Recent Clinical Trials of Asthma

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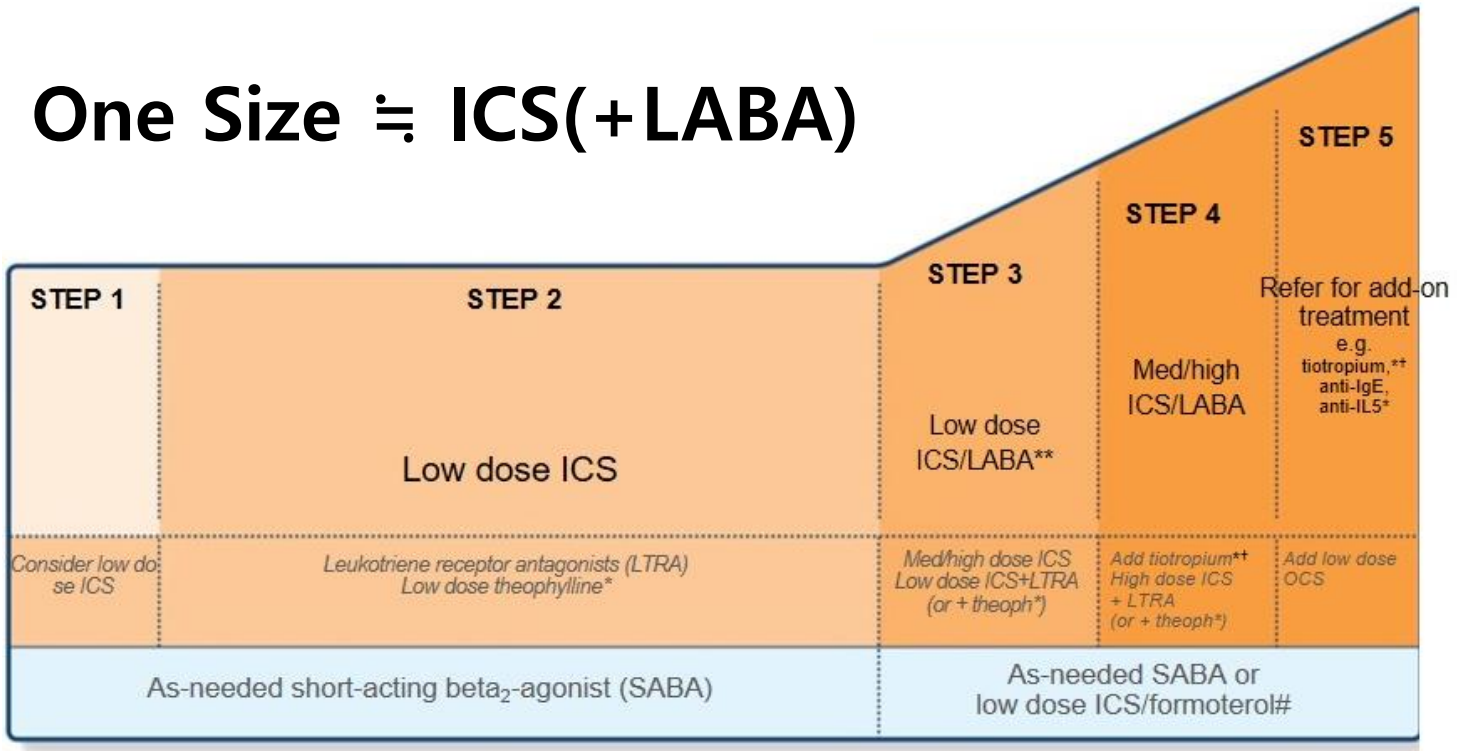
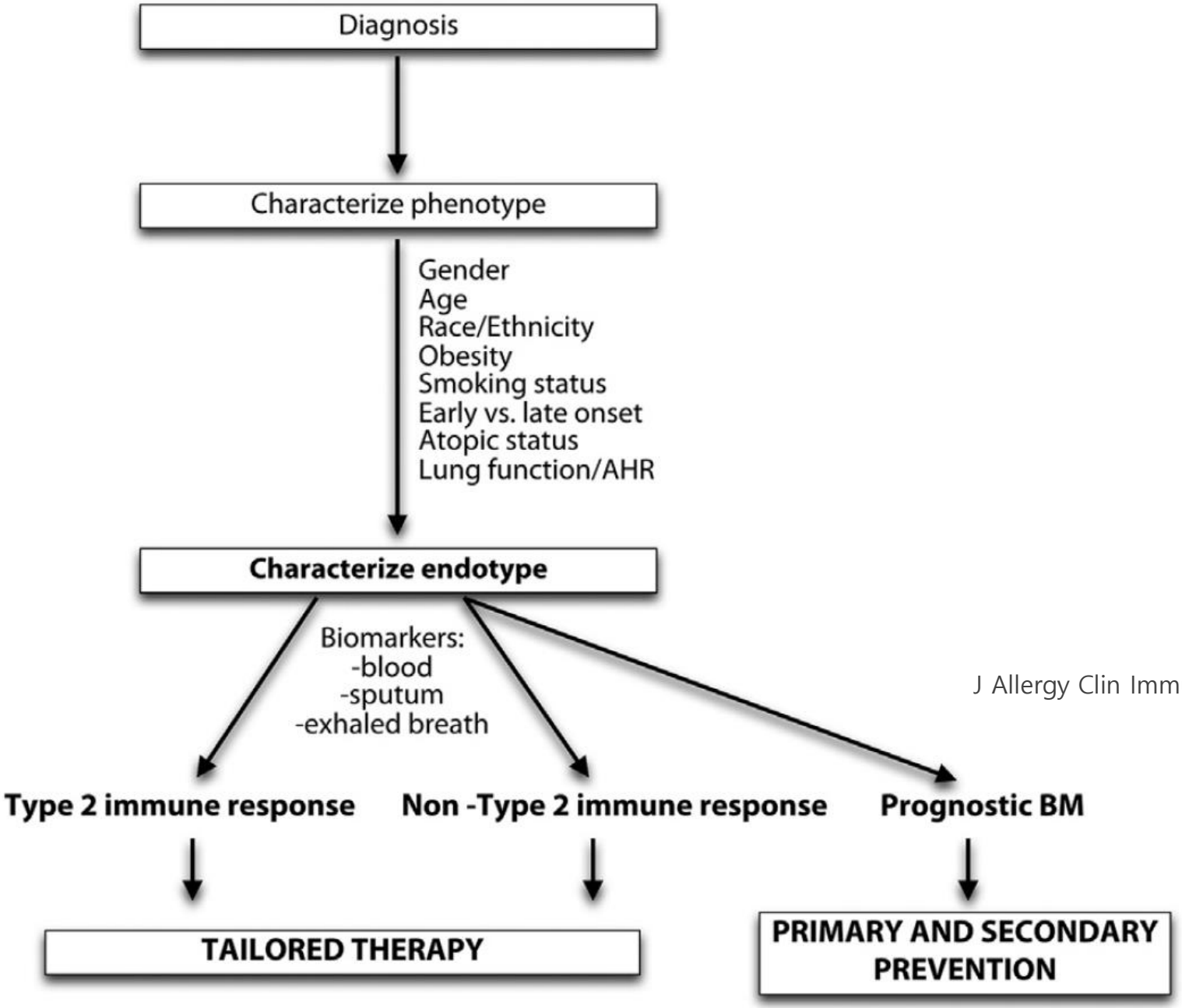
One Size Fits All?

One Size ≒ ICS(+LABA)

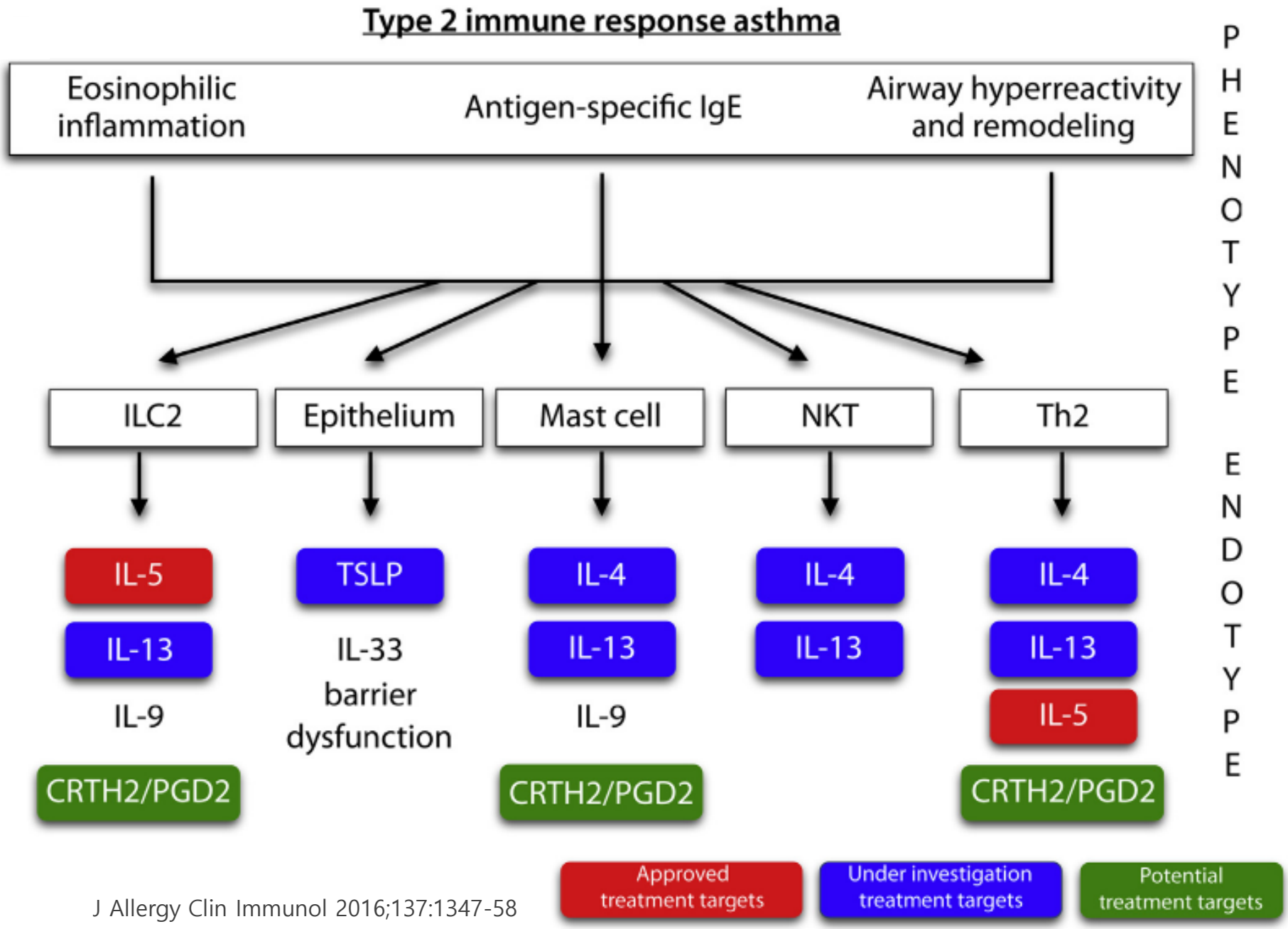


Strategy is NOT "One Size Fits All."

Phenotypes → Endotypes → (Genotypes)



J Allergy Clin Immunol 2016;137:1347-58



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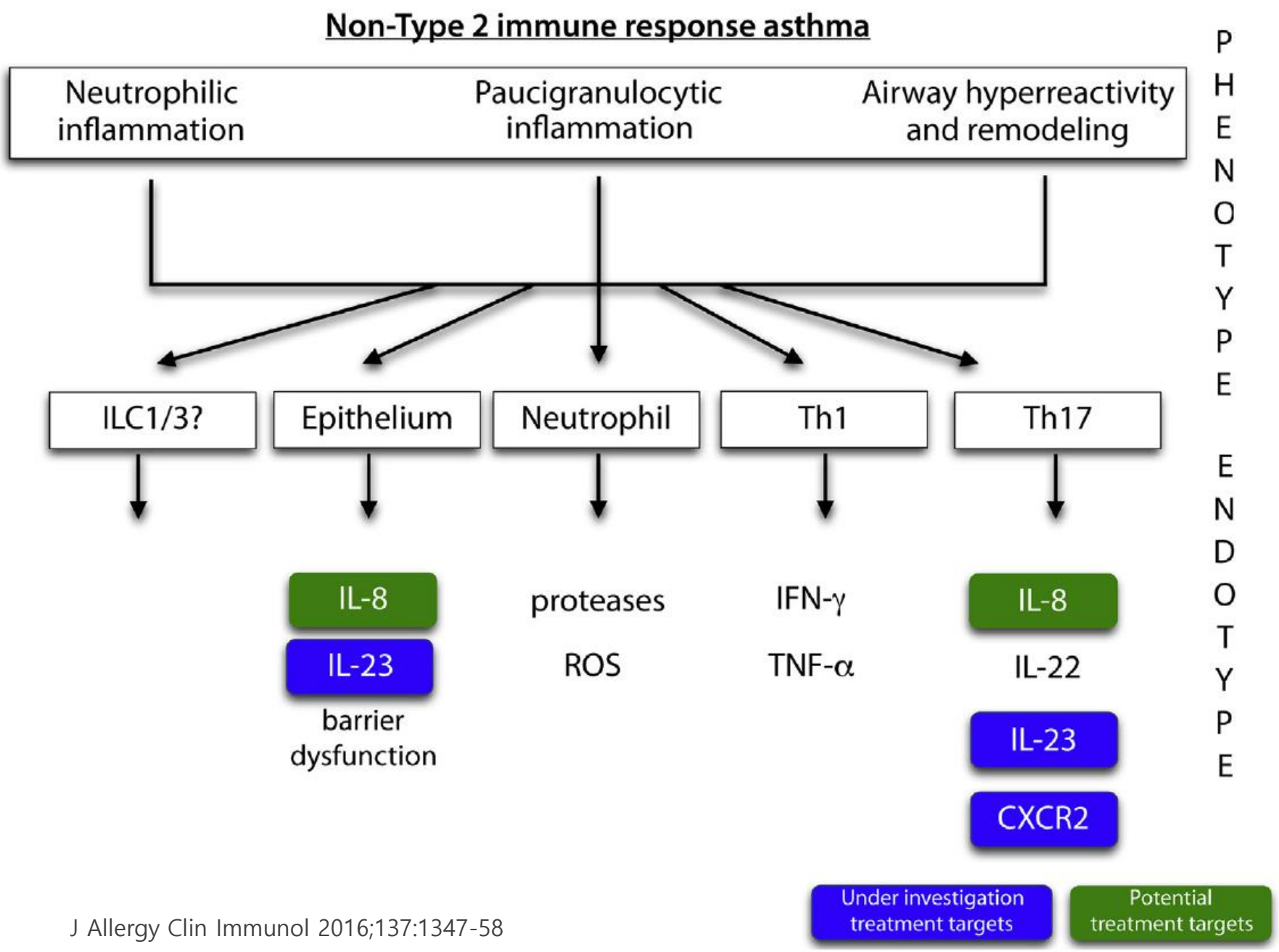


