Pneumo Update Europe 2018

15 - 16 June, Budapest

Asthma

Roland Buhl, Germany

Asthma

- **Diagnosis**
  - **Physician-diagnosis of asthma**
  - **FeNO***

***Fractional exhaled nitric oxide**

Clinical applicability of FeNO

- **FeNO-guided vs. symptom-based treatment reduces exacerbation frequency (OR 0.60, 95% CI 0.43 to 0.84) with no impact on symptoms or ICS dose**
  - ➔ **FeNO measurement in frequent exacerbators**
- **Increased FeNO concentrations in ICS-naïve patients predict response to ICS treatment**

Petsky et al. Cochrane Database Syst Rev 9:CD011440, 2016 Lehtimaki et al. Eur Respir J 48:706-714, 2016 Dweik et al. Am J Respir Crit Care Med 184:602-615, 2011 Chung et al. Eur Respir J 43:343-373, 2014 Price et al. Lancet Respir Med 6(1):29-39, 2018

FeNO as predictor of ICS response in patients with non-specific respiratory symptoms

214 patients with non-specific respiratory symptoms

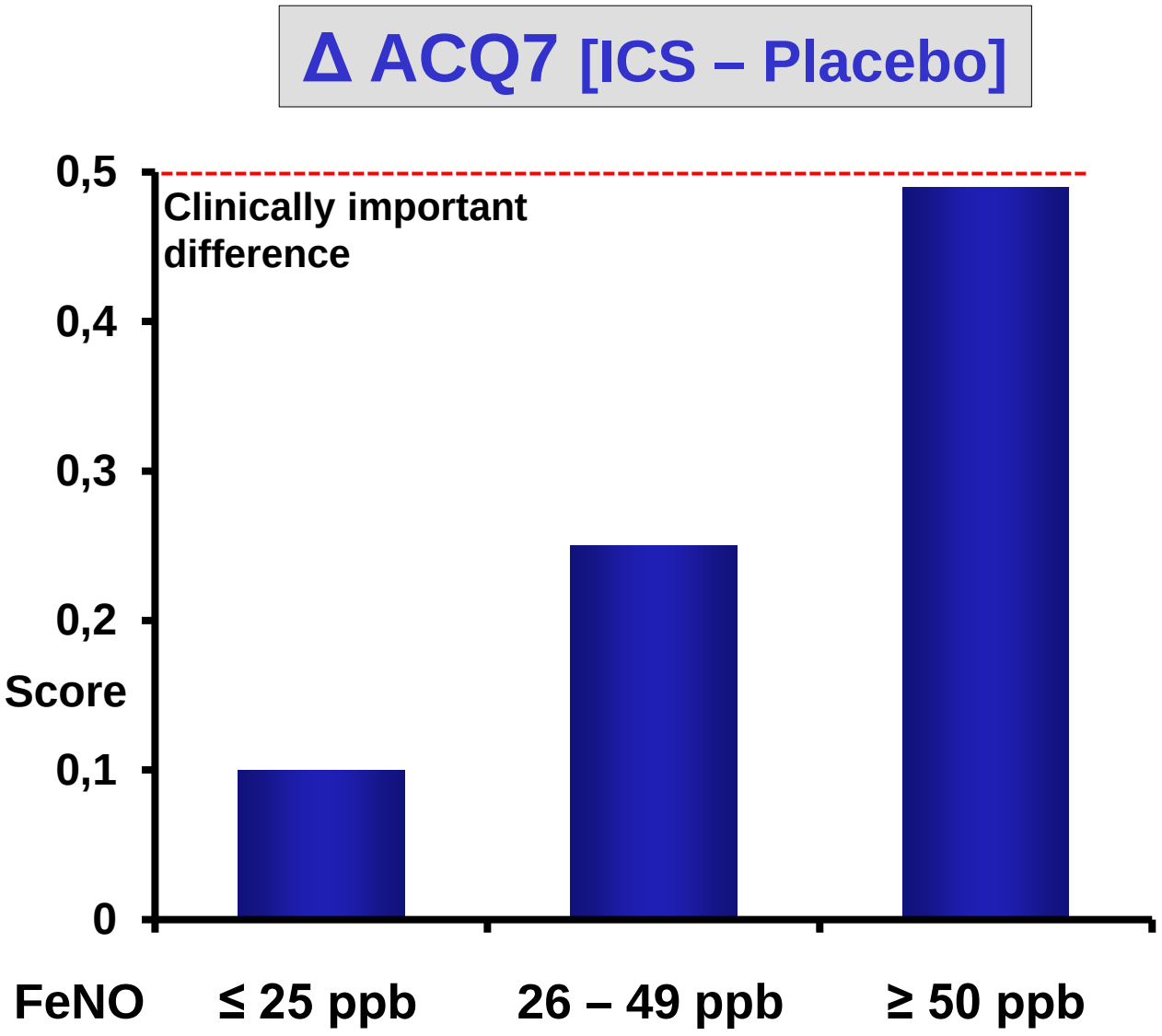
Δ FEV1 post-BD < 20%

- **Beclomethasone 800 µg/day (n=114)**
- **Placebo (n=100)**

4 weeks

- **Asthma Control Questionnaire (ACQ7)**

Price et al. Lancet Respir Med 6(1):20-39, 2018



Clinical applicability of FeNO

- **FeNO-guided vs. symptom-based treatment reduces exacerbation frequency (OR 0.60, 95% CI 0.43 to 0.84) with no impact on symptoms or ICS dose**
  - ➔ **FeNO measurement in frequent exacerbators**
- **Increased FeNO concentrations in ICS-naïve patients predict response to ICS treatment**
- **Low FeNO concentrations indicate low exacerbation risk in ICS-treated patients**
  - ➔ **no indication to increase ICS dose**
- **High FeNO concentrations in ICS-treated patients**
  - ➔ **question inhaler technique and treatment adherence**

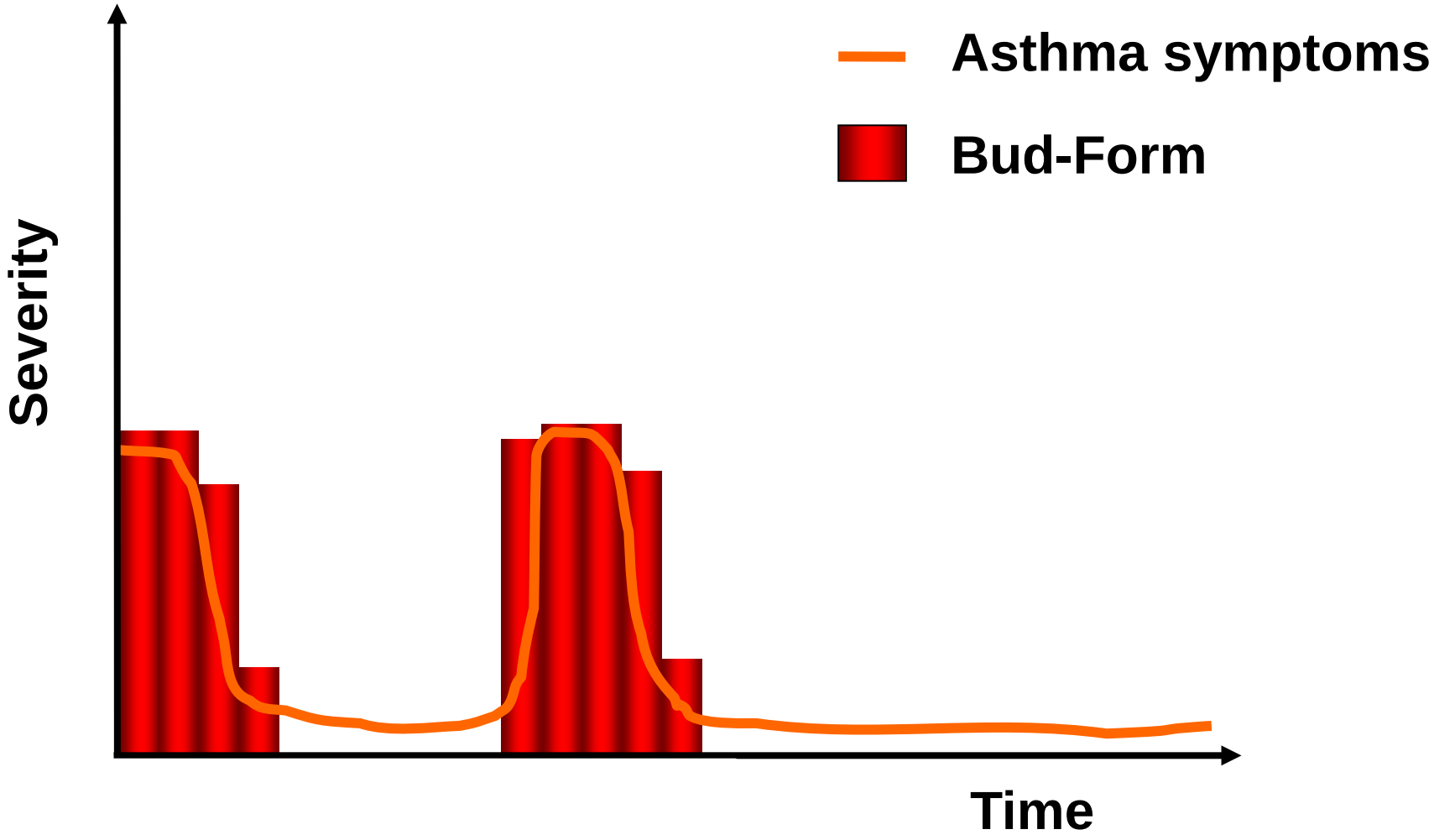
Petsky et al. Cochrane Database Syst Rev 9:CD011440, 2016 Lehtimaki et al. Eur Respir J 48:706-714, 2016 Dweik et al. Am J Respir Crit Care Med 184:602-615, 2011 Chung et al. Eur Respir J 43:343-373, 2014 Price et al. Lancet Respir Med 6(1):29-39, 2018

-------ATS-------
Late Breaking News

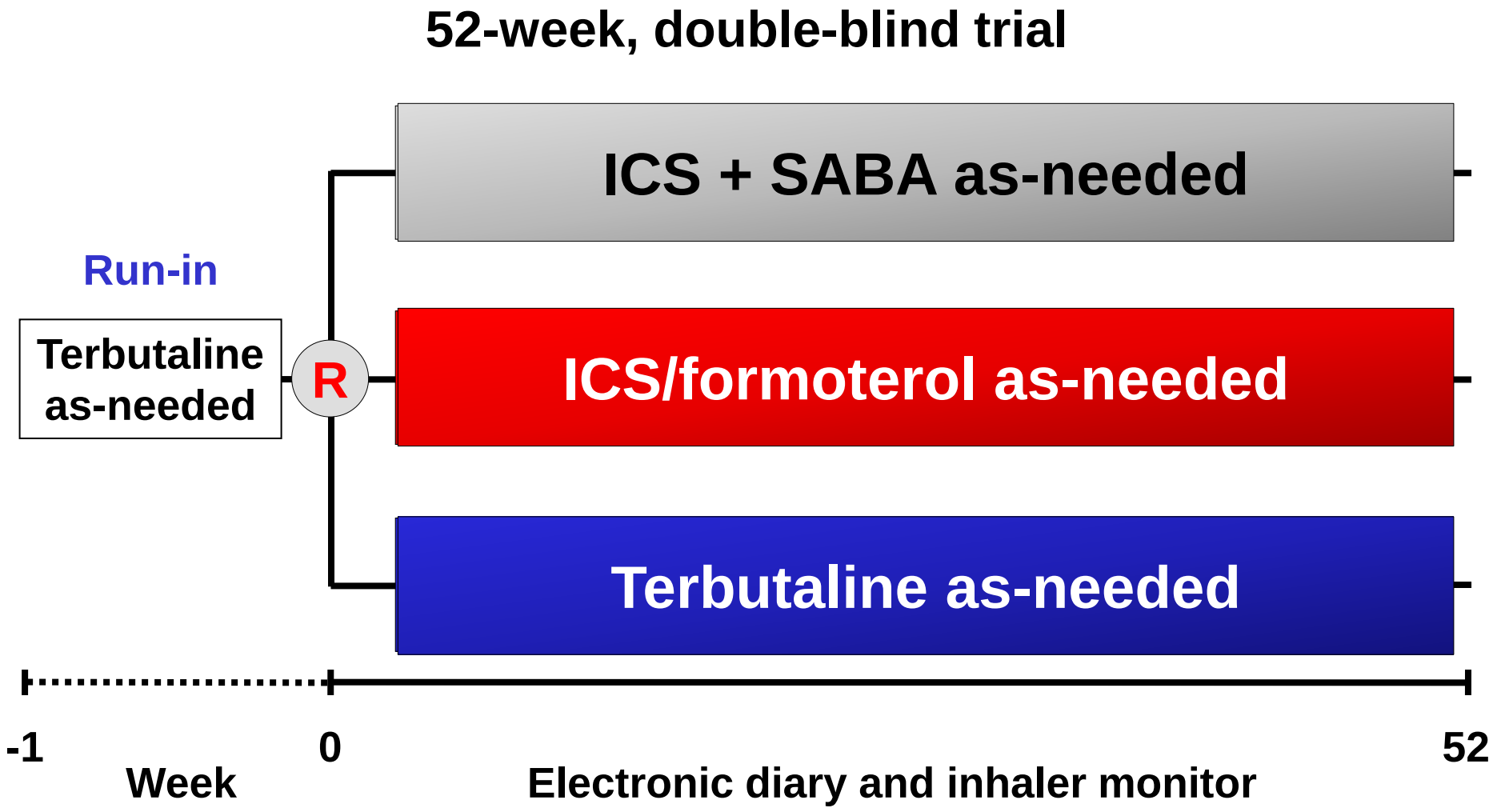
Asthma

- **Diagnosis**
- **Antibiotics for asthma exacerbations**
- **What's new in GINA ?**
- **Mild-to-moderate asthma**
  - **(S)MART light**

Fixed ICS/formoterol combination only as-needed



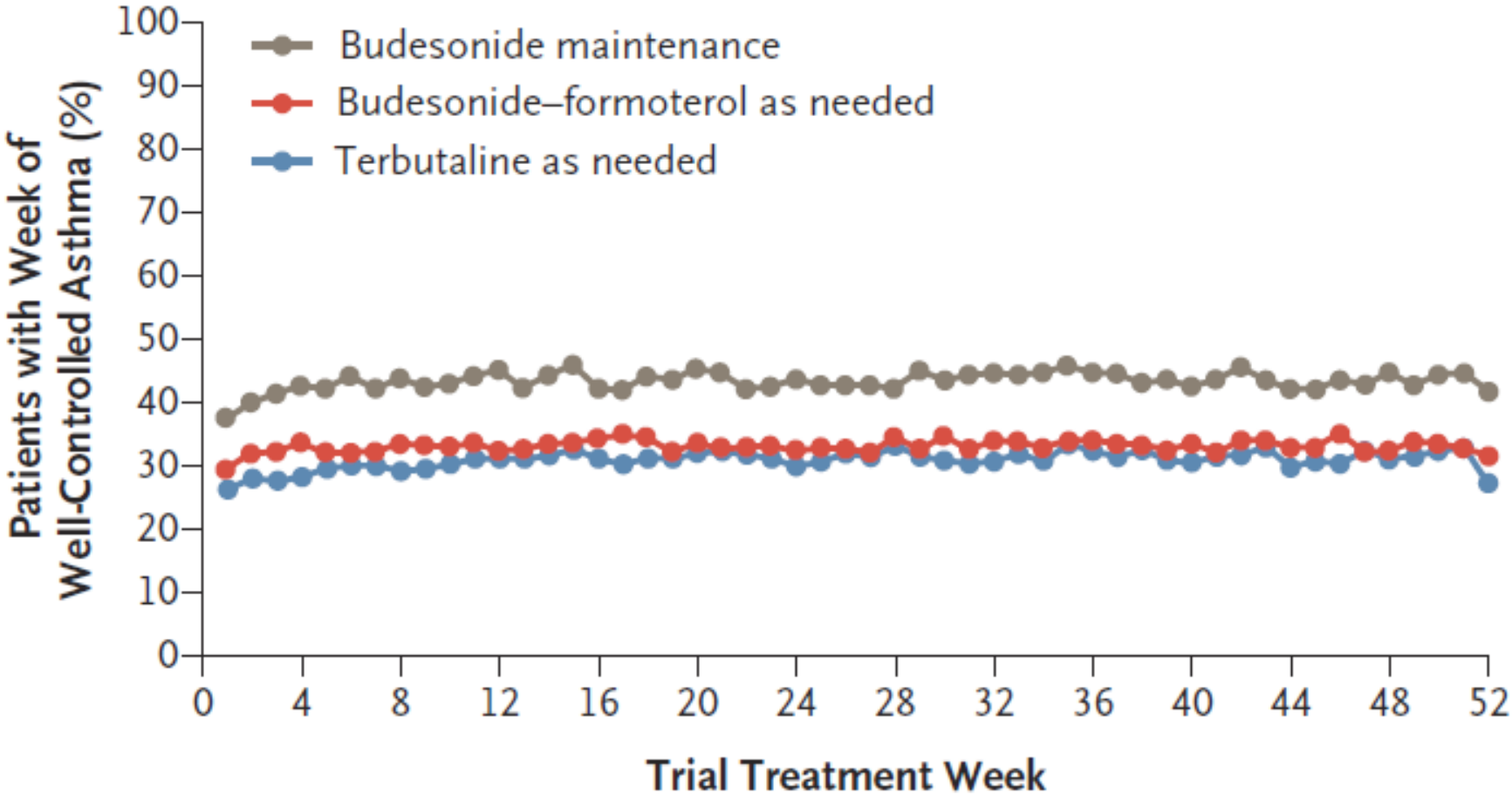
Budesonide/Formoterol as-needed in mild asthma



