# Pneumo Update Europe 2017

## 9 - 10 June, Vienna

# Asthma

Roland Buhl, Germany

# Asthma

- **Asthma prevention**

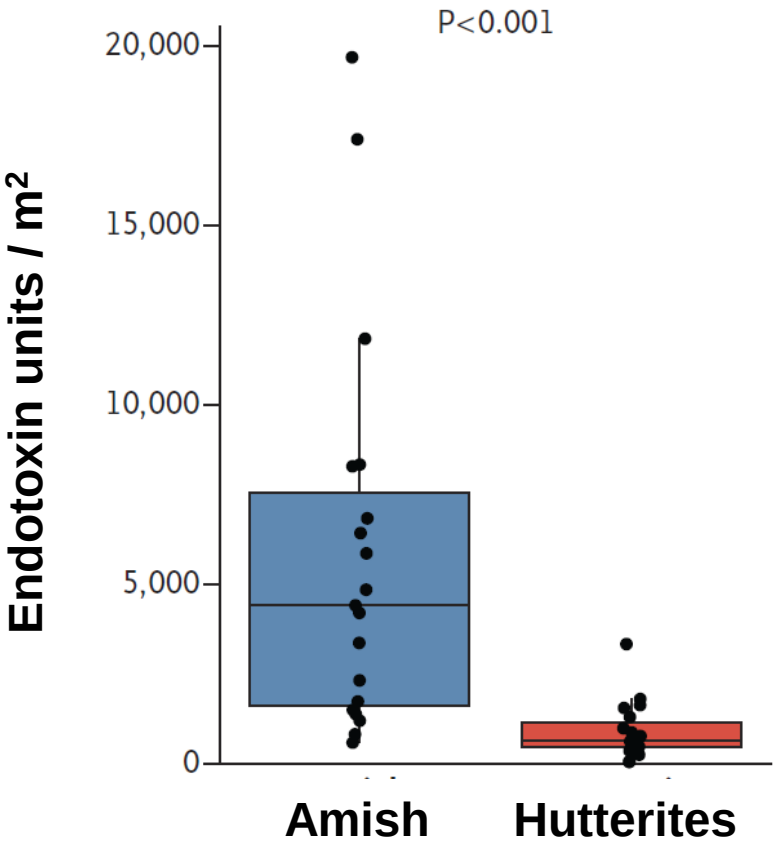
# Innate immunity and asthma risk

| | Amish farm children | | Hutterite farm children |
|---|---|---|---|
| Allergy | 7.2% | vs. | 33.3% |
| Asthma | 5.2% | vs. | 21.3% |

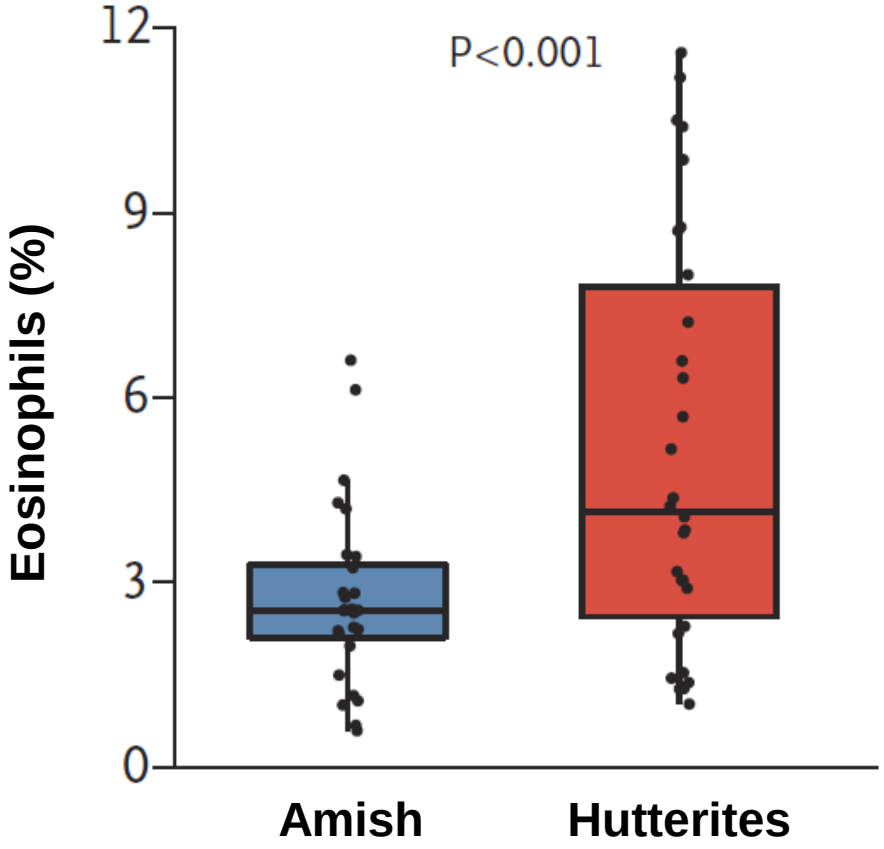
Motika, et al. J Allergy Clin Immunol 128:774-779, 2011; Holbreich, et al. J Allergy Clin Immunol 129:1671-1673, 2012; TA Chatila. N Engl J Med 375(5):477-479, 2016

# Innate immunity and asthma risk

## Endotoxin levels in airborne dust




## Blood eosinophils

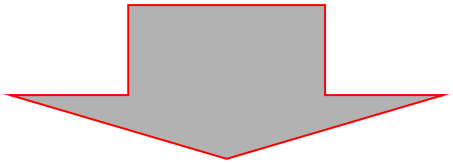





Stein et al. N Engl J Med 375(5):411-421, 2016

# Innate immunity and asthma risk

- **Amish environment and lifestyle protect against allergy and asthma by inducing ong-term, low-level, proinflammatory innate immune responses**



**New preventive approach ?**

**TA Chatila. N Engl J Med 375(5):477-479, 2016**



**Stein et al. N Engl J Med 375(5):411-421, 2016**

# Asthma

- **Asthma prevention**
- **Immunotherapy**
- **LABA safety**

# Safety of adding salmeterol to fluticasone propionate in children with asthma

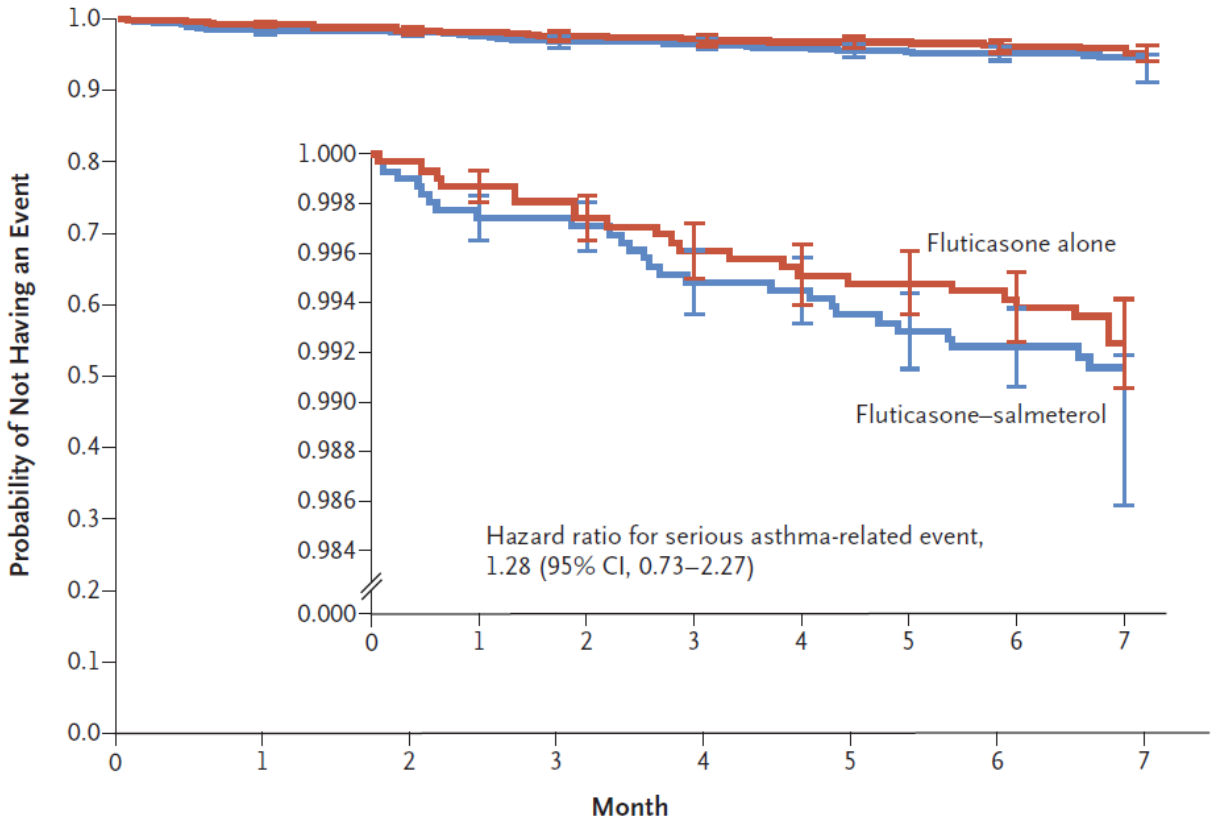
**6208 asthma patients**
**4-11 yrs.,**
**≥ 1 exacerbation**
**in previous year**

- **Salm/FP bid 50/125 µg or 50/250 µg**
- **Fluticasone bid 125 µg or 250 µg**

**26 weeks**

- **First serious asthma-related event (death, intubation, or hospitalization)**

## First serious asthma-related event




Stempel, et al. N Engl J Med 375(9):840-849, 2016

# Safety of adding salmeterol to fluticasone propionate in children with asthma

## Safety endpoints

| Safety End Point | Fluticasone–Salmeterol (N=3107) | Fluticasone Alone (N=3101) |
|---|---|---|
| Composite safety end point — no. (%) | 27 (0.9) | 21 (0.7) |
| Asthma-related death | 0 | 0 |
| Asthma-related intubation | 0 | 0 |
| Asthma-related hospitalization | 27 (0.9) | 21 (0.7) |
| Total no. of asthma-related hospitalizations* | 28 | 22 |

**Stempel et al. N Engl J Med 375(9):840-849, 2016**

**Bush et al. N Engl J Med 375(9):889-891, 2016**

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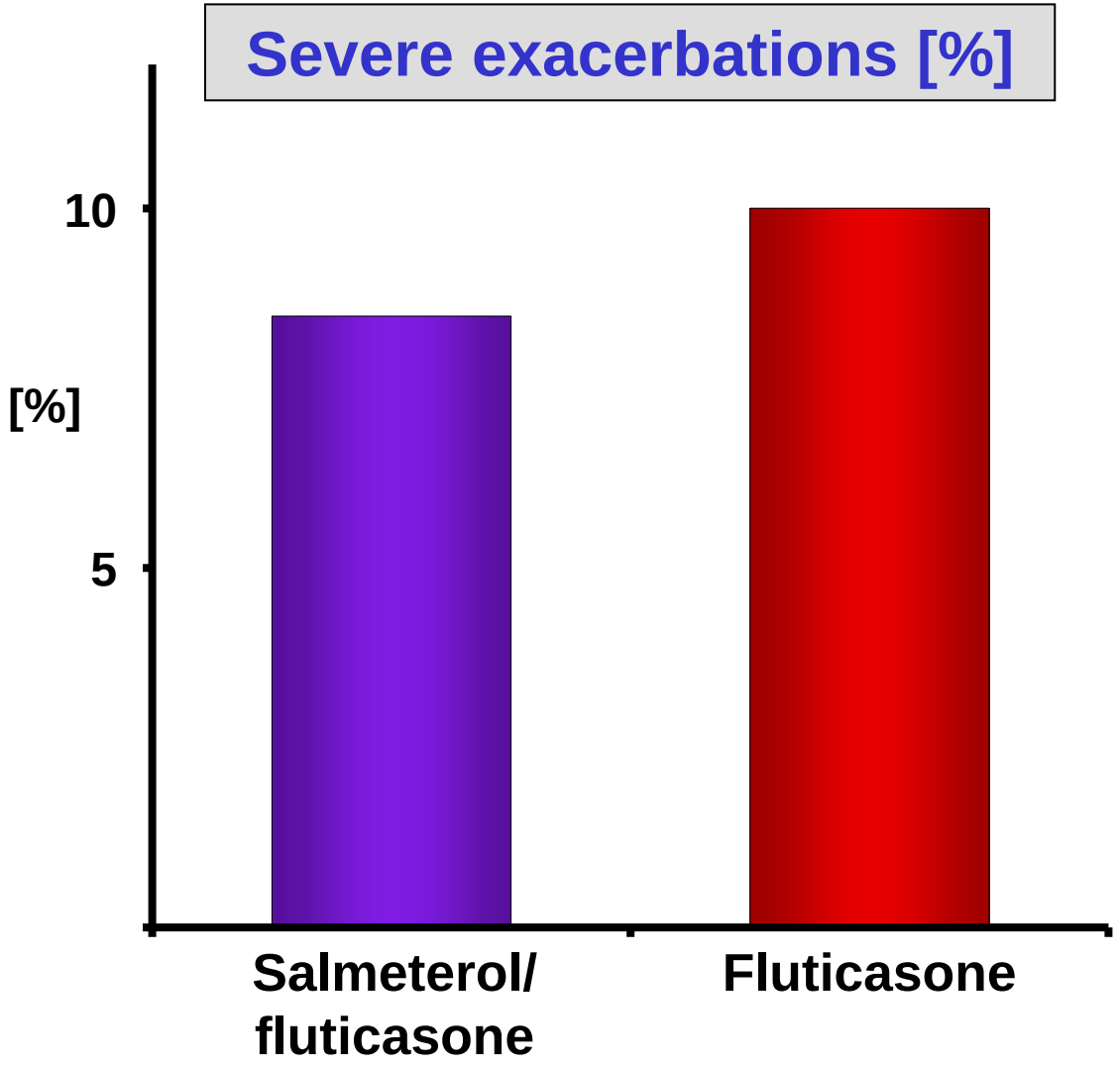




Stempel, et al., N Engl J Med 2016

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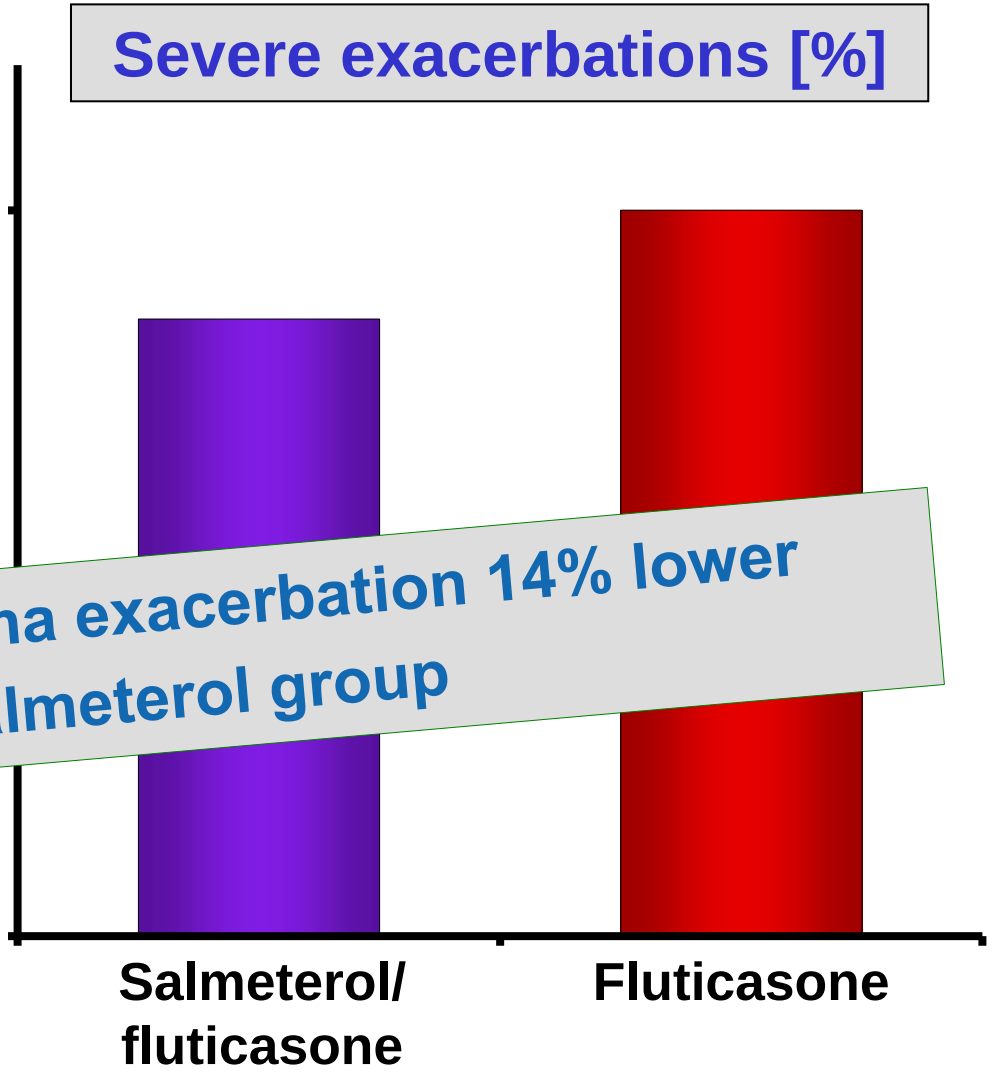