J Allergy Clin Immunol 2016;137:1347-58

Mepolizumab

Nucala®, 100 mg SQ q4w (2015)

DREAM Lancet 2012, 75/250/750 IV, 52 weeks

MENSA NEJM 2014, 75 IV/**100 SQ**, 32 weeks

SIRIUS NEJM 2014, **100 mg, q4w SQ**, 20 weeks

Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies

Hector G Ortega, Steven W Yancey, Bhabita Mayer, Necdet B Gunsoy, Oliver N Keene, Eugene R Bleecker, Christopher E Brightling, Ian D Pavord

Lancet Respir Med 2016;4:549-56

Summary

Background Findings from previous studies showed that mepolizumab significantly reduces the rate of exacerbations in patients with severe eosinophilic asthma. To assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab we did a secondary analysis of data from two studies, stratifying patients by different baseline blood eosinophil thresholds.

	DREAM (n=616)		MENSA (n=569)		Combined* (n=1185)	
	Placebo (n=155)	Mepolizumab (n=461)	Placebo (n=189)	Mepolizumab (n=380)	Placebo (n=344)	Mepolizumab (n=841)
≥150 cells per µL						
n (%)	121 (78%)	346 (75%)	157 (83%)	296 (78%)	278 (81%)	642 (76%)
Exacerbation rate per year	2·47	1·13	1·65	0·78	1·94	0·92
Rate ratio vs placebo (95% CI)	..	0·46 (0·35–0·60)	..	0·47 (0·35–0·63)	..	0·48 (0·39–0·58)
≥300 cells per µL						
n (%)	86 (55%)	216 (47%)	106 (56%)	202 (53%)	192 (56%)	418 (50%)
Exacerbation rate per year	2·66	1·11	1·98	0·78	2·19	0·89
Rate ratio vs placebo (95% CI)	..	0·42 (0·31–0·56)	..	0·39 (0·28–0·55)	..	0·41 (0·33–0·51)
≥400 cells per µL						
n (%)	64 (41%)	149 (32%)	87 (46%)	161 (42%)	151 (44%)	310 (37%)
Exacerbation rate per year	3·12	1·03	2·06	0·66	2·36	0·81
Rate ratio vs placebo (95% CI)	..	0·32 (0·23–0·46)	..	0·32 (0·22–0·46)	..	0·34 (0·27–0·44)
≥500 cells per µL						
n (%)	50 (32%)	114 (25%)	66 (35%)	124 (33%)	116 (34%)	238 (28%)
Exacerbation rate per year	3·34	0·92	2·11	0·58	2·49	0·75
Rate ratio vs placebo (95% CI)	..	0·27 (0·19–0·39)	..	0·27 (0·18–0·41)	..	0·30 (0·23–0·40)

52%

59%

66%

70%

Overall rate of mean exacerbations per person per year

- 1.91(placebo) → 1.91(mepolizumab): [RR] 0.53 (95% CI 0.44-0.62) **47%**

Lancet Respir Med 2016;4:549-56

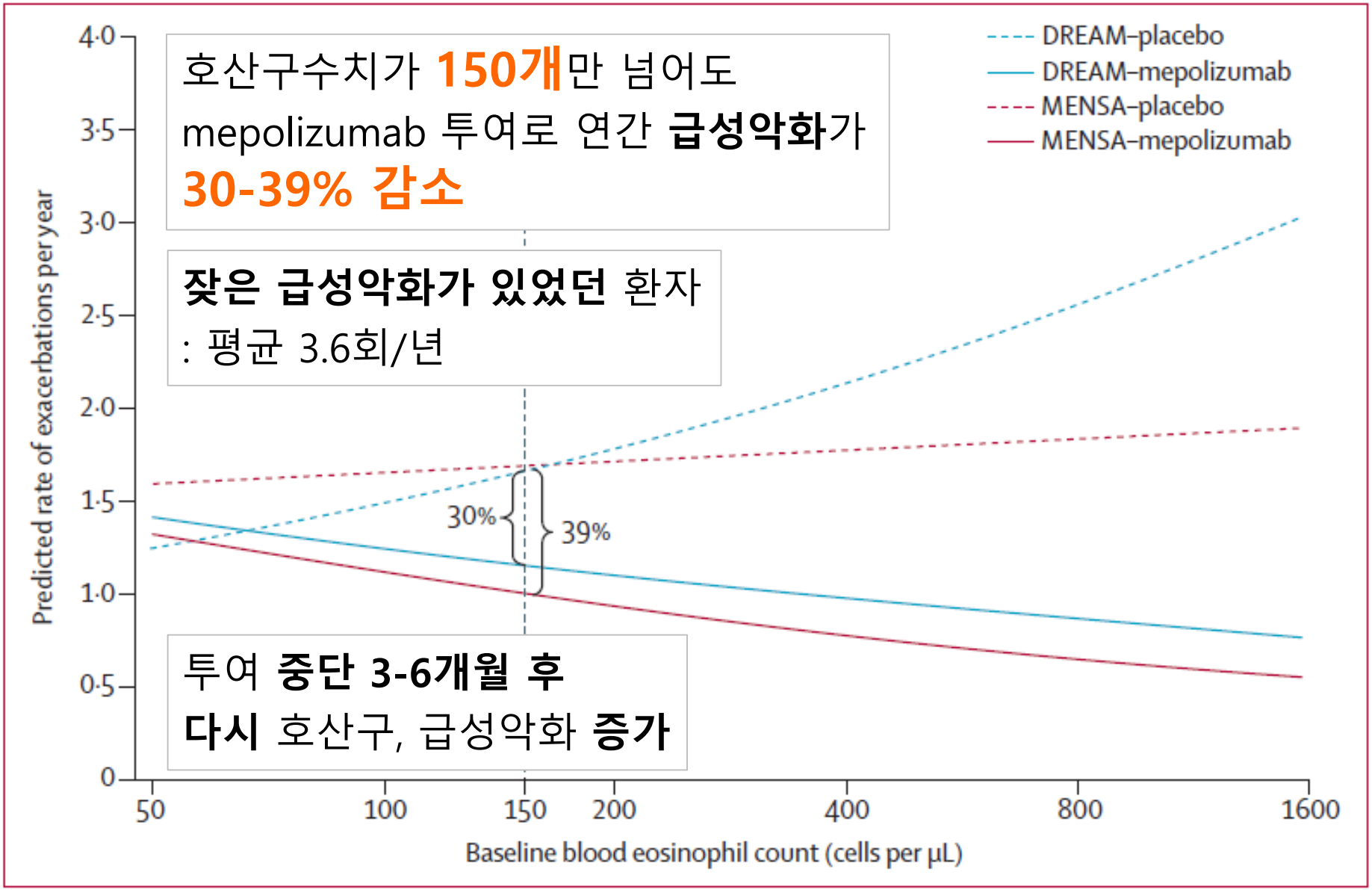


Figure: Predicted rate of clinically significant exacerbations per year against baseline blood eosinophil counts

Lancet Respir Med 2016;4:549-56

Outcome	Placebo (N = 66)	Mepolizumab (N = 69)	Odds Ratio (95% CI)*	P Value
Reduction in oral glucocorticoid dose at 20 to 24 wk: primary outcome — no. (%)†			2.39 (1.25–4.56)	0.008
90 to 100%	7 (11)	16 (23)		
75 to <90%	5 (8)	12 (17)		
50 to <75%	10 (15)	9 (13)		
>0 to <50%	7 (11)	7 (10)		
No decrease in oral glucocorticoid dose, a lack of asthma control, or withdrawal from treatment	37 (56)	25 (36)		
Secondary outcomes				
Reduction in daily oral glucocorticoid dose of ≥50% — no. (%)‡	22 (33)	37 (54)	2.26 (1.10–4.65)	0.03
Reduction in daily oral glucocorticoid dose to a level ≤5 mg — no. (%)‡	21 (32)	37 (54)	2.45 (1.12– 5.37)	0.02
Reduction of 100% in oral glucocorticoid dose — no. (%)‡	5 (8)	10 (14)	1.67 (0.49–5.75)	0.41
Median percent reduction from baseline in daily oral glucocorticoid dose (95% CI)§	0.0 (–20.0 to 33.3)	50.0 (20.0 to 75.0)	NA	0.007

Mepolizumab에 의한 OCS 용량 감소는 위약보다 **2.39배** 높다.

평균적으로 OCS 처음 사용량의 **50% 감소**

SIRIUS study

N Engl J Med 2014;371:1189-97

Reslizumab

Cinqair®, 3 mg/kg IV q4w (2016)

BREATH Lancet Respir Med 2015, **3 mg/kg IV**, 52 weeks

Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials

Mario Castro, James Zangrilli, Michael E Wechsler, Eric D Bateman, Guy G Brusselle, Philip Bardin, Kevin Murphy, Jorge F Maspero, Christopher O'Brien, Stephanie Korn

Summary

Background Elevated numbers of blood eosinophils are a risk factor for asthma exacerbations. Reslizumab is a humanised anti-interleukin 5 monoclonal antibody that disrupts eosinophil maturation and promotes programmed cell death. We aimed to assess the efficacy and safety of reslizumab in patients with inadequately controlled, moderate-to-severe asthma.

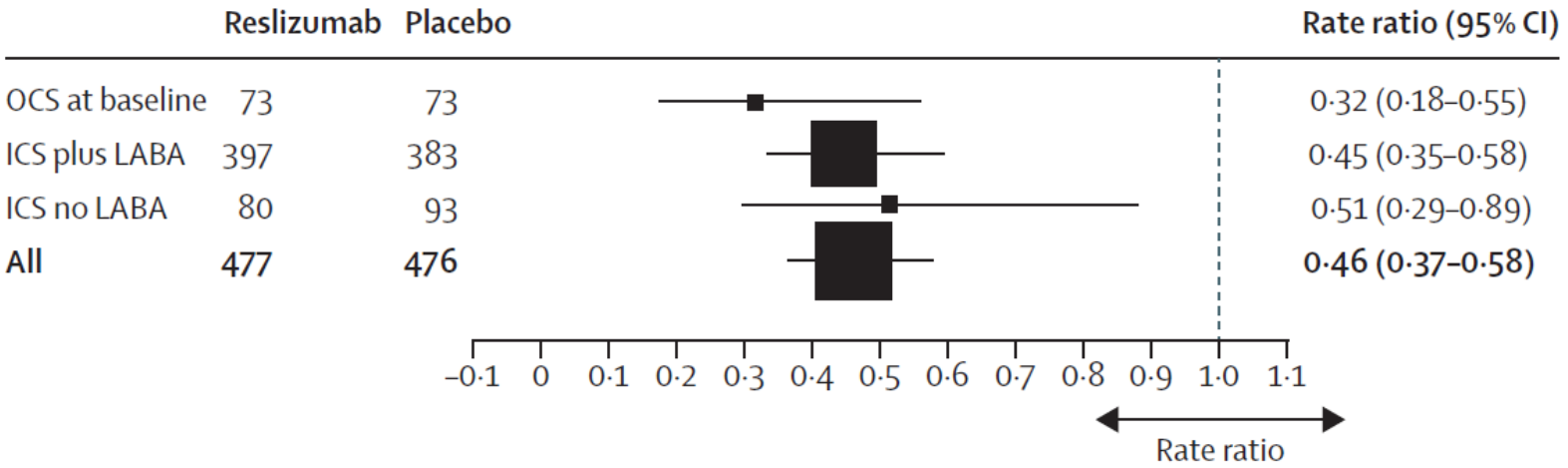
Methods We did two duplicate, multicentre, double-blind, parallel-group, randomised, placebo-controlled phase 3 trials. Both trials enrolled patients with asthma aged 12–75 years (from 128 clinical research centres in study 1 and 104 centres

