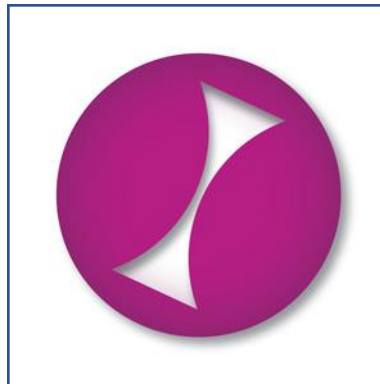


# **Pneumo Update Europe 2016**

**24-25 June, Prague**

---

## **Asthma**



**Roland Buhl, Germany**

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# Asthma

- **What's new in GINA 2016 ?**

# What's new in GINA 2016 ?

- **Step 3**
  - Low-dose fluticasone furoate/vilanterol an option
- **Step 4**
  - Tiotropium add-on option for adolescents (age  $\geq 12$  years) and adults, with a history of exacerbations
- **Step 5**
  - Add-on tiotropium by mist inhaler for patients age  $\geq 12$  years with a history of exacerbations

# Tiotropium in symptomatic asthma despite low- to medium-dose ICS

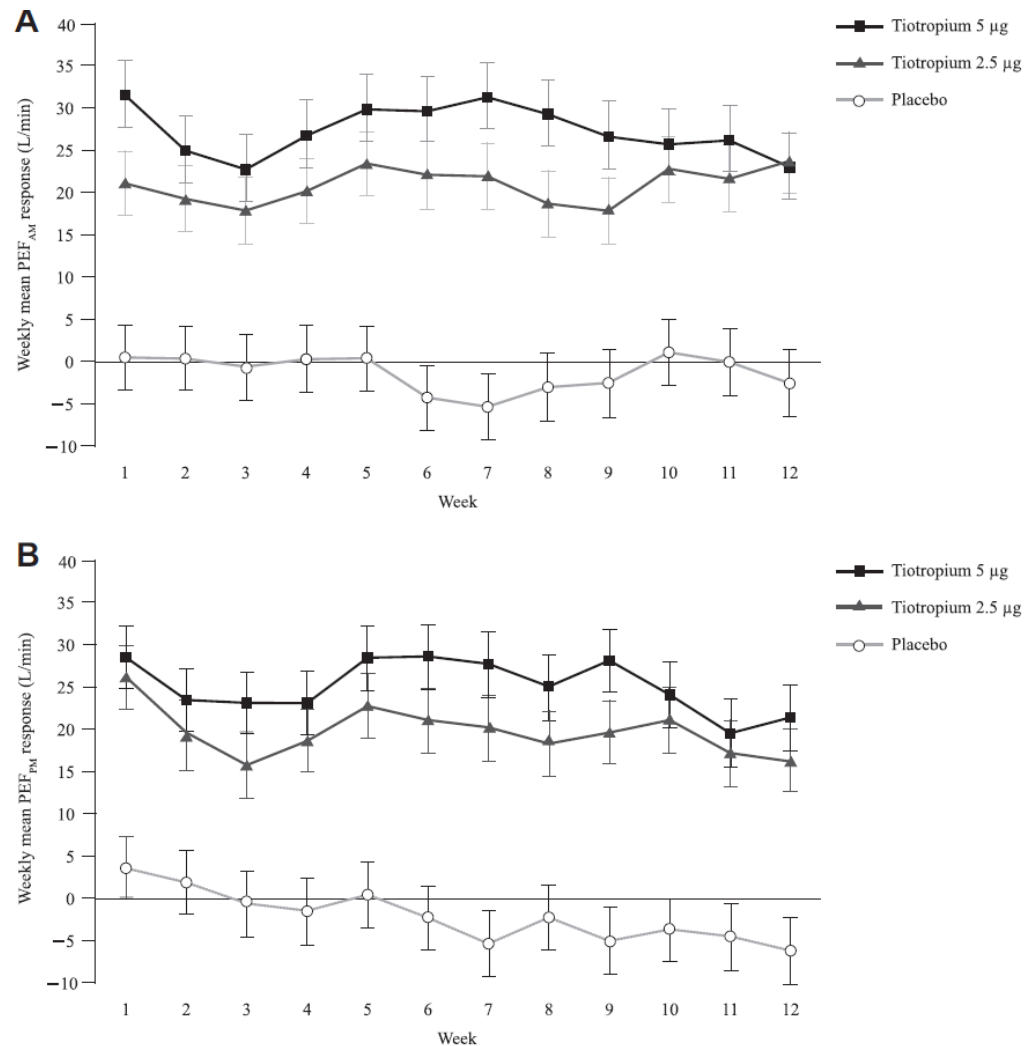
464 asthma patients  
symptomatic despite  
200-400 µg BUD/day  
FEV1 60-90%

