2019.04.13

대한결핵 및 호흡기학회 2019년도 제48차 Workshop

Respiratory Review of 2019

Asthma

문 지 용

한양대학교구리병원 호흡기내과

Contents

- Mild Asthma
- Quadruple of ICS to Abort Exacerbation
- Severe Asthma

The Guidelines for Asthma

- the Global Initiative for Asthma (**GINA**, revised annually)
  - are targeted toward primary care providers and available as management guidance for countries to use in designing their own guidelines, taking socioeconomic issues in consideration
- the National Institute for Health and Care Excellence (**NICE**; United Kingdom, last updated in 2017)
  - are focused on mild-to-moderate asthma and primary care providers
- the Expert Panel Report of the National Asthma Education and Prevention Program (**NAEPP**)
  - the Expert Panel Report 3 (ERP-3 in 2007)

Ballas ZK. J Allergy Clin Immunol 2018;142:787.

Mild Asthma

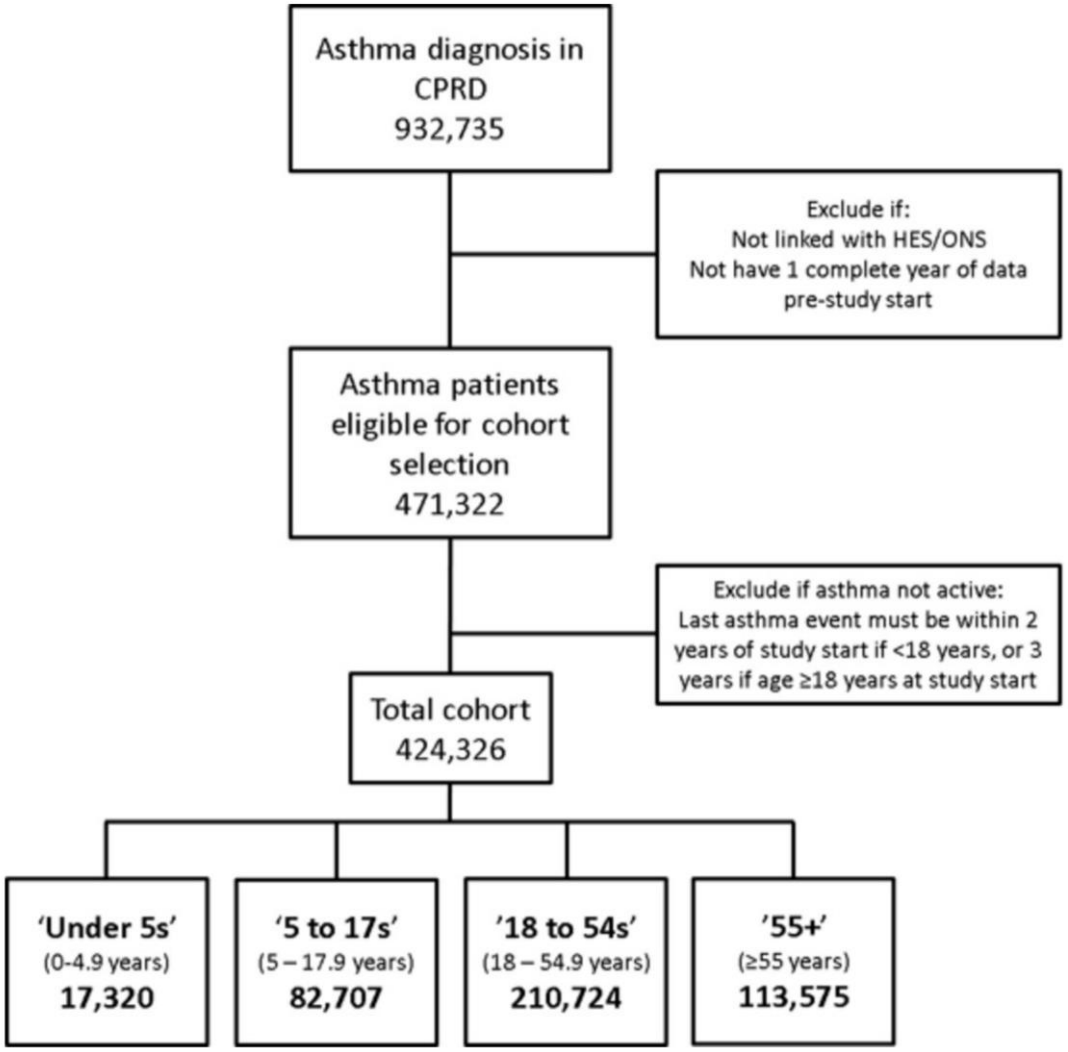
- Definition in the GINA document
  - "Asthma that is well controlled with **Step 1 or Step 2** treatment (Box 3-5, p.44), i.e. with as-needed reliever medication alone, or with **low-intensity controller** treatment such as low dose ICS, leukotriene receptor antagonists or chromones"
- GINA Step 2 in the SYGMA study
  - **uncontrolled** while the patient was using inhaled short-acting bronchodilators (**SABA**) as needed **OR**
  - well **controlled** while the patient was using low-dose inhaled glucocorticoid (**ICS**) or leukotriene-receptor antagonist maintenance therapy plus a SABA as needed

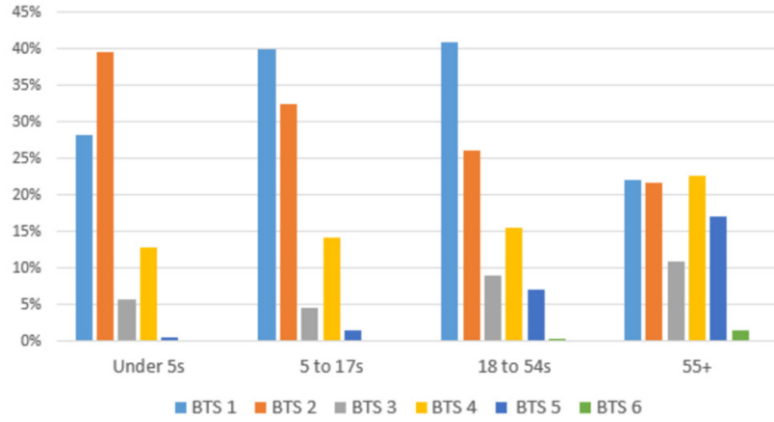
GINA 2018

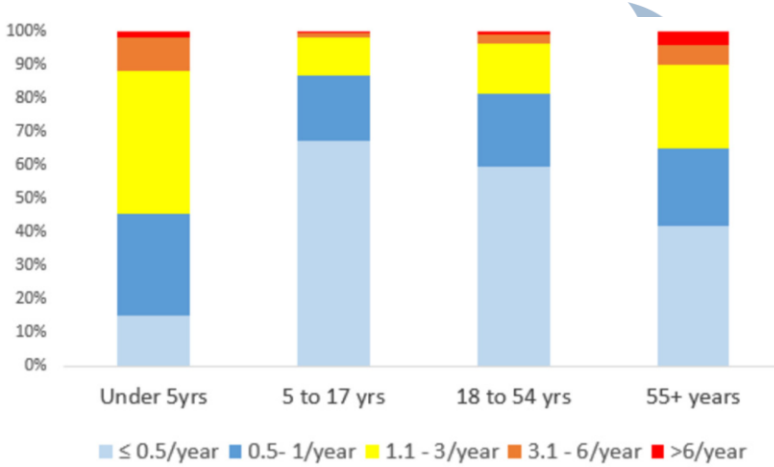
O'Byrne PM, et al. N Engl J Med 2018;378:1865-76

Exacerbation risk and characterisation of the UK's asthma population from infants to old age

Chloe I Bloom,[1] Francis Nissen,[2] Ian J Douglas,[2] Liam Smeeth,[2] Paul Cullinan,[1] Jennifer K Quint[1]

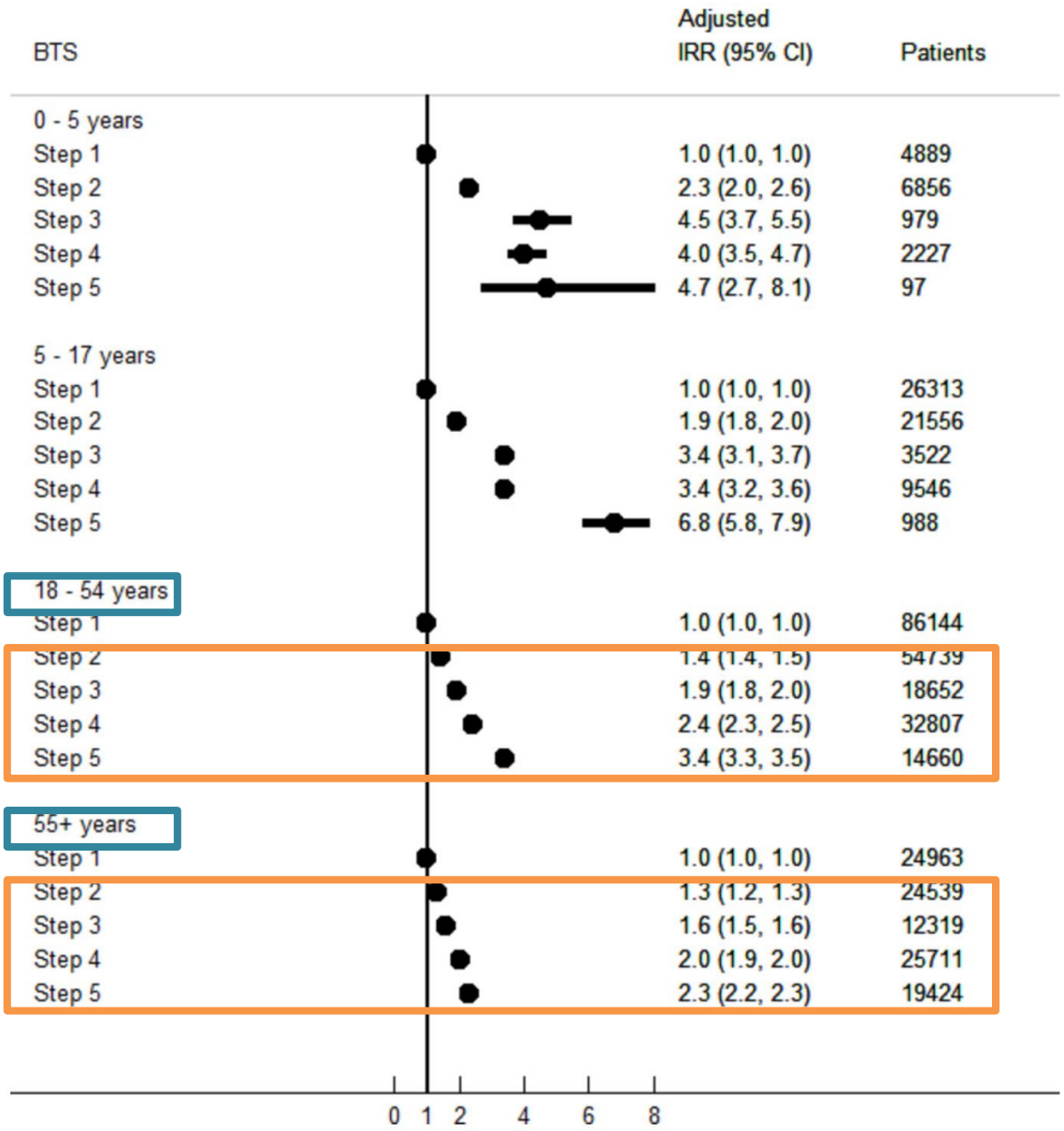






Bloom CI, Thorax 2018;73:313-20.

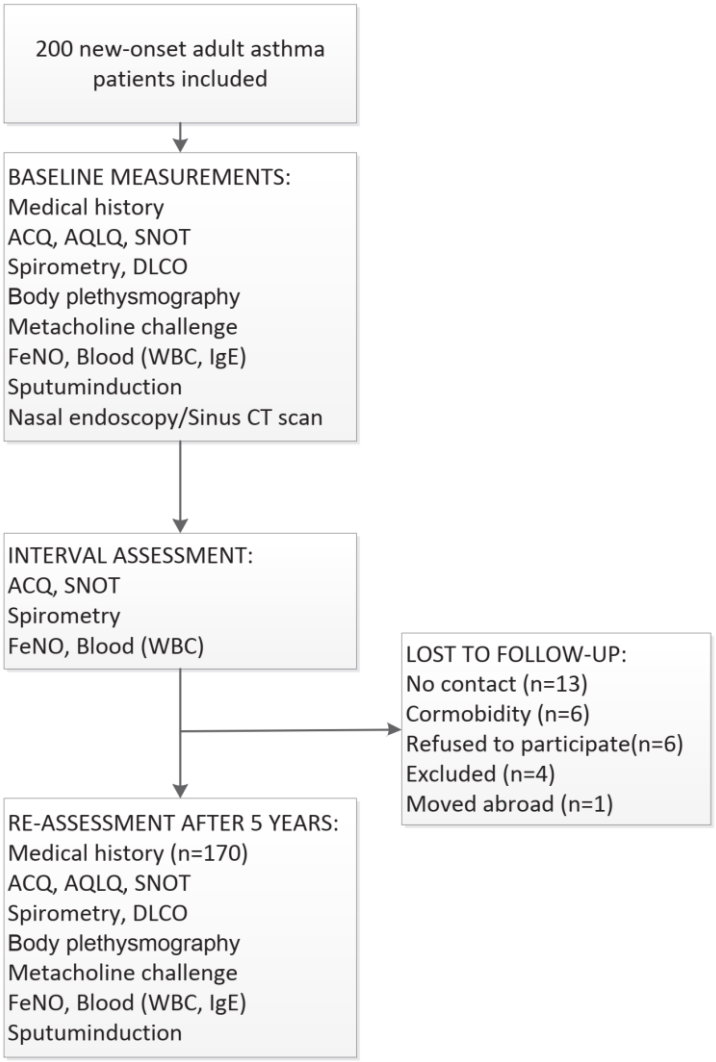
Change in Exacerbation Rates by BTS step



Bloom CI, Thorax 2018;73:313-20.

Clinical predictors of remission and persistence of adult-onset asthma

Guus A. Westerhof, MD, Hanneke Coumou, MD, Selma B. de Nijs, PhD, Els J. Weersink, MD, PhD, and Elizabeth H. Bel, MD, PhD *Amsterdam, The Netherlands*



- to determine which factors predict **remission or persistence** of the disease
- the **ADONIS** (Adult-Onset Asthma and Inflammatory Subphenotypes) study.
- adult patients with **recently diagnosed** (<1 year) asthma
- Asthma **remission**
  - **no symptoms & medication** for **≥1 year**

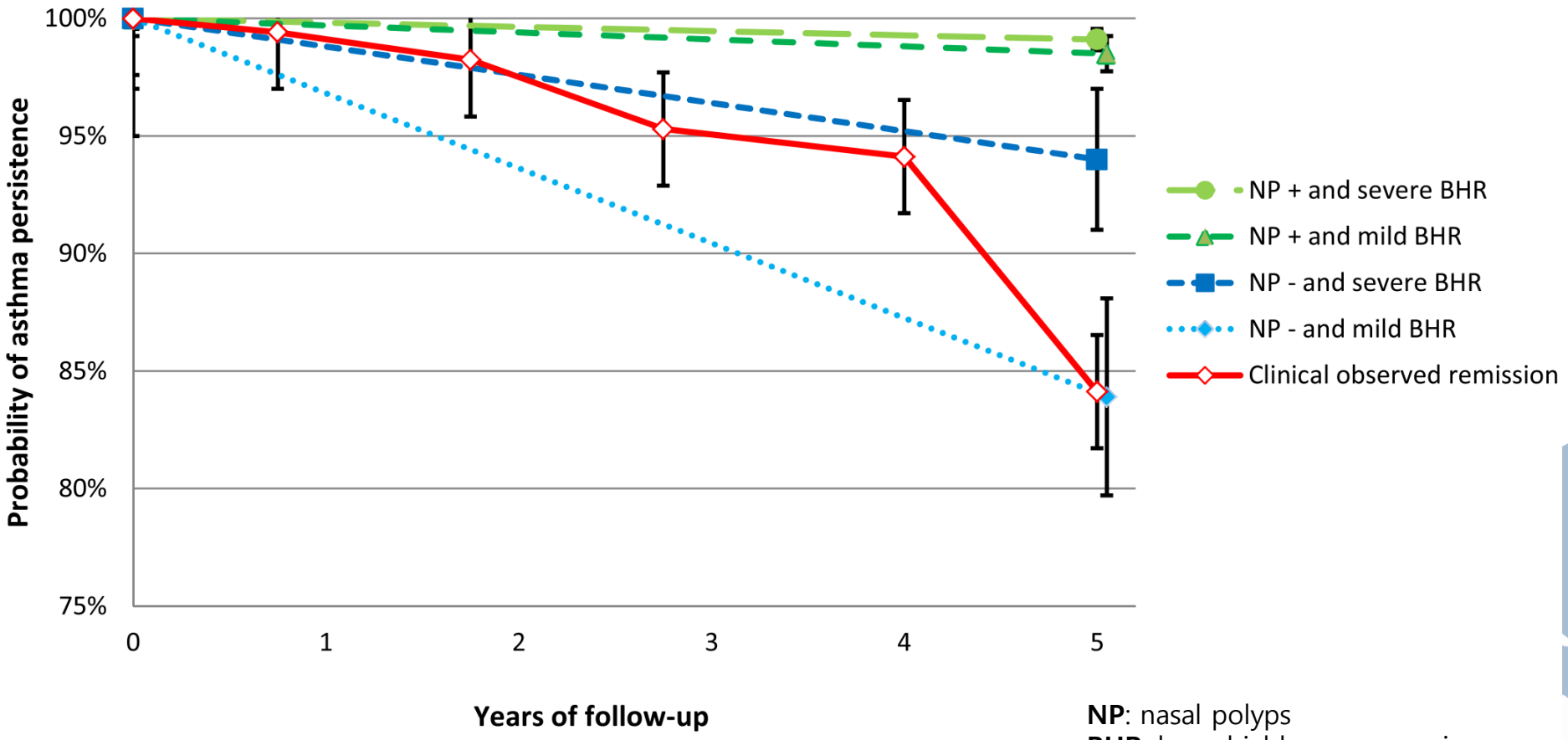
Westerhof GA, J Allergy Clin Immunol 2018;141:104-9 e3.

Baseline characteristics

	Persistent asthma (n = 143)	Clinical remission (n = 27)	*P* value
Female	57	44	.243
Age (y)	50 ± 14	44 ± 15	**.039**
BMI (kg/m^2)	28.2 ± 5.2	26.5 ± 5.0	.132
Ex- or current smoker	58	48	.342
Pack-years	4 (0-15)	1 (0-12)	.266
ACQ-6 score	1.34 ± 0.92	0.89 ± 0.67	**.026**
ICS use	81	70	.212
ICS and second controlller	64	52	.248
Oral corticosteroid use	3	0	.389
ICS dose, fluticasone equivalent	313 (250-500)	250 (0-250)	**.007**
Asthma medication use	92	89	.561
Pre-FEV_1, % predicted	93 ± 17	95 ± 16	.709
Pre-FVC, % predicted	106 ± 16	102 ± 16	.291
Post-FEV_1, % predicted	100 ± 17	99 ± 14	.785
Post FVC, % predicted	108 ± 16	103 ± 17	.107
FEV_1, % reversibility	5 (2-9)	4 (2-6)	.134
Post-FEV_1/FVC, % predicted	95 ± 11	98 ± 10	.158
Post-DLCOc/VA, % predicted	98 ± 15	96 ± 17	.562
Post-RV/TLC ratio, % predicted	88 ± 20	86 ± 13	.527
PC_{20} methacholine (mg/mL)	2.7 (0.8-6.6)	5.8 (2.9-32)	**.003**
Nasal polyps	25	0	**.004**
GERD	39	42	.763
Atopy	44	46	.667
Obesity	33	19	.138
Total IgE (kU/L)	68 (26-236)	59 (30-115)	.497
FeNO (parts/billion)	21 (13-45)	29 (12-44)	.698
Blood neutrophils (10^9/L)	3.7 (3.0-4.6)	3.0 (2.7-4.0)	**.038**
Blood eosinophils (10^9/L)	0.17 (0.1-0.28)	0.15 (0.08-0.26)	.601
Sputum eosinophils (%)	0.5 (0.1-3.8)	0.6 (0.2-1.5)	.688
Sputum neutrophils (%)	71 (50-84)	82 (71-87)	.143

Westerhof GA, J Allergy Clin Immunol 2018;141:104-9 e3.

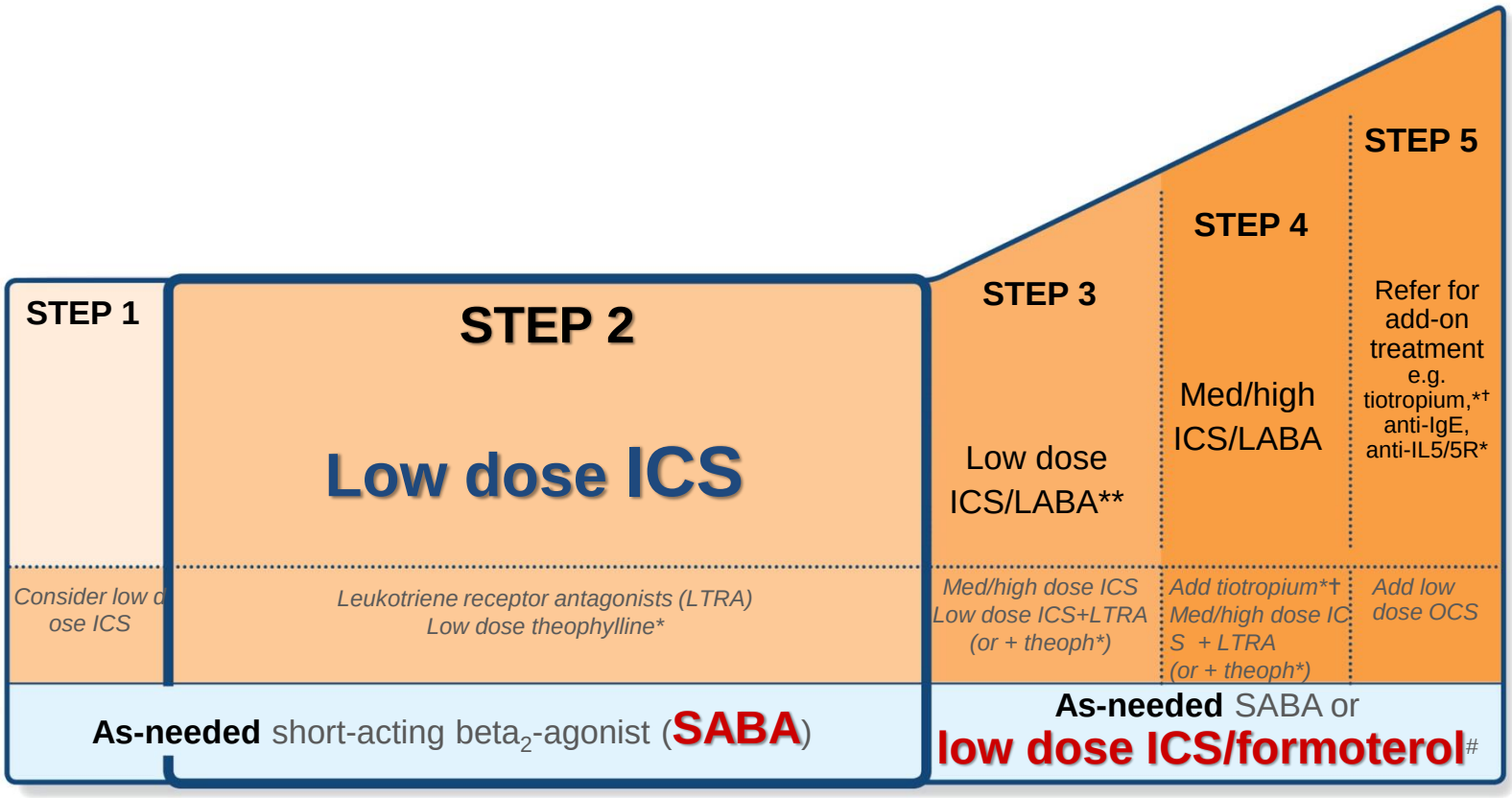
Probability of Asthma Persistence



NP: nasal polyps
BHR: bronchial hyperresponsiveness

Westerhof GA, J Allergy Clin Immunol 2018;141:104-9 e3.

Step 2 – low-dose controller + as-needed inhaled SABA



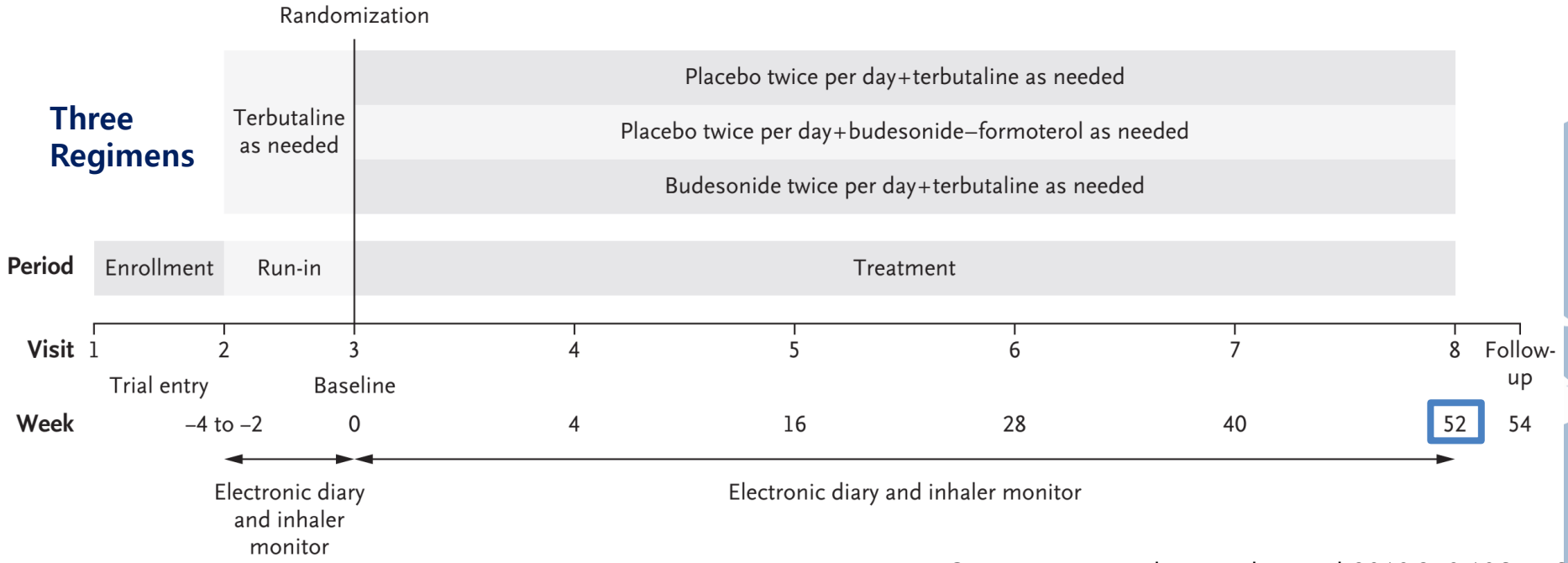
*Not for children <12 years
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

GINA 2018, Box 3-5

- SYGMA 1 -

Symbicort Given as Needed in Mild Asthma 1

- **12 years of age or older (n=3836), 52 weeks**
  - 200 μg of budesonide and 6 μg of formoterol (**Symbicort** Turbuhaler) as needed
  - 200 μg of budesonide (**Pulmicort** Turbuhaler) as twice-daily maintenance therapy plus terbutaline at a dose of 0.5 mg (Turbuhaler) used as needed
  - Terbutaline at a dose of 0.5 mg (Turbuhaler) used as needed.