	Study 1 (Study 3082)				Study 2 (Study 3083)				Pooled data			
	Placebo (n=244)	Reslizumab (n=245)	Rate ratio (95% CI)*	p value	Placebo (n=232)	Reslizumab (n=232)	Rate ratio (95% CI)*	p value	Placebo (n=476)	Reslizumab (n=477)	Rate ratio (95% CI)*	p value
Primary endpoint												
Frequency of CAEs												
Patients with ≥1 CAE	132 (54%)	92 (38%)	..	..	105 (45%)	59 (25%)	..	..	237 (50%)	151 (32%)	..	..
Adjudicated CAE rate (events per patient per year)												
All episodes	1·80	0·90	0·50 (0·37 to 0·67)	<0·0001	2·11	0·86	0·41 (0·28 to 0·59)	<0·0001	1·81	0·84	0·46 (0·37 to 0·58)	<0·0001
Episodes requiring systemic corticosteroids for ≥3 days	1·60	0·72	0·45 (0·33 to 0·62)	<0·0001	1·66	0·65	0·39 (0·26 to 0·58)	<0·0001	1·54	0·66	0·43 (0·33 to 0·55)	<0·0001
Episodes requiring hospital admission or ER treatment	0·21	0·14	0·66 (0·32 to 1·36)	0·257	0·05	0·03	0·69 (0·29 to 1·65)	0·402	0·12	0·077	0·66 (0·38 to 1·16)	0·510

50% 감소

59% 감소

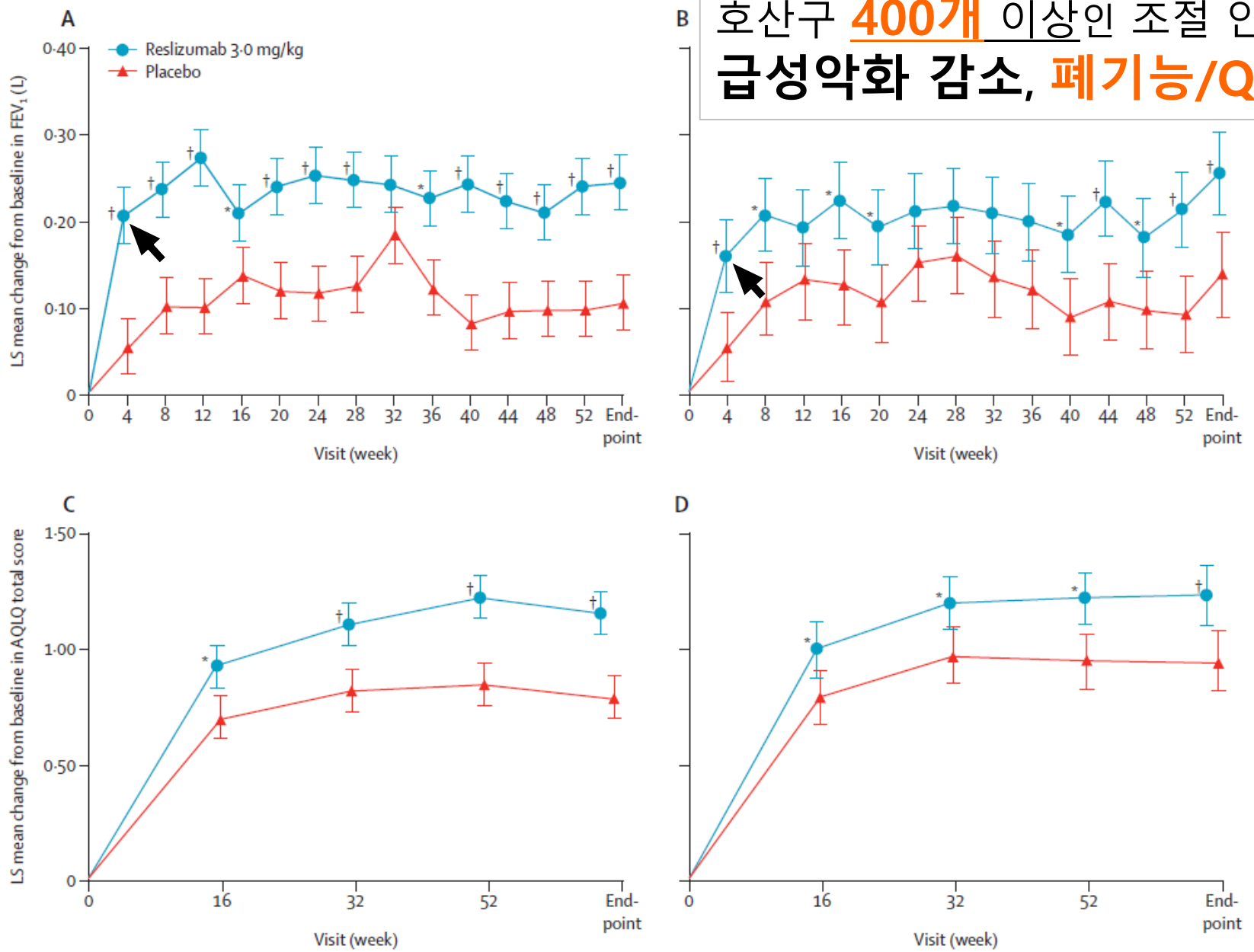
Annual rate of Clinical Asthma Exacerbation : 57% 감소



Major background treatment에 상관없이 CAE 감소

Lancet Respir Med 2015;3:355-66

호산구 **400개** 이상인 조절 안된 천식의
급성악화 감소, 폐기능/QOL 증가



Lancet Respir Med 2015;3:355-66

Benralizumab

Fasenra®, 30 mg SQ q4→8w (2017)

CALIMA Lancet 2016, 30 mg q4w/8w SQ, 56 weeks

SIROCCO Lancet 2016, 30 mg q4w/8w SQ, 56 weeks

ZONDA NEJM 2017, 30 mg q4w/8w SQ, 28 weeks

Depletion of **EOSINOPHILS**

Mepolizumab: humanized monoclonal antibody against **IL-5**

Reslizumab: humanized monoclonal antibody against **IL-5**

Benralizumab: humanized anti-**IL-5 receptor α** monoclonal Ab

→ antibody-dependent cell-mediated cytotoxicity
eosinophil apoptosis by natural killer cells

Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial

*J Mark FitzGerald, Eugene R Bleecker, Parameswaran Nair, Stephanie Korn, Ken Ohta, Marek Lommatzsch, Gary T Ferguson, William W Busse, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Viktoria Werkström, Magnus Aurivillius, Mitchell Goldman, on behalf of the CALIMA study investigators**

Severe asthma uncontrolled by **high-dose ICS** plus LABA

Baseline blood eosinophils **300 cells per μL or greater**

Two or more asthma exacerbations in the 12 months before

Pre-bronchodilator **FEV_1 of less than 80%**

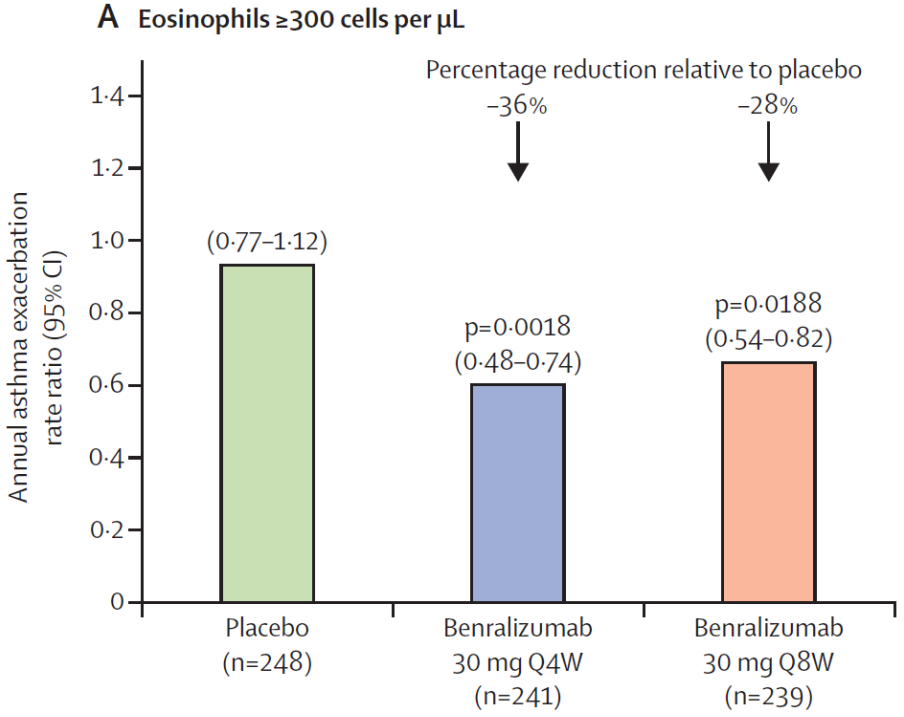
Q4W: benralizumab 30 mg once every 4 weeks

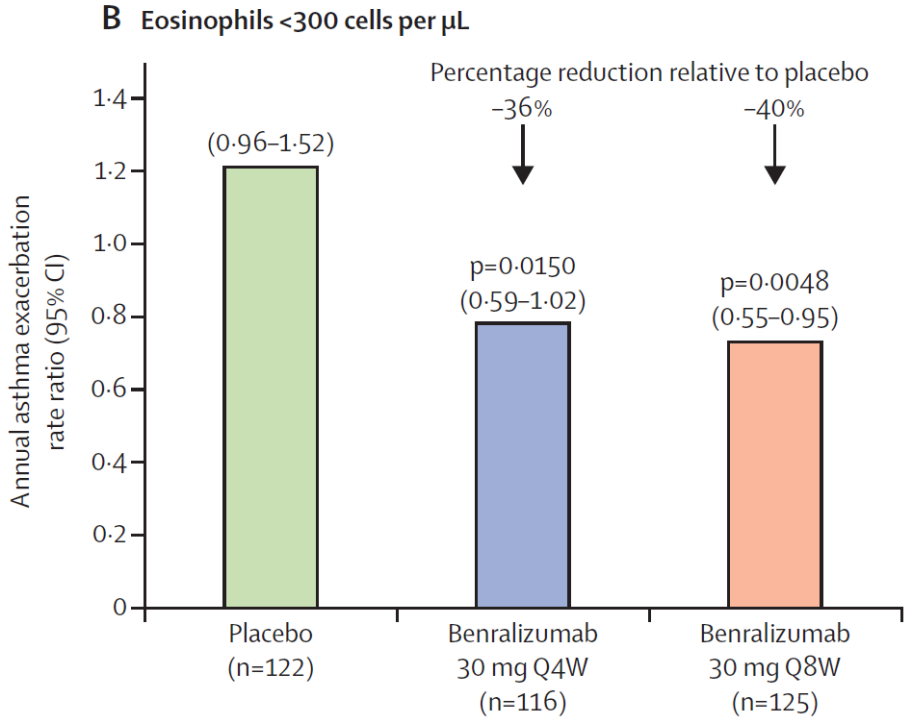
Q8W: once every 4 weeks for the first three doses → once every 8 weeks for the remainder of the treatment period