- Tiotropium 1x 2.5 µg/day
- Tiotropium 1x 5 µg/day
- Placebo

12 weeks

- Lung function

## Morning & evening peak flow [L/min]



# Tiotropium add-on in adolescents with moderate asthma

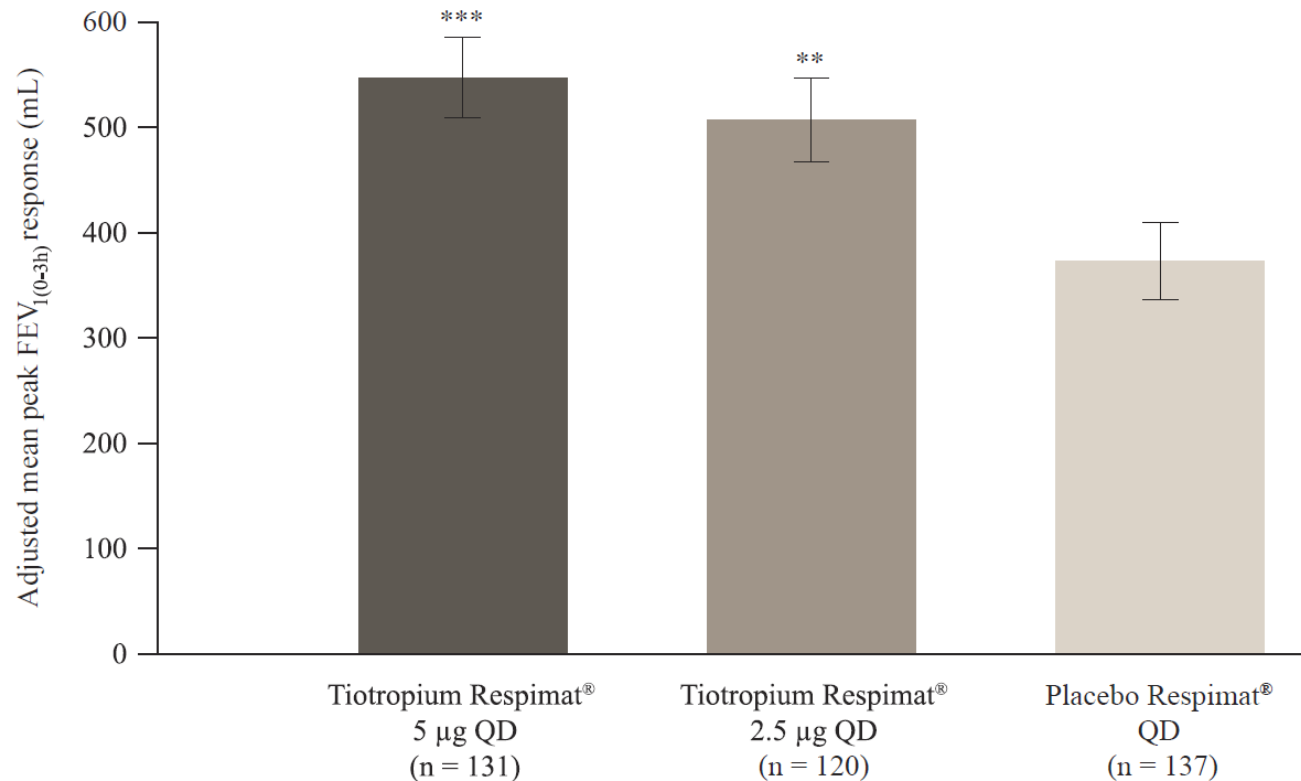
398 asthma patients  
ICS ± LTRA  
12 – 17 years