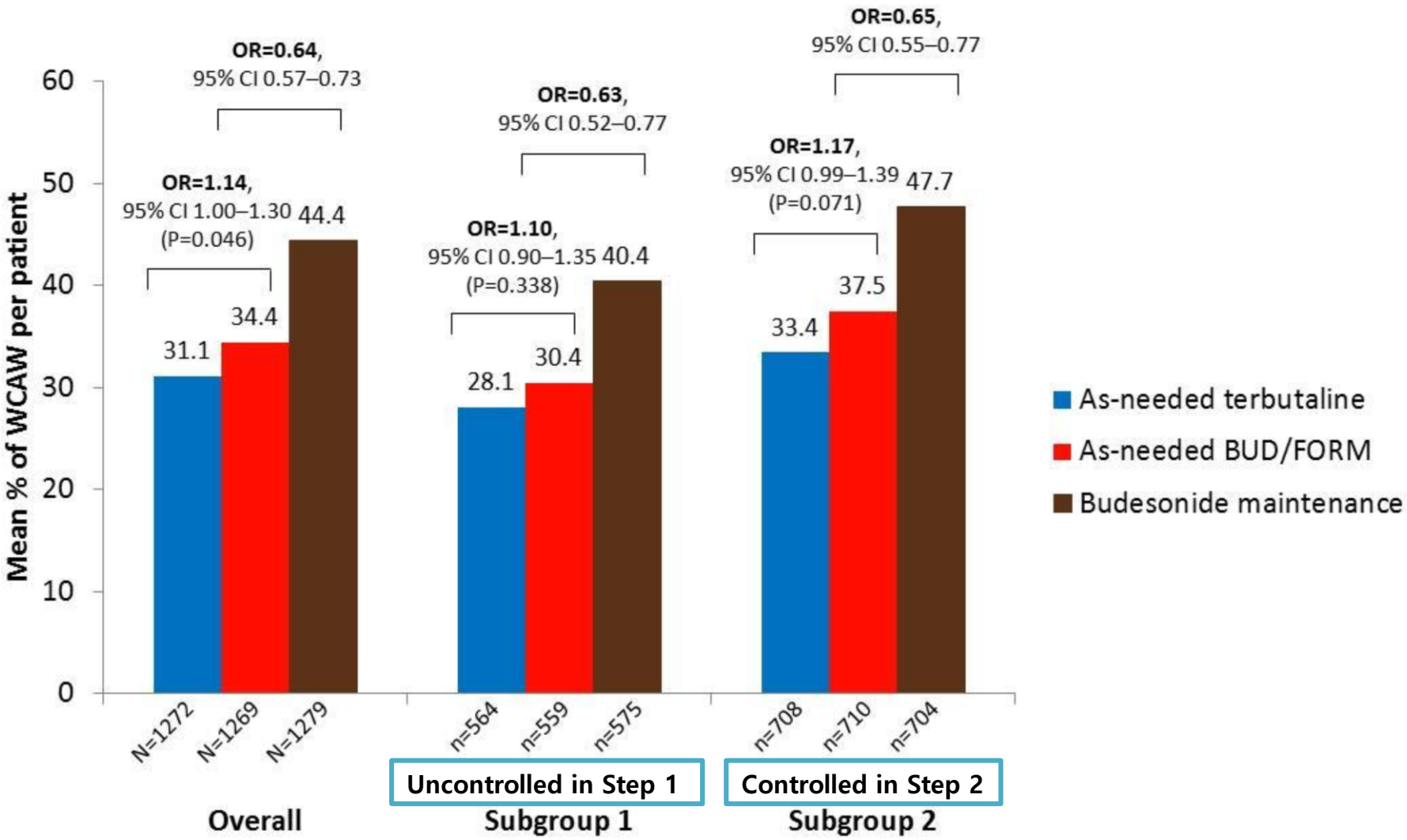
O'Byrne PM, et al. N Engl J Med 2018;378:1865-76.

Baseline Characteristics

Characteristic	Terbutaline as Needed (N=1277)	Budesonide–Formoterol as Needed (N=1277)	Budesonide Maintenance Therapy (N=1282)	Total (N=3836)
Age — yr	40.0±16.3	39.8±16.9	39.0±16.7	39.6±16.6
Female sex — no. (%)	771 (60.4)	777 (60.8)	797 (62.2)	2345 (61.1)
Time since asthma diagnosis — yr				
Median	6.3	6.5	6.3	6.4
Range	0.5–62.4	0.4–65.7	0.5–57.1	0.4–65.7
ACQ-5 score†				
Mean score				
At trial entry	1.52±0.96	1.57±0.97	1.53±0.97	1.54±0.97
At baseline	1.54±0.95	1.61±0.97	1.55±0.96	1.57±0.96
Score ≥1.5 — no./total no. (%)				
At trial entry‡	549/1160 (47.3)	601/1174 (51.2)	568/1177 (48.3)	1718/3511 (48.9)
At baseline	602/1256 (47.9)	649/1257 (51.6)	596/1257 (47.4)	1847/3770 (49.0)
AQLQ score§	5.25±0.99	5.20±1.01	5.27±1.01	5.24±1.00
FEV_1 — % of predicted value				
Before bronchodilator use	84.13±14.08	84.18±14.24	84.23±13.91	84.18±14.07
After bronchodilator use	95.27±13.53	95.86±14.02	95.67±13.43	95.60±13.66
Peak expiratory flow ≥80% of the predicted value every morning — no./total no. (%)¶	362/1276 (28.4)	340/1277 (26.6)	376/1282 (29.3)	1078/3835 (28.1)
Bronchodilator reversibility — %	14.4±11.5	14.9±11.3	14.6±11.6	14.6±11.5
Asthma control according to pretrial treatment — no. (%)‖				
Uncontrolled with short-acting bronchodilator alone	565 (44.2)	565 (44.2)	576 (44.9)	1706 (44.5)
Controlled with inhaled glucocorticoid or leukotriene-receptor antagonist	712 (55.8)	712 (55.8)	706 (55.1)	2130 (55.5)
Severe exacerbation in previous 12 mo — no. (%)	256 (20.0)	257 (20.1)	241 (18.8)	754 (19.7)

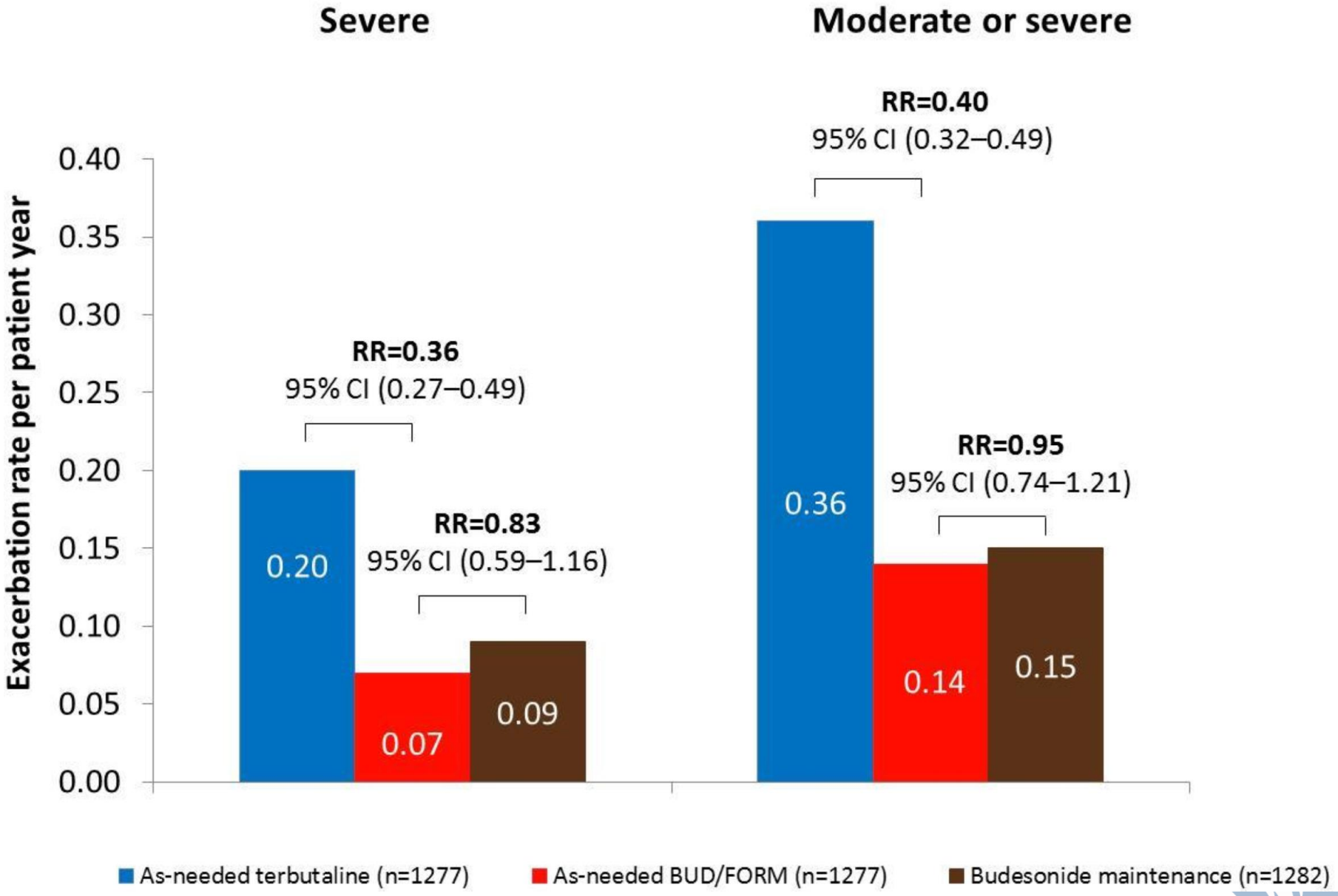
O'Byrne PM, et al. N Engl J Med 2018;378:1865-76.

Primary Outcome: eWCAW
eDiary-Derived Well-Controlled Asthma Weeks



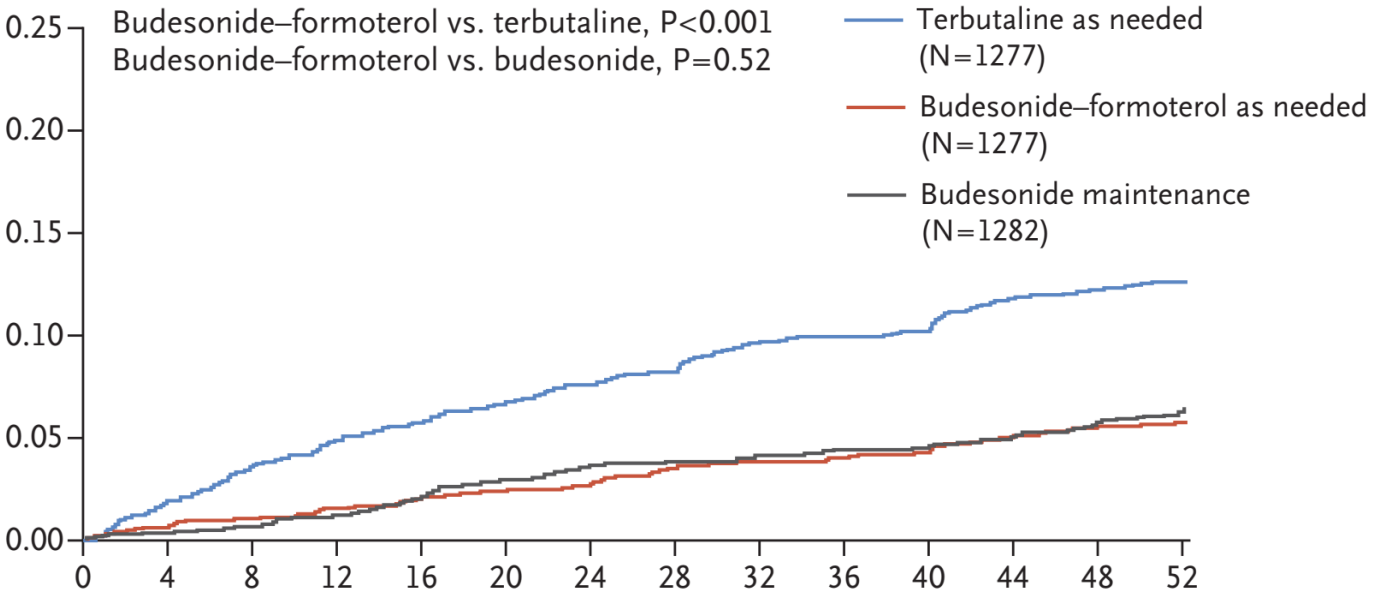
O'Byrne PM, et al. N Engl J Med 2018;378:1865-76.

Annualized Exacerbation Rate

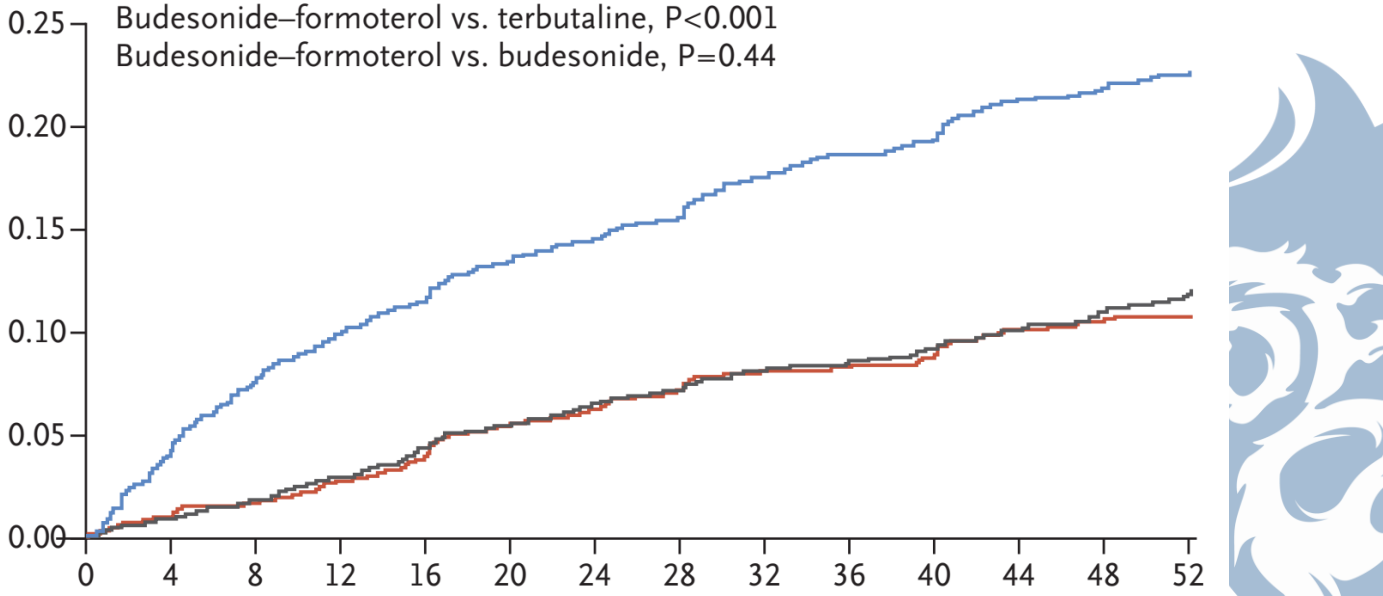


O'Byrne PM, et al. N Engl J Med 2018;378:1865-76.

Severe AE



Moderate or Severe AE

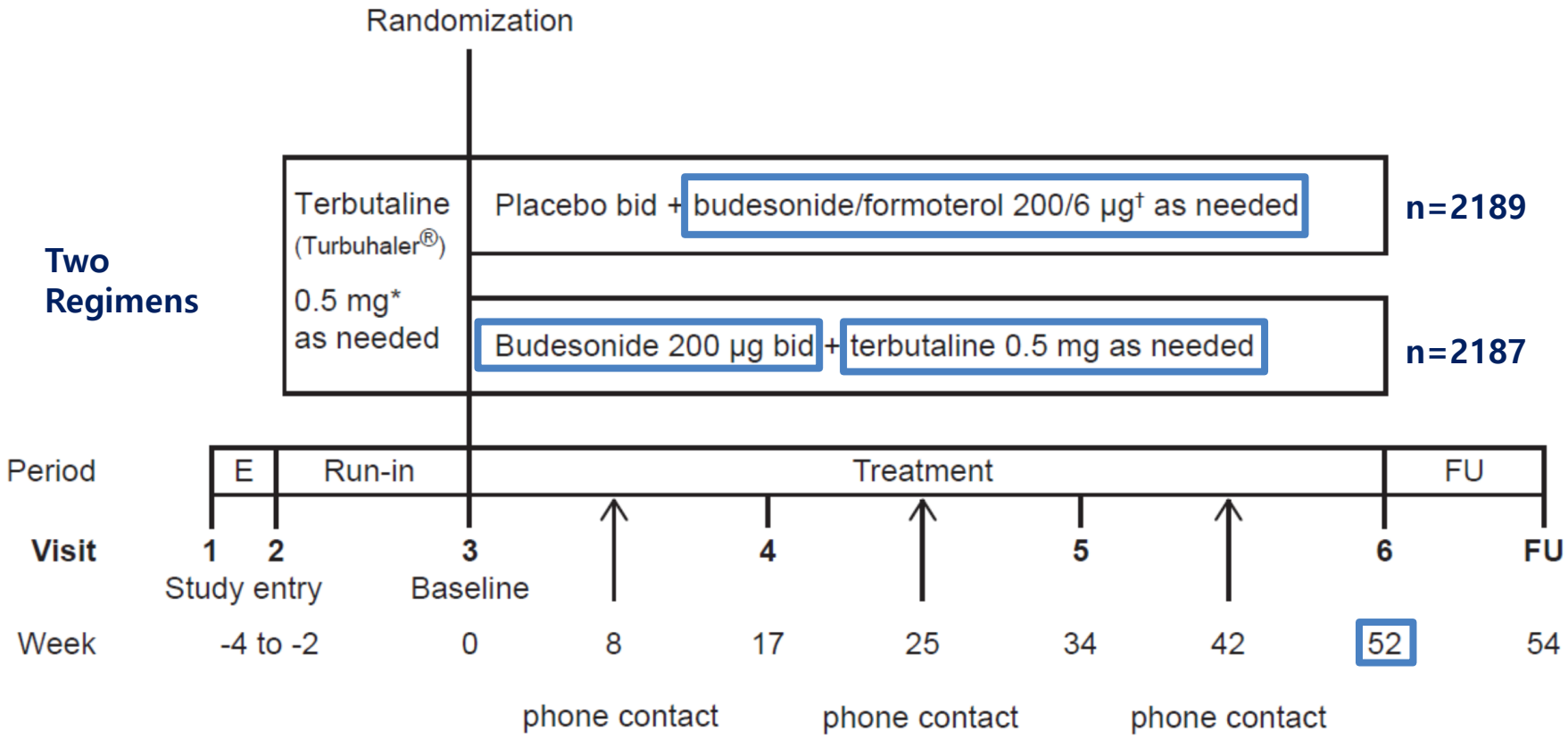


O'Byrne PM, et al. N Engl J Med 2018;378:1865-76.

- SYGMA 2 -

Symbicort Given as Needed in Mild Asthma 2

- A more **pragmatic study** design **without** daily **reminders** to use maintenance med.
- **Noninferiority** in preventing severe **exacerbation** in patients with mild asthma



Bateman ED, et al. N Engl J Med 2018;378:1877-87.

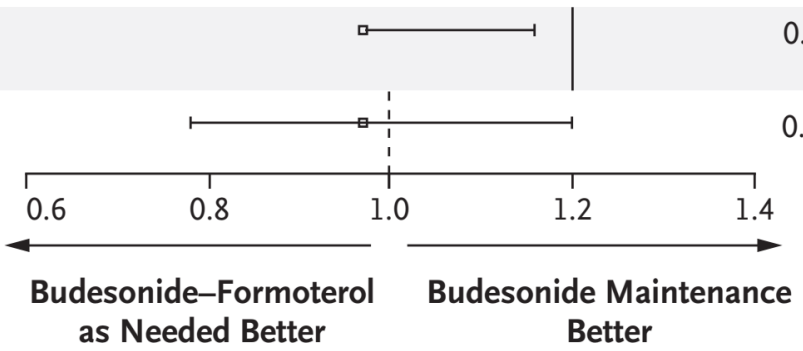
Baseline Characteristics

Characteristic	Budesonide–Formoterol as Needed (N=2089)	Budesonide Maintenance Therapy (N=2087)	Total (N=4176)
Age — yr			
Mean	41.3±16.8	40.7±17.1	41.0±17.0
Range	12–82	12–83	12–83
Female sex — no. (%)	1308 (62.6)	1289 (61.8)	2597 (62.2)
Current smoking — no. (%)	53 (2.5)	54 (2.6)	107 (2.6)
Time since asthma diagnosis — yr			
Median	7.9	7.3	7.6
Range	0.5–62.4	0.4–71.2	0.4–71.2
ACQ-5 score†			
Mean	1.49±0.89	1.53±0.90	1.51±0.90
Score ≥1.5 — no./total no. (%)	943/2043 (46.2)	1000/2037 (49.1)	1943/4080 (47.6)
FEV_1 — % of predicted value			
Before bronchodilator use	84.4±13.9	84.1±13.9	84.3±13.9
After bronchodilator use	96.3±13.8	96.0±13.5	96.1±13.6
Bronchodilator reversibility — %‡	15.1±12.4	15.2±13.0	15.2±12.7
Asthma control according to pretrial treatment — no. (%)§			
Uncontrolled with short-acting bronchodilator	959 (45.9)	975 (46.7)	1934 (46.3)
Controlled with inhaled glucocorticoid or leukotriene-receptor antagonist	1130 (54.1)	1112 (53.3)	2242 (53.7)
No. of severe exacerbations in previous 12 mo — no. (%)			
0	1630 (78.0)	1627 (78.0)	3257 (78.0)
1	365 (17.5)	362 (17.3)	727 (17.4)
≥2	94 (4.5)	98 (4.7)	192 (4.6)

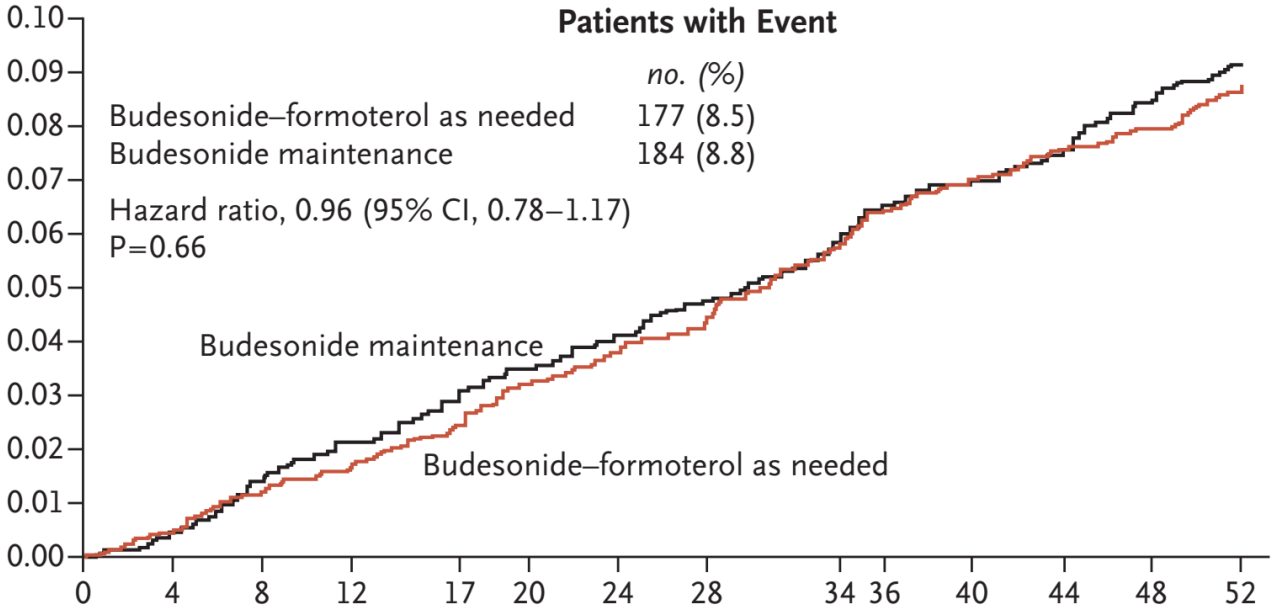
Bateman ED, et al. N Engl J Med 2018;378:1877-87.

Annualized Rate of Severe Exacerbations

Test	Budesonide–Formoterol as Needed	Budesonide Maintenance	Rate Ratio (95% CI)	P Value
Noninferiority test	2084	2083	0.97 (NA–1.16)	—
Superiority test	2089	2087	0.97 (0.78–1.20)	0.75

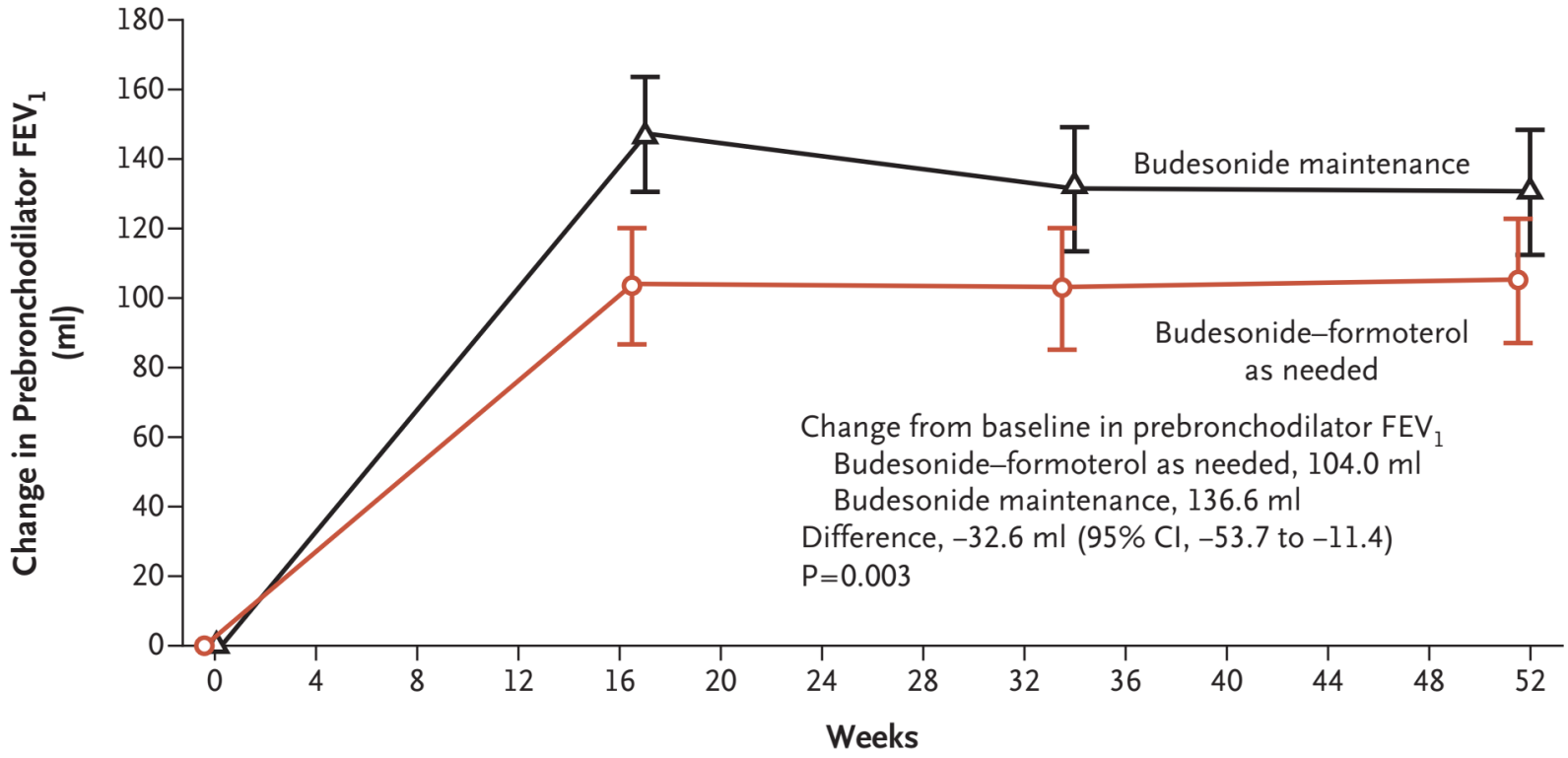


Time to First Severe Exacerbation



Bateman ED, et al. N Engl J Med 2018;378:1877-87.