O'Byrne et al. NEJM 378:1865-1876, 2018

Budesonide/Formoterol as needed in mild asthma

Weeks with well-controlled asthma

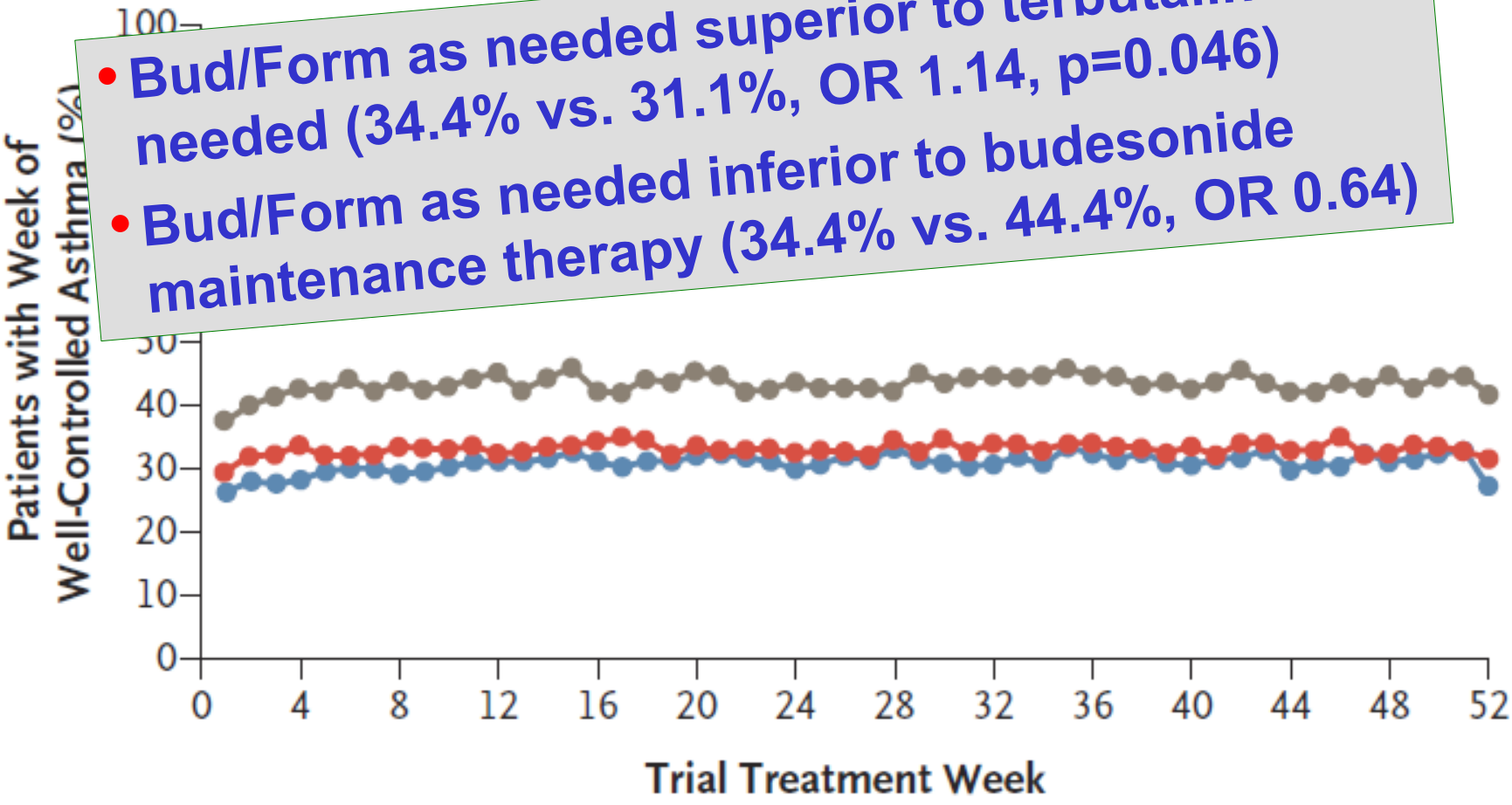


O'Byrne et al. NEJM 378:1865-1876, 2018

Budesonide/Formoterol as needed in mild asthma

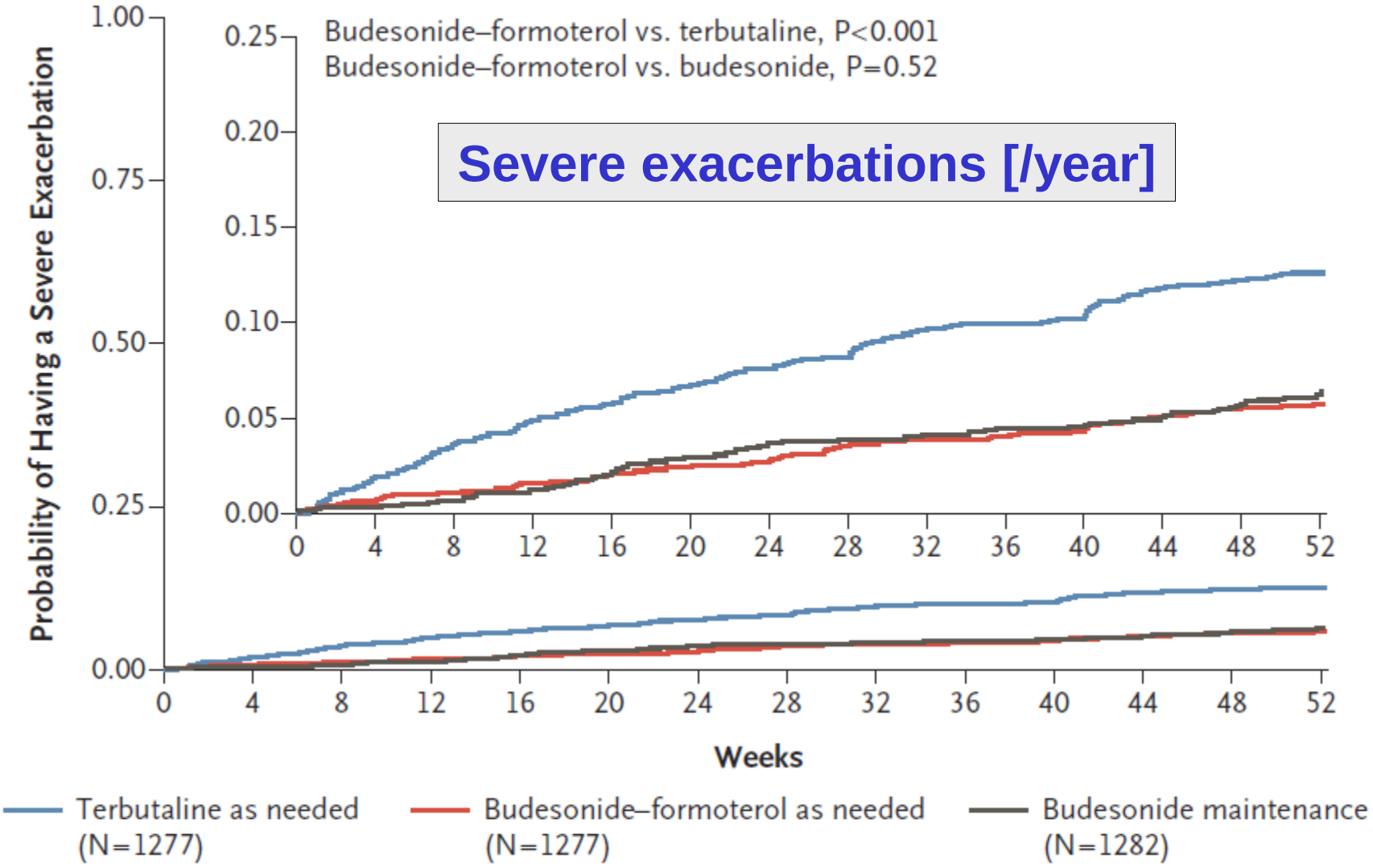
Weeks with well-controlled asthma

- **Bud/Form as needed superior to terbutaline as needed (34.4% vs. 31.1%, OR 1.14, p=0.046)**
- **Bud/Form as needed inferior to budesonide maintenance therapy (34.4% vs. 44.4%, OR 0.64)**



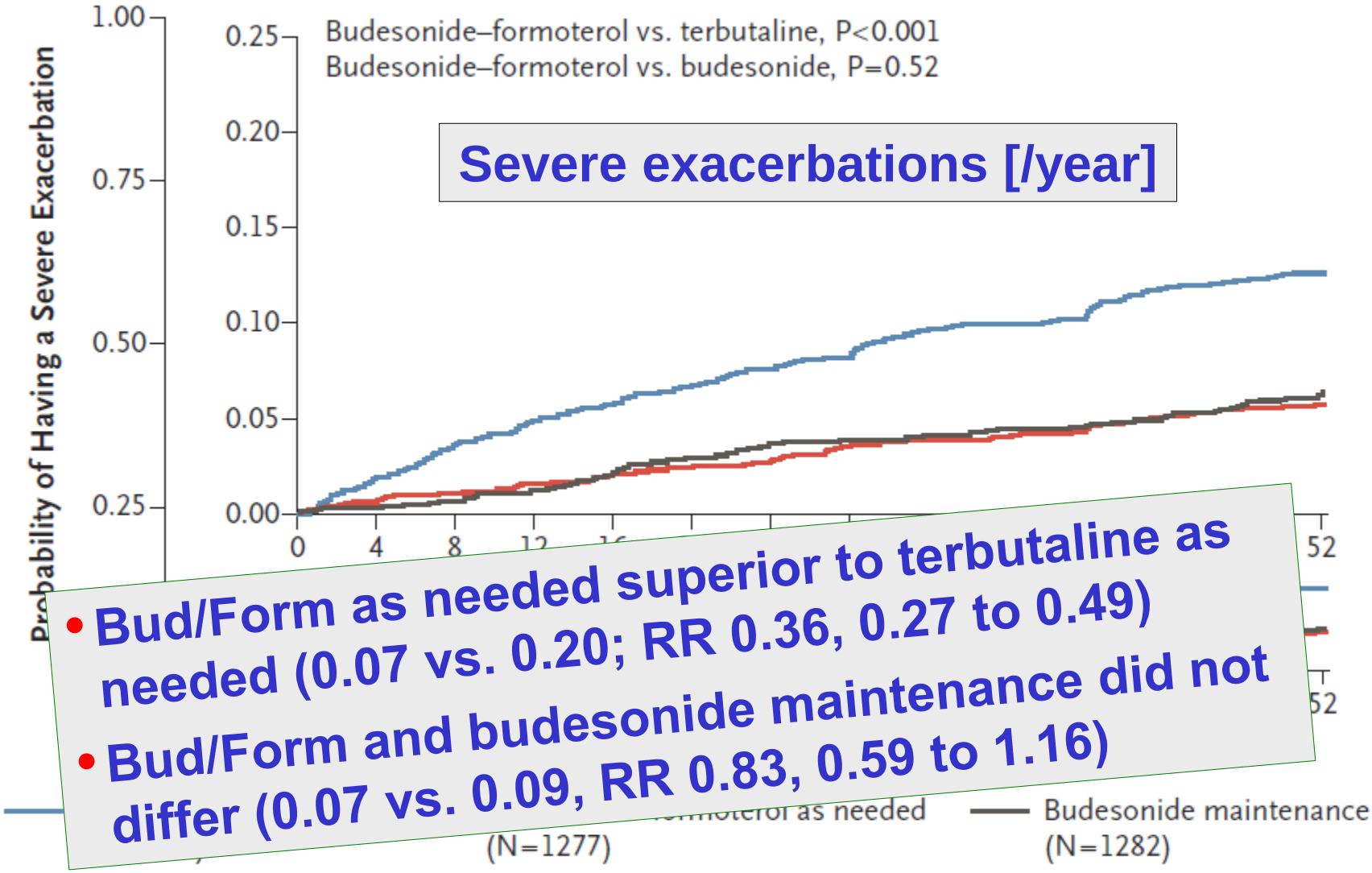
O'Byrne et al. NEJM 378:1865-1876, 2018

Budesonide/Formoterol as needed in mild asthma



O'Byrne et al. NEJM 378:1865-1876, 2018

Budesonide/Formoterol as needed in mild asthma



- **Bud/Form as needed superior to terbutaline as needed (0.07 vs. 0.20; RR 0.36, 0.27 to 0.49)**
- **Bud/Form and budesonide maintenance did not differ (0.07 vs. 0.09, RR 0.83, 0.59 to 1.16)**

O'Byrne et al. NEJM 378:1865-1876, 2018

ICS/Formoterol as-needed in mild asthma

- **BudForm as-needed provided superior asthma symptom control to as-needed terbutaline, but was inferior to budesonide maintenance therapy**
- **Exacerbation rates with the two budesonide containing regimens similar and lower than the rate with terbutaline**
- **Median daily ICS dose in the Bud/Form groups (57 / 66 µg) substantially lower than in the budesonide maintenance groups (340 / 267 µg)**

Lazarus et al. NEJM 378:1940-1942, 2018

ICS/Formoterol as-needed in mild asthma

- **BudForm as-needed provided superior asthma symptom control**
- **This may not be enough for patients who are unhappy with any symptoms or a need for rescue inhaler use**
- **Many others may prefer to accept occasional mild symptoms and inhaler use if it frees them from daily use of inhaled glucocorticoids while preventing loss of lung function and exacerbations**
  For these patients, "Two out of three ain't bad!"

Lazarus et al. NEJM 378:1940-1942, 2018

Asthma

- **Diagnosis**
- **Antibiotics for asthma exacerbations**
- **What's new in GINA ?**
- **Mild-to-moderate asthma**
  - **(S)MART light**
  - **Quadrupling ICS dose**

Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations

1871 asthma patients
≥1 exacerbation last year

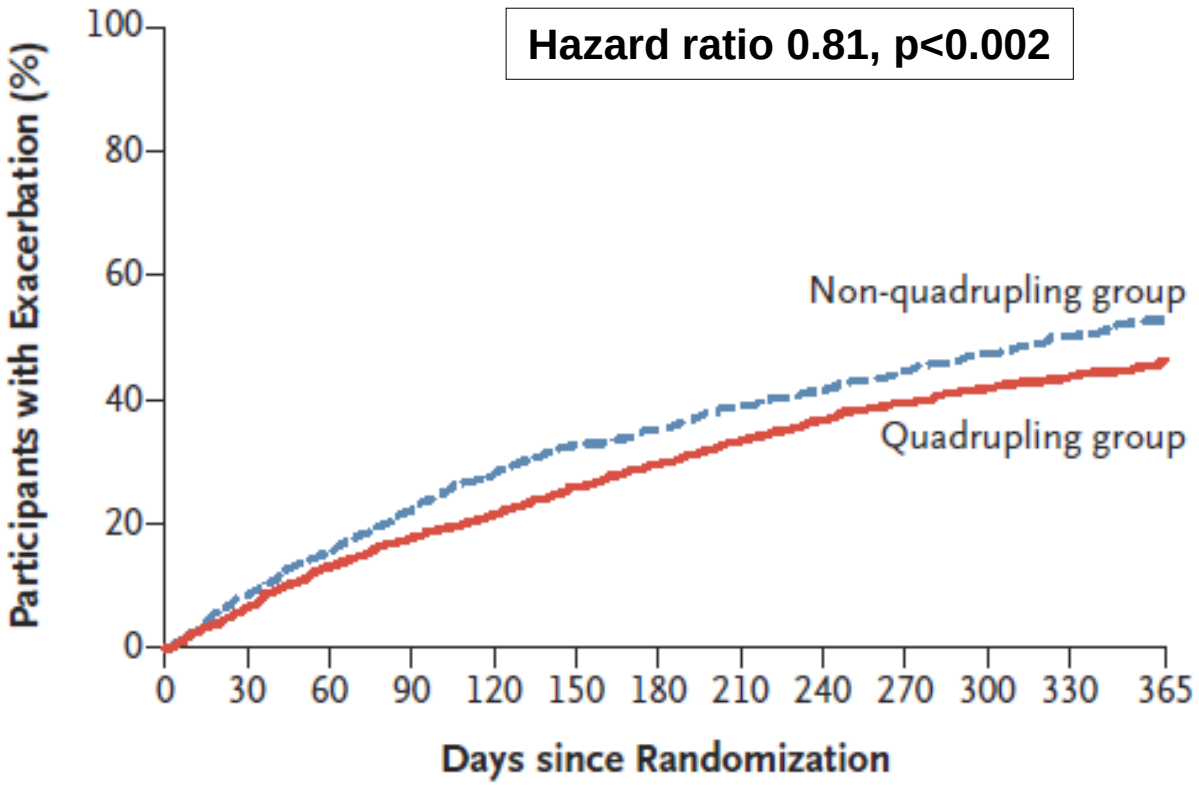
- **Reliever use ↑**
- **Difficulty sleeping**
- **Peak flow < 80% PB**

