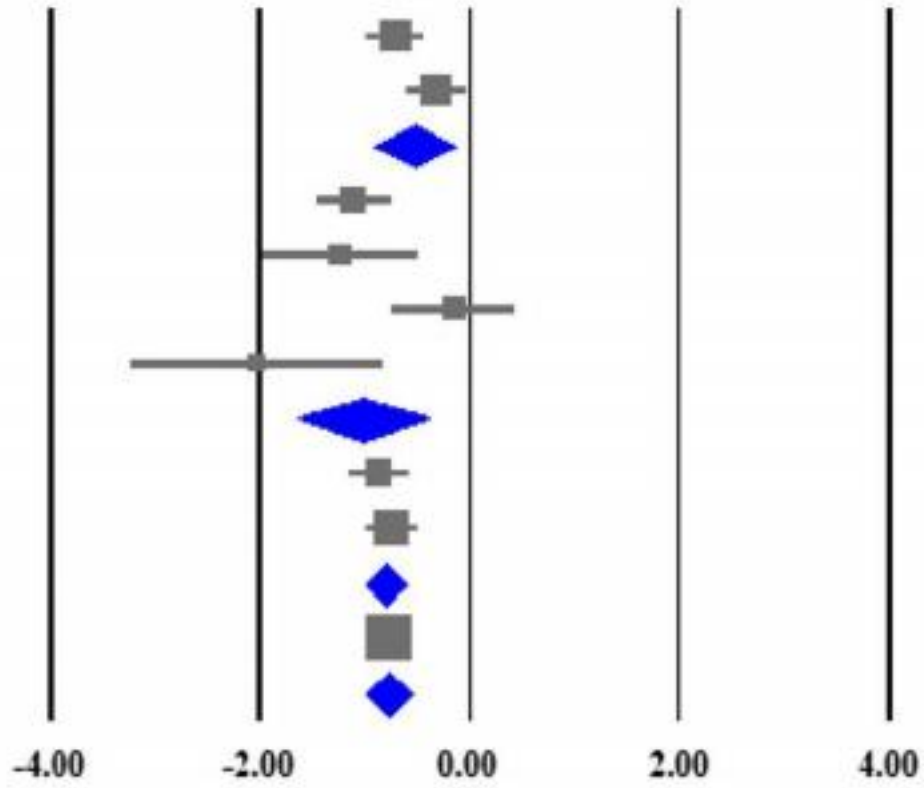
3-2. Effect of Anti-IL5, Anti-IL5R, Anti-IL13 Therapy on Asthma Exacerbations



Ramonell RP. Lung 2020; 198: 95-103.

3-2. Effect of Anti-IL5, Anti-IL5R, Anti-IL13 Therapy on Asthma Exacerbations

Study name		Log rate ratio	Lower limit	Upper limit	p-Value
Bleecker 2016	Benralizumab	-0.713	-0.987	-0.439	0.000
Fitzgerald 2016	Benralizumab	-0.329	-0.611	-0.046	0.023
		-0.523	-0.900	-0.145	0.007
Castro 2018	Dupilumab	-1.109	-1.470	-0.748	0.000
Rabe 2018	Dupilumab	-1.241	-1.973	-0.509	0.001
Wenzel 2016	Dupilumab	-0.157	-0.750	0.437	0.605
Wenzel 2013	Dupilumab	-2.037	-3.240	-0.834	0.001
		-1.024	-1.654	-0.395	0.001
Chupp 2017	Mepolizumab	-0.868	-1.163	-0.572	0.000
Ortega 2014	Mepolizumab	-0.755	-0.997	-0.513	0.000
		-0.800	-0.987	-0.613	0.000
Castro 2015	Reslizumab	-0.777	-1.001	-0.552	0.000
		-0.777	-1.001	-0.552	0.000



Ramonell RP. Lung 2020; 198: 95-103.

3-2. Effect of Anti-IL5, Anti-IL5R, Anti-IL13 Therapy on Asthma Exacerbations

Table 4 Ranking of treatments

	P-score
Dupilumab	0.83
Mepolizumab	0.66
Reslizumab	0.62
Benralizumab	0.36
Placebo	0.00

P-scores are based solely on the point estimates and standard errors of the network estimates

Dupilumab: A Clear Path to Asthma Control

- Dupilumab Is the First Dual Inhibitor of IL-4 and IL-13 Signalling pathway
- Dupixent has shown Significant Exacerbation reduction and Lung Function Improvement during the phase 3 trials (QUEST & VENTURE study)
- Dupixent also demonstrated Significant Reduction of OCS use in VENTURE study
- In addition to significant reduction in OCS use, dupixent has shown Significant Exacerbation Reduction and lung function Improvement.
- In Korea sub-group analysis, Dupixent showed Significant Exacerbation reduction and Lung Function Improvement aligned with global data.
- Dupixent is effective in severe asthma with co-morbid Type 2 inflammatory diseases (e.g. CRSwNP)

FEV_1=forced expiratory volume in 1 second; IL=interleukin; LS=least squares; OCS=oral corticosteroid; SOC=standard of care.