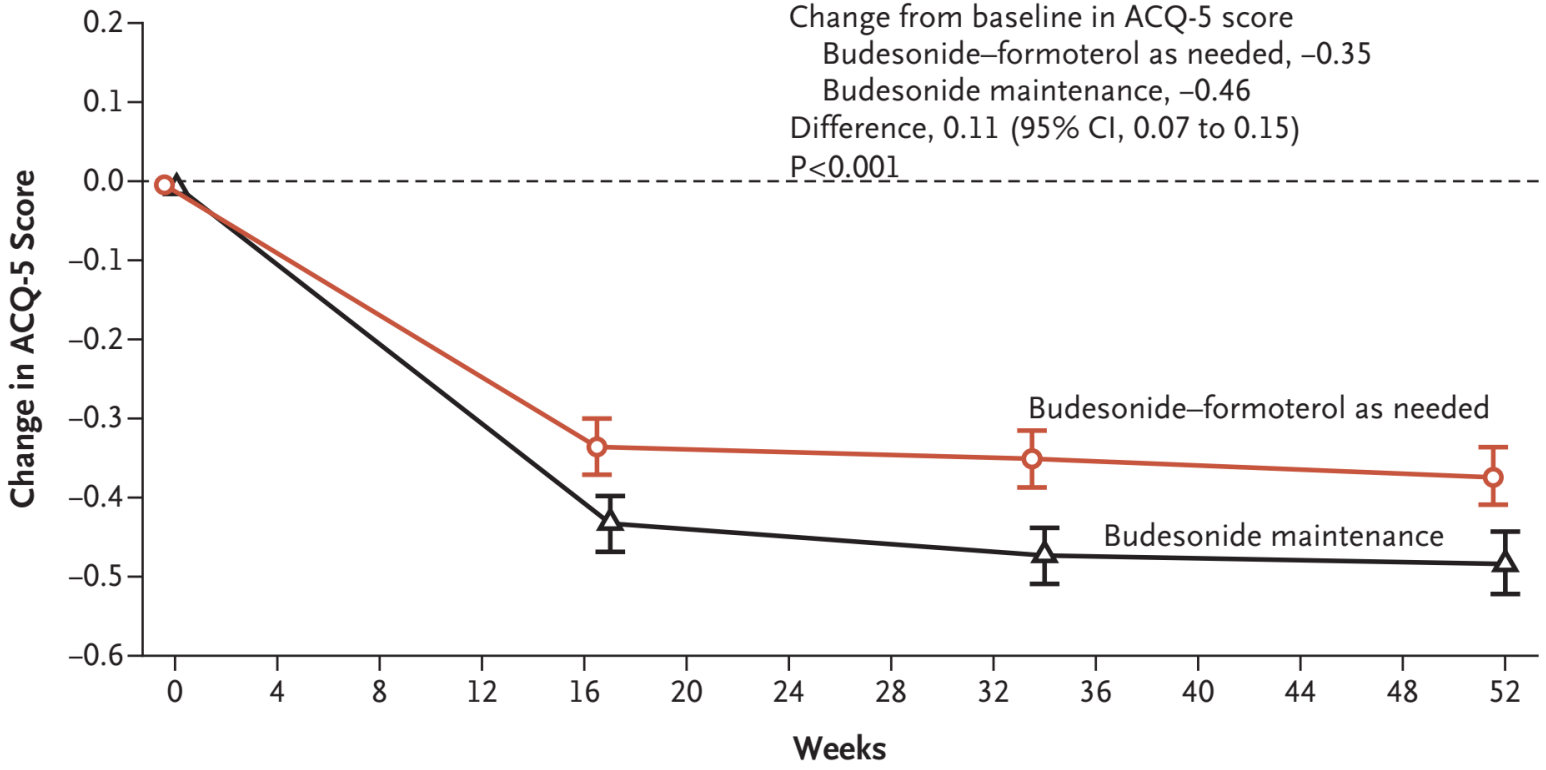
Change in Prebronchodilator FEV1 from Baseline



No. of Patients			
Budesonide–formoterol as needed	1984	1932	1914
Budesonide maintenance	1953	1908	1880

Bateman ED, et al. N Engl J Med 2018;378:1877-87.

Change in ACQ-5 Score from Baseline



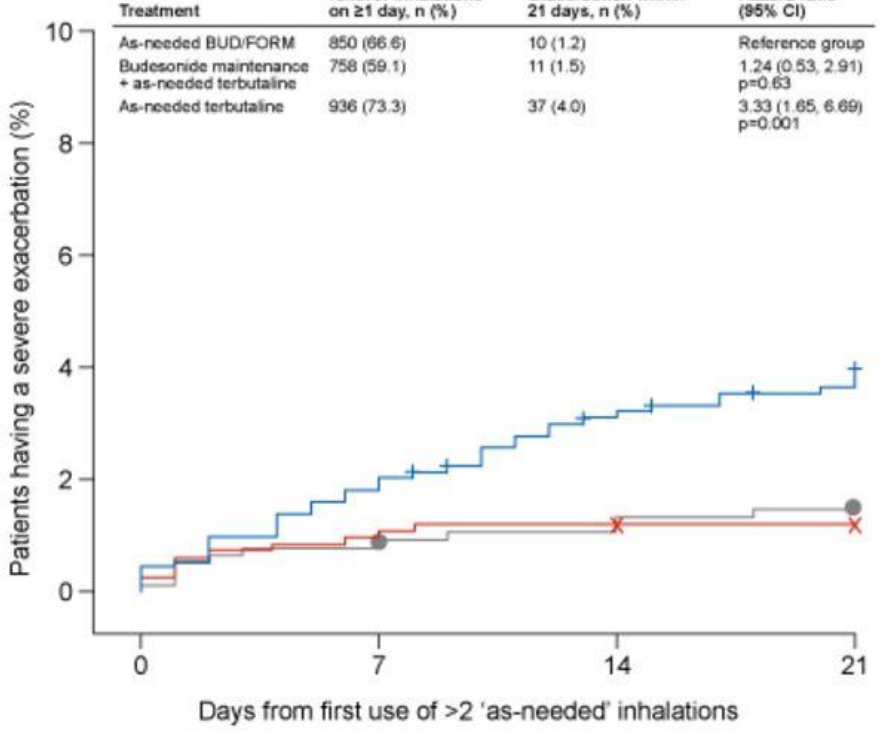
No. of Patients			
Budesonide–formoterol as needed	1941	1898	1862
Budesonide maintenance	1919	1887	1840

Bateman ED, et al. N Engl J Med 2018;378:1877-87.

Risk of a Severe Exacerbation Following Higher Reliever Use: Post-hoc Analysis of SYGMA 1 in Mild Asthma

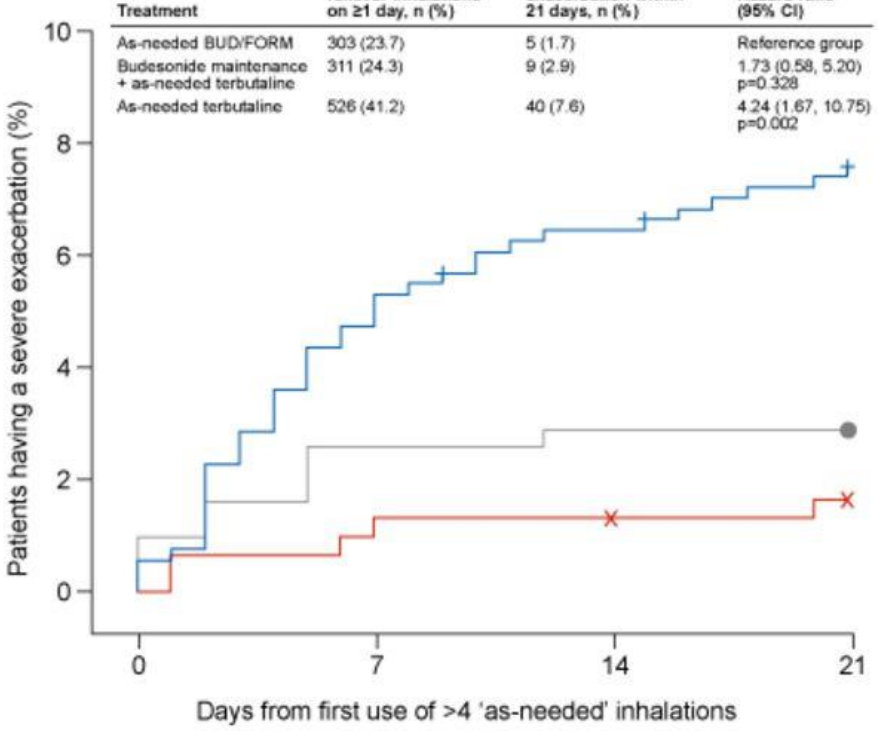
Number of 'as-needed' inhalations >2

Treatment	Patients with >2 reliever inhalations on ≥1 day, n (%)	Patients with severe exacerbation within 21 days, n (%)	Hazard ratio (95% CI)
As-needed BUD/FORM	850 (66.6)	10 (1.2)	Reference group
Budesonide maintenance + as-needed terbutaline	758 (59.1)	11 (1.5)	1.24 (0.53, 2.91) p=0.63
As-needed terbutaline	936 (73.3)	37 (4.0)	3.33 (1.65, 6.69) p=0.001

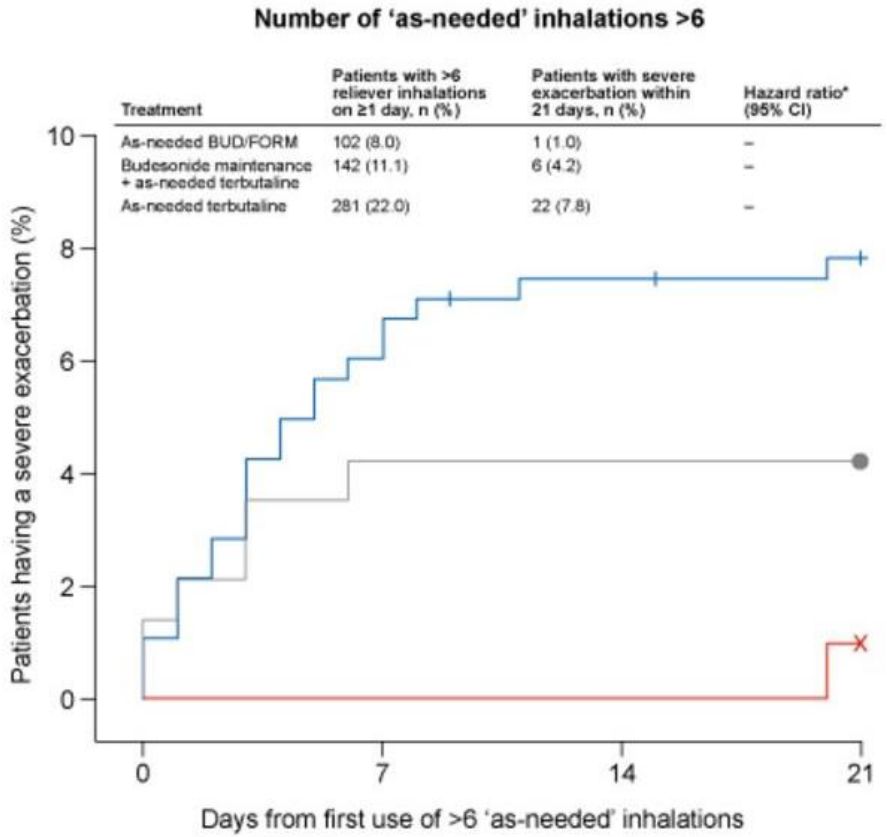


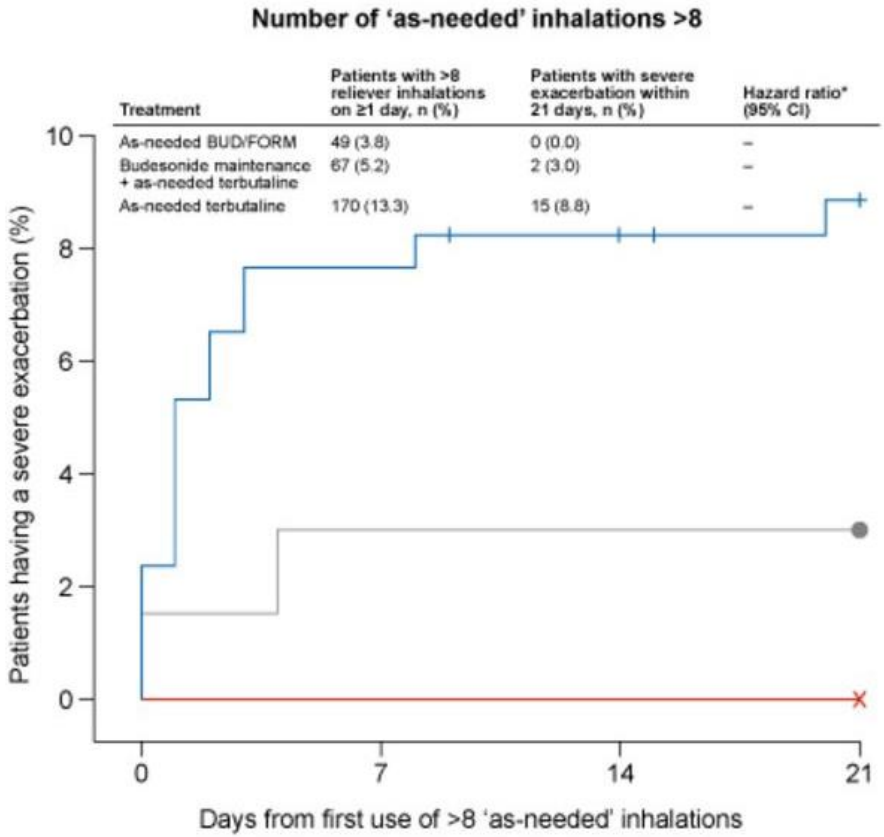
Number of 'as-needed' inhalations >4

Treatment	Patients with >4 reliever inhalations on ≥1 day, n (%)	Patients with severe exacerbation within 21 days, n (%)	Hazard ratio (95% CI)
As-needed BUD/FORM	303 (23.7)	5 (1.7)	Reference group
Budesonide maintenance + as-needed terbutaline	311 (24.3)	9 (2.9)	1.73 (0.58, 5.20) p=0.328
As-needed terbutaline	526 (41.2)	40 (7.6)	4.24 (1.67, 10.75) p=0.002



European Respiratory Journal 2018 52: Suppl. 62, OA1680.





As-needed BUD/FORM — Budesonide maintenance + as-needed terbutaline — As-needed terbutaline

*Hazard ratios were not calculated for the >6 and >8 as-needed inhalations subgroups, in view of the low event rate in the reference group (as-needed BUD/FORM; n=1 and n=0 exacerbations, respectively)

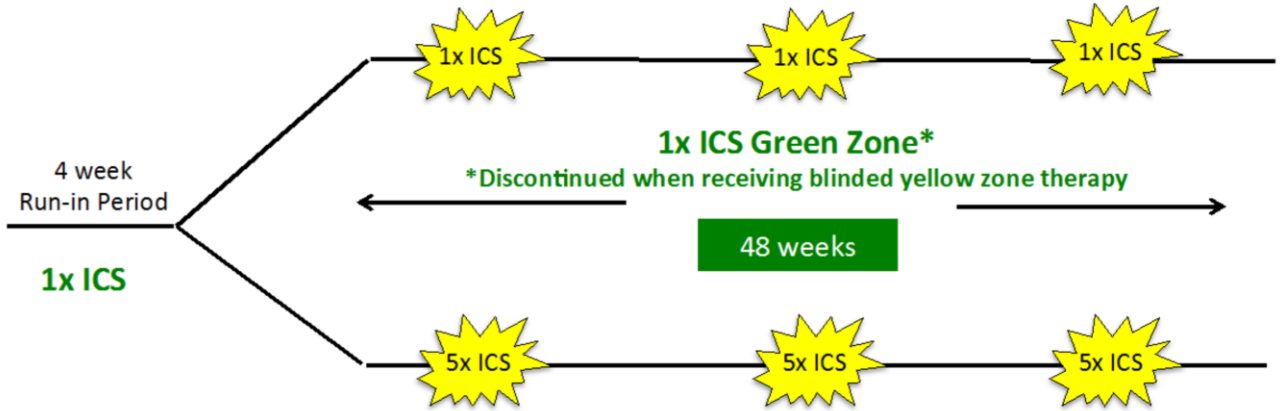
Fig. Kaplan-Meier plots showing time to first severe exacerbation in the 21 days following first day with >2, >4, >6 and >8 reliever inhalations

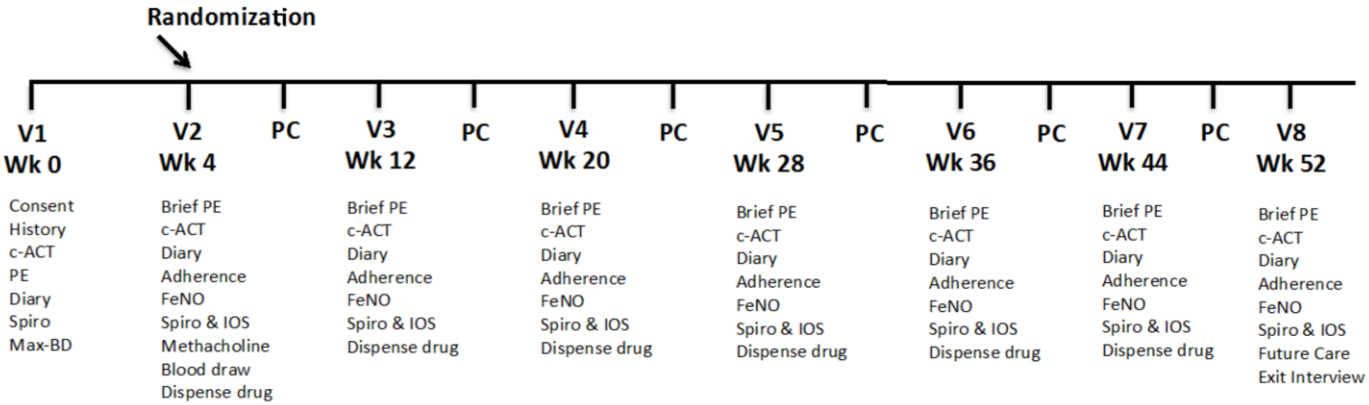
European Respiratory Journal 2018 52: Suppl. 62, OA1680.

- STICS -

the Step Up Yellow Zone ICS to Prevent Exacerbations Trial

- 5 to 11 years of age, n=254, mild-to-moderate persistent asthma,
- at least one exacerbation leading to systemic steroid treatment in the previous year
- fluticasone propionate at a dose of 44 μg per inhalation, two inhalations twice daily



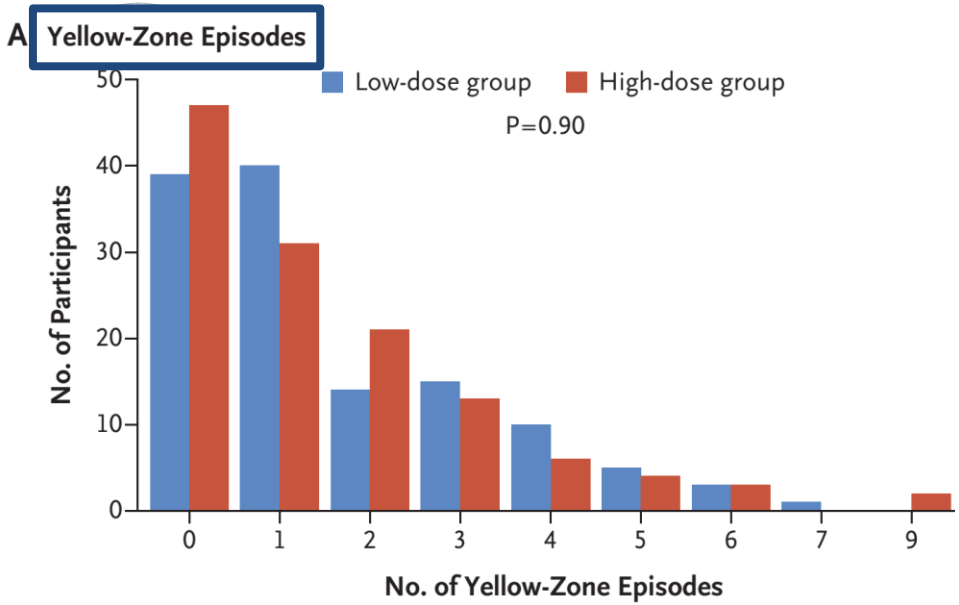


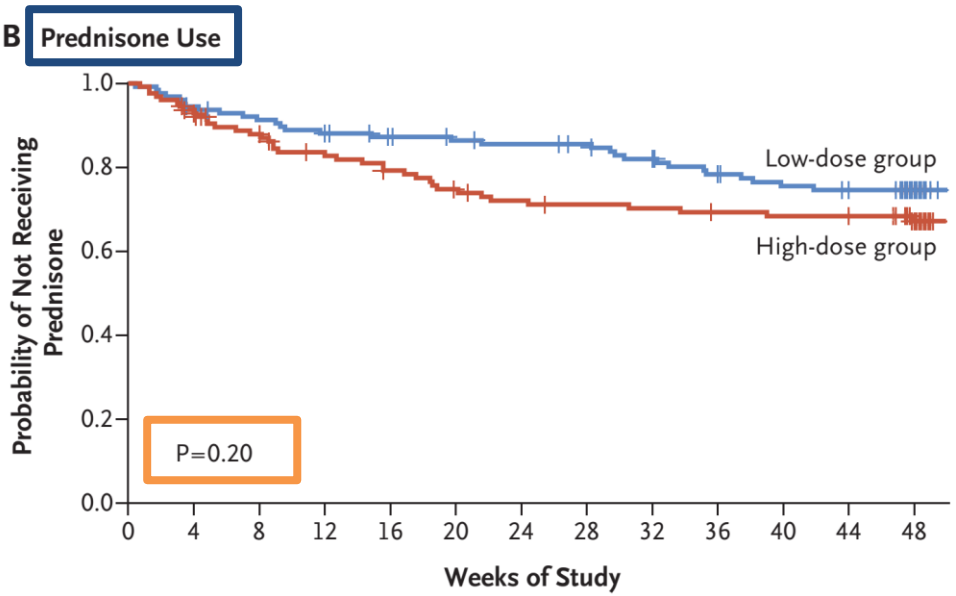
Jackson DJ, N Engl J Med 2018;378:891-901.

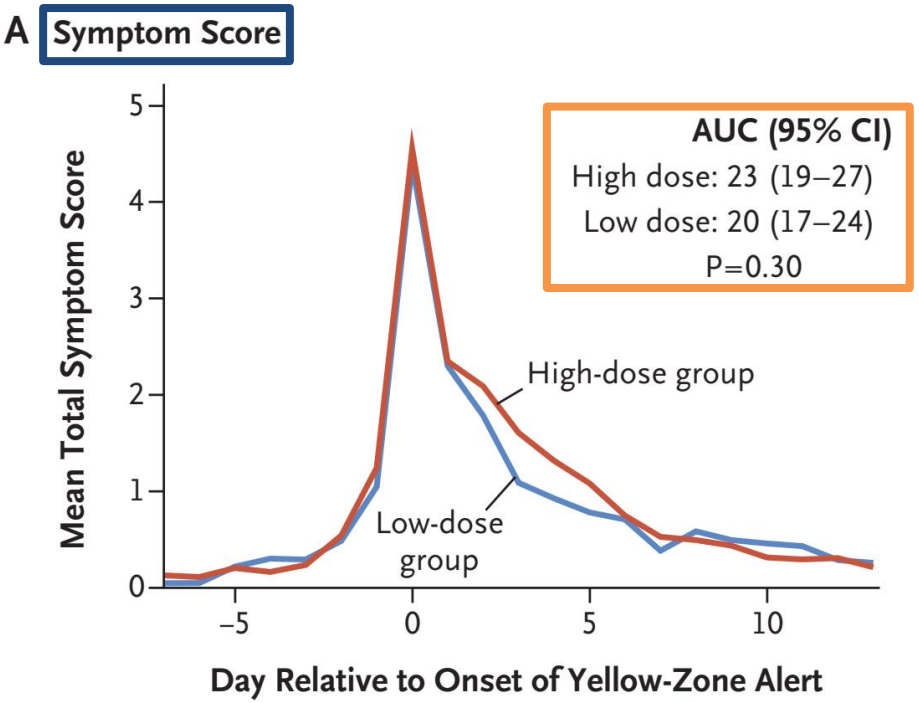
Outcomes & Growth

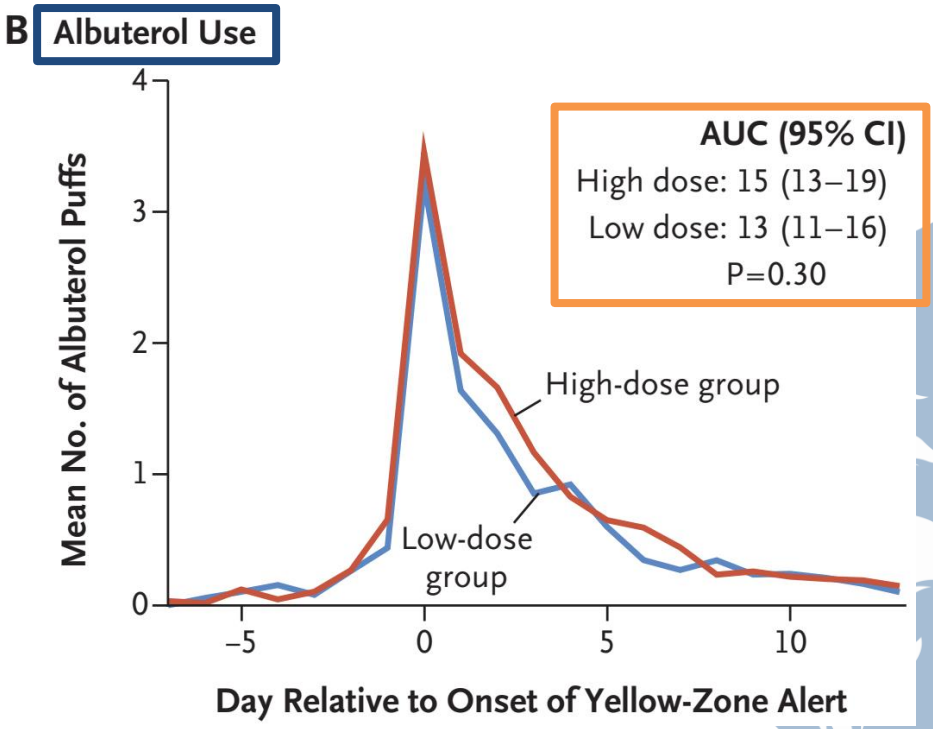
Outcomes	Low-Dose Group (N = 127)	High-Dose Group (N = 127)	Treatment Effect (95% CI)†	P Value
Primary outcome				
No. of exacerbations per year (95% CI)	0.37 (0.25 to 0.55)	0.48 (0.33 to 0.70)	1.3 (0.8 to 2.1)	0.30
Secondary outcomes				
No. of emergency department or urgent care visits per year (95% CI)	0.47 (0.31 to 0.72)	0.64 (0.42 to 0.96)	1.3 (0.8 to 2.4)	0.30
No. of hospitalizations	0	4	—	0.12
Equivalent of hydrocortisone exposure — g/yr (95% CI)				
Fluticasone only	10.6 (10.4 to 10.9)	12.2 (11.9 to 12.4)	1.14 (1.10 to 1.19)	
Fluticasone and prednisone	11.1 (10.6 to 11.4)	12.8 (12.4 to 13.2)	1.16 (1.10 to 1.22)	
Growth — cm/yr (95% CI)				
Mean	5.65 (5.48 to 5.81)	5.43 (5.26 to 5.60)	−0.23 (−0.47 to 0.01)	0.06
Effect per 7-day exposure to high-dose regimen				
Overall	—	−0.07 (−0.17 to 0.03)	−0.07 (−0.17 to 0.03)	0.20
According to age group‡				
5–7 yr	—	−0.12 (−0.22 to −0.02)	−0.12 (−0.22 to −0.02)	0.02
8–11 yr	—	0.02 (−0.21 to 0.26)	0.02 (−0.21 to 0.26)	0.80

Jackson DJ, N Engl J Med 2018;378:891-901.