- **Quadruple ICS dose for ≤ 14 days**
- **Placebo**

12 months

- **Time to first exacerbation**

Time to first severe exacerbation



McKeever et al. N Engl J Med 378(10):902-910, 2018

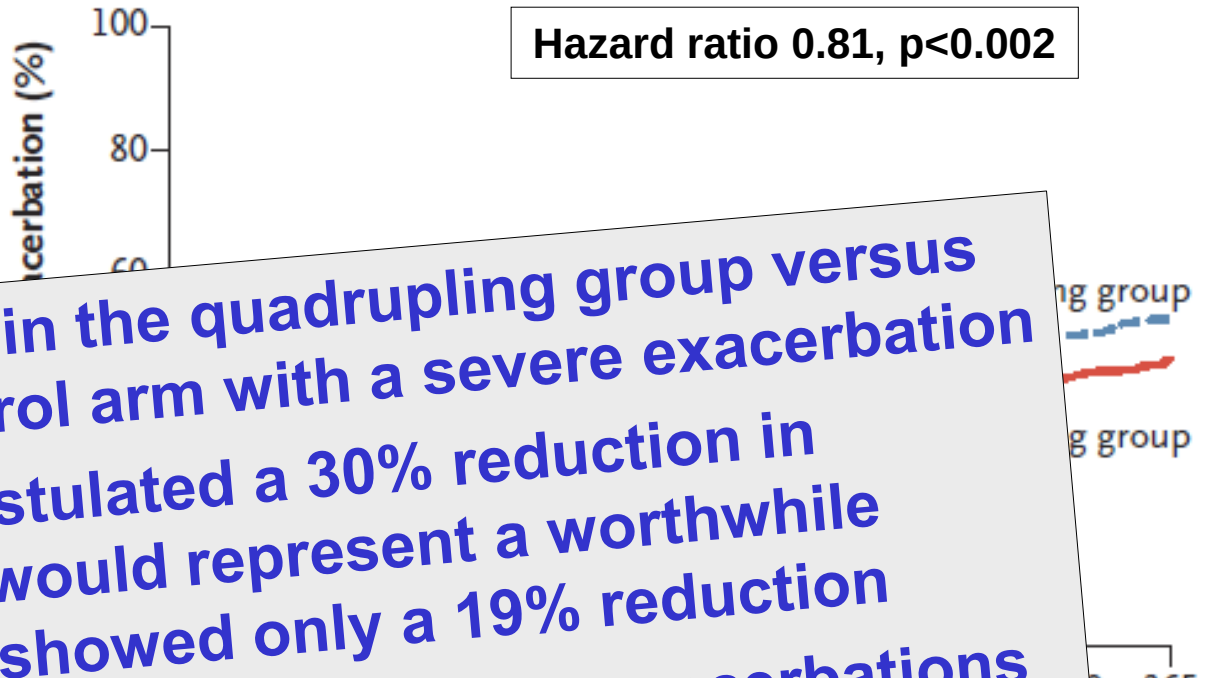
Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations

1871 asthma patients
≥1 exacerbation last year

- **Reliever use ↟**
- **Difficulty sleeping**
- **Peak flow < 80% PB**

- **Quadruple ICS**
-

Time to first severe exacerbation



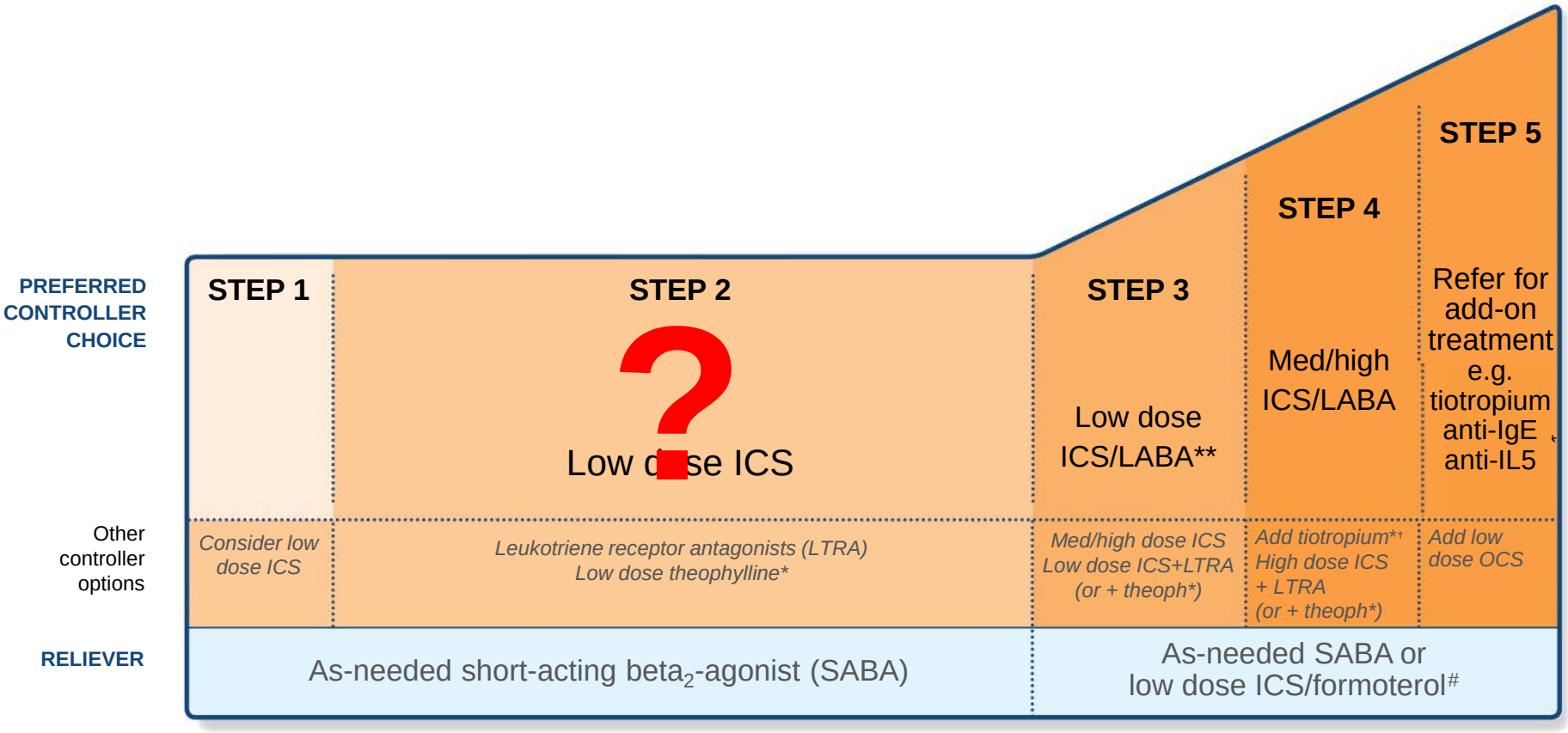
Hazard ratio 0.81, p<0.002

- **45% of patients in the quadrupling group versus 52% in the control arm with a severe exacerbation**
- **The authors postulated a 30% reduction in exacerbations would represent a worthwhile effect, the trial showed only a 19% reduction**
- **Urgent need to phenotype asthma exacerbations**

PG Bardin. N Engl J Med 378(10):950-952, 2018

McKeever et al. N Engl J Med 378(10):902-910, 2018

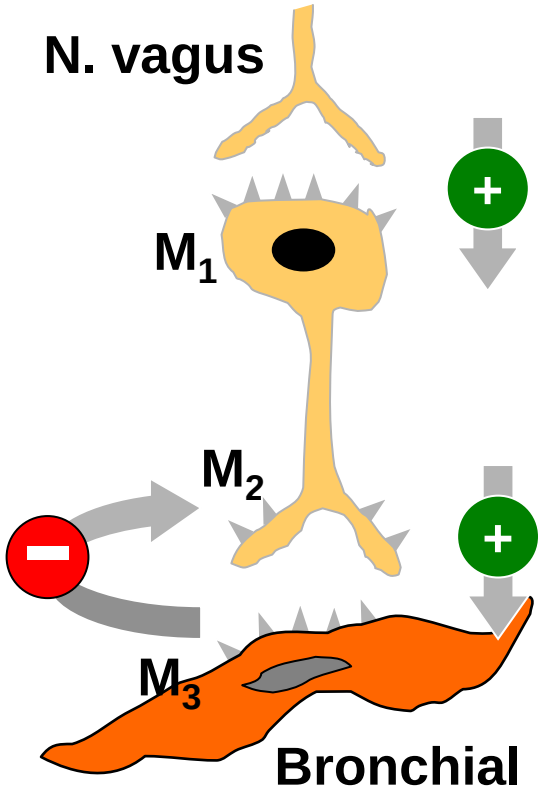
Stepwise asthma treatment for adults and adolescents



*Not for children <12 years. **For children 6–11 years, the preferred Step 3 treatment is medium dose ICS.
Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol for maintenance and reliever therapy.
†Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations (not for children <12 years)
.

www.ginasthma.org

Asthma



- Diagnosis
- Antibiotics for asthma exacerbations
- What's new in GINA ?
- Mild-to-moderate asthma
  - (S)MART light
  - Quadrupling ICS dose
  - Tiotropium

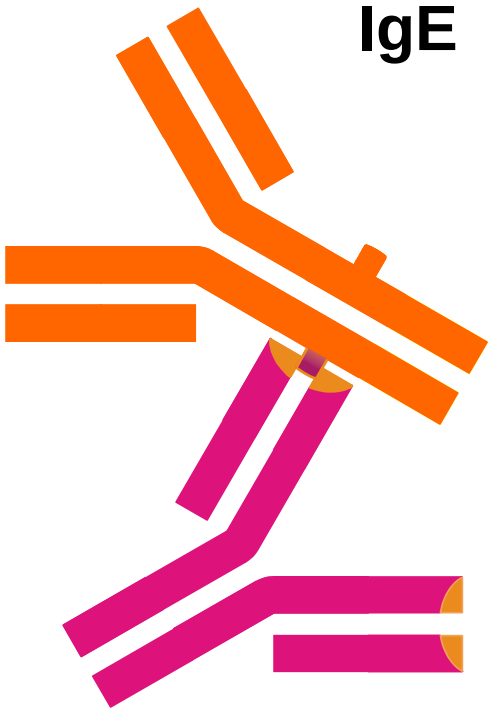
-------ATS-------
Late Breaking News

Asthma

- Diagnosis
- Antibiotics for asthma exacerbations
- What's new in GINA ?
- Mild-to-moderate asthma
- Biologics in severe asthma

Biologics in severe asthma

- **Anti - IgE**
  - **Omalizumab**

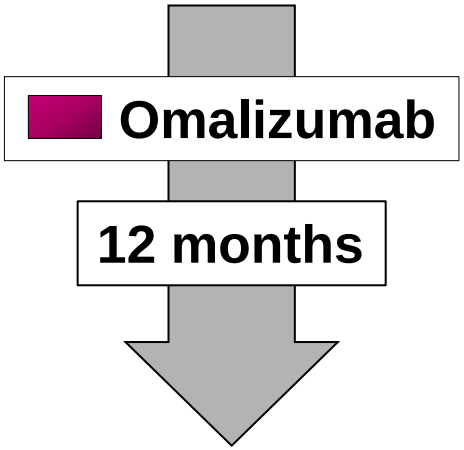


Phenotype ‚allergic asthma‘

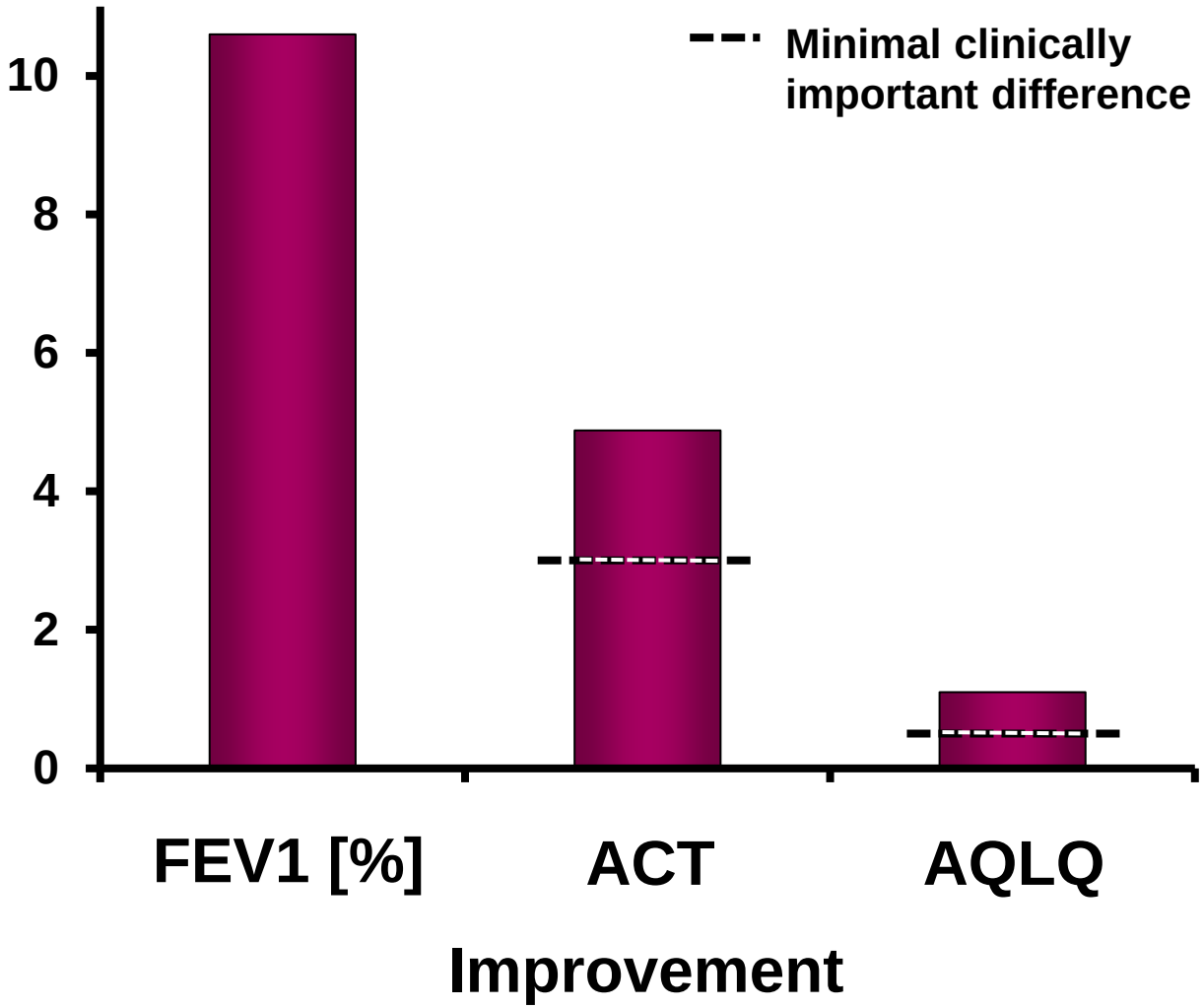
- Usually early disease onset
- Symptoms related to allergen exposure
- Allergic comorbidities
- Skin prick test positive
- Total (and specific) IgE
- Treatment response to glucocorticosteroids and omalizumab

‘Real-life’ effectiveness of omalizumab in severe allergic asthma

9213 asthma patients in 25 controlled trials



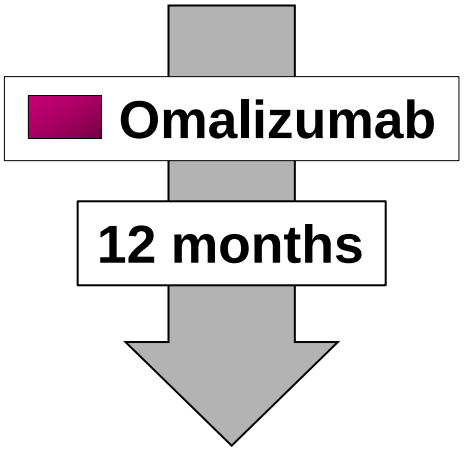
- **Real-life effectiveness**



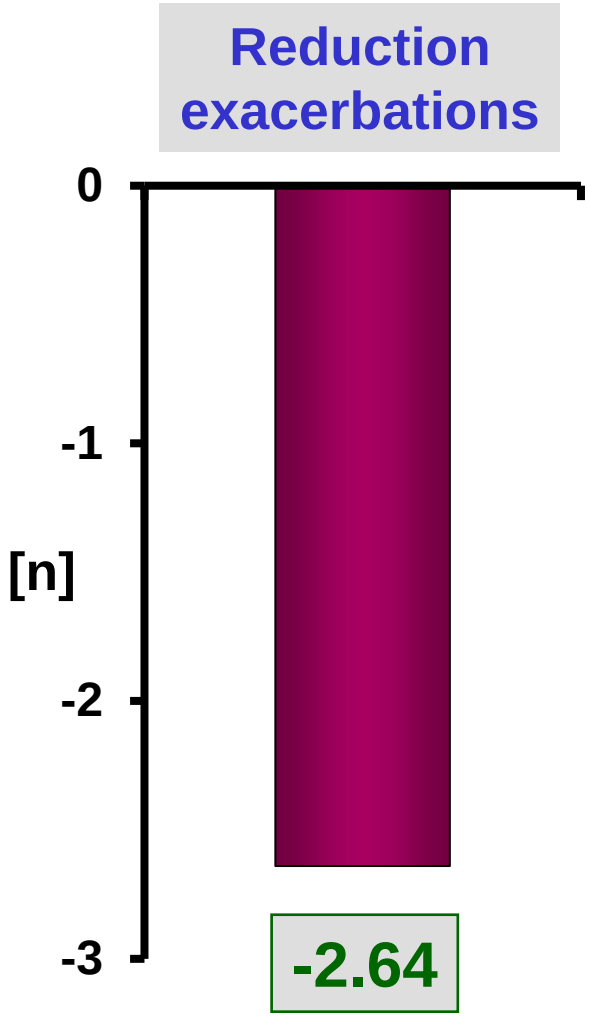
Alhossan et al. J Allergy Clin Immunol Pract 5(5):1362-1370, 2017

