Recent Updates of Dupilumab in Type 2 Asthma

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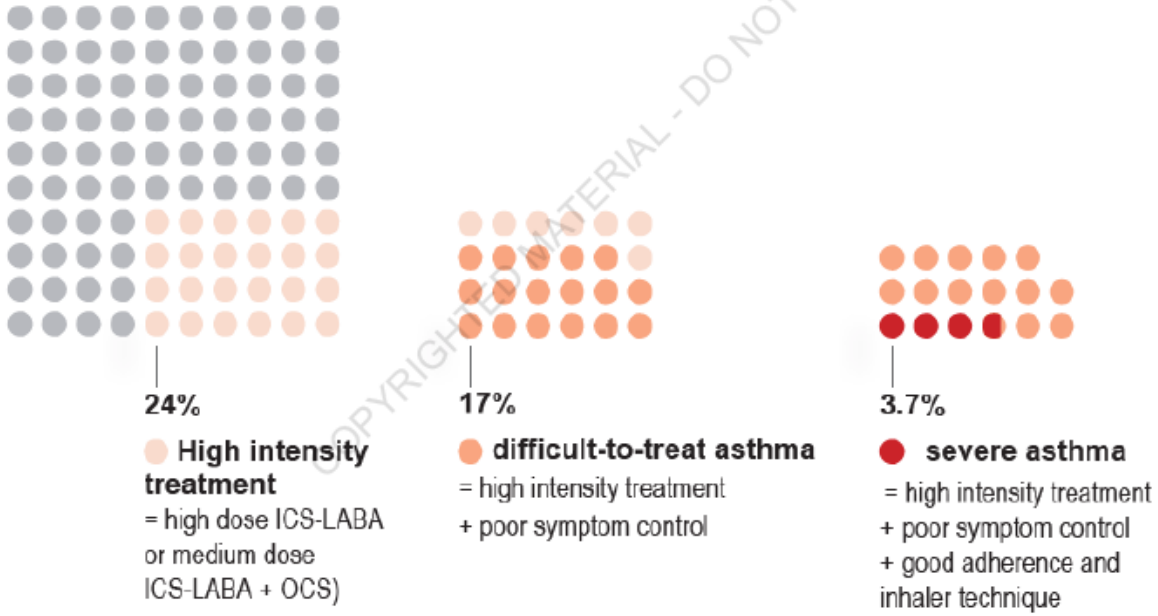
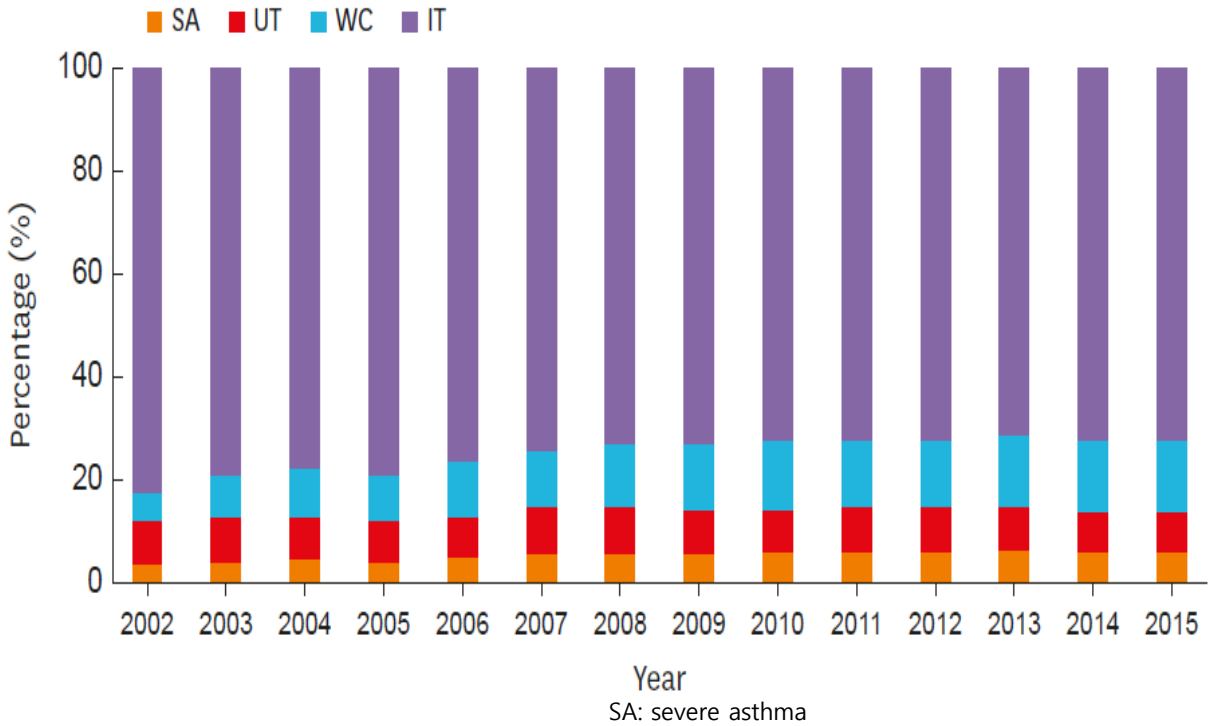
박 혜 윤

중증 천식 환자 비율

3.5% in 2002 → **6.1%** in 2015 (x1.7) in Korea





SA: severe asthma

(frequent asthma exacerbations even with regular treatments)

2021 GINA updated

E Lee et al.Allergy, Asthma & Immunol Res 2020;12(3):467-84

중증 천식

정의

- 고용량 흡입스테로이드 외에 한 가지 이상의 조절제를 쓰고도 조절이 되지 않는 천식이다.
- 중증천식의 진단은 천식 전문가가 최소 6개월 이상의 경과를 보며 정확한 진단 및 약제 사용에 대해 확인한 뒤 이루어져야 한다.

표 6-1. 지침에 따른 중증 천식의 정의

지침	사용 용어	정의
ERS/ATS 2013[1]	Severe asthma	고용량 흡입스테로이드와 2차 조절제 혹은 전신스테로이드를 써야 조절되거나
GINA 2019[3]	Difficult-to-treat asthma	GINA 4-5단계의 치료(중간용량 혹은 고용량 흡입스테로이드와 2차 조절제, 혹은 전신스테로이드 유지)가 필요하거나 이 치료에도 조절되지 않는 천식
	Severe asthma	최대 최적화된 GINA 4-5단계의 치료에 대한 높은 순응도와 천식유발인자 조절도 불구하고 조절되지 않거나 고용량의 천식 약제를 줄이면 악화되는 천식

"**GINA step 4-5** 에서,
적절한 약물/비약물 치료 및 위험인자 조절에도
uncontrolled인 천식"

2020 4차 개정 천식 진료 지침

중증 천식

Table 2. Checklist to distinguish 'severe asthma' from 'difficult-to-treat asthma'

Checklist
Is the patient a current smoker? Have you encouraged him/her to quit smoking?
Do you check how well the patient uses the inhaler and educate them on how to use it properly (at each visit)?
Do you understand the factors that keep patients not adherent to their medications?
Are there any adverse events due to asthma medications? (e.g., oral candidiasis, cough, hoarseness, dry mouth, or palpitation)
Has the patient informed of avoidance of the sensitized allergens or non-specific stimuli?
Environment control (HDM, pollens, molds, fine dust, air pollution, cold air, or other seasonal factors)
Occupational stimuli/work-related symptoms
Pets (dogs, cats, birds)
Drug adverse effects (e.g., cough, chest tightness, or dyspnea due to aspirin, ACEi, or β-blockers)
Does the patient need to be encouraged to exercise or lose weight?
Have you ever considered assessing and managing the comorbidities of the patient?
Chronic rhinosinusitis (with or without nasal polyps) by imaging studies (X-ray or CT scan of the PNS)
GERD by endoscopy or preemptive treatment with proton pump inhibitors
Obstructive sleep apnea by polysomnography
Obesity
Psychological distress (anxiety and depression)
Structural lung diseases (COPD or bronchiectasis) by imaging studies (chest CT scan)

HDM, house dust mites; ACEi, angiotensin-converting enzyme inhibitors; PNS, paranasal sinuses; GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary diseases; CT, computed tomography.

흡연

흡입기 사용법

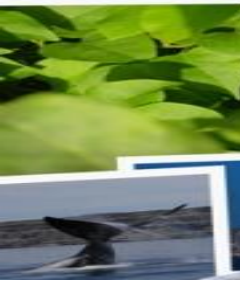
순응도

부작용

알러젠이나 비특이적 자극 물질에 대한 회피

동반질환 (축농증, GERD, 수면무호흡증, 비만, 스트레스, COPD 등)

Kim et al. Allergy Asthma Immunol Res 2020;12:910-33



Uncontrolled asthma

- Uncontrolled asthma symptom (3 or 4 of criteria)
  - ≥ 2 daytime symptoms/weeks in the past 4 weeks
  - Any night-waking in the past 4 weeks
  - Reliever used ≥ 2 times/week in the past 4 weeks
  - Any activity limitation in the past 4 weeks

or

- Partly controlled asthma symptom (1 or 2 criteria) plus one risk factor for poor outcome
  - Reduced lung function (FEV1 predicted value ≤ 80%)
  - History of asthma exacerbation (oral corticosteroid bursts ≥ 2/year or hospitalization ≥ 1/year)

Difficult-to-treat asthma

- Uncontrolled with GINA step 4 or 5 treatment

Consider referral to an asthma specialist or asthma specialty center

- Confirmation of asthma diagnosis
  Consider examinations for differential diagnosis: chest CT, bronchoscopy, laryngoscopy, serum ANCA, skin prick test, or serum specific IgE to *Aspergillus*
- Correction of modifiable risk factors
  - Smoking
  - Inhaler technique
  - Medication non-adherence
  - Exposure to sensitized allergen or stimuli
    : environment control, occupational stimuli/work-related symptoms, pets
- Control of comorbidities
  - CRS, GERD, OSA, obesity, depression/anxiety disorder

Still uncontrolled after 3–6 months of optimizing treatment
- Non-pharmacological interventions
- Pharmacological interventions

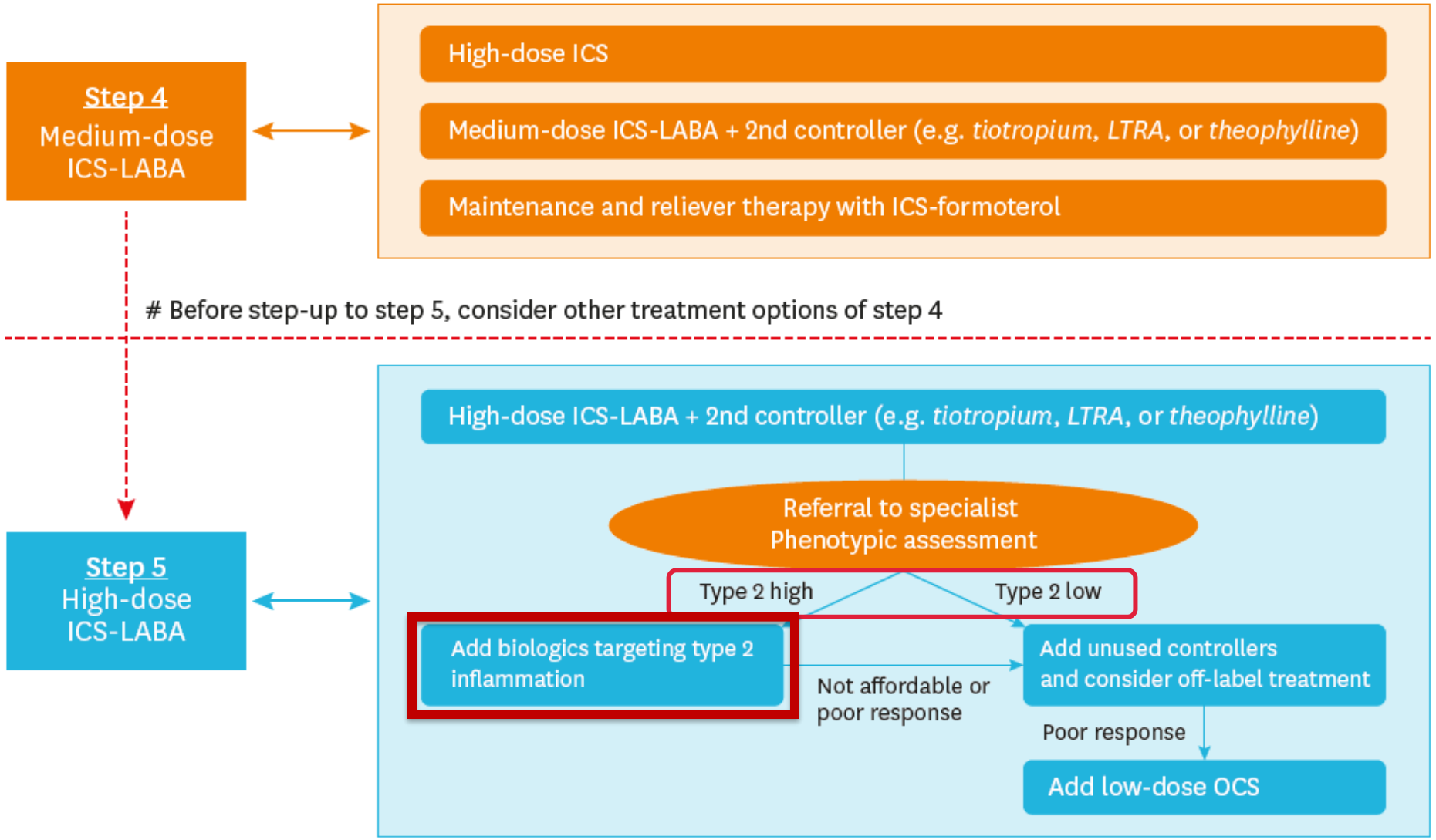
Severe asthma

Consider referral to an asthma specialist or asthma specialty center

- Assessment of phenotype
  : blood eosinophils, sputum eosinophils, FeNO, skin prick test, and/or specific IgE test
- Type 2 inflammation (one or more criteria)
  - Blood eosinophils ≥ 150/μ
  - Sputum eosinophils ≥ 2%
  - FeNO ≥ 20 ppb
  - Allergen-driven

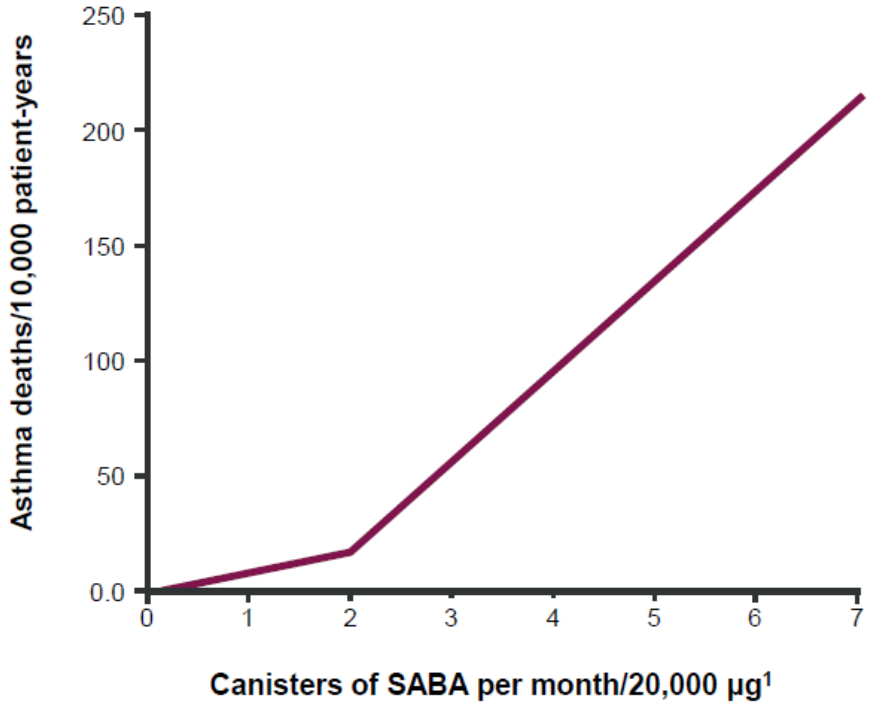
Kim et al. Allergy Asthma Immunol Res 2020;12:910-33

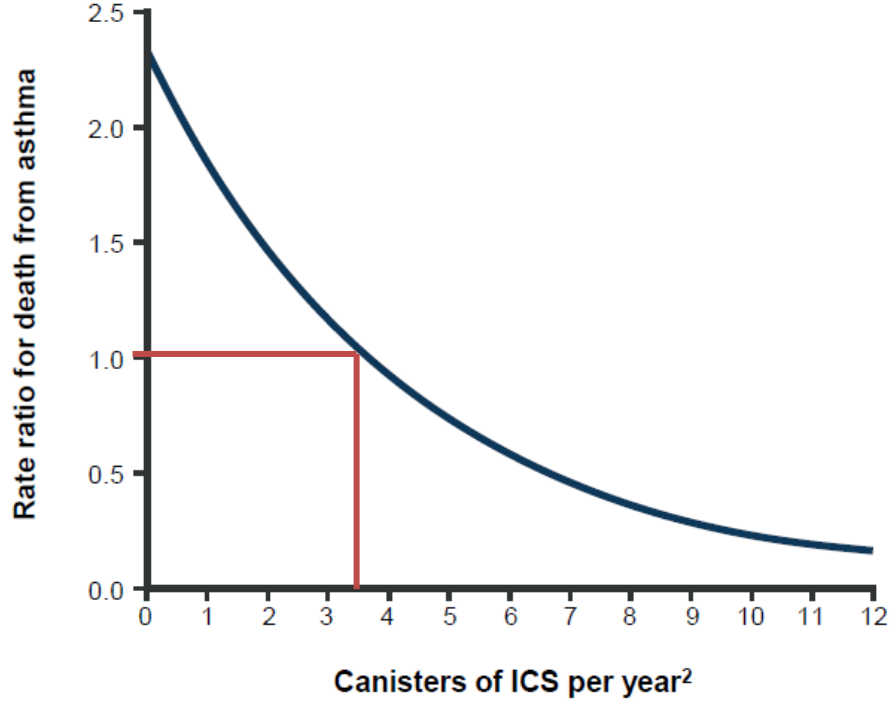
중증 천식


Step 4
Medium-dose
ICS-LABA
High-dose ICS
Medium-dose ICS-LABA + 2nd controller (e.g. tiotropium, LTRA, or theophylline)
Maintenance and reliever therapy with ICS-formoterol
Before step-up to step 5, consider other treatment options of step 4
Step 5
High-dose
ICS-LABA
High-dose ICS-LABA + 2nd controller (e.g. tiotropium, LTRA, or theophylline)
Referral to specialist
Phenotypic assessment
Type 2 high
Type 2 low
Add biologics targeting type 2 inflammation
Not affordable or poor response
Add unused controllers and consider off-label treatment
Poor response
Add low-dose OCS

ICS 사용을 해야 하는 이유

The rate of death from asthma decreased by 21 % with each additional canister of inhaled corticosteroids used in the previous year.

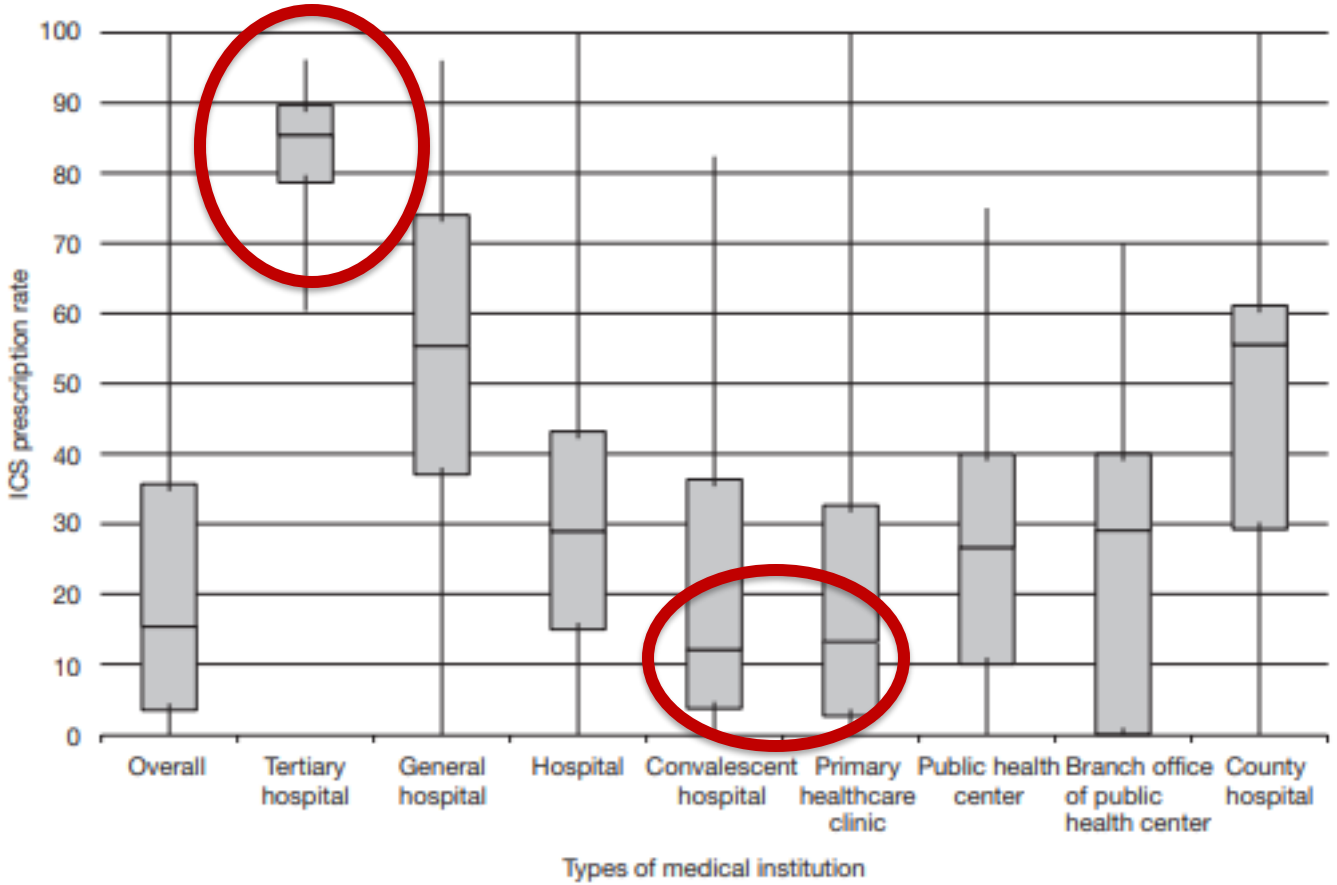




꾸준한 염증 치료는 천식 사망률을 감소시킴

1. SuissaS, et al. Am J Respir CritCare Med 1994;149:604–10; 2. SuissaS, et al. N EnglJ Med 2000;343:332–6

ICS 처방 비율



Tertiary hospital: General hospitals (≥100 beds) with specialized medical practice for disease with high severity

JY Choi et al, J Thorac Dis 2018;10(9):5405-5413

중증 천식 환자 (한국)

Characteristic	Data
Sex, No. (%) (n = 4,986)	
Female	2,957 (59.3)
Male	2,029 (40.7)
Age, y (n = 4,967)	
Mean (SD)	55.0 (15.9)
18-34, No. (%)	658 (13.2)
35-54, No. (%)	1,510 (30.4)
55-79, No. (%)	2,588 (52.1)
≥ 80, No. (%)	211 (4.2)
Ethnicity, No. (%) (n = 4,912)	
White	3,568 (72.6)
Asian	589 (12.0)
African	263 (5.4)
Mixed	31 (0.6)
Other	130 (2.6)
Unknown	331 (6.7)
BMI, No. (%), kg/m^2 (n = 4,901)	
Underweight (< 18.5)	105 (2.1)
Normal (≥ 18.5 to < 25)	1,345 (27.4)
Overweight (≥ 25 to < 30)	1,531 (31.2)
Obese (≥ 30)	1,920 (39.2)
Smoking status, No. (%) (n = 4,947)	
Current smoker	294 (5.9)
Exsmoker	1,656 (33.5)
Never smoked	2,997 (60.6)

The number refers to the total number of patients with nonmissing data. Percentages may not total 100% because of rounding. ISAR = Internal Severe Asthma Registry.