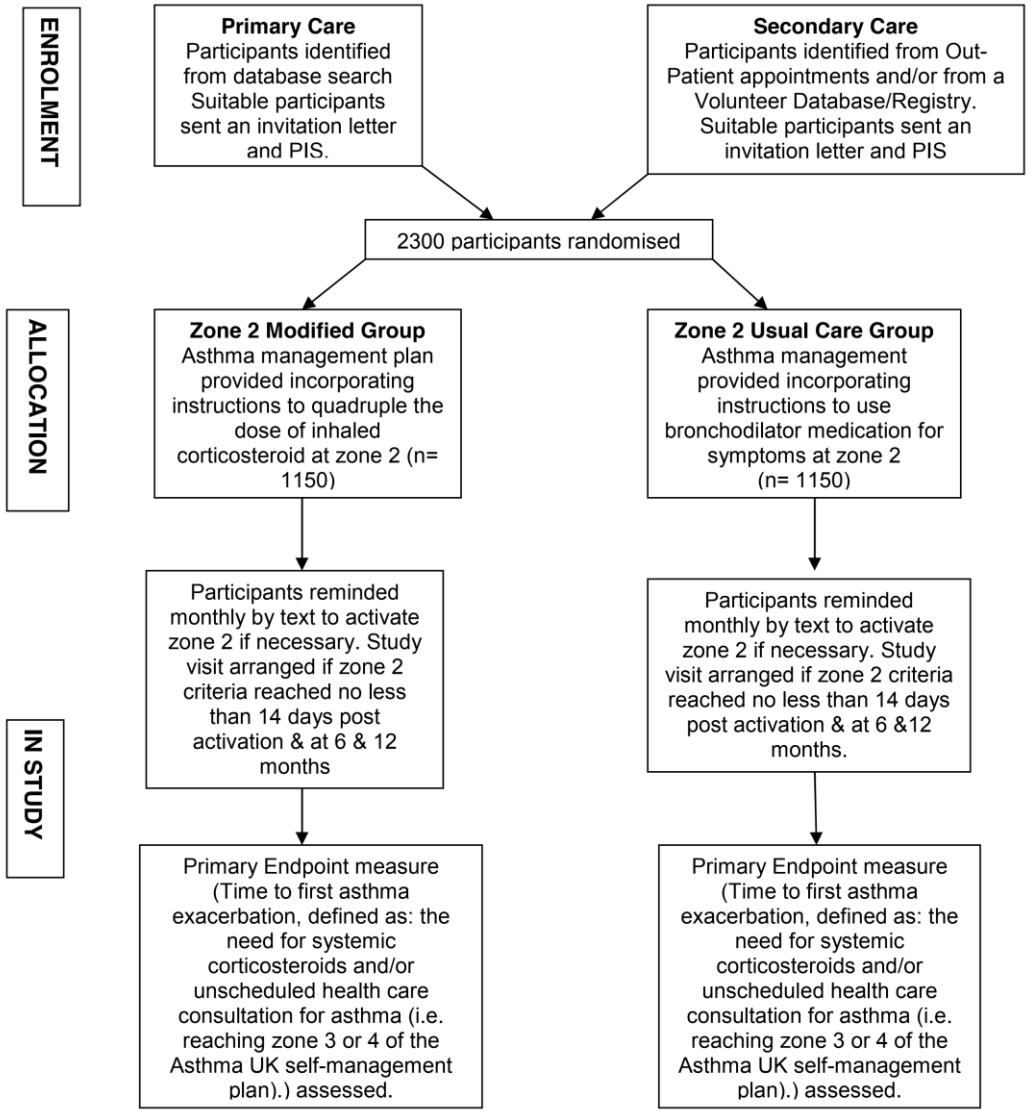






Jackson DJ, N Engl J Med 2018;378:891-901.

Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations



- **16 years** of age or older
- at least one **exacerbation** leading to systemic steroid treatment in the **previous year**
- The primary **outcome**: the time to a **first severe exacerbation**
  - systemic corticosteroid
  - unscheduled health care visit

McKeever T, N Engl J Med 2018;378:902-10.

Baseline Characteristics

Characteristic	Non-Quadrupling Group (N=965)	Quadrupling Group (N=957)
Age — yr		
Mean	56.7±15.2	56.2±15.5
Range	19–94	16–91
Sex — no. (%)		
Male	316 (33)	301 (31)
Female	649 (67)	656 (69)
Source of recruitment — no. (%)		
Primary care	774 (80)	785 (82)
Secondary care	191 (20)	172 (18)
Mean peak expiratory flow at screening — liters/min	381.1±112.2	386.9±110.8
Type of inhaler — no. (%)		
Glucocorticoid	303 (31)	275 (29)
Combination	662 (69)	682 (71)
Type of inhaled glucocorticoid — no. (%)		
Beclomethasone	388 (40)	325 (34)
Budesonide	220 (23)	225 (24)
Fluticasone	350 (36)	401 (42)
Ciclesonide	7 (1)	6 (1)
Maintenance dose of inhaled glucocorticoids		
Median (IQR) — μg/day of beclomethasone or equivalent	800 (400–1000)	800 (400–1000)
Range — μg/day of beclomethasone or equivalent	100–4000	80–4000
Low: ≤1000 μg/day of beclomethasone or equivalent — no. (%)	752 (78)	743 (78)
High: >1000 μg/day of beclomethasone or equivalent — no. (%)	213 (22)	214 (22)
Smoking status — no. (%)		
Never smoked	552 (57)	564 (59)
Current smoker	66 (7)	59 (6)
Former smoker	347 (36)	334 (35)
Pack-years among current or former smokers		
No. of participants	413	393
Mean pack-yr	13.9±16.1	12.3±14.5
Mini-AQLQ overall score†		
No. of participants	959	944
Mean score	5.0±1.2	5.1±1.2

McKeever T, N Engl J Med 2018;378:902-10.

Asthma Self-management Plan

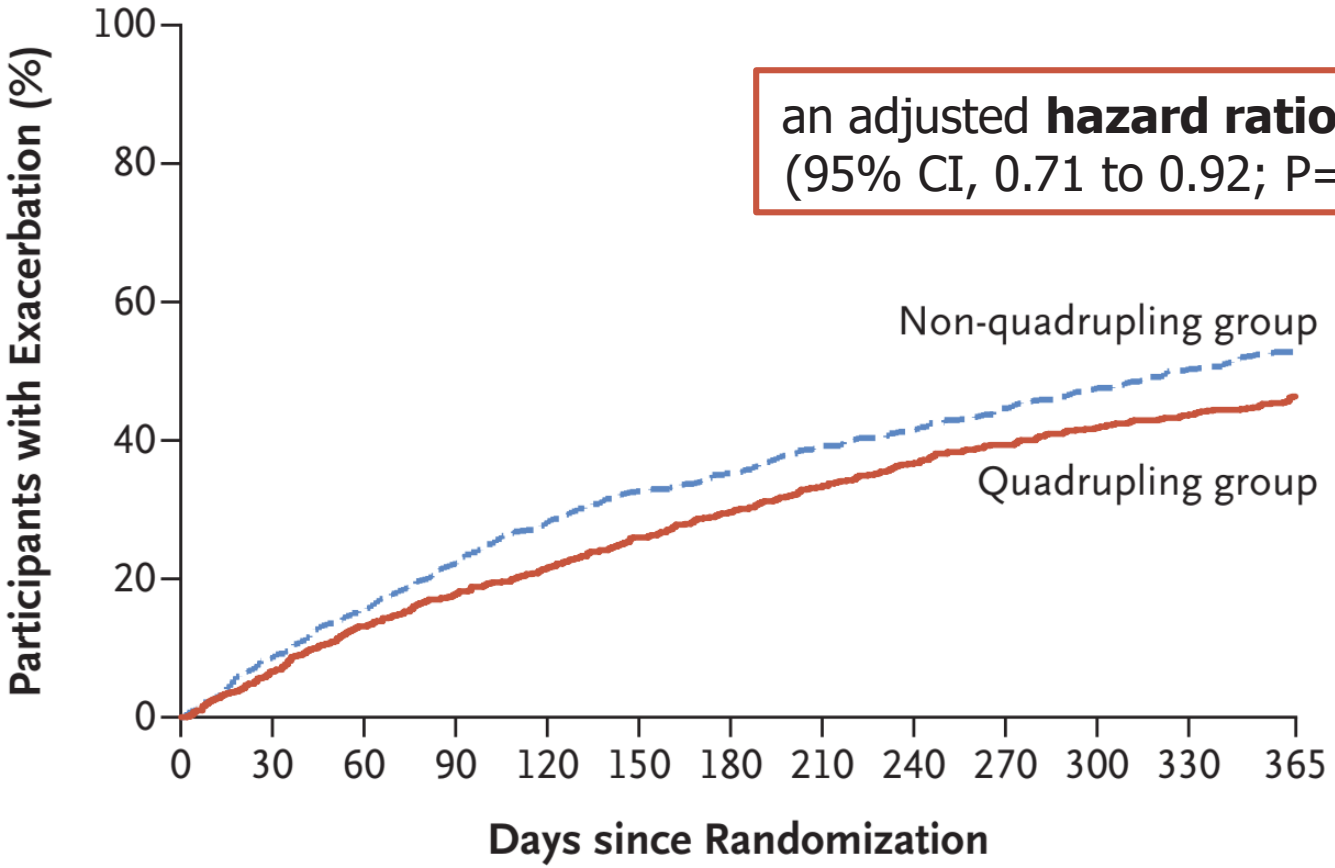
Zone 2

ZONE 1	ZONE 2	ZONE 3	ZONE 4
Your asthma is under control if: • You have no or minimal symptoms during the day and night (wheezing, coughing, shortness of breath or tightness in the chest) • You can do all of your normal activities without asthma symptoms • Your peak flow reading is normal or near normal for you: _____	**Your asthma is getting worse if you have ONE or MORE of the following:** • You need your reliever inhaler more than usual • You have more difficulty sleeping because of your asthma • Your peak flow is below **80**	**Your asthma is much more severe if you have ONE or MORE of the following:** • You need to take your reliever inhaler every four hours or more often • You are unable to manage your normal activities • You have symptoms during the day or night • Your peak flow reading is below _____	**It is an asthma emergency if any of the following happen:** • Your reliever inhaler (usually blue) does not help. • One or more of your symptoms get worse (wheezing, coughing, shortness of breath or tightness in the chest) • You are too breathless to speak • Your peak flow reading isbelow _____
Action	**Action**	**Action**	**Action**
Take your preventer inhaler every day, even when you are feeling well. Your preventer inhaler is:_____ Take your reliever inhaler if you have symptoms. Your reliever inhaler is:_____	Use your reliever inhaler to relieve your symptoms and increase your preventer medication as described below: Write the plan here: **Reliever inhaler ± Quadruple ICS** Once your symptoms or peak flow have returned to normal or after a maximum of 14 days return to your normal treatment. **If your symptoms get worse follow Zone 3 instructions**	Continue taking your medicine as shown in Zone 2. Continue to take your reliever medicine when needed. If you have been prescribed steroid tablets, start taking them and let your doctor or asthma nurse know within 24 hours If you have not been prescribed steroid tablets see a doctor or asthma nurse urgently Take____5mg Predinisolone tablets immediately and again every morning for_____ days or until your symptoms have improved and your peak flow is back to normal (as in Zone 1). For you this means _____.	1.Take one to two puffs of your reliever inhaler (usually blue) 2.Sit up and take slow steady breaths 3.If you don't feel better, continue to take two puffs of your reliever inhaler every two minutes. You can take up to ten puffs 4.If you do not feel better after taking your reliever inhaler as above or if you are worried at any time call 999 5.If an ambulance does not arrive within 15 minutes, and you do not feel any better, repeat step 3
If you are always in Zone 1, your doctor or asthma nurse may want to reduce your regular medicines.	**Start to record your morning peak flow, symptoms and medication in the study diary.**	**If you are in Zone 3 ask your doctor or asthma nurse for an asthma review, even if you feel better.**	**If your symptoms improve and you do not need to call 999 you will need to see your doctor or asthma nurse within 24 hours** **Do not delay calling for help if your asthma is getting worse, day or night**
If you have stopped your treatment for any reason you should restart it at the first sign of asthma	**Phone you research nurse to arrange a study visit.**	**Do not ignore worsening asthma. Get medical help**	**This information does not apply to people using Symbicort SMART regime who should discuss their advice with their doctor or asthma nurse**

Zone 2 or above : **562/957** in the **quadrupling** group,
552/965 in the **non-quadrupling** group

McKeever T, N Engl J Med 2018;378:902-10.

Time to the First Severe Asthma Exacerbation



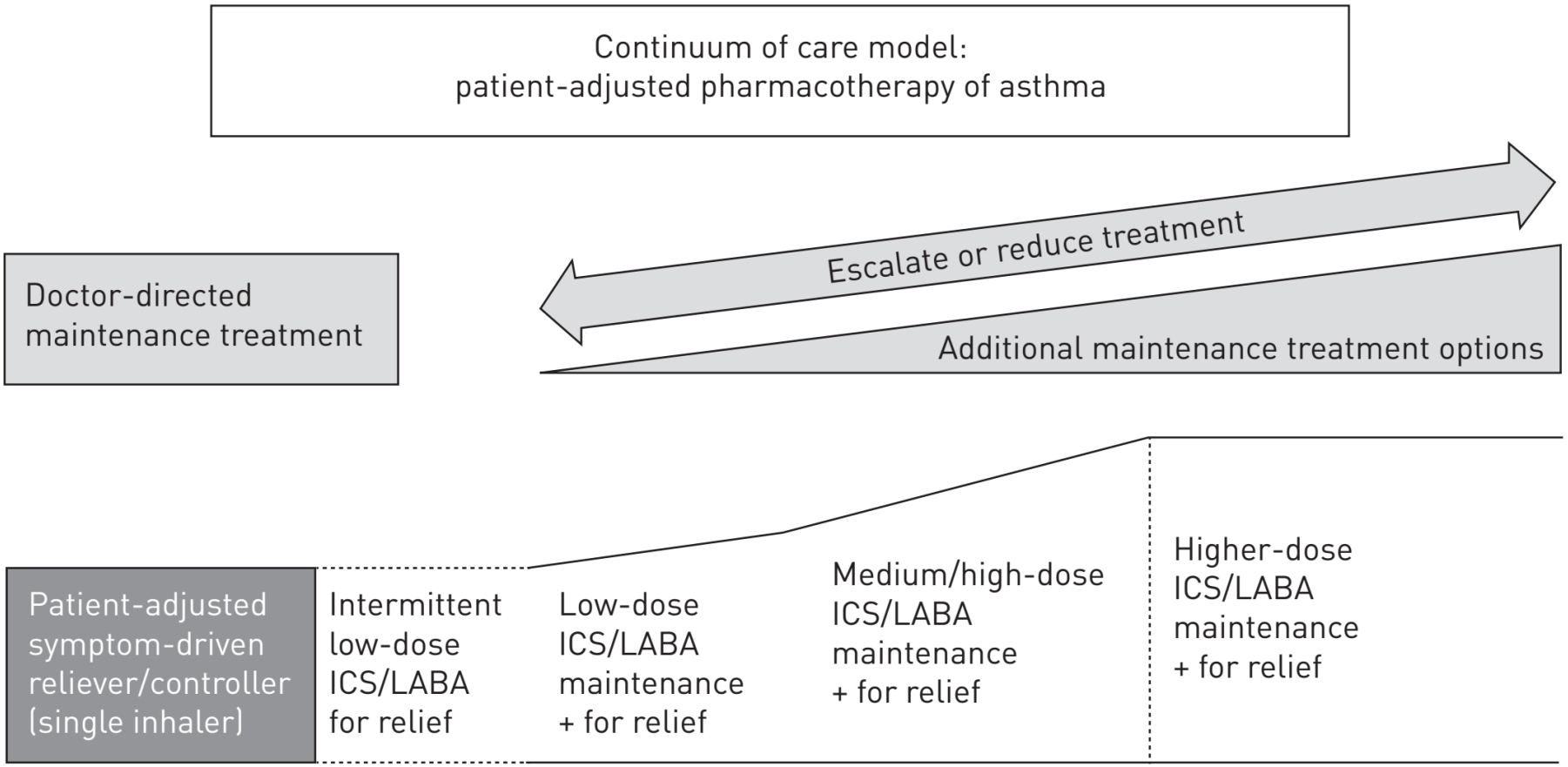
an adjusted **hazard ratio: 0.81**
(95% CI, 0.71 to 0.92; P=0.002)

No. at Risk							
Non-quadrupling group	938	791	671	592	521	463	349
Quadrupling group	933	806	727	644	558	508	366

McKeever T, N Engl J Med 2018;378:902-10.

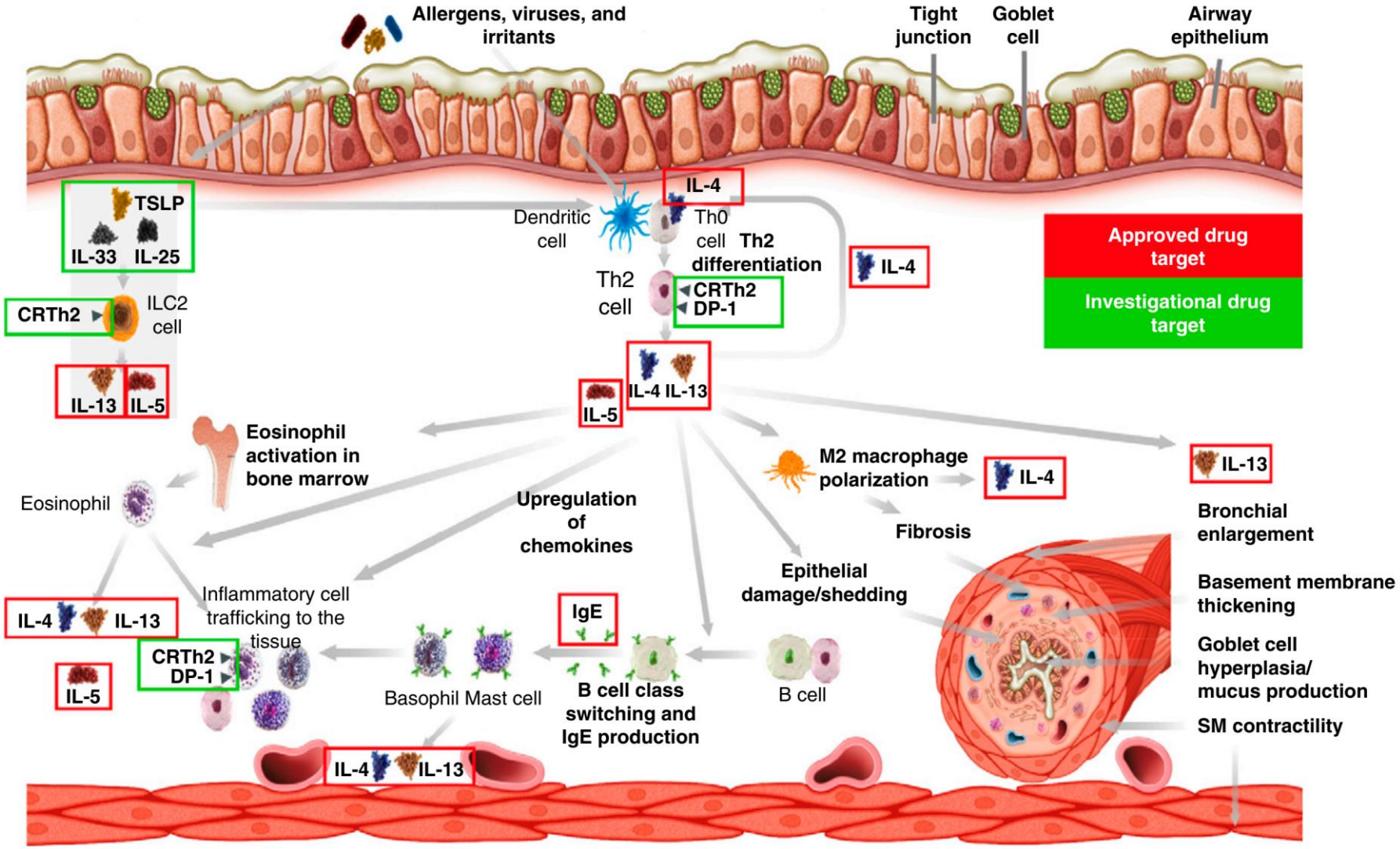
Continuum of Care

Patient-adjusted Plus Physician-directed Step-wedge Approach to Pharmacotherapy in Asthma



O'Byrne PM, Eur Respir J 2017;50.

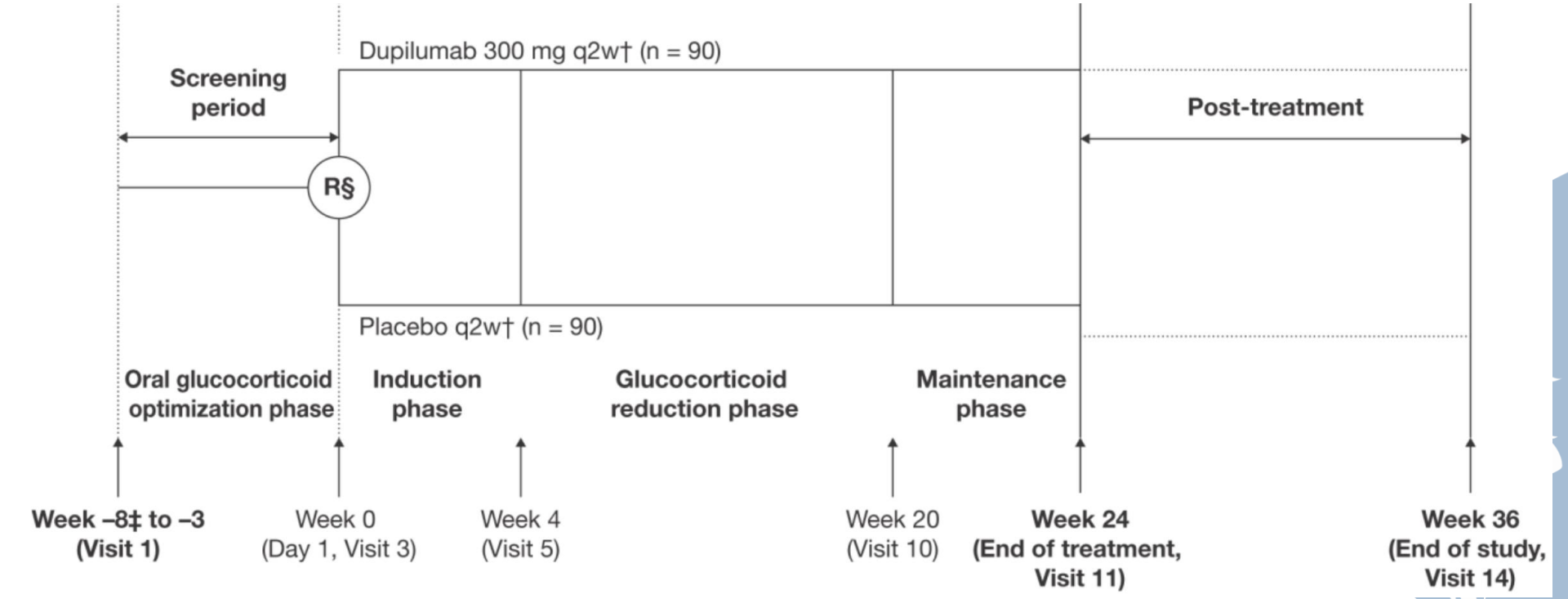
the Immunopathobiology of Asthma



McGregor MC, et al. Am J Respir Crit Care Med 2019;199:433-45.

LIBERTY ASTHMA VENTURE

- 210 patients with **oral glucocorticoid–dependent severe asthma**
- **Dupilumab** (at a dose of **300 mg**) or placebo every 2 weeks for 24 weeks
- adjusting glucocorticoid in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks.
- the primary end point: the percentage **reduction in the glucocorticoid dose** at week 24



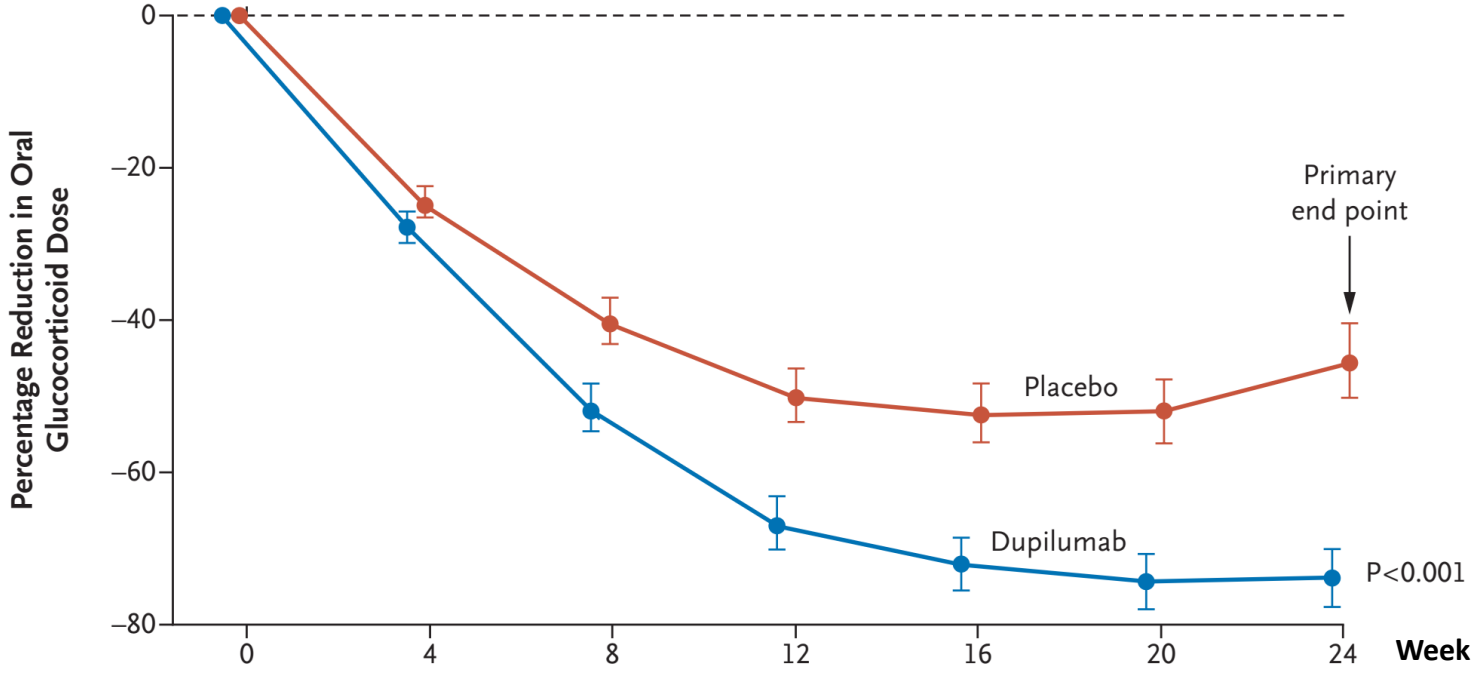
Rabe KF, N Engl J Med 2018;378:2475-85.

Baseline Characteristics

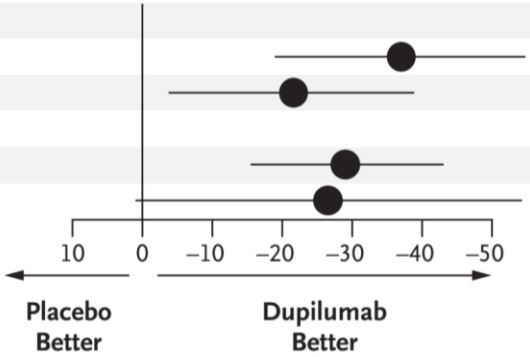
Characteristic	Placebo Group (N = 107)	Dupilumab Group (N = 103)	Total (N = 210)
Age — yr	50.7±12.8	51.9±12.5	51.3±12.6
Male sex — no. (%)	42 (39)	41 (40)	83 (40)
No. of severe asthma exacerbations in previous year	2.17±2.24	2.01±2.08	2.09±2.16
Time since first oral glucocorticoid prescription — yr	1.64±3.54	1.77±3.52	1.70±3.52
Daily oral glucocorticoid dose — mg/day			
Dose before adjustment phase	11.83±6.02	11.79±6.40	11.81±6.20
Adjusted dose	11.75±6.31	10.75±5.90	11.26±6.12
Prebronchodilator FEV_1 — liters	1.63±0.61	1.53±0.53	1.58±0.57
Prebronchodilator FEV_1 — % of predicted value	52.69±15.14	51.64±15.28	52.18±15.18
FEV_1 reversibility — liters†	0.28±0.32	0.29±0.31	0.28±0.31
Any relevant medical history — no. (%)‡	86 (80)	76 (74)	162 (77)
Nasal polyposis	38 (36)	33 (32)	71 (34)
Food allergy	10 (9)	10 (10)	20 (10)
Former smoker — no. (%)	17 (16)	24 (23)	41 (20)
Time since cessation of smoking — yr	16.98±11.01	13.99±10.96	15.23±10.94
ACQ-5 score§	2.58±1.09	2.42±1.24	2.50±1.16
Blood eosinophil count — cells/mm^3	325±298	370±316	347±307
F_{ENO} — ppb	39.62±34.12	35.55±28.34	37.61±31.38

Rabe KF, N Engl J Med 2018;378:2475-85.