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

48 weeks

- Lung function

Peak FEV<sub>1</sub>(0-3 h) in week 24



# **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**

# What's new in GINA 2016 ?

- **Step 3**
  - Low-dose fluticasone furoate/vilanterol an option
- **Step 4**
  - Tiotropium add-on option for adolescents (age  $\geq 12$  years) and adults, with a history of exacerbations
- **Step 5**
  - Add-on tiotropium by mist inhaler for patients age  $\geq 12$  years with a history of exacerbations
  - Add-on omalizumab (anti-IgE) for severe allergic asthma
  - Add-on mepolizumab (anti-IL5) for severe eosinophilic asthma ( $\geq 12$  years)
  - Sputum-guided treatment, if available



Reduce

# GINA 2016: Asthma treatment



Increase

## Step 1

Consider  
low dose  
ICS

As-needed short-acting  
 $\beta_2$ -agonist (SABA)

## Step 2

Low dose  
ICS

LTRA  
Low dose  
theophylline

## Step 3

Low dose  
ICS / LABA

Medium/high  
dose ICS  
Low dose ICS  
+ LTRA (or  
+ theophylline)

As-needed SABA or  
low-dose ICS/formoterol

## Step 4

Medium -  
high dose  
ICS / LABA

Plus tiotropium  
High dose ICS  
+ LTRA (or  
+ theophylline)

## Step 5

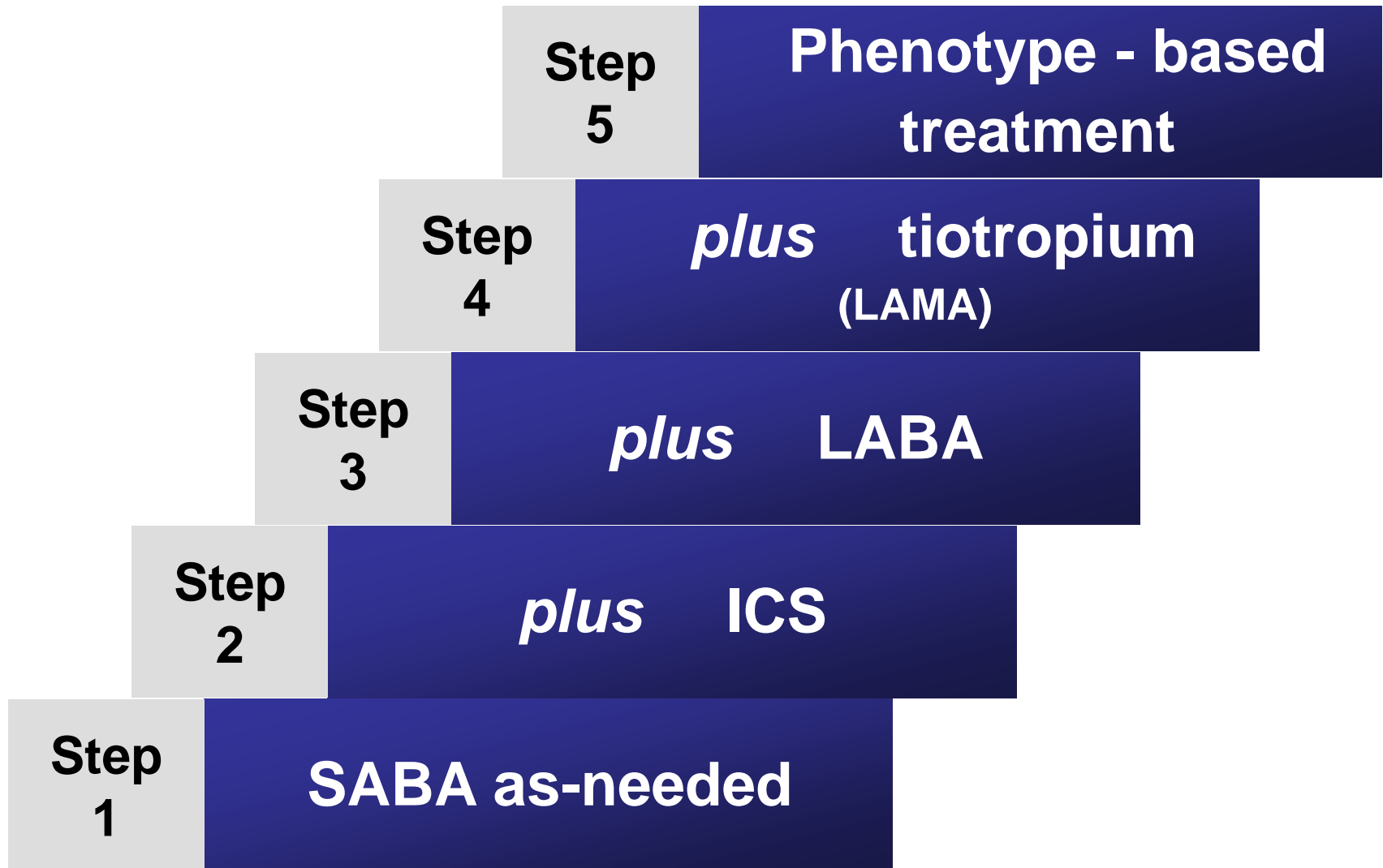
Add-on  
treatment  
Tiotropium  
Omalizumab  
Mepolizumab