- **Risk of severe asthma exacerbation 14% lower in the fluticasone/salmeterol group**



Stempel, et al., N Engl J Med 2016

# Serious asthma events with budesonide plus formoterol vs. budesonide alone

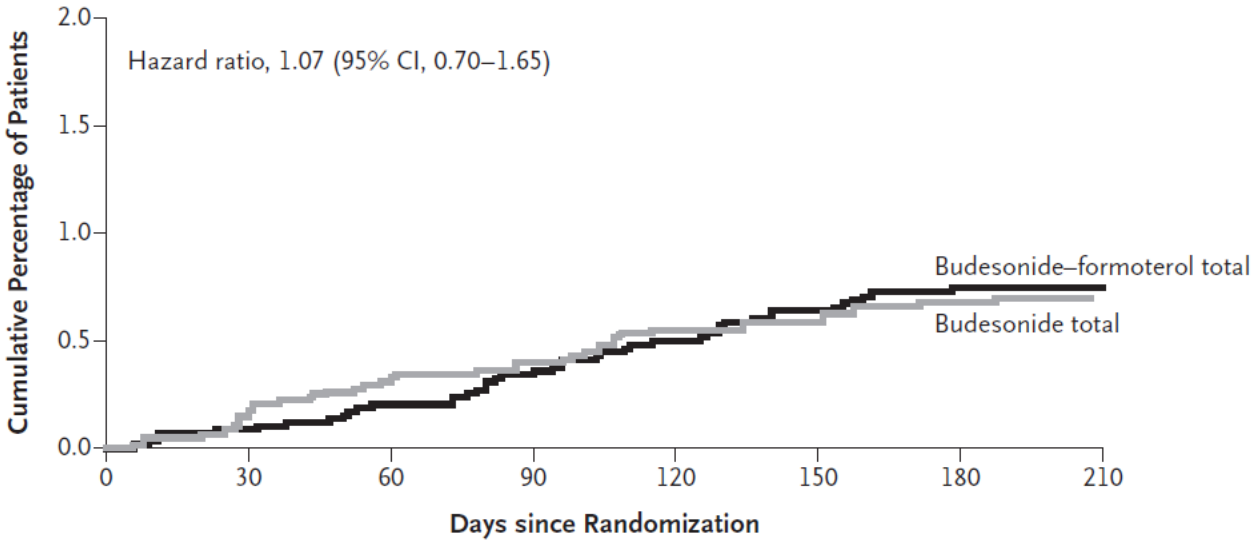
**11693 asthma patients**
**≥ 1 exacerbation**
**in previous year**

- **Bud/Form**
  **2x 80/4.5 µg or**
  **160/4.50 µg bid**
- **Budesonide**
  **2x 80 µg or**
  **160 µg bid**

**26 weeks**

- **First serious asthma-related event (death, intubation, or hospitalization)**

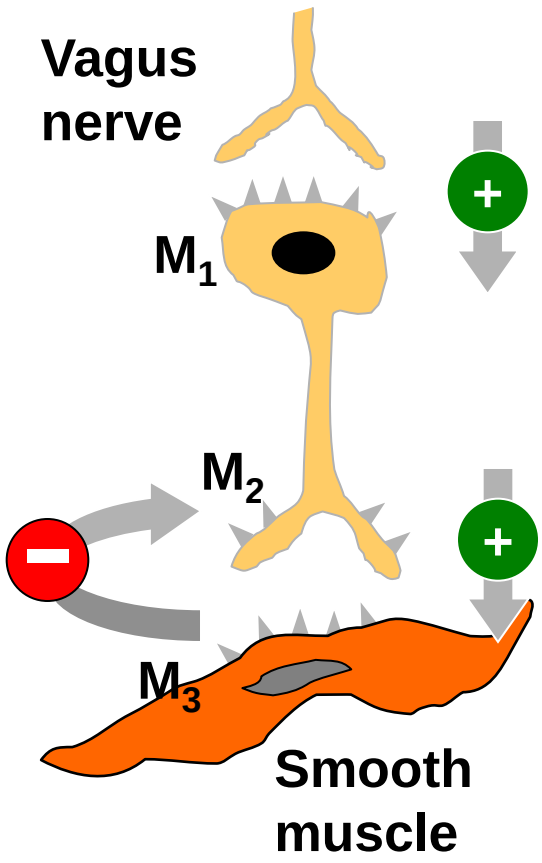
## Time to first serious asthma-related event





Peters, et al. N Engl J Med 375(9):850-860, 2016

# Asthma




- Asthma prevention
- Immunotherapy
- LABA safety
- Tiotropium in asthma

# Tiotropium add-on in adolescents with moderate asthma

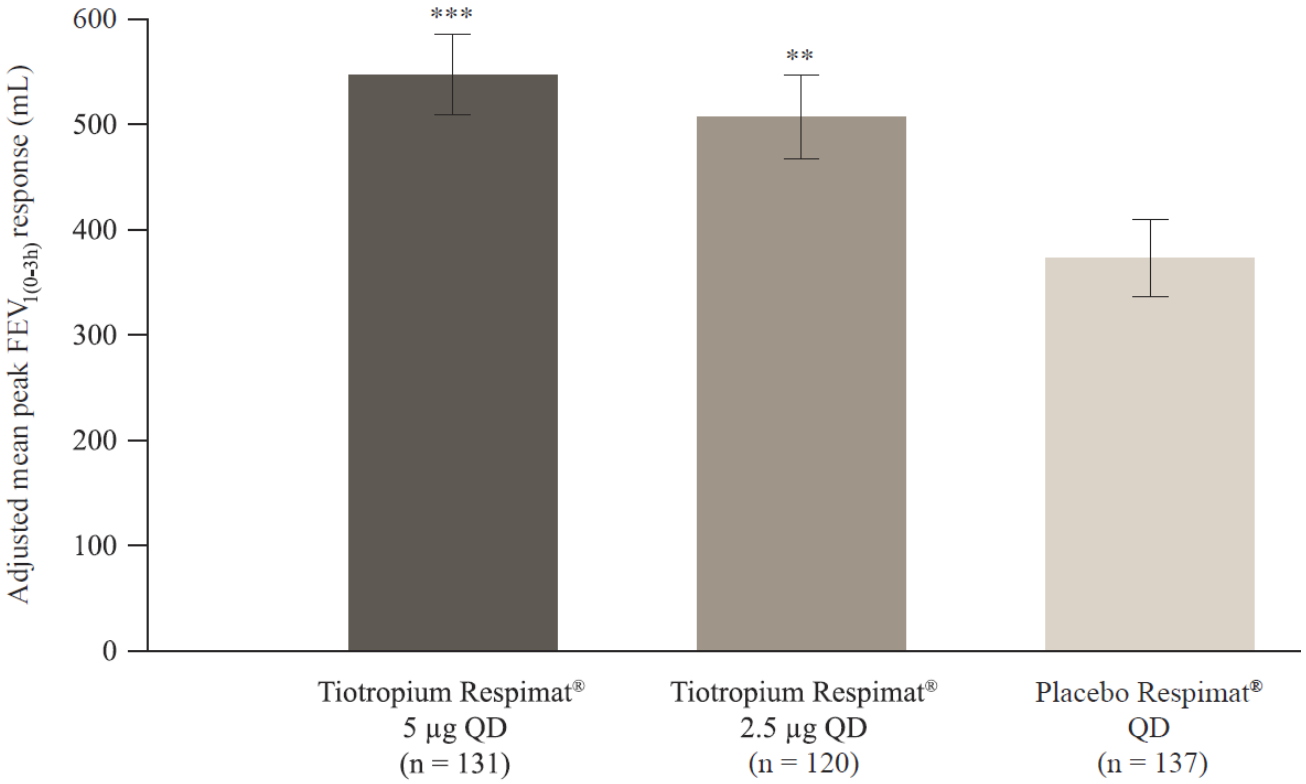
**398 asthma patients**
**ICS ± LTRA**
**12 – 17 years**

- **Tiotropium**
  - **1x 5 µg**
  - **1x 2.5 µg**
- **Placebo**

**48 weeks**

- **Lung function**

## Peak FEV1(0-3 h) in week 24






Hamelmann, et al. J Allergy Clin Immunol 2016

# Tiotropium add-on in adolescents with severe symptomatic asthma

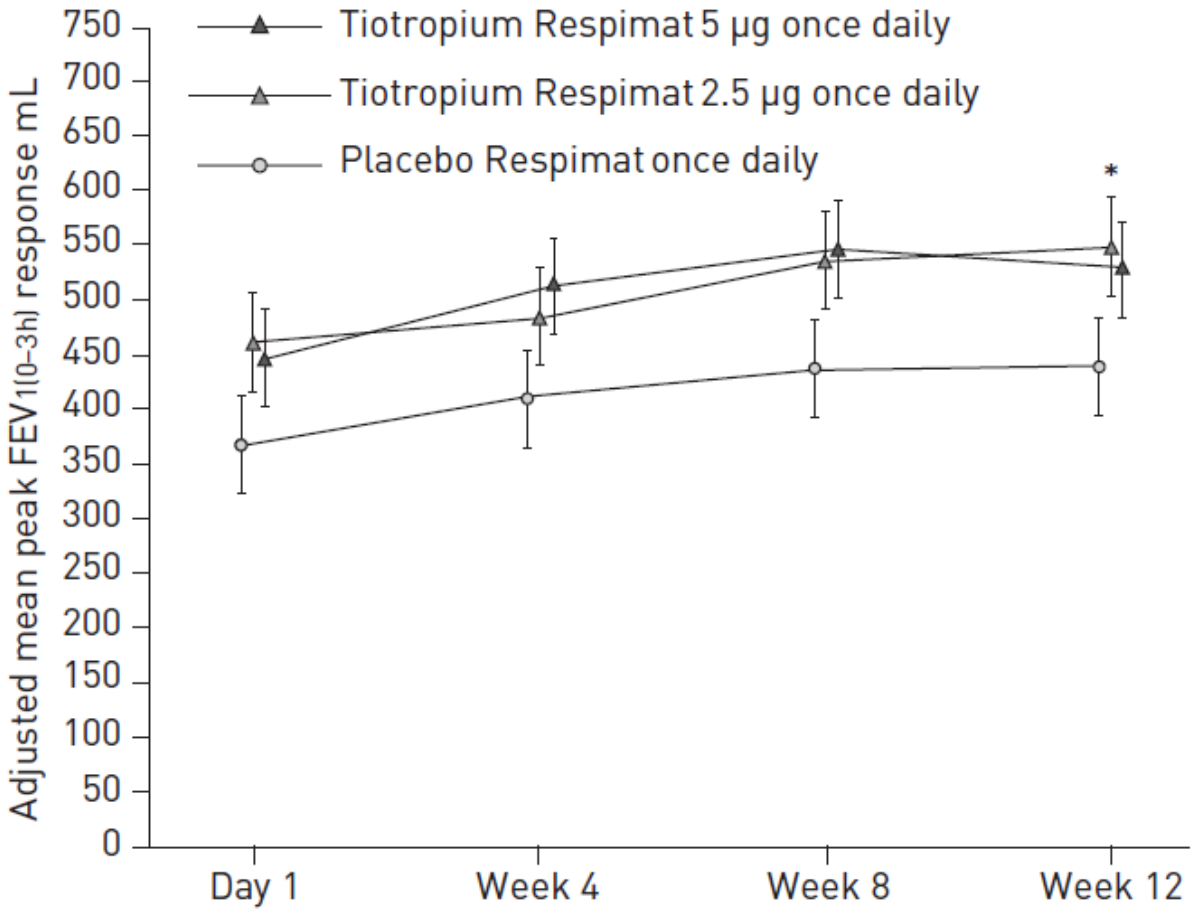
**392 asthma patients**
**ICS + other controller(s)**
**12 – 17 years**

- **Tiotropium**
  - **1x 5 µg**
  - **1x 2.5 µg**
- **Placebo**

**12 weeks**

- **Lung function**

## Peak FEV1(0-3 h) in week 12





Hamelmann, et al. Eur Respir J, 11;49, Jan. 2017

# Tiotropium: Asthma indication in the US

- **The proposed indication for tiotropium Respimat is the longterm, once-daily, add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids**

# Tiotropium add-on improves lung function in children with severe symptomatic asthma

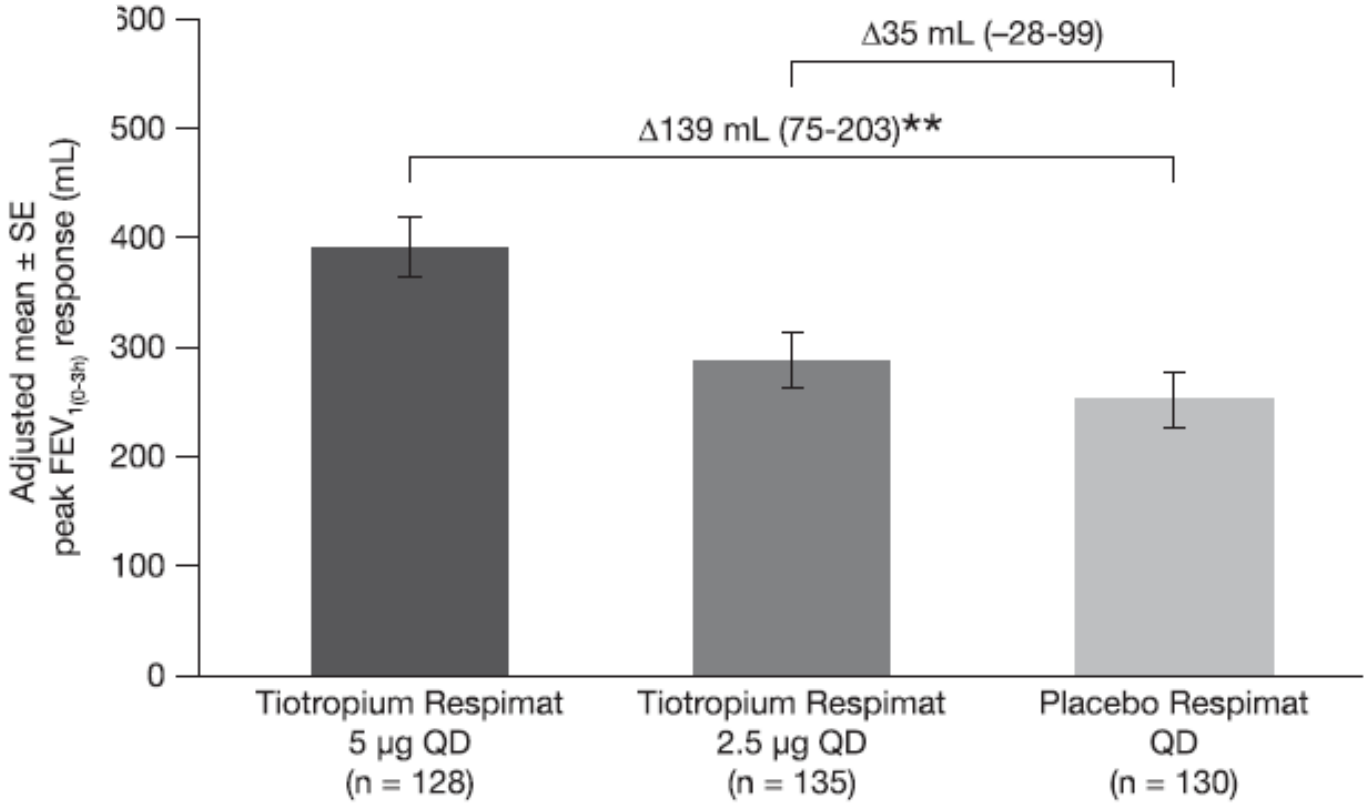
**401 asthma children**
**6 - 11 yrs., ACQ ≥ 1.5**
**FEV1 81.6 ± 11.5 %**
**ICS + LABA ± LTRA**

- **Tiotropium**
  - **1x 5 µg**
  - **1x 2.5 µg**
- **Placebo**

**12 weeks**

- **Lung function in week 12**

**Peak FEV1(0-3 h)**





Szefler, et al. J Allergy Clin Immunol 2017 [epub]

# Safety and tolerability of tiotropium in children with severe symptomatic asthma

## Adverse events (AE)

| N (%) | Tiotropium 5 mg QD (n = 130) | Tiotropium 2.5 mg QD (n = 136) | Placebo QD (n = 134) |
|---|---|---|---|
| Any AE | 56 (43.1) | 59 (43.4) | 66 (49.3) |
| Drug-related AEs | 1 (0.8) | 0 | 2 (1.5) |
| AEs leading to discontinuation | 2 (1.5) | 0 | 2 (1.5) |
| Serious AEs | 4 (3.1) | 2 (1.5) | 2 (1.5) |
| AEs in >2% of participants | | | |
| Asthma | 24 (18.5) | 20 (14.7) | 30 (22.4) |
| Decreased PEF | 15 (11.5) | 15 (11.0) | 20 (14.9) |
| Nasopharyngitis | 6 (4.6) | 6 (4.4) | 11 (8.2) |
| Viral RTI | 5 (3.8) | 2 (1.5) | 4 (3.0) |
| Respiratory tract infection (RTI) | 3 (2.3) | 1 (0.7) | 5 (3.7) |