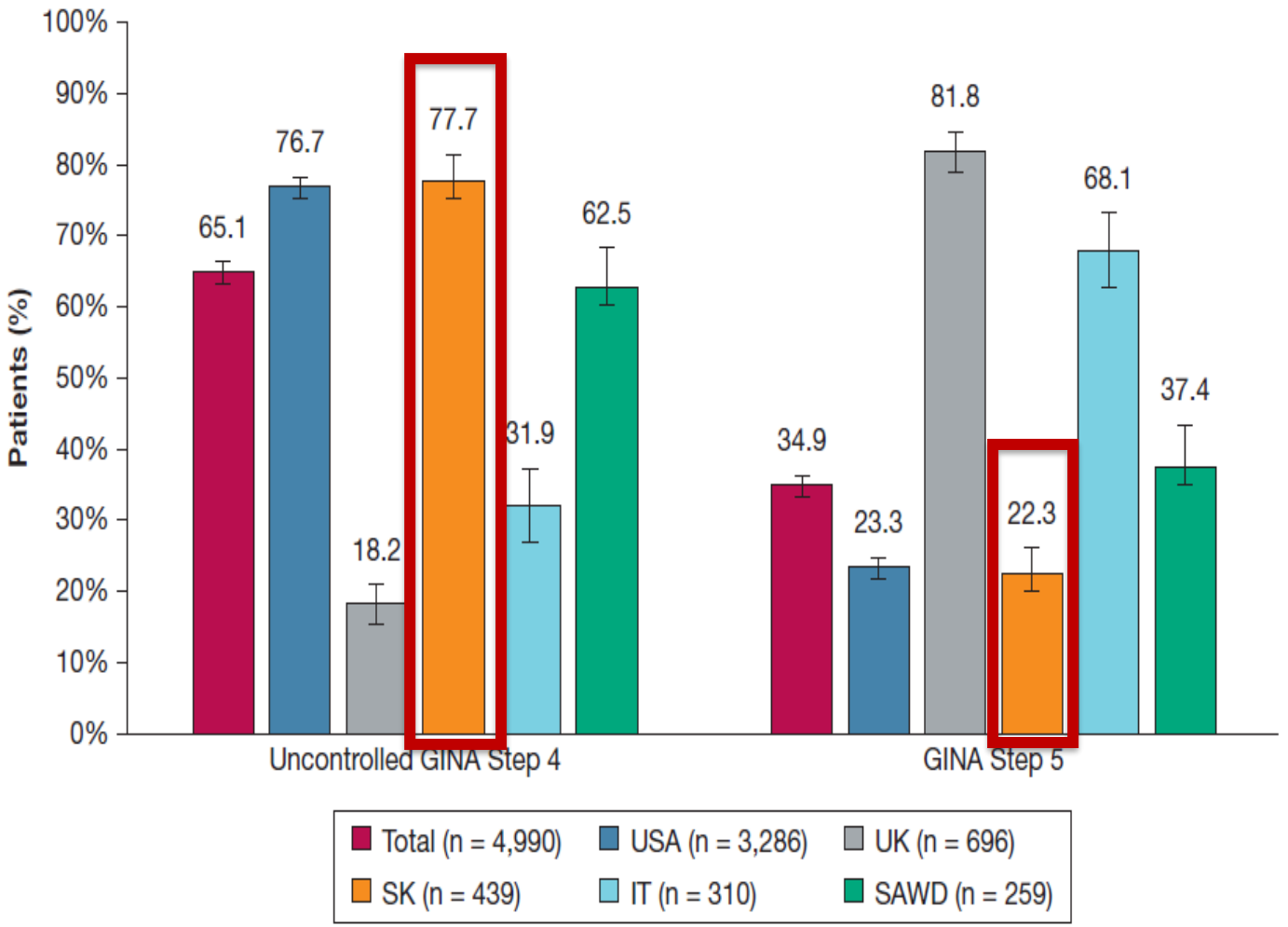
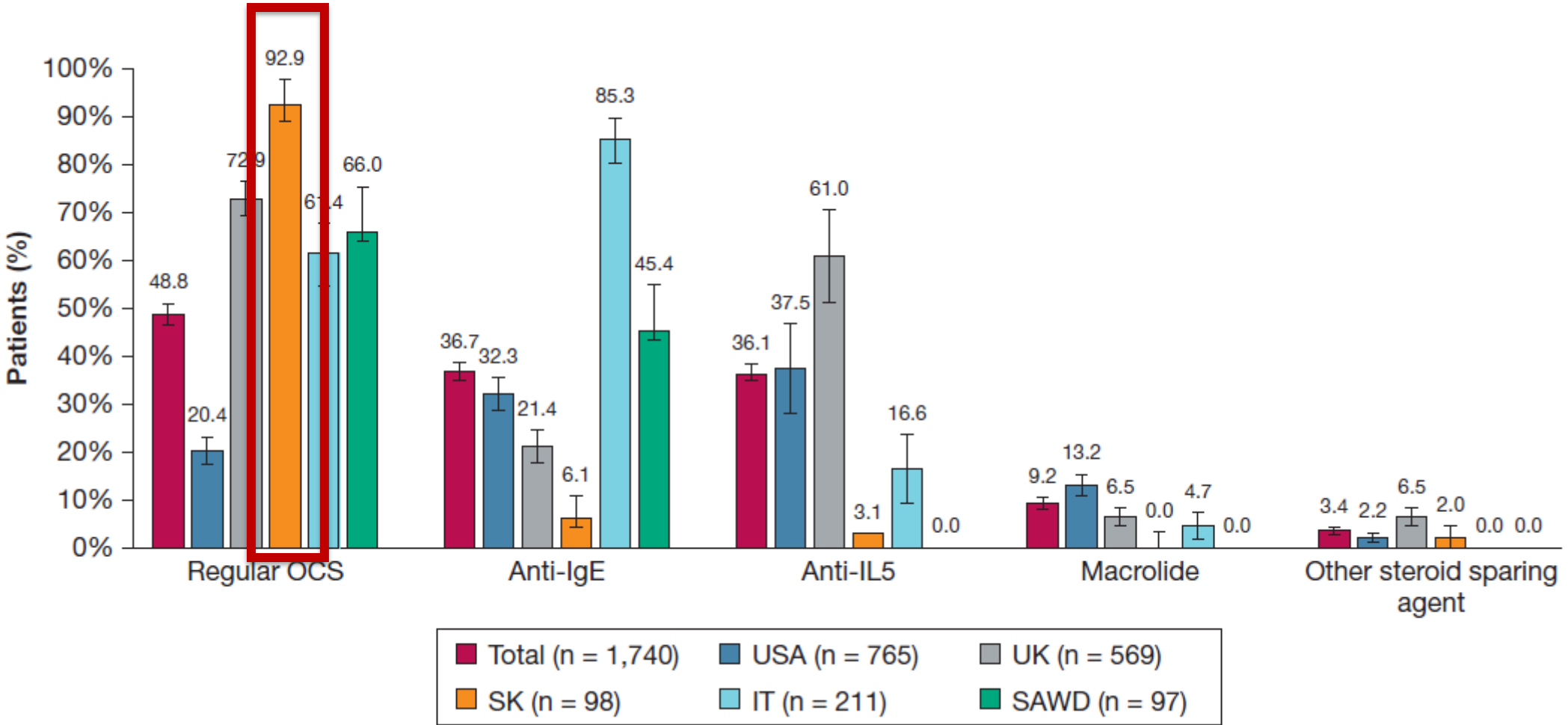


Figure 1 – *Asthma severity distribution in the total International Severe Asthma Registry population and by country. GINA = Global Initiative for Asthma; IT = Italy; SAWD = Severe Asthma Web-based Database; SK = South Korea; UK = United Kingdom; USA = United States.*

중증 천식 환자 (한국)

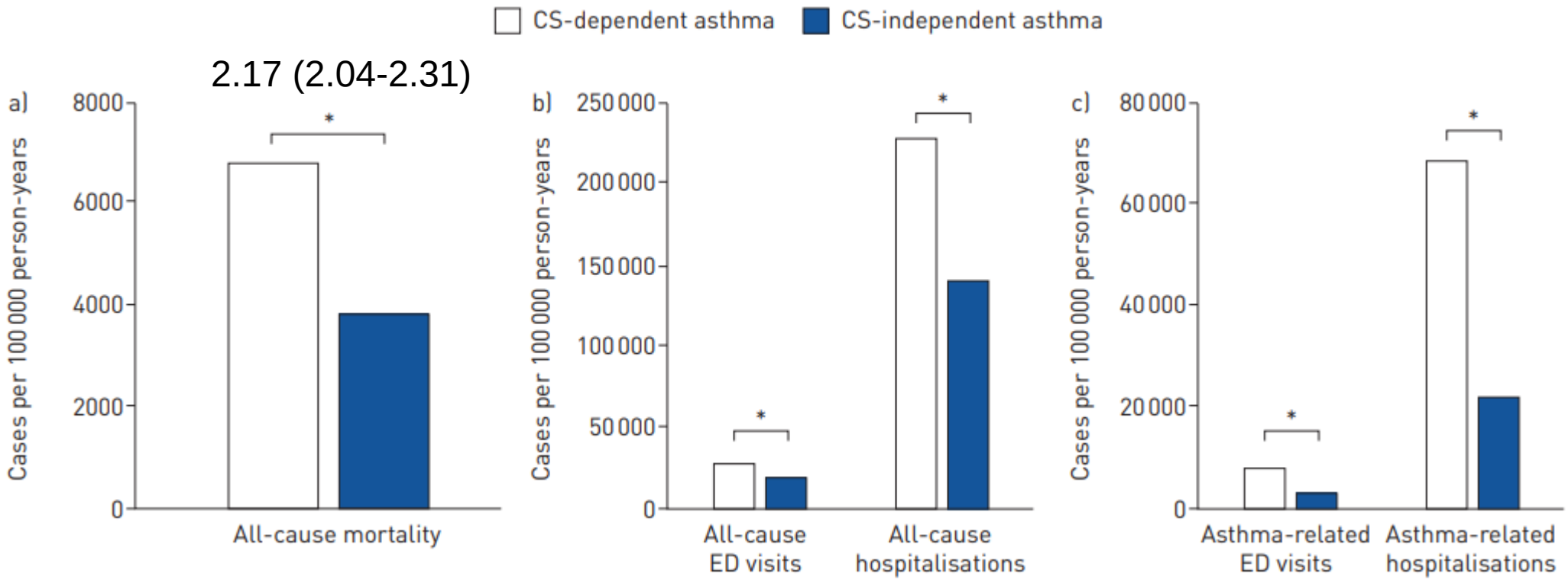
For those at GINA Step 5 in the total International Severe Asthma Registry population and by country



Increased Mortality in Patients with Corticosteroid-dependent Asthma: A Nationwide Population-based Study

Hyun Lee, Jiin Ryu, Eunwoo Nam, Sung Jun Chung, Yoomi Yeo, Dong Won Park, Tai Sun Park, Ji-Yong Moon, Tae-Hyung Kim, Jang Won Sohn, Ho Joo Yoon, Sang-Heon Kim

From January 1, 2005, to December 31, 2005, there were 751,180 asthma patients aged 18 years or older. CS-dependent cohort (CS use ⩾6 months) vs. the CS-independent cohort (CS use < 6 months) during baseline period : 1: 1



GINA 2021

STARTING TREATMENT
in adults and adolescents with a diagnosis of asthma

Track 1 is preferred if the patient is likely to be poorly adherent with daily controller ICS-containing therapy is recommended even if symptoms are infrequent, as it reduces the risk of severe exacerbations and need for OCS.

FIRST ASSESS:

- Confirm diagnosis
- Symptom control and modifiable risk factors, including lung function
- Comorbidities
- Inhaler technique and adherence
- Patient preferences and goals

START HERE IF:

CONTROLLER and PREFERRED RELIEVER (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

Symptoms less than 4–5 days a week

STEPS 1 – 2
As-needed low dose ICS-formoterol

Symptoms most days, or waking with asthma once a week or more

STEP 3
Low dose maintenance ICS-formoterol

Daily symptoms, or waking with asthma once a week or more, and low lung function

STEP 4
Medium dose maintenance ICS-formoterol

Short course OCS may also be needed for patients presenting with severely uncontrolled asthma

STEP 5
Add-on LAMA
Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R
Consider high dose ICS-formoterol

거의 매일 증상,
주1회 이상 야간증상

As-needed low-dose ICS-formoterol

START HERE IF:

CONTROLLER and ALTERNATIVE RELIEVER (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller therapy

Symptoms less than twice a month

STEP 1
Take ICS whenever SABA taken

Symptoms twice a month or more, but less than 4–5 days a week

STEP 2
Low dose maintenance ICS

Symptoms most days, or waking with asthma once a week or more

STEP 3
Low dose maintenance ICS-LABA

Daily symptoms, or waking with asthma once a week or more, and low lung function

STEP 4
Medium/high dose maintenance ICS-LABA

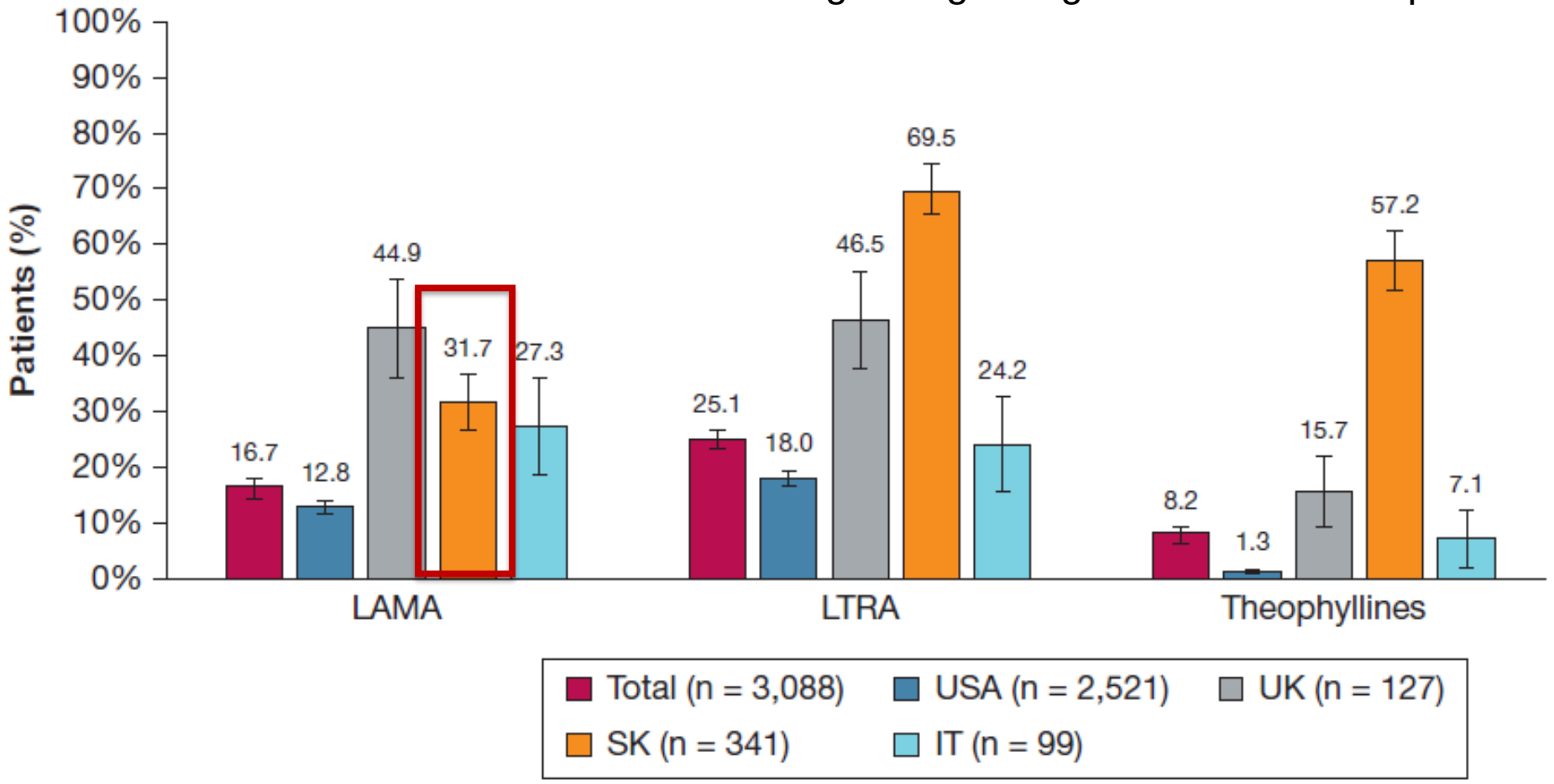
Short course OCS may also be needed for patients presenting with severely uncontrolled asthma

STEP 5
Add-on LAMA
Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R
Consider high dose ICS-LABA

RELIEVER: As-needed short-acting β2-agonist

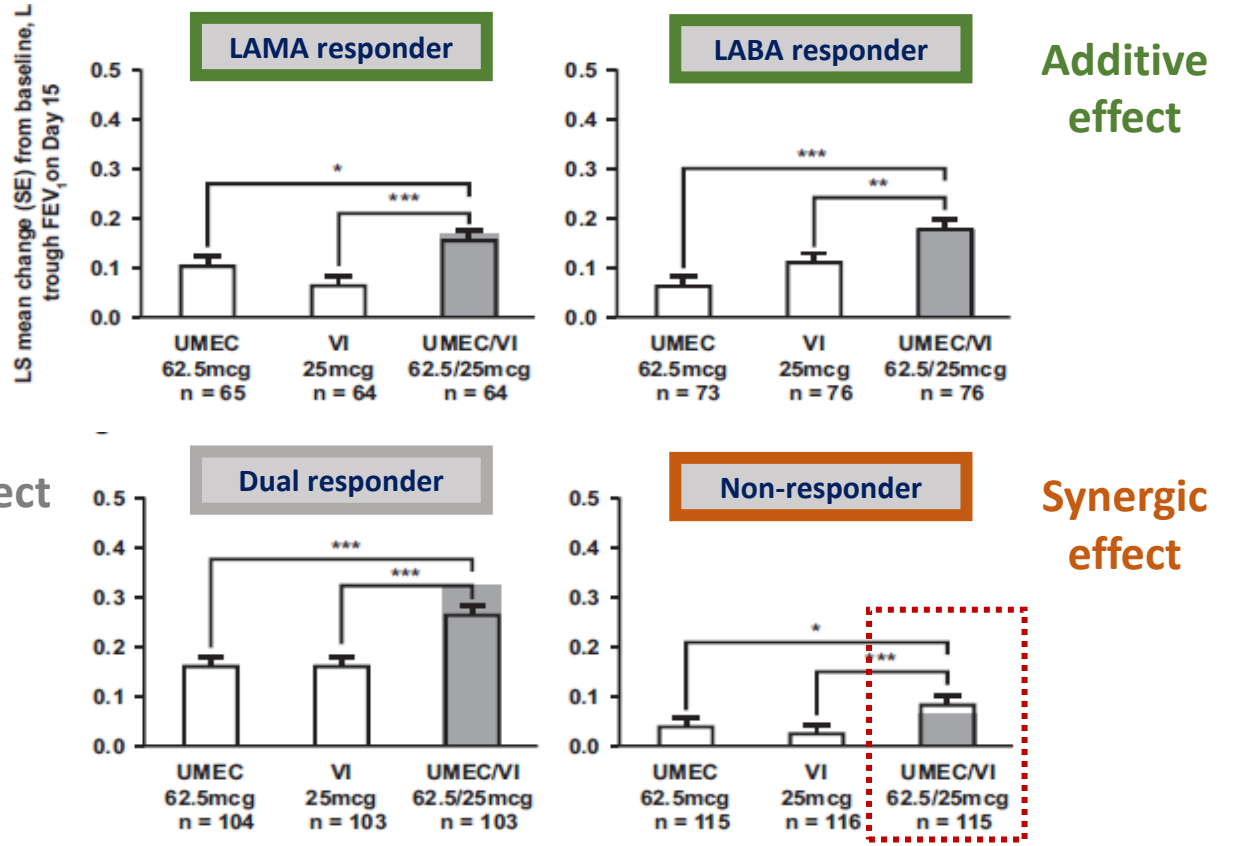
중증 천식 환자 (한국): LAMA

for those with uncontrolled asthma at GINA Step 4 who were receiving inhaled corticosteroid and long-acting b2-agonist add-on therapies



Positive interactions between LABA and LAMA

Trough FEV_1 on 15 day



Additive effect

Ceiling effect

Synergic effect

Grey bars: expected fully additive effect of both monotherapies

Donohue et al, Respir Med. 2016 Mar;112:65-74.

천식에서의 LAMA?