Percentage Reduction in Oral Glucocorticoid Dose



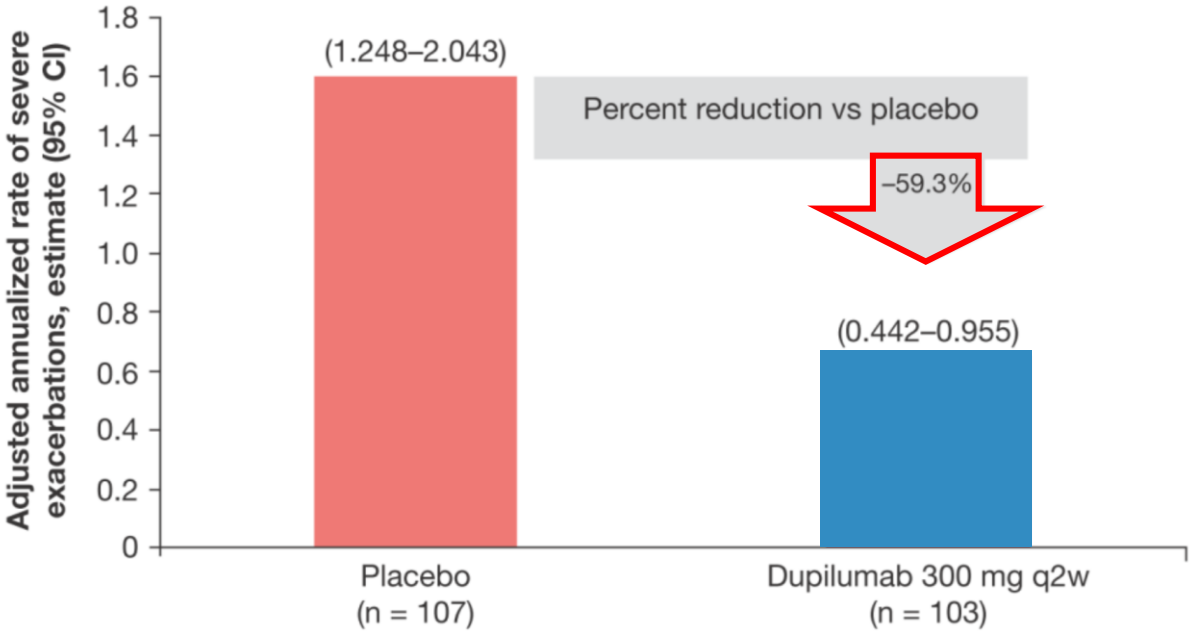
Subgroup	Placebo (N=107)	Dupilumab (N=103)	Least-Squares Mean Difference (95% CI)	P Value for Interaction
	no. of patients		*percentage points*	
≥300 or <300 cells/mm³				0.24
≥300	41	48	−36.8 (−54.7 to −18.9)	
<300	66	55	−21.3 (−38.8 to −3.9)	
≥150 or <150 cells/mm³				0.71
≥150	69	81	−29.4 (−43.1 to −15.7)	
<150	38	22	−26.9 (−54.5 to 0.7)	



Rabe KF, N Engl J Med 2018;378:2475-85.

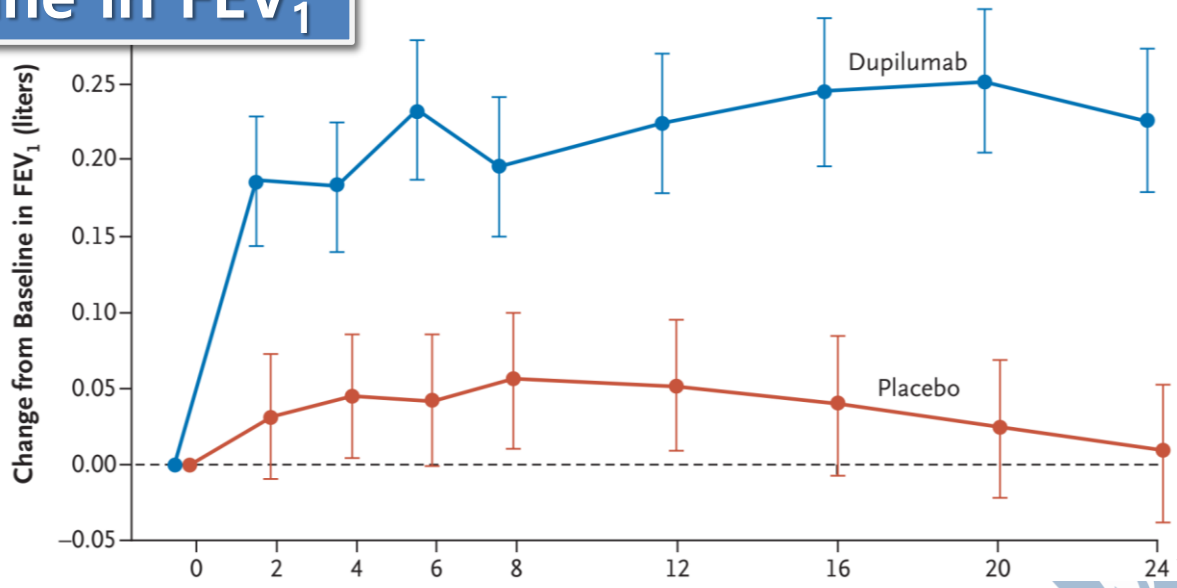
Rate of Severe Exacerbations

Reduced exacerbation **59%** (95% CI, 37 to 74)



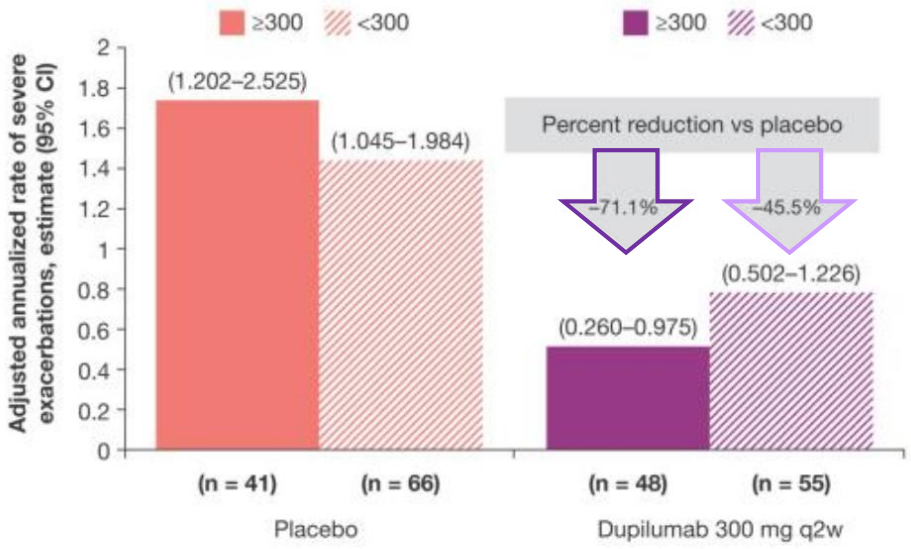
Change from Baseline in FEV_1

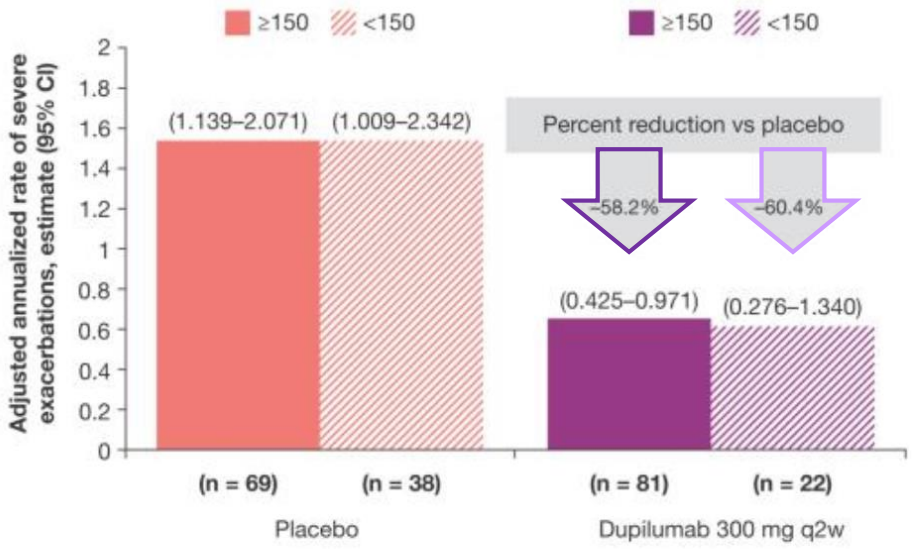
Higher by a mean value of **0.22 liters** (95% CI, 0.09 to 0.34)

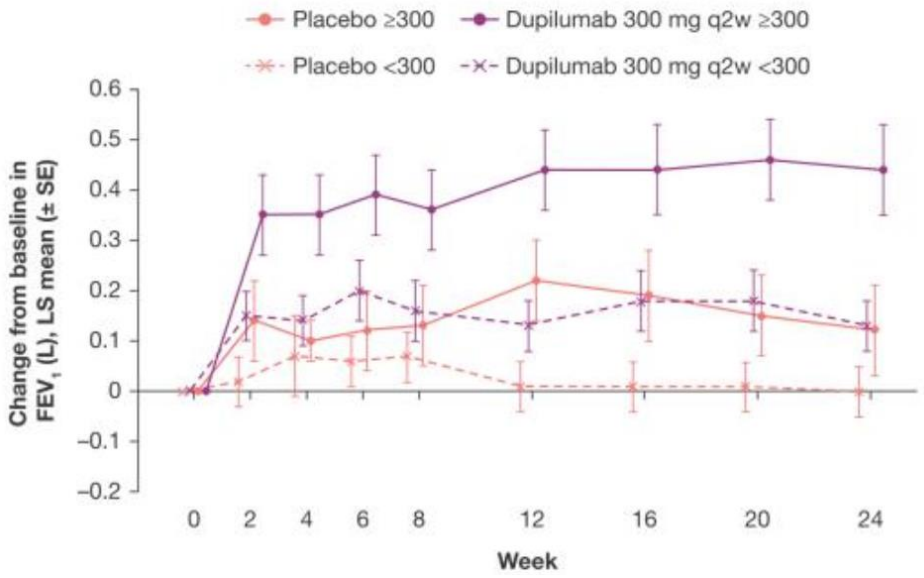


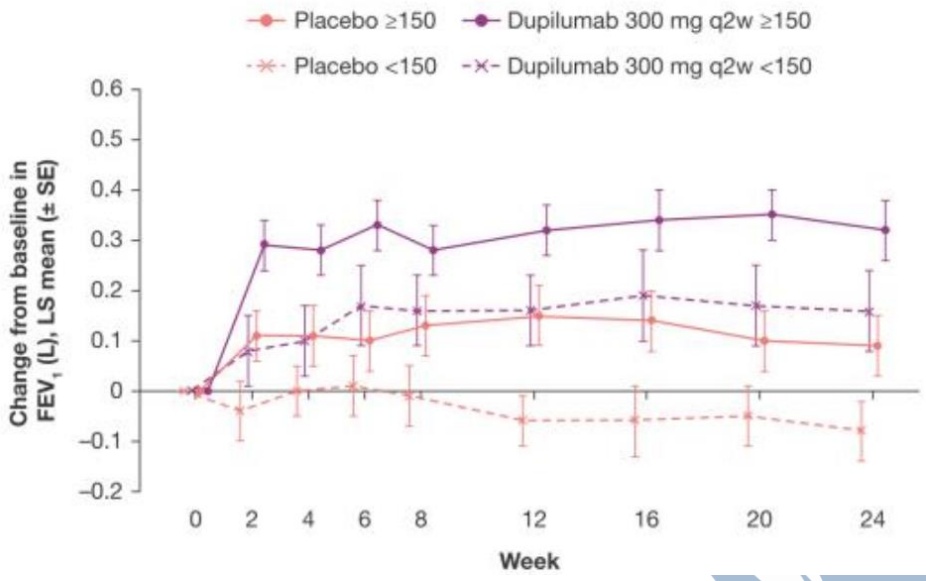
Rabe KF, N Engl J Med 2018;378:2475-85

Severe Exacerbation & FEV_1 by Baseline Blood Eosinophil Subgroups









Rabe KF, N Engl J Med 2018;378:2475-85

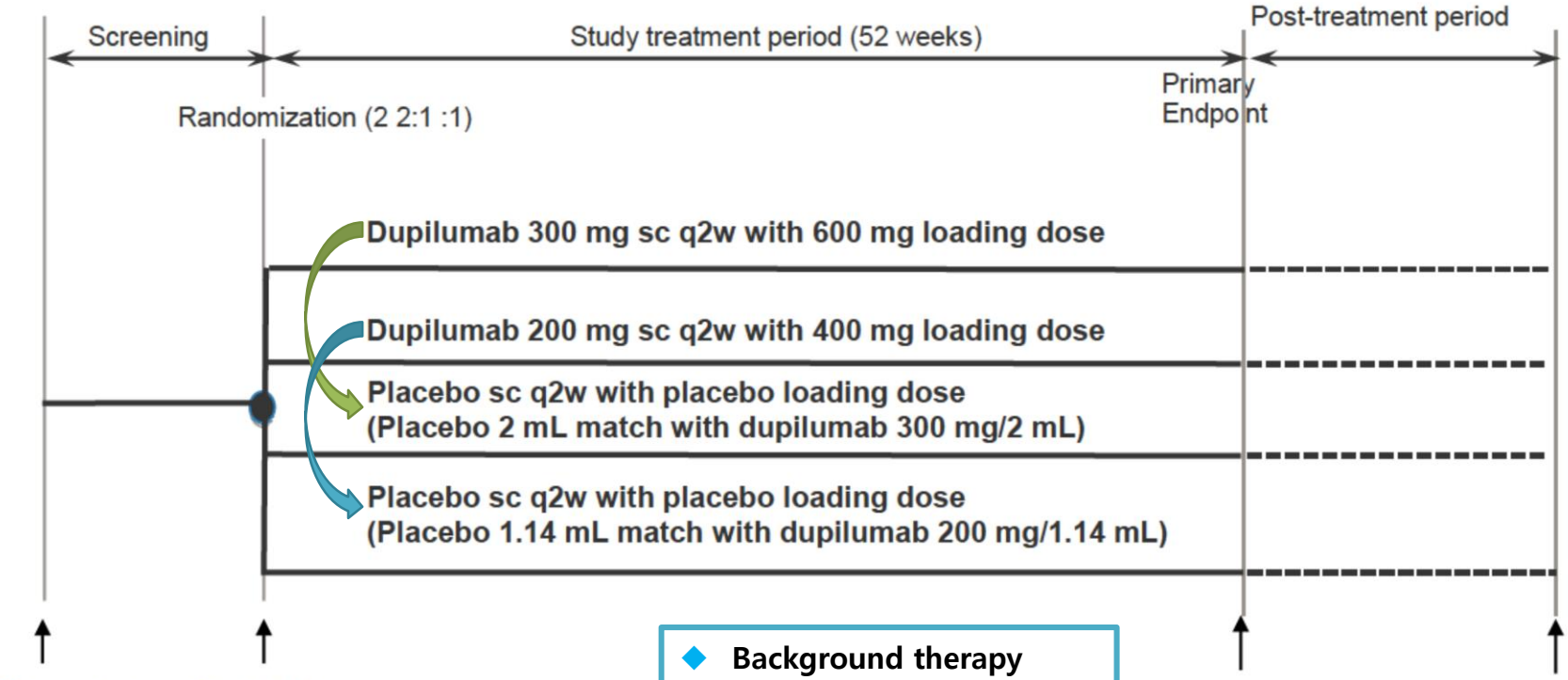
Overview of Adverse Events

Event	Placebo Group (N = 107)	Dupilumab Group (N = 103)
	number (percent)	
Any adverse event	69 (64)	64 (62)
Any serious adverse event	6 (6)	9 (9)
Any adverse event leading to death	0	0
Any adverse event leading to permanent discontinuation of trial regimen	4 (4)	1 (1)
Adverse event occurring in ≥5% of patients in either group†		
Viral upper respiratory tract infection	19 (18)	9 (9)
Bronchitis	6 (6)	7 (7)
Sinusitis	4 (4)	7 (7)
Influenza	6 (6)	3 (3)
Eosinophilia‡	1 (1)	14 (14)
Injection-site reaction§	4 (4)	9 (9)
≥1 measurement of blood eosinophil count >3000 cells/mm^3	1 (1)	13 (13)

Rabe KF, N Engl J Med 2018;378:2475-85.

LIBERTY ASTHMA QUEST

- 1902 patients 12 years of age or older with uncontrolled asthma
- The primary **end points**: the annualized **rate** of severe asthma **exacerbations**
  the absolute change from baseline to week 12 in the **FEV1**



- **Background therapy**

Medium to high dose of ICS + controllers (LABA/LTRA)

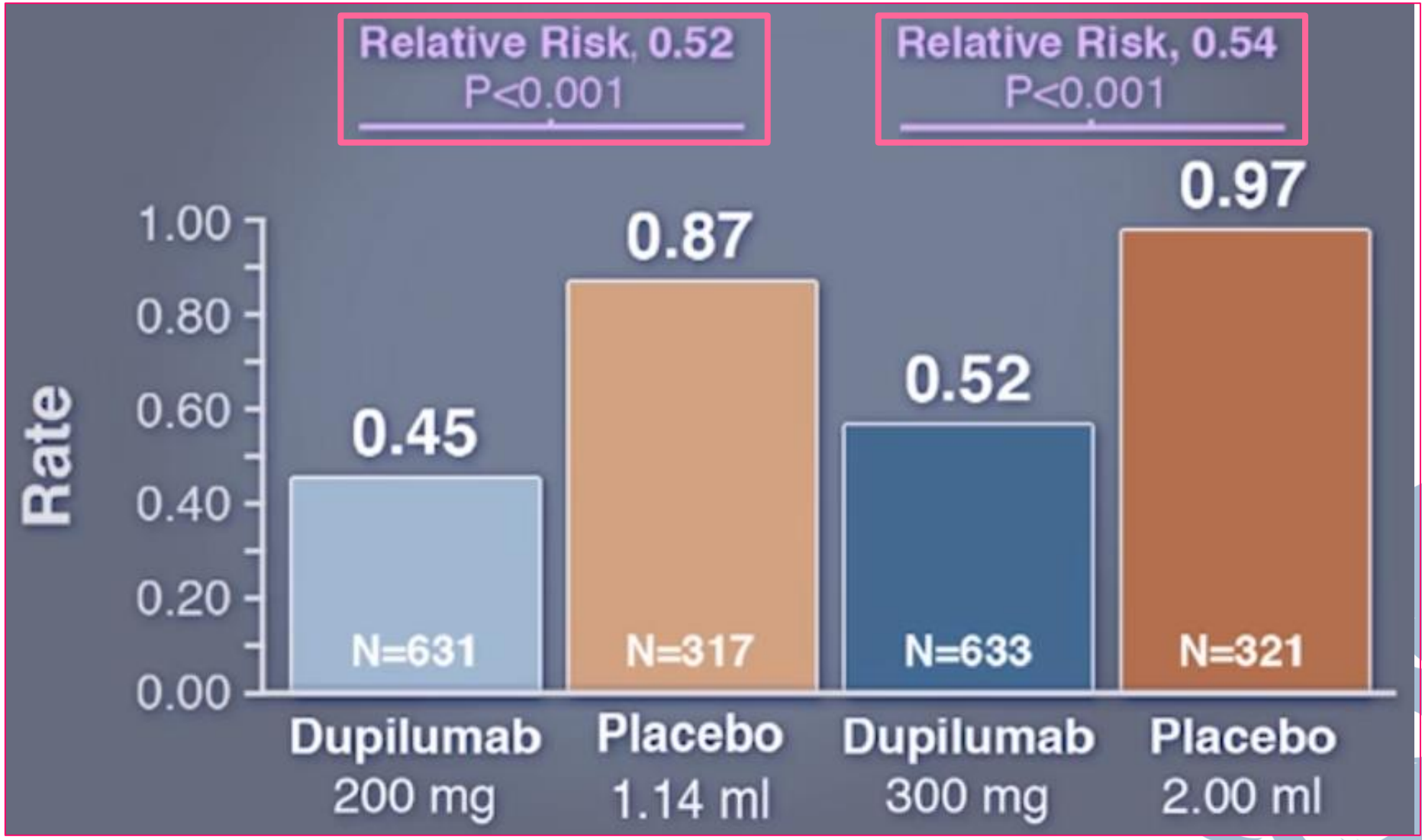
Castro M, N Engl J Med 2018;378:2486-96.

Baseline Characteristics

Characteristic	Placebo, 1.14 ml (N=317)	Dupilumab, 200 mg (N=631)	Placebo, 2.00 ml (N=321)	Dupilumab, 300 mg (N=633)	Overall Population (N=1902)
Age — yr	48.2±15.6	47.9±15.3	48.2±14.7	47.7±15.6	47.9±15.3
Female sex — no. (%)	198 (62.5)	387 (61.3)	218 (67.9)	394 (62.2)	1197 (62.9)
Prebronchodilator FEV_1 — liters	1.76±0.61	1.78±0.62	1.75±0.57	1.78±0.60	1.78±0.60
Percent of predicted normal value	58.43±13.22	58.38±13.52	58.35±13.87	58.51±13.52	58.43±13.52
FEV_1 reversibility — %	25.06±18.76	27.39±22.79	26.45±17.65	25.73±23.79	26.29±21.73
No. of exacerbations in past year	2.07±1.58	2.07±2.66	2.31±2.07	2.02±1.86	2.09±2.15
Use of high-dose inhaled glucocorticoid — no. (%)	172 (54.3)	317 (50.2)	167 (52.0)	323 (51.0)	979 (51.5)
ACQ-5 score†	2.71±0.73	2.76±0.80	2.77±0.77	2.77±0.76	2.76±0.77
Ongoing atopic or allergic condition — no. (%)	266 (83.9)	509 (80.7)	266 (82.9)	524 (82.8)	1565 (82.3)
Nasal polyposis or chronic rhinosinusitis — no. (%)	73 (23.0)	141 (22.3)	80 (24.9)	145 (22.9)	439 (23.1)
Former smoker — no. (%)	59 (18.6)	126 (20.0)	67 (20.9)	116 (18.3)	368 (19.3)
No. of pack-yr	3.96±2.81	3.89±2.69	4.07±3.12	4.15±3.04	4.02±2.89
Biomarker levels					
Blood eosinophil count — cells/mm^3					
Mean	370±338	349±345	391±419	351±369	360±366
Median (range)	270 (0–2200)	250 (0–3610)	265 (0–3580)	250 (0–4330)	255 (0–4330)
FE_{NO} — ppb	34.47±28.54	34.45±34.91	38.39±38.00	34.01±29.74	34.97±32.85
Total IgE — IU/ml	394±625	461±818	448±797	415±701	432±747

Castro M, N Engl J Med 2018;378:2486-96.

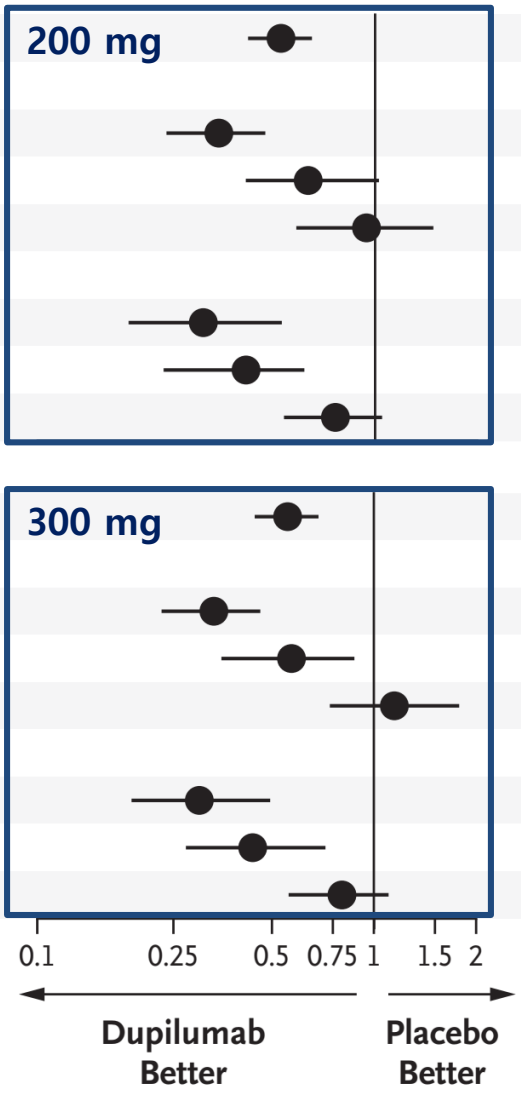
Annualized Rate of Severe Asthma Exacerbations



Castro M, N Engl J Med 2018;378:2486-96.

Forest Plots of the Risk of Severe Exacerbation

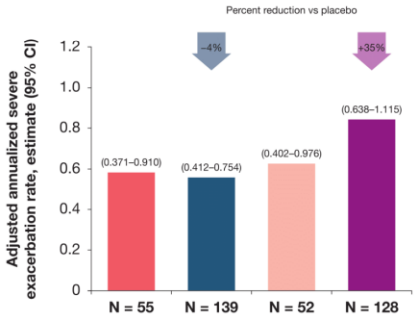
Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
Fe_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)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



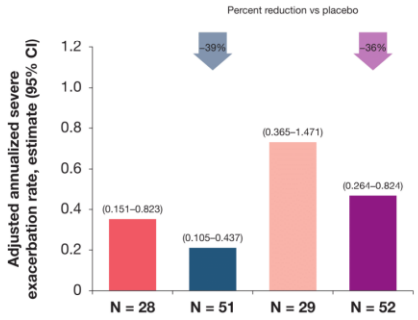
Castro M, N Engl J Med 2018;378:2486-96.

Severe Exacerbation by Baseline FENO & Blood Eosinophil Subgroups

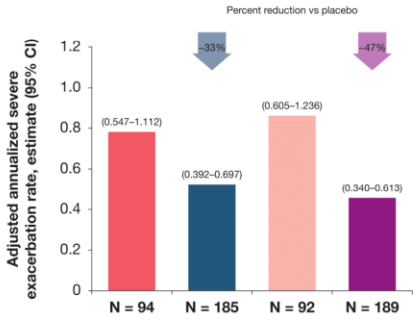
FE_{NO} <25 ppb and eosinophils <150 cells/μL (19.9% of ITT population)



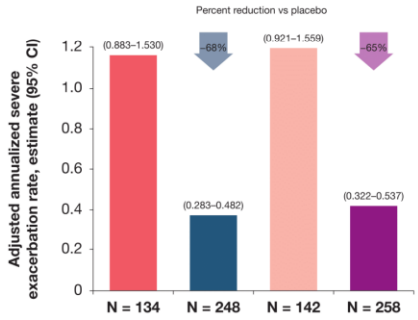
FE_{NO} ≥25 ppb and eosinophils <150 cells/μL (8.5% of ITT population)



FE_{NO} <25 ppb and eosinophils ≥150 cells/μL (29.9% of ITT population)

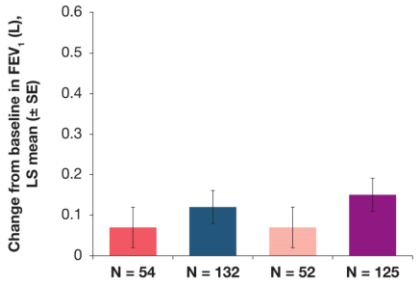


FE_{NO} ≥25 ppb and eosinophils ≥150 cells/μL (41.7% of ITT population)

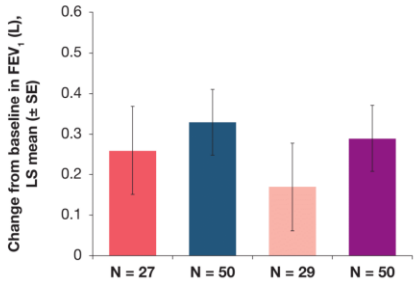


Change of FEV_1 by Baseline FENO & Blood Eosinophil Subgroups

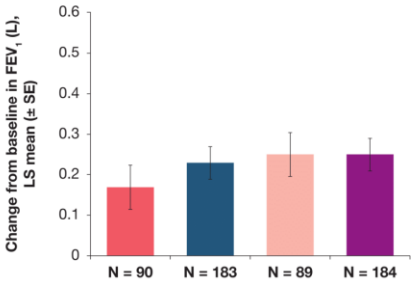
FE_{NO} <25 ppb and eosinophils <150 cells/μL (19.9% of ITT population)



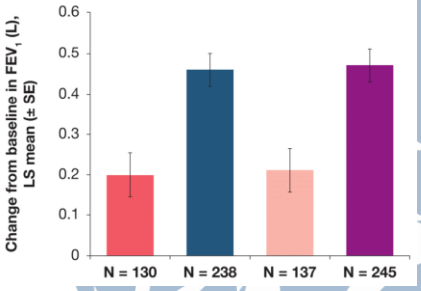
FE_{NO} ≥25 ppb and eosinophils <150 cells/μL (8.5% of ITT population)



FE_{NO} <25 ppb and eosinophils ≥150 cells/μL (29.9% of ITT population)



FE_{NO} ≥25 ppb and eosinophils ≥150 cells/μL (41.7% of ITT population)

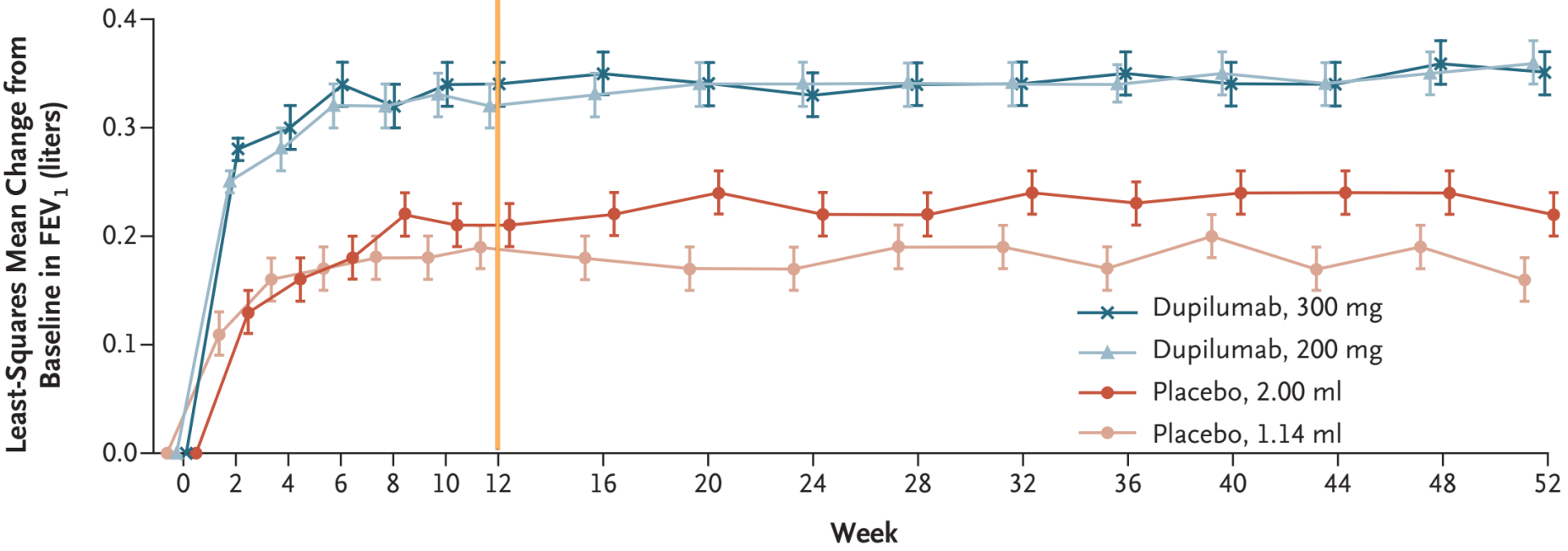


Castro M, N Engl J Med 2018;378:2486-96.