Szefler, et al. J Allergy Clin Immunol 2017 [epub]

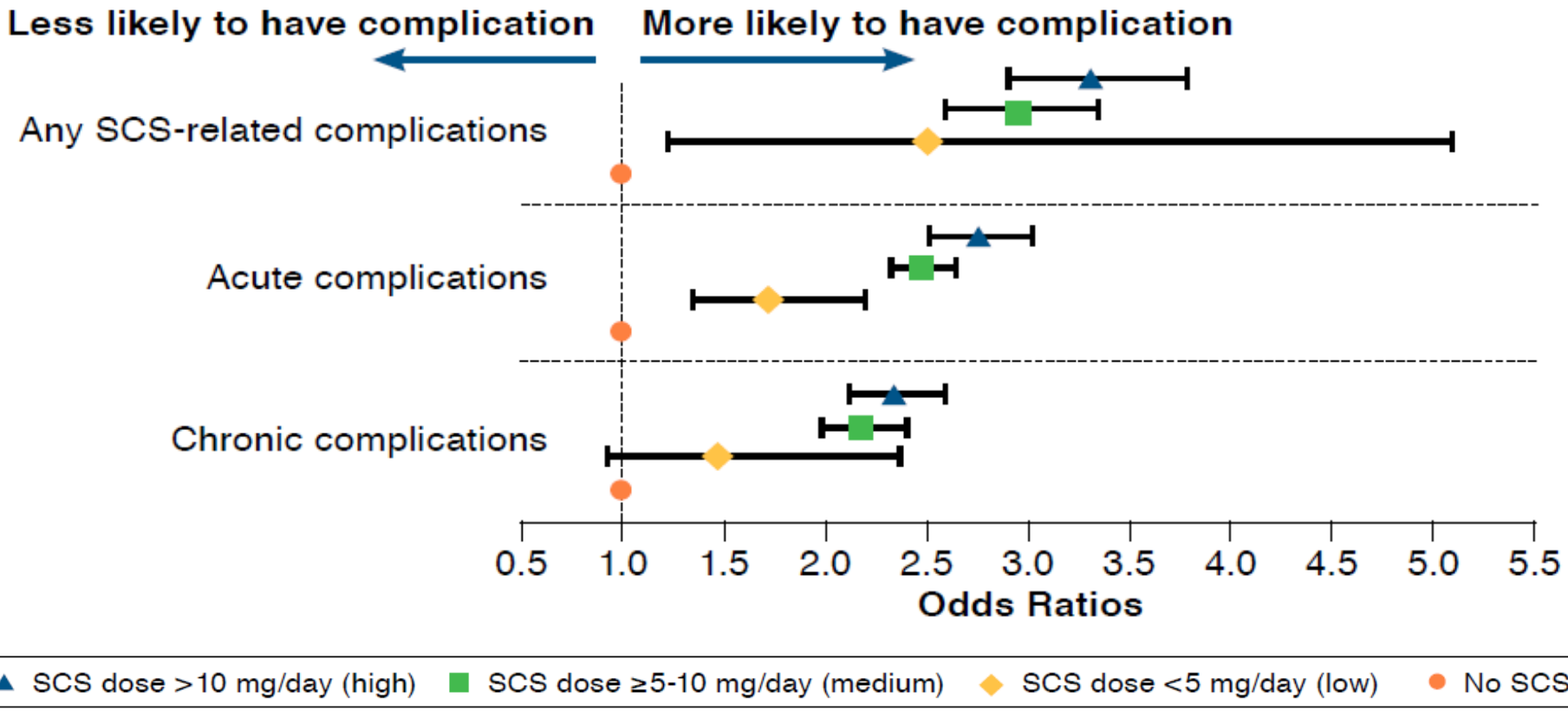
# Asthma

- Asthma prevention
- Immunotherapy
- LABA safety
- Tiotropium in asthma
- OCS side effects

http://columbiasurgery.org/conditions-and-treatments/cushings-syndrome

# Risk of developing SCS-related complications with SCS exposure

## Acute and chronic complications




**SCS: Systemic corticosteroids**



Dalal et al. J Manag Care Spec Pharm 22(7):833-847, 2016

# Morbidity associated with oral corticosteroids in severe asthma

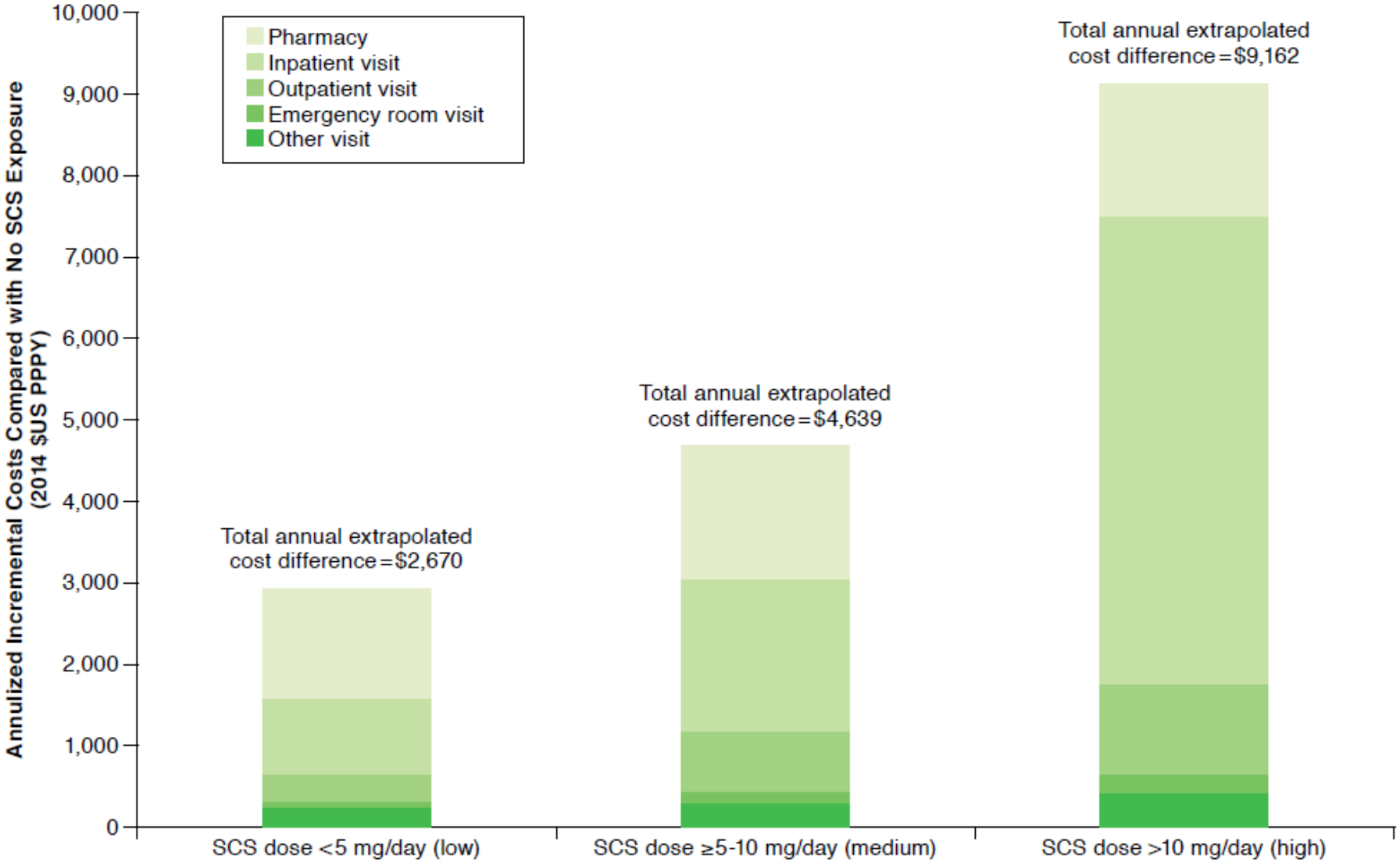
- **93% of patients with severe asthma had one or more condition linked to systemic corticosteroid exposure**

**Compared with mild/moderate asthma**

| | |
|---|---|
| • Diabetes (type II) | 10% vs. 7%<br>OR=1.46, p<0.01 |
| • Osteoporosis | 16% vs. 4%<br>OR=5.23, p<0.001 |
| • Dyspeptic disorders | 65% vs. 34%<br>OR=3.99, p<0.001 |
| • Cataracts | 9% vs. 5%<br>OR=1.89, p<0.001 |

Lefebvre, et al. JACI 136(6): 1488-1495, 2015; Sweeney, et al. Thorax 71(4):339-346, 2016; Choo & Pavord. Thorax 71(4): 302-304, 2016

# Incremental costs of SCS-related complications




**SCS: Systemic corticosteroids**



Dalal et al. J Manag Care Spec Pharm 22(7):833-847, 2016

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

# Asthma

- Asthma prevention
- Immunotherapy
- LABA safety
- Tiotropium in asthma
- OCS side effects
- What's new in GINA 2017 ?

# What's new in GINA 2017 ?

- **Step 1**
  - **Consider low dose inhaled corticosteroids (ICS)**

# Inhaled corticosteroids for mild asthma and symptom frequency

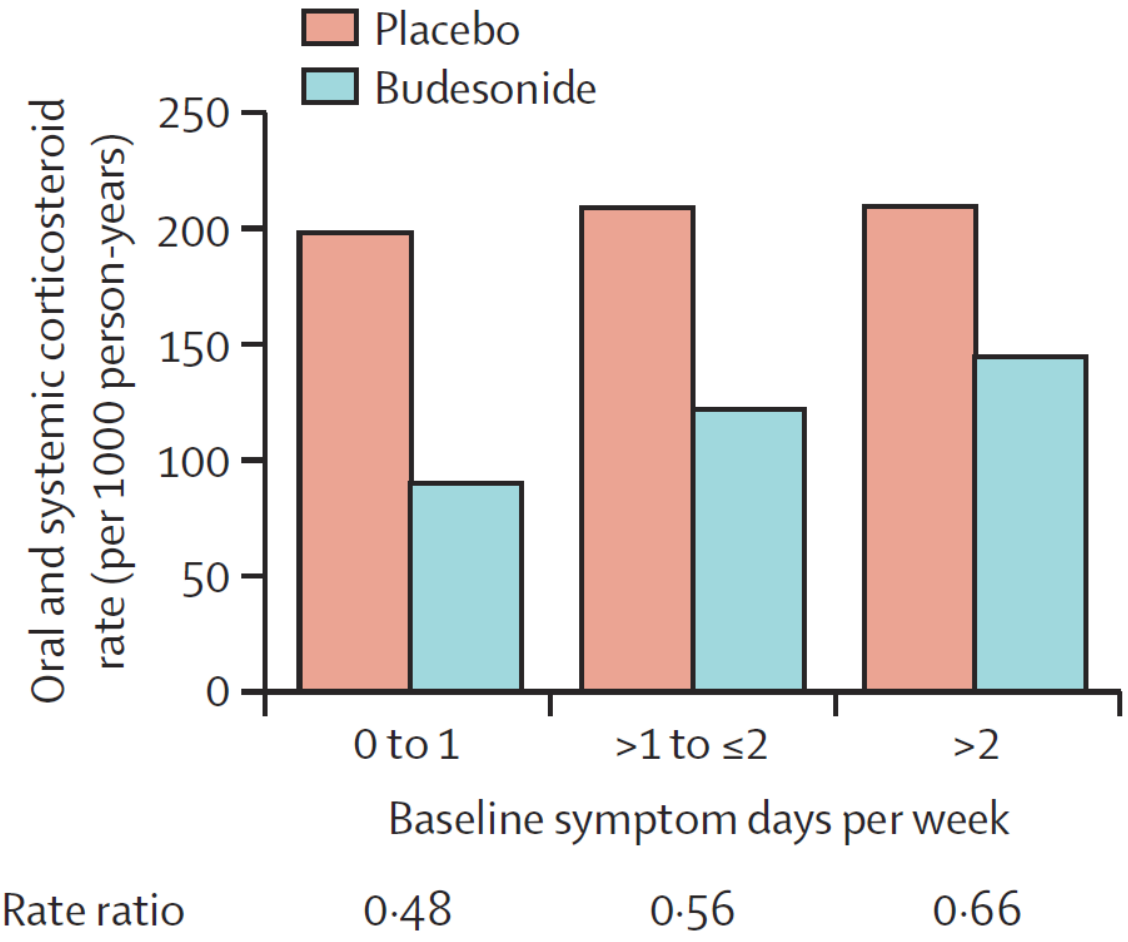
**7165 asthma patients**

- **Individual asthma therapy *plus***
  - **budesonide (400 µg/d.)**
  - **placebo**

**3 years**

**Severe asthma-related events (hospital admission, emergency treatment, or death)**

**Severe exacerbations**



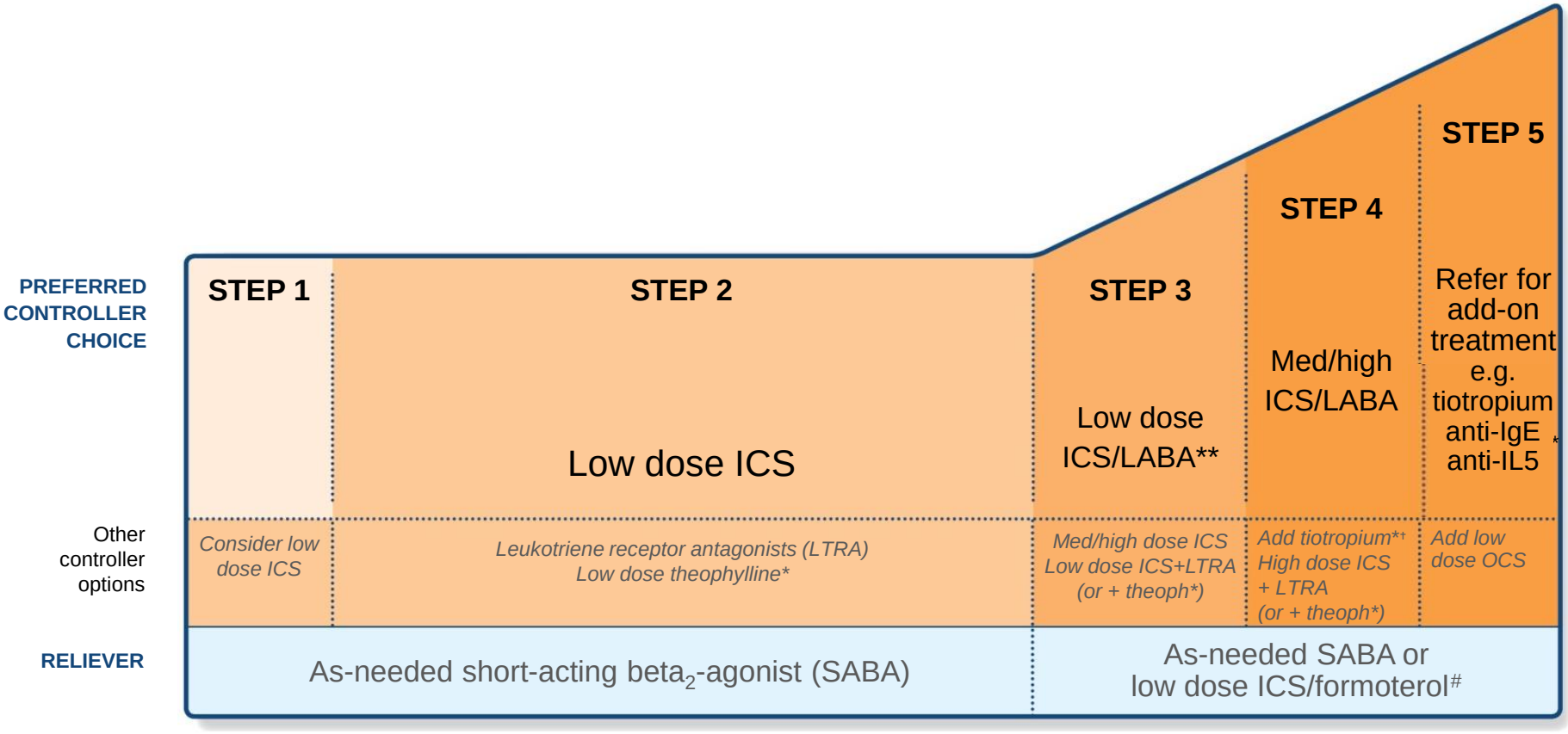



Reddel et al. Lancet, 389:157-166, 2017

# What's new in GINA 2017 ?

- **Step 1**
  - **Consider low dose inhaled corticosteroids (ICS)**
- **Steps 3 - 4**
  - **Add-on immunotherapy can now be considered in adult house dust mite-sensitive patients with asthma and allergic rhinitis uncontrolled despite ICS treatment, provided FEV1 is >70%**
- **Step 5**
  - **Add-on reslizumab (anti-IL5) for severe eosinophilic asthma (≥ 18 years)**