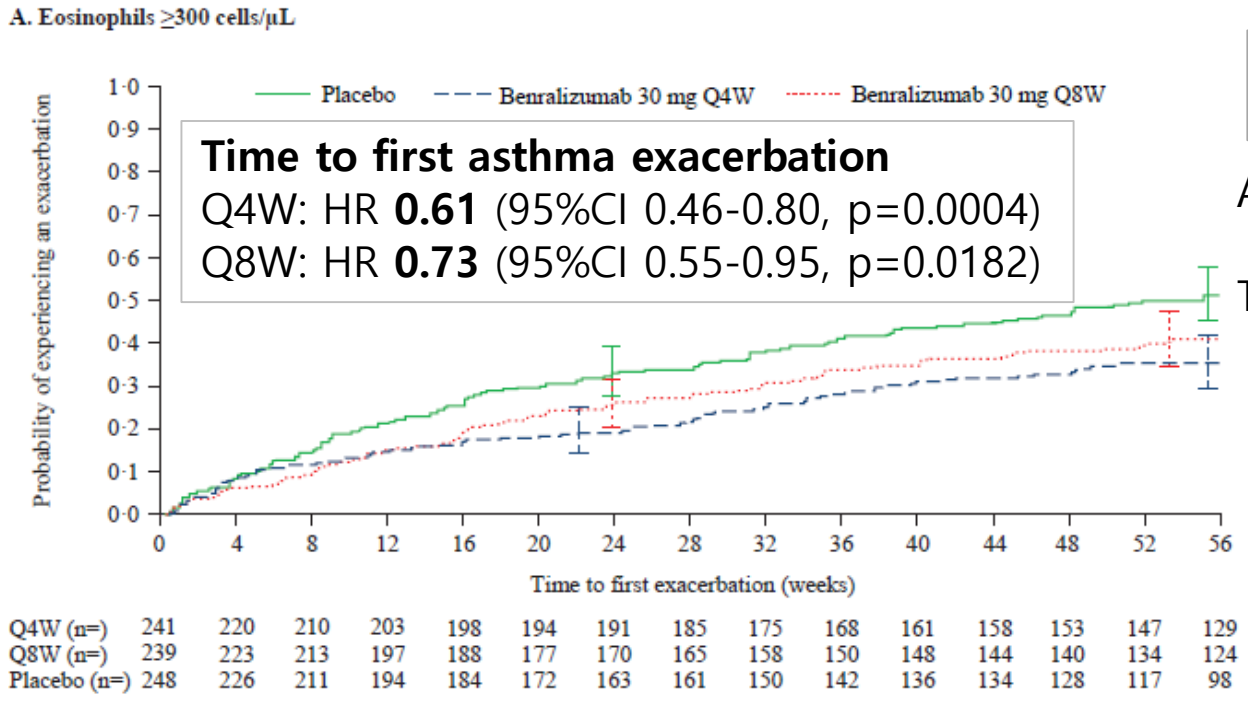
Lancet 2016;388:2128-41

	All patients (n=1306)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL (n=728)			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per µL (n=363)		
	Placebo (n=440)	Benralizumab 30 mg Q4W (n=425)	Benralizumab 30 mg Q8W (n=441)	Placebo (n=248)	Benralizumab 30 mg Q4W (n=241)	Benralizumab 30 mg Q8W (n=239)	Placebo (n=122)	Benralizumab 30 mg Q4W (n=116)	Benralizumab 30 mg Q8W (n=125)
Age (years)	48·8 (15·1)	50·0 (13·6)	49·0 (14·3)	48·5 (14·1)	50·1 (13·1)	49·6 (13·0)	52·4 (14·4)	51·9 (12·2)	51·1 (13·8)
Local eosinophil count (cells per µL)†	371 (0–4494)	370 (20–2420)	400 (0–2600)	510 (300–4494)	500 (300–2420)	500 (300–2600)	190 (0–298)	160 (20–293)	180 (0–295)
Missing data	7	7	6	1	4	3	2	0	2
Central eosinophil count (cells per µL)†	370 (0–4150)	350 (0–2800)	350 (0–2260)	490 (30–4150)	470 (0–2800)	475 (10–2260)	170 (0–700)	150 (10–880)	140 (0–440)
Missing data	11	9	9	8	4	5	3	5	2
Prebronchodilator FEV_1 (L)†	1·771 (0·645)	1·757 (0·602)	1·759 (0·641)	1·815 0·648)	1·75 (0·570)	1·758 (0·622)	1·639 (0·615)	1·717 (0·626)	1·665 (0·616)
Missing data	6	5	1	3	2	0	3	2	1
Prebronchodilator FEV_1 (% predicted normal)†	58·0% (14·9)	58·9% (14·8)	57·9% (14·9)	58·2% (13·9)	59·1% (13·7)	57·0% (14·2)	56·1% (16·3)	57·4% (16·2)	56·7% (15·2)
Missing data	6	5	1	3	2	0	3	2	1
Number of exacerbations in the past 12 months	2·7 (1·6)	2·7 (1·9)	2·7 (1·4)	2·8 (1·7)	2·8 (1·7)	2·7 (1·3)	2·7 (1·9)	2·6 (1·6)	2·7 (1·7)
Number resulting in emergency department visit	0·3 (1.2)	0·3 (0·8)	0·2 (0.7)	0·4 (1·4)	0·3 (0·9)	0·2 (0·6)	0·2 (0·8)	0·2 (0·5)	0·2 (0·6)
Patients with ≥1 exacerbations resulting in emergency department visit	62 (14%)	60 (14%)	56 (13%)	36 (15%)	35 (15%)	31 (13%)	18 (15%)	15 (13%)	13 (10%)
Number resulting in hospital admission	0·3 (0·8)	0·2 (0·5)	0·3 (0·7)	0·3 (0·7)	0·2 (0·5)	0·3 (0·6)	0·3 (1.0)	0·3 (0·6)	0·2 (0·6)
Patients with ≥1 exacerbations resulting in hospital admission	72 (16%)	65 (15%)	78 (18%)	44 (18%)	42 (17%)	43 (18%)	21 (17%)	20 (17%)	18 (14%)

Lancet 2016;388:2128-41





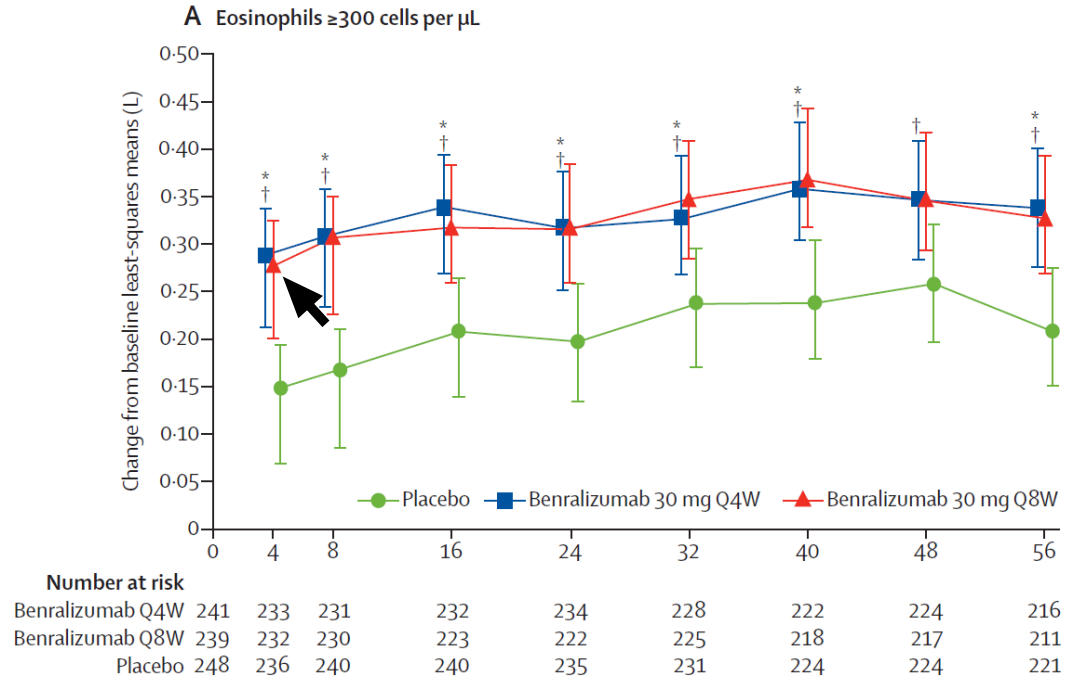


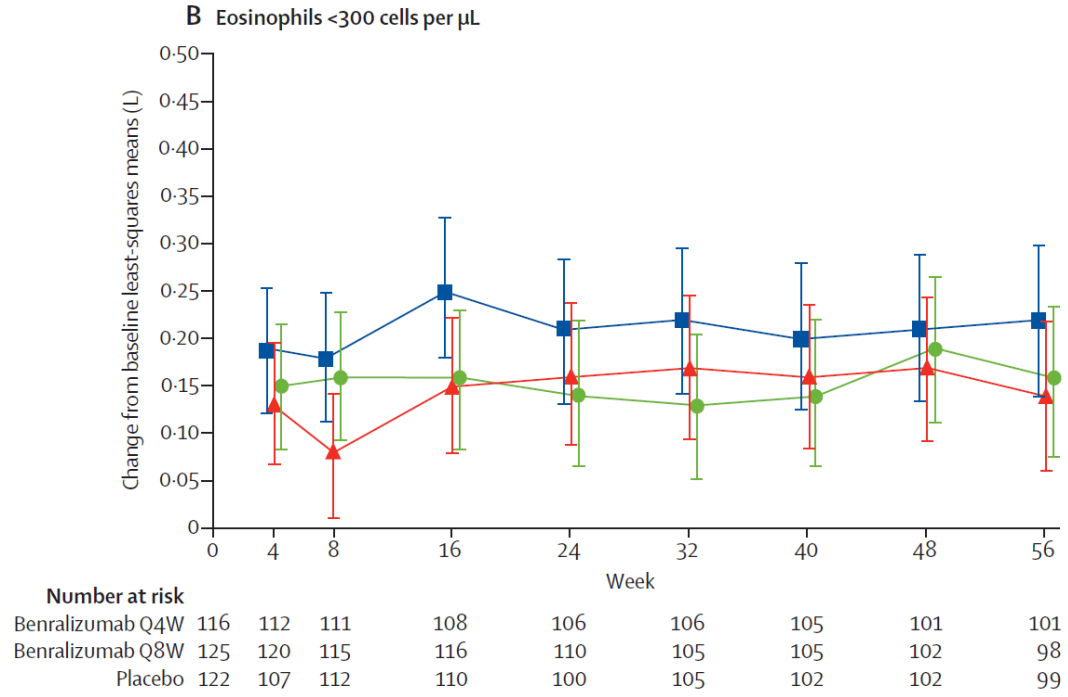
천식 급성악화

Annual exacerbation rates: **36%** ↓

Time to first exacerbation: **39%** ↓

Lancet 2016;388:2128-41





폐기능 개선

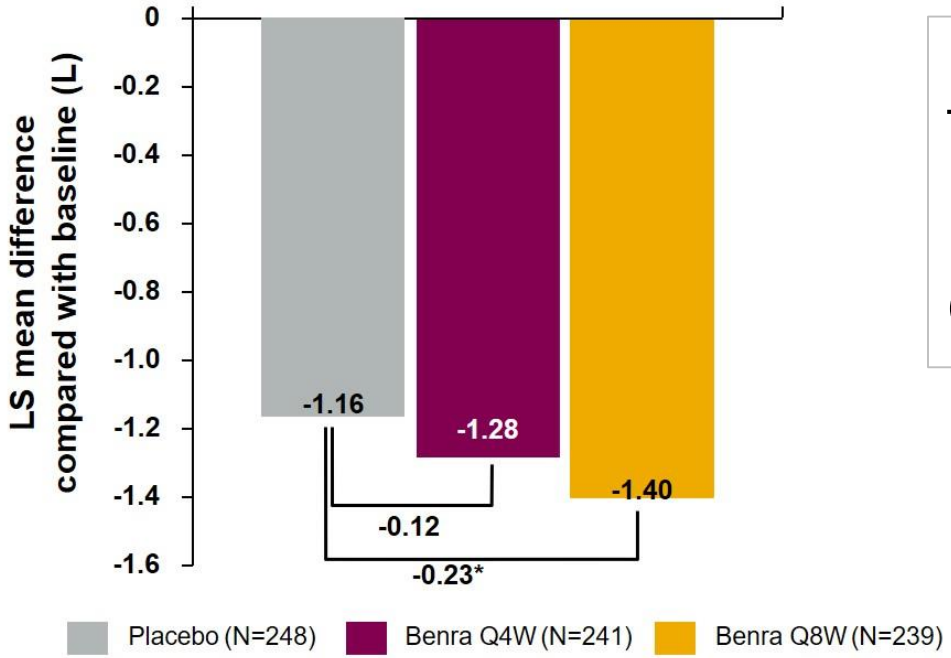
호산구 **300개** 이상인 경우,

4주부터 증가가 관찰되어

56주 치료기간 내내 지속

Lancet 2016;388:2128-41

	High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per µL		
	Placebo (n=248)	Benralizumab 30 mg Q4W (n=241)	Benralizumab 30 mg Q8W (n=239)	Placebo (n=122)	Benralizumab 30 mg Q4W (n=116)	Benralizumab 30 mg Q8W (n=125)
Total asthma symptom score†‡						
Number of patients analysed (baseline and at least one post-baseline assessment)	247	241	237	122	115	124
LS mean change§	−1·16; 187	−1·28; 184	−1·40; 185	−0·95; 89	−1·11; 88	−0·95; 85
LS mean difference *vs* placebo	..	−0·12 (−0·32 to 0·07)	−0·23 (−0·43 to −0·04)	..	−0·16 (−0·44 to 0·13)	0·01 (−0·28 to 0·29)
p value *vs* placebo	..	0·2241	0·0186		0·2868	0·9663



천식증상 점수

호산구 **300개** 이상인 경우,

Q8W에서 **의미 있는 개선 관찰**

Lancet 2016;388:2128-41

	High-dosage ICS/LABA + baseline blood eosinophils ≥300 cells/μL		
	Placebo (n=248)	Benralizumab 30 mg Q4W (n=241)	Benralizumab 30 mg Q8W (n=239)
Baseline blood eosinophil count (cells/μL)	470 (340–695); 248	470 (320–720); 241	480 (350–700); 239
Week 4 blood eosinophil count (cells/μL)	430 (290–620); 238	0 (0–10); 234	0 (0–10); 231–97·1%
LS mean change	7·9%	–96·2%	–105·0% (–115·1 to –95·0)
LS means difference *vs* placebo	–	–104·2% (–114·2 to –94·2)	<0·0001
P-value *vs* placebo	–	<0·0001	
Week 56 blood eosinophil count (cells/μL)	390 (265–570); 200	0 (0–10); 203	0 (0–10); 193
LS mean change	17·7%	–94·5%	–89·0%
LS means difference *vs* placebo	–	–112·3% (–155·0 to –69·5)	–106·8% (–149·7 to –63·9)
P-value *vs* placebo	–	<0·0001	<0·0001

High-dosage ICS/LABA + baseline blood eosinophils <300 cells/μL		
Placebo (n=122)	Benralizumab 30 mg Q4W (n=116)	Benralizumab 30 mg Q8W (n=125)
170 (110–240); 122	150 (95–230); 116	150 (90–230); 125
180 (120–270); 117	0 (0–10); 110	0 (0–10); 117
34·2%	–95·8%	–90·1%
–	–129·9% (–148·3 to –111·5)	–124·2% (–142·3 to –106·1)
–	<0·0001	<0·0001
180 (110–260); 95	0 (0–10); 85	0 (0–10); 84
229·5%	–98·3%	–100·1%
–	–327·8% (–635·1 to –20·5)	–329·6% (–636·6 to –22·7)
–	0·0366	0·0354

호산구 수치

치료 4주부터 감소

(470→ 0개)되어

56주 치료완료 때까지

감소되어 유지

Lancet 2016;388:2128-41 (Supplimentary Appendix)

	CALIMA		SIROCCO[28]	
	Benralizumab Q4W	Benralizumab Q8W	Benralizumab Q4W	Benralizumab Q8W
Annual rate of exacerbations	↓ 36%	↓ 28%	↓ 45%	↓ 51%
Prebronchodilator FEV_1 (L)	↑ 0·125	↑ 0·116	↑ 0·106	↑ 0·159
Total asthma symptom score (score 0–6)‡	↓ 0·12§	↓ 0·23	↓ 0·08§	↓ 0·25

FEV_1=forced expiratory volume in 1 s. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W). *See Bleecker and colleagues.[28] †All results are differences from placebo; week 56 results presented for CALIMA and week 48 results presented for SIROCCO. ‡Reduced score indicates improvement. §Non-significant.