Change in the Prebronchodilator FEV_1

0.34 vs. **0.21 L** (Dupilumab 300 mg vs. Placebo, 2.00 ml)

0.32 vs. **0.18 L** (Dupilumab, 200 mg vs. Placebo, 1.14 ml)



P<0.001 for the comparisons of each Dupilumab dose with matched placebo at week 12

Castro M, N Engl J Med 2018;378:2486-96.

Overview of Adverse Events

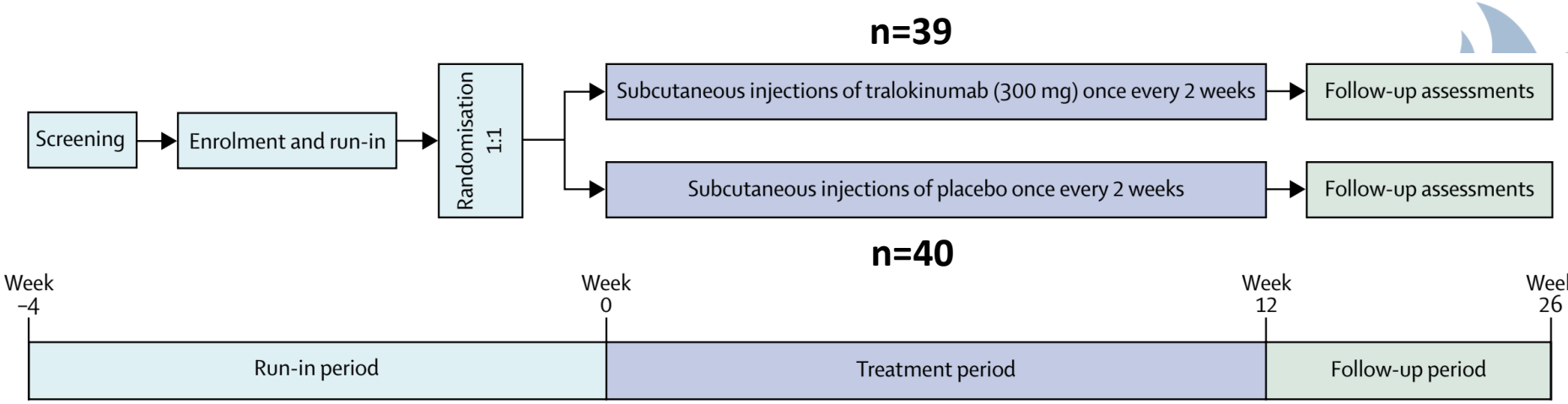
Event	Placebo, 1.14 ml (N=313)	Dupilumab, 200 mg (N=631)	Placebo, 2.00 ml (N=321)	Dupilumab, 300 mg (N=632)	Combined Placebo (N=634)	Combined Dupilumab (N=1263)
	number of patients (percent)					
Any adverse event	257 (82.1)	508 (80.5)	270 (84.1)	515 (81.5)	527 (83.1)	1023 (81.0)
Any serious adverse 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)

Castro M, N Engl J Med 2018;378:2486-96.

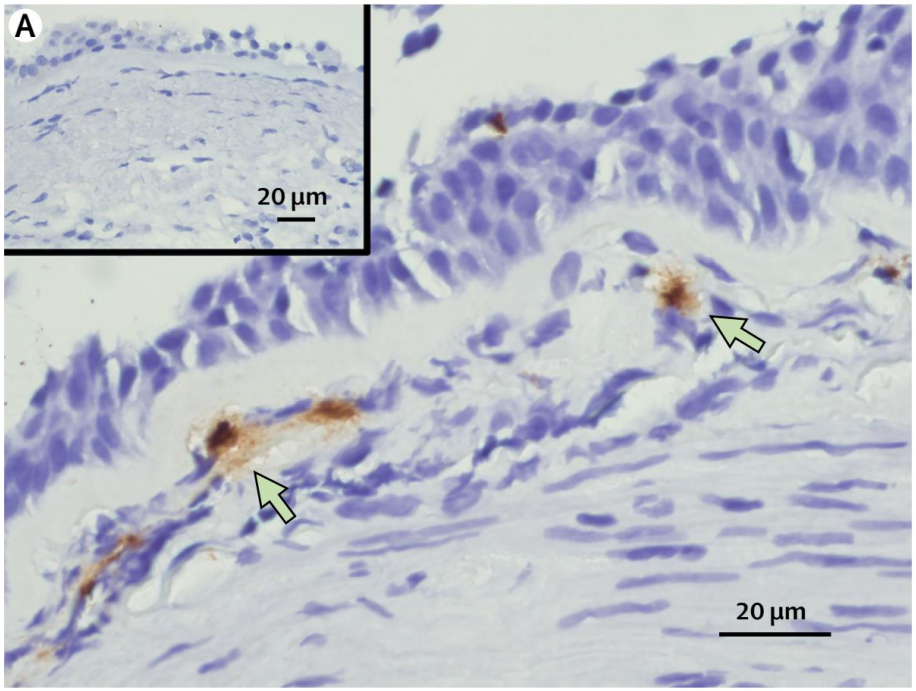
- MESOS -

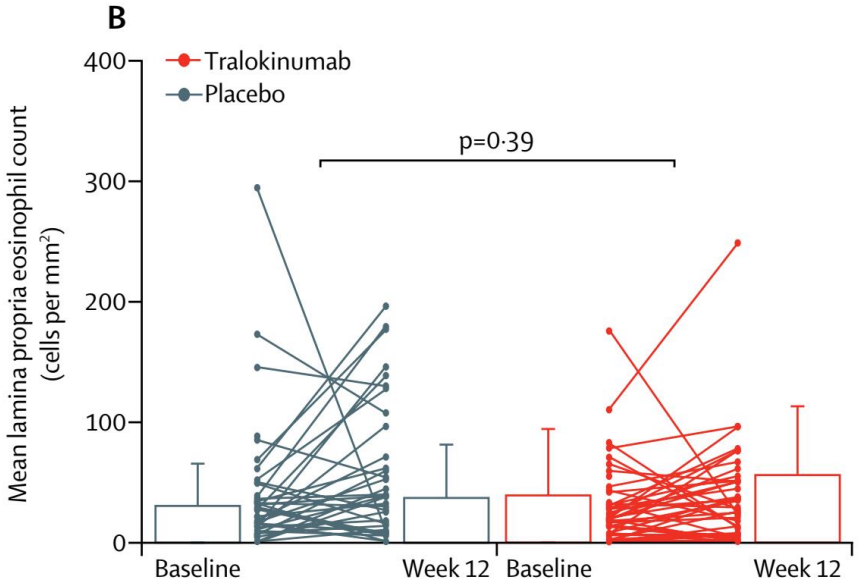
Tralokinumab on Eosinophilic Airway Inflammation in Uncontrolled Moderate-to-severe Asthma

- **Tralokinumab**: a human monoclonal antibody that neutralizes interleukin 13
- **MESOS**: a multicentre, double-blind, randomised, placebo-controlled phase 2 trial
- aged 18–75 years with **uncontrolled moderate-to-severe asthma** for 12 months or more
- Primary outcome: change from baseline to week 12 in **bronchial biopsy eosinophil count**

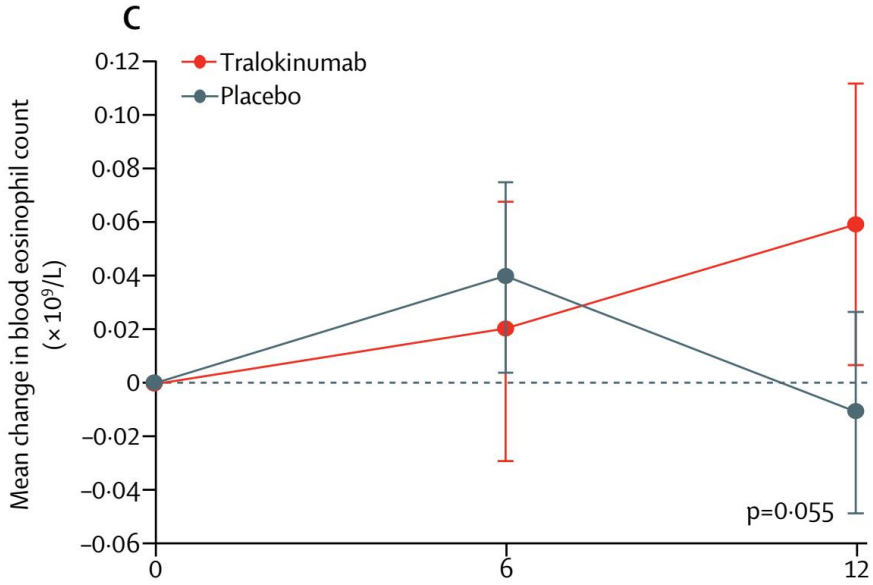


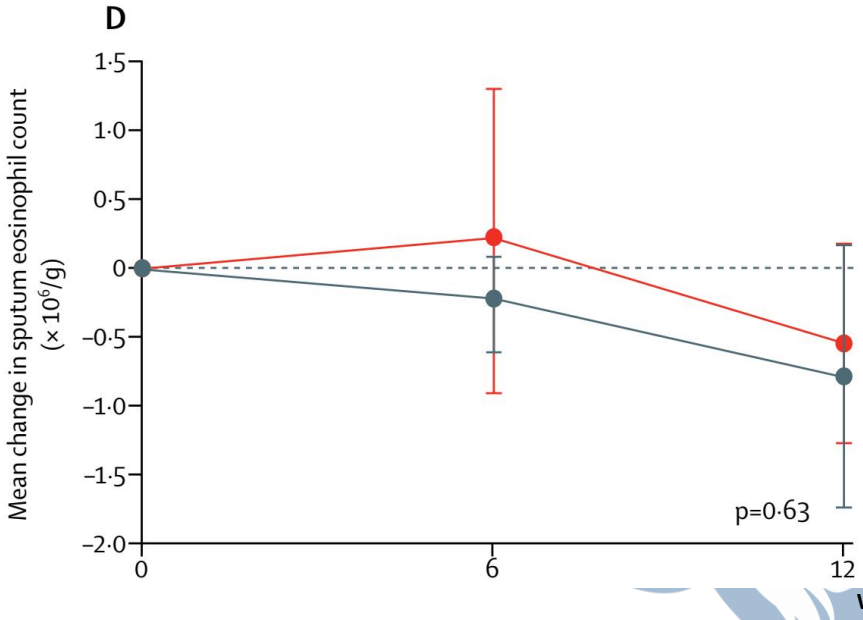
Russell RJ, Lancet Respir Med 2018;6:499-510.





Participants treated with tralokinumab showed an **increase in blood eosinophil count**





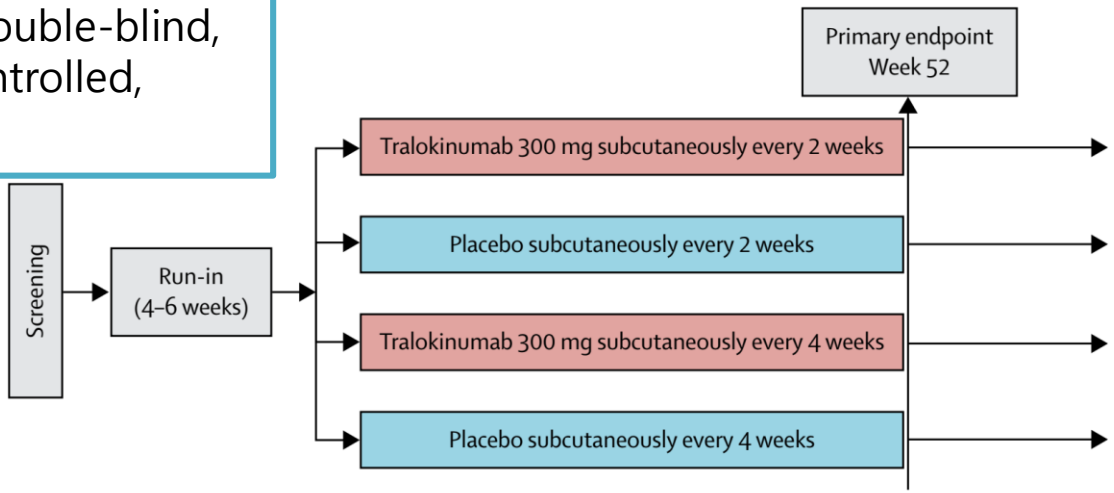
Russell RJ, Lancet Respir Med 2018;6:499-510.

- STRATOS 1 & 2 -

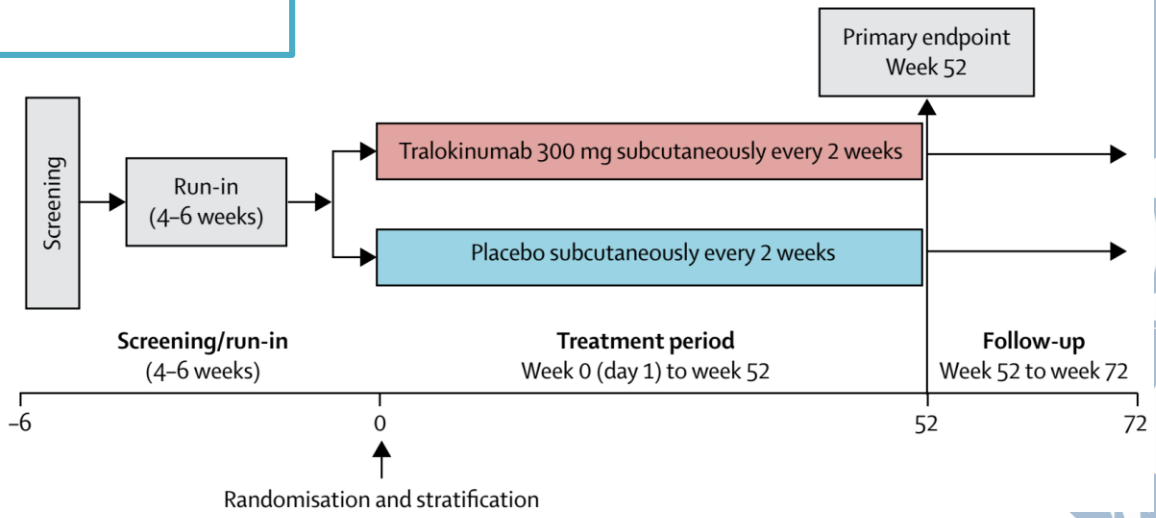
Tralokinumab for severe, uncontrolled asthma

- STRATOS 1: randomized, double-blind, parallel-group, placebo-controlled, phase 3 clinical trials

aged 12–75 years with **severe asthma** that was uncontrolled despite use of ICS (**≥500 µg**/d **fluticasone** or equivalent) and **LABA** (but not OCS)



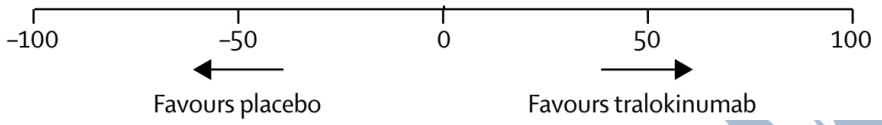
- STRATOS 2



Panettieri RA, Jr., Lancet Respir Med 2018;6:511-25.

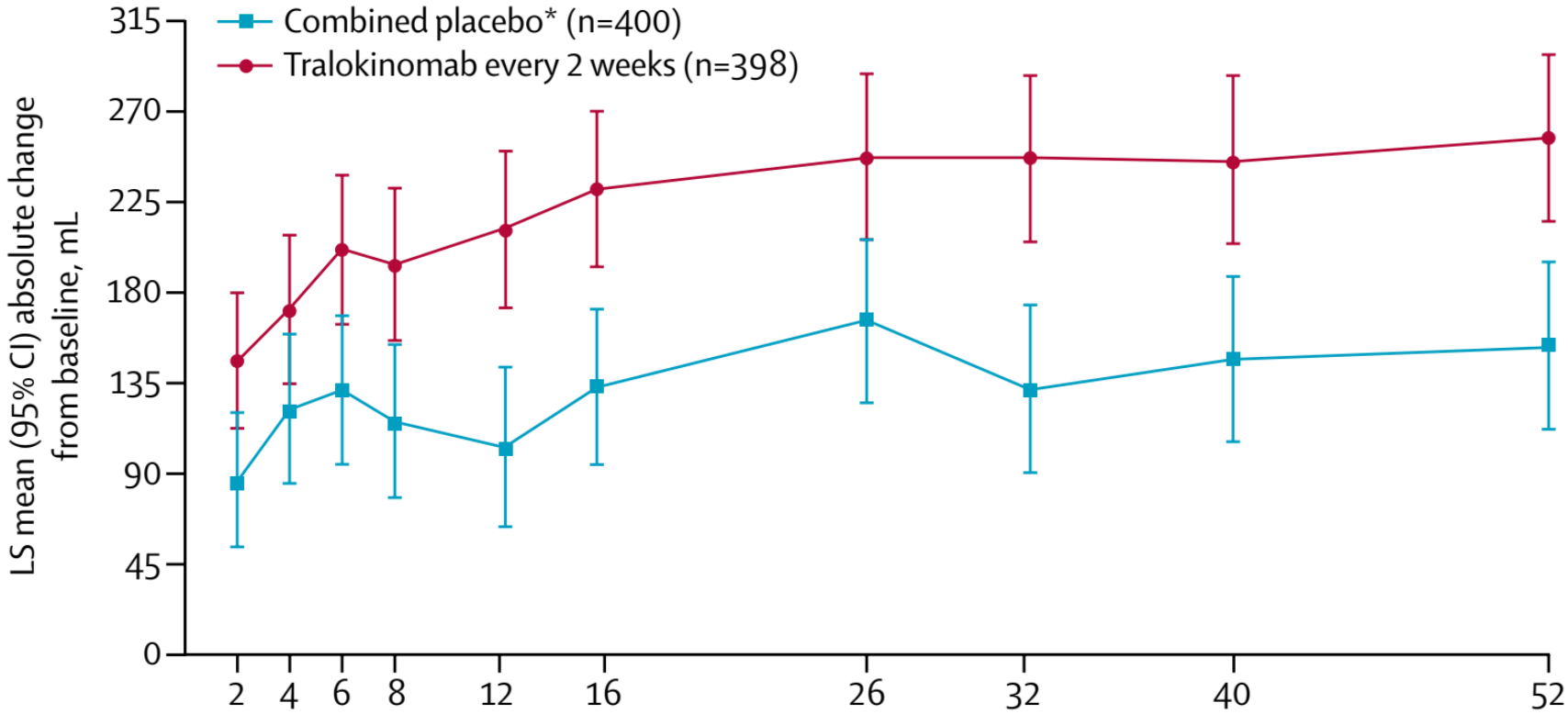
Annualized Asthma Exacerbation Rate (AAER)

	n	AAER (95% CI)	Rate ratio (95% CI)	Treatment effect on AAER (95% CI)	p value
STRATOS 1					
All-comers			0·93 (0·72 to 1·21)	7·0% (–20·8 to 28·4)	0·59
Combined placebo*	400	0·6 (0·5 to 0·7)			
Tralokinumab every 2 weeks	398	0·6 (0·5 to 0·7)			
FENO-high (≥37 ppb)			0·56 (0·34 to 0·94)	44·0% (6·0 to 66·0)	0·028†
Combined placebo*	102	0·9 (0·6 to 1·2)			
Tralokinumab every 2 weeks	97	0·5 (0·3 to 0·7)			
FENO-low (<37 ppb)			1·14 (0·84 to 1·56)	–14·0% (–56·0 to 16·0)	0·39†
Combined placebo*	296	0·5 (0·4 to 0·6)			
Tralokinumab every 2 weeks	298	0·6 (0·5 to 0·7)			
STRATOS 2					
All-comers			1·03 (0·81 to 1·31)	–3·1% (–31·5 to 19·1)	0·80‡
Placebo	417	0·8 (0·7 to 1·0)			
Tralokinumab every 2 weeks	420	0·8 (0·7 to 1·0)			
FENO-high (≥37 ppb)			0·84 (0·53 to 1·34)	15·8% (–33·7 to 47·0)	0·47‡
Placebo	121	1·0 (0·7 to 1·3)			
Tralokinumab every 2 weeks	108	0·8 (0·6 to 1·1)			
FENO-low (<37 ppb)			1·13 (0·85 to 1·50)	–13·0% (–50·0 to 15·0)	0·41§
Placebo	290	0·8 (0·6 to 1·0)			
Tralokinumab every 2 weeks	308	0·9 (0·7 to 1·1)			



Panettieri RA, Jr., Lancet Respir Med 2018;6:511-25.

Mean Absolute Change in FEV_1



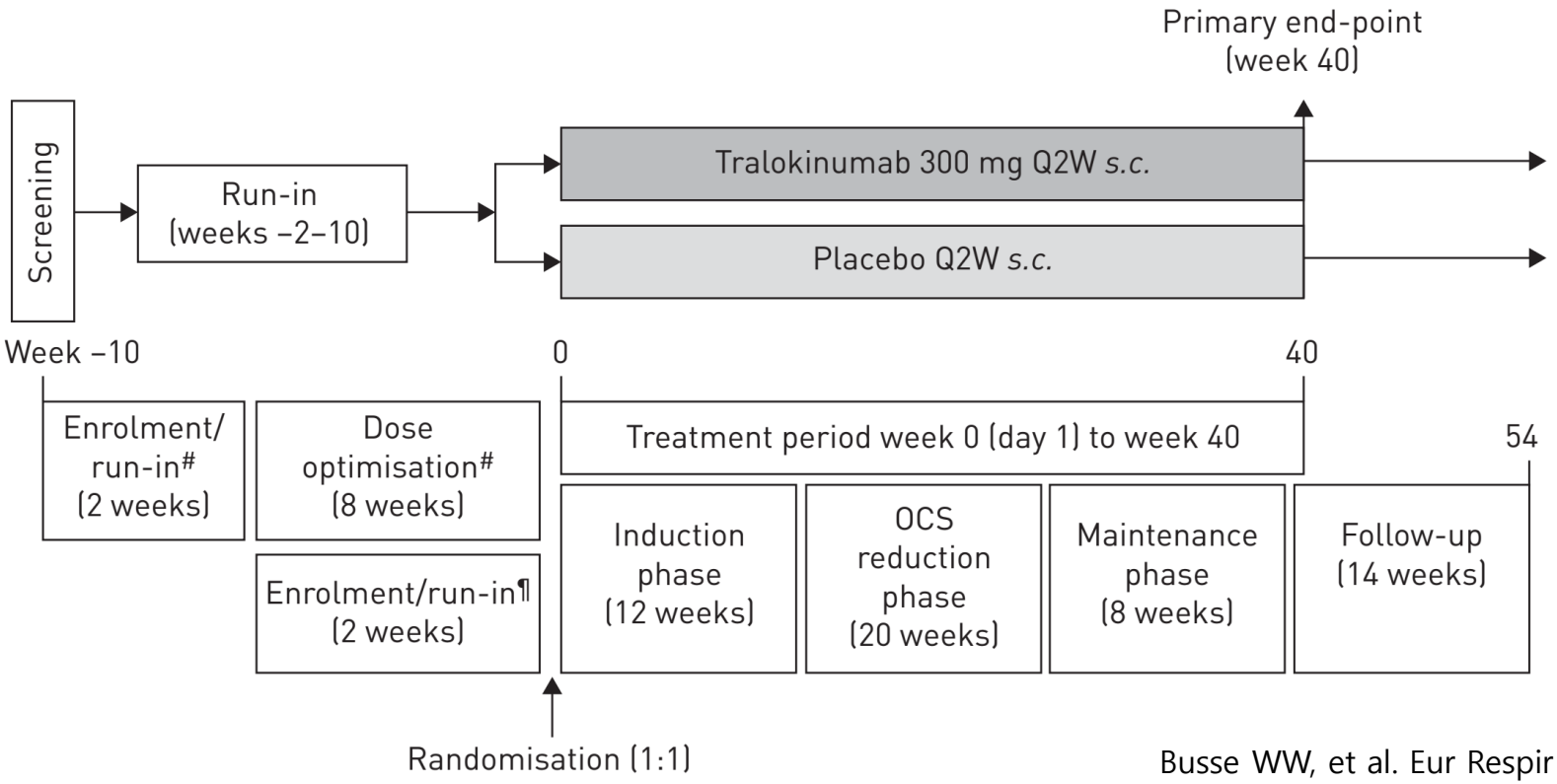
Combined placebo*	382	386	378	379	375	373	365	357	357	363
Tralokinumab every 2 weeks	384	388	379	374	374	373	360	352	349	357

Panettieri RA, Jr., Lancet Respir Med 2018;6:511-25.

- TROPOS -

Tralokinumab Did Not Demonstrate Oral Corticosteroid-sparing Effects in Severe Asthma

- 40-week, randomized, double-blind trial
- **severe, uncontrolled asthma** requiring **maintenance OCS** treatment plus ICS/LABA
- primary end-point: **% change** from baseline in average **OCS** dose at week 40



Busse WW, et al. Eur Respir J 2019;53.