# 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)

# What's new in GINA 2017 ?

- **Step 1**
  - **Consider low dose inhaled corticosteroids (ICS)**
- **Steps 3 - 4**
  - **Add-on immunotherapy can now be considered in adult house dust mite-sensitive patients with asthma and allergic rhinitis uncontrolled despite ICS treatment, provided FEV1 is >70%**
- **Step 5**
  - **Add-on reslizumab (anti-IL5) for severe eosinophilic asthma (≥ 18 years)**
- **Add-on leukotriene receptor antagonist as an option for helping to down-titrate ICS**

# Stepping down medications in patients with controlled asthma

| Asthma control | Level of asthma control | | |
|---|---|---|---|
| In the past 4 weeks, has the patient had: | Well controlled | Partly controlled | Uncontrolled |
| • Daytime asthma symptoms more than twice a week?<br>• Any night waking due to asthma?<br>• Reliever needed for symptoms more than twice a week?<br>• Any activity limitation due to asthma? | None of these symptoms | 1 - 2 of these symptoms | 3 - 4 of these symptoms |

- **Once good asthma control has been achieved and maintained for ≥ 3 months, treatment can often be successfully reduced, without loss of asthma control**

Rank, et al. JACI 137(5):1373-1379, 2016

# GINA & GOLD: ACOS no longer advised

- **'Asthma-COPD overlap syndrome', or ACOS, is no longer advised, because this term has often been used as if it was a separate disease**

- **'Asthma-COPD overlap' is the term recommended by GINA and GOLD to describe patients who have features of both asthma and COPD**

# Asthma and COPD are 2 different diseases

- **Asthma and COPD may occur in the same patient**

**P Barnes. Am J Respir Crit Care Med 174(3):240-243, 2006**
**& Postma & Boezen. Chest 126(2 Suppl):96S-104S, 2004**

# Accurate diagnosis does matter !

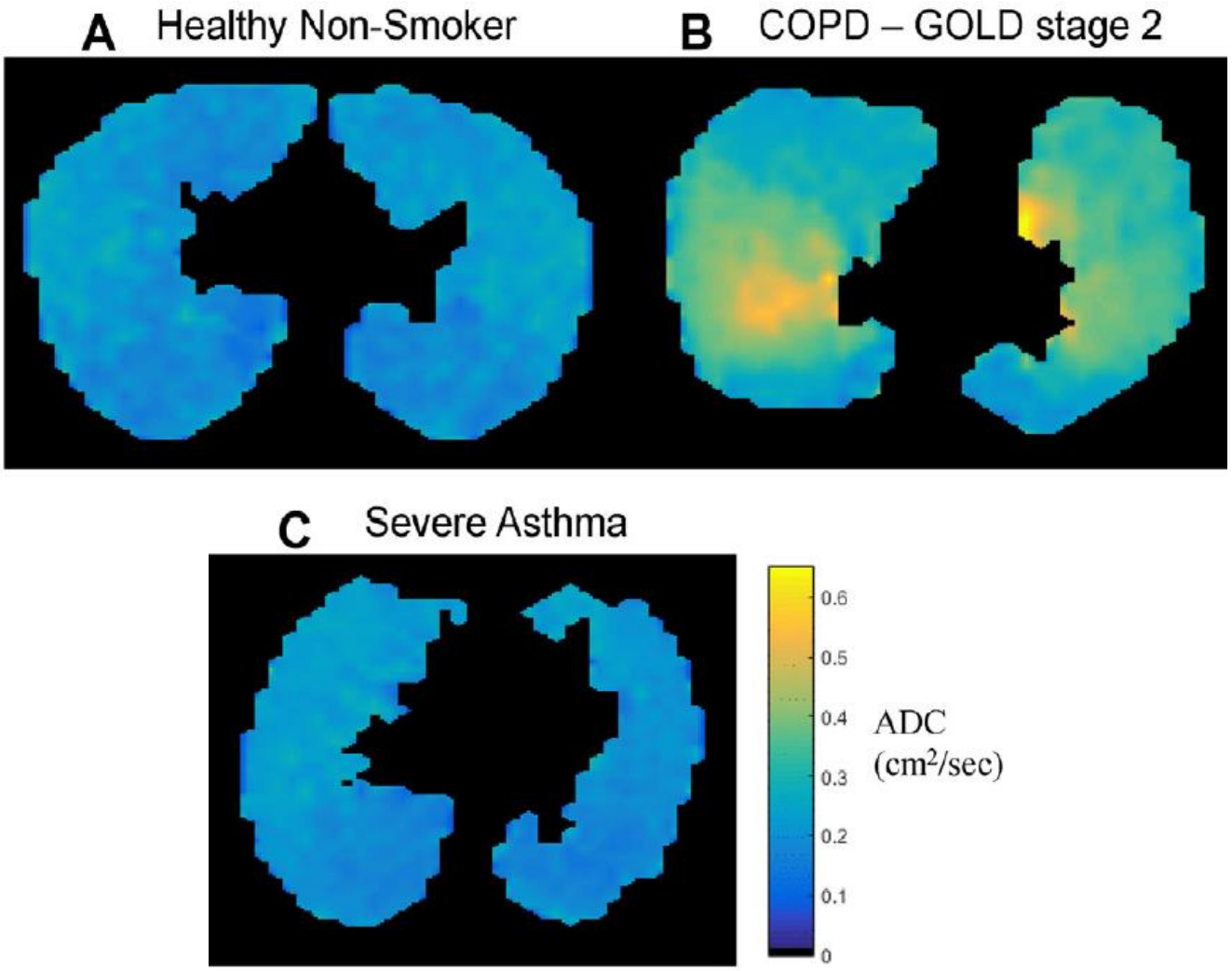
| Treatment | Asthma | COPD |
|---|---|---|
| Inhaled corticosteroids | Mandatory first line treatment | Third line treatment in subpopulation |
| LABAs | No monotherapy ! | First line treatment |
| LAMAs | Tiotropium 2nd or 3rd line | First line treatment |
| LABA + LAMA | Not without an ICS ! | First line treatment |
| Oral corticosteroids | Severe asthma, exacerbations | Treatment of exacerbations |
| Montelukast, omalizumab | Effective and approved | Not approved, efficacy questionable |
| Roflumilast | Not approved | Approved |
| New biologics | Highly effective | No or disappointing data |
| Immunotherapy | Promising new data | No data |
| Beta-blocker | High risk | Recommended |

# Asthma and COPD - a few simple rules

- **Asthma and COPD cannot (yet!) be easily defined based on simple and easy to measure clinical, physiological or imaging parameters**
- **In a minority of patients it may not be possible to make a final or exclusive diagnosis of COPD or asthma**
  - **regular reassessment and ongoing monitoring may help to confirm or change the initial diagnosis**
- **Precise diagnosis is mandatory to guide treatment**
- **Patients with co-existing asthma and COPD should be treated as having asthma but with COPD-expected outcomes**

# Imaging as a biomarker for asthma

## Quantitative computed tomographie



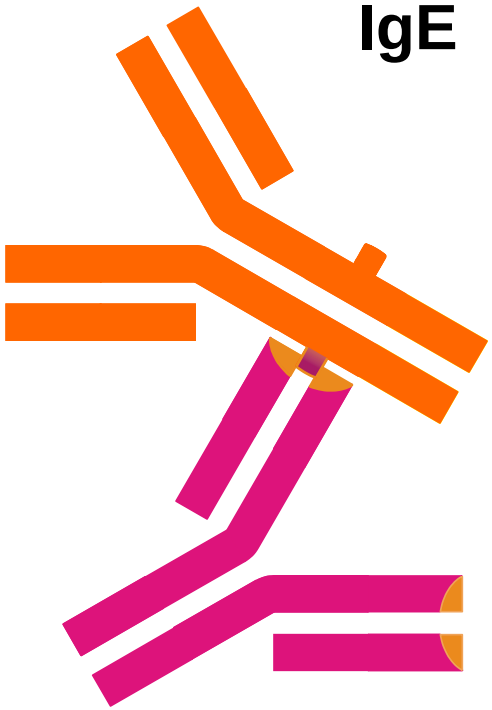

 Trivedi et al. J Allergy Clin Immunol 139(1):1-10, 2017

# Asthma

- Asthma prevention
- Immunotherapy
- LABA safety
- Tiotropium in asthma
- OCS side effects
- What's new in GINA 2017 ?
- Severe asthma
- Biologics

# Biologics in severe asthma

- **Anti - IgE**
  - **Omalizumab**
  - **Ligelizumab (QGE031) >>**
  - **Quilizumab >>**




**Novartis termination letter, 21.12.2015**

**Harris et al. Respir Res 17(1):29, 2016**

# Phenotype ‚allergic asthma‘

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

# Persistence of omalizumab response after long-term therapy

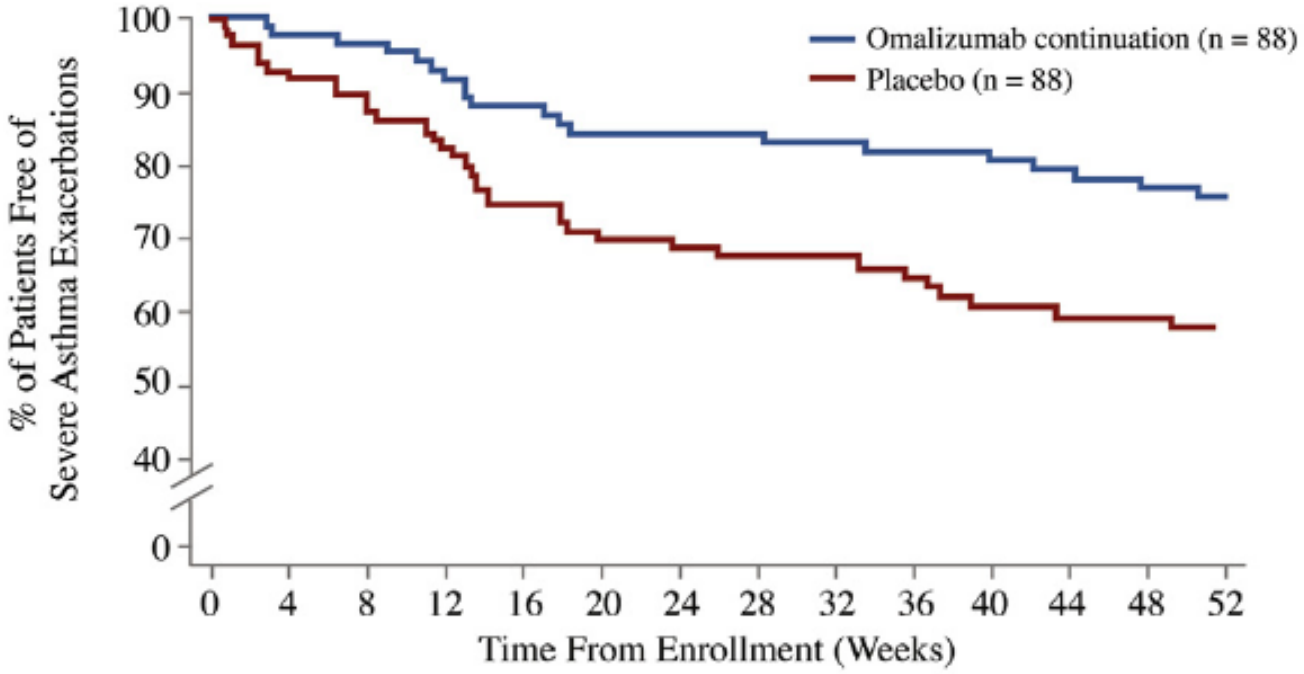
- Moderate-to-severe asthma
- Omalizumab for ~ 5 yr.

- Continue omalizumab
- Withdraw to placebo

1 year

- Severe asthma exacerbation
- Asthma control

**Time to 1st exacerbation**






Ledford et al. J Allergy Clin Immunol 2016 [epub]

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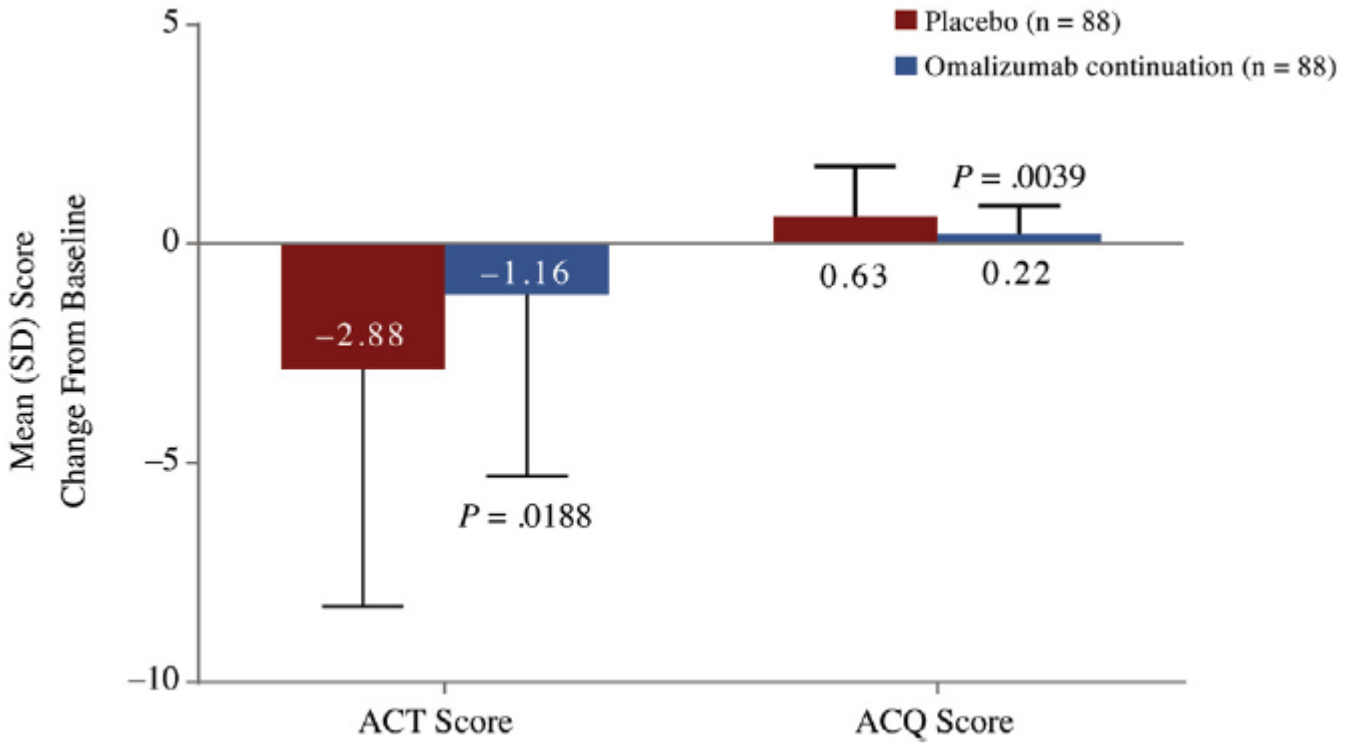
**Asthma control**



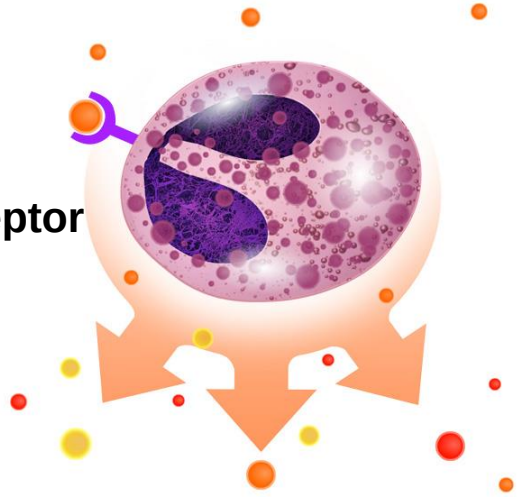


Ledford et al. J Allergy Clin Immunol 2016 [epub]

# Biologics in severe asthma

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

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




**Eosinophil granulocyte**

# The role of eosinophils in asthma

- **< 50% of severe asthmatics suffer from eosinophilic asthma**
- **Activated eosinophils release various mediators which can damage lung tissue and induce airway hyperresponsiveness and mucus hypersecretion**
- **Numbers of airway and blood eosinophils correlate with asthma severity**
- **IL-5 mediates eosinophil mobilization, maturation, activation, and survival**

# Reslizumab indication in the EU

- **Reslizumab is indicated as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment**
- **The recommended dose of reslizumab is 3.0 mg/kg every 4 weeks, given as an intravenous infusion**