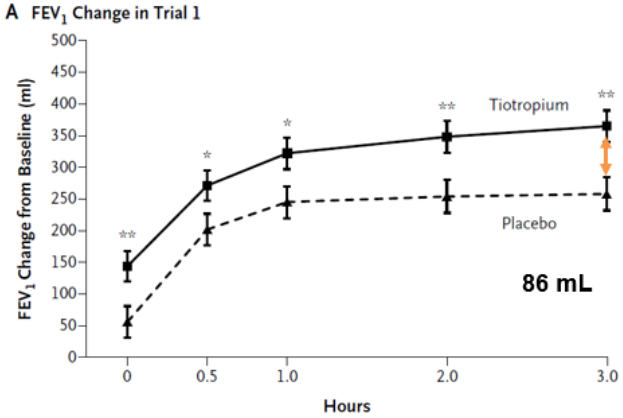
ICS + LABA

LAMA

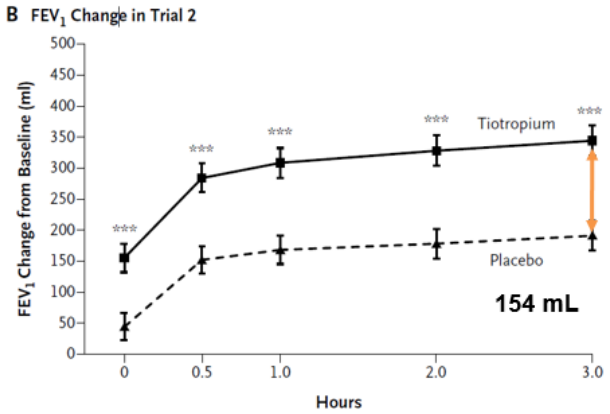
ICS-LABA vs. ICS-LABA-LAMA

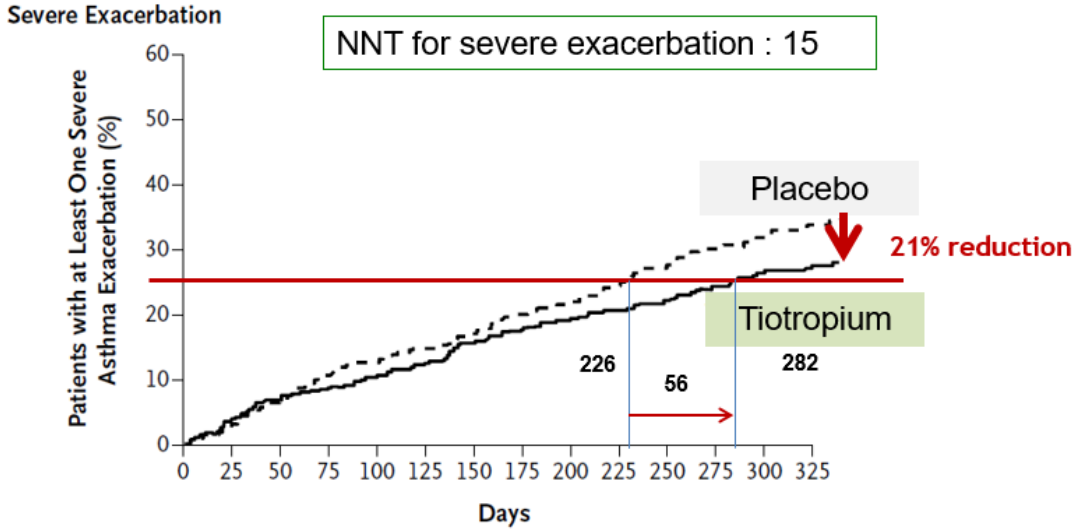
- **PRIMO TinA study** (ICS-LABA+placebo vs. ICS-LABA+**tiotrpoium**)
- Symptomatic asthma despite med- or high-dose ICS-LABA, at least one exacerbation in the previous year, and post-BD FEV_1<80%

Trial 1



Trial 2





(Trough) **FEV_1** 호전 +86-154 ml (*P*=0.01 and <0.001)
Severe exacerbation 21% 감소 (*P*=0.03)

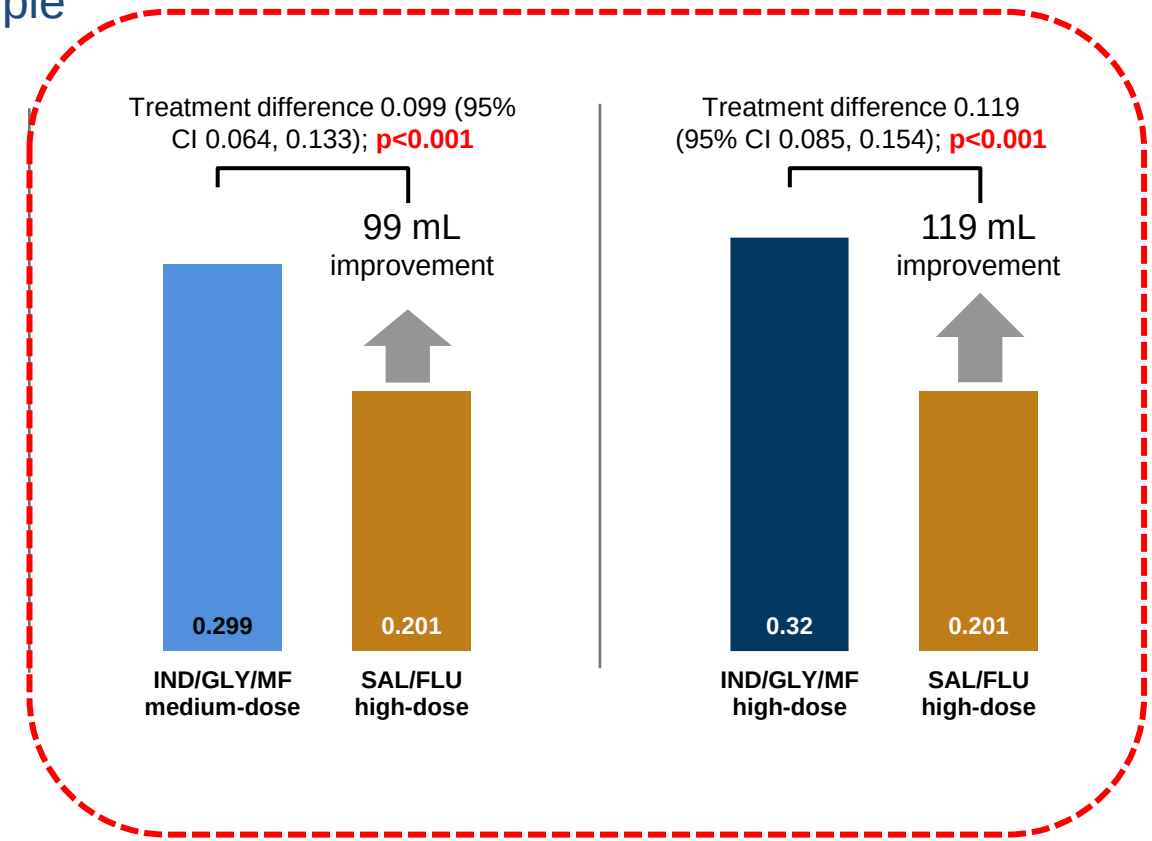
Kerstjens et al. N Eng J Med 2012; 356(13):1198-207

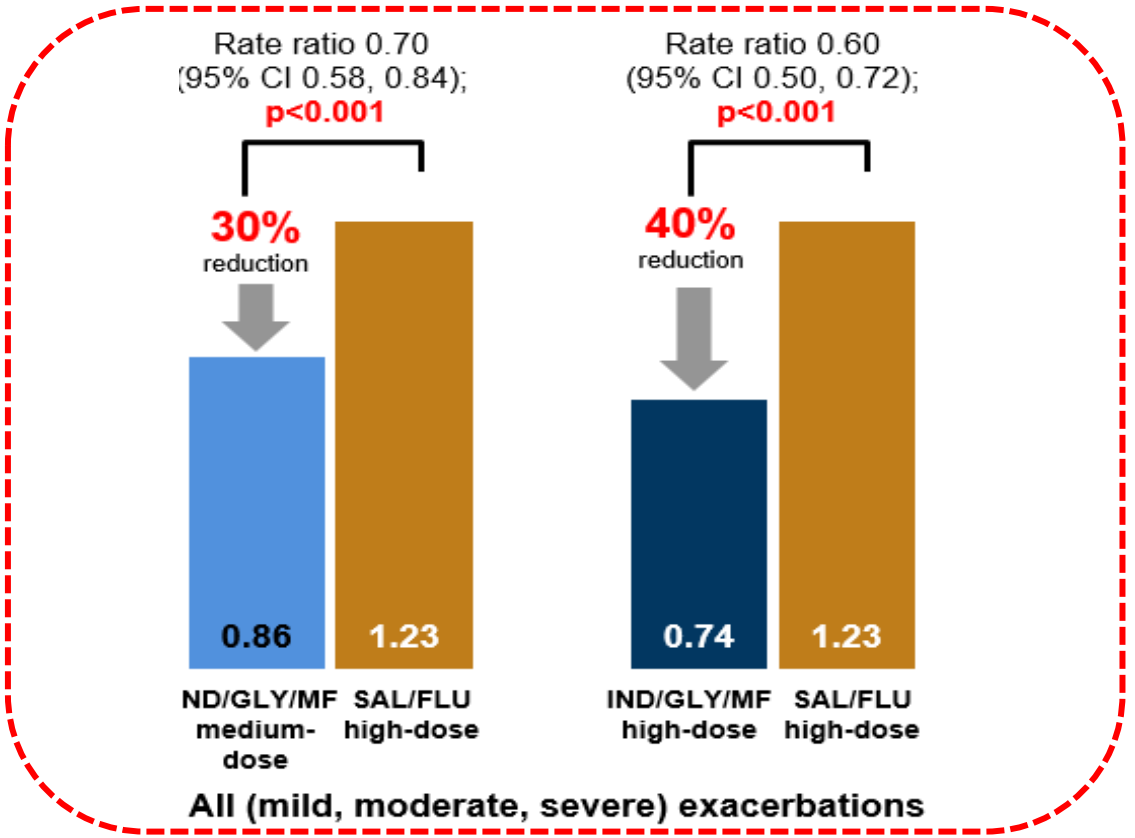
ICS-LABA vs. ICS-LABA-LAMA

- **IRIDIUM study**

Primary endpoint met (p<0.001 for all treatment comparisons): Superiority of medium or high doses of IND/GLY/MF to corresponding doses of IND/MF in terms of trough FEV_1 at **26 weeks**

Triple



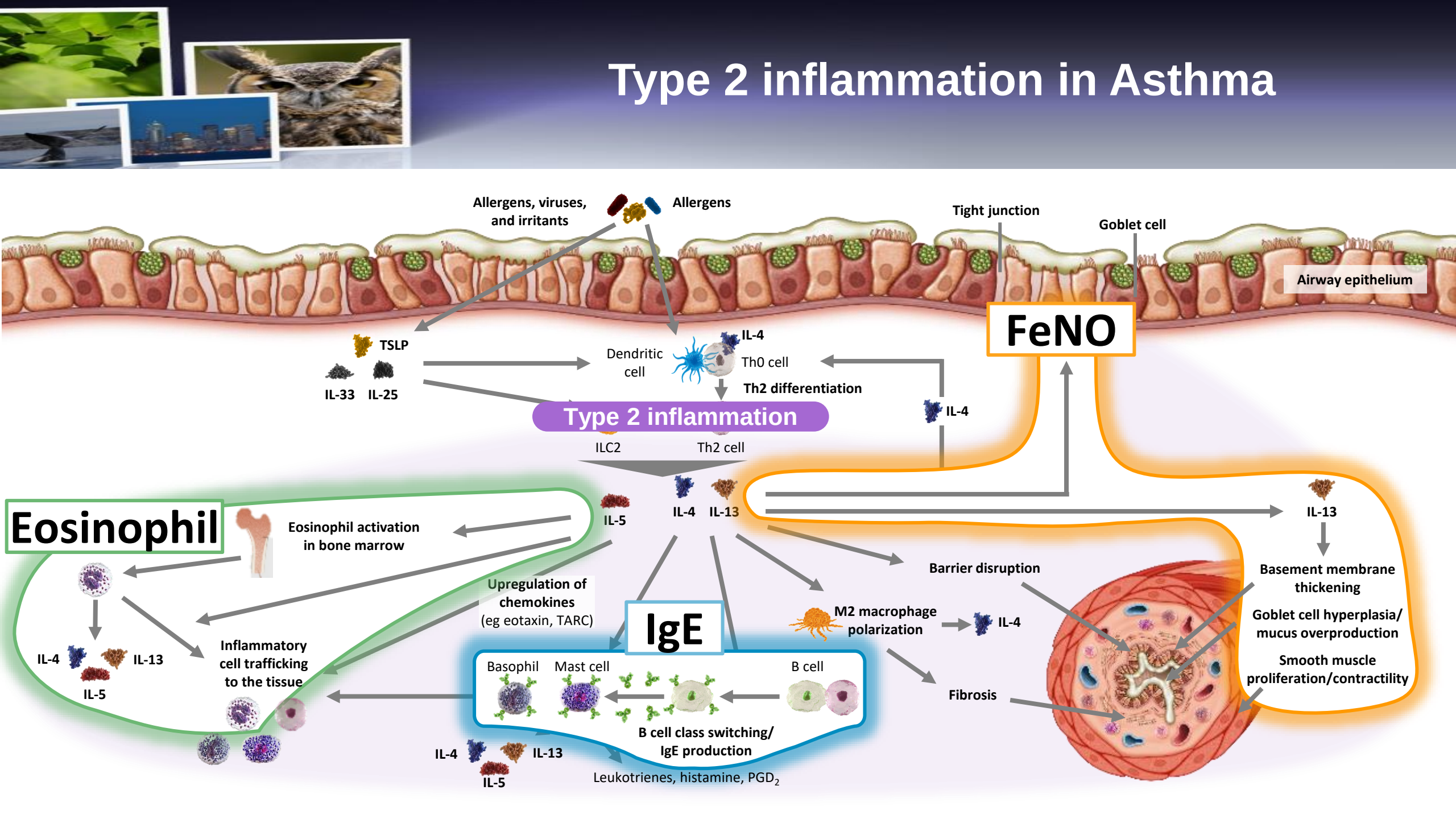


Type 2 inflammation in Asthma

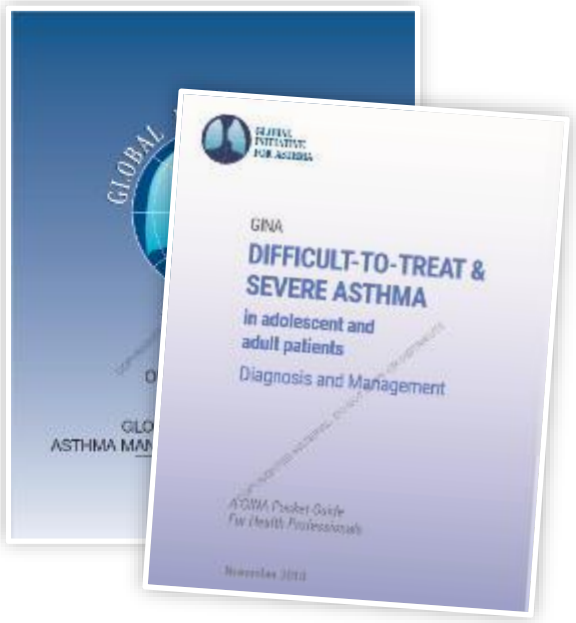
GINA: What is type 2 inflammation?

- It is **characterized by cytokines such as IL-4, IL-5, and IL-13**, which are often produced by the adaptive immune system on recognition of allergens
- **Type 2 inflammation is often characterized by eosinophils or increased FeNO, and may be accompanied by atopy**, whereas non-type 2 inflammation is often characterized by neutrophils

Type 2 inflammation in Asthma



Type 2 inflammation in Asthma

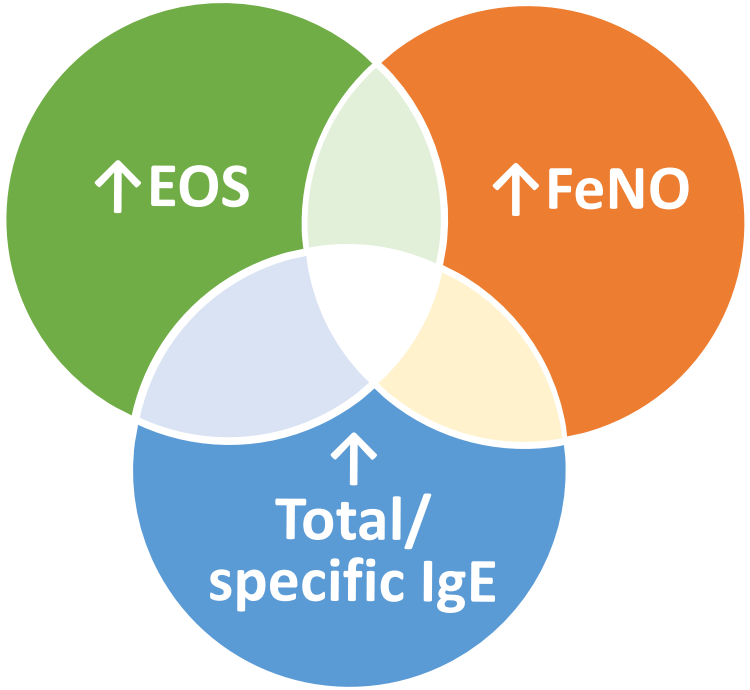


GINA criteria for type 2 inflammation

- Blood eosinophils ≥150 cells/µL and/or
- FeNO ≥20 ppb and/or
- Sputum eosinophils ≥2% and/or
- Asthma clinically allergen driven
- Need for maintenance OCS

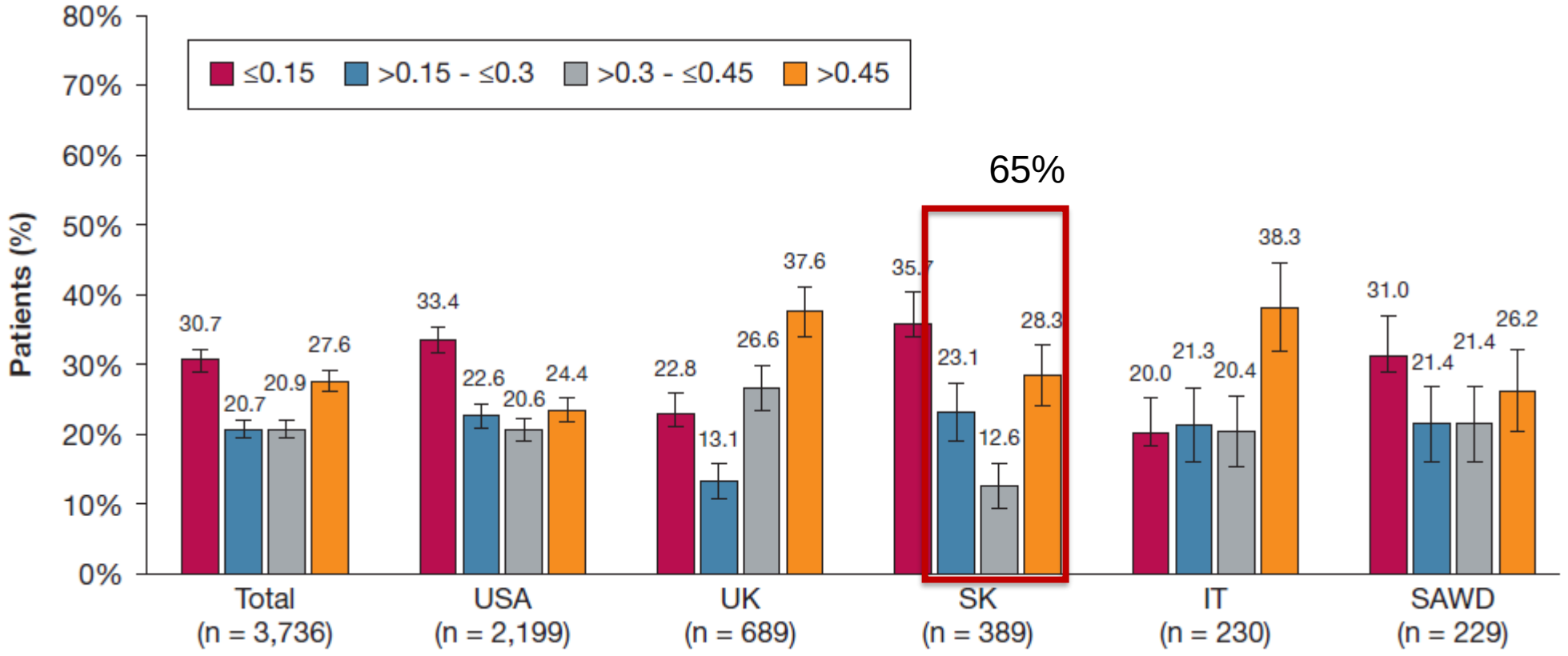
(Repeat blood eosinophils and FeNO up to 3×, on lowest possible OCS dose)

Type 2 inflammation



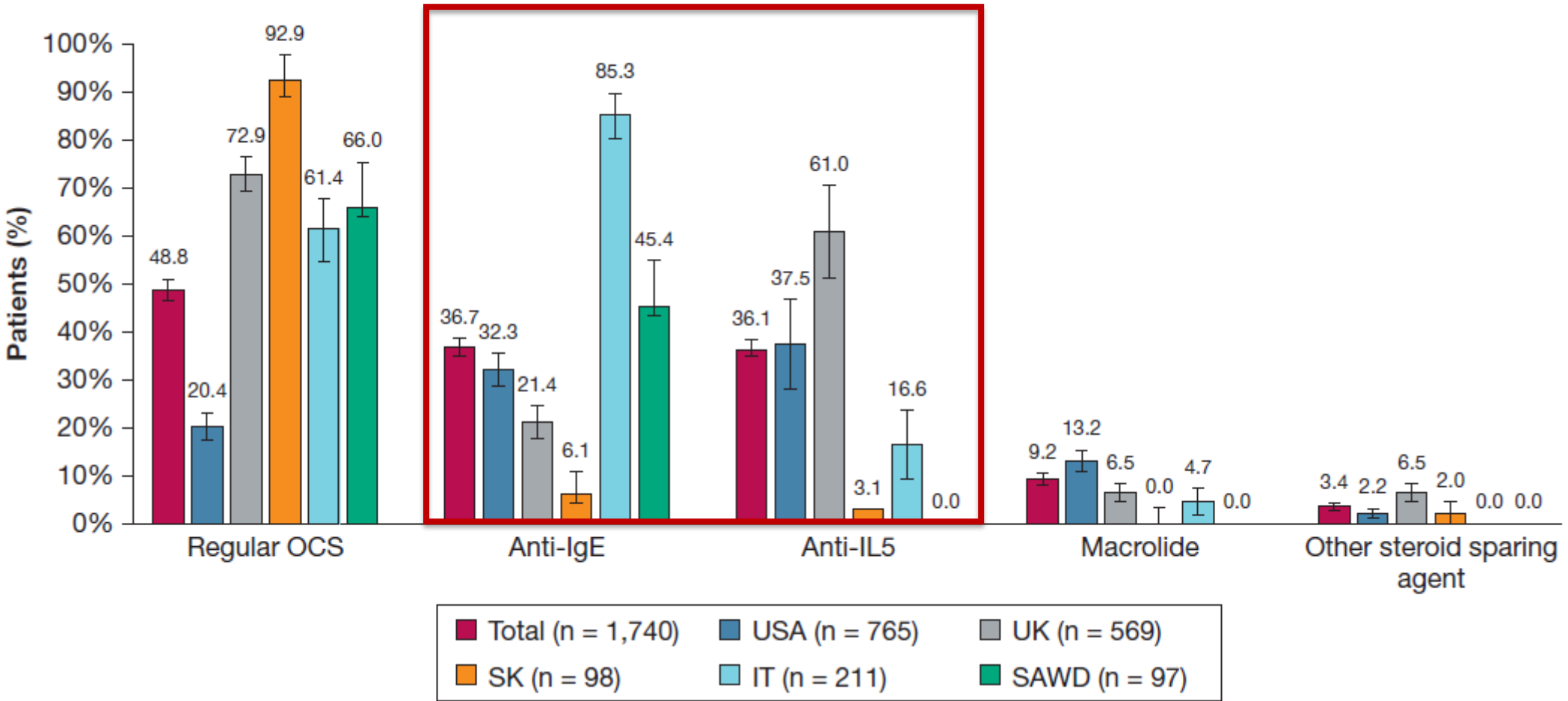
OCS use rapidly reduces biomarkers of type 2 inflammation, eg FeNO, blood eosinophils

Blood Eosinophil Count



Medication regimen

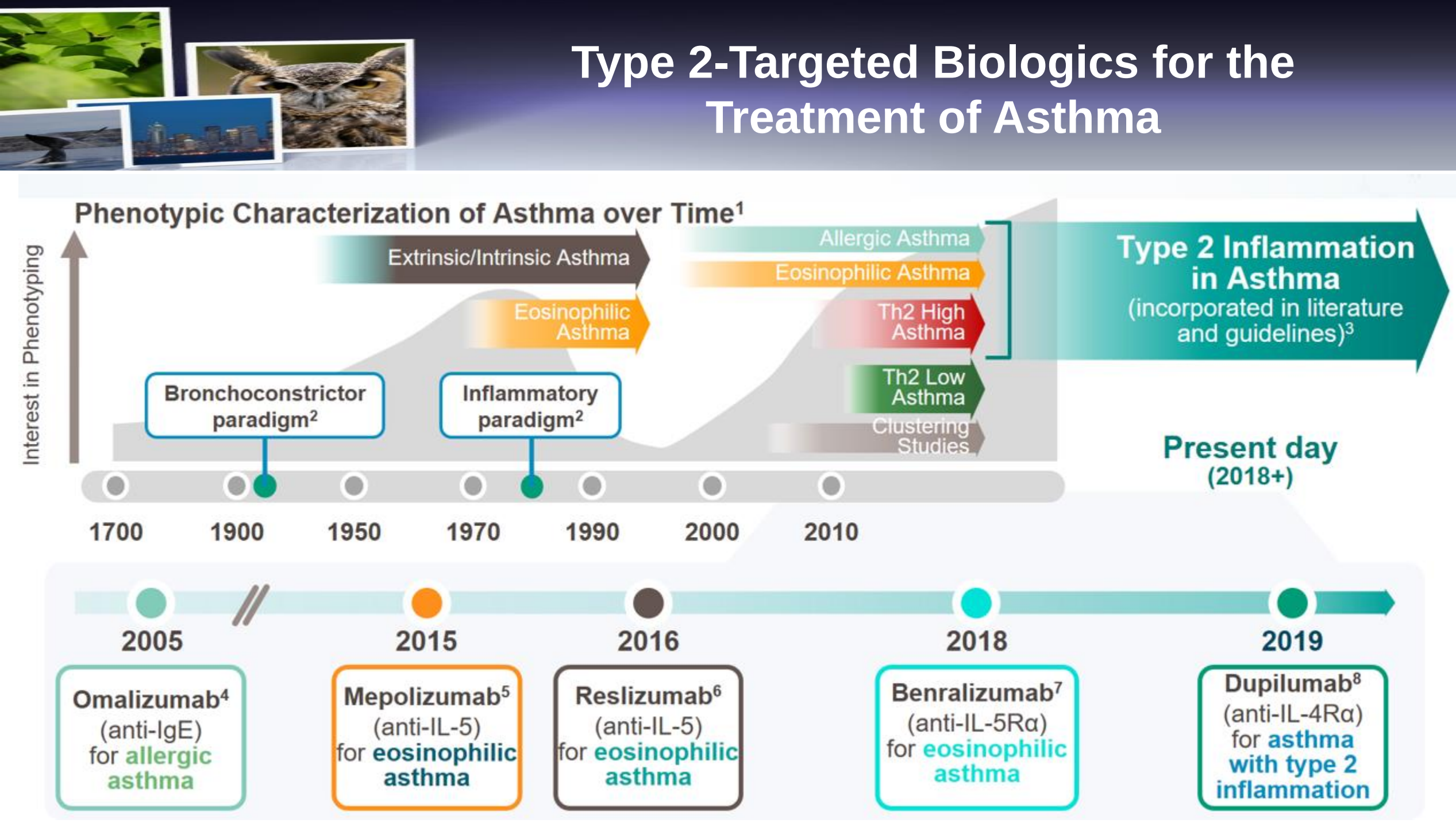
For those at GINA Step 5 in the total International Severe Asthma Registry population and by country