Baseline Characteristics

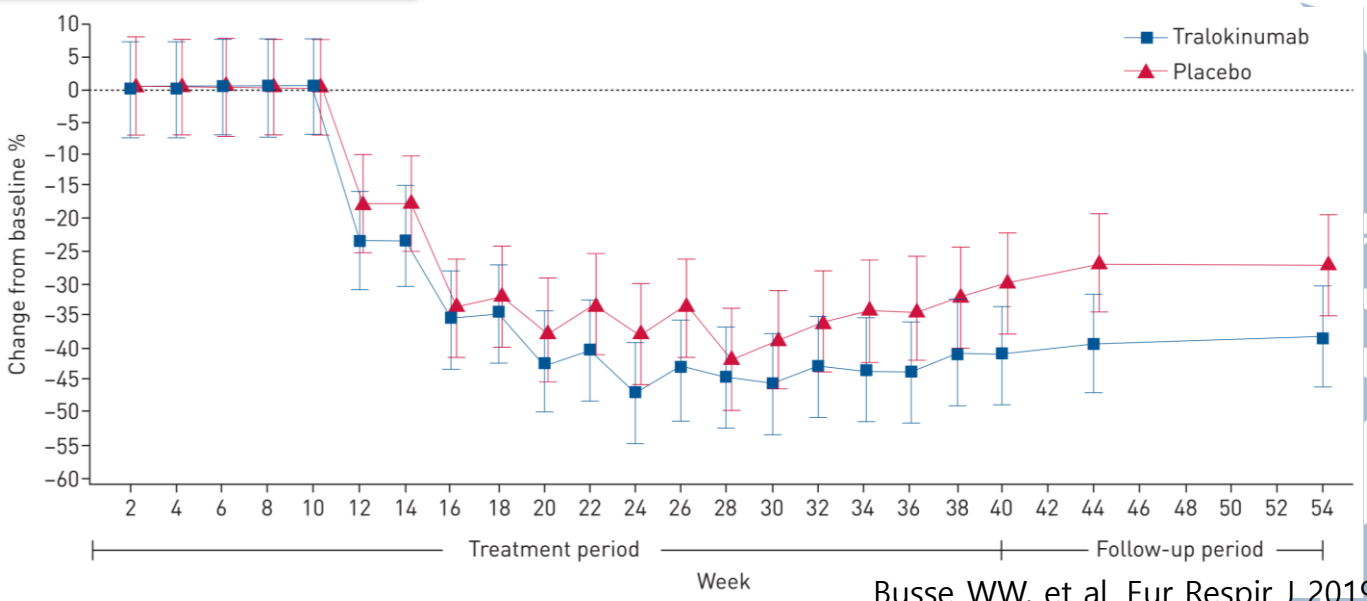
	Tralokinumab	Placebo	Total
Patients	70	70	140
Age years	54.0±11.05	55.4±10.26	54.7±10.65
Female	48 (68.6)	39 (55.7)	87 (62.1)
BMI kg·m^{-2}	28.1±5.07	30.8±6.84	29.4±6.15
Race			
Caucasian	66 (94.3)	63 (90.0)	129 (92.1)
Other	4 (5.7)	7 (10.0)	11 (7.8)
Smoking history			
Never-smokers	57 (81.4)	50 (71.4)	107 (76.4)
Ex-smokers[¶]	13 (18.6)	20 (28.6)	33 (23.6)
Pack-years[+]	4.5±2.37	4.7±3.10	4.6±2.79
Time since asthma diagnosis[§] years	21.5 (3–52)	25.5 (1.6–55.0)	24.0 (1.6–55.0)
Exacerbations in the past 1 year			
0	9 (12.9)	11 (15.7)	20 (14.3)
1	19 (27.1)	24 (34.3)	43 (30.7)
2	21 (30.0)	17 (24.3)	38 (27.1)
⩾3	21 (30.0)	18 (25.7)	39 (27.8)
Asthma medications at baseline			
ICS[f]	69 (98.6)	70 (100)	139 (99.3)
LABA	70 (100)	70 (100)	140 (100)
OCS dose at trial entry mg	14.14±6.03	13.50±5.18	13.82±5.61
Optimised total daily OCS dose[##] mg	13.21±6.17	12.82±4.96	13.02±5.58
Prebronchodilator FEV_1			
Volume L	1.69±0.59	1.65±0.68	1.67±0.63
% predicted	56.67±15.58	54.74±17.67	55.71±16.63
Prebronchodilator FVC L	2.87±0.84	2.81±0.98	2.84±0.91
Percentage reversibility of FEV_1[¶¶]	17.22±14.04	18.19±19.24	17.71±16.79
Total asthma symptom score	2.3±1.14	2.3±1.25	Not done
ACQ-6 score	2.4±1.12	2.5±1.26	Not done
AQLQ score	4.4±1.15	4.4±1.29	Not done
F_{ENO} ppb	28.3 (6.4–175.2)	23.9 (4.2–134.9)	27.55 (4.1–175.2)
F_{ENO} distribution			
High ⩾37 ppb	23 (32.9)	21 (30.0)	44 (31.4)
Mid ⩾30 and <37 ppb	11 (15.7)	11 (15.7)	22 (15.7)
Low <30 ppb	36 (51.4)	36 (51.4)	72 (51.4)
No baseline assessment	0	2 (2.9)	2 (1.4)

Busse WW, et al. Eur Respir J 2019;53.

Primary & Secondary End-points

	Tralokinumab	Placebo
Patients	70	70
Primary end-point		
Percentage change in final daily average OCS dose from baseline		
Percentage reduction in LS mean	−37.62±4.98	−29.85±4.98
Difference in LS mean (95% CI)	−7.78 (−21.70–6.15)	
p-value	0.271	
Secondary end-points		
Proportion of patients with final daily average OCS dose ⩽5 mg		
Patients with OCS dose ⩽5 mg	32 (45.7)	28 (40.0)
OR (95% CI)	1.33 (0.65–2.73)	
p-value	0.442	
Proportion of patients with ⩾50% reduction from baseline in final daily average OCS dose		
Patients with ⩾50% reduction in OCS dose	31 (44.3)	26 (37.1)
OR (95% CI)	1.38 (0.70–2.74)	
p-value	0.356	
Asthma exacerbations		
AAER (95% CI)	1.84 (1.43–2.36)	2.31 (1.83–2.92)
Rate ratio (95% CI)	0.80 (0.57–1.12)	
p-value	0.186	

Percentage Change of OCS



Busse WW, et al. Eur Respir J 2019;53.

Anti-Interleukin-5 Antibodies for Eosinophilic Asthma

	Benralizumab (Fasenra)	Mepolizumab (Nucala)	Reslizumab (Cinqair)	Dupilumab (Dupixent)
Mechanism of Action	IL-5 receptor antagonist	IL-5 antagonist	IL-5 antagonist	IL-4 receptor alpha subunit antagonist (inhibits IL-4 and IL-13 signaling)
Formulation	30 mg/mL soln in single-dose prefilled syringes	100 mg lyophilized powder in single-dose vials	100 mg/10 mL soln in single-use vials	200 mg/1.14 mL, 300 mg/2 mL soln in single-dose prefilled syringes
Dosage	30 mg SC q4 wks × 3, then q8 wks	100 mg SC q4 wks	3 mg/kg IV q4 wks	400 mg SC then 200 mg q2 wks or 600 mg SC then 300 mg q2 wks
FDA-approved age	≥12 years	≥12 years	≥18 years	≥12 years
Cost	$4752	$2868	$2588	$1466

JAMA 2019;321:1000-1.

Efficacy of the Biologics

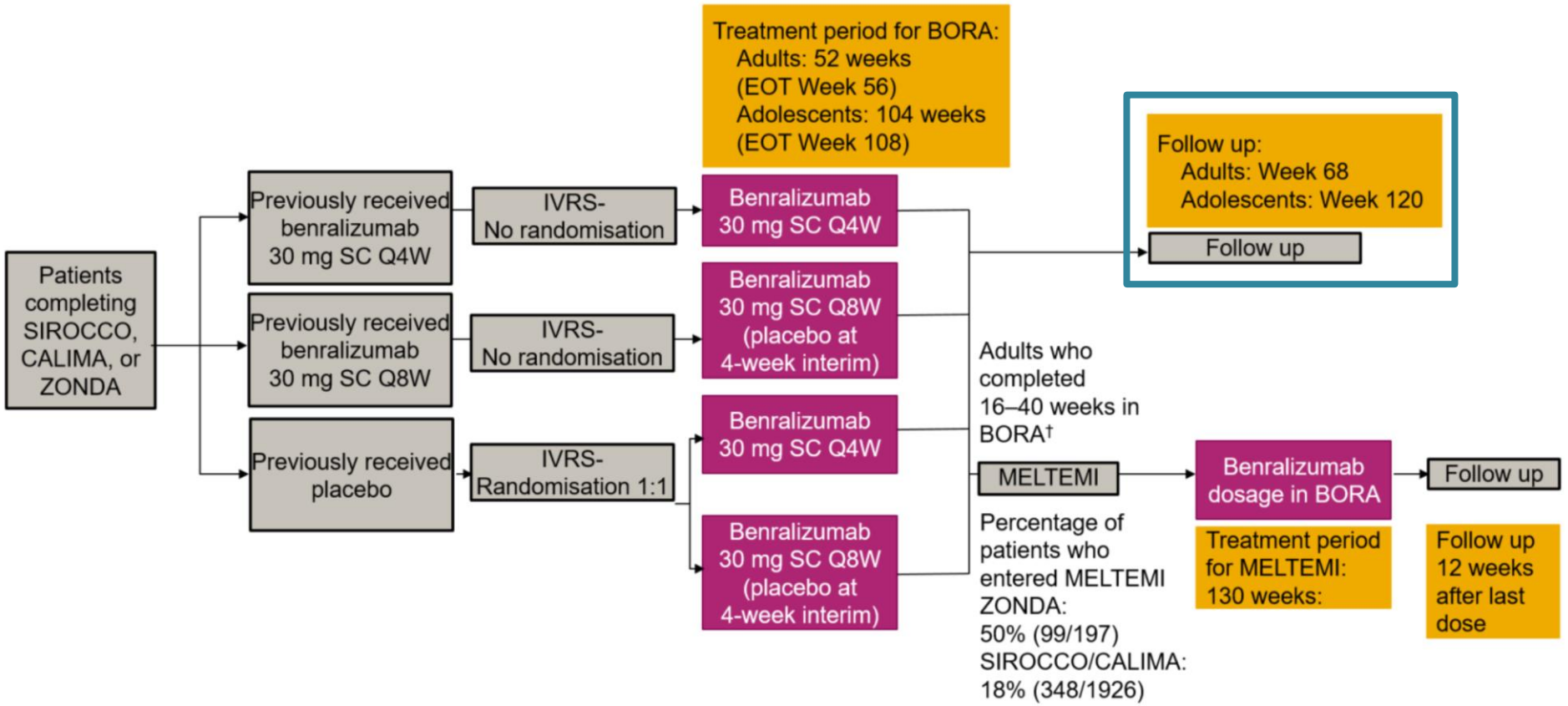
Therapy	Asthma Exacerbation	Lung Function	Corticosteroid Weaning	Special Considerations
Omalizumab	Reduces by **25%**	**Minimal** or equivocal improvement	Decreases use of ICS, but **no data** that it helps with **OCS weaning**	Only s.c. biologic approved for **children** 6–11 yr old
Mepolizumab	Reduces by **~50%**	**Inconsistent** effect	**Decreases** total use of OCS and has been shown to facilitate complete **weaning** from chronic OCS (**14%)**	Standard s.c. dosing has **not been shown to decrease sputum eosinophilia**; approved at higher dosing for EGPA
Reslizumab	Reduces by **~50–60%**	**Improved**	Has **not** been **specifically evaluated** for this indication	Only **weight-based dosing** i.v. biologic approved for asthma
Benralizumab	Reduces by **~25–60%**	**Improved**	**Decreases** total use of OCS and has been shown to facilitate complete **weaning** from chronic OCS (**50%**)	Only s.c. biologic that offers **every-8-wk** dosing
Dupilumab	Reduces by **~50–70%**	**Improved**	**Decreases** total use of OCS and has been shown to facilitate complete **weaning** from chronic OCS (**50%**)	Only biologic that can be **self-administered** s.c.; showed benefit with **FENO > 25** ppb **regardless of eosinophil** count

McGregor MC, et al. Am J Respir Crit Care Med 2019;199:433-45.

- BORA -

Long-term Safety and Efficacy of Benralizumab

- Eligible patients: completed the **SIROCCO** or **CALIMA** trials and remained on subcutaneous benralizumab 30 mg every 4 weeks (Q4W) or every 8 weeks (Q8W) (**no placebo**)
- The primary endpoint: the **safety and tolerability** of the two dosing regimens of benralizumab



Busse WW, Lancet Respir Med 2019;7:46-59.

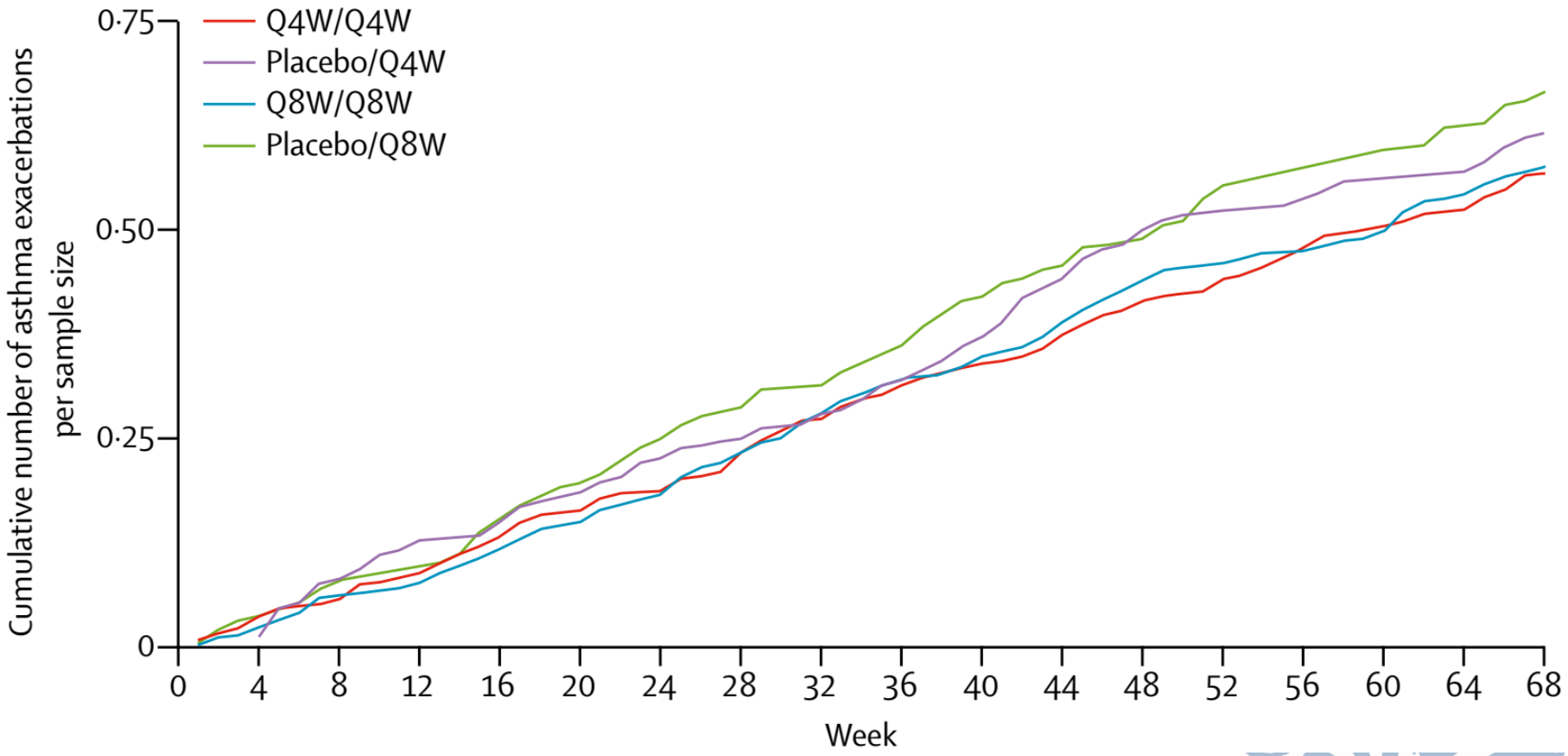
Adverse Events

	Benralizumab 30 mg Q4W			Benralizumab 30 mg Q8W		
	Q4W/Q4W group (n=518)	Placebo/Q4W group (n=265)	Total (n=783)	Q8W/Q8W group (n=512)	Placebo/Q8W group (n=281)	Total (n=793)
Any AE	364 (70%)	181 (68%)	545 (70%)	361 (71%)	183 (65%)	544 (69%)
Any AE leading to treatment discontinuation	10 (2%)	8 (3%)	18 (2%)	8 (2%)	5 (2%)	13 (2%)
AEs in ≥5% of patients*						
Viral upper respiratory tract infection	78 (15%)	36 (14%)	114 (15%)	80 (16%)	41 (15%)	121 (15%)
Asthma	49 (9%)	27 (10%)	76 (10%)	41 (8%)	19 (7%)	60 (8%)
Upper respiratory tract infection	30 (6%)	21 (8%)	51 (7%)	31 (6%)	20 (7%)	51 (6%)
Bronchitis	26 (5%)	18 (7%)	44 (6%)	33 (6%)	15 (5%)	48 (6%)
Headache	25 (5%)	13 (5%)	38 (5%)	31 (6%)	9 (3%)	40 (5%)
Acute sinusitis	18 (3%)	9 (3%)	27 (3%)	27 (5%)	13 (5%)	40 (5%)
Any SAE	58 (11%)	29 (11%)	87 (11%)	53 (10%)	30 (11%)	83 (10%)
SAEs in ≥1% of patients						
Worsening asthma	19 (4%)	10 (4%)	29 (4%)	16 (3%)	9 (3%)	25 (3%)
Pneumonia	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	2 (1%)	3 (<1%)
Pneumonia caused by bacterial infection	1 (<1%)	0	1 (<1%)	2 (<1%)	2 (1%)	4 (1%)
Influenza	1 (<1%)	1 (<1%)	2 (<1%)	0	2 (1%)	2 (<1%)
Ischaemic stroke	0	0	0	0	2 (1%)	2 (<1%)
SAEs associated with infections	7 (1%)	4 (2%)	11 (1%)	9 (2%)	8 (3%)	17 (2%)
Deaths	1 (<1%)	3 (1%)	4 (1%)	2 (<1%)	1 (<1%)	3 (<1%)
Injection-site reactions	8 (2%)	6 (2%)	14 (2%)	10 (2%)	3 (1%)	13 (2%)
Hypersensitivity AEs†	12 (2%)	7 (3%)	19 (2%)	6 (1%)	7 (2%)	13 (2%)
Causally related‡	1 (<1%)	0	1 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)
Urticaria	0	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Anaphylactic reaction	1 (<1%)	0	1 (<1%)	0	0	0

Busse WW, Lancet Respir Med 2019;7:46-59.

Cumulative number of new exacerbations

- **patients** with baseline **blood eosinophil counts ≥300 cells per μL**



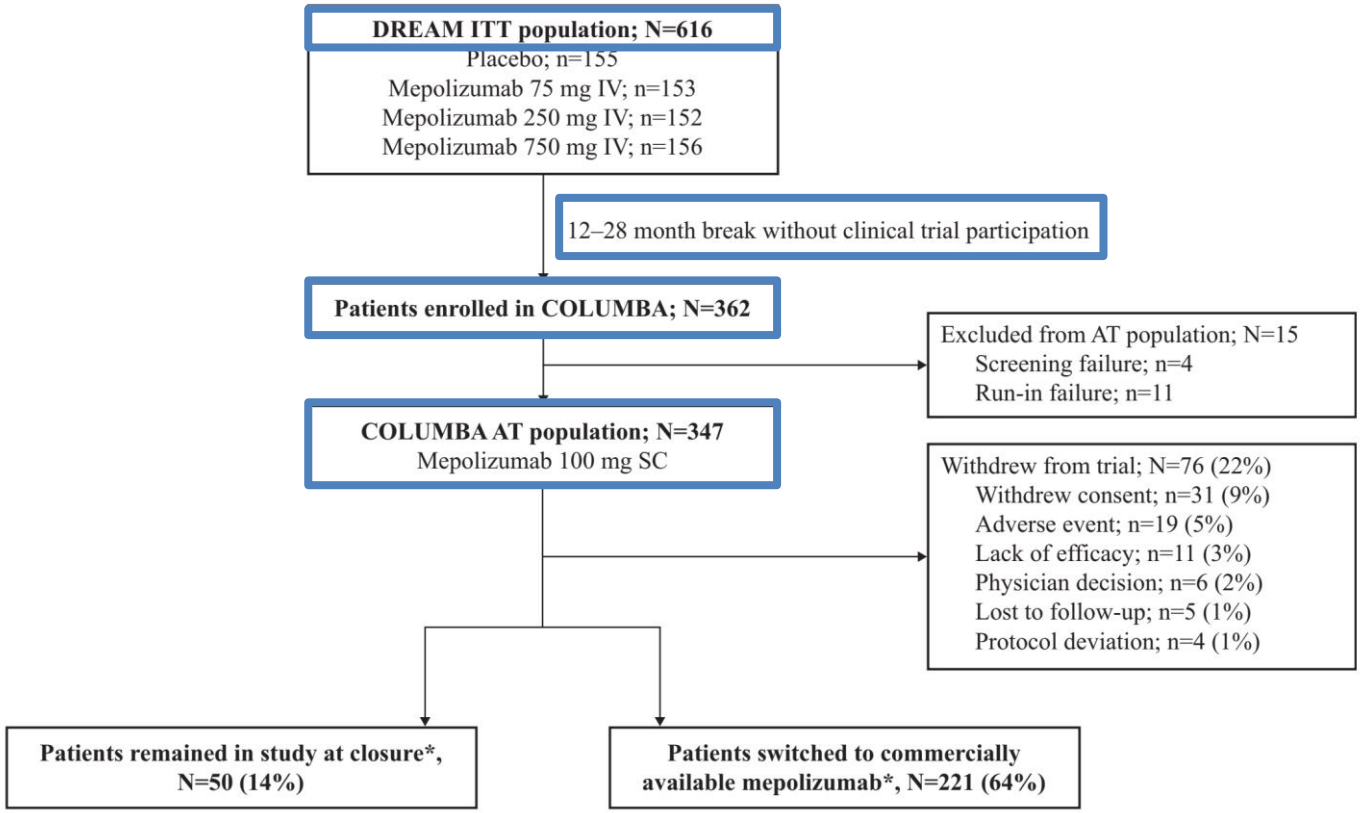
- 37 (**4%**) of 1046 patients who received benralizumab in **BORA** had **exacerbations** that led to hospital **admission**, which is **similar** to the percentages in **SIROCCO** and **CALIMA** (**4–6%**)

Busse WW, Lancet Respir Med 2019;7:46-59.

- COLUMBA -

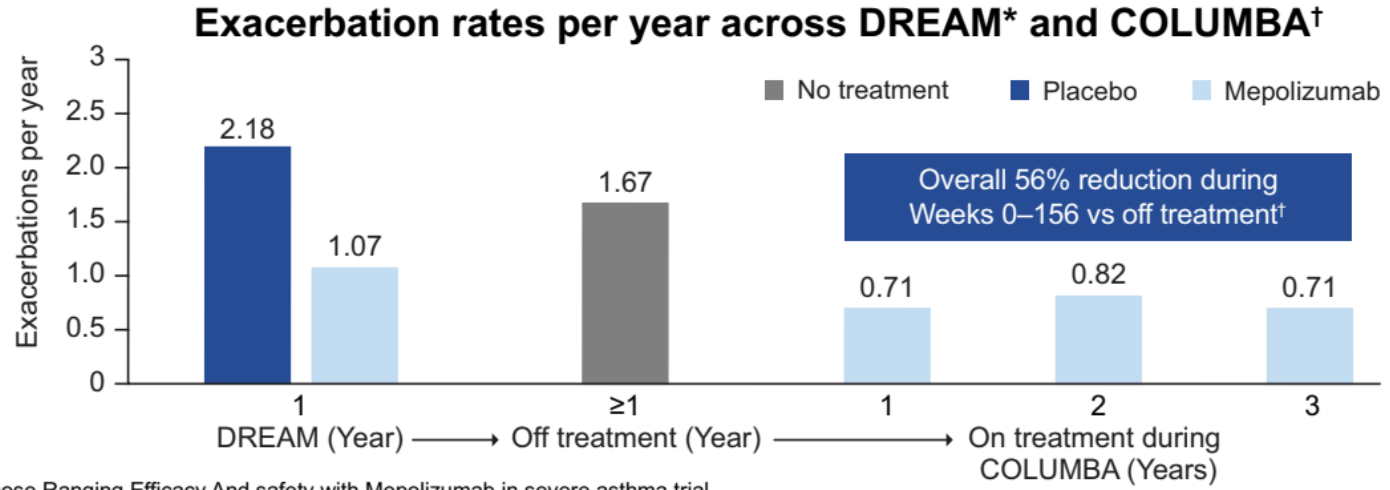
Long-term Safety and Durability of Mepolizumab Response in Patients with Severe Eosinophilic Asthma

- Open label, single arm, multi-center, extension study
- 347 patients treated for up to 4.5 years by Mepolizumab 100 mg SC every 4 weeks



Khatri S, et al. J Allergy Clin Immunol 2018 (ePub)

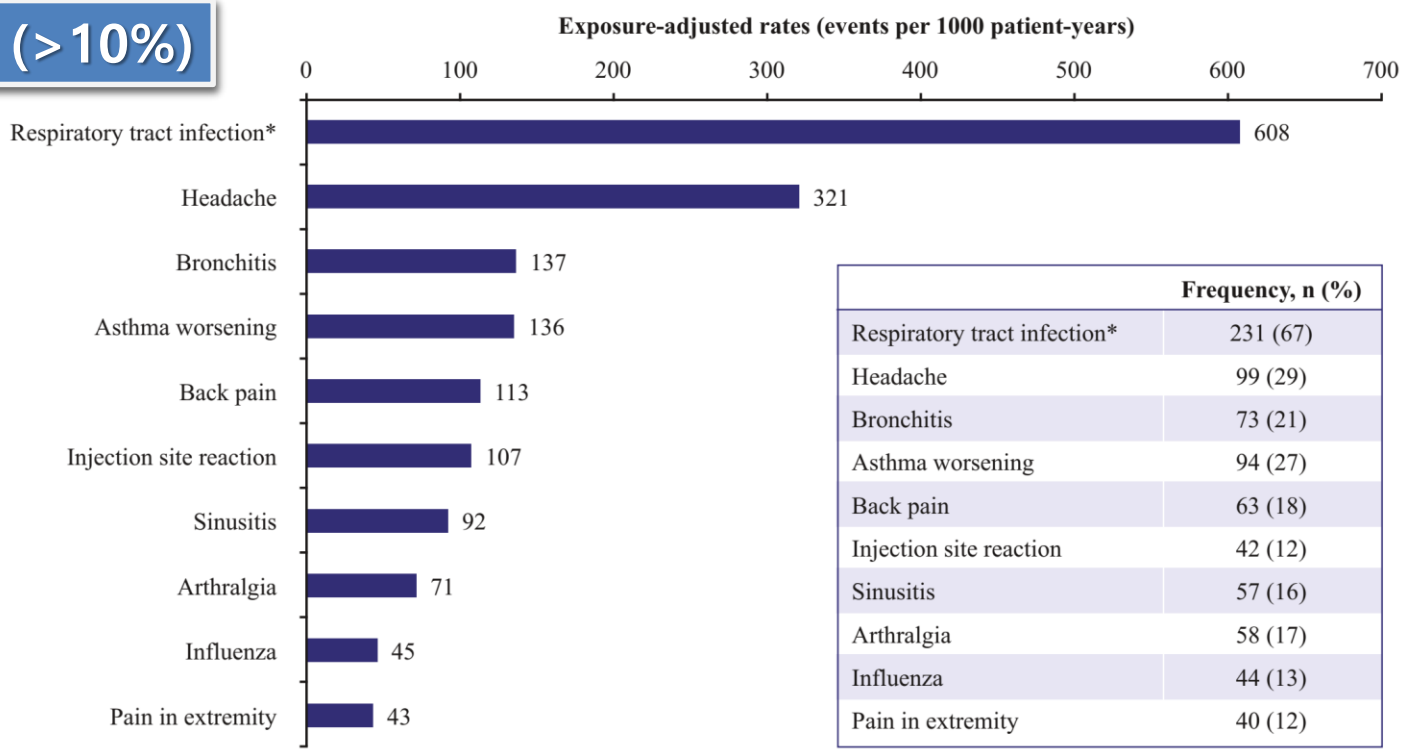
Exacerbation Rates



*Dose Ranging Efficacy And safety with Mepolizumab in severe asthma trial

†Based on 286 patients with ≥156 weeks of open-label data in COLUMBA

Adverse Events (>10%)



	Frequency, n (%)
Respiratory tract infection*	231 (67)
Headache	99 (29)
Bronchitis	73 (21)
Asthma worsening	94 (27)
Back pain	63 (18)
Injection site reaction	42 (12)
Sinusitis	57 (16)
Arthralgia	58 (17)
Influenza	44 (13)
Pain in extremity	40 (12)

Khatri S, et al. J Allergy Clin Immunol 2018 (ePub)

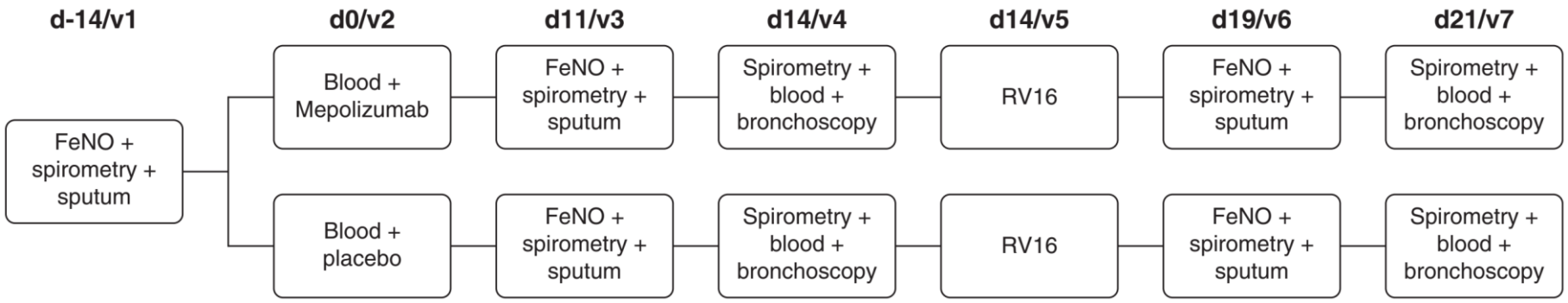
Anti–IL-5 in Mild Asthma Alters Rhinovirus-induced Macrophage, B-Cell, and Neutrophil Responses (MATERIAL)