# Reslizumab for inadequately controlled eosinophilic asthma

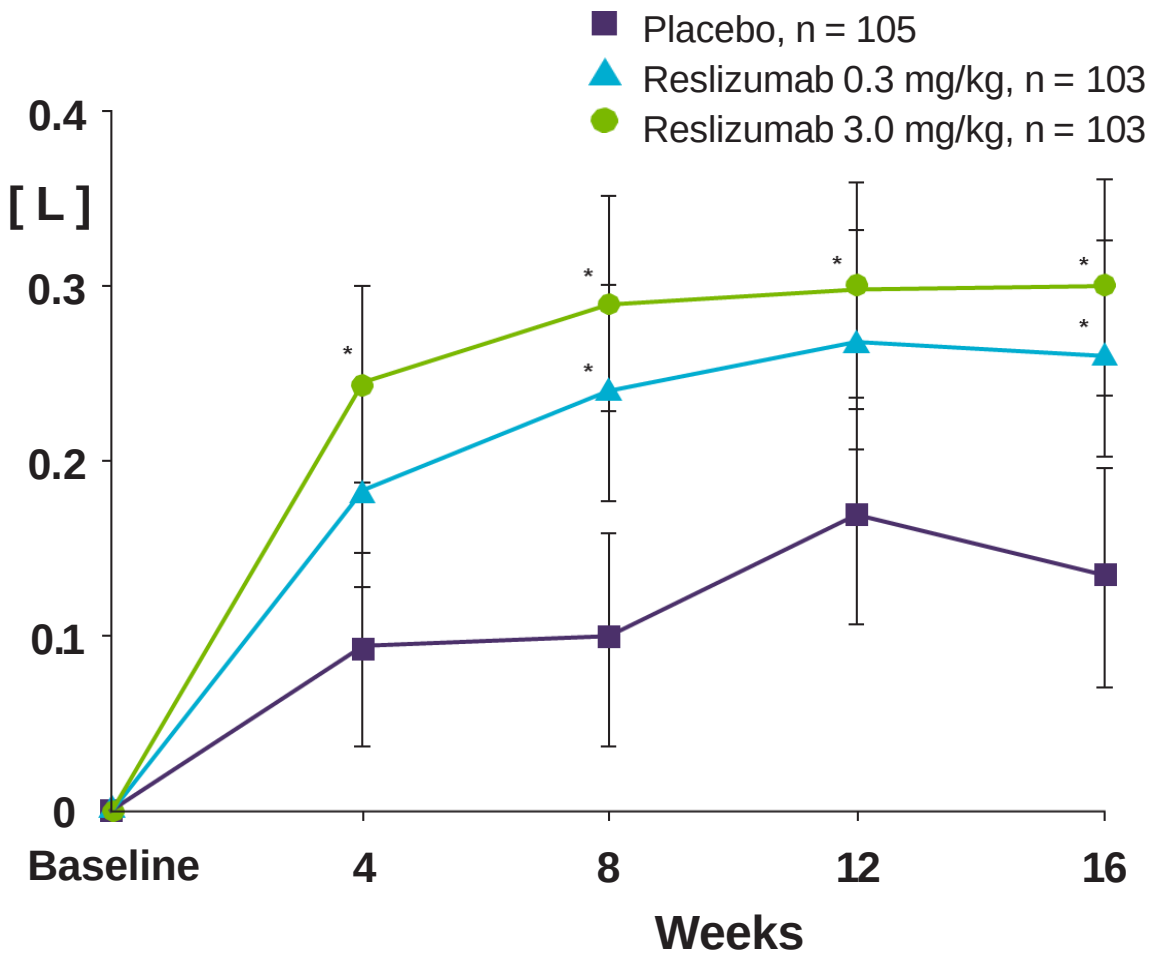
**315 asthma patients uncontrolled on MD-ICS ≥ 400 eosinophils/µl**

- **Reslizumab 0.3 or 3 mg/Kg iv every 4 weeks**
- **Placebo**

**16 weeks**

- **Lung function**

## Lung function [FEV1, L]

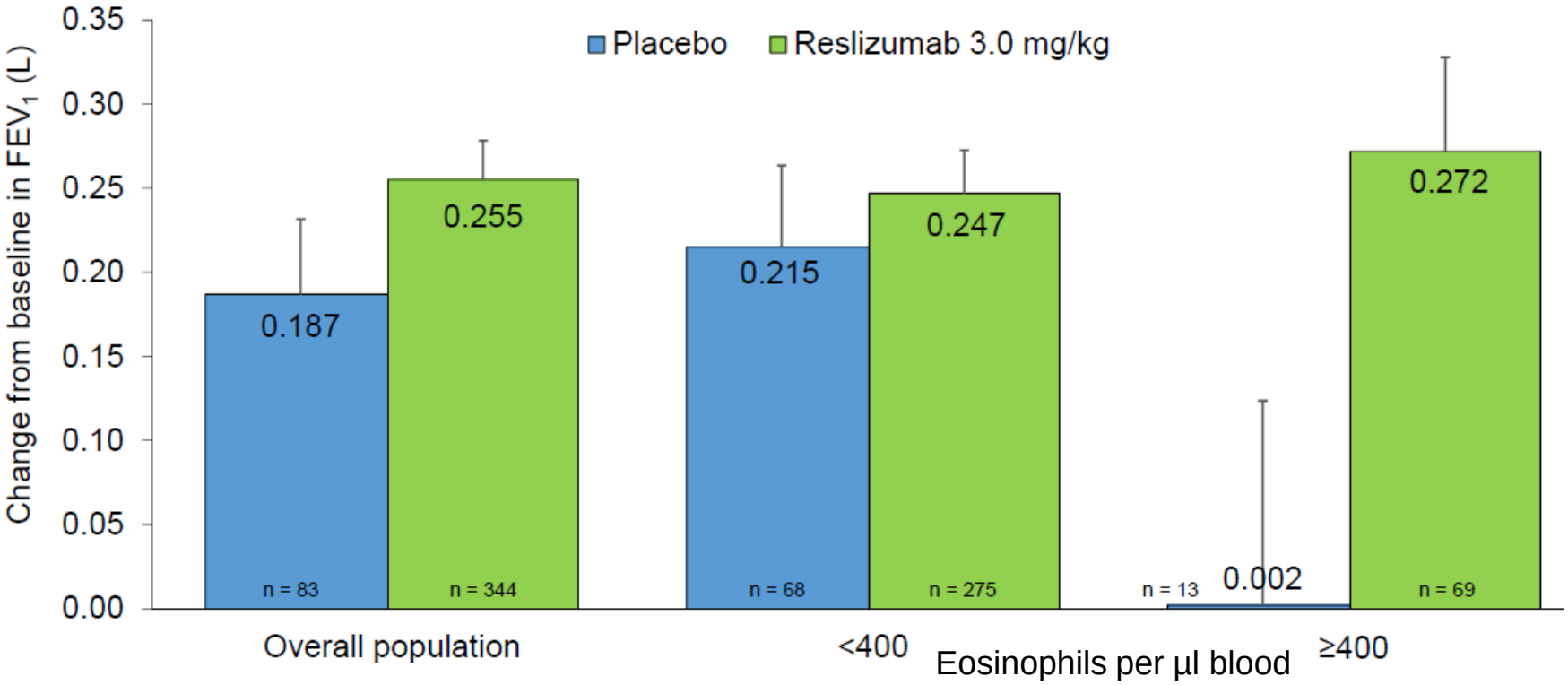





Bjermer, et al. Chest, 150(4):789-798, 2016

# Effects of reslizumab on lung function stratified by baseline eosinophil thresholds

- **492 asthma pts. (18-65 yrs.) with an ACQ-7 score ≥ 1.5 inadequately controlled by fluticasone propionate ≥ 440 µg/day or equivalent**
- **16-week double-blind (4:1 randomisation) treatment with reslizumab 3.0 mg/kg or placebo once every 4 weeks**






Corren, et al. Chest 150(4):799-810, 2016

# Benralizumab for severe asthma uncontrolled with high-dose ICS and LABA (SIROCCO)

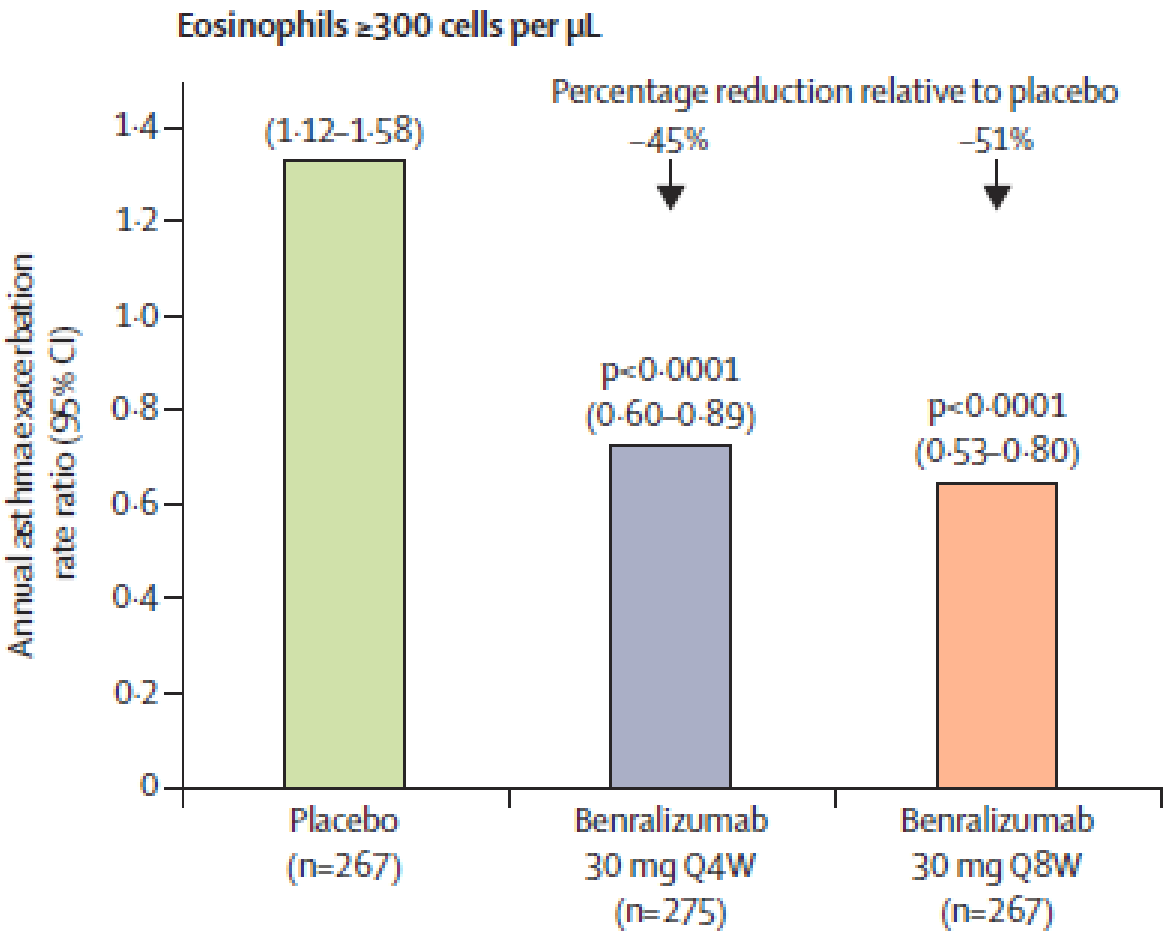
**1205 asthma patients**
**12-75 yrs., HD ICS + LABA**
**≥ 2 exac./prev. year**

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

**48 weeks**

- **Exacerbation rate**

## Exacerbations / year





Bleecker et al. Lancet 388 (10056):2115-2127, 2016

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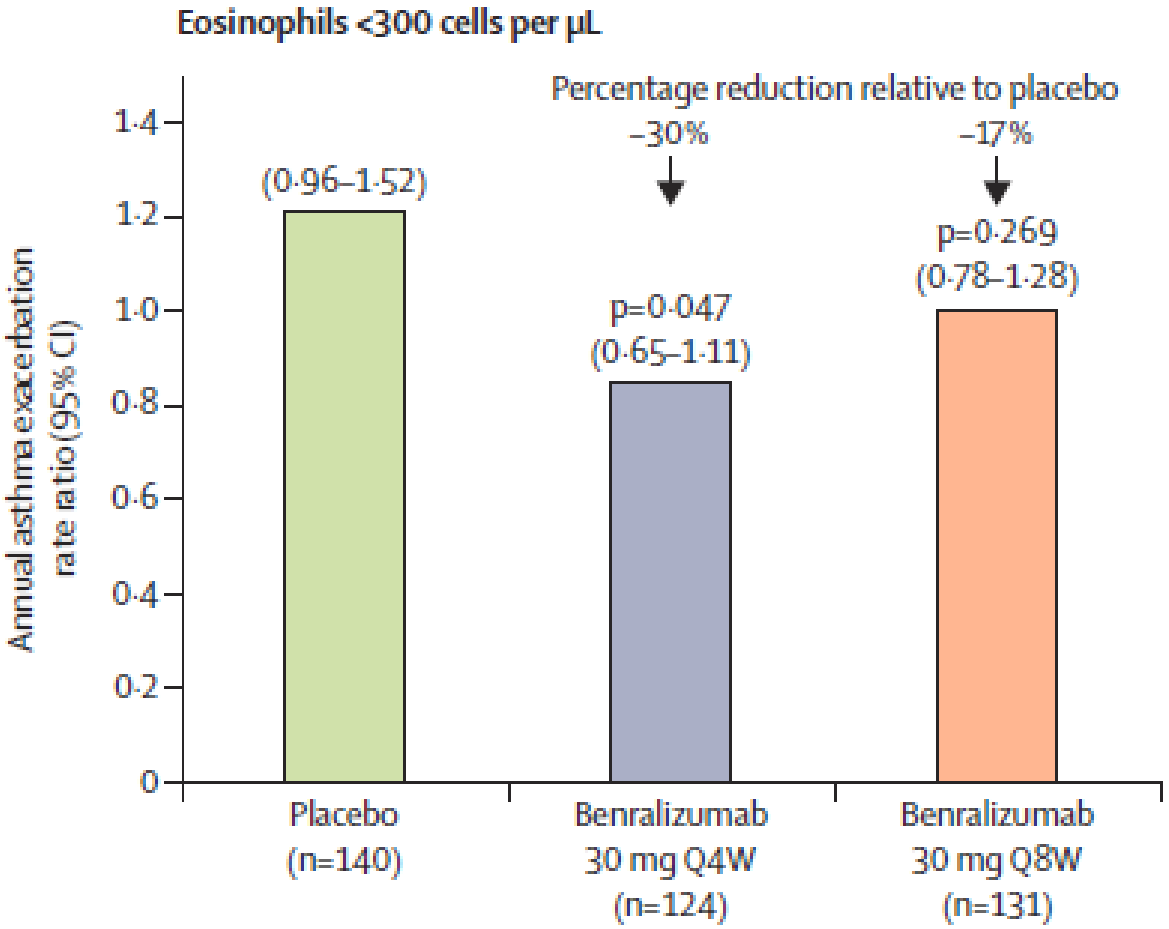



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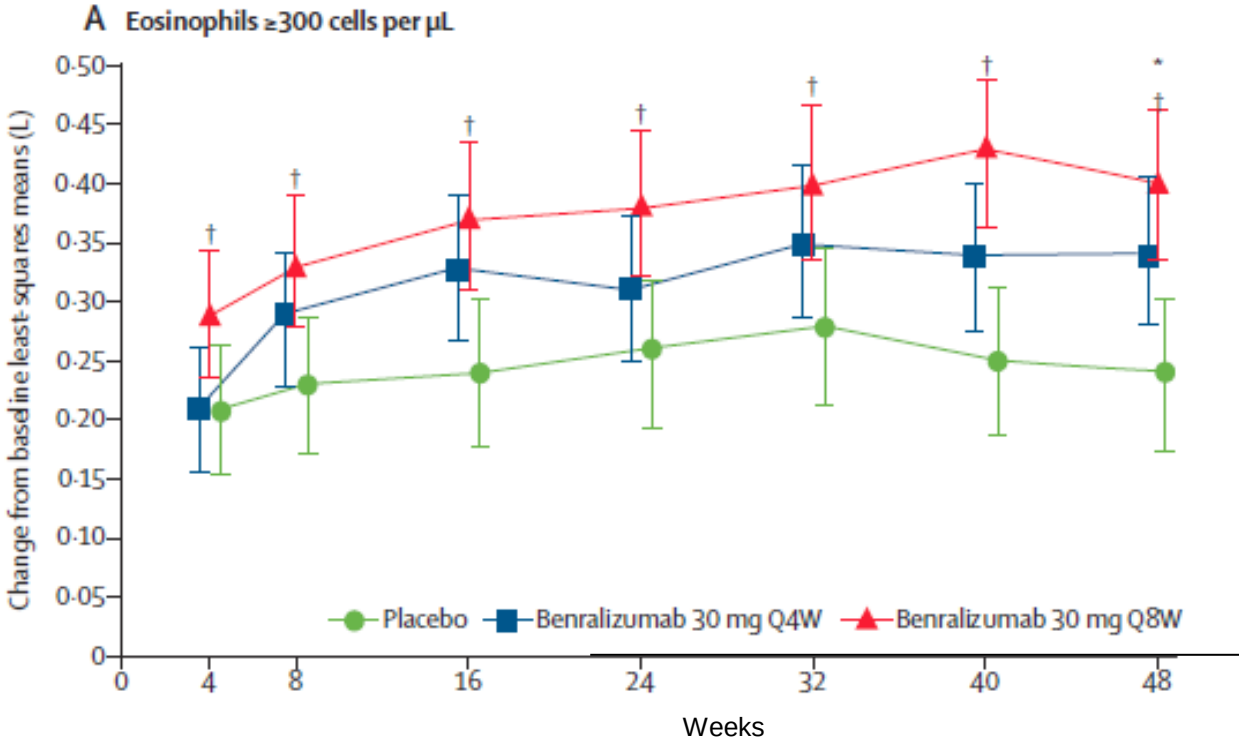
- **Lung function**