Add-on low  
dose oral  
corticosteroid

ICS: inhaled corticosteroid, LABA: long-acting inhaled  $\beta_2$ -agonist, LTRA: leukotriene receptor antagonist



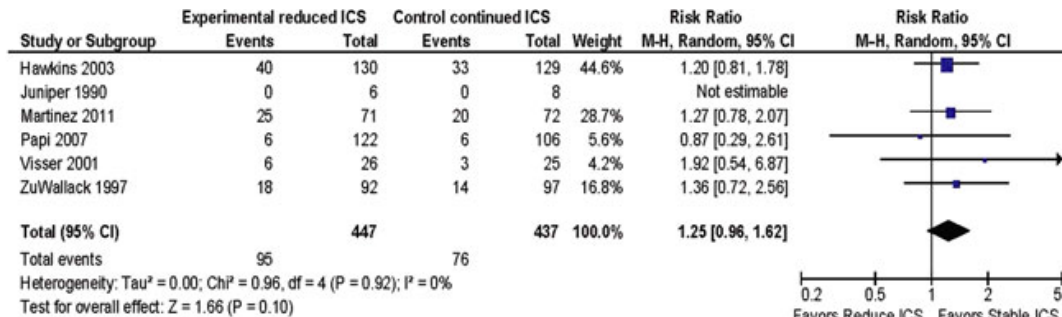
# Stepwise asthma treatment



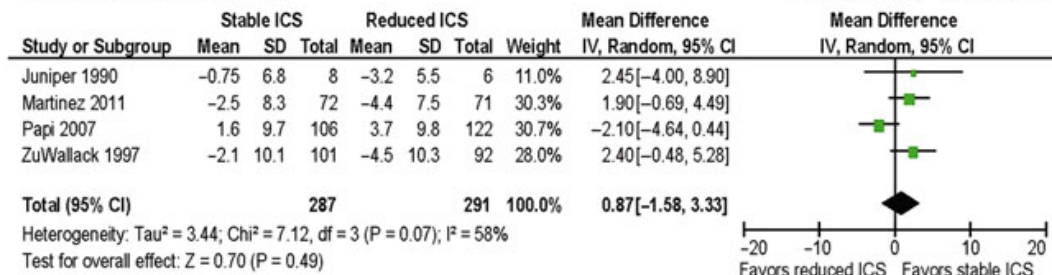
# What's new in GINA 2016 ?