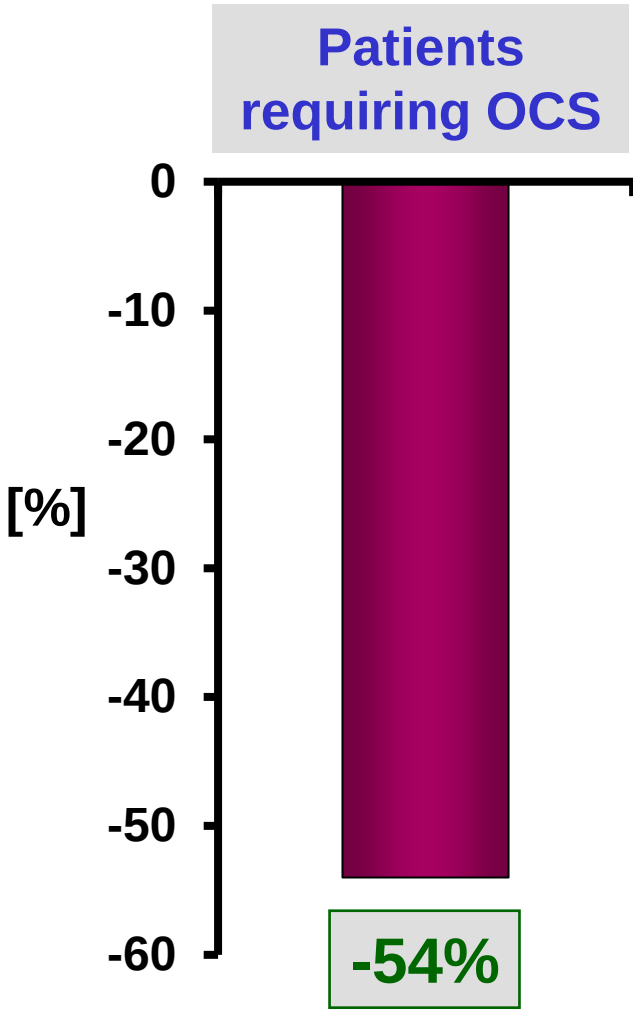
‘Real-life’ effectiveness of omalizumab in severe allergic asthma

9213 asthma patients in 25 controlled trials



- **Real-life effectiveness**





Alhossan et al. J Allergy Clin Immunol Pract 5(5):1362-1370, 2017

Persistence of omalizumab response after long-term therapy

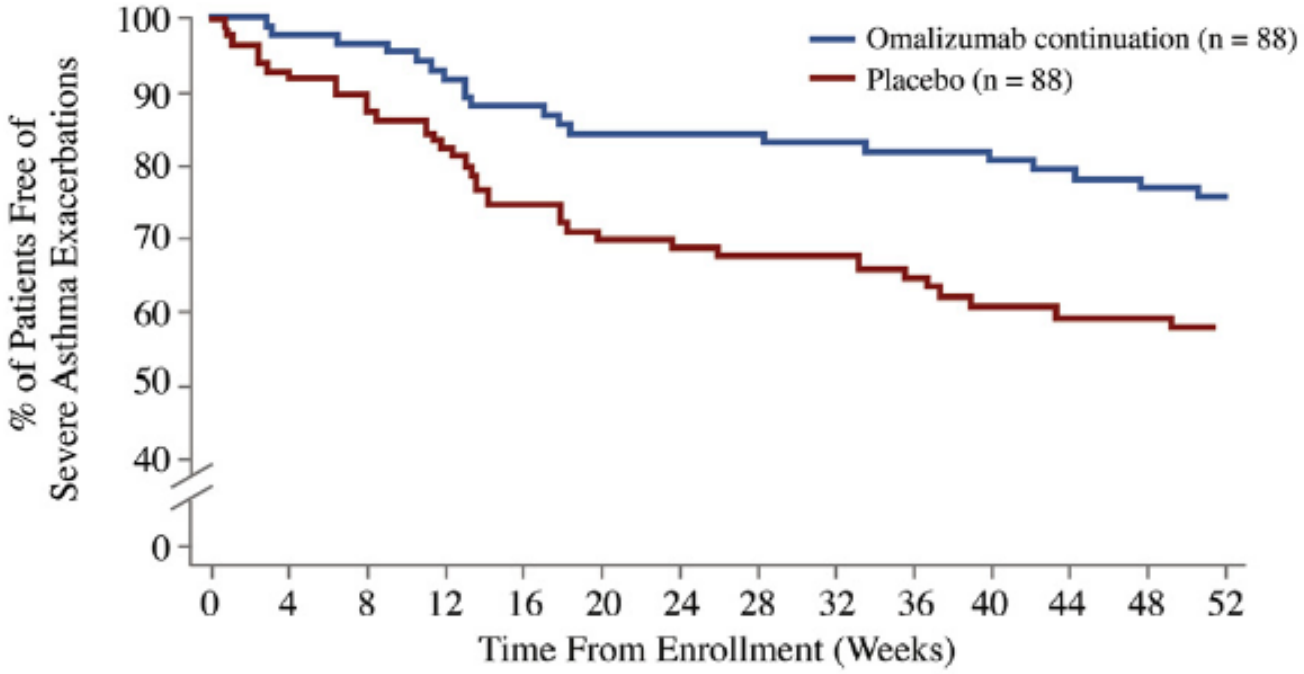
- Moderate-to-severe asthma
- Omalizumab for ~ 5 yr.

- Continue omalizumab
- Withdraw to placebo

1 year

- Severe asthma exacerbation
- Asthma control

Time to 1st exacerbation



Ledford et al. J Allergy Clin Immunol 140(1):162-169, 2017

Persistence of omalizumab response after long-term therapy

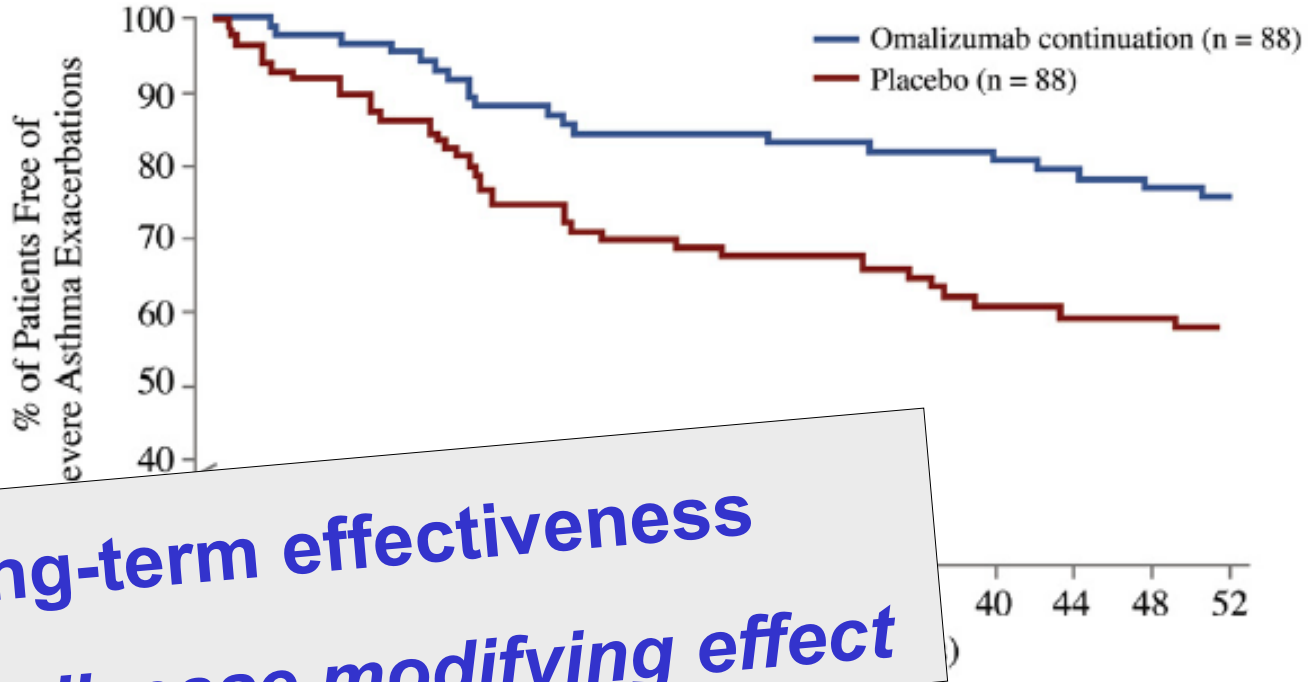
- Moderate-to-severe asthma
- Omalizumab for ~ 5 yr.

- Continue omalizumab
- Withdraw to placebo

1 year

- Severe asth… exacerbatio…
- Asthma cont…

Time to 1st exacerbation



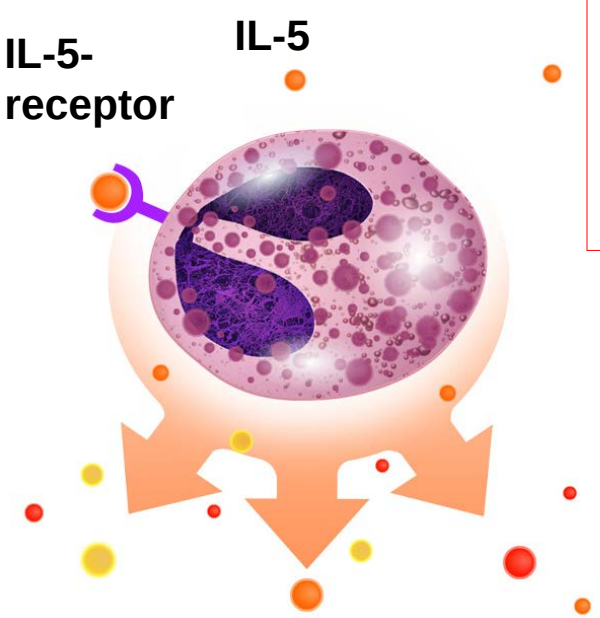
- **Long-term effectiveness**
- **No *disease modifying effect***

Ledford et al. J Allergy Clin Immunol 140(1):162-169, 2017

Biologics in severe asthma

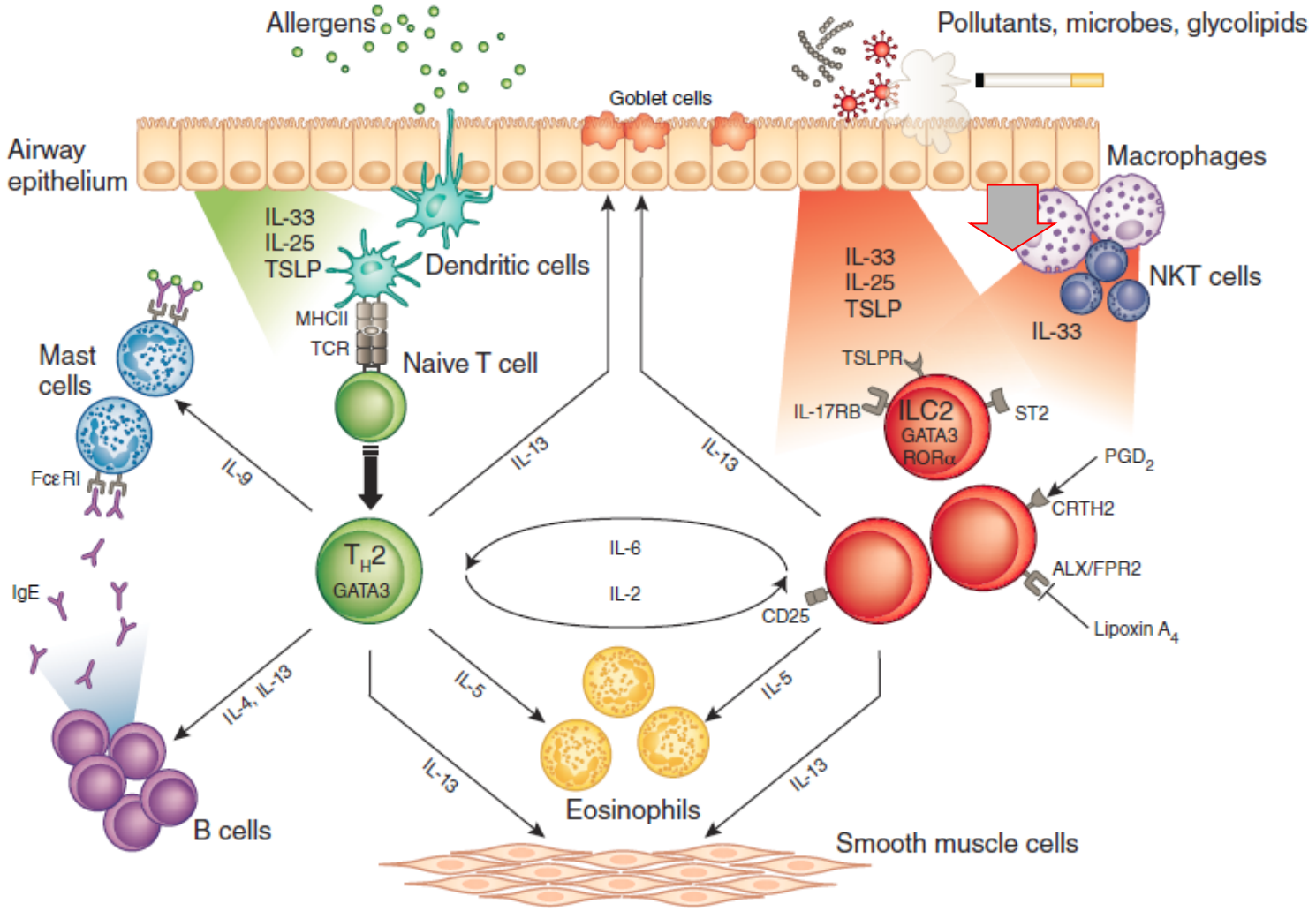
- **Anti - IgE**
  - **Omalizumab**

- **Anti - IL-5**
  - **Mepolizumab**
  - **Reslizumab**
  - **Benralizumab (anti-IL-5 receptor)**



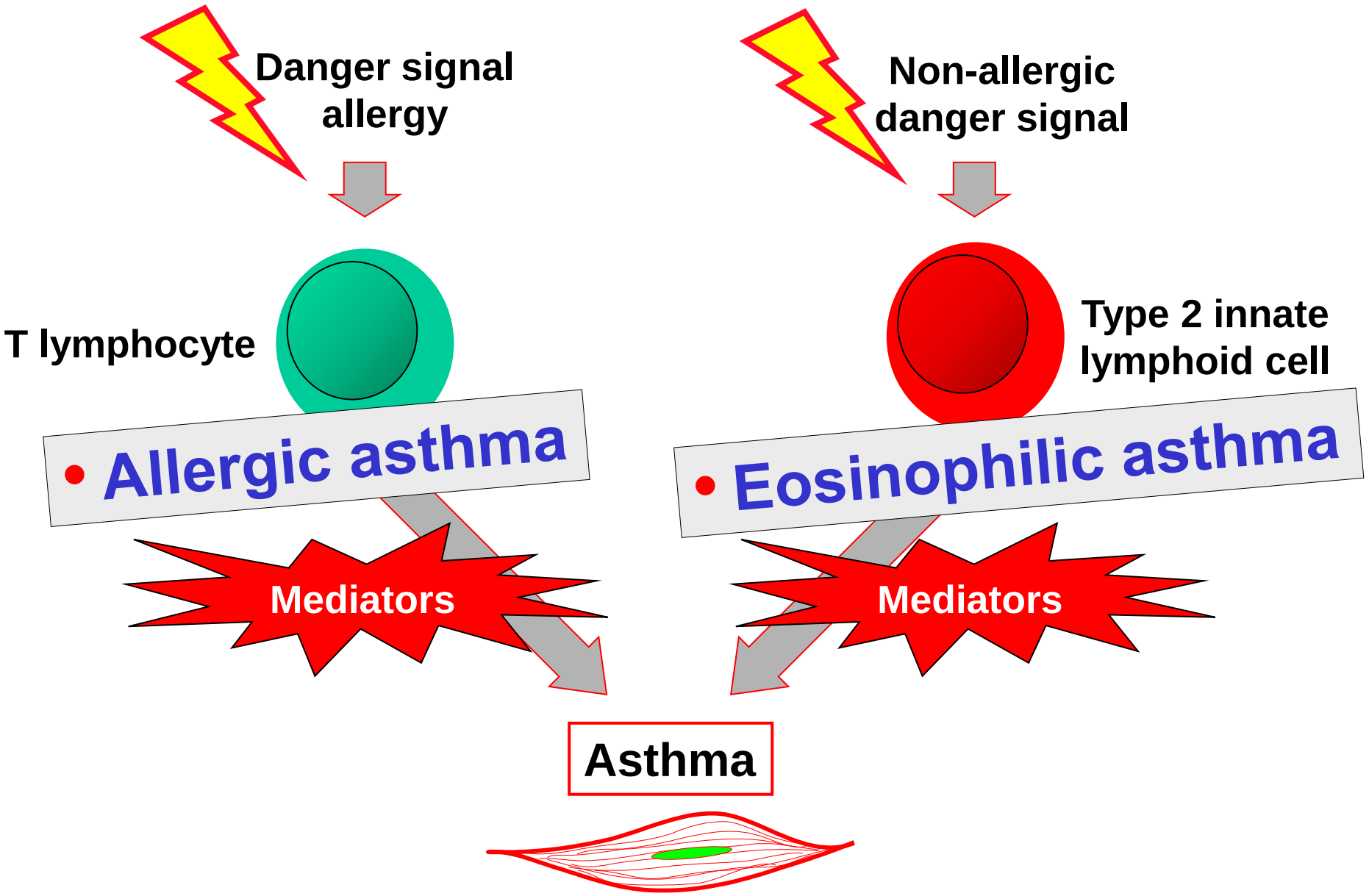
Eosinophil granulocyte

Airway inflammation in asthma



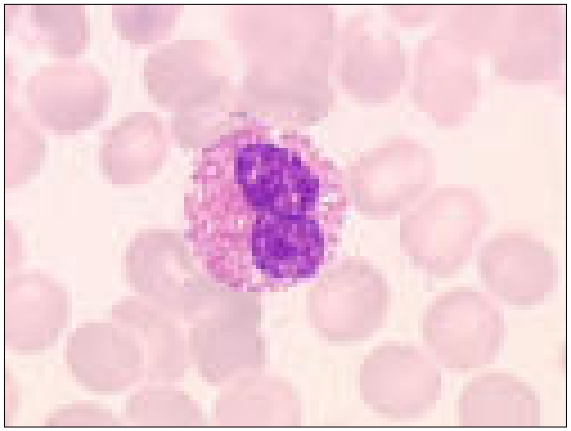
Brusselle, et al. Nat Med 19(8):977-979, 2013