## Δ FEV1 (vs. baseline)





Bleecker et al. Lancet 388 (10056):2115-2127, 2016

# Benralizumab for severe asthma uncontrolled with high-dose ICS and LABA (SIROCCO)

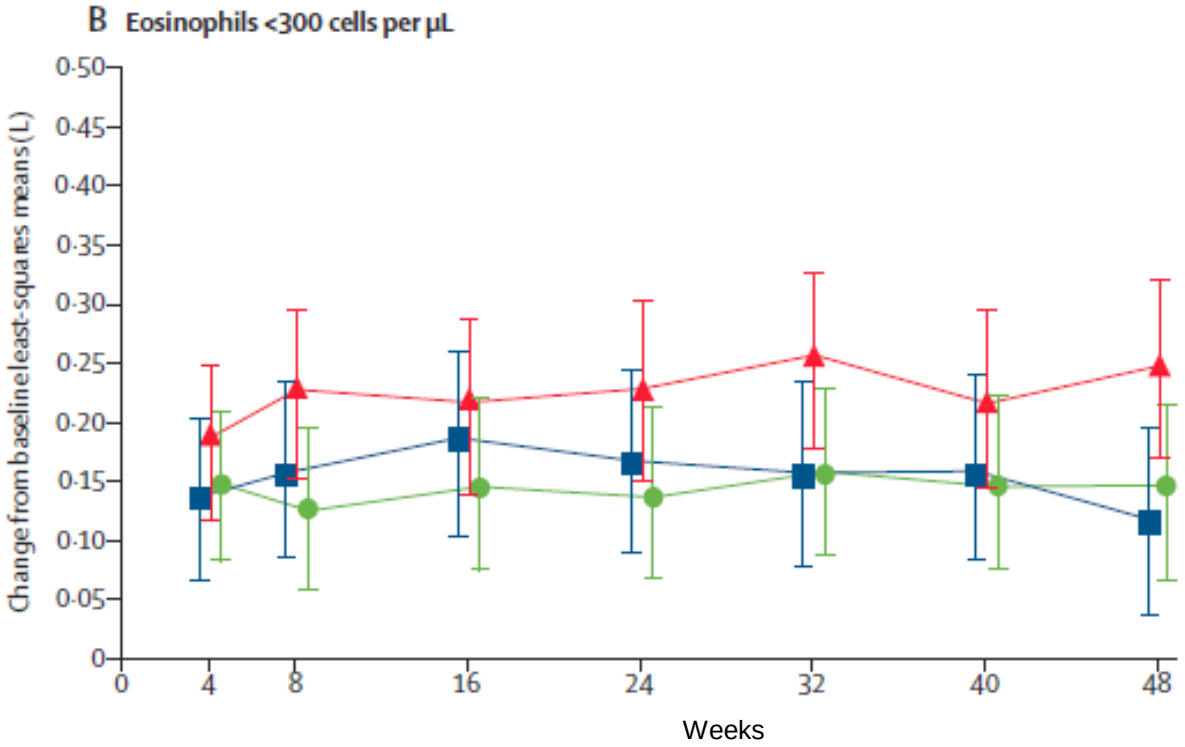
**1205 asthma patients**
**12-75 yrs., HD ICS + LABA**
**≥ 2 exac./prev. year**

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

**48 weeks**

- **Lung function**

## Δ FEV1 (vs. baseline)





Bleecker et al. Lancet 388 (10056):2115-2127, 2016

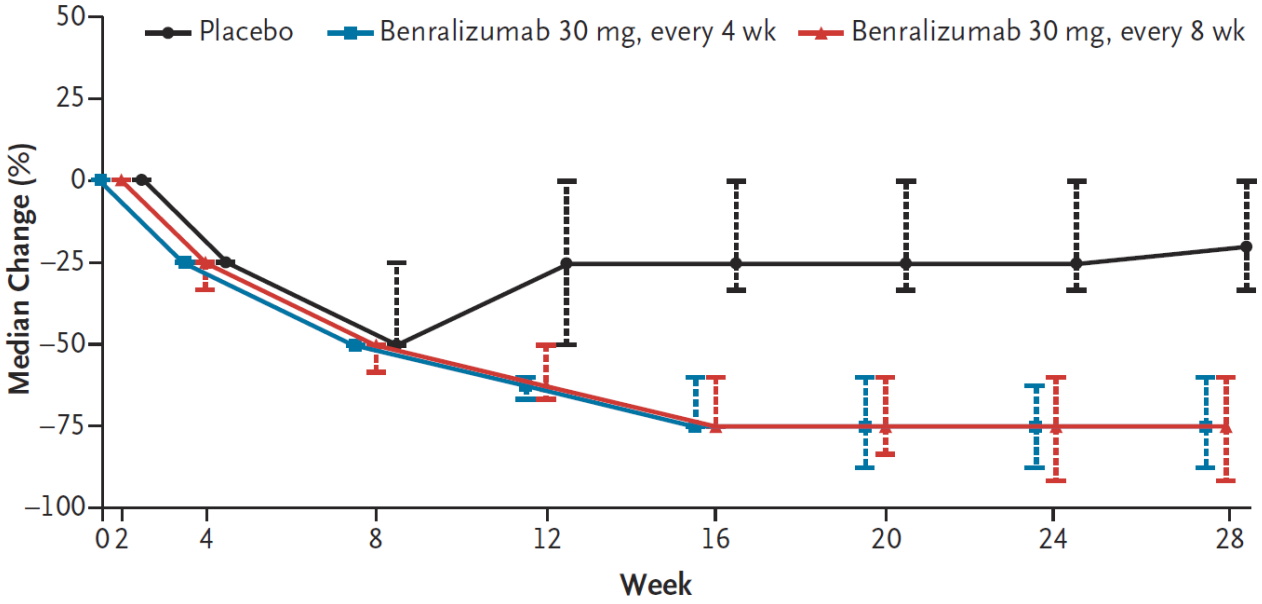
# ZONDA: Oral glucocorticoid-sparing effect of benralizumab in severe asthma

**220 asthma patients**
**≥150 blood eos/µL**
**despite GINA step 5**
**incl. predniso(lo)ne**
**7.5-40 mg/day**

- **Benralizumab 30 mg sc 4- / 8-weekly**
- **Placebo**

**28 weeks**

## Change in OCS dose [%]



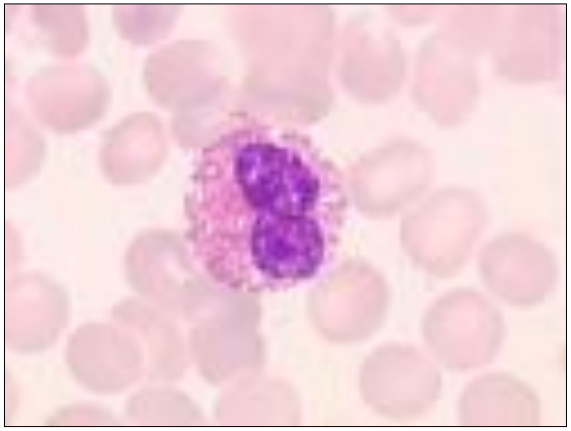

- **Change in OCS dose**

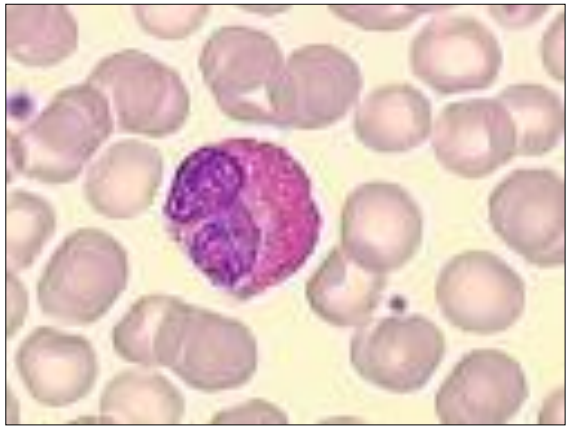

Nair et al. NEJM 2017 [epub]

# Anti - IL-5 antibodies: Clinical efficacy

| | Mepolizumab | Reslizumab | Benralizumab |
|---|---|---|---|
| Exazerbations ↓ (vs. placebo) | | | |
| $FEV_1$ ↑ | | | |
| Asthma symptoms (ACQ-5/6) | | | |
| Oral steroids ↓ | | | |
| Dosage | **q4w 100 mg s.c.** | **q4w 3 mg/kg i.v.** | **q8w 30 mg s.c.** |

# Phenotype ‚eosinophilic' asthma





- **Late onset of disease**
- **Symptoms ↑, exacerbations ↑**
- **Eosinophilia in blood** (± sputum)
- **± FeNO > 50 ppb**
- **No *clinically relevant* allergy**
- **± Nasal polyposis**
  **- smell ↓ & taste ↓**
- **Response to (oral) gluco-corticoids and anti - IL-5**

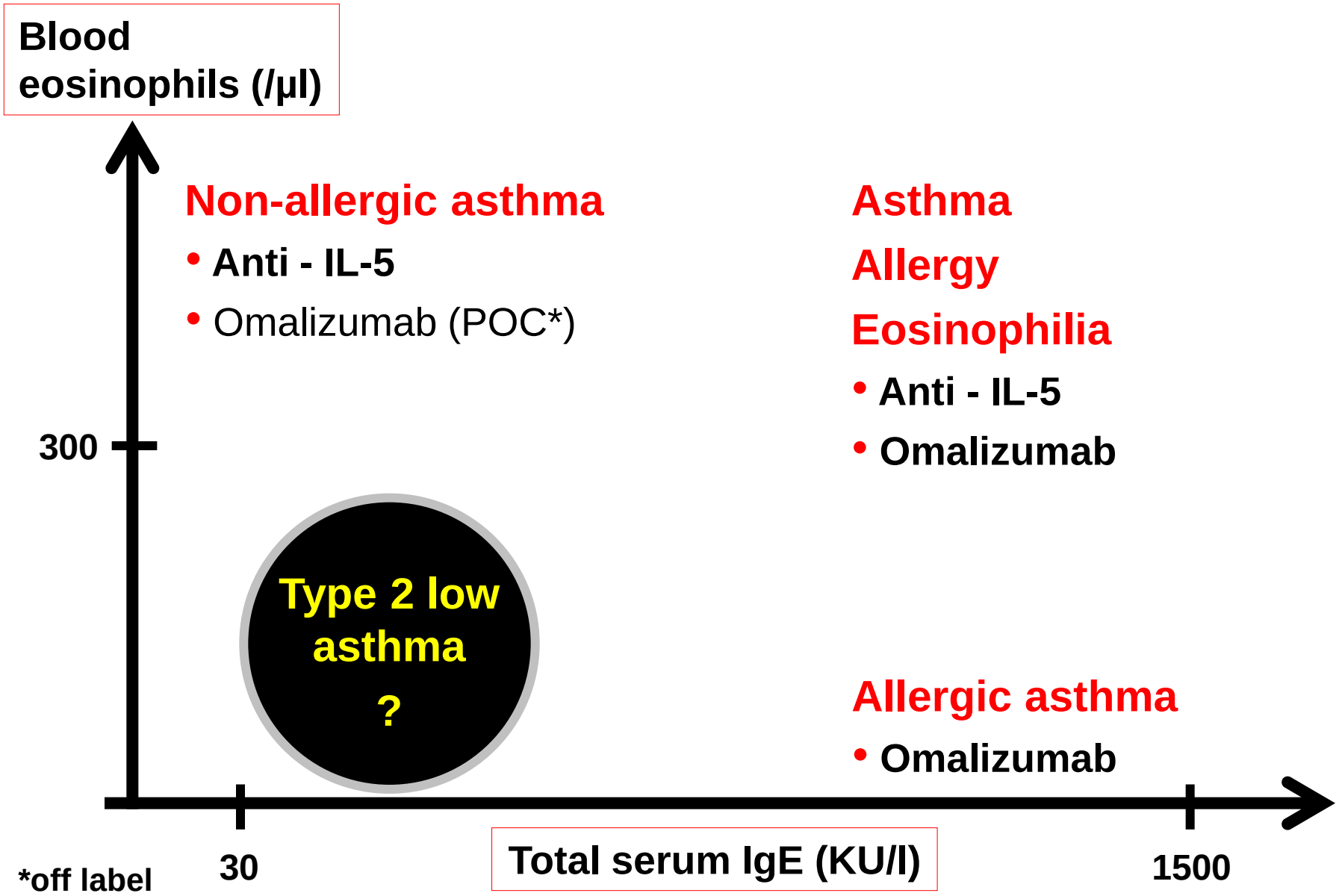
# Diagnosis of severe eosinophilic asthma

| 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 2017 [epub]

# Severe asthma



# Biologics in severe asthma

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

**Human interleukin-13**

**AstraZeneca Media Release**
**STRATOS-1, 10.5.2017**

**Roche Media Release**
**LAVOLTA, 29.2.2016**

# Lebrikizumab in uncontrolled asthma

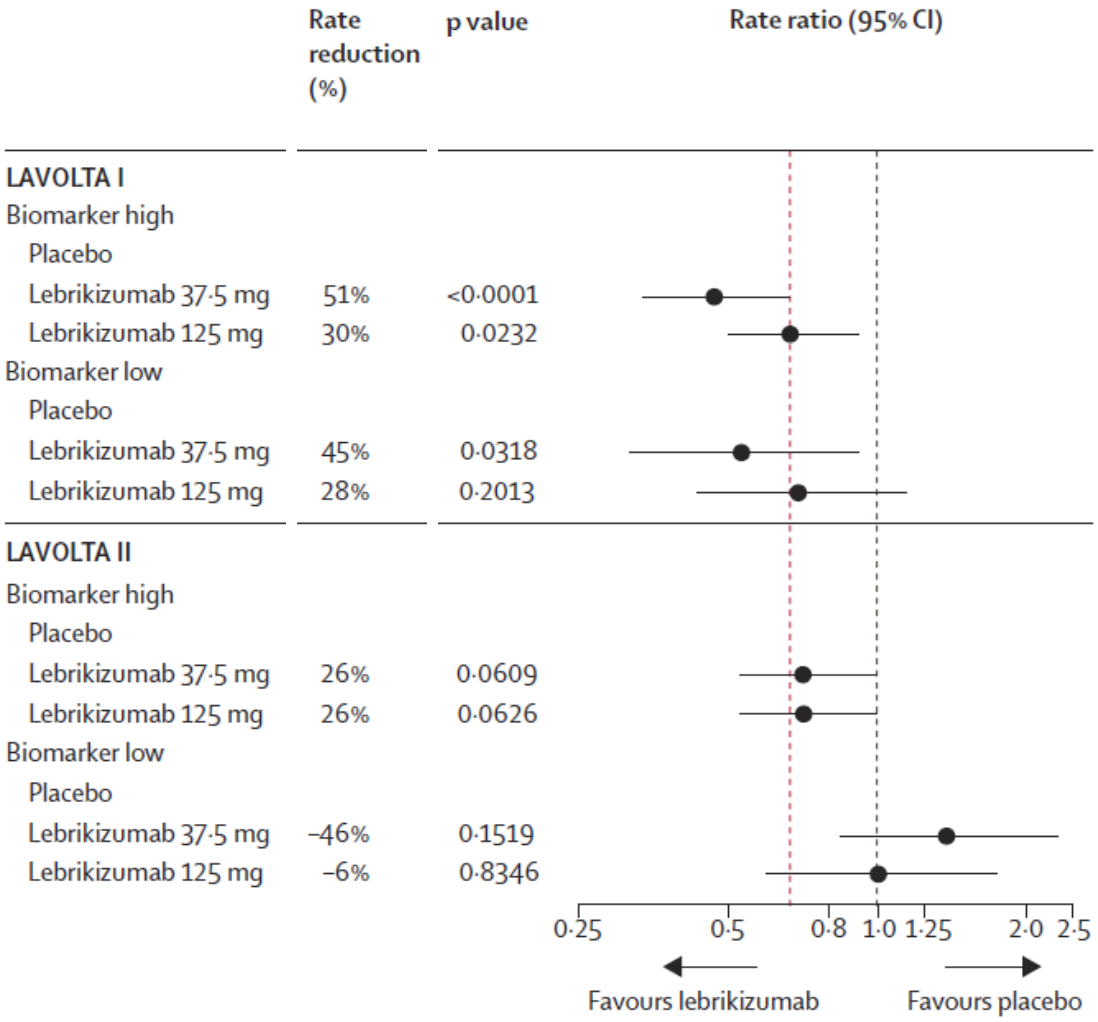
**1081 patients with uncontrolled asthma, pre-BD FEV1 40-80%**

- **Lebrikizumab s.c. 37.5 mg or 125 mg every 4 weeks**
- **Placebo**

**52 weeks**

- **Asthma exacerbations in biomarker-high pts. (periostin ≥50 ng/mL or blood eosinophils ≥300 cells/µl)**