***Table* 5: Efficacy results for patients receiving high-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per μL in the CALIMA and SIROCCO studies*†**

CALIMA: USA, Canada, Germany, Sweden, Poland, Romania, Ukraine, Argentina, Chile, Japan, Philippines / 2013.8.21- 2015.3.16

SIROCCO: Australia, Brazil, Bulgaria, Czech Republic, France, Italy, Mexico, Peru, Poland, Russia, South Africa, **South Korea**, Spain, Turkey, UK, USA, Vietnam / 2013.9.19- 2015.3.16

Lancet 2016;388:2128-41

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

Parameswaran Nair, M.D., Ph.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., Ph.D., Arnaud Bourdin, M.D., Ph.D., Njira L. Lugogo, M.D., Piotr Kuna, M.D., Ph.D., Peter Barker, Ph.D., Stephanie Sproule, M.Math., Sandhia Ponnarambil, M.D., and Mitchell Goldman, M.D., for the ZONDA Trial Investigators*

Medium to high-dose ICS + LABA for at least 12 months

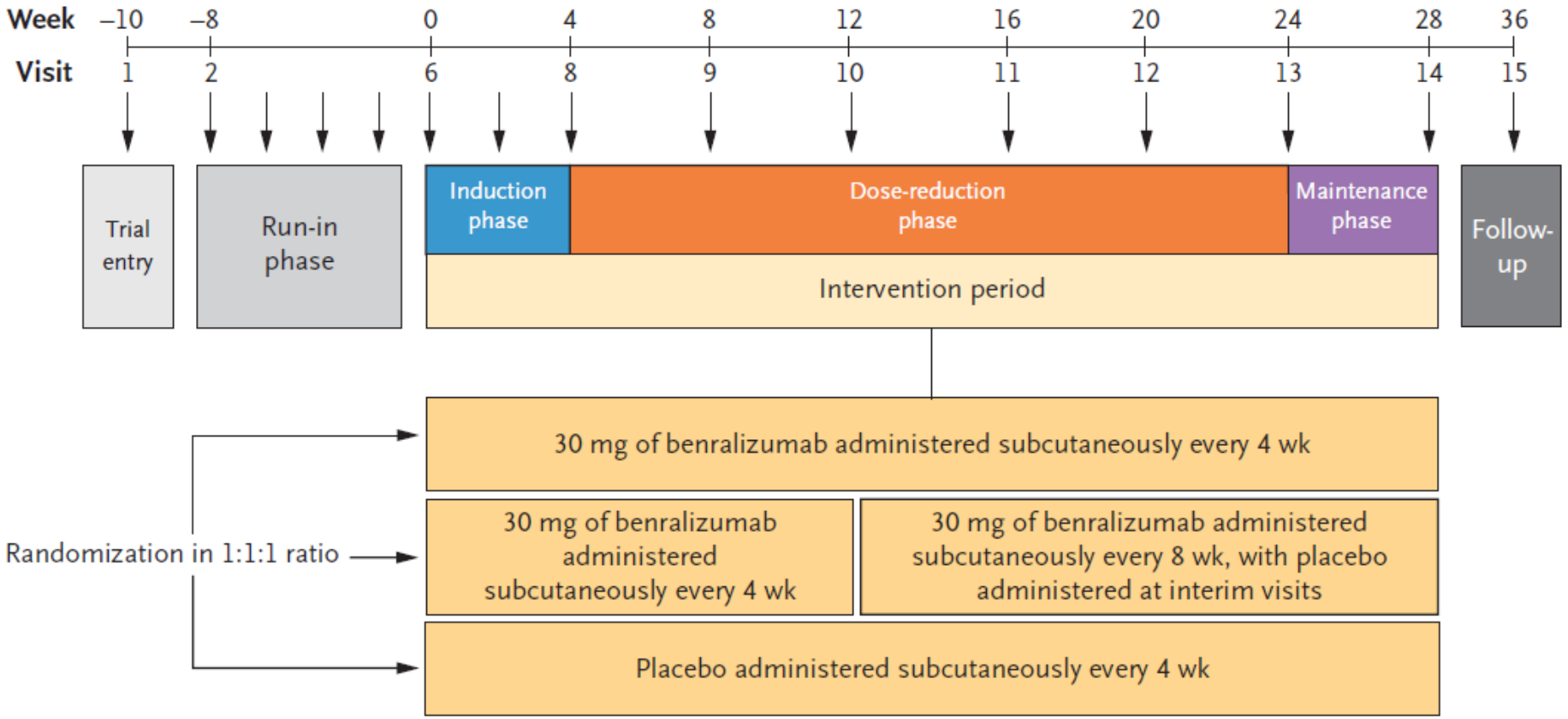
Chronic **OCS** therapy (**7.5–40 mg/day** of prednisolone/ prednisone equivalents) for **≥6 continuous months**

Baseline blood eosinophils **150 cells per μL or greater**

One or more asthma exacerbations in the 12 months before

Pre-bronchodilator **FEV_1 of less than 80%**

N Engl J Med 2017;376:2448-58



Optimization

2주마다 확인

OCS 감량: **2.5-5.0 mg/day**

Treatment period reduction

4주마다 확인/ 24주까지

OCS 감량: **2.5-5.0 mg/day**

ZONDA study

N Engl J Med 2017;376:2448-58

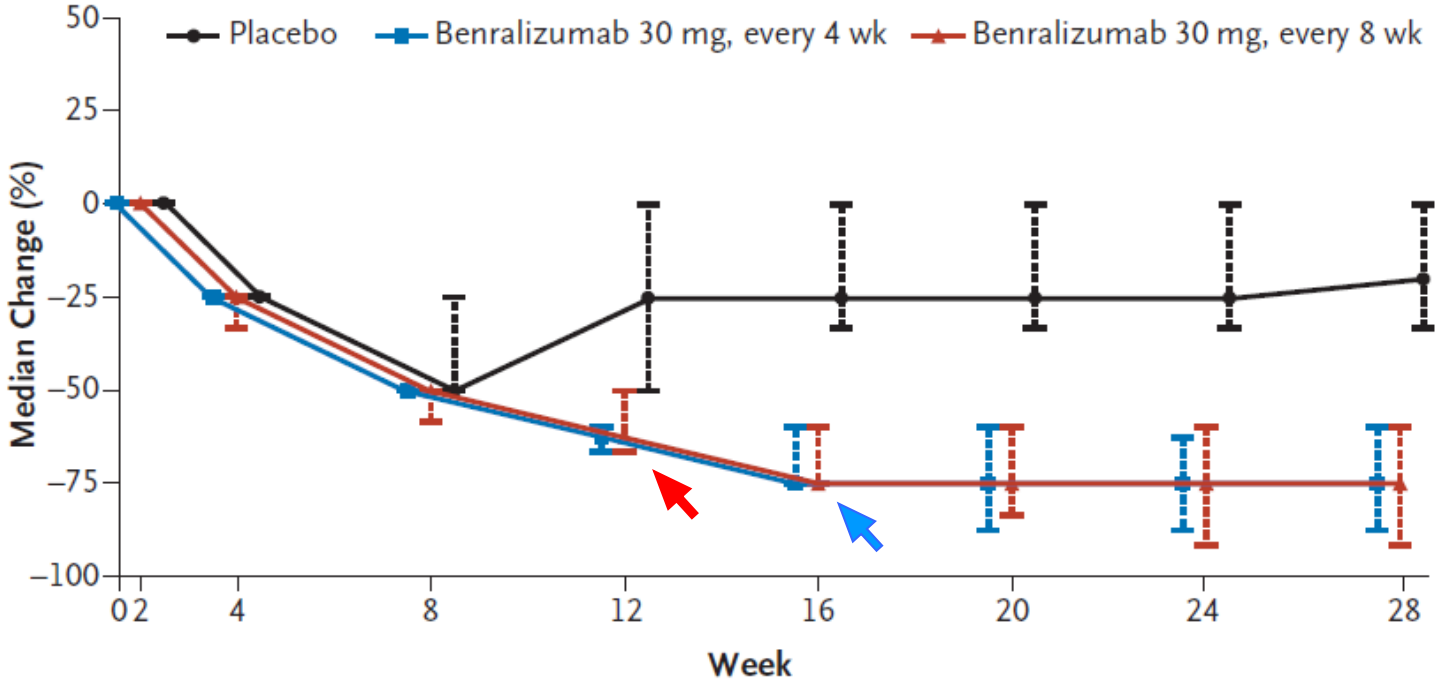
Outcome	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
Primary outcome			
Median oral glucocorticoid dose (range) — mg/day*			
At baseline	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
At final visit	10.0 (0.0 to 40.0)	5.0 (0.0 to 45.0)	5.0 (0.0 to 30.0)
Median reduction from baseline (range) — % of baseline value†	25.0 (–150 to 100)	75.0 (–100 to 100)	75.0 (–50 to 100)
P value†	—	<0.001	<0.001
Reduction from baseline in final oral glucocorticoid dose — no. (%)			
≥90%	9 (12)	24 (33)	27 (37)
≥75%	15 (20)	38 (53)	37 (51)
≥50%	28 (37)	48 (67)	48 (66)
>0%	40 (53)	55 (76)	58 (79)
Any increase or no change in dose	35 (47)	17 (24)	15 (21)
Analysis of percentage reduction from baseline in oral glucocorticoid dose			
Odds ratio (95% CI)	—	4.09 (2.22 to 7.57)	4.12 (2.22 to 7.63)
P value	—	<0.001	<0.001

* The baseline oral glucocorticoid dose was the daily dose at which the patient's asthma was stabilized at randomization (after the run-in phase), and the final oral glucocorticoid dose was the final daily dose at week 28.
† Negative values indicate an increase in the final oral glucocorticoid dose from baseline. The P values were calculated with the use of a Wilcoxon rank-sum test.

Benralizumab은 위약에 비하여
OCS 용량 감소가 4배 높다.

N Engl J Med 2017;376:2448-58

Change from Baseline in Oral Glucocorticoid Dose



No. at Risk

Benralizumab 30 mg, every 4 wk	72	70	70	69	69	68	66	68
Benralizumab 30 mg, every 8 wk	70	72	67	69	69	66	69	68
Placebo	74	75	73	74	74	73	73	72

Benralizumab사용으로
Q8W은 OCS 사용 **12주부터**
Q4W은 **16주부터** OCS 사용 용량의 감소

처음 사용량의 평균 **75% 감소**

N Engl J Med 2017;376:2448-58

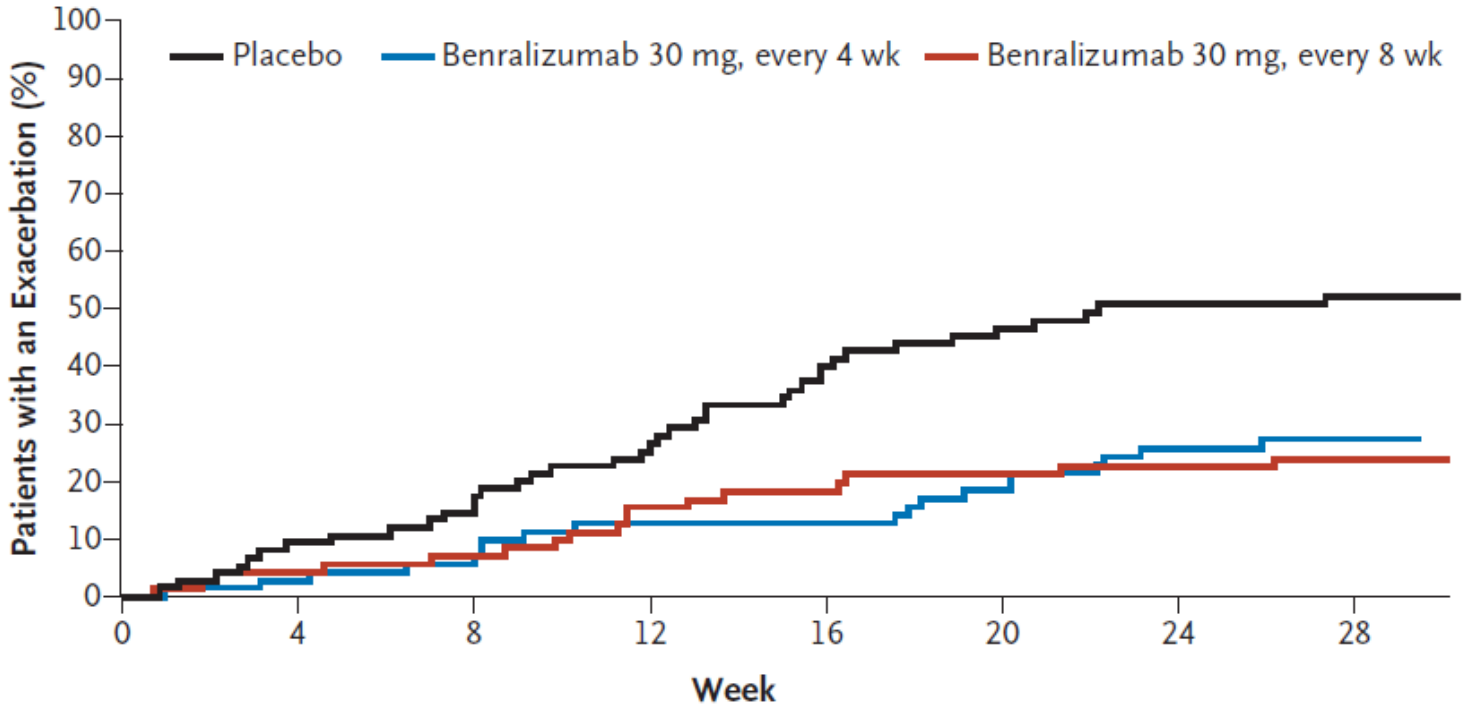
Outcome	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
Secondary outcomes			
Reduction from baseline in final oral glucocorticoid dose, according to percentage reduction			
100% Reduction — no./total no. (%)‡	8/42 (19)	22/39 (56)	22/42 (52)
Odds ratio (95% CI)	—	5.23 (1.92 to 14.21)	4.19 (1.58 to 11.12)
P value	—	<0.001	0.002
≥50% Reduction — no. (%)	28 (37)	48 (67)	48 (66)
Odds ratio (95% CI)	—	3.59 (1.79 to 7.22)	3.03 (1.57 to 5.86)
P value	—	<0.001	<0.001
≥25% Reduction — no. (%)	38 (51)	54 (75)	57 (78)
Odds ratio (95% CI)	—	2.89 (1.45 to 5.79)	3.25 (1.62 to 6.52)
P value	—	0.002	<0.001
Final oral glucocorticoid dose of ≤5.0 mg/day — no. (%)§	25 (33)	44 (61)	43 (59)
Odds ratio (95% CI)	—	3.16 (1.60 to 6.23)	2.74 (1.41 to 5.31)
P value	—	<0.001	0.002