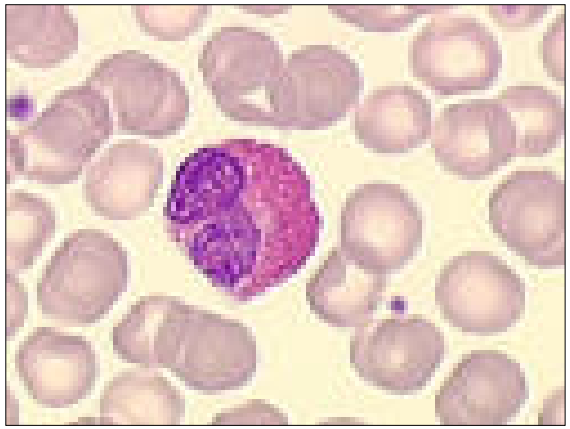
Airway inflammation in asthma



Brusselle, et al. Nat Med 19(8):977-979, 2013

Phenotype ‚eosinophilic' asthma



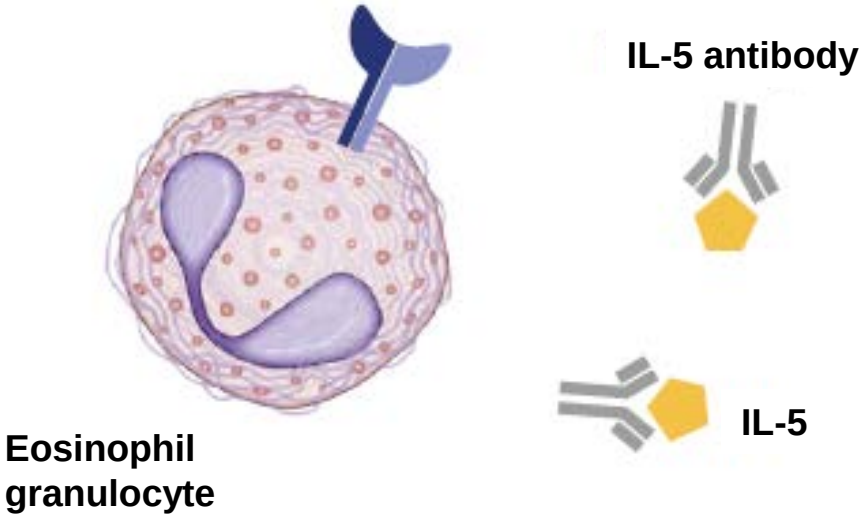


- **Late onset of disease**
- **Symptoms ↑, exacerbations ↑**
- **Eosinophilia in blood** (± sputum)
- **No *clinically relevant* allergy**
- **± Nasal polyposis**
  - smell ↓ & taste ↓
- **Response to (oral) gluco-corticoids and anti - IL-5**

Eosinophil depletion by monoclonal antibodies

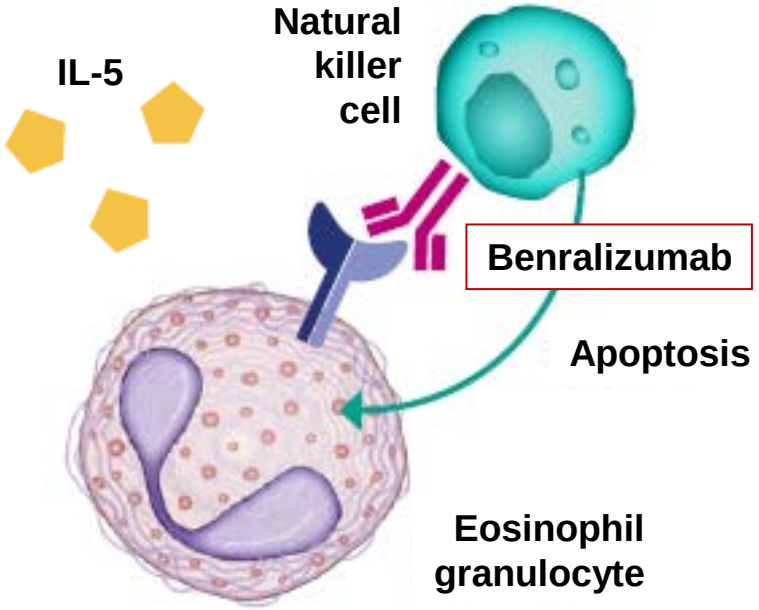
Anti-IL-5 antibodies mepolizumab & reslizumab

- **IL-5 essential for eosinophil mobilisation, maturation, activation, and survival**



Anti-IL-5-receptor antibody benralizumab

- **Binds to IL-5Rα and depletes eosinophils via antibody-dependent cell-mediated cytotoxicity**



Anti - IL-5 antibodies: Clinical efficacy

	Mepolizumab	Reslizumab	Benralizumab
Exacerbations ↓ (vs. placebo)	54% sc, 47% iv (80% at ≥500 eos)	50–60% at ≥400 eos	28–51% at ≥300 eos
FEV_1 ↑ (%)	98 mL (6%)	160 mL (7%) and 270 mL (12%)	106 - 159 mL at ≥300 eos
Asthma symptoms (ACQ5/6)	0.44 (0.75 at ≥500 eos)	0.36	0.19 - 0.29 at >300 eos
Oral steroids ↓	50% median	No study	50% median
Dosage	q4w 100 mg sc	q4w 3 mg/kg iv	30 mg q4/8w sc

1. Ortega et al. N Engl J Med 2014 **2. Bel et al. N Engl J Med 2014**
3. Bjermer et al. Chest 2016 **4. Corren et al. Chest 2016**
5. Fitzgerald et al. Lancet 2016 **6. Bleecker et al. Lancet 2016**
7. Nair et al. N Engl J Med 376(25):2448-2458, 2017

Benralizumab for mild-to-moderate asthma

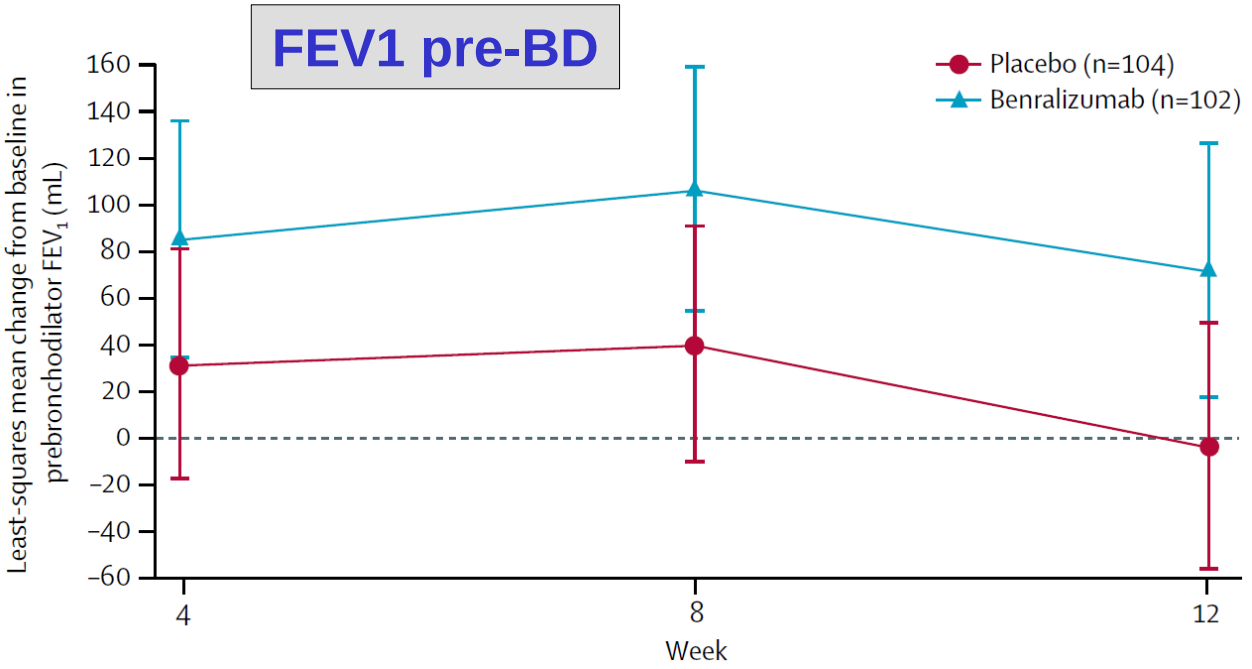
211 asthma patients
FEV1 pre-BD >50-90%,
uncontrolled despite
LD-MD ICS or
LD ICS + LABA

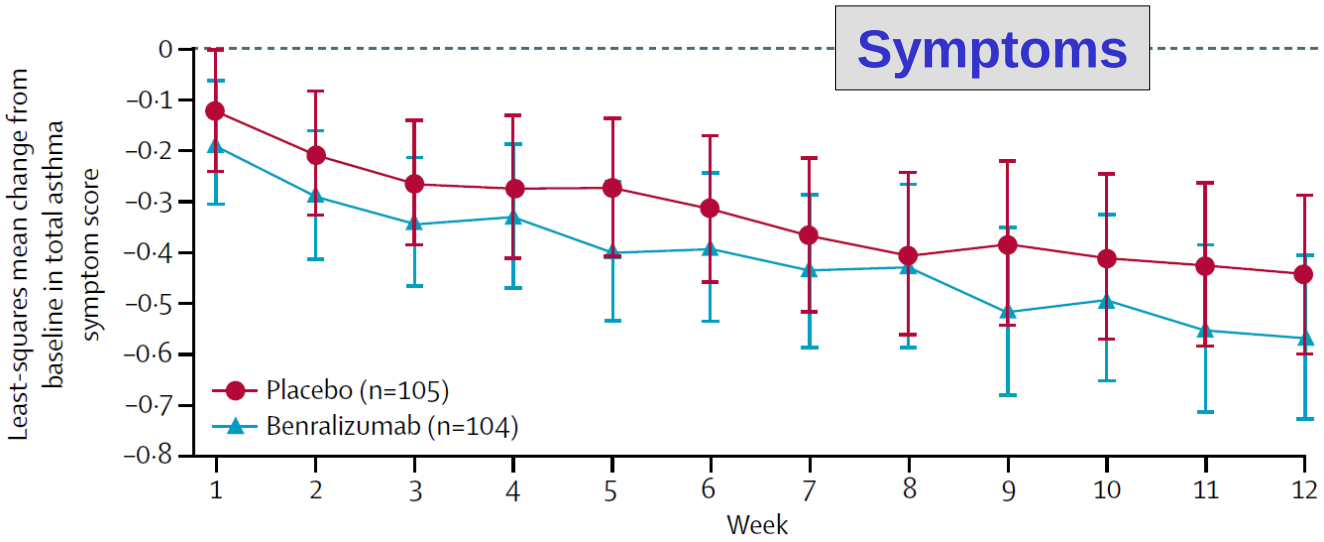
- **Benralizumab 30 mg sc every 4 weeks**
- **Placebo**

12 weeks

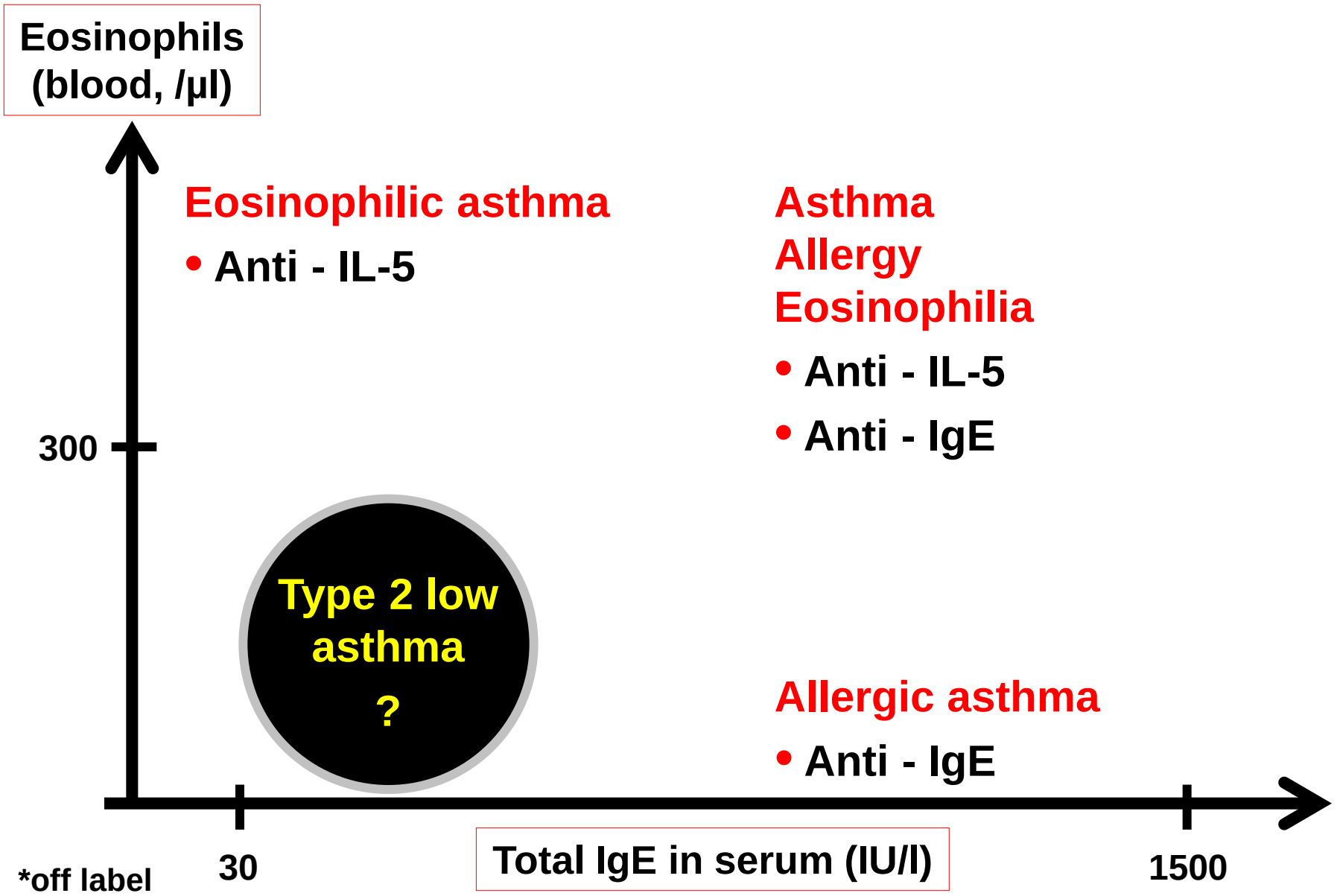
- **ΔFEV1 pre-BD**
- **Symptoms**

Ferguson et al.
Lancet Respir Med
5(7):568-576, 2017





Targeted treatments in severe asthma



Diagnosis of severe eosinophilic asthma

Major criteria	Minor criteria
• Severe asthma	• Late onset of disease
• Blood eosinophilia (≥ 2 occasions)	• Upper airway disease (chronic rhinosinusitis, often with nasal polyposis)
• Frequent exacerbations (≥ 2 per year)	• Other biomarkers (FeNO?)
• Dependence (continuous or intermittent) on oral corticosteroids	• Fixed airflow obstruction
	• Air trapping / presence of mucus plugs