## Asthma exacerbations






Hanania et al. Lancet Respir, Med 4(10):781-796, 2016

# Lebrikizumab in uncontrolled asthma

**1081 patients with uncontrolled asthma, pre-BD FEV1 40-80%**

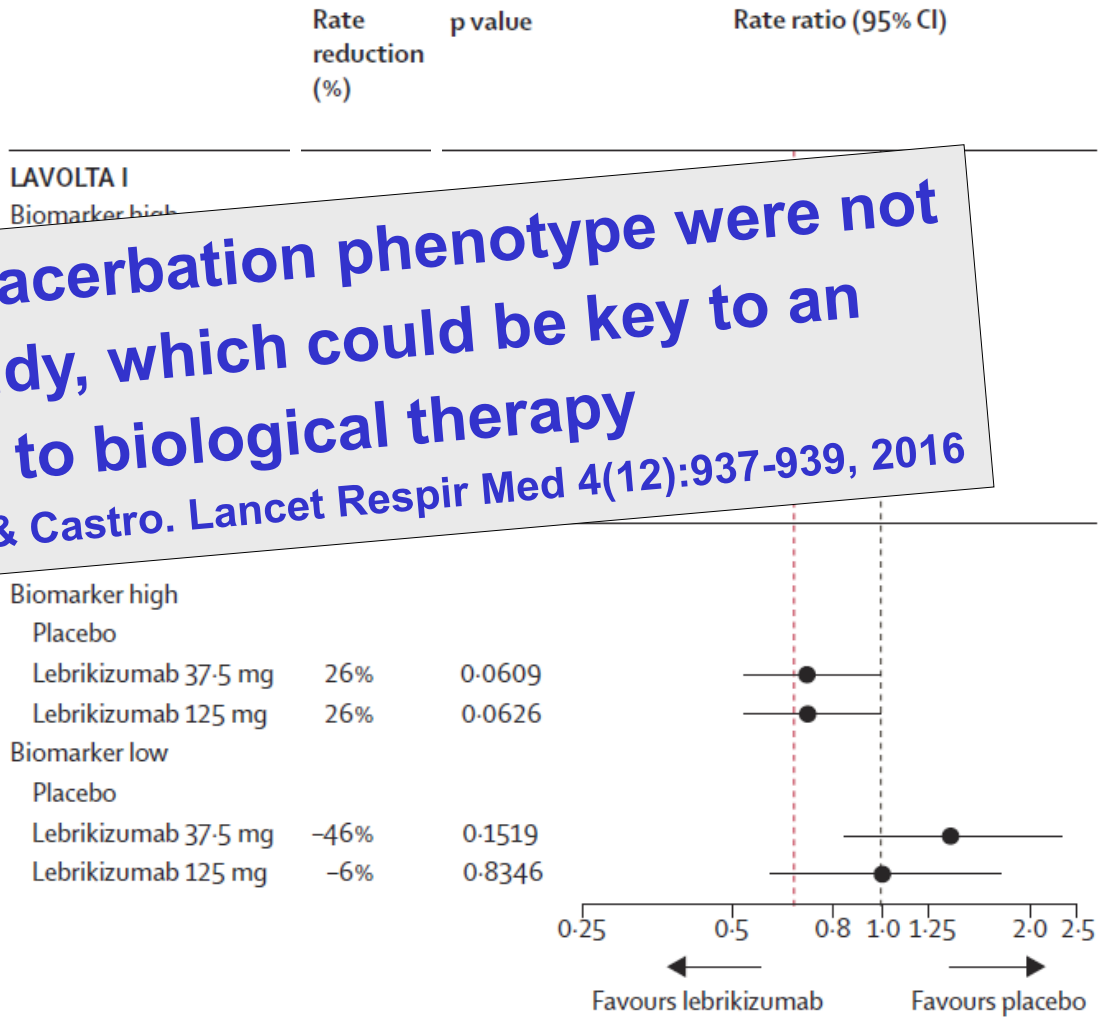
- **Lebrikizumab s.c. 37.5 mg or 125 mg every 4 weeks**
- **P**

- **Patients with an exacerbation phenotype were not selected in this study, which could be key to an effective response to biological therapy**

**Sood & Castro. Lancet Respir Med 4(12):937-939, 2016**

- **Asthma exacerbations in biomarker-high pts. (periostin ≥50 ng/mL or blood eosinophils ≥300 cells/µl)**

## Asthma exacerbations



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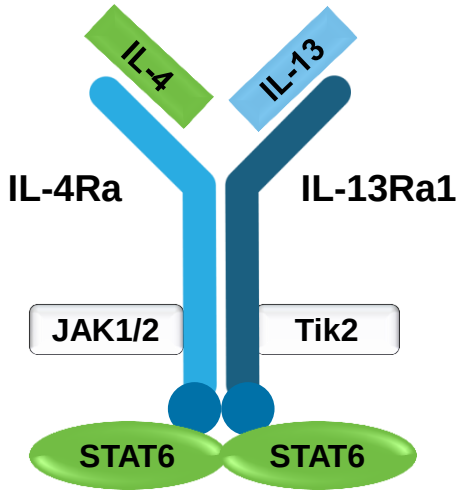
# Biologics in severe asthma

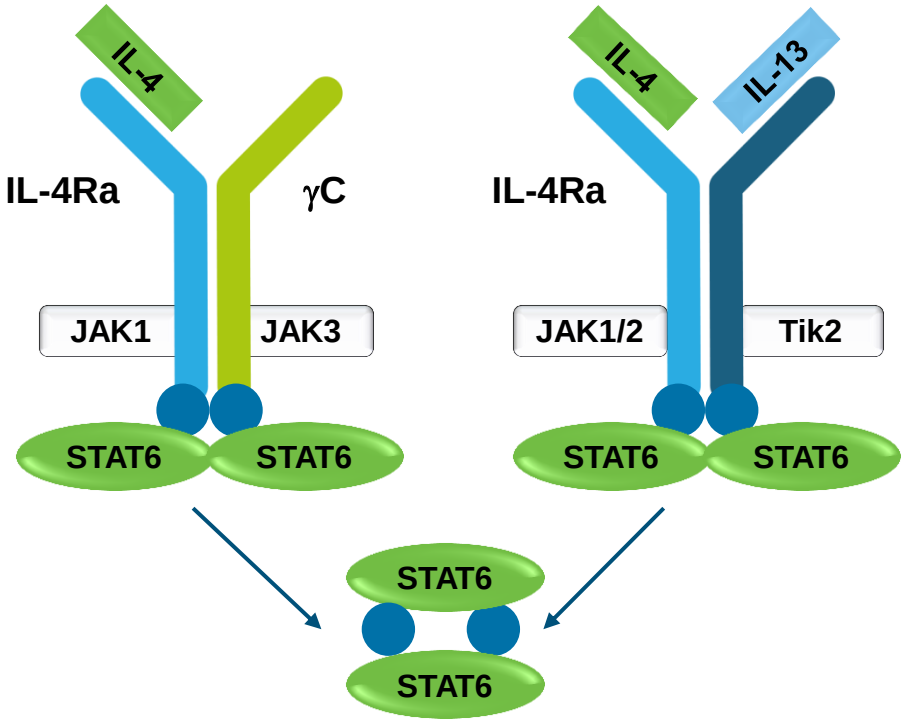



Interleukin-4/13 receptor

- **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)


Wenzel, et al. N Engl J Med 368(26):2455-2466, 2013

# Dupilumab in uncontrolled asthma despite ICS + LABA




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

Thaçi, et al. Lancet 387:40-52, 2016

Wenzel, et al. Lancet 388:31-44, 2016

Bachert, et al. JAMA 315(5):469-479, 2016

Simpson, et al. NEJM 375(24):2335-2348, 2016

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

# Asthma

- Asthma prevention
- Immunotherapy
- LABA safety
- Tiotropium in asthma
- OCS side effects
- What's new in GINA 2017 ?
- Severe asthma
- Biologics
- Two more things

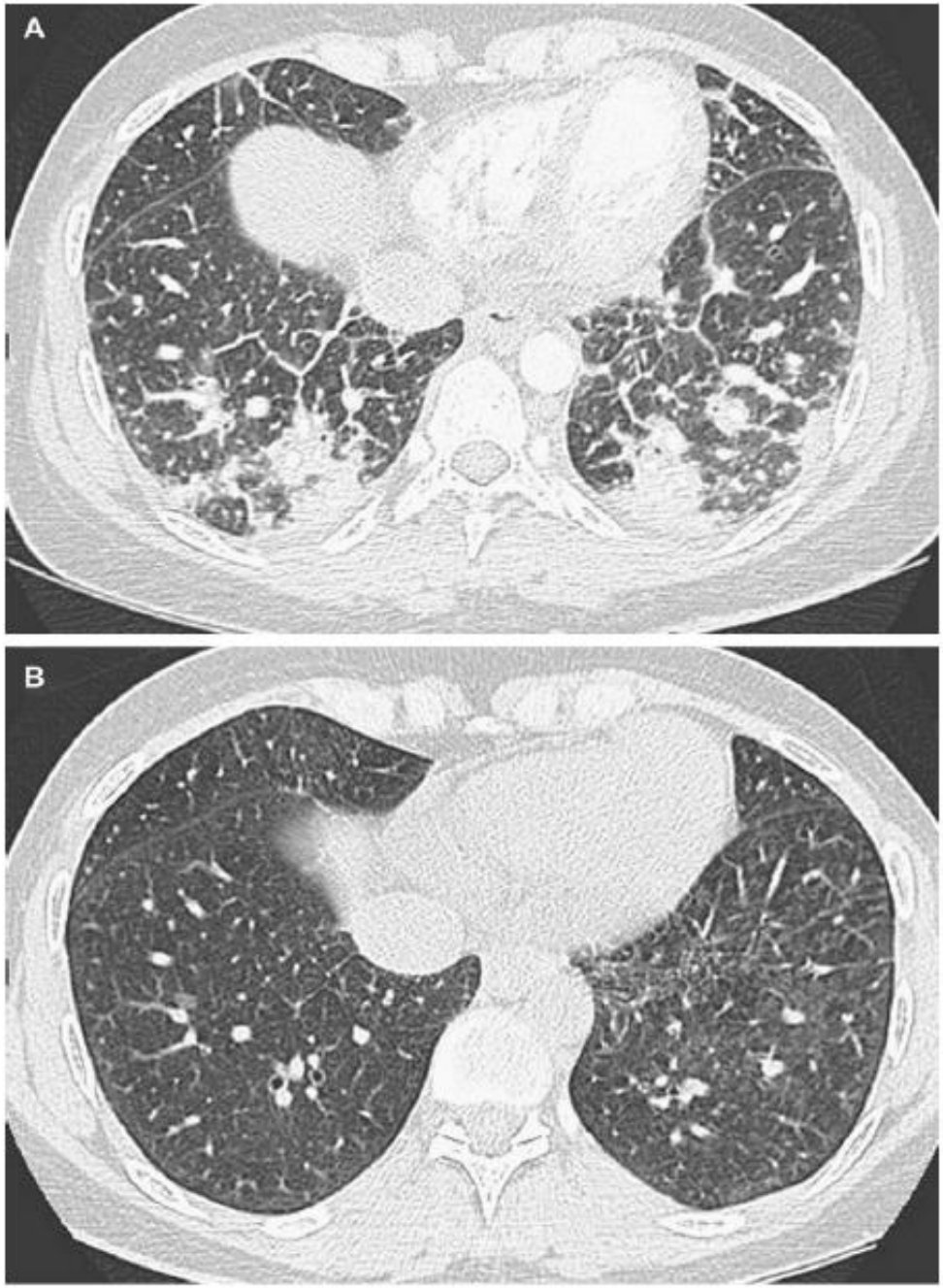
# Eosinophilic granulomatosis with polyangitis (Churg-Strauss-syndrome)

## Diagnostic criteria

- Asthma
- Blood eosinophilia > 10%
- Polyneuropathy or Mononeuritis multiplex
- Pulmonary infiltrates, non-fixed
- Paranasal sinus abnormality
- Extravascular eosinophils (biopsy)

**If at least 4 of this 6 criteria are positive, a patient shall be said to have Churg-Strauss-syndrome**


Groh et al. Eur J Intern Med 26 (7):545-553, 2015




# Anti-interleukin-5 (mepolizumab) in a patient with Churg-Strauss-syndrome



Kahn et al. J Allergy, Clin Immunol 2010, Jan;125(1):267-70.

# Mepolizumab for eosinophilic granulomatosis with polyangiitis

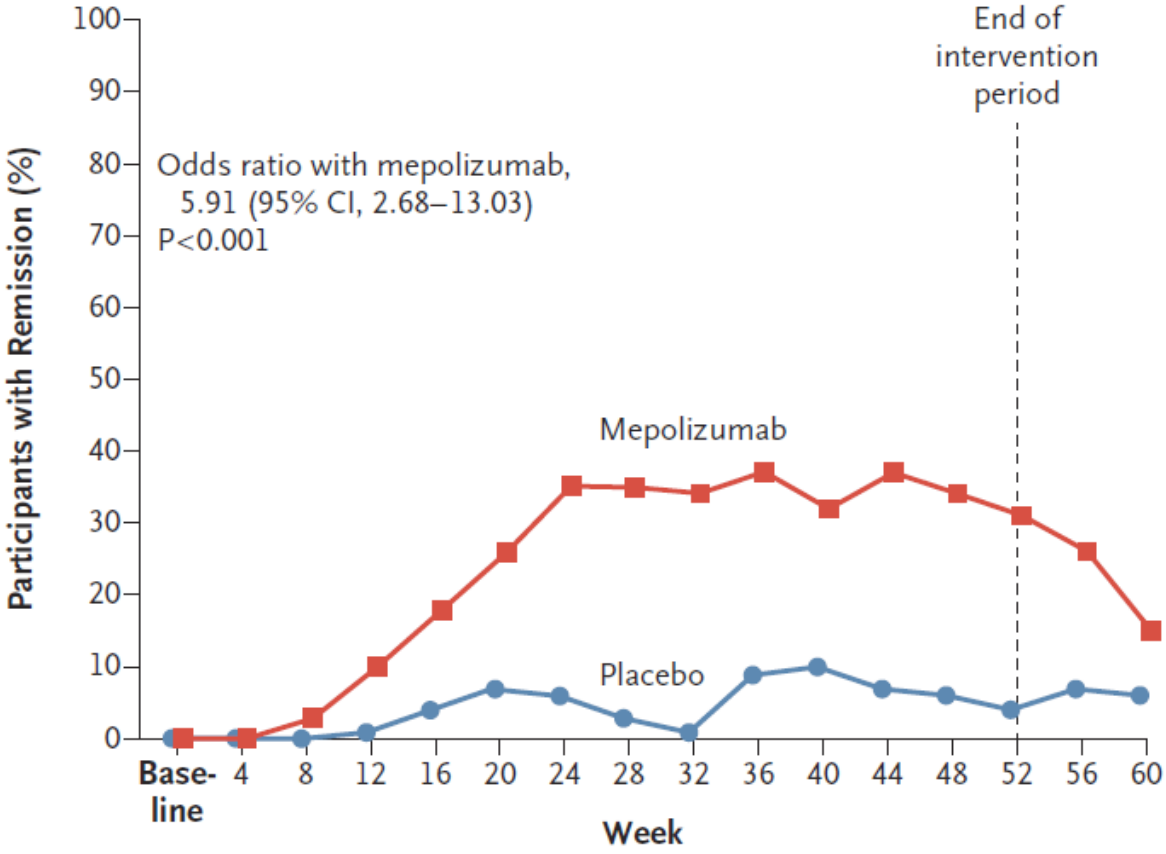
**136 EGPA-Patienten**
**Predniso(lo)ne ≥ 7.5 mg/day**

- **Mepolizumab 300 mg sc 4-weekly**
- **Placebo**

**52 weeks**

- **Weeks of remission**
- **Patients in remission at weeks 36 and 48**

## Patients in remission






Wechsler et al. N Engl J Med 376(20):1921-1932, 2017

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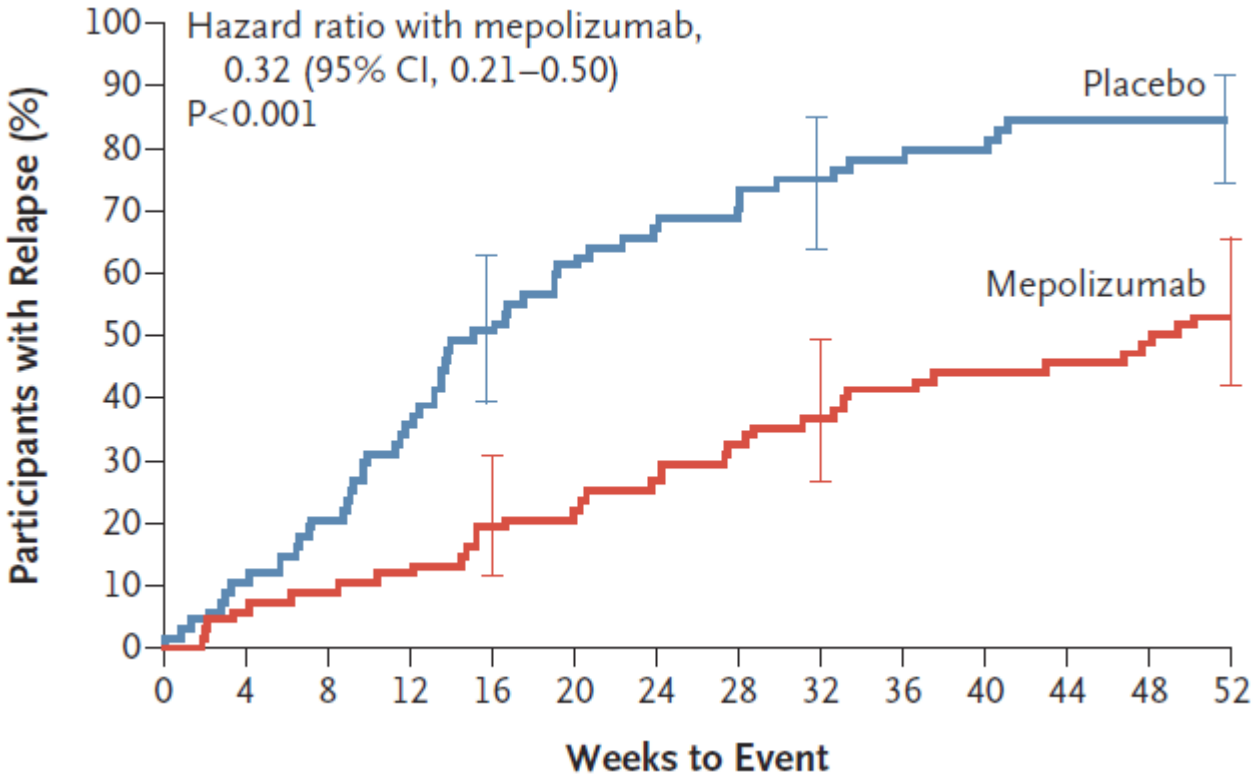
- **Patients in remission at weeks 36 and 48**