- **Step 3**
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- **Step 4**
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- **Step 5**
  - Add-on tiotropium by mist inhaler for patients age  $\geq 12$  years with a history of exacerbations
  - Add-on omalizumab (anti-IgE) for severe allergic asthma
  - Add-on mepolizumab (anti-IL5) for severe eosinophilic asthma ( $\geq 12$  years)
  - Sputum-guided treatment, if available
- Low, medium and high ICS doses
  - Fluticasone furoate: 100  $\mu\text{g}$  (low dose); 200  $\mu\text{g}$  (high dose)
- **Stepping down ICS when asthma well-controlled**  
**now Evidence A**

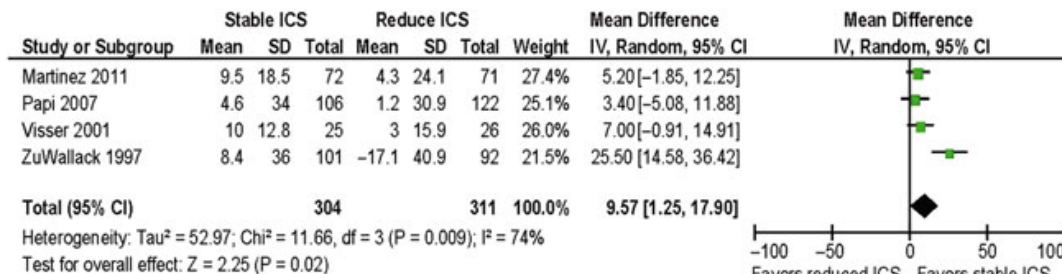
# Risk of reducing ICS in stable asthma



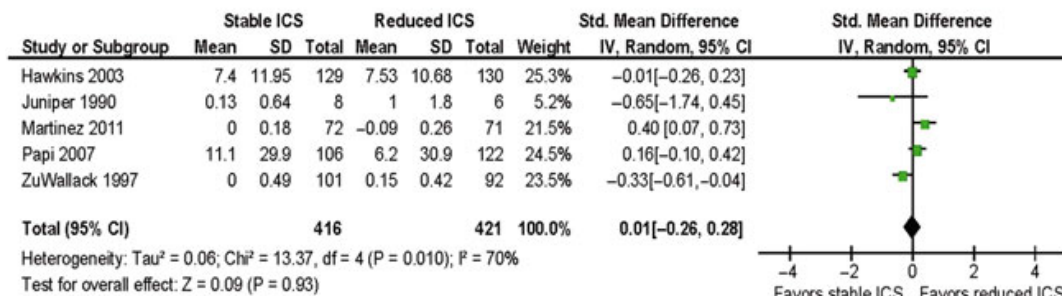
**Asthma  
exacerbation**



**FEV1 (%)**



**PEF  
(AM, L/min)**



**Symptoms**

# Safety of stepping down medications in patients with controlled asthma

4235 asthma patients  
US Medical Expenditure  
Panel Survey  
Years 2000 - 2010



## Eligibility for step-down

- no hospitalizations or ED visits for asthma
- no systemic corticosteroid and  $\leq 3$  rescue inhalers dispensed