‡ Patients with a baseline oral glucocorticoid dose of 12.5 mg or less per day at the end of the run-in phase were eligible for a 100% dose reduction (discontinuation of oral glucocorticoid therapy).
§ All the patients with a final oral glucocorticoid dose of 5.0 mg or less per day also had a reduction of at least 25% from baseline in the final oral glucocorticoid dose.

OCS **12.5 mg 이하 사용인 환자중**에서,
완전히 끊을 수 있는 환자: **52-56%**

N Engl J Med 2017;376:2448-58

Time to First Asthma Exacerbation



No. at Risk

Benralizumab 30 mg, every 4 wk	72	69	67	62	61	56	51	45
Benralizumab 30 mg, every 8 wk	73	68	66	60	58	56	55	51
Placebo	75	68	64	56	45	40	37	31

Benralizumab 사용으로

Q4W은 천식악화를 **78%**, Q8W은 **68%**를 감소시킴

N Engl J Med 2017;376:2448-58

Dupilumab

Human monoclonal antibody against **IL-4 receptor α subunit**
→ inhibits both **IL-4** and **IL-13** signaling

Dupixent®, Atopic dermatitis (2017)

Phase 2b

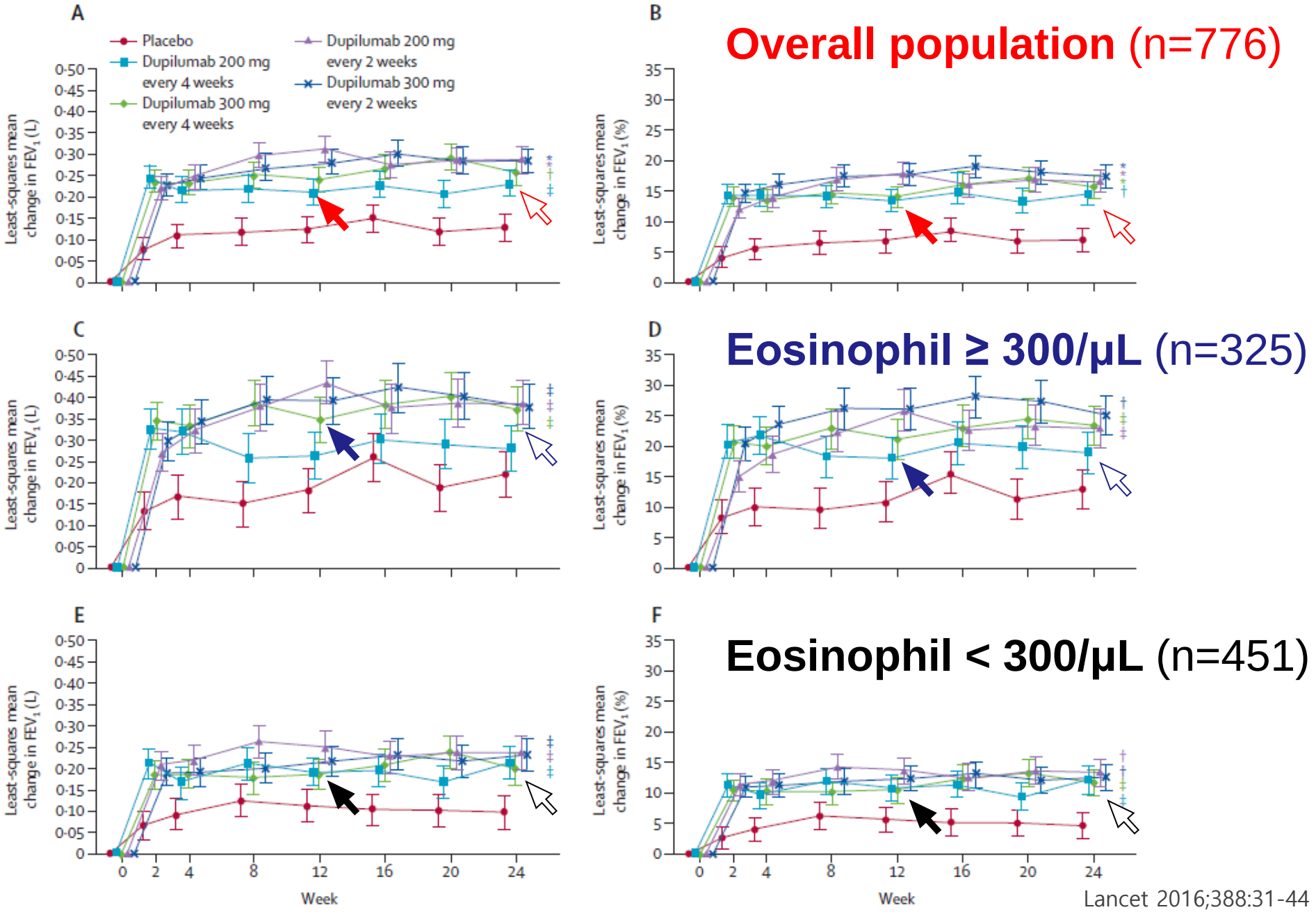
Lancet 2016, 200/**300 mg**, **Q2W**/4W SQ, 24 weeks

Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial

Sally Wenzel, Mario Castro, Jonathan Corren, Jorge Maspero, Lin Wang, Bingzhi Zhang, Gianluca Pirozzi, E Rand Sutherland, Robert R Evans, Vijay N Joish, Laurent Eckert, Neil M H Graham, Neil Stahl, George D Yancopoulos, Mariana Louis-Tisserand, Ariel Teper

Summary

Background Dupilumab, a fully human anti-interleukin-4 receptor α monoclonal antibody, inhibits interleukin-4 and interleukin-13 signalling, key drivers of type-2-mediated inflammation. Adults with uncontrolled persistent asthma who are receiving medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist require additional treatment options as add-on therapy. We aimed to assess the efficacy and safety of dupilumab as add-on therapy in patients with uncontrolled persistent asthma on medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist, irrespective of baseline eosinophil count.



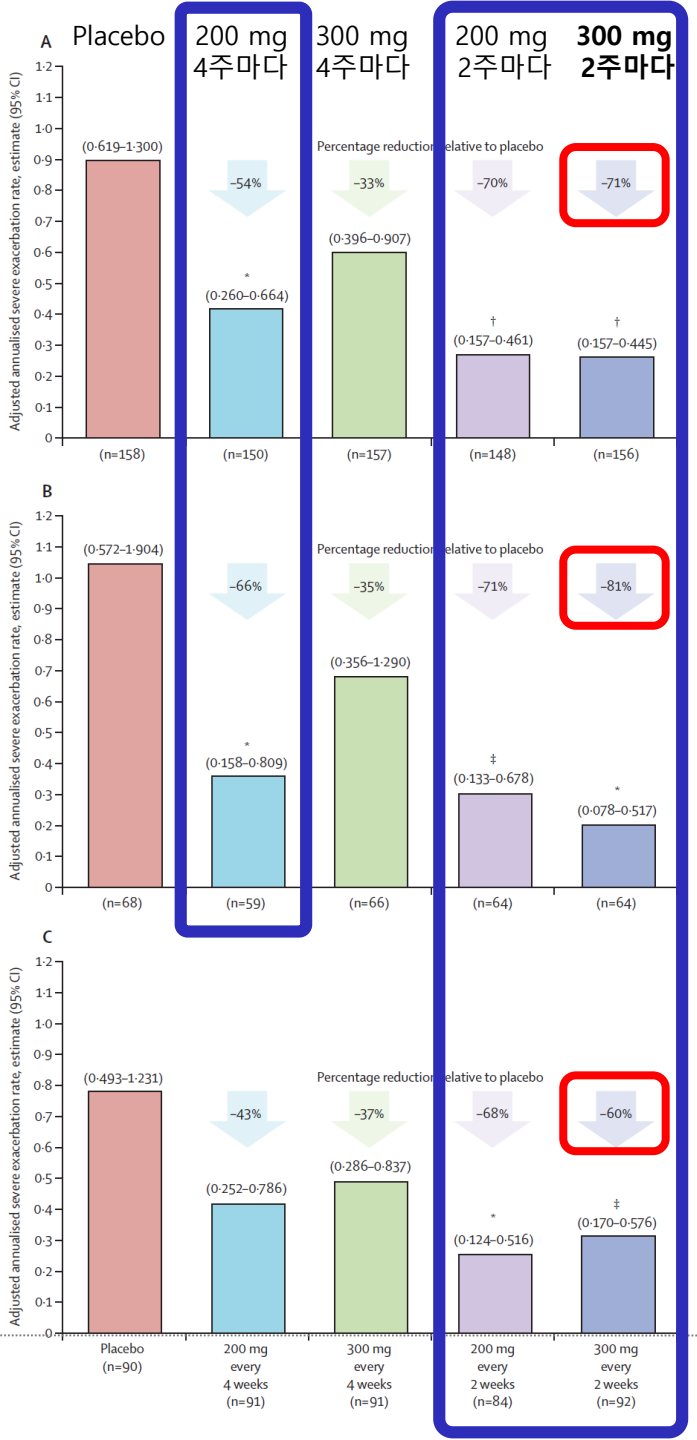
Overall population (n=776)

Eosinophil ≥ 300/μL (n=325)

Eosinophil < 300/μL (n=451)

Lancet 2016;388:31-44

1° endpoint: 12주 사용 후 **FEV_1** 변화, **Eos ≥ 300/μL**



Overall population

Eosinophil ≥ 300/μL

Eosinophil < 300/μL

Dupilumab는 medium-high dose ICS + LABA 사용으로 조절되지 않는 천식에 추가 사용하여 **폐기능의 개선**과 **급성악화 감소**

60-80% 감소

Lancet 2016;388:31-44

Tezepelumab

70/210 mg q4w, 280 mg q2w SQ

PATHWAY

N Engl J Med **2017**, 70/210 mg q4w, 280 mg q2w SQ, 52 weeks

TLSP: an epithelial-cell-derived cytokine

Tezepelumab: human IgG2 monoclonal antibody against TSLP

Tezepelumab in Adults with Uncontrolled Asthma

Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

Phase 2 trial

Uncontrolled by **medium or high-dose ICS** plus LABA

Two or more asthma exacerbations in the 6 months before

Pre-bronchodilator **FEV_1 of 40~80%**

Characteristic	Placebo (N=148)	Low-Dose Tezepelumab (N=145)	Medium-Dose Tezepelumab (N=145)	High-Dose Tezepelumab (N=146)	Total Tezepelumab (N=436)
Age — yr	52.2±11.5	50.6±12.4	52.6±12.5	50.1±12.2	51.1±12.4
Blood eosinophil count — cells/μl					
Mean	366±323	345±284	359±347	378±423	361±356
Median (range)	270 (0–1870)	270 (10–1600)	275 (0–3180)	255 (0–3990)	270 (0–3990)
Total serum IgE — IU/ml					
Mean	447±1232	314±870	464±1366	344±579	374±992
Median (range)	135 (4–11,860)	109 (2–7423)	135 (2–11,430)	138 (2–3814)	127 (2–11,430)
FENO					
No. of patients evaluated	146	144	143	141	428
Mean — ppb	36.3±38.9	34.5±46.9	30.4±29.4	32.6±33.9	32.5±37.5
Median (range) — ppb	21.5 (3.5–276.3)	22.0 (2.5–349.0)	20.5 (4.0–152.5)	19.7 (2.0–217.5)	21.0 (2.0–349.0)