**Patients with relapse [%]**






Wechsler et al. N Engl J Med 376(20):1921-1932, 2017

# Mepolizumab for eosinophilic granulomatosis with polyangiitis

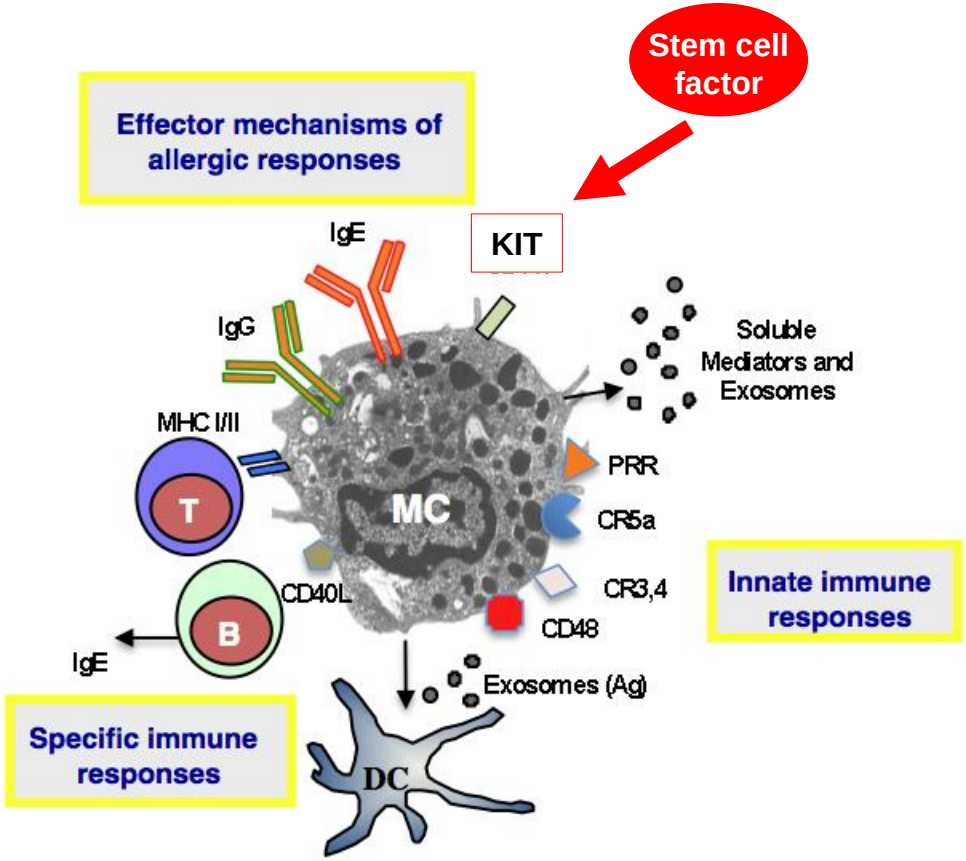
- **Definition of relapse**
  - **asthma**
  - **sinonasal disease**
  - **combination**
- **Fewer exacerbating asthma- or sinonasal-based relapses**
  - **mepolizumab response of vasculitic component?**
- **Relapses after remission raise questions**
  - **mechanism(s) of relapses ➔ role of eosinophils?**
  - **dose of mepolizumab?**

**Djukanovic & O'Byrne. N Engl J Med 376 (20):1985-1986, 2017**



**Wechsler et al. N Engl J Med 376(20):1921-1932, 2017**

# Mast cells and KIT

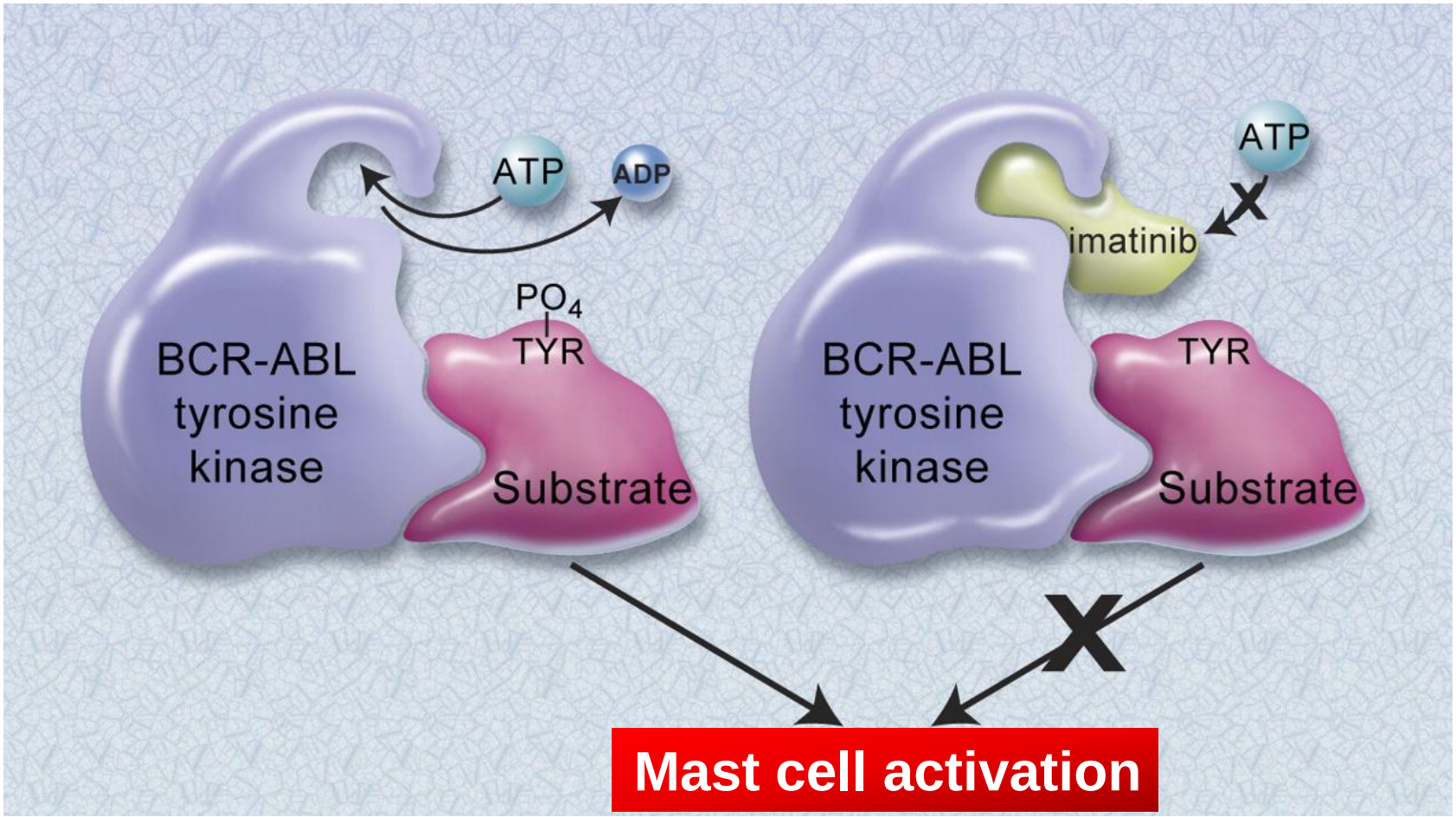



- **Stem cell factor and its receptor KIT regulate mast cell survival, differentiation, proliferation, and modulate the activation of mast cells through Fc εRI receptors**



SJ Galli. Adv Immunol 126:45-127, 2015

# Mast cell inhibition by imatinib




Druker, Blood 2008

Cahill et al. N Engl J Med 376(20):1911-1920, 2017
SJ Galli. N Engl J Med 376(20):1983-1984, 2017

# KIT inhibition by imatinib in severe asthma

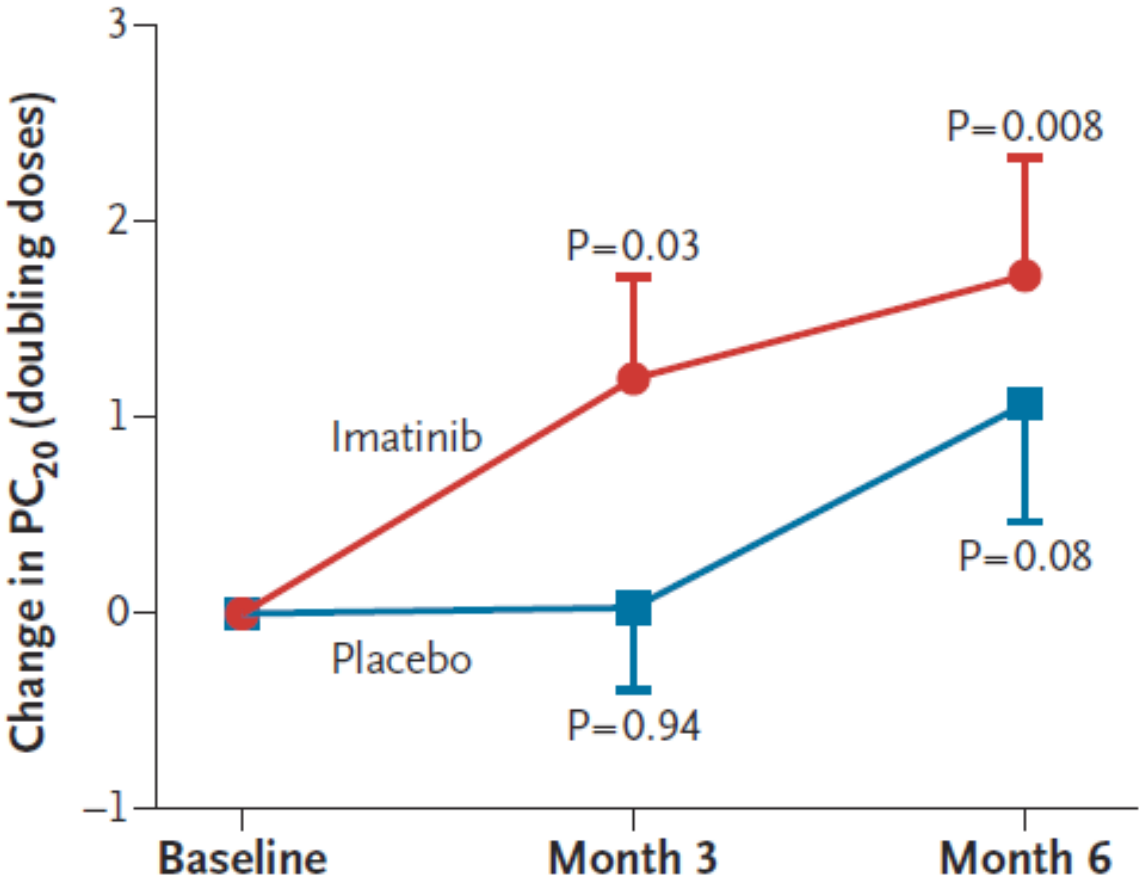
**62 asthma patients**
**on high dose ICS**
**+ 2nd controller**
**ACQ ≥ 1.5**

- **Imatinib 400 mg/day**
- **Placebo**

**24 weeks**

- **Airway hyperreactivity**
- **Lung function**

## Airway hyperreactivity





Cahill et al. N Engl J Med 376(20):1911-1920, 2017

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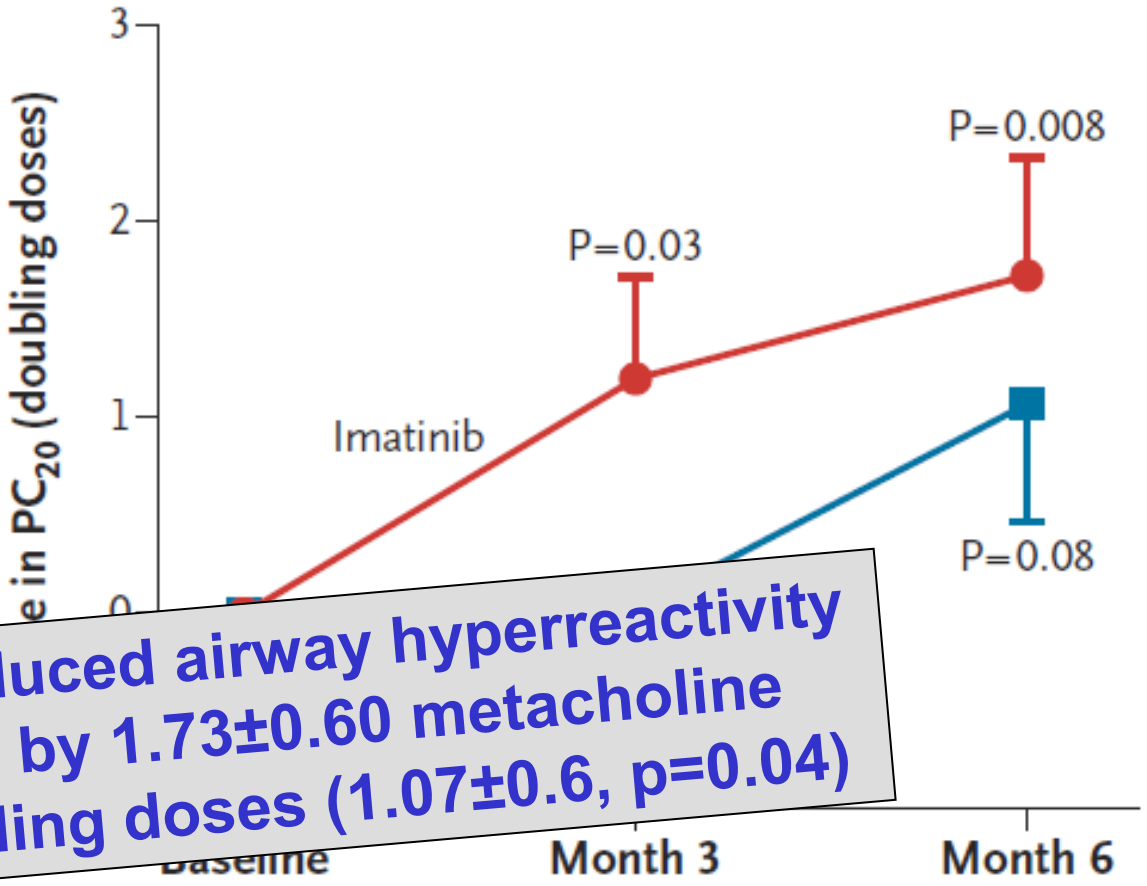
- **Lung fun**

## Airway hyperreactivity




- **Imatinib reduced airway hyperreactivity vs. placebo by 1.73±0.60 metacholine PC20 doubling doses (1.07±0.6, p=0.04)**



Cahill et al. N Engl J Med 376(20):1911-1920, 2017

# KIT inhibition by imatinib in severe asthma

| Measure | Change from Baseline | | P Value |
|---|---|---|---|
| | Imatinib | Placebo | |
| PEF (liters/min) | | | |
| Morning | 7.3±46.1 | −6.4±39.3 | 0.38 |
| Evening | 8.3±53.6 | −8.2±37.2 | 0.31 |
| $FE_{NO}$ (ppb) | 7.89±33.0 | −5.92±33.2 | 0.11 |
| Maximum post-bronchodilation $FEV_1$ (liters) | 0.01±0.2 | −0.08±0.26 | 0.10 |
| ACQ-6 score | −0.62±0.96 | −0.49±0.89 | 0.31 |
| AQLQ score | 0.55±1.0 | 0.25±0.80 | 0.11 |

- **Improvements of FEV1 (+46 ml (95% CI 36 to 56), fewer asthma exacerbations, higher peak expiratory flows, and improvements in patient-reported outcomes in the imatinib group**


Cahill et al. N Engl J Med 376(20):1911-1920, 2017

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- **Improvements of FEV1 (…) asthma exacer… …vements in patie… …the imatinib group**

- **Mast cells are a potential treatment target (not only?) in severe asthma**


Cahill et al. N Engl J Med 376(20):1911-1920, 2017

# Asthma

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- Immunotherapy
- LABA safety
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