Buhl et al. Eur Respir J 49, 2017

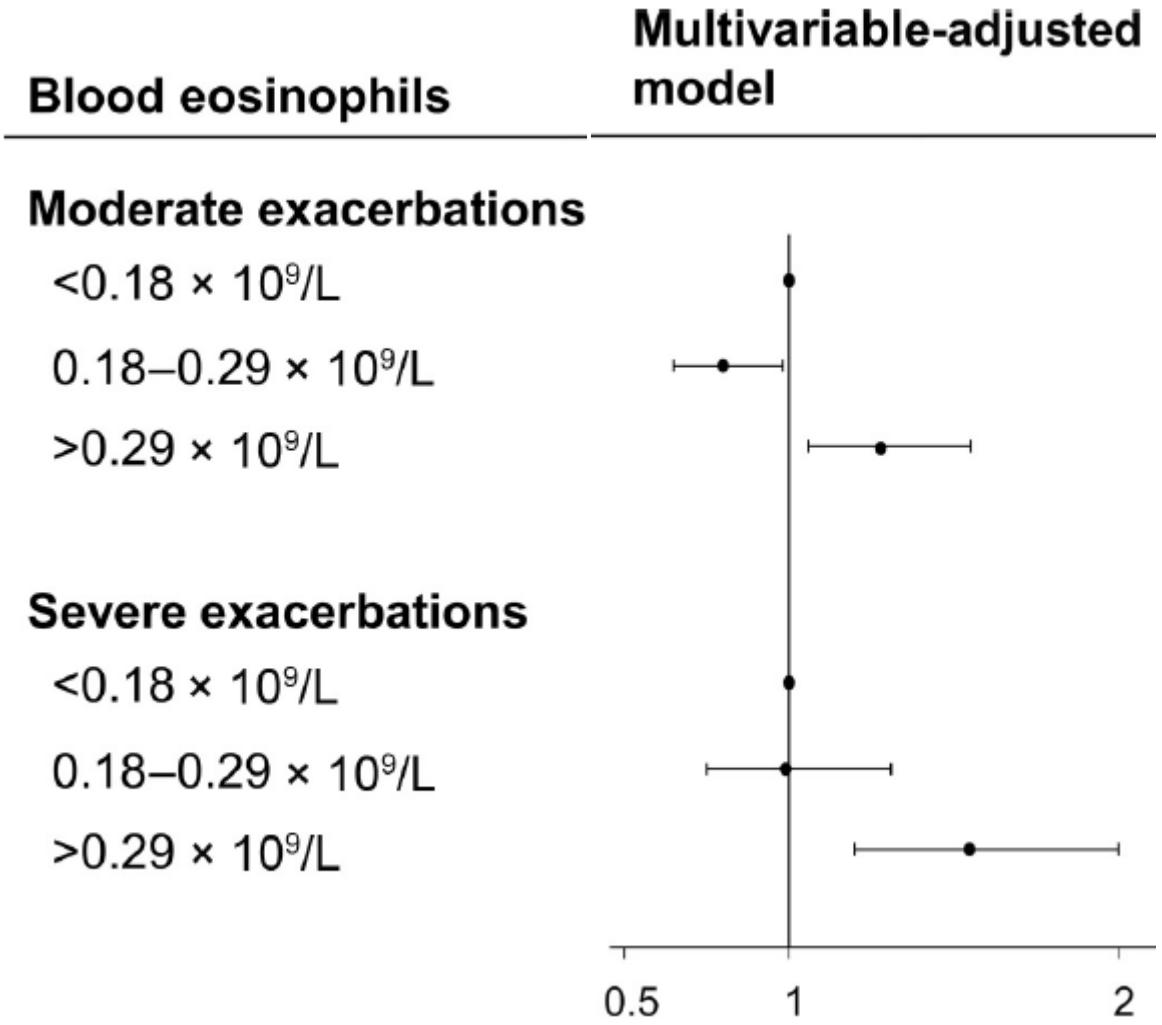
Blood eosinophils and asthma exacerbations

Copenhagen General Population Study

- **81351 participants**
- **4838 with self-reported asthma**

2003 - 2011

- **Blood eosinophils**
- **Asthma exacerbations**



Vedel-Krogh et al. Clin Chem 63(4):823-832, 2017

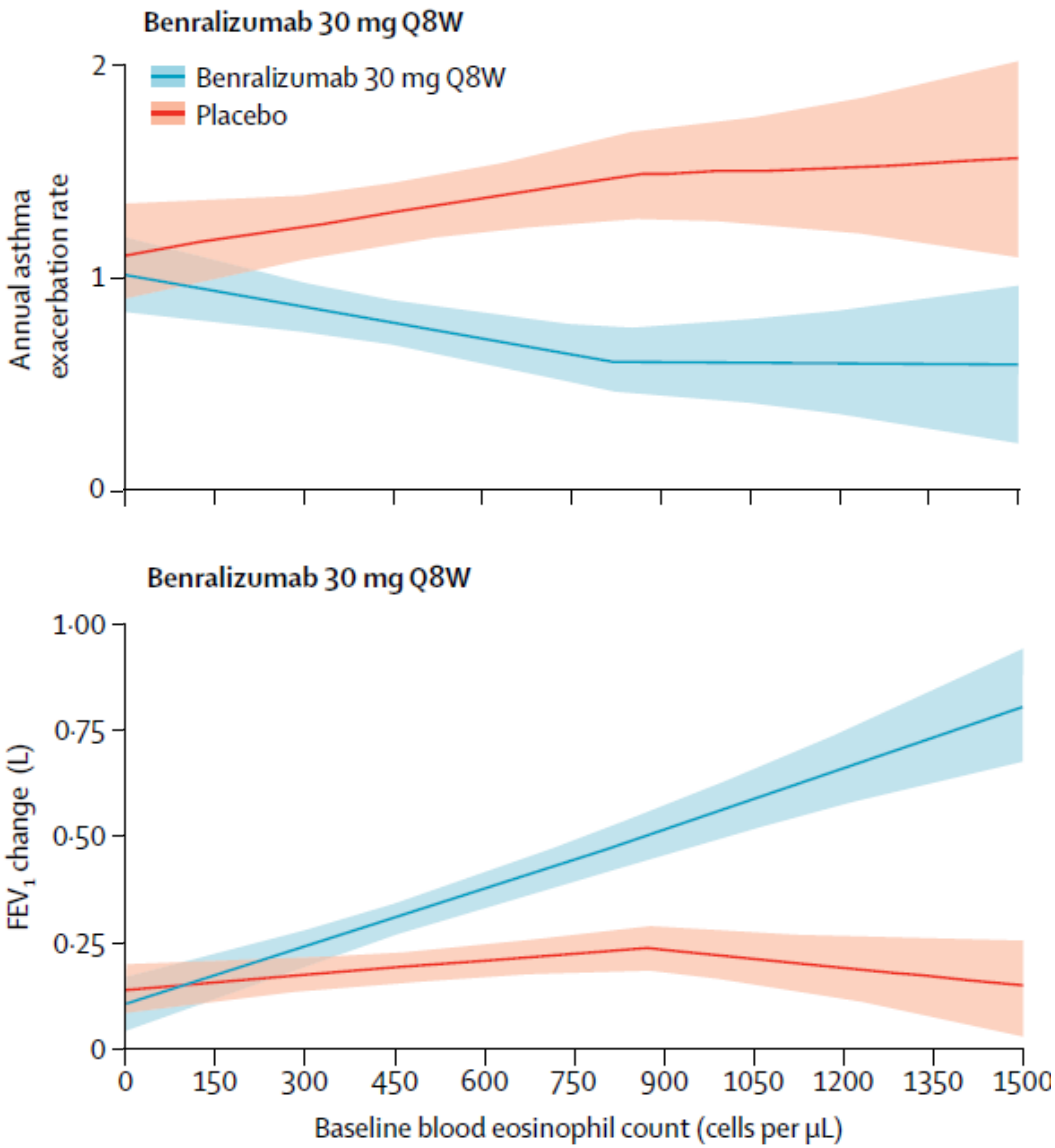
Predictors of response with benralizumab for severe asthma: SIROCCO and CALIMA

2295 asthma patients
12-75 yrs., MD - HD ICS + LABA, ≥ 2 exac./prev. year

- **Benralizumab 30 mg s.c. Q4W**
- **Benralizumab 30 mg s.c. 3x Q4W➔Q8W**
- **Placebo**

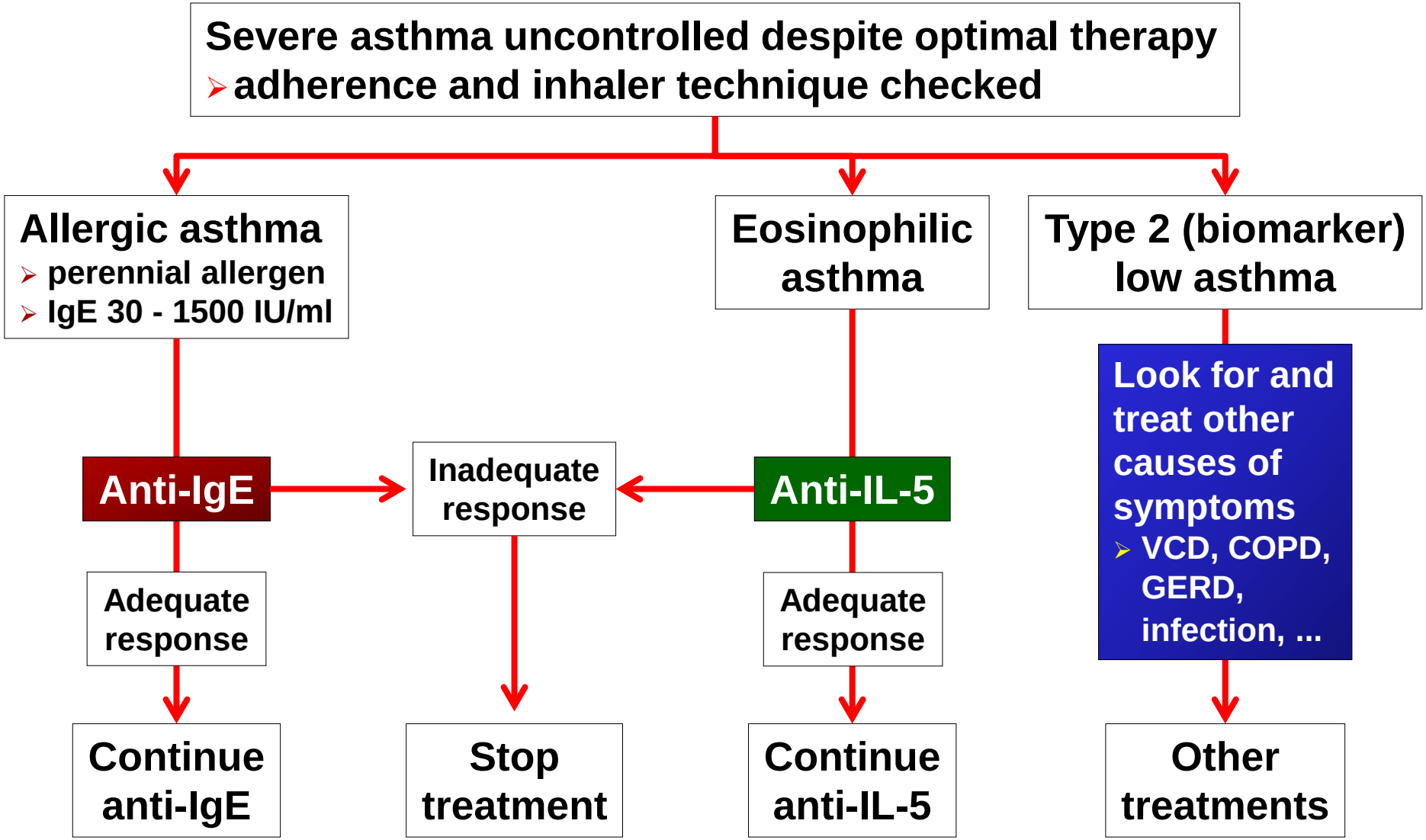
48 / 56 weeks

- **Exacerbation rate**
- **Lung function**



FitzGerald et al. Lancet Respir Med 6(1):51-64, 2018

Care pathways for biologics in asthma

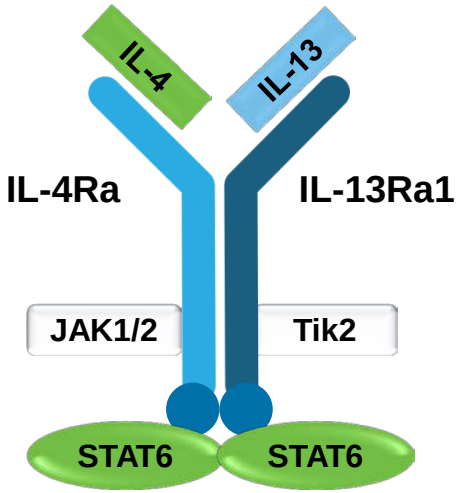


Anti-IL-5: Monitoring for response

- **No universally accepted definition of response to treatment of severe asthma with biologics**
- **Physicians routinely evaluate multiple aspects of response using a range of clinical tools**
  - **symptom control (ACT, ACQ)**
  - **use of reliever therapy & oral corticosteroids**
  - **number and severity of exacerbations**
  - **lung function parameters**
  - **side effects**
  - **patient satisfaction**
- **The relative importance of these measures may vary depending on the individual patient**

-------ATS-------
Late Breaking News

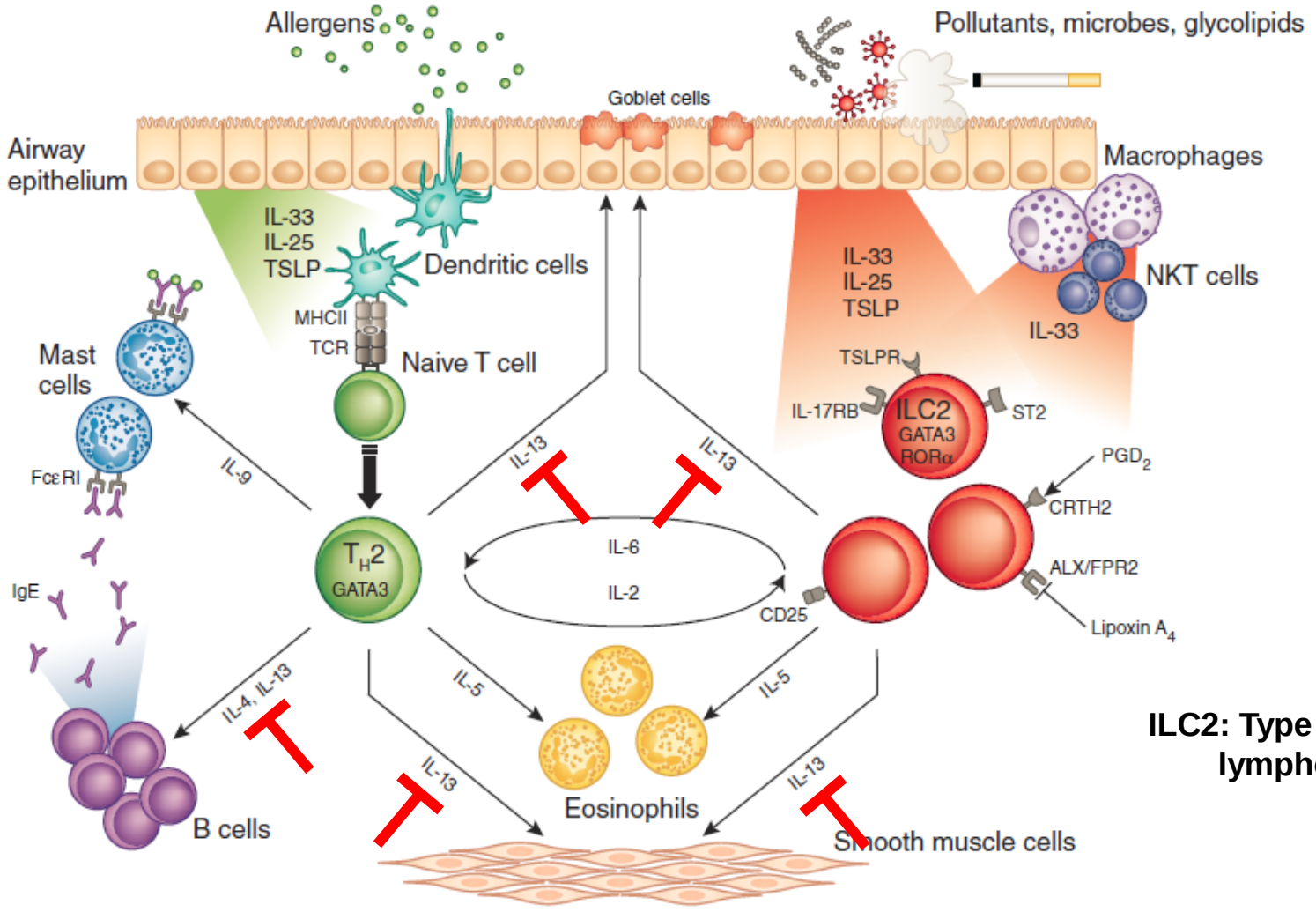
Biologics in severe asthma



Interleukin-4/13 receptor

- **Anti - IgE**
  - Omalizumab
- **Anti - IL-5**
  - Mepolizumab
  - Reslizumab
  - Benralizumab (anti-IL-5 receptor)
- **Anti - IL-13**
  - Lebrikizumab >>
  - Tralokinumab >>
- **Anti - IL-4 / IL-13**
  - Dupilumab (anti-IL-4/IL-13 receptor)

Airway inflammation in asthma



ILC2: Type 2 innate lymphoid cells

Brusselle et al. Nat Med 19(8):977-979, 2013

Dupilumab in uncontrolled moderate-to-severe asthma (LIBERTY ASTHMA QUEST)

1902 asthma patients uncontrolled on medium-to-high dose ICS + up to 2 additional controllers