A Placebo-controlled, Double-Blind Study

- MATERIAL -

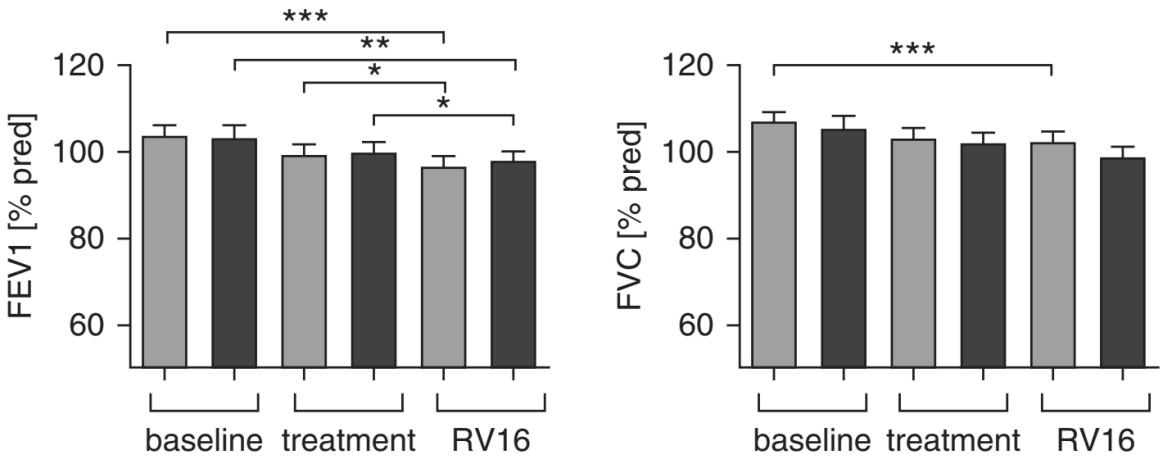
Yanaika S. Sabogal Piñeros[1,2], Suzanne M. Bal[1,2], Marianne A. van de Pol[2], Barbara S. Dierdorp[2], Tamara Dekker[2], Annemiek Dijkhuis[2], Paul Brinkman[1], Koen F. van der Sluijs[2], Aeilko H. Zwinderman[3], Christof J. Majoor[1], Peter I. Bonta[1], Lara Ravanetti[1,2], Peter J. Sterk[1], and René Lutter[1,2]

- **Mild** steroid-naive patients with **asthma**: (irrespective of the blood eosinophil levels)
  - either **750 mg intravenous mepolizumab** or placebo
  - experimentally infected with **rhinovirus** 16 **after 2 weeks**
- Primary outcomes: The prebronchodilator FEV1 before and after RV16 challenge

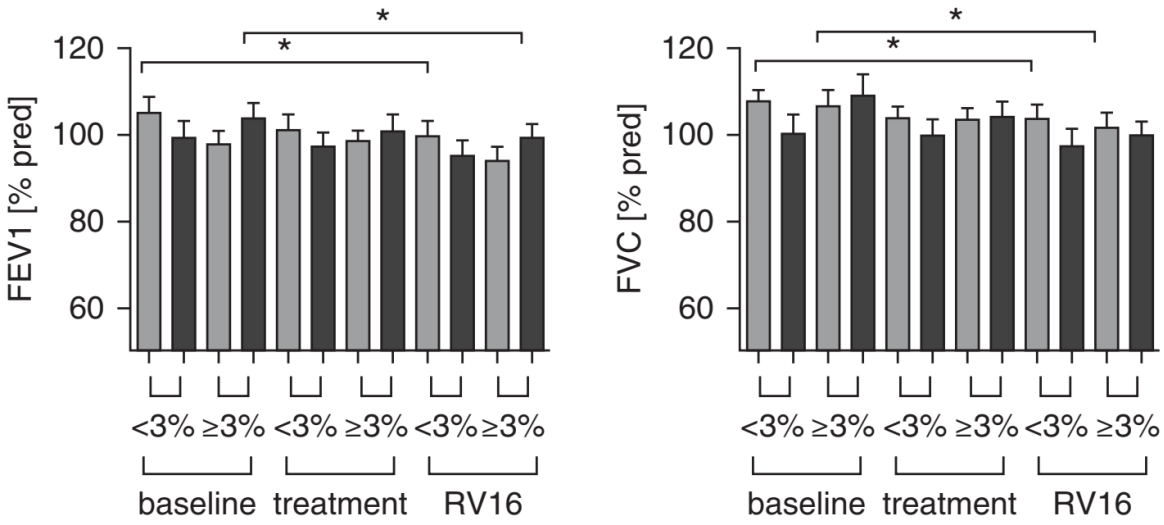


Sabogal Pineros YS, Am J Respir Crit Care Med 2019;199:508-17.

Lung Function Parameters



Placebo Mepolizumab

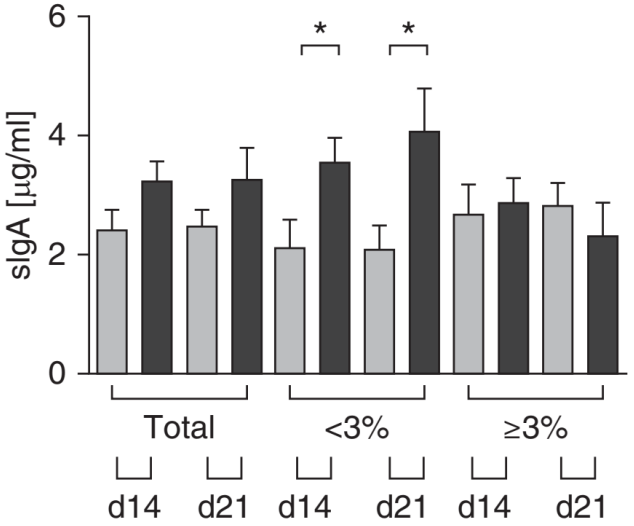


P n=13, M n=7,
<3% P n=6, ≥3% P n=7,
<3% M n=2, ≥3% M n=5;

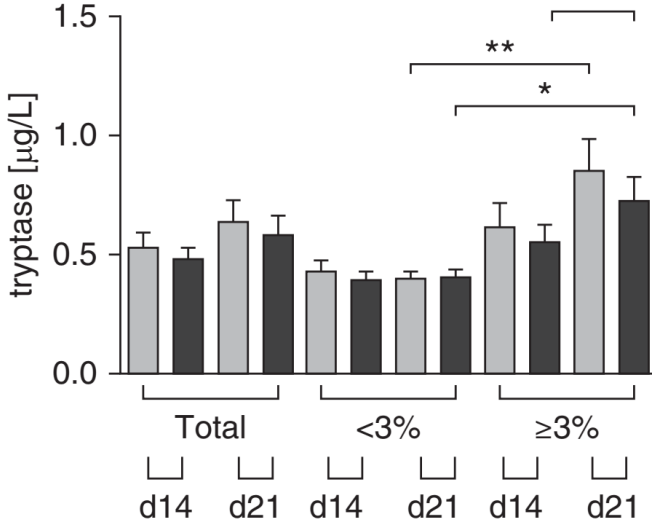
P n=13, M n=7,
<3% P n=6, ≥3% P n=7,
<3% M n=2, ≥3% M n=5;

Sabogal Pineros YS, Am J Respir Crit Care Med 2019;199:508-17.

sIgA and Mast Cell Activation

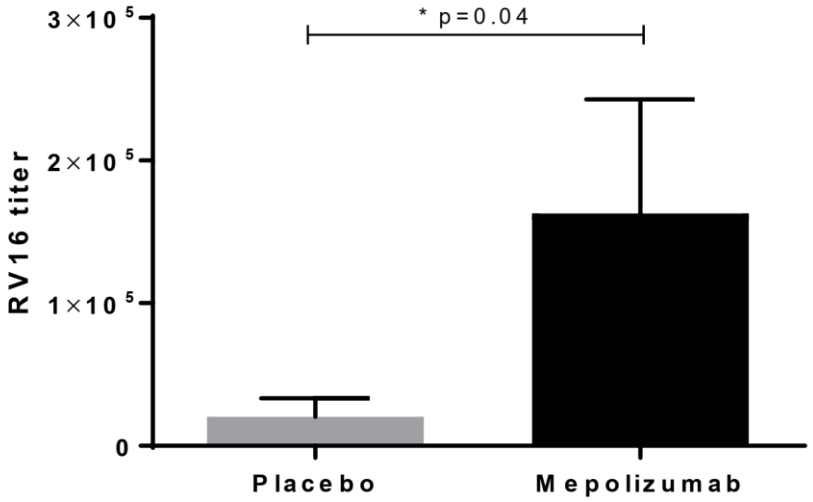


P n=17, M n=11
<3% P n=8, ≥3% P n=9
<3% M n=6, ≥3% M n=5



P n=17, M n=9
<3% P n=8, ≥3% P n=9
<3% M n=4, ≥3% M n=5

Placebo Mepolizumab



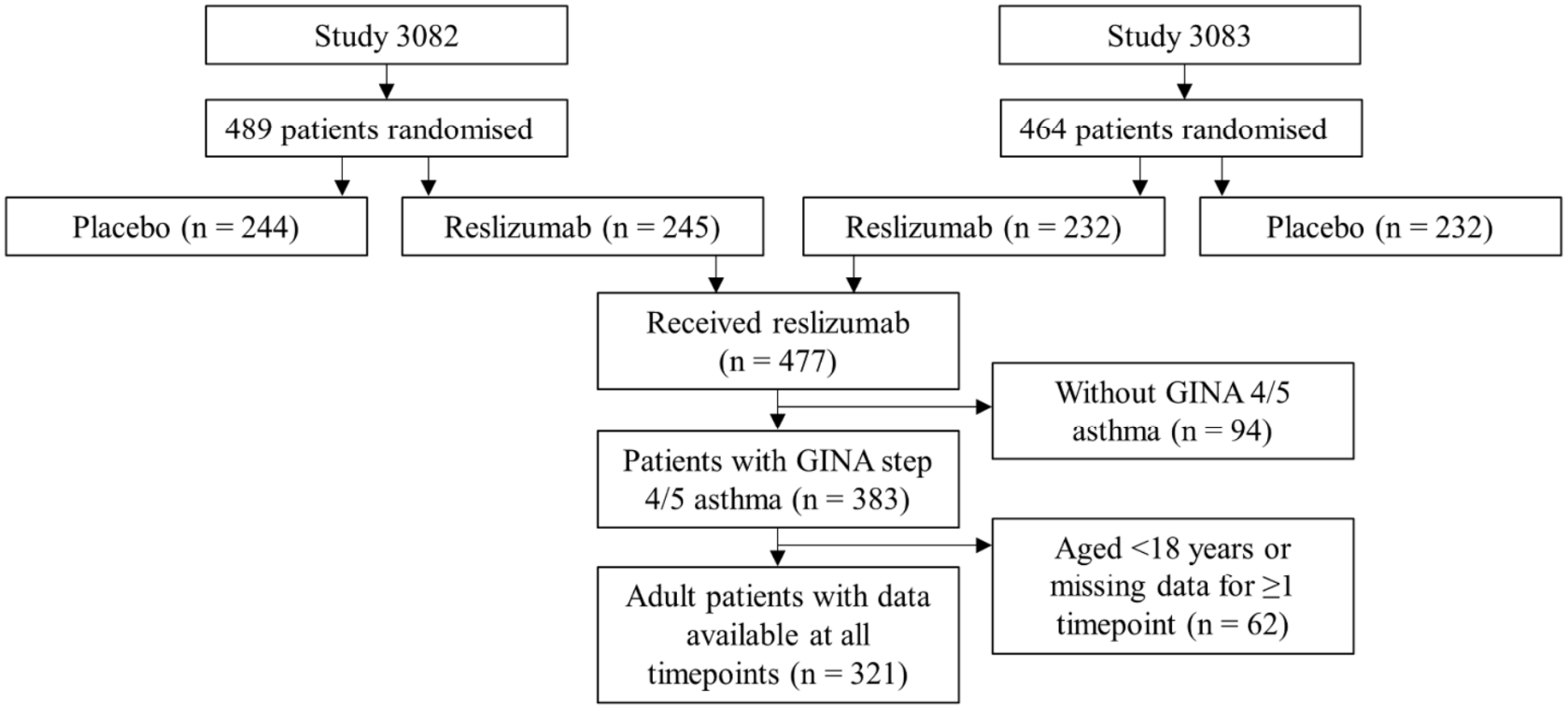
Viral Titer in Nasal Swab

Sabogal Pineros YS, Am J Respir Crit Care Med 2019;199:508-17.

Predicting Responders to Reslizumab after 16 Weeks of Treatment Using an Algorithm Derived from Clinical Studies of Patients with Severe Eosinophilic Asthma

Eric D. Bateman[1], Ratko Djukanović[2], Mario Castro[3], Janice Canvin[4], Matthew Germinaro[5], Robert Noble[5], Margaret Garin[5], and Roland Buhl[6]

- To predict response and nonresponse to intravenous reslizumab at 52 weeks at 16 weeks of treatment



Bateman ED, Am J Respir Crit Care Med 2019;199:489-95.

Definitions of Responders, Nonresponders, and Indeterminate

Nonresponders	Responders	Indeterminate
Two or more CAEs at 52 wk unless at least one of the following criteria are met*: • >10% improvement in FEV_1 and ACQ-6 improvement† at 52 wk • >10% improvement in FEV_1 and AQLQ improvement‡ at 52 wk • 50% reduction from historical§ number of CAEs at 52 wk	At least one CAE at 52 wk and at least one of the following criteria are met: • >10% improvement in FEV_1 at 52 wk • ACQ-6 improvement† at 52 wk • AQLQ improvement at 52 wk	Criteria not met for either responders or nonresponders

ACQ = Asthma Control Questionnaire
AQLQ = Asthma Quality of Life Questionnaire
CAE = clinical asthma exacerbation

Comparison of Actual Week 52 Responses versus Those Predicted from Week 16 Data

	Predicted			
	Non-responder	Indeterminate	Responder	Total
Actual				
NR	13	8	11	32 (10%)
I	8	4	17	29 (9%)
R	5	7	248	260 (81%)
Total	26 (8%)	19 (6%)	276 (86%)	321 (100%)

Bateman ED, Am J Respir Crit Care Med 2019;199:489-95.

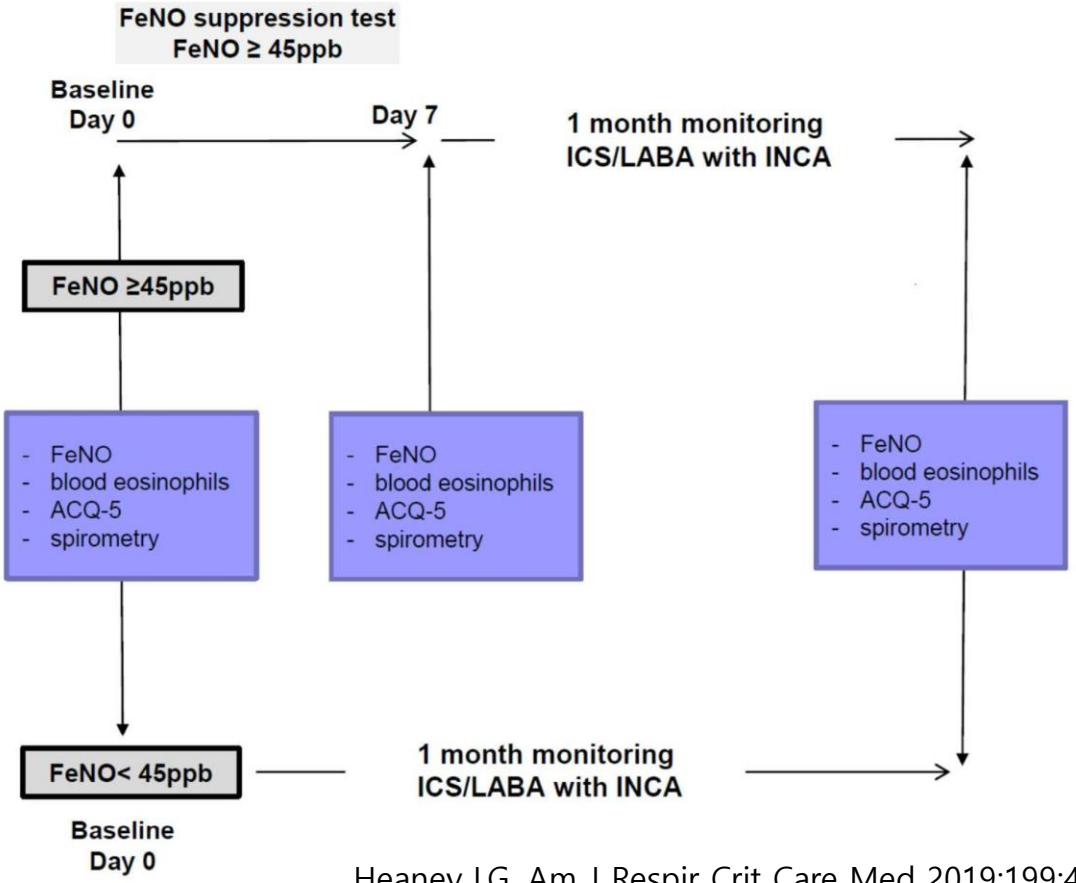
Remotely Monitored Therapy and Nitric Oxide Suppression Identifies Nonadherence in Severe Asthma

Liam G. Heaney[1], John Busby[1], Peter Bradding[2], Rekha Chaudhuri[3], Adel H. Mansur[4], Robert Niven[5], Ian D. Pavord[6], John T. Lindsay[7], and Richard W. Costello[8]; on behalf of the Medical Research Council UK Refractory Asthma Stratification Programme (RASP-UK)

- To **distinguishing** patients with **difficult-to-control asthma** who respond to ICS from **refractory asthma**

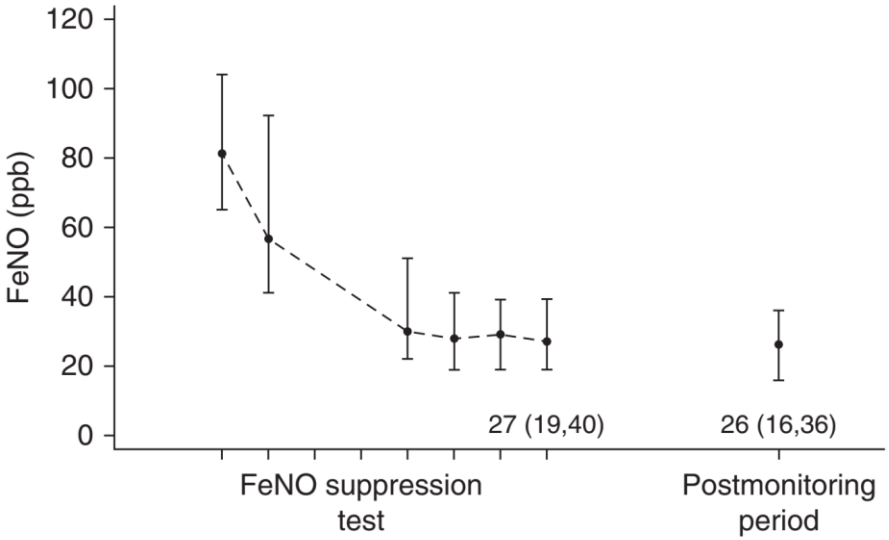
Study population

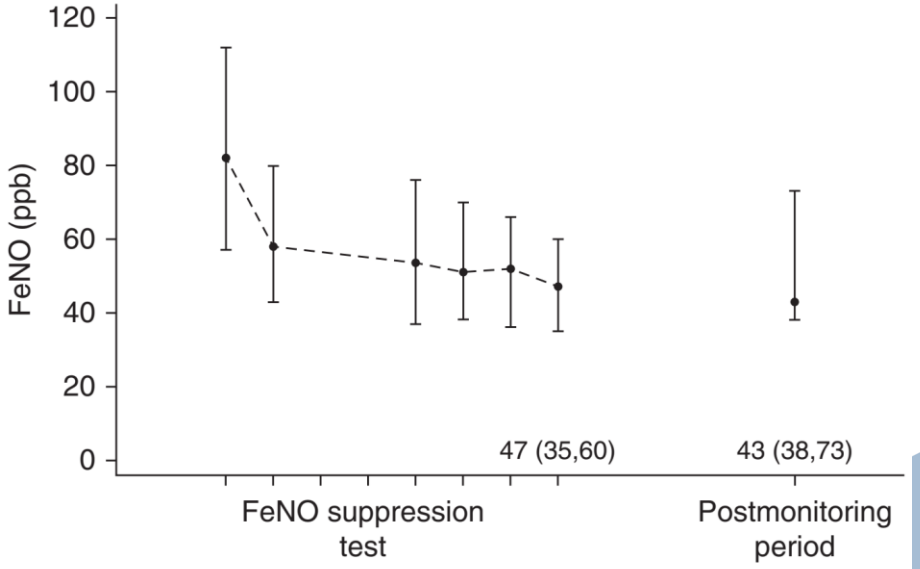
- GINA Step 4/5 severe asthma
- attending UK Specialist Severe Asthma Service
- clinical and demographic details
- serum prednisolone / cortisol (subjects on maintenance prednisolone)
- instructed in use of INCA enabled Accuhaler



Heaney LG, Am J Respir Crit Care Med 2019;199:454-64.

Relationship Between FENO after 7-day Suppression Testing and FEBO after 1-month Monitoring for Subject with Good Adherence

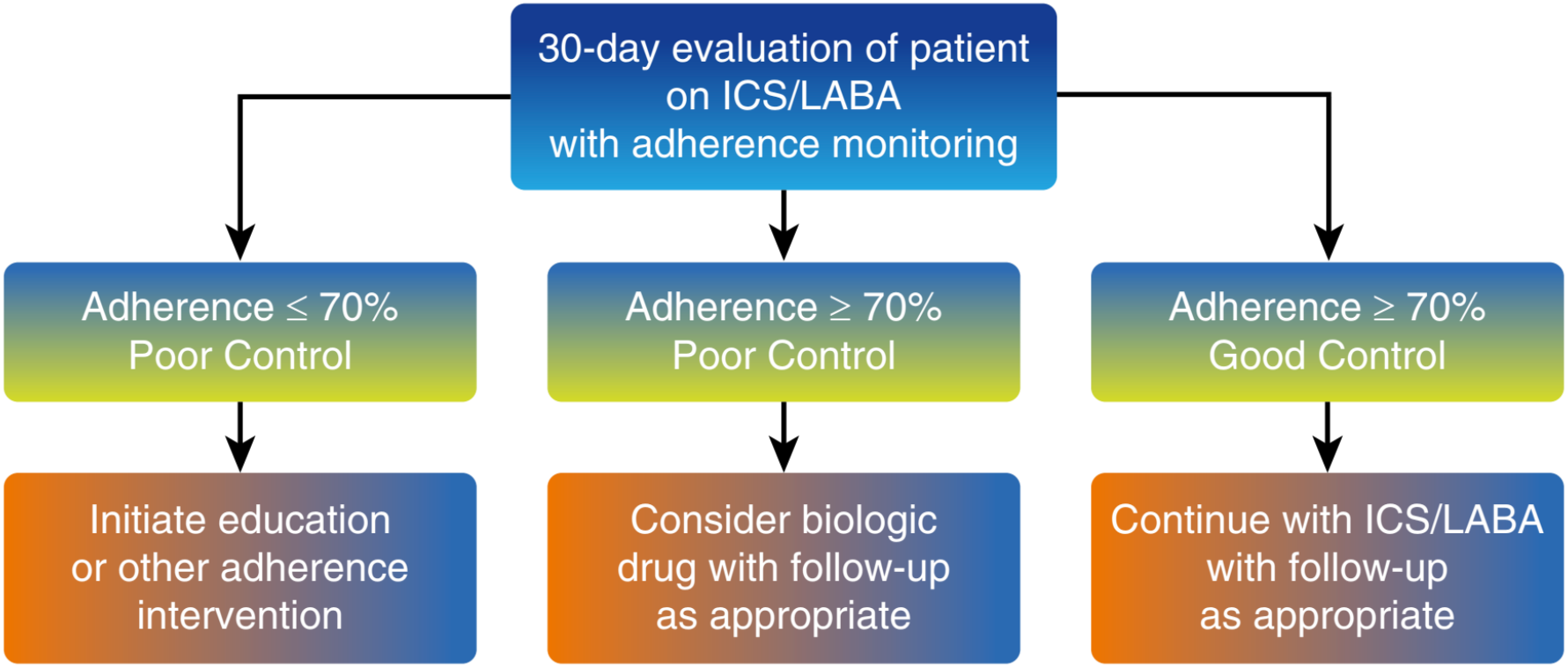




- Remote FENO suppression testing is an effective means of identifying nonadherence to ICS in subjects with difficult-tocontrol asthma

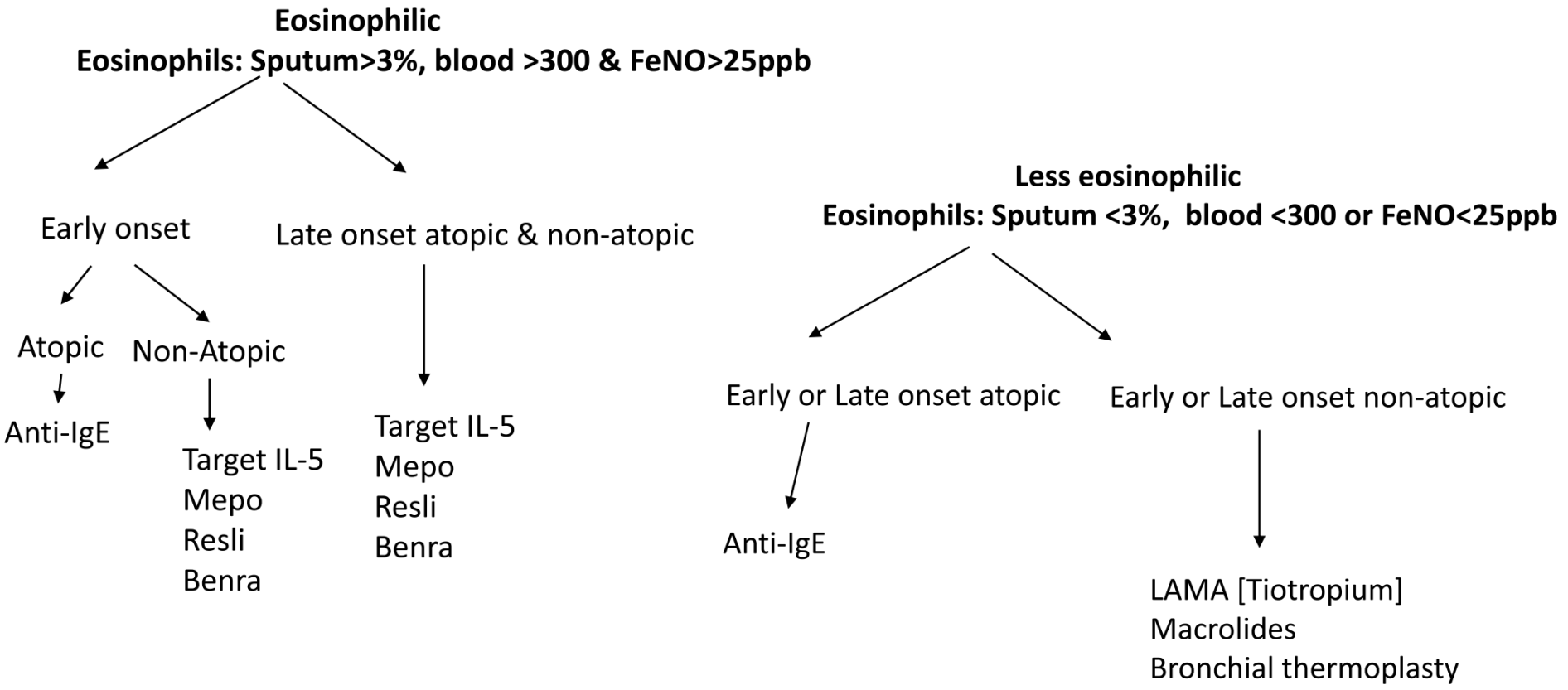
Heaney LG, Am J Respir Crit Care Med 2019;199:454-64.

Assessment Protocol in Consideration of Biologic Therapy



Bender BG, Am J Respir Crit Care Med 2019;199:400-2.

Severe Asthma Algorithm Approach: A Simple Approach



Papaioannou AI, et al. Respir Med 2018;142:15-22.