Dupilumab

- **Completed Pivotal clinical trials**
- **Long term data of Dupilumab**
- **Post-hoc analysis: QUEST Korea subgroup**

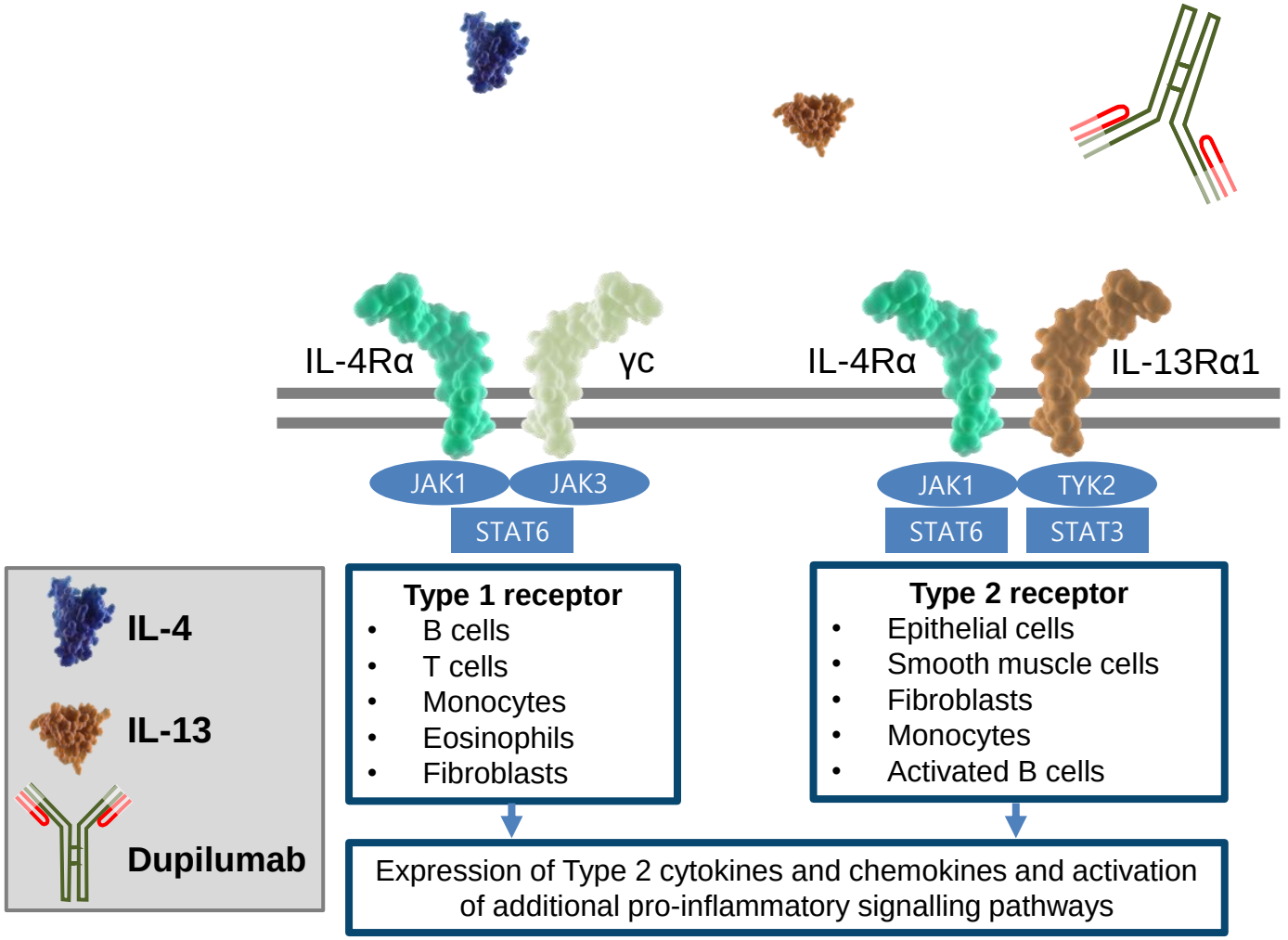
Type 2-Targeted Biologics for the Treatment of Asthma



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

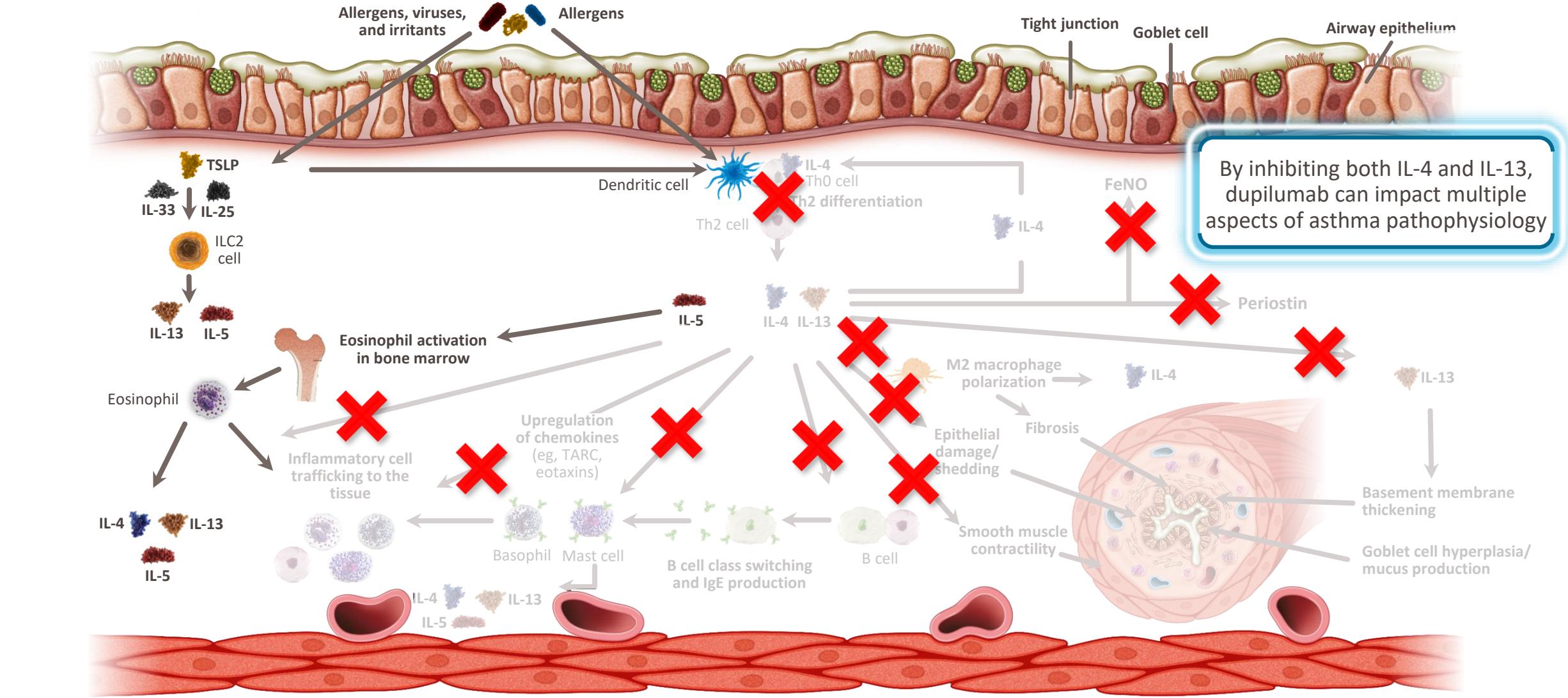
2. Dupilumab, a human monoclonal IgG4 antibody, binds to IL-4Rα, blocking both IL-4 and IL-13 signalling pathway



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

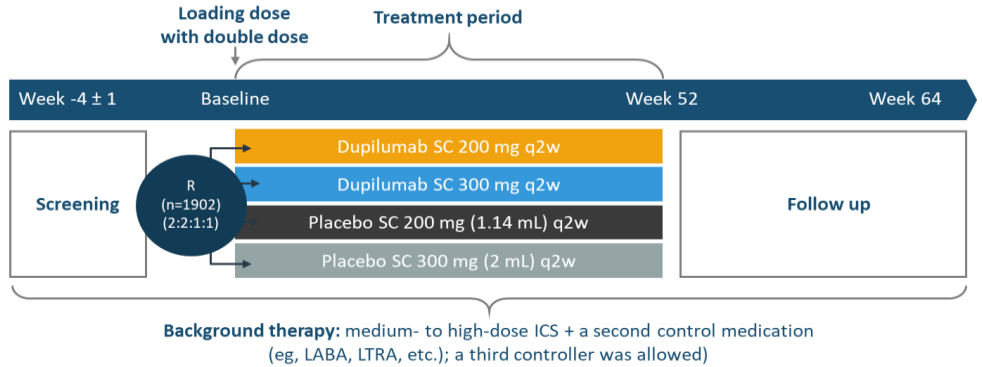
Gandhi NA, et al. *Nat Rev Drug Discov.* 2016;15(1):35–50

Dupilumab Inhibits IL-4 and IL-13, Important Drivers of the Type 2 Inflammatory Pathway Associated With Multiple Downstream Effects[1-10]



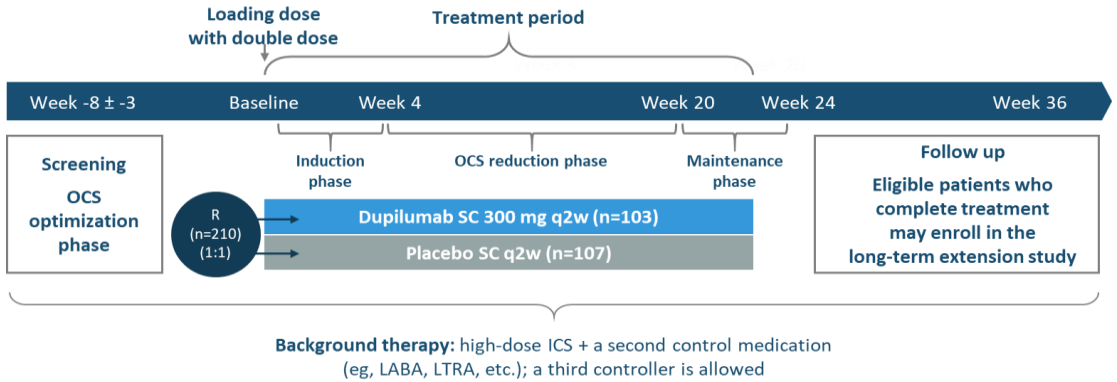
✕=inhibition by dupilumab.

Ongoing and completed Pivotal clinical trials of Dupilumab in Asthma

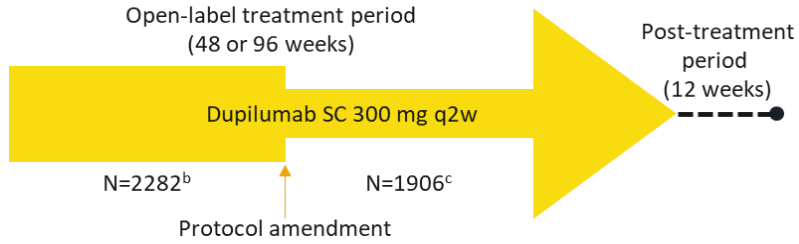


QUEST[1] in patients with uncontrolled persistent asthma despite use of medium- to high-dose ICS plus up to two additional controllers

Adults and adolescents (≥ 12 years old)



VENTURE[2] in <u>OCS dependent</u> patients with severe refractory asthma



TRAVERSE[3]

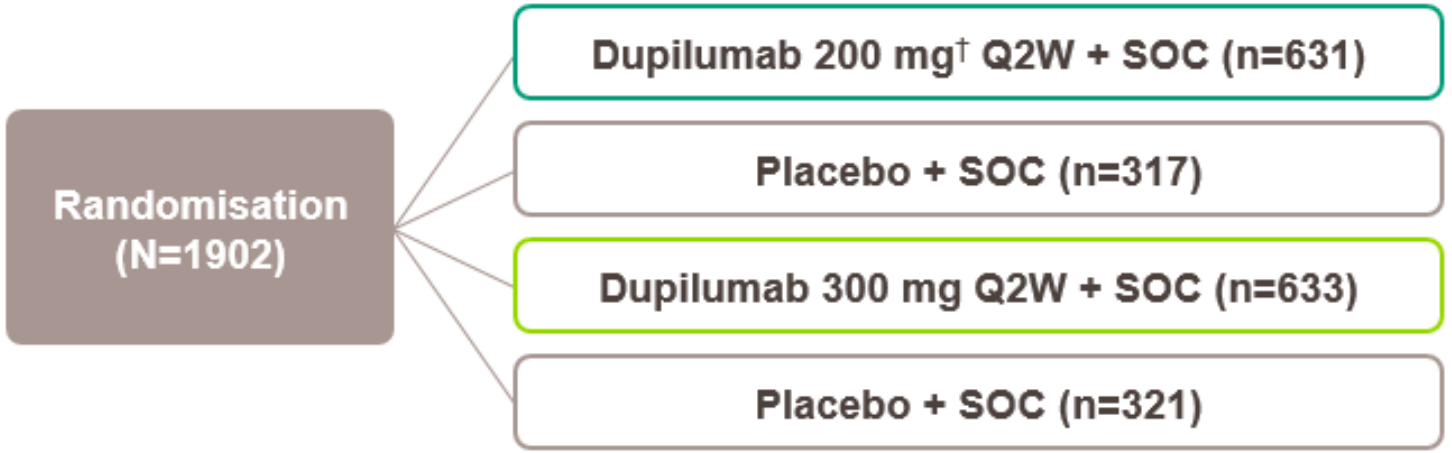
Open Label extension study of Phase 3 and Phase 2 studies in patients aged ≥ 12 years old

*Dupilumab 국내 허가사항은 성인 (만 18세 이상) 및 청소년 (만 12-17세)에서 기존 치료에 적절하게 조절되지 않는 중증 천식 (제2형 염증성 천식)의 추가 유지 치료입니다.

1. Castro M, et al. *N Engl J Med*. 2018;378:2486–2496. 2. Rabe KF, et al. N Engl J Med. 2018;378:2475–2485. 3. Michael E Wechsler et al. Lancet Respir Med. 2022 Jan;10(1):11-25

Dupilumab Asthma Program: Study Design

QUEST: 52-Week Phase 3 Study



Primary Endpoints

- Annualised rate of severe exacerbation‡ events over 52 weeks
- Change from baseline to Week 12 in FEV_1 (L)

Key Secondary Endpoints

- Primary endpoints assessed in subgroups based on baseline blood EOS and FeNO
- Asthma control and quality-of-life scores

CS=corticosteroid; EOS=eosinophil; FeNO=fractional exhaled nitric oxide; FEV_1=forced expiratory volume in 1 second; Q2W=every 2 weeks; SOC=standard of care.
*Patients were enrolled without requiring a minimum baseline blood eosinophil or other Type 2 inflammatory biomarker (eg, FeNO or IgE) level. Asthma treatment guidelines define Type 2 inflammation as eosinophilia ≥150 cells/μL and/or FeNO ≥20 ppb. The primary endpoints were analysed in the overall population (unrestricted by minimum baseline eosinophils or other Type 2 inflammatory biomarkers) and subgroups based on baseline blood eosinophils and FeNO.[1]
†The Dupilumab 200-mg group was initially given a 400-mg loading dose. The Dupilumab 300-mg group was initially given a 600-mg loading dose.[2] ‡Deterioration of asthma leading to treatment for ≥3 days with systemic CS or hospitalisation/emergency department visit leading to treatment with systemic CS.[2]

1. Dupixent (dupilumab) [summary of product characteristics]. Paris, France: sanofi-aventis groupe; 2019. 2. Castro M, et al. *N Engl J Med.* 2018;378(26):2486-2496.

QUEST in patients aged ≥ 12 yrs old with uncontrolled persistent asthma

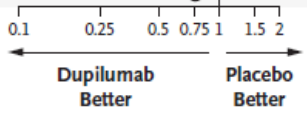
Primary endpoints

Annualized rate of severe asthma exacerbations

According to Baseline Blood Eosinophil Count and Baseline FeNO

Dupilumab **200mg** EOW vs Placebo

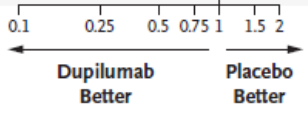
Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
FE_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥25 to <50 ppb	91	180	0.39 (0.24–0.62)
<25 ppb	149	325	0.75 (0.54–1.05)



48% REDUCTION

Dupilumab **300mg** EOW vs Placebo

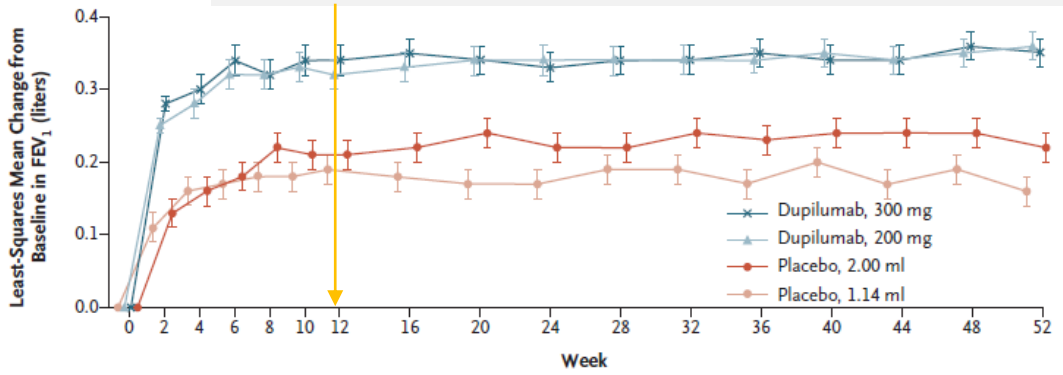
Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm³	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm³	95	175	0.56 (0.35–0.89)
<150 cells/mm³	83	181	1.15 (0.75–1.77)
FE_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)



46% REDUCTION

Change from baseline to week 12 in pre-BD FEV_1

At week 12,
+0.14L *p<0.001* (0.32L Dupilumab 200mg EOW vs 0.18L Placebo)
+0.13L *p<0.001* (0.34L Dupilumab 300mg EOW vs 0.21L Placebo)



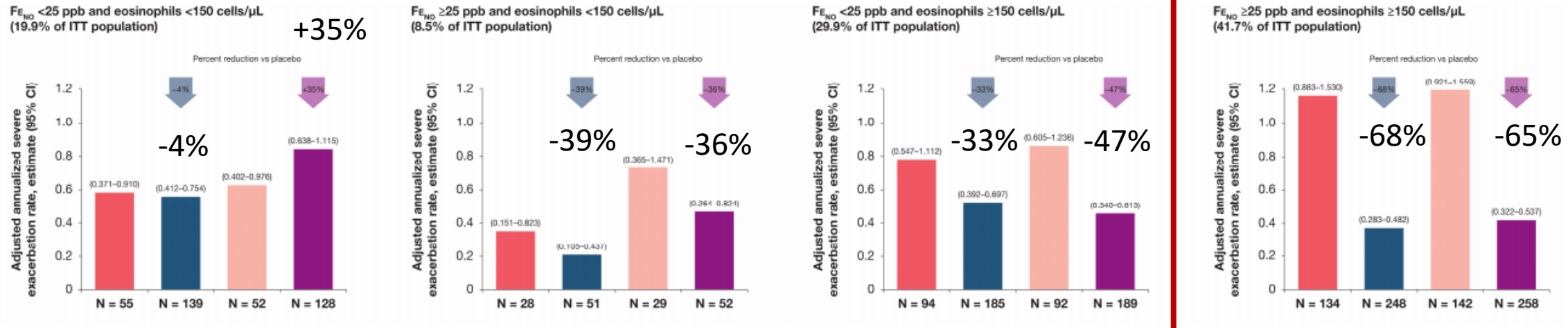
No. at Risk																	
Dupilumab, 300 mg	633	625	614	612	609	598	610	611	593	596	586	579	584	584	570	562	488
Dupilumab, 200 mg	631	610	613	615	604	607	611	605	601	599	589	585	590	577	581	570	477
Placebo, 2.00 ml	321	313	311	313	311	309	313	310	304	296	304	301	301	297	292	290	250
Placebo, 1.14 ml	317	315	307	301	305	301	307	300	303	300	290	286	289	287	288	281	240

Figure 2. Change in the Prebronchodilator FEV_1 from Baseline over the 52-Week Intervention Period in the Intention-to-Treat Population.
Patients received dupilumab at a dose of 200 or 300 mg every 2 weeks or a matched-volume placebo. For the lower dose of dupilumab, the matched placebo had a volume of 1.14 ml. For the higher dose of dupilumab, the matched placebo had a volume of 2.00 ml. P<0.001 for the comparisons of each dupilumab dose with matched placebo at week 12. I bars represent the standard error. FEV_1 denotes forced expiratory volume in 1 second.