- **Dupilumab 200 / 300 mg sc every 2 weeks**
- **Placebo**

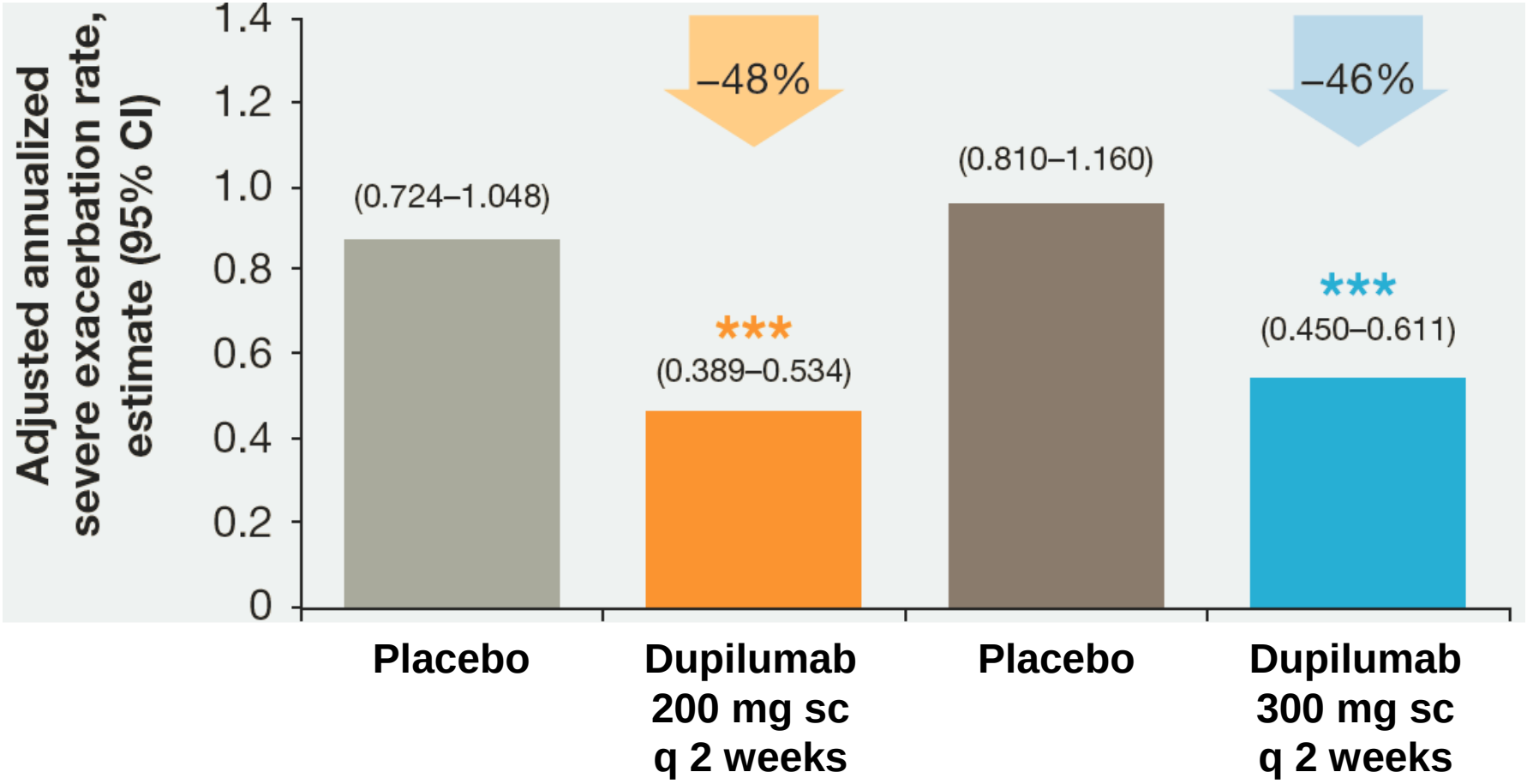
52 weeks

- **Severe exacerbations**
- **FEV1 pre-BD [mL]**

Castro et al. N Engl J Med 2018 [epub]

Dupilumab in uncontrolled moderate-to-severe asthma (LIBERTY ASTHMA QUEST)

Exacerbations [/year]



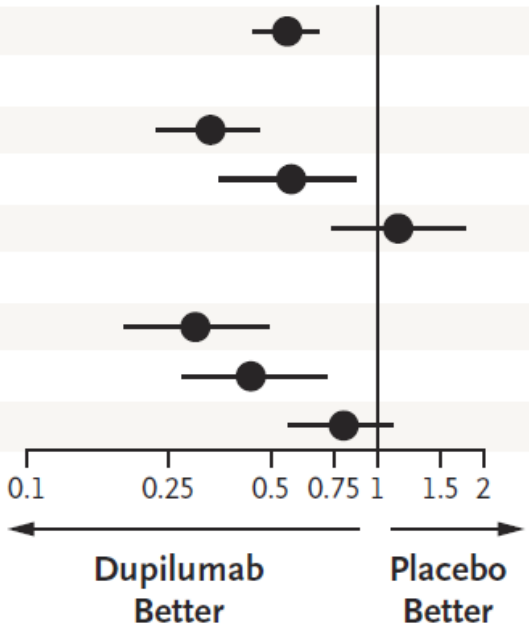
Castro et al. N Engl J Med 2018 [epub]

Dupilumab in uncontrolled moderate-to-severe asthma (LIBERTY ASTHMA QUEST)

Risk of severe exacerbations

Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

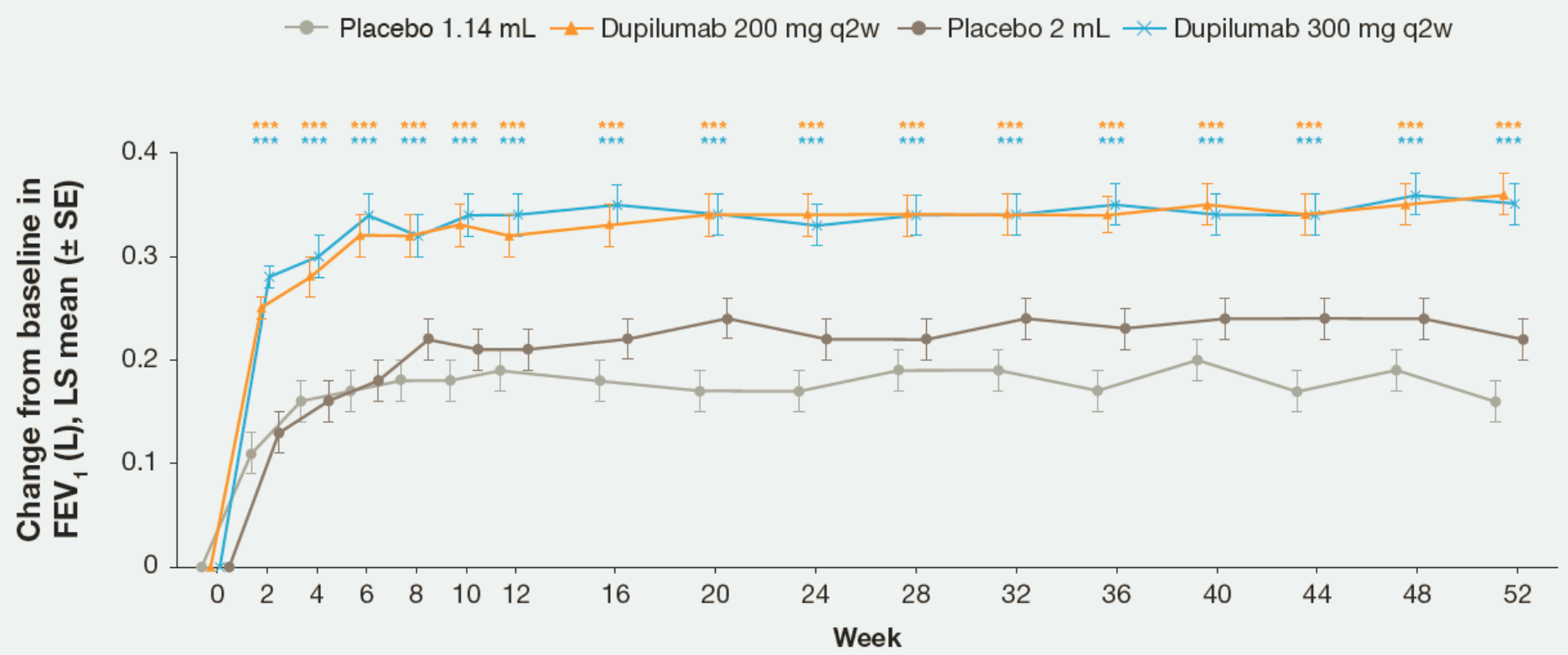
Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm³	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm³	95	175	0.56 (0.35–0.89)
<150 cells/mm³	83	181	1.15 (0.75–1.77)
FE_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)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



Castro et al. N Engl J Med 2018 [epub]

Dupilumab in uncontrolled moderate-to-severe asthma (LIBERTY ASTHMA QUEST)

Δ prebronchodilator FEV1



Castro et al. N Engl J Med 2018 [epub]

Dupilumab in corticosteroid-dependent severe asthma (LIBERTY ASTHMA VENTURE)

220 patients with OCS-dependent severe asthma

- Dupilumab 300 mg sc every 2 weeks
- Placebo

24 weeks

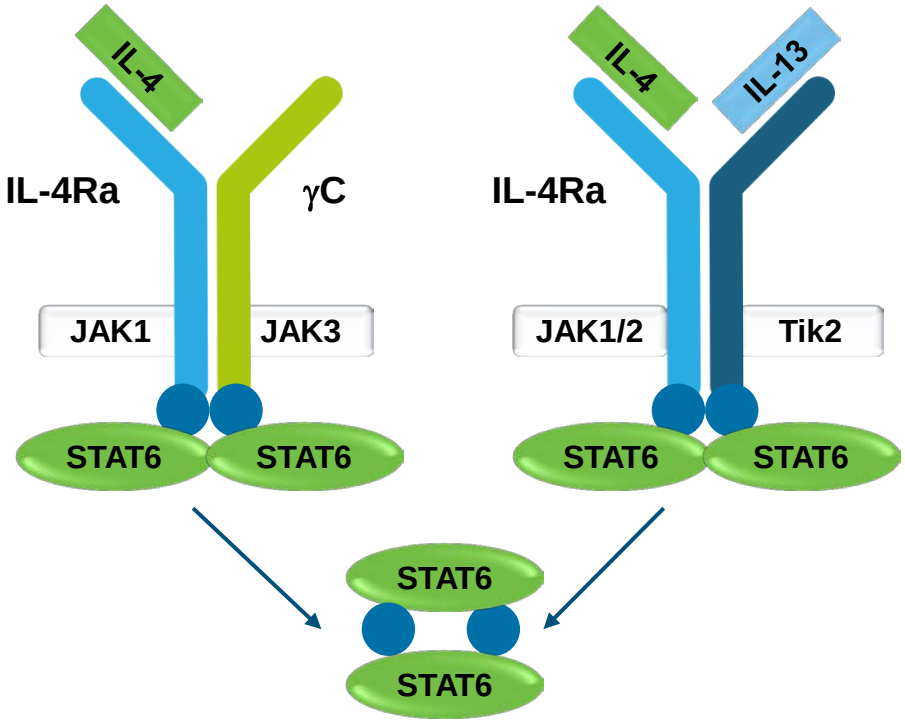
- OCS dose reduction [%] at week 24

Dupilumab vs placebo [week 24]

• OCS dose	-28.24%	p<0.0001
• OCS reduction	-2.81 mg/d.	p<0.0002
≥50%	80% vs 50%	
100%	48% vs 25%	
• Severe exacerbations	-59.3%	p<0.0001
• FEV1	+0.22 L	p<0.0007

Rabe et al. N Engl J Med 2018 [epub]

Dupilumab in uncontrolled asthma despite ICS + LABA



- FEV1 ↑
- Exacerbations ↓
- Nasal polyps ↓
- Atopic dermatitis ↓

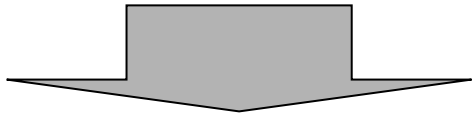
Thaçi et al. Lancet 387:40-52, 2016; Bachert et al. JAMA 315(5):469-479, 2016
Wenzel et al. Lancet 388:31-44, 2016; Simpson et al. NEJM 375(24):2335-2348, 2016;
Blauvelt et al. Lancet 389 (10086):2287-2303, 2017

Monoclonal antibodies in severe asthma

Mepolizumab	• **100 mg sc every 4 weeks**
Reslizumab	• **3 mg per Kg body weight iv every 4 weeks**
Benralizumab	• **30 mg sc**
Dupilumab	• **300 mg sc every 2 weeks 600 mg loading dose**

Individualised precision medicine in asthma

- **Improved treatment results in patients with severe asthma by optimal use of biologics**
  - **Identification of responsive patient populations**
  - **A realistic goal from the patients' perspective is to reduce exposure to regular and rescue oral corticosteroids by 50%**



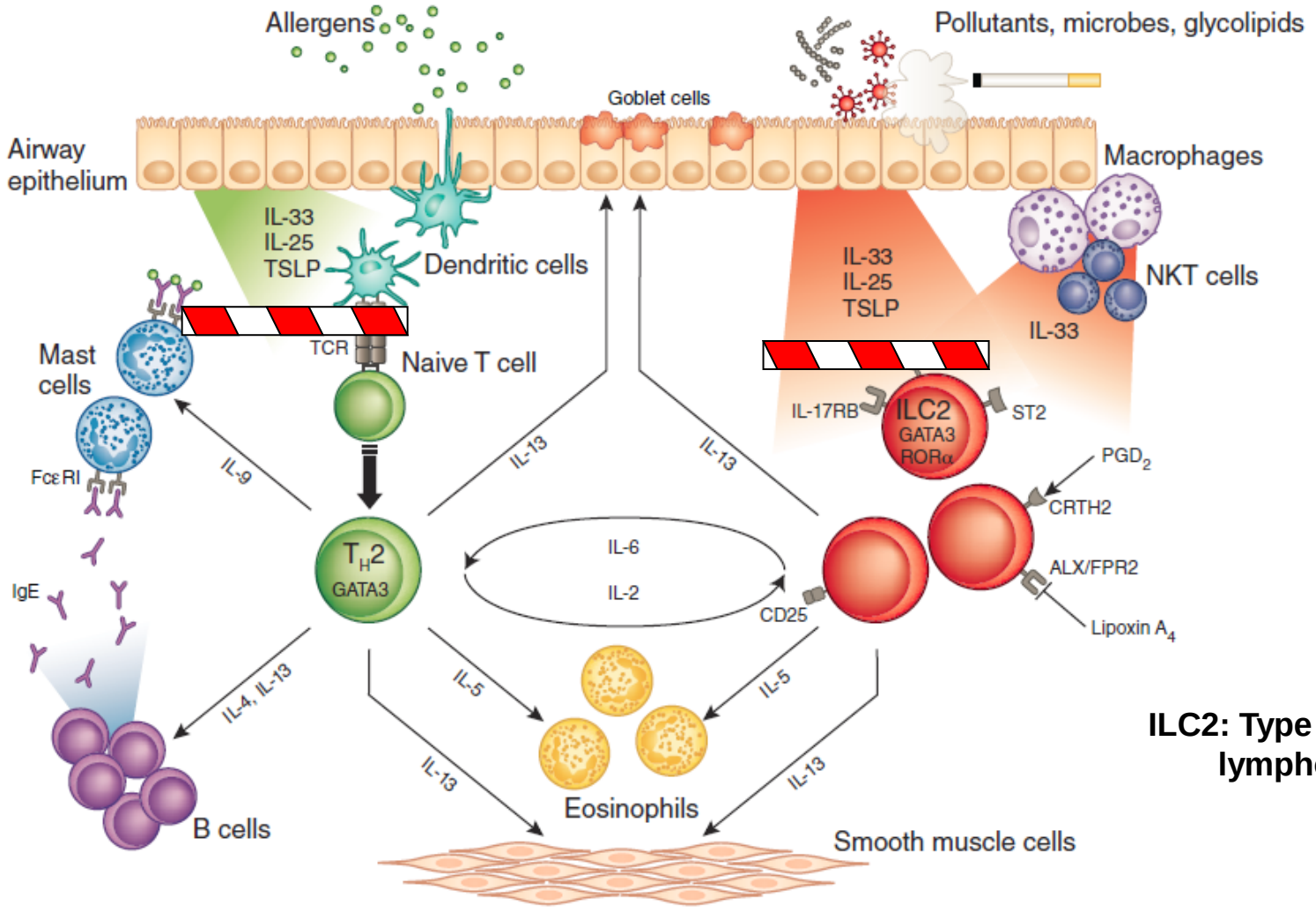
‚Deliver the right drugs to the right lungs rather than more drugs to more lungs'

Pavord et al. Lancet 391(10118):350-400, 2018

Biologics in severe asthma

- **Anti - IgE**
  - **Omalizumab**
- **Anti - IL-5**
  - **Mepolizumab**
  - **Reslizumab**
  - **Benralizumab (anti-IL-5 receptor)**
- **Anti - IL-13**
  - **Lebrikizumab >>**
  - **Tralokinumab >>**
- **Anti - IL-4 / IL-13**
  - **Dupilumab (anti-IL-4/IL-13 receptor)**
- **Anti - thymic stromal lymphopoietin**
  - **Tezepelumab**