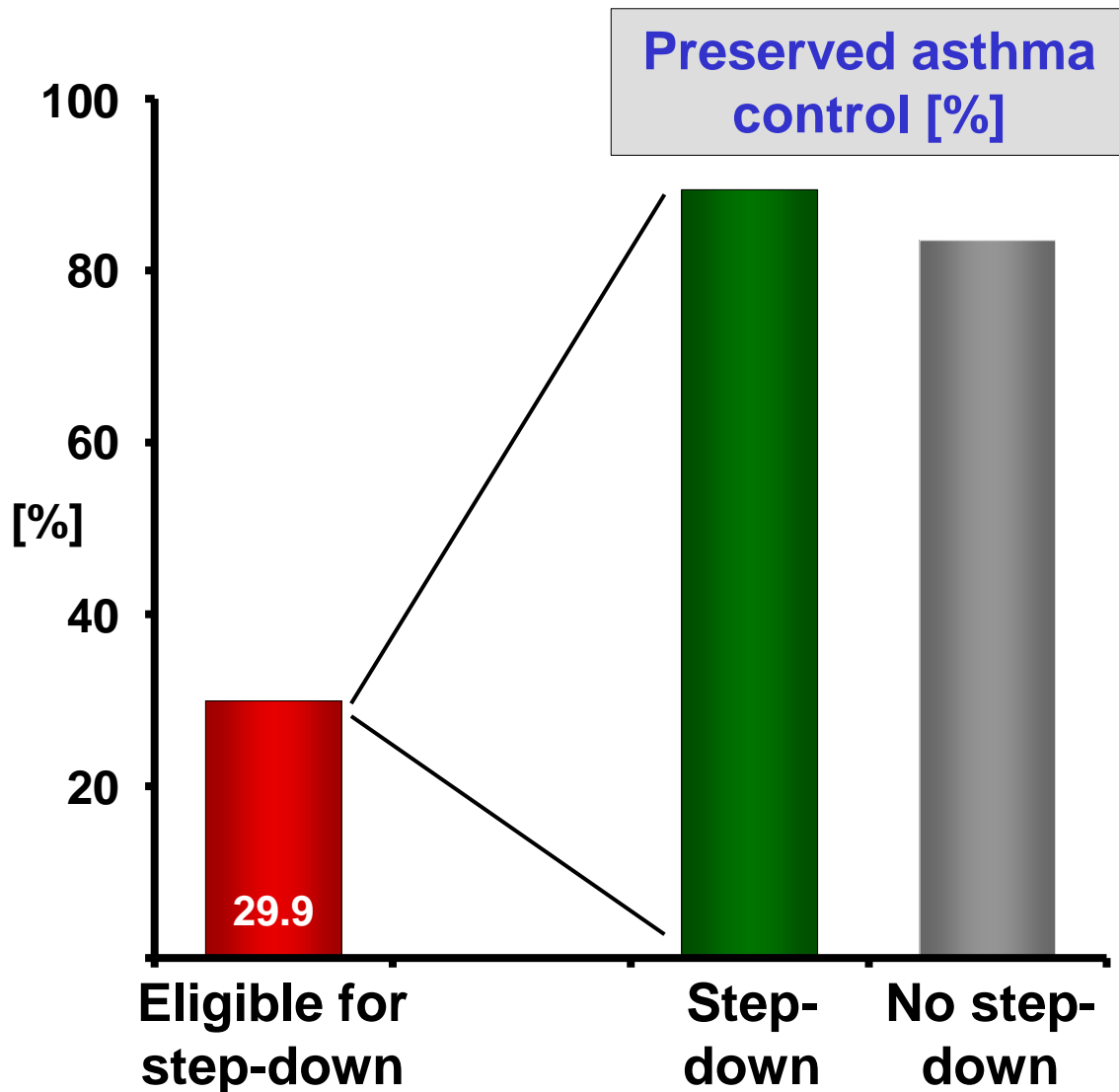
- Asthma control after step down versus unchanged treatment

# Safety of stepping down medications in patients with controlled asthma

4235 asthma patients  
US Medical Expenditure  
Panel Survey  
Years 2000 - 2010

• Eligibility for  
step-down?  
~ 14 months

- Asthma control after  
step-down versus  
unchanged treatment



# Asthma

- **What's new in GINA 2016 ?**
- **LABA safety**

# **Safety of salmeterol $\pm$ ICS in the treatment of asthma**

- **35 asthma deaths in 215 studies  
with 106 575 subjects**
  - **30 / 35 (86%) deaths in 2 clinical trials**
- **Risk of death from asthma in salmeterol patients  
not prescribed ICS 7.3 (OR, 95% CI 1.8 bis 29.4)**
- **No asthma deaths among 22 600 patients  
receiving salmeterol/fluticasone or ICS**