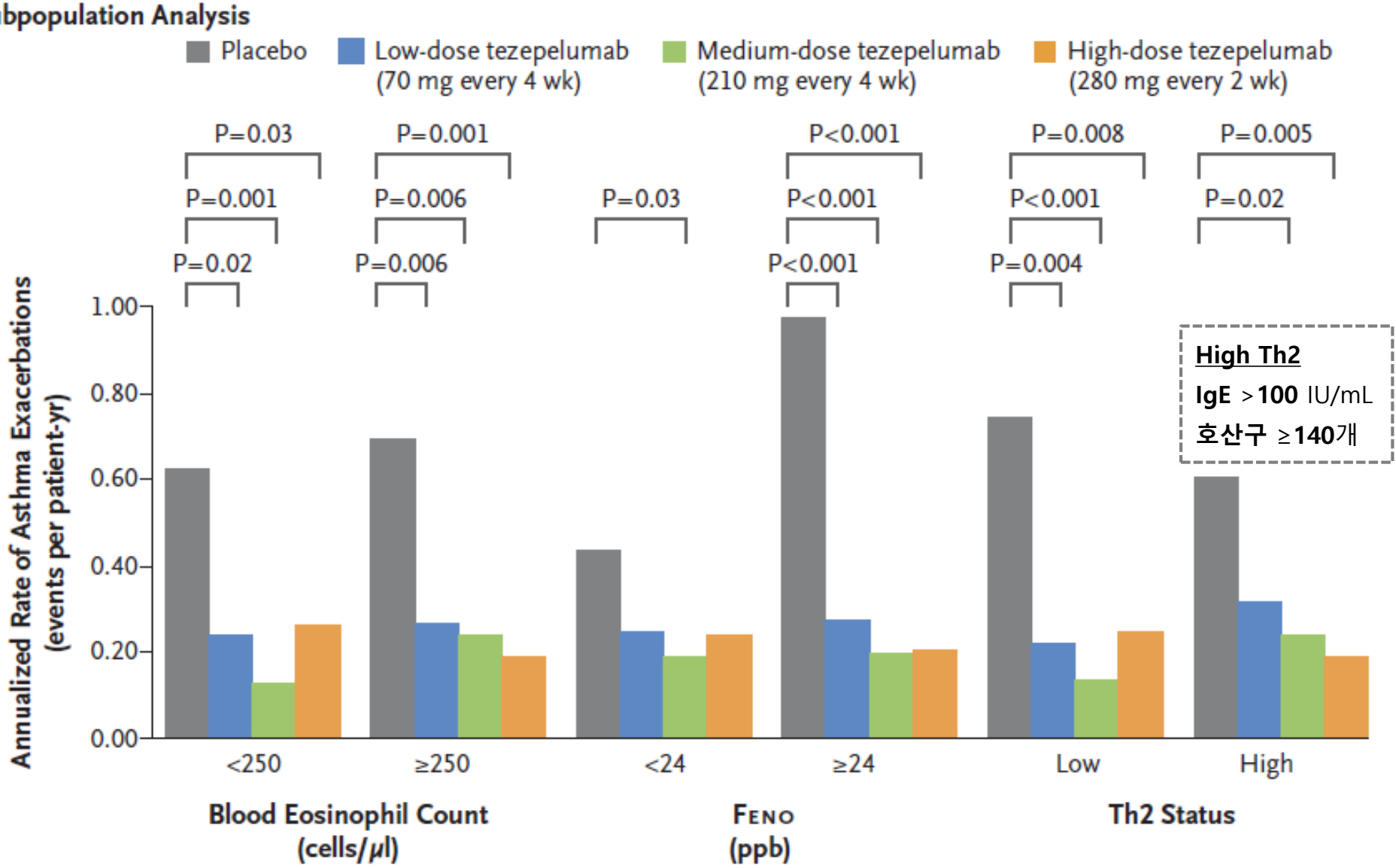
N Engl J Med 2017;377:936-46

Variable	Placebo (N=148)	Low-Dose Tezepelumab (N=145)	Medium-Dose Tezepelumab (N=145)	High-Dose Tezepelumab (N=146)
Annualized rate of asthma exacerbations through wk 52 — events per patient-yr (90% CI)	0.67 (0.57 to 0.80)	0.26 (0.19 to 0.34)	0.19 (0.13 to 0.27)	0.22 (0.16 to 0.30)
Relative reduction vs. placebo — % (90% CI)	—	61 (39 to 75)	71 (53 to 82)	66 (47 to 79)
P value	—	<0.001	<0.001	<0.001
FEV_1 before bronchodilation				
No. of patients evaluated	141	137	128	125
Least-squares mean change from baseline at wk 52 — % of predicted value	−0.99	7.11	7.27	9.37
Difference vs. placebo (95% CI)	—	8.11 (2.39 to 13.82)	8.26 (2.50 to 14.03)	10.36 (4.60 to 16.13)
P value*	—	0.006	0.005	<0.001
Least-squares mean change from baseline at wk 52 — liters	−0.05	0.07	0.06	0.11
Difference vs. placebo (95% CI)	—	0.12 (0.02 to 0.21)	0.11 (0.02 to 0.20)	0.15 (0.06 to 0.25)
P value*	—	0.01	0.02	0.002

Annual rate of Clinical Asthma Exacerbation : 61-71% 감소

PreFEV$_1$ at week 52 : 110-150 mL 증가

N Engl J Med 2017;377:936-46



"**Broader** physiological effects"