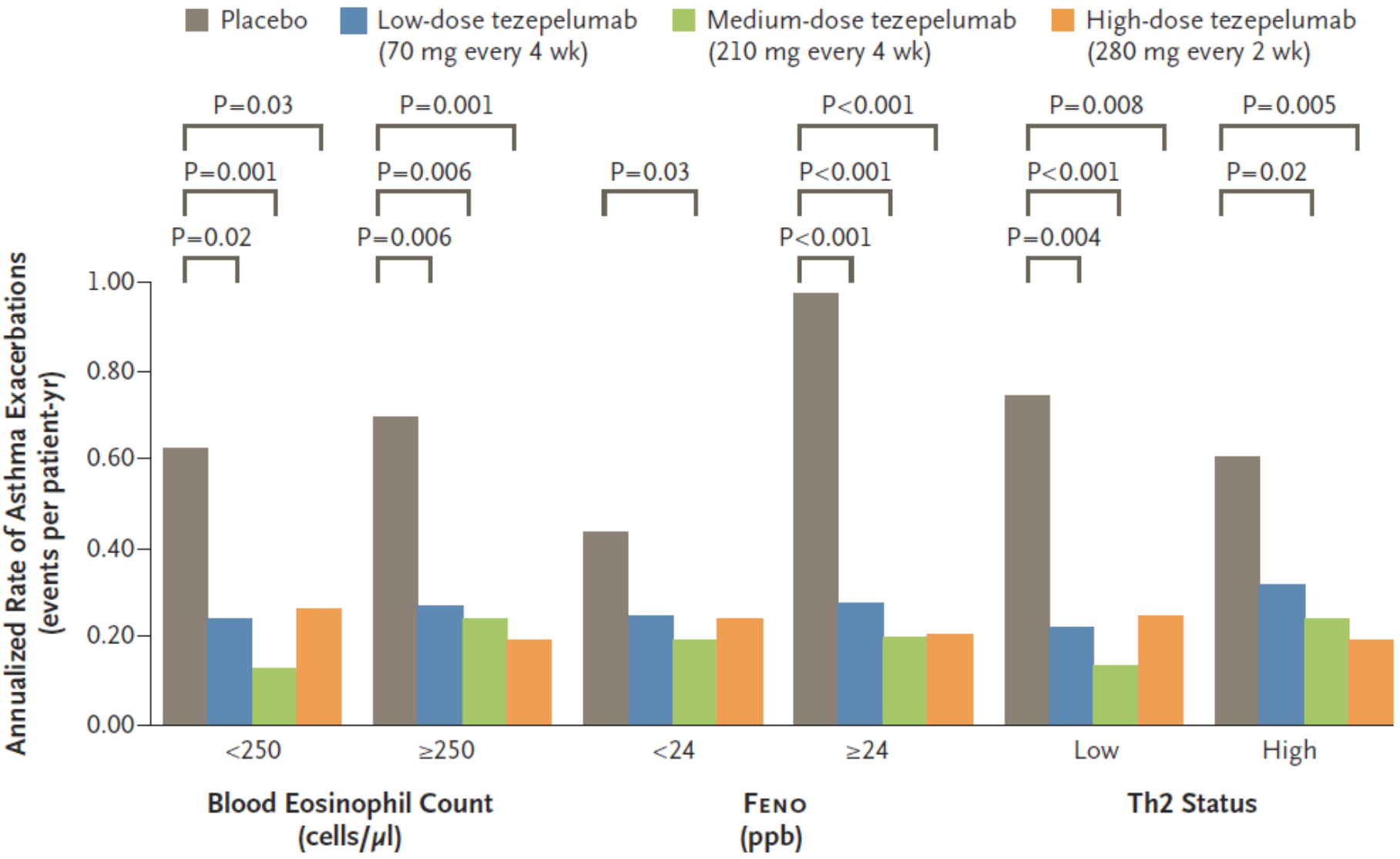
Airway inflammation in asthma



ILC2: Type 2 innate lymphoid cells

Brusselle et al. Nat Med 19(8):977-979, 2013

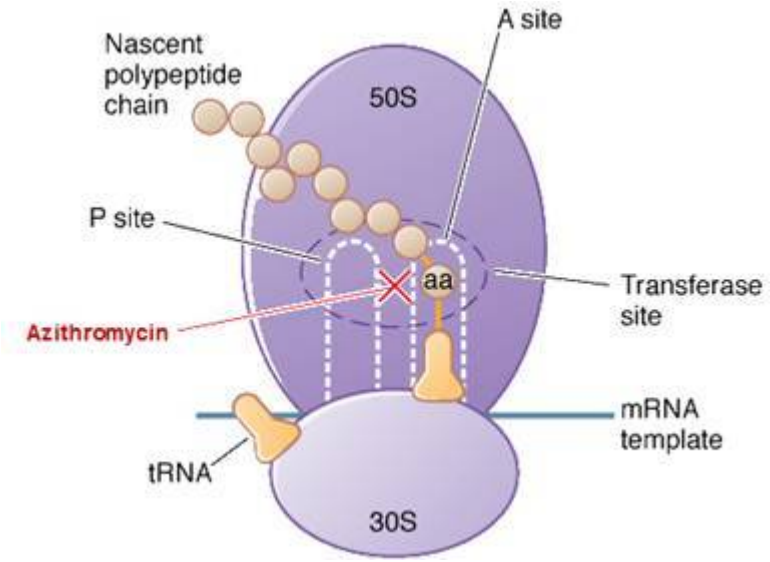
Anti-TSLP in uncontrolled asthma



Corren et al. N Engl J Med 377:936-946, 2017

Asthma

Macrolides



- antibiotic
- antiinflammatory
- immunmodulatory

- Diagnosis
- Antibiotics for asthma exacerbations
- What's new in GINA ?
- Mild-to-moderate asthma
- Biologics in severe asthma
- Macrolides

Effect of azithromycin on exacerbations in uncontrolled asthma

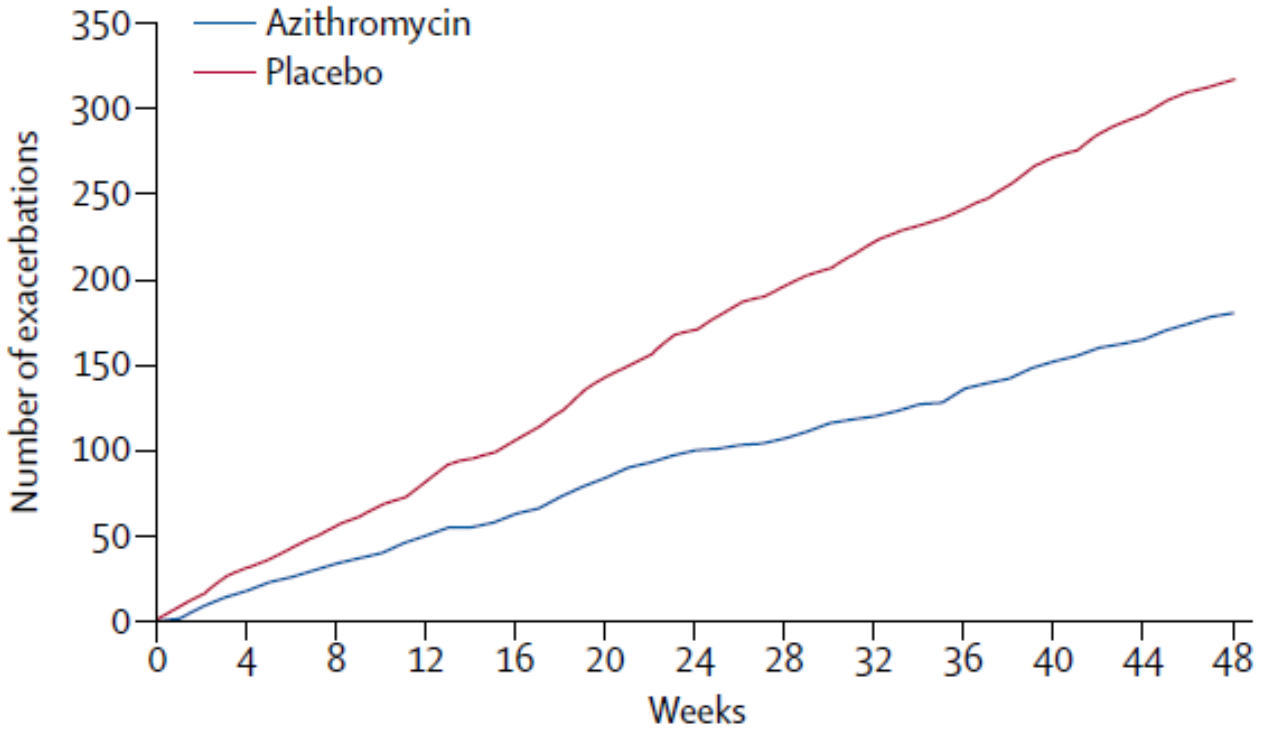
420 asthma patients uncontrolled despite ICS + LABA

- **Azithromycin 500 mg 3x per week**
- **Placebo**

48 weeks

- **Asthma exacerbations**

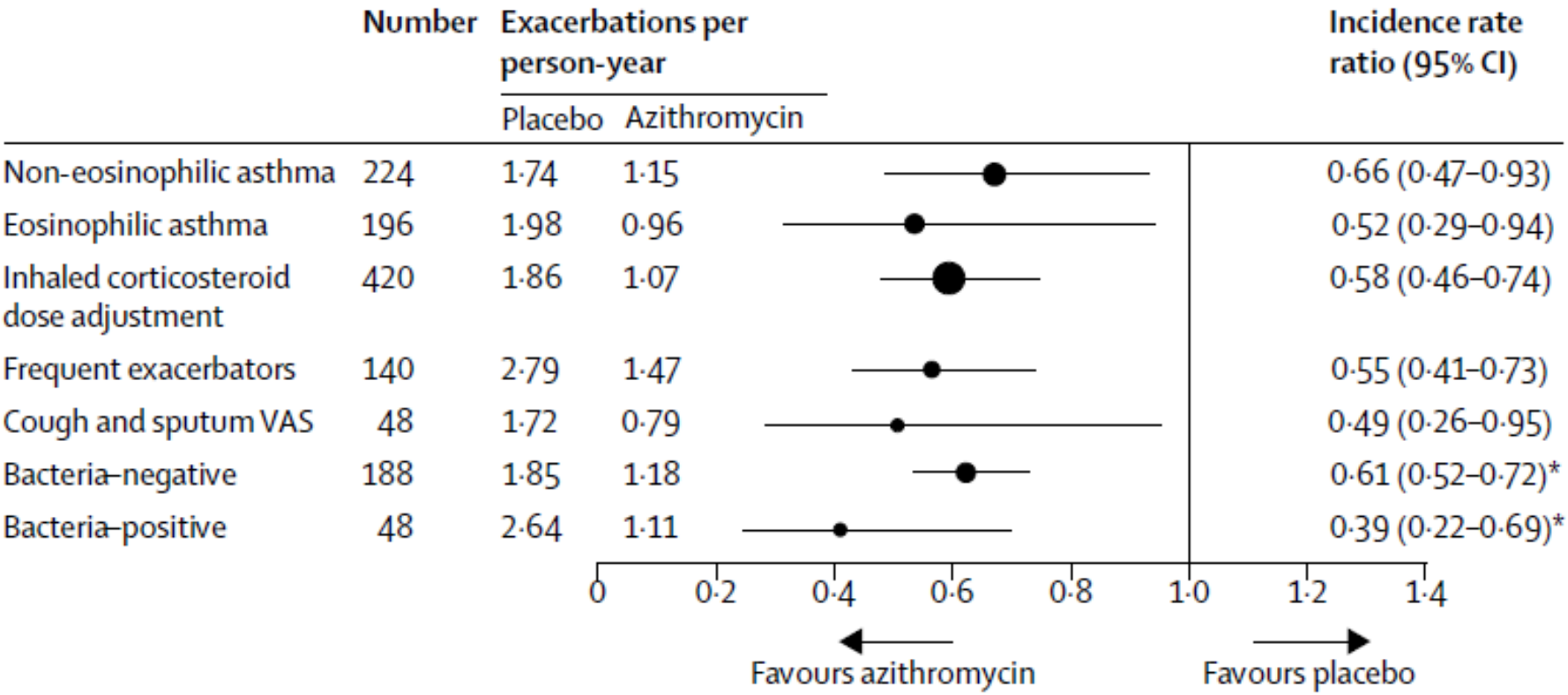
Moderate and severe exacerbations



Gibson et al. Lancet 390(10095):659-668, 2017

Effect of azithromycin on exacerbations in uncontrolled asthma

Asthma exacerbations



Gibson et al. Lancet 390(10095):659-668, 2017

Effect of azithromycin on exacerbations in uncontrolled asthma

Asthma exacerbations

	Number	Exacerbations per person-year		Incidence rate ratio (95% CI)
		Placebo	Azithromycin	
Non-eosinophilic asthma	224	1·74	1·15	0·66 (0·47–0·93)
Eosinophilic asthma	196	1·98	0·96	29–0·94)
Inhaled corticosteroid dose ad	420			16–0·74)
Frequer				1–0·73)
Cough a				5–0·95)
Bacteria				–0·72)*
Bacteria				–0·69)*

Favours placebo

- Azithromycin is effective and safe in asthma uncontrolled despite ICS and LABA, both in eosinophilic and non-eosinophilic asthma
- Effects of long-term therapy with macrolides on community microbial resistance?

Brusselle & Pavord. Lancet, 390(10095):629-630, 2017

Gibson et al. Lancet 390(10095):659-668, 2017

List of References

1. Backman et al. Clin Exp Allergy 47(11): 1426-1435, 2017
2. Aaron et al. JAMA 317 (3):269-279, 2017
3. Aaron et al. CMAJ 179:1121–1131, 2008
4. Luks et al. Eur Respir J 36(2):255-260, 2010
5. GINA 2018, www.ginasthma.com
6. Brusselle et al. Nat Med 19(8):977-979, 2013
7. Wadsworth et al. J Asthma Allergy 4:77-86, 2011
8. Vijverberg et al. Clin Exp Allergy 41:615-29, 2011
9. Petsky et al. Cochrane Database Syst Rev 9:CD011440, 2016
10. Lehtimaki et al. Eur Respir J 48:706-714, 2016
11. Dweik et al. Am J Respir Crit Care Med 184:602-615, 2011
12. Chung et al., Eur Respir J 43:343-373, 2014
13. Price et al. Lancet Respir Med 6(1):29-39, 2018
14. Johnston et al. JAMA Intern Med 176(11):1630-1637, 2016
15. Reddel et al. Lancet, 389:157-166, 2017
16. O'Byrne et al. Eur Respir J 50:1701103, 2017
17. Papi et al. NEJM 356:2040-2052, 2007
18. Papi et al. Lancet Respir Med 2015
19. Kerstjens & van den Berge, Lancet Respir Med 2015
20. O'Byrne et al. NEJM 378:1865-1876, 2018
21. Bateman et al. NEJM 378:1877-1887, 2018

List of References

22. McKeever et al. N Engl J Med 378(10):902-910, 2018
23. https://www.fda.gov
24. Bruton et al. Lancet Respir, Med 6(1):19-28, 2018
25. Normansell et al. Cochrane Database Syst Rev 2014
26. Alhossan et al. J Allergy Clin Immunol Pract 5(5):1362-1370, 2017
27. Ledford et al. J Allergy Clin Immunol 140(1):162-169, 2017
28. Ferguson et al. Lancet Respir Med 5(7):568-576, 2017
29. Ortega et al. N Engl J Med 2014
30. Bel et al. N Engl J Med 2014
31. Bjermer et al. Chest 2016
32. Corren et al. Chest 2016
33. Fitzgerald et al. Lancet 2016
34. Bleecker et al. Lancet 2016
35. Nair et al. N Engl J Med 376(25):2448-2458, 2017
36. Buhl et al. Eur Respir J 49, 2017
37. Bleecker et al. AJRCCM 197:A7703, 2018
38. Vedel-Krogh et al. Clin, Chem 63(4):823-832, 2017
39. H. Morrow Brown. Lancet 272:1245-1247, 1958
40. FitzGerald et al. Lancet Respir, Med 6(1):51-64, 2018
41. Magnan et al. Allergy 71(9):1335-1344, 2016
42. Garcia et al. Chest 144(2):411-419, 2013

List of References

43. Humbert et al. ERS Milan PA4696, 2017
44. Chipps et al. Ann Allergy Asthma Immunol 2018 [epub]
45. Bousquet et al. Eur Respir J 50(6), 2017
46. Stephen Holgate, ERS Milan 11.9.2017
47. Brusselle et al. Nat Med 19(8):977-979, 2013
48. Castro et al. N Engl J Med 2018 [epub]
49. Rabe et al. N Engl J Med 2018 [epub]
50. Sidhu, et al. Proc Natl Acad Sci USA 107:14170-14175, 2010
51. Suresh, et al. Am J Respir Cell Mol Biol 37:97-104, 2007
52. Menzies-Gow , et al. J Allergy Clin Immunol 111:714-719, 2003
53. Hershey. J Allergy Clin Immunol 111:677-690, 2003
54. Thaçi et al. Lancet 387:40-52, 2016;
55. Bachert et al. JAMA 315(5):469-479, 2016
56. Wenzel et al. Lancet 388:31-44, 2016;
57. Simpson et al. NEJM 375(24):2335-2348, 2016;
58. Blauvelt et al. Lancet 389 (10086):2287-2303, 2017
59. Pavord et al. Lancet 391(10118):350-400, 2018
60. Corren et al. N Engl J Med 377:936-946, 2017
61. Demenais et al. Nature Genetics 50(1):42-53, 2018
62. Gibson et al. Lancet 390(10095):659-668, 2017