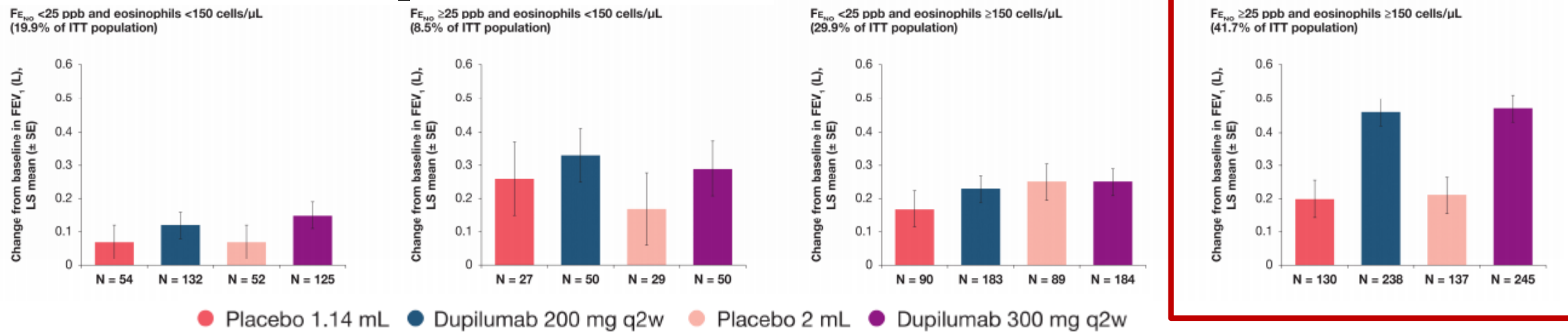
Castro M, et al. N Engl J Med. 2018;378:2486–2496

QUEST:
Baseline Blood Eosinophil Count and FeNO

Annualized rate of severe asthma exacerbations



Change From Baseline in FEV_1



QUEST: ACQ-5 Improvements

Improvements in ACQ-5 following treatment with Dupixent were seen in:

70%-73%
of patients with
EOS ≥150 cells/µL (n=803)
vs 64%-65% with placebo (n=418)

71%-75%
of patients with
EOS ≥300 cells/µL (n=487)
vs 64%-67% with placebo (n=253)

74%-76%
of patients with
FeNO ≥25 ppb (n=539)
vs 64%-65% with placebo (n=300)

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

QUEST: Safety Profile

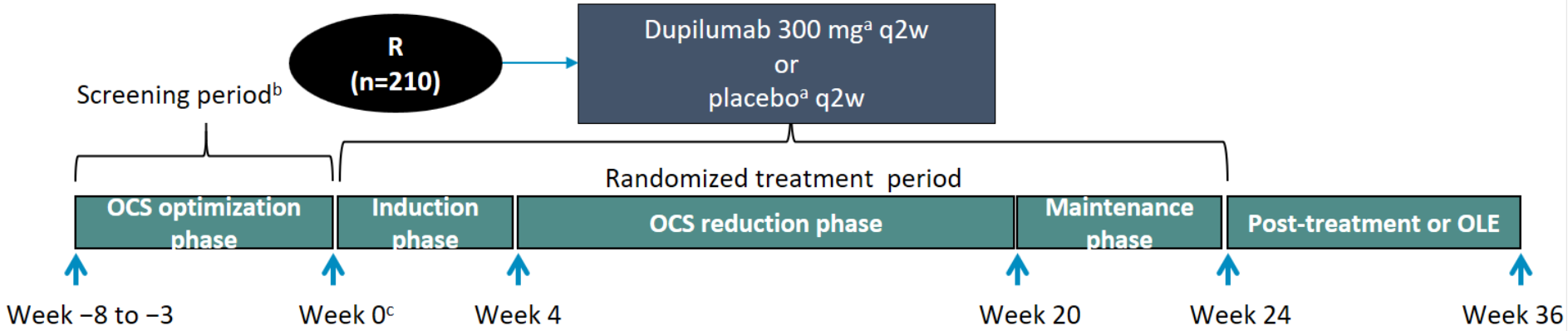
Table 2. Adverse Events That Emerged during the Intervention Period (Safety Population).*

Event	Placebo, 1.14 ml (N=313)	Dupilumab, 200 mg (N=631)	Placebo, 2.00 ml (N=321)	Dupilumab, 300 mg (N=632)	Combined Placebo (N=634)	Combined Dupilumab (N=1263)
			number of patients (percent)			
Any adverse event	257 (82.1)	508 (80.5)	270 (84.1)	515 (81.5)	527 (83.1)	1023 (81.0)
Any serious adverse event	26 (8.3)	49 (7.8)	27 (8.4)	55 (8.7)	53 (8.4)	104 (8.2)
Any adverse event leading to death†	3 (1.0)	1 (0.2)	0	4 (0.6)	3 (0.5)	5 (0.4)
Any adverse event leading to permanent discontinuation of the intervention	19 (6.1)	19 (3.0)	10 (3.1)	44 (7.0)	29 (4.6)	63 (5.0)
Adverse events occurring in ≥5% of patients in any group‡						
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)
Influenza	29 (9.3)	36 (5.7)	22 (6.9)	38 (6.0)	51 (8.0)	74 (5.9)
Sinusitis	27 (8.6)	36 (5.7)	29 (9.0)	26 (4.1)	56 (8.8)	62 (4.9)
Urinary tract infection	17 (5.4)	17 (2.7)	12 (3.7)	19 (3.0)	29 (4.6)	36 (2.9)
Headache	26 (8.3)	46 (7.3)	25 (7.8)	40 (6.3)	51 (8.0)	86 (6.8)
Rhinitis allergic	16 (5.1)	21 (3.3)	15 (4.7)	18 (2.8)	31 (4.9)	39 (3.1)
Back pain	16 (5.1)	30 (4.8)	7 (2.2)	25 (4.0)	23 (3.6)	55 (4.4)
Accidental overdose§	16 (5.1)	33 (5.2)	16 (5.0)	33 (5.2)	32 (5.0)	66 (5.2)
Injection-site reaction¶	17 (5.4)	96 (15.2)	33 (10.3)	116 (18.4)	50 (7.9)	212 (16.8)

VENTURE in OCS dependent patients with severe refractory asthma

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

- **Percent reduction of OCS dose at weeks 20 to 24** versus baseline while maintaining asthma control

Key Secondary Endpoints

- OCS dose reduction ≥50%, <5 mg/day, complete elimination of use, and absolute dose reduction
- Annualised severe exacerbation‡ rates and changes in FEV_1 (L) at week 24

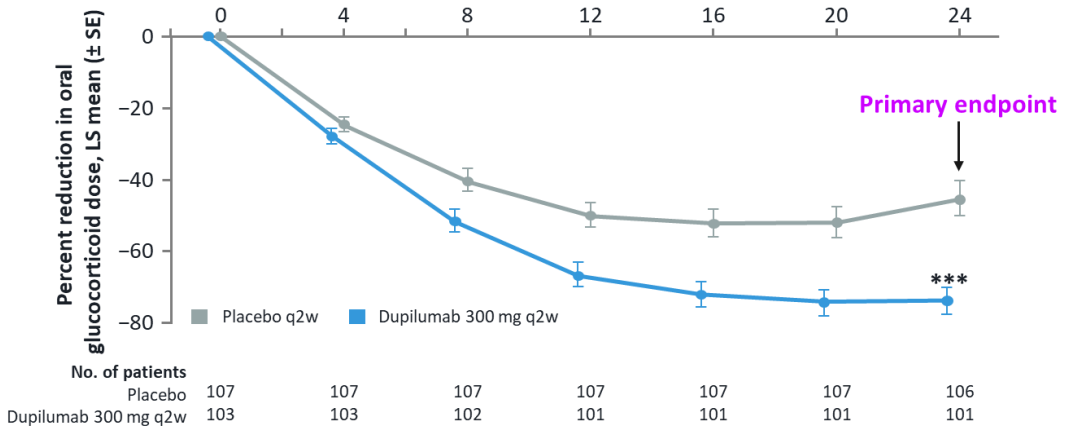
FEV_1=forced expiratory volume in 1 second; OCS=oral corticosteroid; Q2W=every 2 weeks; Q4W=every 4 weeks; SOC=standard of care.
*The dupilumab 300-mg group was initially given a 600-mg loading dose.[1] †OCS dose was reduced Q4W during OCS reduction phase (weeks 4-20) as long as asthma control was maintained.[1,2]
‡Events leading to hospitalisation, an emergency department visit, or treatment for ≥3 days with systemic glucocorticoids at ≥2 times the current dose of oral glucocorticoid.[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.

VENTURE in OCS dependent patients with severe refractory asthma

Main outcomes

Percentage Reduction in OCS Dose* from Baseline to Week 24 (Primary endpoint)

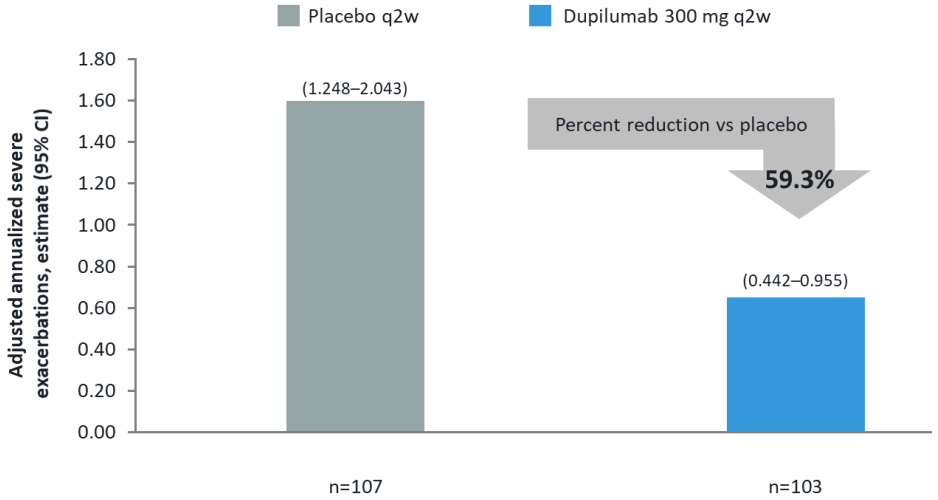
*LS mean OCS reduction from baseline to Week 24, while maintaining asthma control



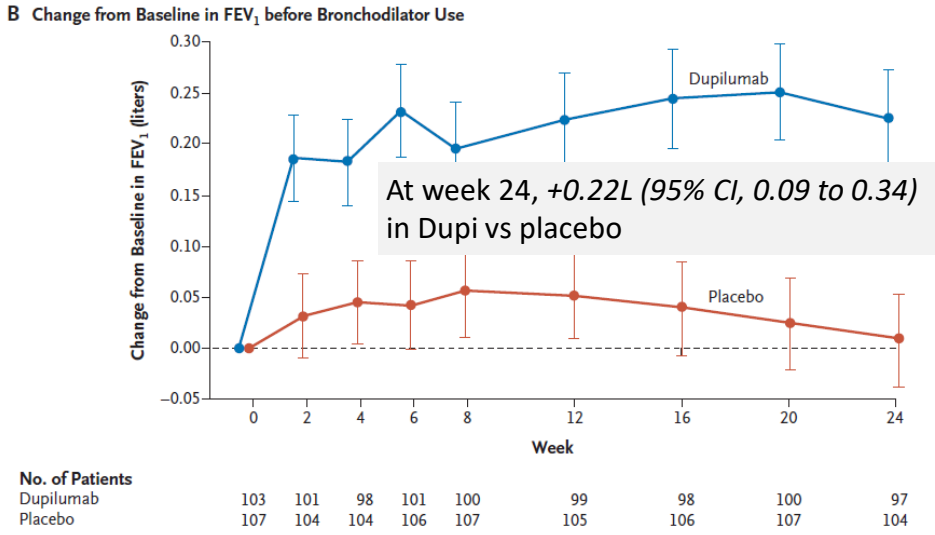
70.1% on dupilumab vs 41.9% on placebo

***p<0.001 vs placebo.

Annualized Rate of Severe Exacerbations over 24-Week



Change from baseline in pre-BD FEV_1



Rabe KF, et al. N Engl J Med. 2018;378:2475–2485

VENTURE in OCS dependent patients with severe refractory asthma

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)

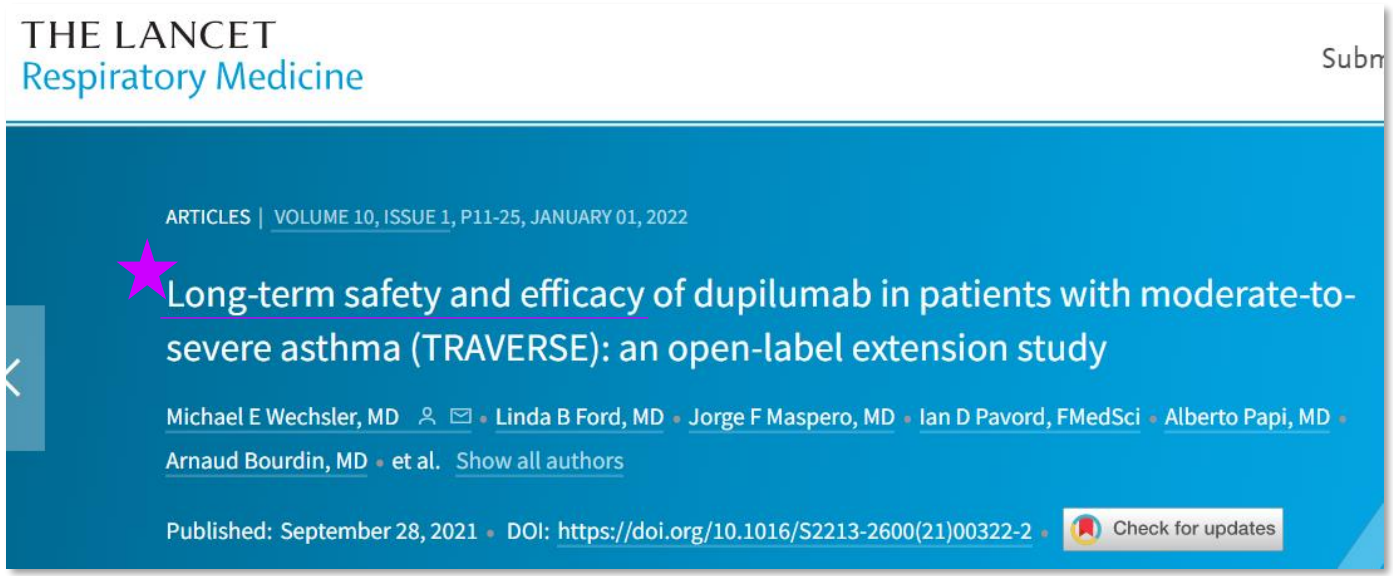
69% reduced OCS dose to <5 mg/day
versus 33% in placebo (*P*<0.001)

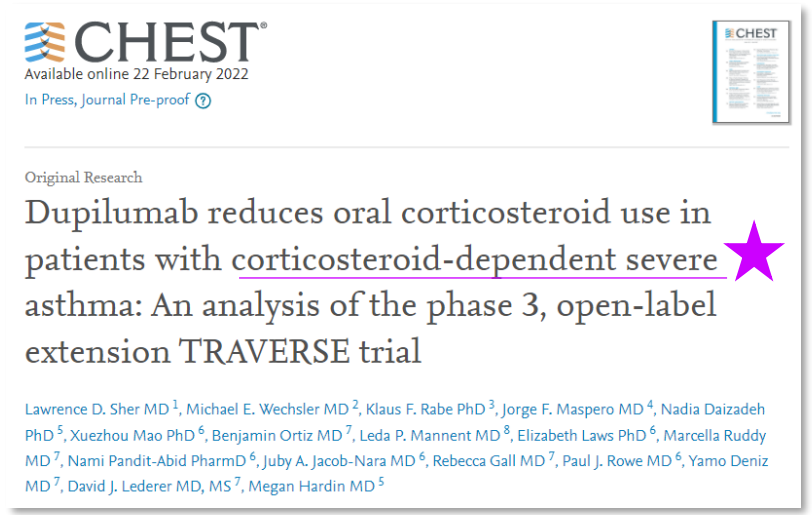
52% completely eliminated OCS use
versus 29% in placebo (*P*=0.002)

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)

New 2022 publication updates – **Long-term over 148 wks**





The primary endpoint: the number and percentage of patients with any treatment-emergent adverse events.

1. Michael E Wechsler et al. Lancet Respir Med. 2022 Jan;10(1):11-25. 2. Lawrence D Sher et al. Chest. 2022 Feb 22;S0012-3692(22)00388-9.

TRAVERSE - Lancet Respir Med. 2022 (1)

Dupilumab was **well tolerated** by adolescents and adults with moderate-to-severe asthma over **148 (52+96) weeks**

THE LANCET Respiratory Medicine

✓ The safety profile was consistent with the known dupilumab safety profile.

non-OCS-dependent: from QUEST | **OCS-dependent: from VENTURE**

	Patients from P2b		Patients from QUEST		Patients from VENTURE	
	Placebo–dupilumab (n=111)	Dupilumab–dupilumab (n=421)	Placebo–dupilumab (n=517)	Dupilumab–dupilumab (n=1013)	Placebo–dupilumab (n=97)	Dupilumab–dupilumab (n=90)
Patients with any treatment-emergent adverse event	88 (79·3%)	369 (87·6%)	414 (80·1%)	789 (77·9%)	74 (76·3%)	70 (77·8%)
Per patient-year (per 100 patient-years)*	88/72·5 (121·4)	369/228·7 (161·4)	414/293·6 (141·0)	789/613·6 (128·6)	74/57·0 (129·8)	70/53·8 (130·0)
Patients with any treatment-emergent serious adverse event	14 (12·6%)	42 (10·0%)	48 (9·3%)	106 (10·5%)	12 (12·4%)	10 (11·1%)
Per patient-year (per 100 patient-years)*	14/207·0 (6·8)	42/794·2 (5·3)	48/747·9 (6·4)	106/1457·6 (7·3)	12/125·3 (9·6)	10/119·4 (8·4)
Patients with any treatment-emergent adverse event leading to death†	0	3 (0·7%)	0	1 (0·1%)	0	0
Per patient-year (per 100 patient-years)*	0/222·3	3/827·6 (0·4)	0/780·5	1/1543·4 (<0·1)	0/137·6	0/124·8
Patients with any treatment-emergent adverse event leading to permanent treatment discontinuation	3 (2·7%)	19 (4·5%)	12 (2·3%)	31 (3·1%)	4 (4·1%)	5 (5·6%)
Per patient-year (per 100 patient-years)*	3/221·5 (1·4)	19/822·4 (2·3)	12/777·1 (1·5)	31/1534·4 (2·0)	4/136·4 (2·9)	5/123·5 (4·0)
Treatment-emergent adverse events occurring in ≥10% in any treatment group by preferred term‡						
Nasopharyngitis	27 (24·3%)	109 (25·9%)	99 (19·1%)	191 (18·9%)	17 (17·5%)	16 (17·8%)
Bronchitis	15 (13·5%)	80 (19·0%)	63 (12·2%)	118 (11·6%)	9 (9·3%)	14 (15·6%)
Upper respiratory tract infection	18 (16·2%)	60 (14·3%)	65 (12·6%)	130 (12·8%)	8 (8·2%)	6 (6·7%)
Influenza	5 (4·5%)	45 (10·7%)	30 (5·8%)	69 (6·8%)	9 (9·3%)	7 (7·8%)
Pharyngitis	16 (14·4%)	37 (8·8%)	26 (5·0%)	59 (5·8%)	1 (1·0%)	4 (4·4%)
Headache	13 (11·7%)	47 (11·2%)	47 (9·1%)	74 (7·3%)	4 (4·1%)	5 (5·6%)
Injection-site erythema	26 (23·4%)	55 (13·1%)	35 (6·8%)	50 (4·9%)	5 (5·2%)	2 (2·2%)
Injection-site pruritus	12 (10·8%)	16 (3·8%)	15 (2·9%)	7 (0·7%)	2 (2·1%)	0

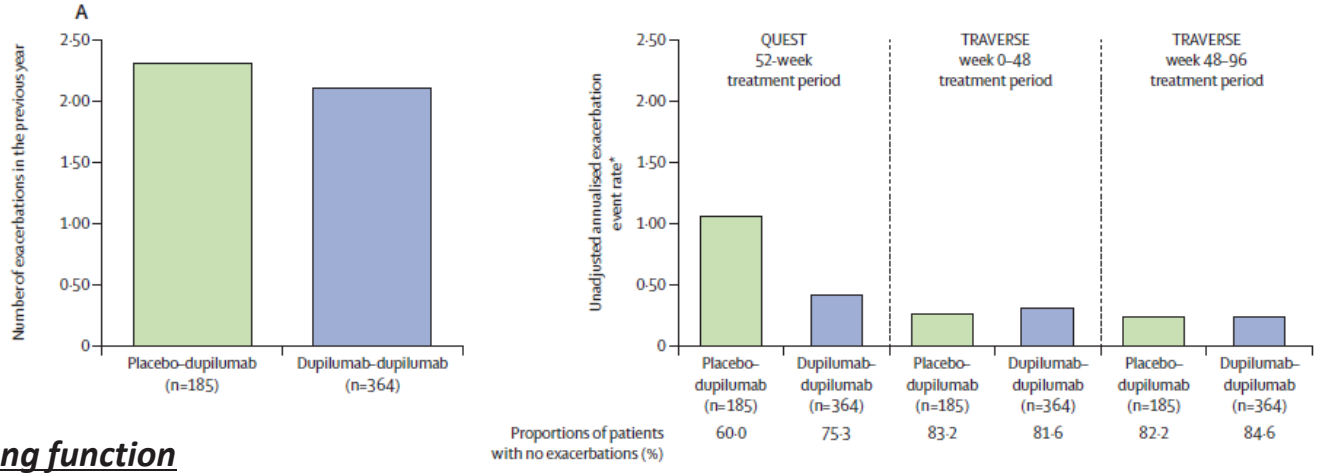
MedDRA=Medical Dictionary for Regulatory Activities. OCS=oral corticosteroid. P2b=phase 2B DRI.

1. Michael E Wechsler et al. Lancet Respir Med. 2022 Jan;10(1):11-25.

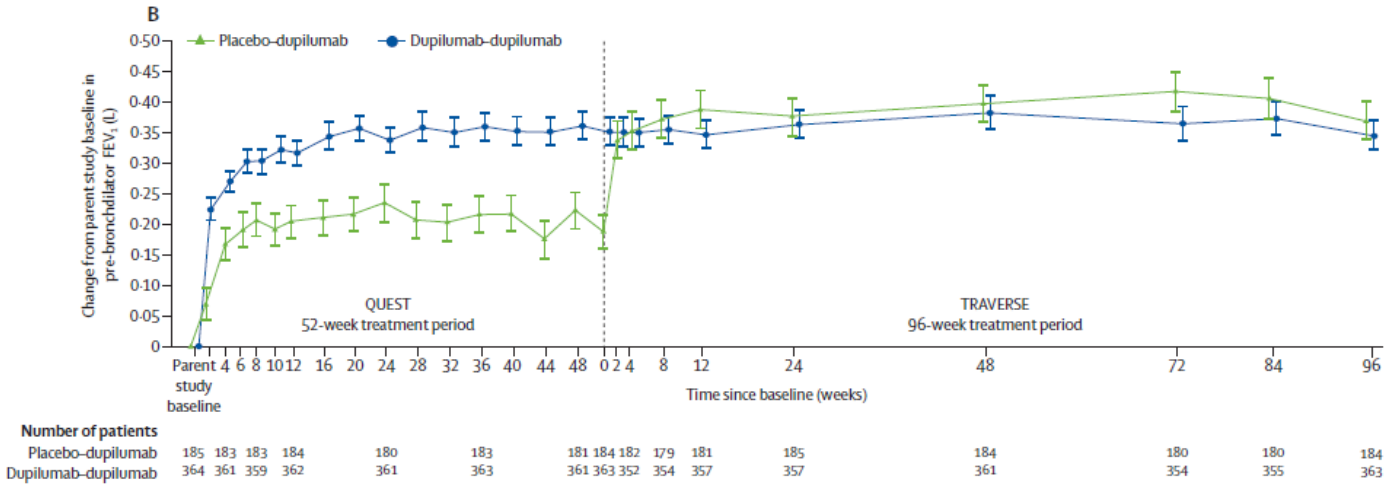
TRAVERSE - Lancet Respir Med. 2022 (2)

In **non-OCS dependent type 2 asthma***, Dupilumab showed **sustained efficacy** over the subsequent 148 weeks

Exacerbation rates *A type 2 inflammatory phenotype was defined as blood eosinophils 150 cells per µL or more or FeNO 25 ppb or more from QUST/TRAVERSE population.



Lung function



Exacerbation rates and lung function in patients from QUEST with a type 2 inflammatory phenotype followed-up for 148 weeks

(A) Number of exacerbations in the year before the parent study and AER during the parent and open-label extension treatment periods (mean [SD]) and (B) change from parent study baseline in pre-bronchodilator FEV1 in patients from QUEST with a type 2 inflammatory phenotype followed-up for 148 weeks (ie, given dupilumab for 52 weeks during QUEST and an additional 96 weeks during TRAVERSE; mean [SE]).
AER was assessed in the overall exposed population (observed cases). Pre-bronchodilator FEV1 was assessed in the overall exposed population (observed cases) using descriptive statistics.
Week 0 represents the start of the open-label extension.

*The total number of events that occurred during the treatment period divided by the total number of patient-years followed-up in the treatment period.