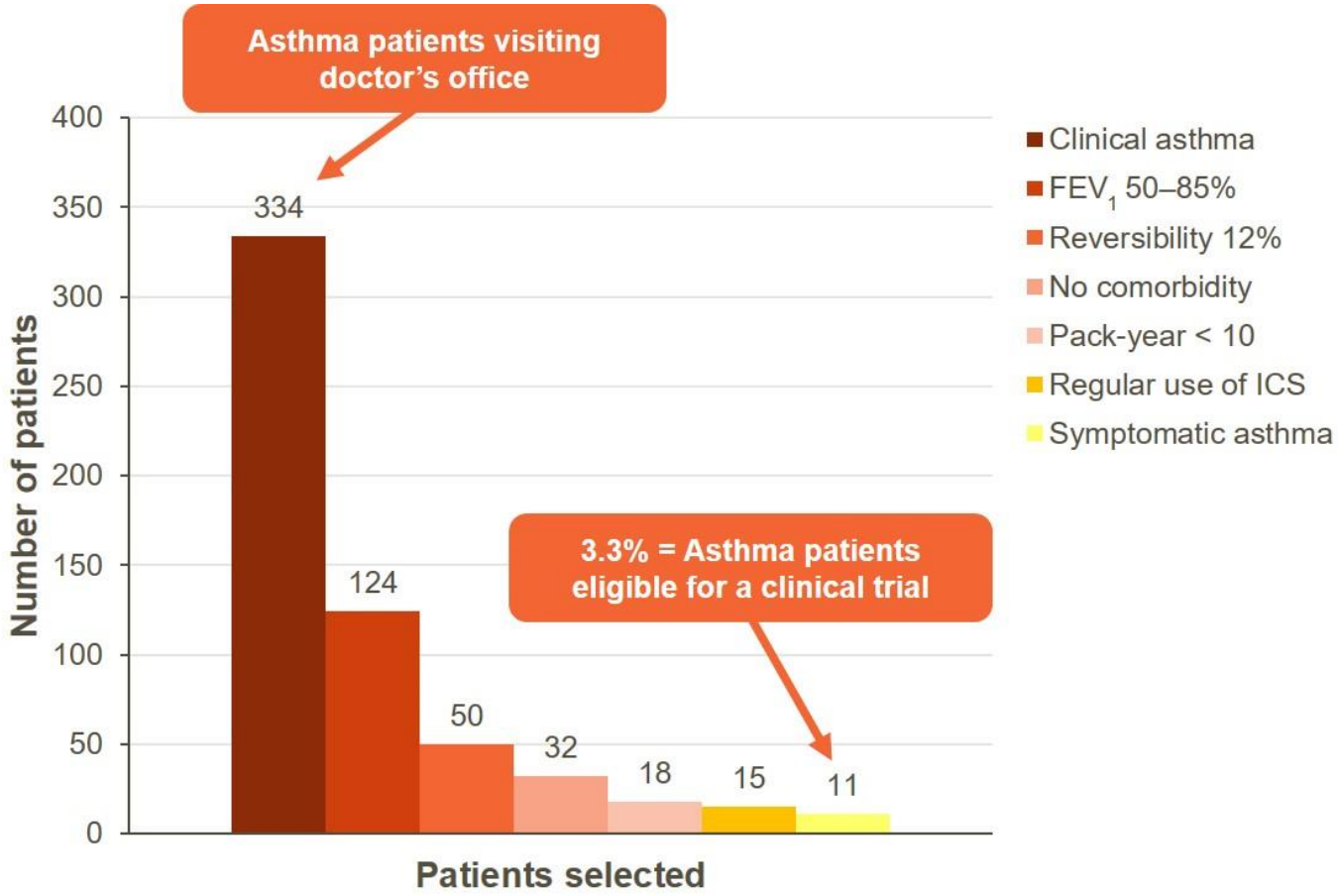
N Engl J Med 2017;377:936-46

Real-World

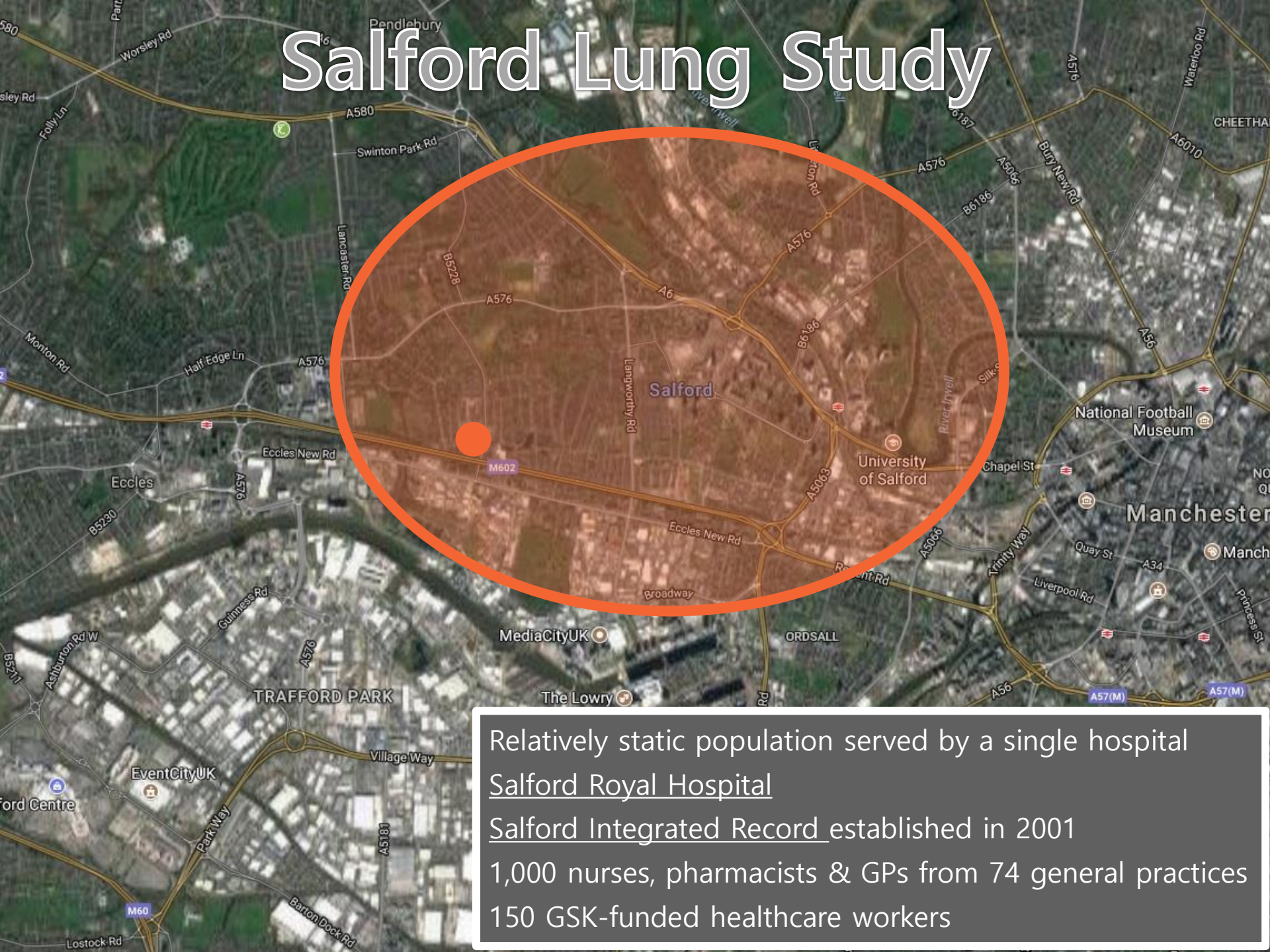
Effectiveness analysis, 12 months

SALFORD Lung Study

Lancet **2017**



Salford Lung Study



Relatively static population served by a single hospital

Salford Royal Hospital

Salford Integrated Record established in 2001

1,000 nurses, pharmacists & GPs from 74 general practices

150 GSK-funded healthcare workers

Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial

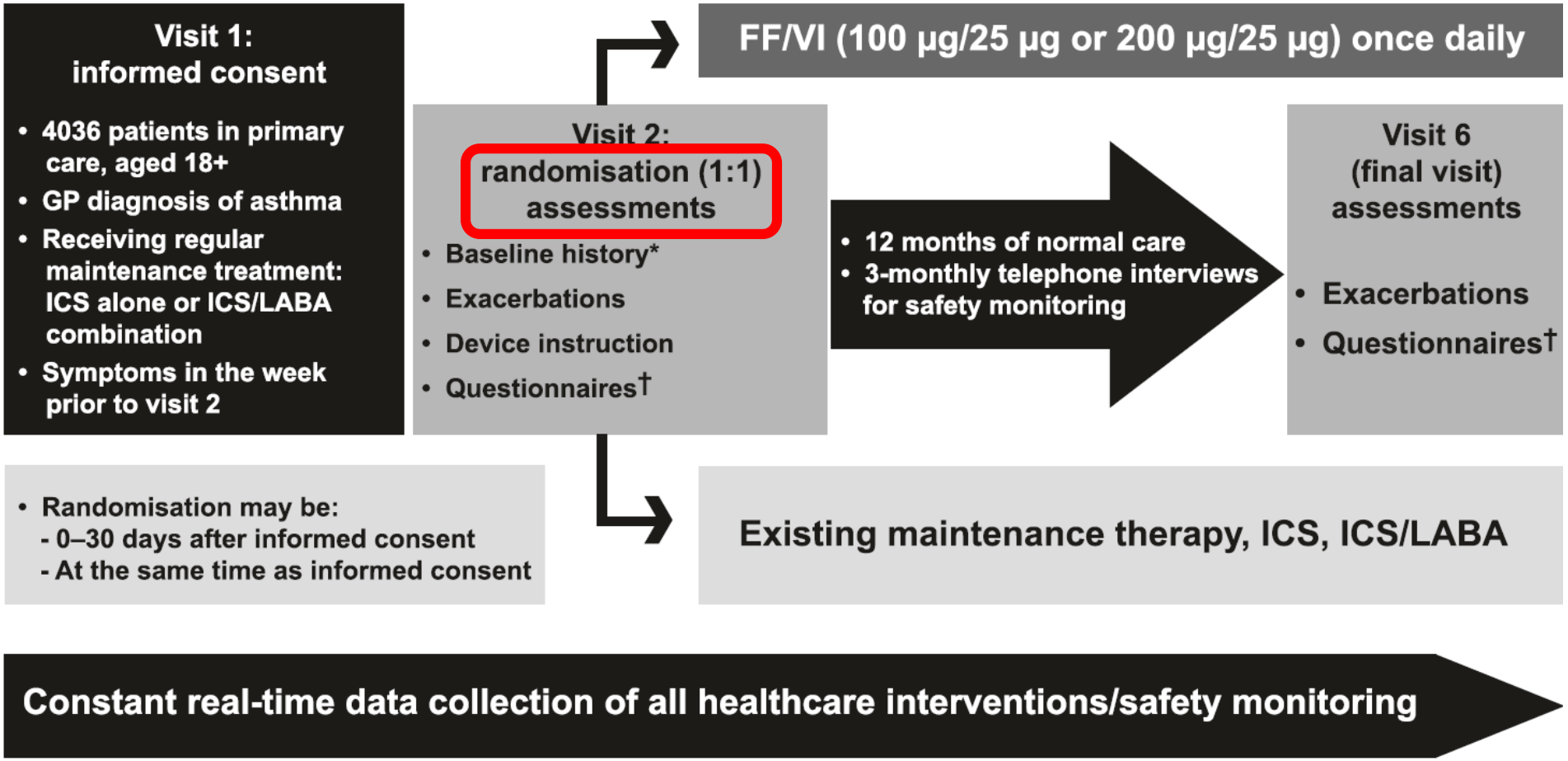
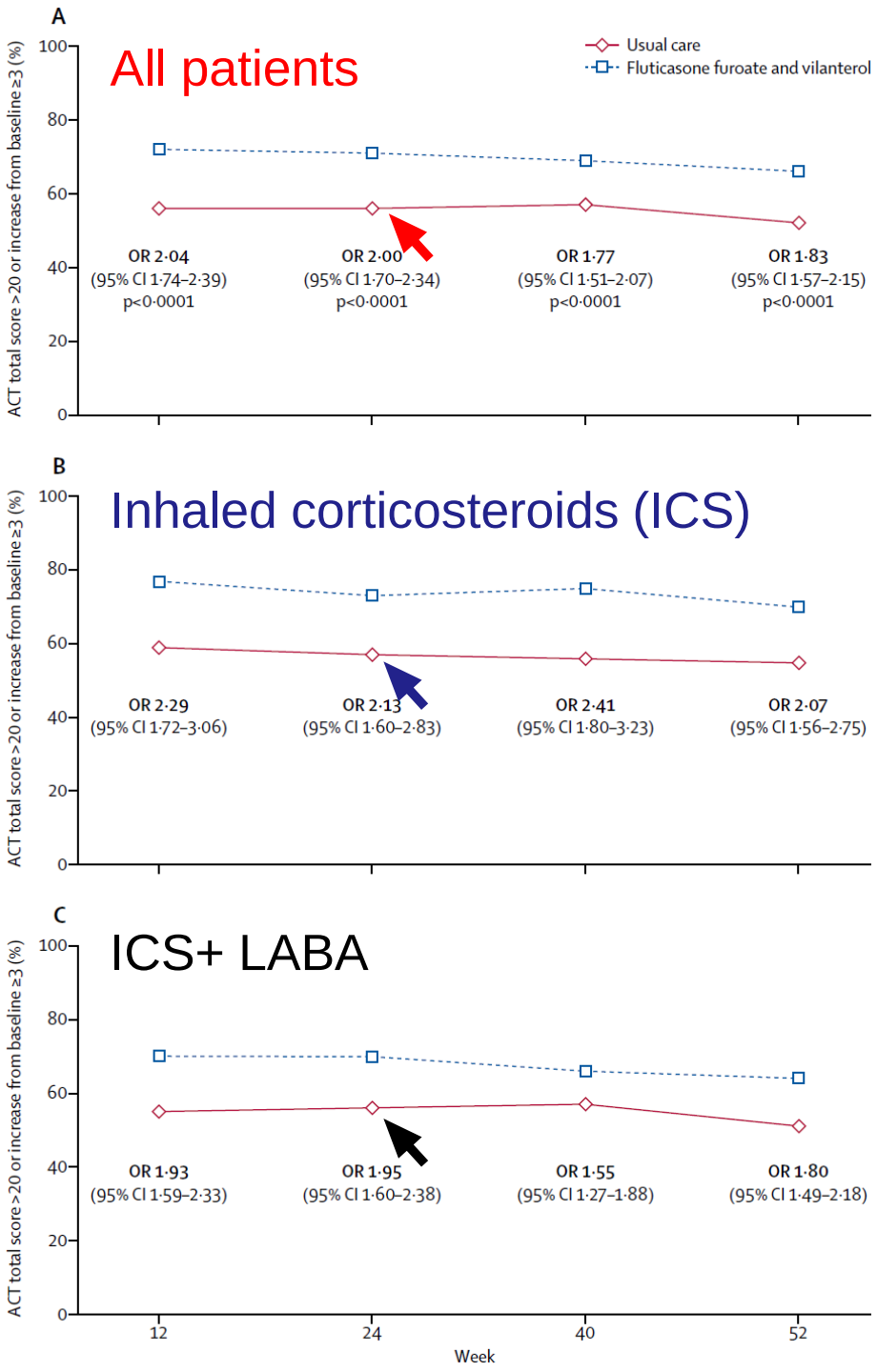
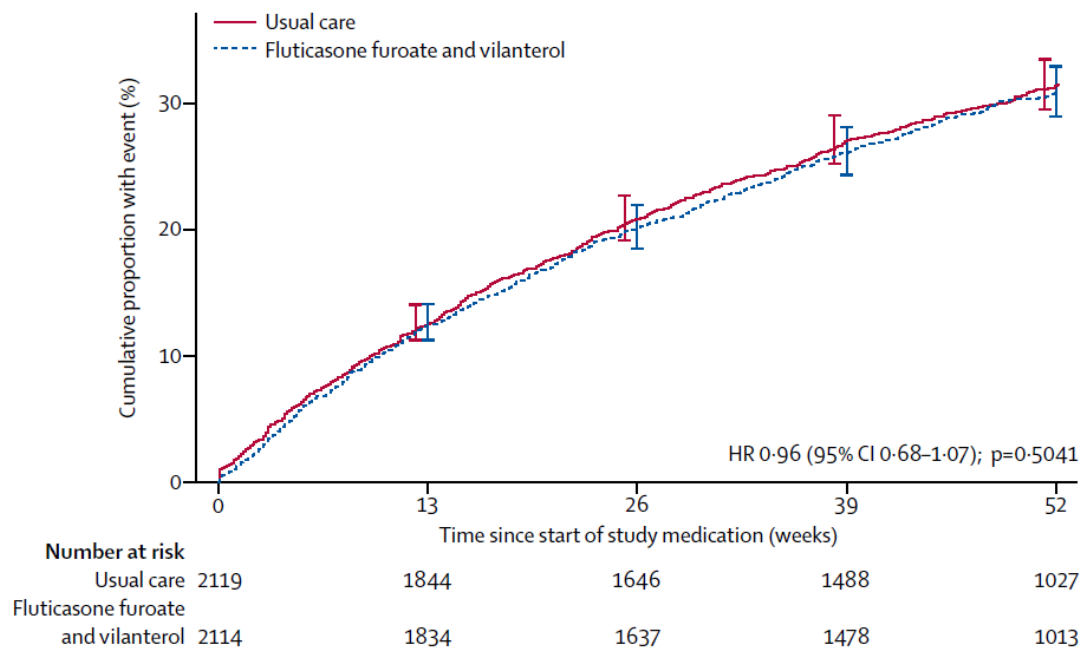


Fig. 1 Study design. *Cardiovascular risk factors collected. †Comprises: Asthma Control Test; Asthma Quality of Life Questionnaire(s); EuroQol questionnaire; Medication Adherence Report Scale for Asthma; Work Productivity and Activity Impairment Questionnaire: Asthma. *FF* fluticasone furoate; *GP* general practitioner; *ICS* inhaled corticosteroid; *LABA* long-acting β_2-agonist; *VI* vilanterol

	Usual care (n=2119)	Fluticasone furoate and vilanterol (n=2114)
Age, years	50 (17)	50 (16)
Female	1241 (59%)	1257 (59%)
Body-mass index >30 kg/m²	903 (43%)	870 (42%)
Current smokers	429 (20%)	420 (20%)
Asthma control test score at baseline		
≥20 **n=1,514**	605 (29%)	601 (28%) **1,512**
16–19	653 (31%)	655 (31%)
<15	861 (41%)	857 (41%)
Duration of asthma ≥5 years	1844 (87%)	1819 (86%)
Daytime symptoms more than twice per week	1926 (91%)	1904 (90%)
Nocturnal symptoms in past week	1053 (50%)	1064 (50%)
Number of exacerbations 12 months before randomisation		
0	1314 (62%)	2692 (65%)
1	501 (24%)	973 (22%)
>1	304 (14%)	568 (12%)
Comorbidities		
Any	812 (38%)	813 (38%)
Cardiac	164 (8%)	182 (9%)
Vascular	559 (26%)	540 (26%)
Diabetes	201 (9%)	205 (10%)

Lancet 2017;390:2247-55





	Usual care	Fluticasone furoate and vilanterol
Cardiovascular disease	69 (29·6)	42 (23·3)
Asthma and bronchospasm	40 (17·2)	24 (13·3)
Pneumonia	21 (8·4)	21 (10·7)
Lower respiratory tract infection (excluding pneumonia)	8 (3·4)	7 (3·9)
Decreased bone mineral density and associated fractures	52 (22·3)	35 (19·4)
Effects on glucose	22 (9·4)	18 (10·0)
Hypersensitivity	5 (2·1)	7 (3·9)
Effects on potassium	1 (0·4)	4 (2·2)
Corticosteroid-associated eye disease	7 (3·0)	9 (5·0)
Adrenal suppression	1 (0·4)	0
Local steroid effects	0	1 (0·6)
Tremors	0	0

<u>천식조절(ACT socre) 개선</u>: FF+vilanterol이 **2배** 높다

급성악화: 두 군간에 차이가 없다

폐렴발생: FF+vilanterol이 높은 경향이나 통계적 차이 없다

Lancet 2017;390:2247-55

요 약

Phenotypes → **Endotypes**

Precision

Mepolizumab

Reslizumab

Benralizumab

Duplimab

Tezepelumab

- Asthma Exacerbation -

- Steroid Sparing -

- Uncontrolled Asthma -

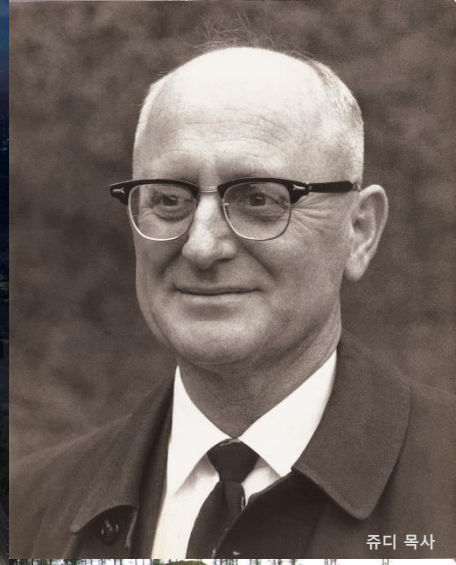
Efficacy → **Effectiveness**

Real-World

SALFORD LUNG STUDY

- Asthma Control -

- Nonallergic, Smoking, Virus,.. -


쥬디 목사


기공식
1957. 11. 15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