**No evidence that salmeterol/fluticasone therapy  
is associated with an increased asthma mortality**

# Serious asthma events with fluticasone plus salmeterol versus fluticasone alone

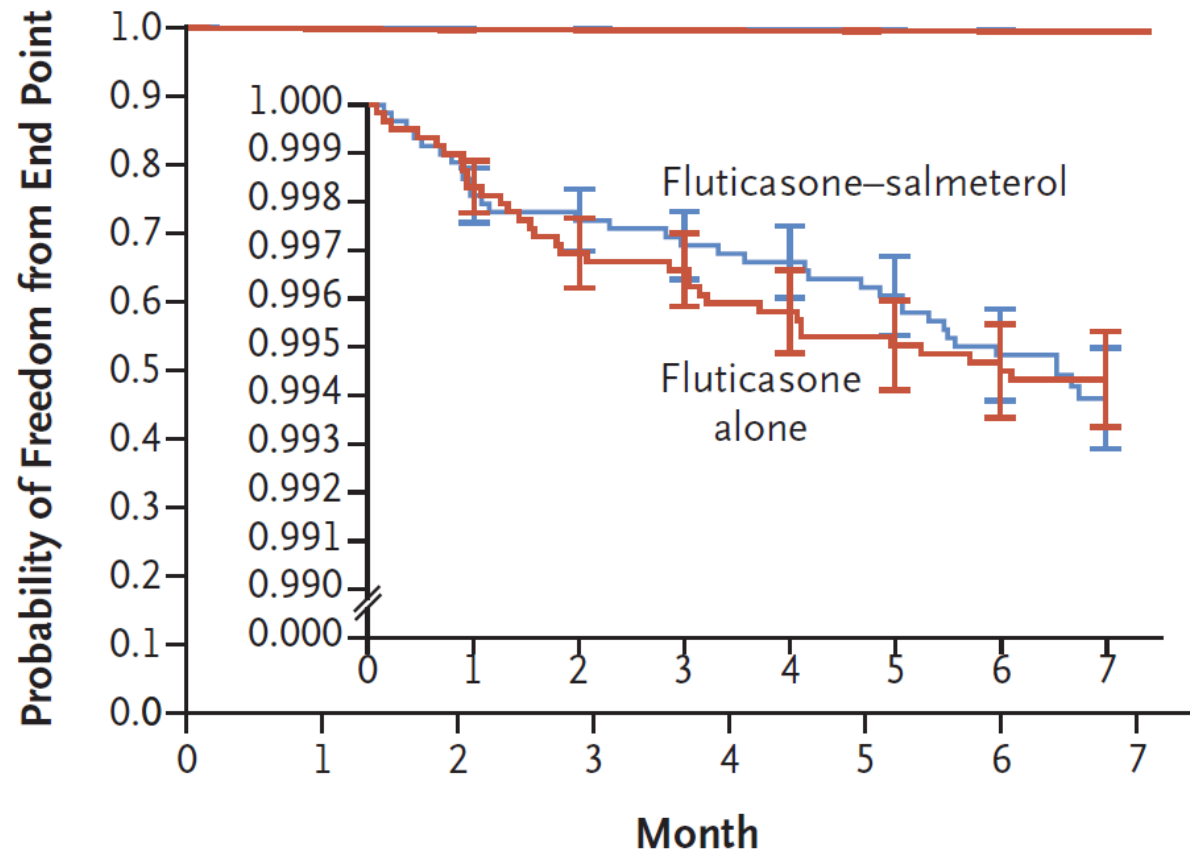
11679 asthma patients  
≥ 1 exacerbation  
in previous year

- Salm/FP bid  
50/125 µg, 50/250 µg or 50/500 µg
- Fluticasone bid  
125 µg, 250 µg or 500 µg

26 weeks

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

## First serious asthma-related event





# Serious asthma events with fluticasone plus salmeterol versus fluticasone alone

## Safety endpoints

Safety End Point	Fluticasone– Salmeterol (N = 5834)	Fluticasone Alone (N = 5845)
Composite safety end point — no. (%)	34 (<1)	33 (<1)
Asthma-related death	0	0
Asthma-related intubation	0	2 (<1)
Asthma-related hospitalization	34 (<1)	33 (<1)
Total no. of asthma-related hospitaliza- tions	36	36
Death from any cause — no. (%)†	3 (<1)	6 (<1)