1. Michael E Wechsler et al. Lancet Respir Med. 2022 Jan;10(1):11-25.

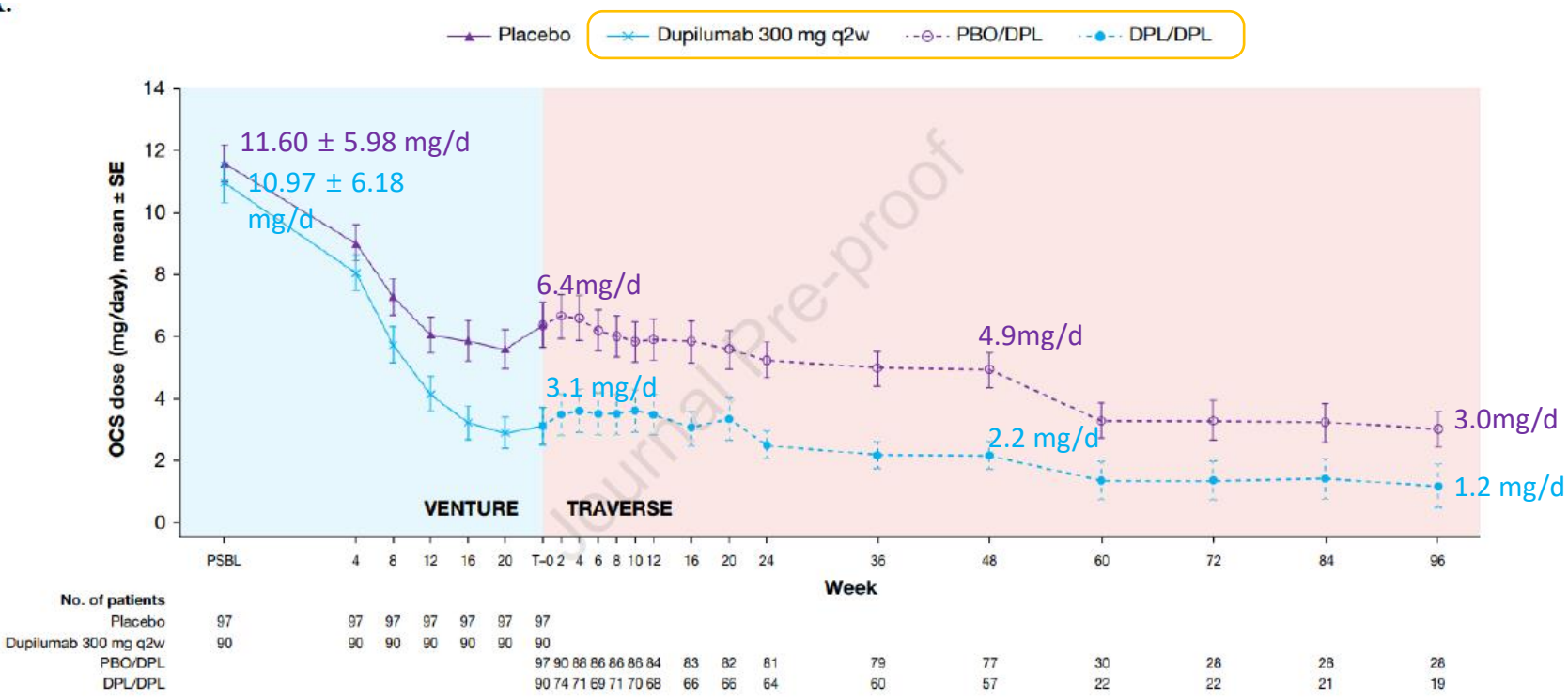
TRAVERSE subanalysis - Chest. 2022

Dupilumab demonstrated the ability to **sustain the OCS dose reduction*** from VENTURE to TRAVERSE

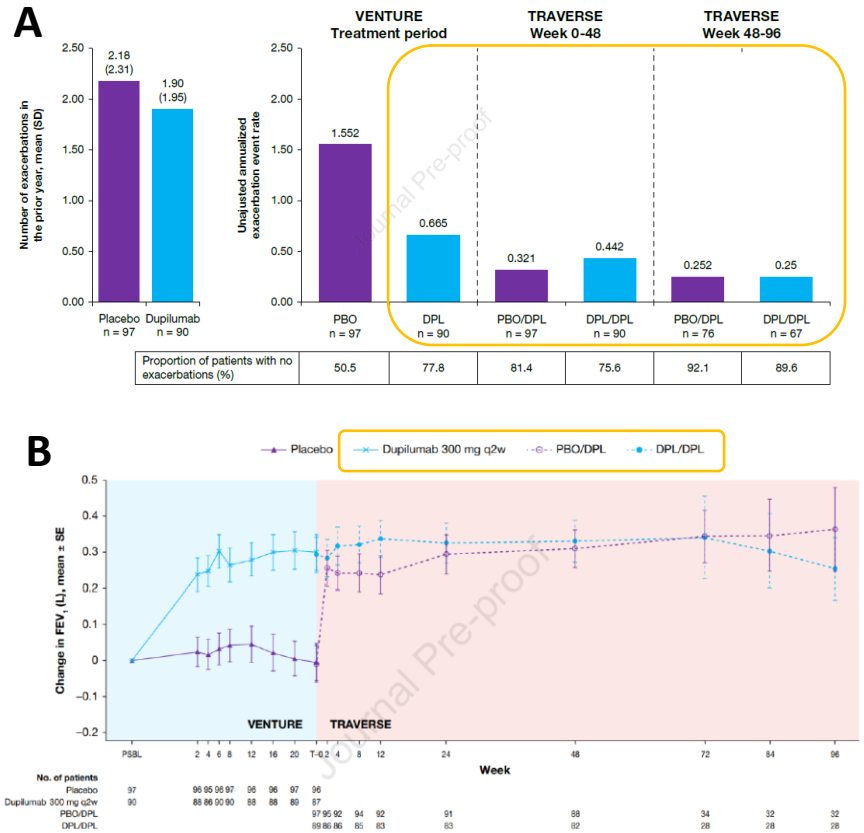
CHEST
Available online 22 February 2022
In Press, Journal Pre-proof

*while maintaining a low exacerbation rate and improved lung function

Mean OCS use (mg/day) from VENTURE and TRAVERSE



Efficacy analysis: **exacerbation rates** (A) and **mean change in FEV1** (B).



DPL = dupilumab; OCS = oral corticosteroid; PBO = placebo; PSBL = parent study baseline; q2w = every 2 weeks; SE = standard error; T = TRAVERSE

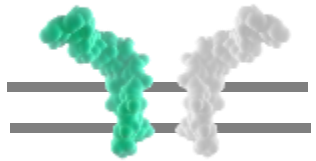
Lawrence D Sher et al. Chest. 2022 Feb 22;S0012-3692(22)00388-9.

FeNO, Eosinophils, and IgE Are Targeted by Type 2 Biologics for Severe Asthma

GINA recommendations for add-on biologic type 2-targeted treatment

Severe type 2/ eosinophilic asthma ★

Blood eosinophils ≥150 cells/µL
OR FeNO ≥25 ppb

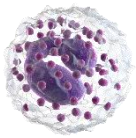


Patient eligible for anti-IL-4R

Need for maintenance OCS

Severe eosinophilic asthma

Blood eosinophils
≥300 cells/µL



Patient eligible for anti-IL-5/anti-IL-5R

Severe allergic asthma

Sensitization on skin prick testing or specific IgE
Total serum IgE and weight within dosage range

Patient eligible for anti-IgE

Only blockade of IL-4Rα (through which IL-4 and IL-13 signal) is recommended for treatment of patients with type 2 asthma

ppb, parts per billion

1. GINA. Global strategy for asthma management and prevention. 2019; 2. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15:35–50

Indirect comparison of efficacy of dupilumab *versus* mepolizumab and omalizumab for severe type 2 asthma

	Percentage of patients without exacerbations	10%	B: −10.6 (−21.9–4.5), p=0.12	B: 0.80 (0.60–1.08), p=0.14	B: 2.6 (−5.6; 12.2), p=0.58	B: 1.05 (0.90–1.21), p=0.53
OCS maintenance treatment	Mean % reduction of daily OCS dose	20% (at least 2.5 mg prednisolone equivalent)				
	Percentage of patients able to eliminate daily OCS treatment	5%	C: −0.5 (−9.9–27.6), p=0.94	C: 0.97 (0.31–2.91), p=0.96		
	Percentage of patients with a reduction of OCS daily dose⩾50%	10%	C: −1.4 (−21.0–29.9), p=0.92	C: 0.97 (0.61–1.57), p=0.91		
Lung function, FEV_1	Mean difference in FEV_1	200 mL	A: +100 (13–188), p=0.025 B: +189 (62–316), p=0.004 C: +106 (−122–334), p=0.37		B: +96 (11–182), p=0.028	
	Percentage of patients who achieved an improvement in FEV_1 ⩾200 mL	15%				
ACQ	Mean difference in ACQ	0.5	A: −0.02 (−0.22–0.18), p=0.86 C: 0.05 (−0.41–0.51), p=0.84		A: −0.11 (−0.42–0.20), p=0.50	
AQLQ	Mean difference in AQLQ	0.5	A: −0.13 (−0.32–0.06), p=0.18 C: −0.01 (−0.41–0.40), p=0.96		A: −0.08 (−0.30–0.15), p=0.50	
SAEs	Total incidence of SAEs	5%	A: 6.5 (−1.6–27.5), p=0.39 B: 2.0 (−5.7–17.6), p=0.75 C: 26.0 (1.5–257.1), p=0.013	A: 1.97 (0.76–5.13), p=0.16 B: 1.15 (0.57–2.35), p=0.71 C: 19.55 (2.10–184.6), p=0.009	A: 3.0 (−1.8–14.9), p=0.49 B: 0.2 (−2.7–5.3), p=0.93	A: 1.61 (0.64–4.05), p=0.32 B: 1.04 (0.60–1.80), p=0.90
	Specific subtypes of SAEs, *e.g.* anaphylaxis		No analysis	No analysis		

All estimates are for dupilumab compared to mepolizumab and omalizumab. MCID: minimal clinically important difference; OCS: oral corticosteroids; FEV_1: forced expiratory volume in 1 s; ACQ: Asthma Control Questionnaire; AQLQ: Asthma quality of life Questionnaire; SAE: serious adverse events. A: severe asthma, 24–32 weeks treatment; B: severe asthma, 48–52 weeks treatment; C: OCS-dependent asthma, 24 weeks treatment. #: dupilumab studies: [10–14]; ¶: mepolizumab studies: [15–18]; +: omalizumab studies: [19–40].

ERJ open research 2021

Dupilumab

- Completed Pivotal clinical trials
- Long term data of Dupilumab
- **Post-hoc analysis: QUEST Korea subgroup**

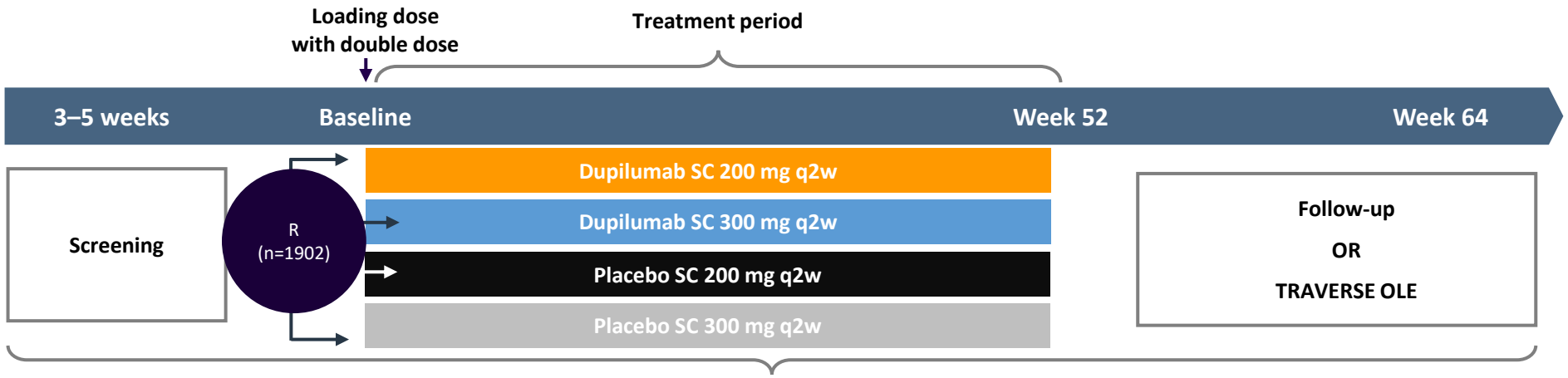
Phase 3 Asthma QUEST: Design

Parent study

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

QUEST (uncontrolled persistent asthma)



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

Primary endpoint(s)	Key secondary endpoints
▪ Annualized rate of severe exacerbation events[a] over 52 weeks ▪ Δ in pre-BD FEV_1 at Week 12	▪ 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

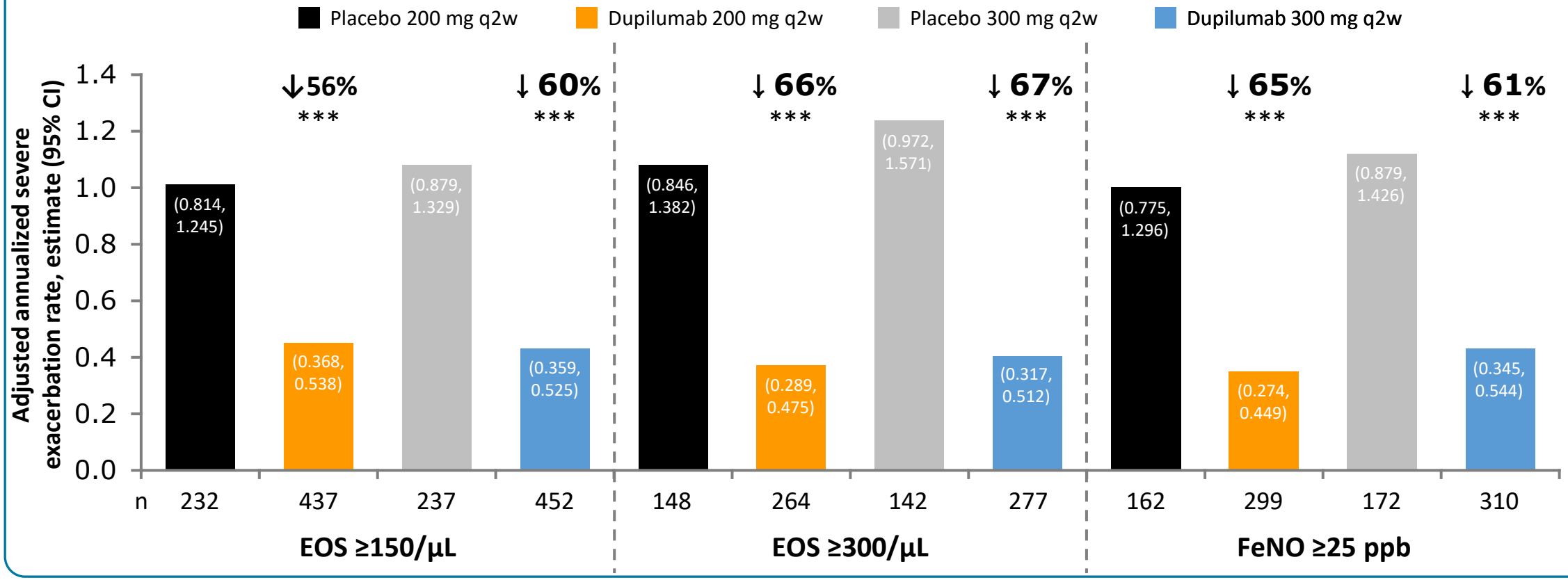
1. Castro M, et al. *N Engl J Med*. 2018;378:2486–2496;

QUEST

Severe Exacerbations over 52 weeks (1° endpoint)

Parent study

Severe asthma exacerbations over 52 weeks in patients with a range of elevated type 2 biomarkers at baseline



***p<0.001 vs placebo

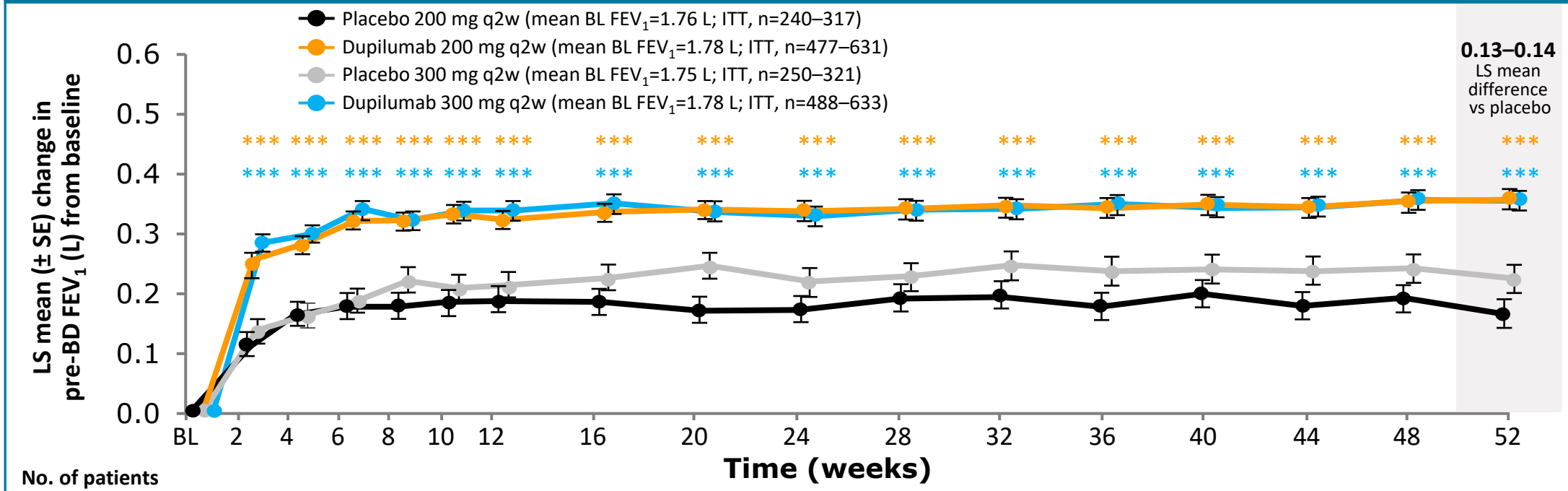
1. Castro M, et al. *N Engl J Med*. 2018;378:2486–2496; 2. Ford LB, et al. *EAACI*. 2018; 3. Wenzel S, et al. *ATS*. 2018; 4. Castro M, et al. *ATS*. 2018

QUEST

Pre-BD FEV_1 at wk 12 (1° endpoint) and over 52-wk

Parent study

Week 52 (ITT); Phase 3 (QUEST)[1,2]



No. of patients																		
Placebo 200 mg	317	315	307	301	305	301	307	300	303	300	290	286	289	287	288	281	240
Dupilumab 200 mg	631	610	613	615	604	607	611	605	601	599	589	585	590	577	581	570	477
Placebo 300 mg	321	313	311	313	311	309	313	310	304	296	304	301	301	297	292	290	250
Dupilumab 300 mg	633	625	614	612	609	598	610	611	593	596	586	579	584	584	570	562	488

MCID for changes in FEV_1 of 0.1–0.2 L are likely to be clinically important – per NIH-organized workshop[3]

***p<0.001

NIH, National Institutes of Health

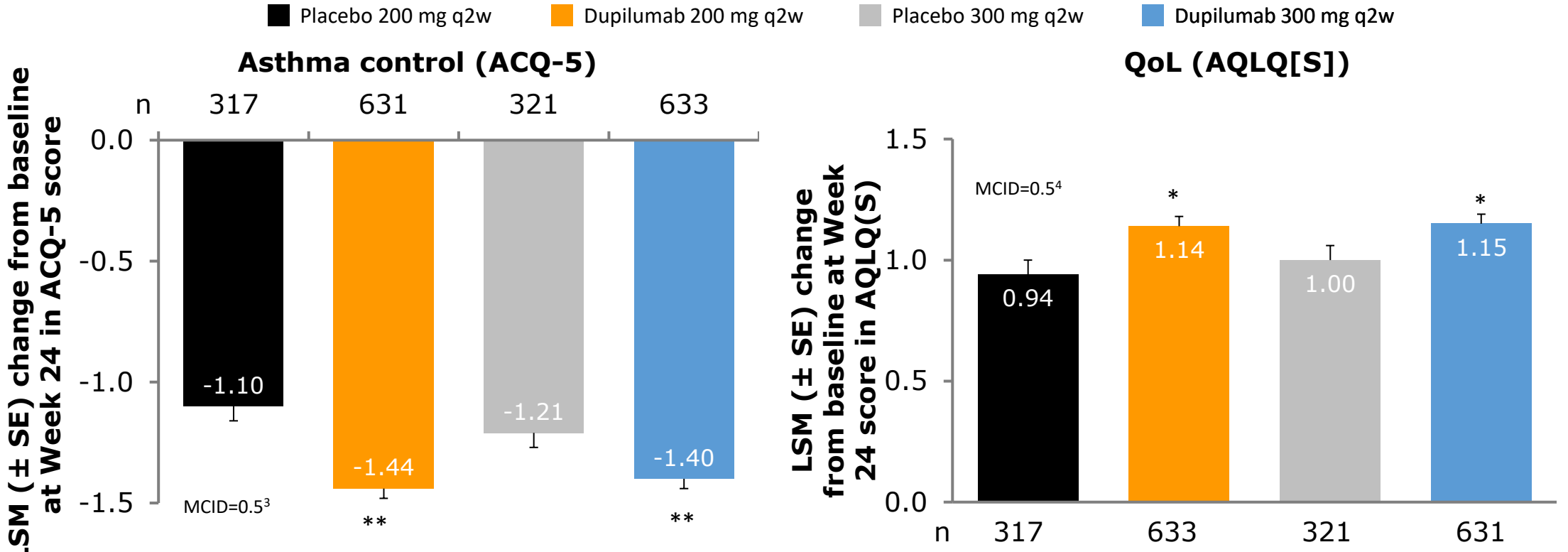
1. Castro M, et al. *N Engl J Med*. 2018;378:2486–2496; 2. Castro M, et al. *ATS*. 2018; 3. Tepper RS, et al. *J Allergy Clin Immunol*. 2012;129(3 suppl):S65–S87

QUEST

Asthma Control and Quality of Life at week 24

Parent study

Change in PRO measures at Week 24 in the ITT population[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

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Allergy, Asthma & Immunology Research AAIR

Original Article

Effect of Dupilumab in Korean Patients With Uncontrolled Moderate-to-Severe Asthma: A LIBERTY ASTHMA QUEST Sub-analysis

Chin Kook Rhee [1], Jung-Won Park [2], Heung-Woo Park [3], You Sook Cho [4*]

QUEST Korean sub-analysis

Background & Objective

Background

- In the LIBERTY ASTHMA QUEST study, dupilumab significantly decreases exacerbations compared with placebo in patients with severe asthma; however, little is known regarding the effect of dupilumab in Korean patients with severe asthma.

Objective

- To assess the effect of dupilumab on the annualized rate of severe exacerbations and change in FEV_1 of the Korean patients.

CK Rhee et al. Allergy Asthma Immunol Res. 2022 Mar: 14(2):182-195

Methods

Study Assessment

- This was a post-hoc analysis of the subgroup of Korean patients in QUEST.
  - The number of Korean patients enrolled was 74 (4% of total patients).

- Dupilumab 200mg or 300mg was administrated every 2 weeks in treatment group.

- Outcomes assessed were effect of treatment over the 52-week treatment period on annualized rate of severe exacerbation, pre-bronchodilator FEV1, asthma control, asthma related quality of life, and markers of type 2 inflammation.

QUEST Korean sub-analysis - Results

Baseline Characteristics

Table 1. Demographic and clinical characteristics at baseline (ITT population)

Parameters	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined		Total (n = 74)
	Placebo (n = 12)	Dupilumab (n = 24)	Placebo (n = 13)	Dupilumab (n = 25)	Placebo (n = 25)	Dupilumab (n = 49)	
Age (yr)	59.8 (7.8)	46.8 (11.3)	51.6 (8.3)	53.3 (13.0)	55.5 (8.9)	50.1 (12.5)	51.9 (11.6)
Sex							
Women	8 (66.7)	15 (62.5)	9 (69.2)	15 (60.0)	17 (68.0)	30 (61.2)	47 (63.5)
Men	4 (33.3)	9 (37.5)	4 (30.8)	10 (40.0)	8 (32.0)	19 (38.8)	27 (36.5)
BMI (kg/m²)							
< 25	7 (58.3)	10 (41.7)	8 (61.5)	12 (48.0)	15 (60.0)	22 (44.9)	37 (50.0)
≥ 25 and < 30	4 (33.3)	12 (50.0)	3 (23.1)	8 (32.0)	7 (28.0)	20 (40.8)	27 (36.5)
≥ 30	1 (8.3)	2 (8.3)	2 (15.4)	5 (20.0)	3 (12.0)	7 (14.3)	10 (13.5)
Age at asthma onset (yr)	45.4 (10.2)	35.0 (11.5)	37.1 (14.9)	42.9 (13.0)	41.1 (13.3)	39.0 (12.8)	39.7 (12.9)
Time since the first asthma diagnosis (yr)	14.31 (8.4)	11.92 (8.5)	14.48 (10.6)	10.49 (5.7)	14.40 (9.4)	11.19 (7.2)	12.7 (8.1)
Pre-bronchodilator FEV1 (L)	1.46 (0.4)	1.59 (0.5)	1.30 (0.2)	1.56 (0.4)	1.38 (0.3)	1.57 (0.4)	1.51 (0.4)
Pre-bronchodilator FEV1 percent predicted	63.83 (9.0)	58.96 (12.9)	54.77 (15.1)	62.56 (9.7)	59.12 (13.2)	60.80 (11.4)	60.23 (12.0)
Post-bronchodilator FEV1 (L)	1.80 (0.5)	1.93 (0.6)	1.58 (0.2)	1.94 (0.5)	1.69 (0.4)	1.94 (0.6)	1.85 (0.5)
FEV1 reversibility (%), [median (range)]	23.8 (11.2 to 50.5)	15.4 (2.8 to 97.5)	21.2 (−3.1 to 70.2)	19.7 (2.9 to 81.4)	23.6 (−3.1 to 70.2)	18.8 (2.8 to 97.5)	19.6 (−3.1 to 97.5)
No. of asthma exacerbation experienced in the past year, median (range)	2.0 (1.0 to 3.0)	2.0 (1.0 to 8.0)	2.0 (1.0 to 6.0)	2.0 (1.0 to 4.0)	2.0 (1.0 to 6.0)	2.0 (1.0 to 8.0)	2.0 (1.0 to 8.0)

The majority of Korean patients were women (63.5%) and the mean (SD) age was 51.9 (11.6) years.

QUEST Korean sub-analysis - Results

Baseline Characteristics

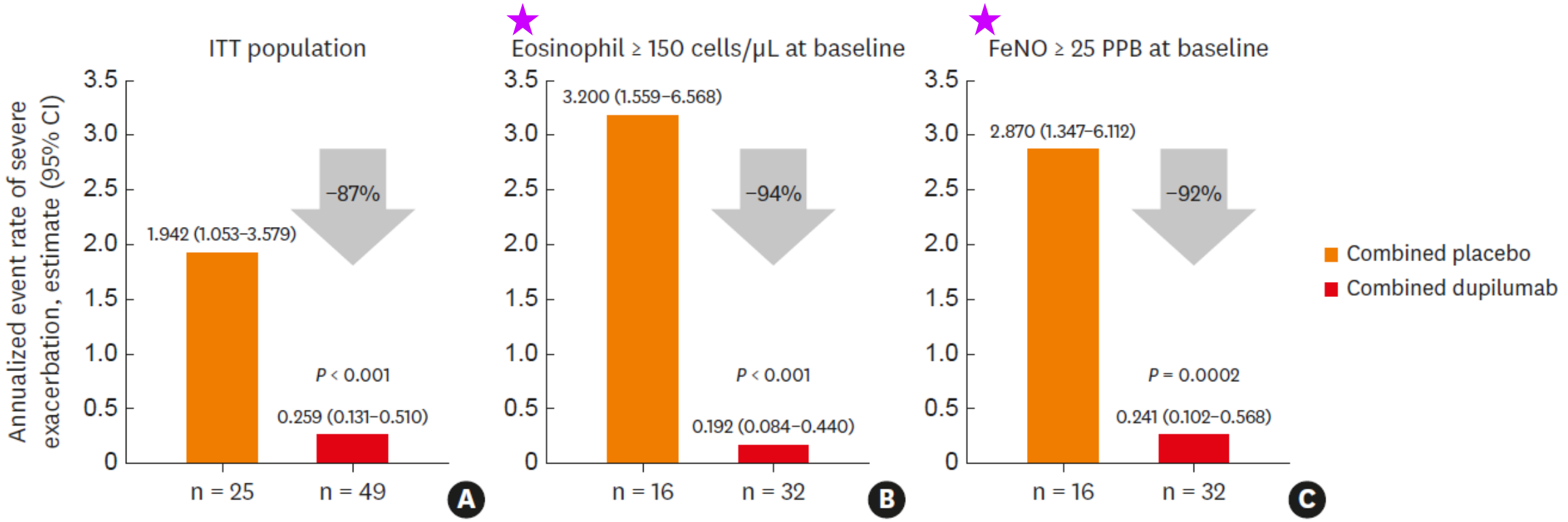
Parameters	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined		Total (n = 74)
	Placebo (n = 12)	Dupilumab (n = 24)	Placebo (n = 13)	Dupilumab (n = 25)	Placebo (n = 25)	Dupilumab (n = 49)	
ICS dose at baseline, mg, median (range)	500.0 (400.0 to 1,250.0)	500.0 (400.0 to 1,300.0)	500.0 (400.0 to 1,300.0)	500.0 (400.0 to 1,500.0)	500.0 (400.0 to 1,300.0)	500.0 (400.0 to 1,500.0)	500.0 (400.0 to 1,500.0)
ICS dose level at baseline							
High	4 (33.3)	6 (25.0)	6 (46.2)	11 (44.0)	10 (40.0)	17 (34.7)	27 (36.5)
Medium	8 (66.7)	18 (75.0)	7 (53.8)	14 (56.0)	15 (60.0)	32 (65.3)	47 (63.5)
Atopic medical condition	8 (66.7)	20 (83.3)	12 (92.3)	21 (84.0)	20 (80.0)	41 (83.7)	61 (82.4)
Atopic dermatitis	-	1 (4.2)	-	-	-	1 (2.0)	1 (1.4)
Allergic conjunctivitis	-	3 (12.5)	2 (15.4)	3 (12.0)	2 (8.0)	6 (12.2)	8 (10.8)
Allergic rhinitis	8 (66.7)	16 (66.7)	10 (76.9)	20 (80.0)	18 (72.0)	36 (73.5)	54 (73.0)
Food allergy	-	3 (12.5)	2 (15.4)	1 (4.0)	2 (8.0)	4 (8.2)	6 (8.1)
Hives	-	1 (4.2)	-	-	-	1 (2.0)	1 (1.4)
IgE (IU/mL), [median (IQR range)]	95.5 (3.0 to 962.0)	160.5 (13.0 to 2,907.0)	257.0 (16.0 to 1,268.0)	300.0 (16.0 to 2,583.0)	210.0 (3.0 to 1,268.0)	223.0 (13.0 to 2,907.0)	218.0 (3.0 to 2,907.0)
Blood eosinophil group (cells/μL)							
< 300	5 (41.7)	12 (50.0)	6 (46.2)	13 (52.0)	11 (44.0)	25 (51.0)	36 (48.6)
≥ 300	7 (58.3)	12 (50.0)	7 (53.8)	12 (48.0)	14 (56.0)	24 (49.0)	38 (51.4)
Blood eosinophil group (cells/μL)							
< 150	5 (41.7)	8 (33.3)	4 (30.8)	9 (36.0)	9 (36.0)	17 (34.7)	26 (35.1)
≥ 150	7 (58.3)	16 (66.7)	9 (69.2)	16 (64.0)	16 (64.0)	32 (65.3)	48 (64.9)
FeNO (ppb)	31.5 (9.0 to 197.0)	37.0 (9.0 to 269.0)	57.0 (12.0 to 127.0)	36.0 (9.0 to 168.0)	34.0 (9.0 to 197.0)	36.0 (9.0 to 269.0)	35.0 (9.0 to 269.0)
FeNO group (ppb)							
< 25	5 (41.7)	10 (41.7)	3 (25.0)	7 (28.0)	8 (33.3)	17 (34.7)	25 (34.2)
≥ 25 and < 50	4 (33.3)	6 (25.0)	2 (16.7)	11 (44.0)	6 (25.0)	17 (34.7)	23 (31.5)
≥ 50	3 (25.0)	8 (33.3)	7 (58.3)	7 (28.0)	10 (41.7)	15 (30.6)	25 (34.2)

Data shown as number (%) or mean (SD), unless otherwise specified.
ITT, Intent-to-treat; BMI, body mass index; FEV1, forced expiratory volume at first second; ICS, inhaled corticosteroids; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide; SD, standard deviation.

- ✓ 64.9% of patients had **blood eosinophil count ≥150 cells/μL (520 vs. 360 cells/μL original)**
- ✓ 65.7% of patients had **FeNO ≥ 25 ppb (49.6% in overall; 51.25 vs. 34.97 ppb original)**

QUEST Korean sub-analysis - Results

Annualized Severe Exacerbations over 52-week

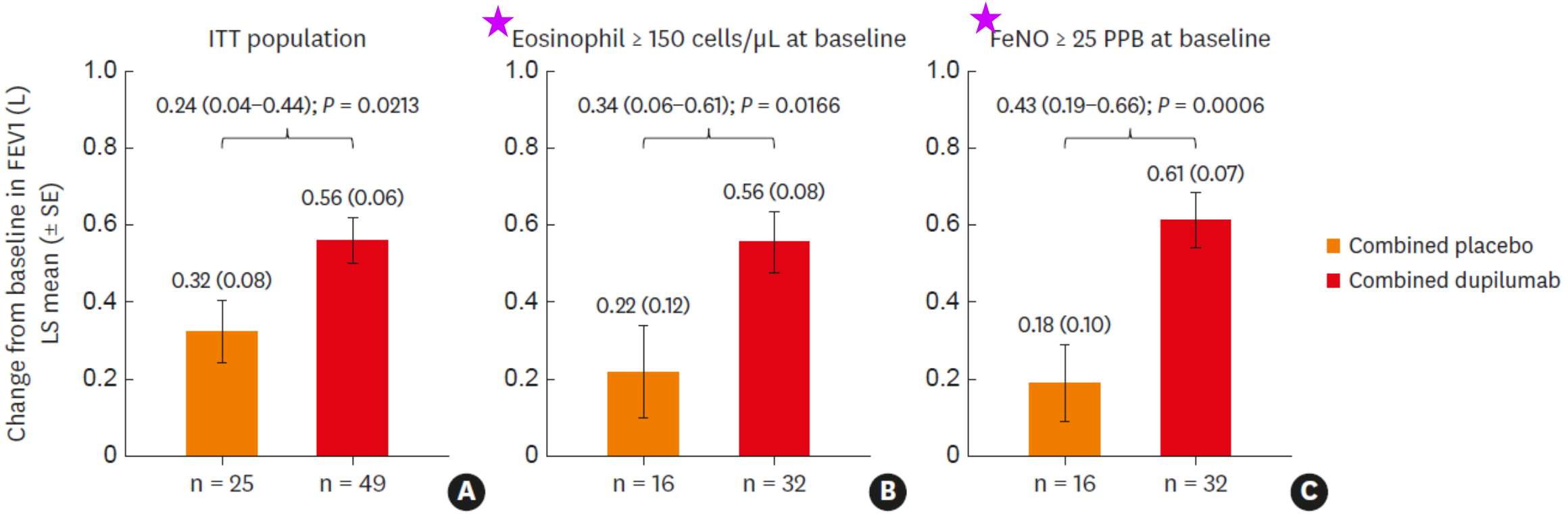


Dupilumab significantly reduced the annualized rate of severe exacerbations compared to placebo in Korean population over 52-week

ITT, intention-to-treat; CI, confidence interval; FeNO, fractional exhaled nitric oxide; ppb, parts per billion

QUEST Korean sub-analysis - Results

Pre-BD FEV_1 at week 12

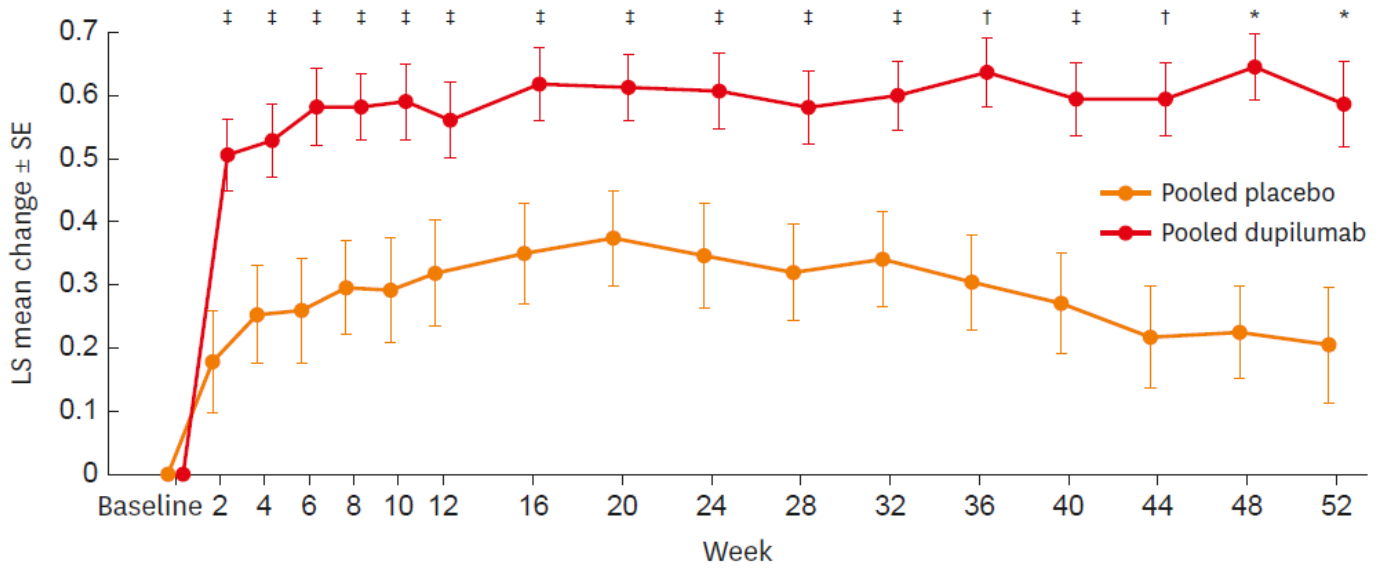


Dupilumab significantly improved pre-bronchodilator FEV1 at week 12 compared to placebo in Korean population

ITT, intention-to-treat; FEV1, forced expiratory volume at first second; LS, least squares; SE, standard error; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

QUEST Korean sub-analysis - Results

Pre-BD FEV_1 during 52 weeks: ITT



Pooled placebo	25	25	25	25	25	25	25	25	22	23	24	24	24	24	24	24	17
Pooled dupilumab	49	48	47	49	49	48	48	49	49	47	47	44	46	45	46	46	31

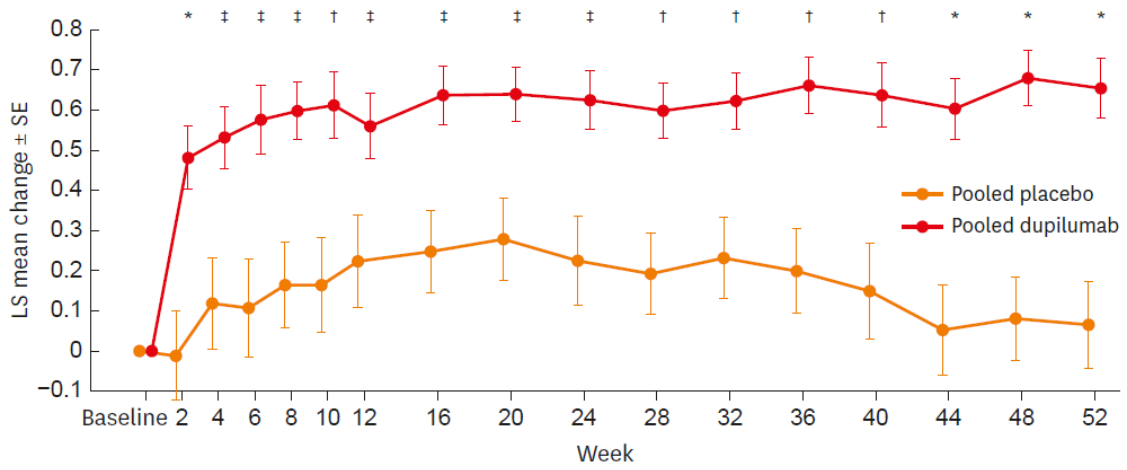
Dupilumab significantly improved Pre-BD FEV1 since week 2 and sustained over 52-week compared to placebo in Korean population

LS, least squares; SE, standard error; FEV1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat.
*P≤0.0001; †P≤0.001; ‡P≤0.05.

QUEST Korean sub-analysis - Results

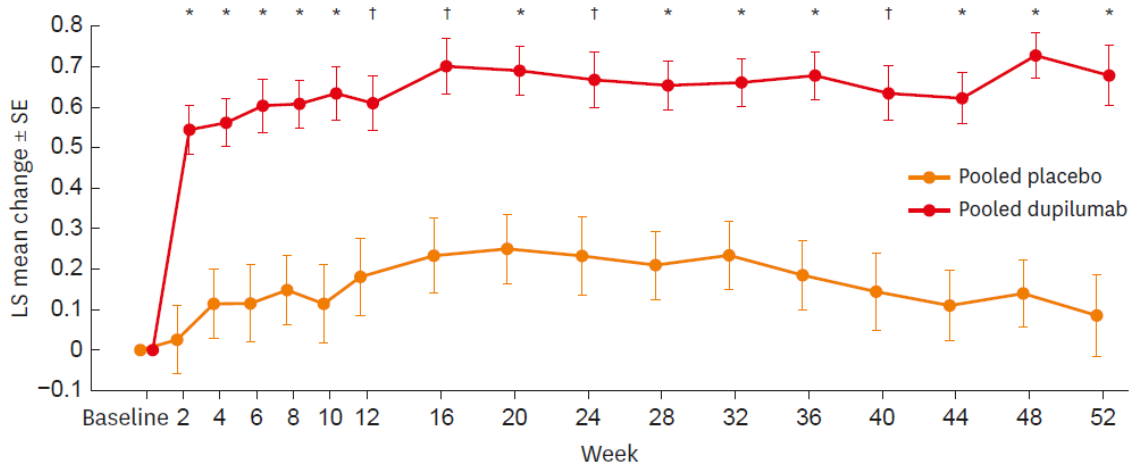
Pre-BD FEV_1 during 52 weeks: in Type 2 asthma

Patients with EOS ≥150 cells/µL



Pooled placebo	16	16	16	16	16	16	16	16	13	14	15	15	15	15	15	15	11
Pooled dupilumab	32	31	31	32	32	31	31	32	32	31	30	28	30	29	31	30	20

Patients with FeNO ≥25 ppb



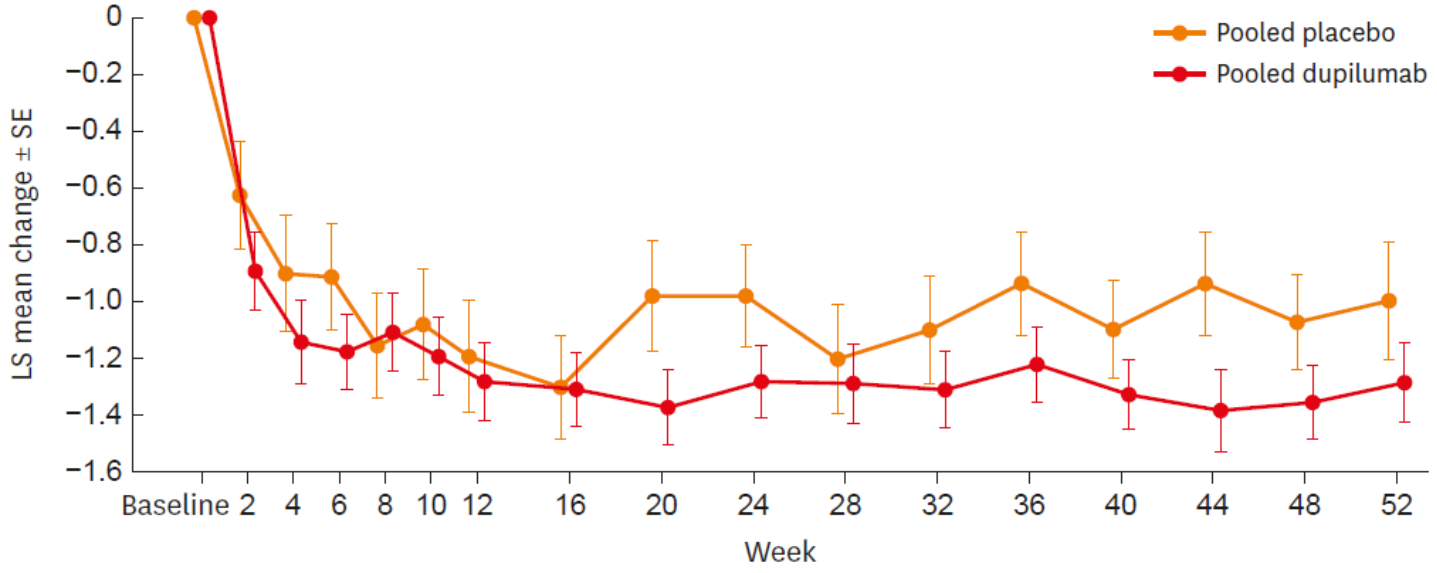
Pooled placebo	16	16	16	16	16	16	16	16	14	14	15	15	15	15	15	15	12
Pooled dupilumab	32	32	31	32	32	31	31	32	32	31	31	30	30	29	31	30	22

Dupilumab significantly improved Pre-BD FEV1 since week 2 and sustained over 52-week compared to placebo in Korean population with type 2 inflammation phenotype

LS, least squares; SE, standard error; FEV1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat.
*P≤0.0001; †P≤0.001; ‡P≤0.05.

QUEST Korean sub-analysis - Results

ACQ-5 during 52 weeks: ITT



Pooled placebo	25	23	25	25	25	25	25	25	22	23	24	24	24	24	24	24	17
Pooled dupilumab	49	48	46	49	49	47	48	49	49	47	46	45	43	44	45	44	31

Dupilumab showed greater improvements in ACQ-5 scores over 52-week compared to placebo in Korean population

LS, least squares; SE, standard error; ACQ-5, 5-item asthma control questionnaire; ITT, intention-to-treat; FeNO, fractional exhaled nitric oxide.
*P < 0.001; †P < 0.05 vs. matched placebo.

QUEST Korean sub-analysis - Results

Safety profile Summary

Table 2. Summary of treatment-emergent adverse events (safety population)

Events	Placebo (n = 25)	Dupilumab (n = 49)
TEAE	22 (88.0)	44 (89.8)
Treatment emergent SAE	3 (12.0)	5 (10.2)
TEAE leading to a permanent treatment discontinuation	-	4 (8.2)
Injection site reactions		
TEAE	-	11 (22.4)
TEAE related to IMP reported by investigator	-	11 (22.4)
Patients with ISR (n = 11)		
1 episode	-	2 (18.2)
2 episodes	-	1 (9.1)
3 episodes	-	2 (18.2)
≥ 4 episodes	-	6 (54.5)
ISRs duration (hour) (n = 63)		
< 24	-	24 (38.1)
≥ 24 and < 72	-	15 (23.8)
≥ 72	-	24 (38.1)

Data shown as number (%).

TEAE, treatment-emergent adverse events; SAE, serious adverse event; IMP, investigational medicinal product; ISR, injection site reaction.

QUEST Korean sub-analysis

Conclusions

- A significant reduction of the annualized severe exacerbation rates and a significant improvement in lung function with the acceptable safety in severe asthma patients on the 52-week dupilumab treatment in Korea are the key findings of the current study.

- Compared with the overall Korean ITT group, the reductions in the risk of severe exacerbations and the improvements in pre-BD FEV1 were greater in those with elevated baseline blood eosinophils 150 cells/μL and FeNO levels 25 ppb.

- This posthoc analysis of the Korean subgroup in the QUEST study indicates the substantial efficacy and acceptable safety of dupilumab as an add-on therapy in severe asthma for a period of over one year.

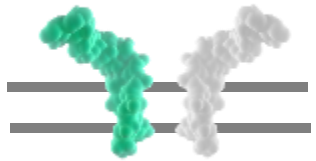
- The study demonstrates a significant decrease in severe exacerbations and enhanced FEV1 in dupilumab-treated versus placebo-treated Korean patients, suggesting no negative impact of Korean ethnicity on the efficacy of dupilumab.

FeNO, Eosinophils, and IgE Are Targeted by Type 2 Biologics for Severe Asthma

GINA recommendations for add-on biologic type 2-targeted treatment

Severe type 2/ eosinophilic asthma ★

Blood eosinophils ≥150 cells/µL
OR FeNO ≥25 ppb

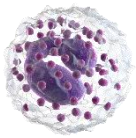


Patient eligible for anti-IL-4R

Need for maintenance OCS

Severe eosinophilic asthma

Blood eosinophils
≥300 cells/µL



Patient eligible for anti-IL-5/anti-IL-5R

Severe allergic asthma

Sensitization on skin prick testing or specific IgE
Total serum IgE and weight within dosage range

Patient eligible for anti-IgE

Only blockade of IL-4Rα (through which IL-4 and IL-13 signal) is recommended for treatment of patients with type 2 asthma

ppb, parts per billion

1. GINA. Global strategy for asthma management and prevention. 2019; 2. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15:35–50

경청해 주셔서

감사합니다.

Asthma and CRSwNP Driven by Type 2 Inflammation Often Coexist

Of adult patients with severe asthma:

- ~30%–45% have coexisting CRSwNP[1-6]*
- ~44%–62% have coexisting allergic rhinitis[1-3]
- ~15% have coexisting NSAID-ERD[7]

Of adult patients with CRSwNP:

- ~48%–56% have coexisting asthma[8-11]
- ~46% have coexisting allergic rhinitis[12]
- ~10%–21% have coexisting NSAID-ERD[7-9]

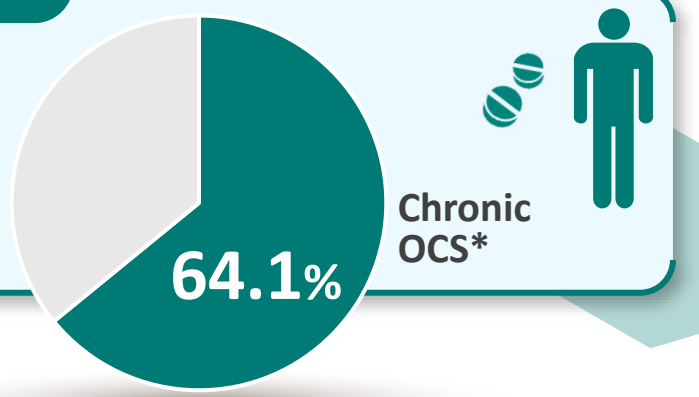
*CRSwNP or NP only.

1. Heffler E, et al. *J Allergy Clin Immunol Pract*. 2019;7:1462-1468. 2. Shaw DE, et al. *Eur Respir J*. 2015;46:1308-1321. 3. Maio S, et al. *Allergy*. 2018;73:683-695. 4. Micheletto C, et al. *Eur Ann Allergy Clin Immunol*. 2010;42:120-124. 5. Matsusaka M, et al. *Allergol Int*. 2015;64(2):175-180. 6. Novelli F, et al. *Clin Mol Allergy*. 2018;16:25. 7. Rajan JP, et al. *J Allergy Clin Immunol*. 2015;135:676-681. 8. Khan A, et al. *Rhinology*. 2019;57(1):32-42. 9. Stevens WW, et al. *J Allergy Clin Immunol Pract*. 2017;5(4):1061-1070. 10. Promsopa C, et al. *Int Forum Allergy Rhinol*. 2016; 6(4):373-377. 11. Benjamin MR, et al. *J Allergy Clin Immunol Pract*. 2019;7(3):1010-1016. 12. Rondon C, et al. *J Investig Allergol Clin Immunol*. 2015;25(4):276-282.

Systemic Steroid Exposure and Associated Adverse Risks Are Greater in Patients With Coexisting Asthma + CRSwNP

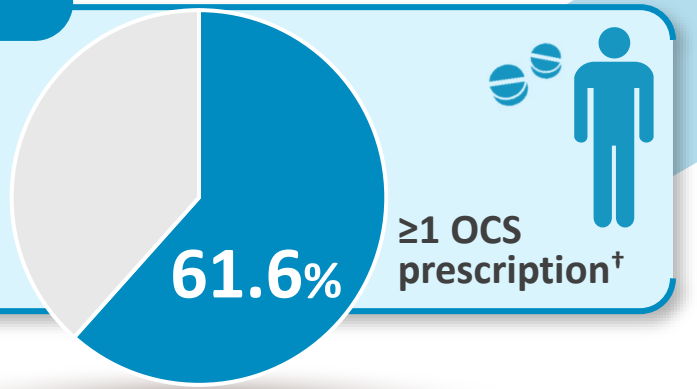
Severe asthma

Severe Asthma Network in Italy (n=437)[1]



CRSwNP

US Truven Health Claims database (n=10,841)[2]



*Compared with **12.8%** of patients without CRS/NP (reference group)†*

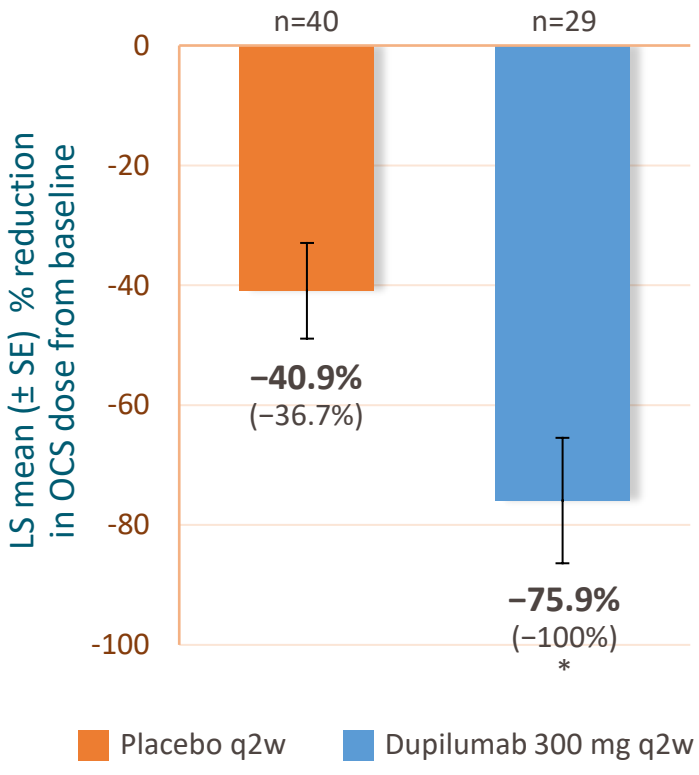
*Treatment with OCS for ≥6 months in the previous year.[1] †During 1-year follow-up period (2.14 mean number of prescriptions in CRSwNP group and 1.58 in reference group).[2]

1. Heffler E, et al. *J Allergy Clin Immunol Pract*. 2019;7(5):1462-1468. 2. Bhattacharyya N, et al. *Laryngoscope*. 2019;129(9):1969-1975. 3. Heffler E, et al. *Curr Opin Allegy Clin Immunol*. 2019;19:61-67.

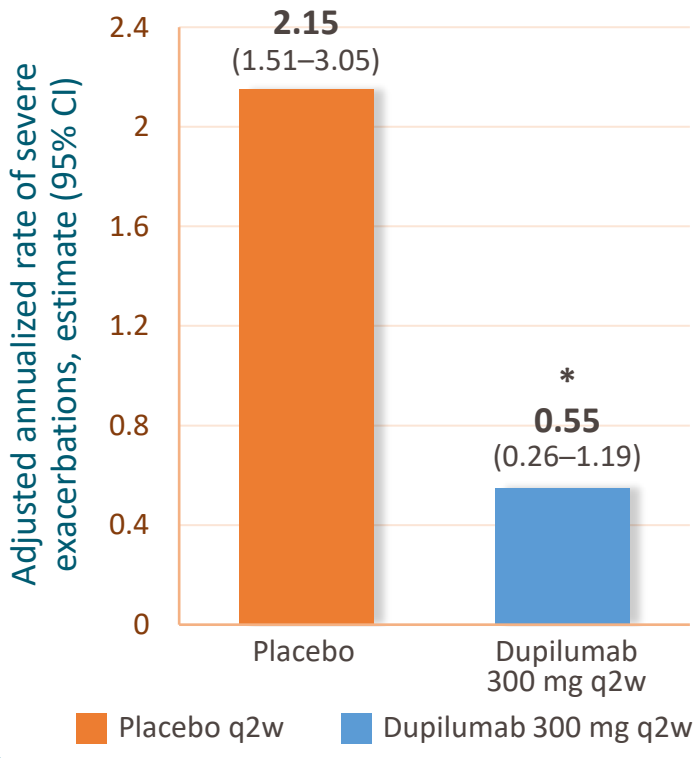
Dupilumab Significantly Reduced Exacerbations and Improved Lung Function Despite OCS Dose Reduction (OCS-Dependent Asthma + CRS/NP)

Asthma + comorbid CRS/NP; phase 3 VENTURE (post-hoc analysis)

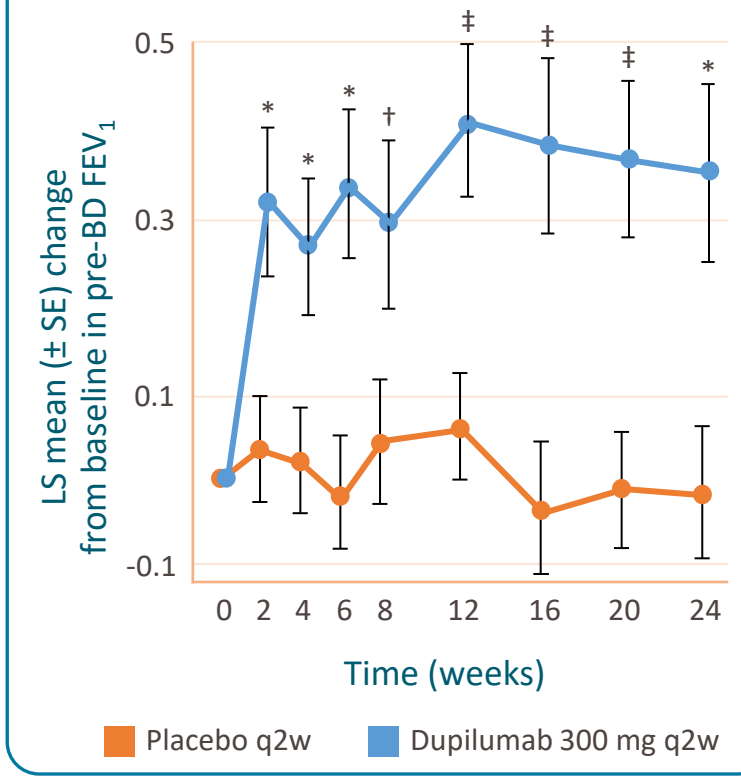
OCS dose reduction



Exacerbations



Lung function



*P<0.01, †P<0.05, ‡P<0.001, vs placebo.

1. Rabe KF, et al. Presented at: the Annual Congress of the European Academy of Allergy and Clinical Immunology (EAACI); June 1-5, 2019; Lisbon, Portugal.

Comparative efficacy and safety of monoclonal antibodies and aspirin desensitization for chronic rhinosinusitis with nasal polyposis: A systematic review and network meta-analysis

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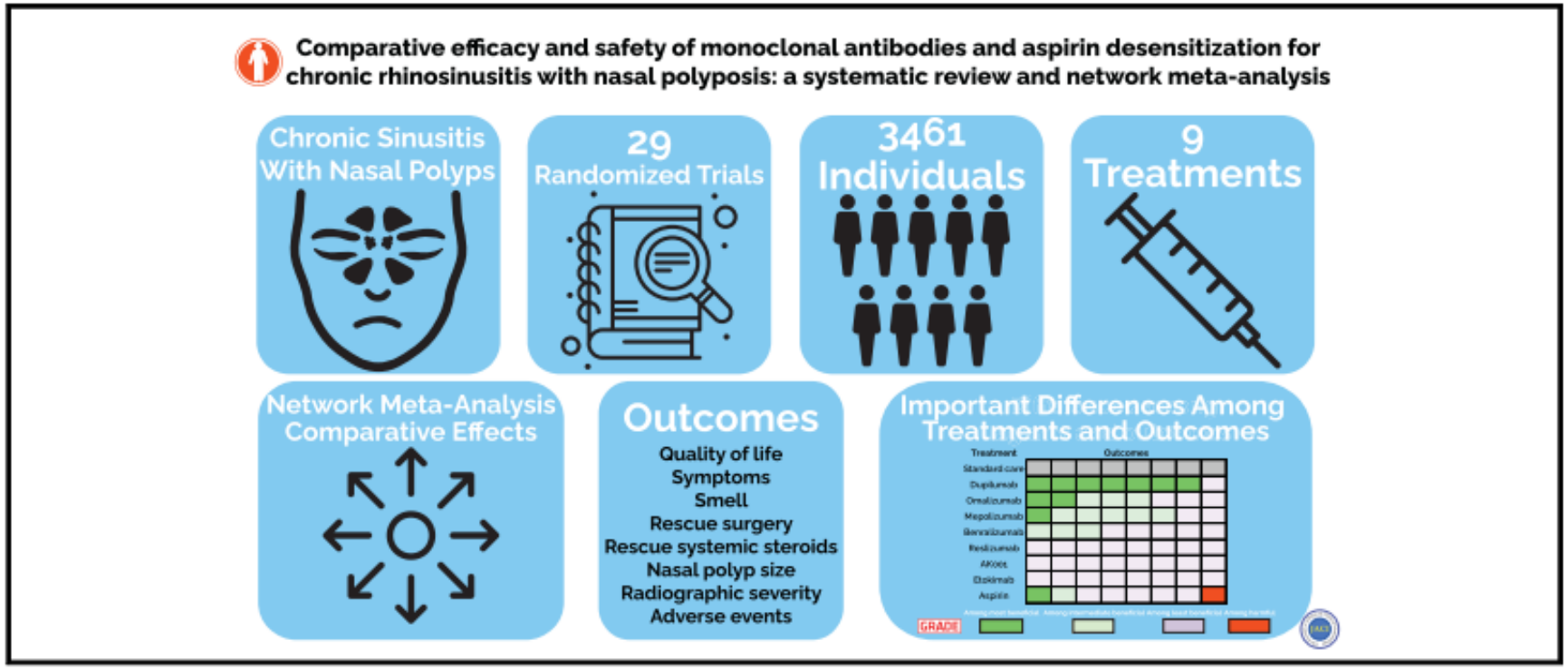
Hamilton, Ontario, Canada; Berlin, Germany; Montpellier, France; and Philadelphia, Pa

GRAPHICAL ABSTRACT



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Chronic rhinosinusitis with nasal polyposis (CRSwNP)

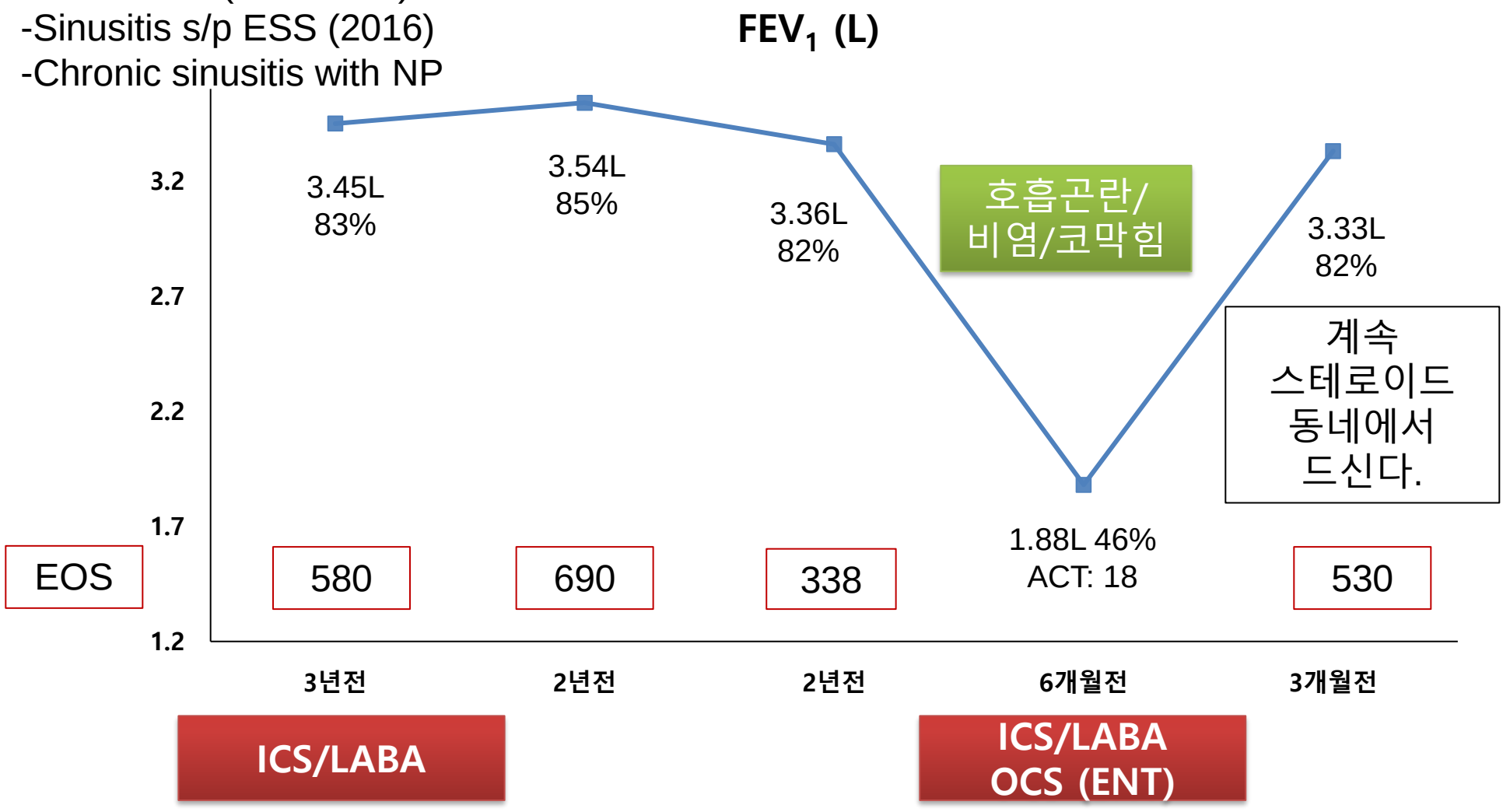
	Patient-important outcomes						Surrogate outcomes	
	HRQoL SNOT-22 (0-110)‡	Symptoms VAS (0-10 cm)	Smell UPSIT (0-40)†	Rescue OCS	Rescue polyp surgery	Adverse events	Nasal polyp size (0-8)	CT score LMK (0-24)
Standard care*	50.11	6.84	14.04	31.96%	21.05%	73.78%	5.94	18.35
Dupilumab	**-19.91** (-22.50, -17.32)	**-3.25** (-4.31, -2.18)	**10.96** (9.75, 12.17)	**-21.73** (-24.61, -18.22) RR 0.32 (0.23, 0.43)	**-16.35** (-18.13, -13.48) RR 0.22 (0.14, 0.36)	**0.13** (-8.12, 9.88) RR 1.00 (0.88, 1.13)	**-2.04** (-2.73, -1.35)	**-7.51** (-10.13, -4.89)
Omalizumab	**-16.09** (-19.88, -12.30)	**-2.09** (-3.15, -1.03)	**3.75** (2.14, 5.35)	**-12.46** (-23.65, 12.78) RR 0.61 (0.26, 1.40)	**-7.40** (-11.04, -2.43) RR 0.65 (0.48, 0.88)	**-2.60** (-15.58, 13.28) RR 0.96 (0.79, 1.18)	**-1.09** (-1.70, -0.49)	**-2.66** (-5.70, 0.37)
Mepolizumab	**-12.89** (-16.58, -9.19)	**-1.82** (-3.13, -0.50)	**6.13** (4.07, 8.19)	**-10.23** (-15.98, -2.88) RR 0.68 (0.50, 0.91)	**-12.33** (-15.56, -7.22) RR 0.41 (0.26, 0.66)	**-3.07** (-13.44, 9.07) RR 0.96 (0.82, 1.12)	**-1.06** (-1.79, -0.34)	
Benralizumab	**-7.68** (-12.09, -3.27)	**-1.15** (-2.47, 0.17)	**2.95** (1.02, 4.88)	**-9.91** (-16.30, -0.96) RR 0.69 (0.49, 0.97)	**-2.53** (-9.05, 7.16) RR 0.88 (0.57, 1.34)	**-1.48** (-13.28, 12.54) RR 0.98 (0.82, 1.17)	**-0.64** (-1.39, 0.12)	**-1.00** (-3.83, 1.83)
Reslizumab					**-18.82** (-20.93, 20.56) RR 0.11 (0.01, 1.98)	**-2.55** (-19.49, 19.18) RR 0.97 (0.74, 1.26)		
AK001						**2.54** (-27.11, 51.03) RR 1.03 (0.63, 1.69)	**-0.20** (-1.61, 1.21)	
Etokimab	**-1.30** (-8.99 to 6.40)					**188.14** (-59.76, 4879.1) RR 3.55 (0.19, 67.13)	**-0.33** (-1.58, 0.92)	
ASA Desensitization	**-10.61** (-14.51, -6.71)	**-2.74** (-3.92, -1.57)	**2.72** (-1.17, 6.61)		**-16.00** (-19.79, 0.21) RR 0.24 (0.06, 1.01)	**209.21** (8.30, 901.87) RR 3.84 (1.11, 13.22)	**-0.95** (-2.44, 0.55)	**-0.31** (-3.50, 2.88)

Classification of intervention (colour)[24]				Certainty (shading)[24, 29]
Among most beneficial	Among intermediate beneficial	Among least beneficial/not clearly different from placebo	No data (blank)	High/moderate (solid)
Among most harmful	Among intermediate harmful			Low/very low (shaded)

In conclusion,
Multiple biologics and ASA-D credibly improve patient-important outcomes, with clinically important differences in effects among agents; dupilumab uniquely ranks among the most beneficial for all outcomes studied.

50세 남자 천식으로 치료

-Ex-smoker (21세 끊음)
-Sinusitis s/p ESS (2016)
-Chronic sinusitis with NP



2주후

스테로이드 다 끊었고, 지금 너무 편하다. 냄새도 맡을 수 있다.

듀피젠트® 허가 사항 - 천식

제품명	듀피젠트® 프리필드주 300밀리그램 (두필루맙,유전자재조합) 듀피젠트® 프리필드주 200밀리그램 (두필루맙,유전자재조합)
주성분 및 함량	두필루맙 (Dupilumab) 300 mg / 주 두필루맙 (Dupilumab) 200 mg / 주
효능효과 (천식)	**성인(만 18세 이상) 및 청소년(만 12-만 17세)에서 기존 치료에 적절하게 조절되지 않는 중증 천식으로 다음 중 하나에 해당하는 제2형 염증성 천식의 추가 유지 치료** 1) 중증 호산구성 천식(혈중 호산구 ≥150/㎕ 또는 호기산화질소(FeNO) ≥25 ppb) 2) 경구 코르티코스테로이드 의존성의 중증 천식
용법•용량 (천식)	이 약은 다음의 한 가지 방법으로 피하 투여한다. • 초회 용량으로 400 mg(200 mg을 다른 투여부위로 연속 2회 투여) 투여 후 유지 용량으로 **200 mg을 2주 간격**으로 투여 혹은 • 초회 용량으로 600 mg(300 mg을 다른 투여부위로 연속 2회 투여) 투여 후 유지 용량으로 **300 mg을 2주 간격**으로 투여 혹은 • 경구 코르티코스테로이드 의존성이 있거나 중등도에서 중증 아토피 피부염을 동반하고 있는 경우 초회 용량으로 600 mg(300 mg을 다른 투여부위로 연속 2회 투여) 투여 후 유지 용량으로 **300 mg을 2주 간격**으로 투여

1. 듀피젠트 300 mg 국내 허가사항 https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetail?itemSeq=201801406 (as of 2022-03-25)
2. 듀피젠트 200mg 국내 허가사항 https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetail?itemSeq=202003302 (as of 2022-03-25)