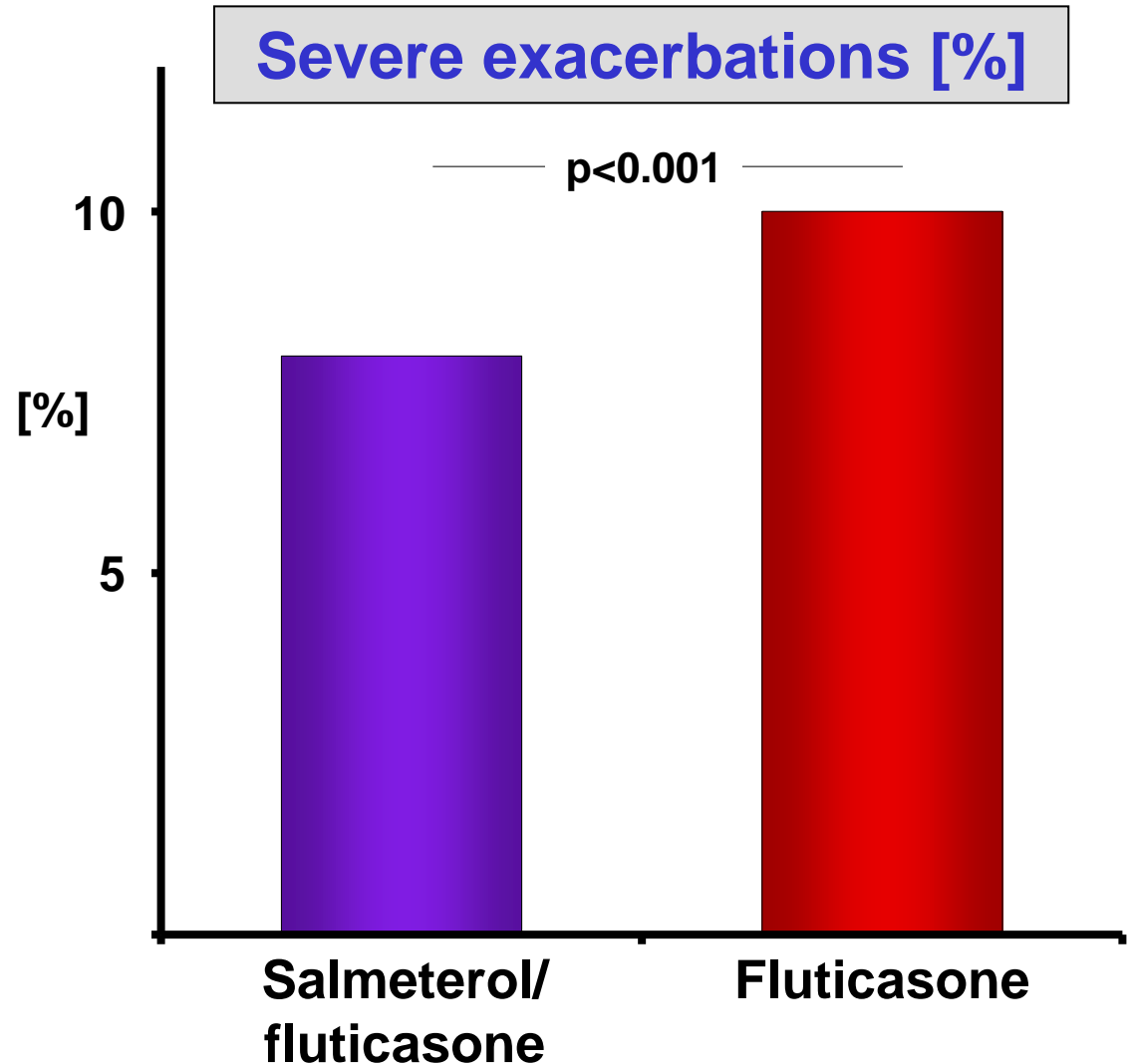
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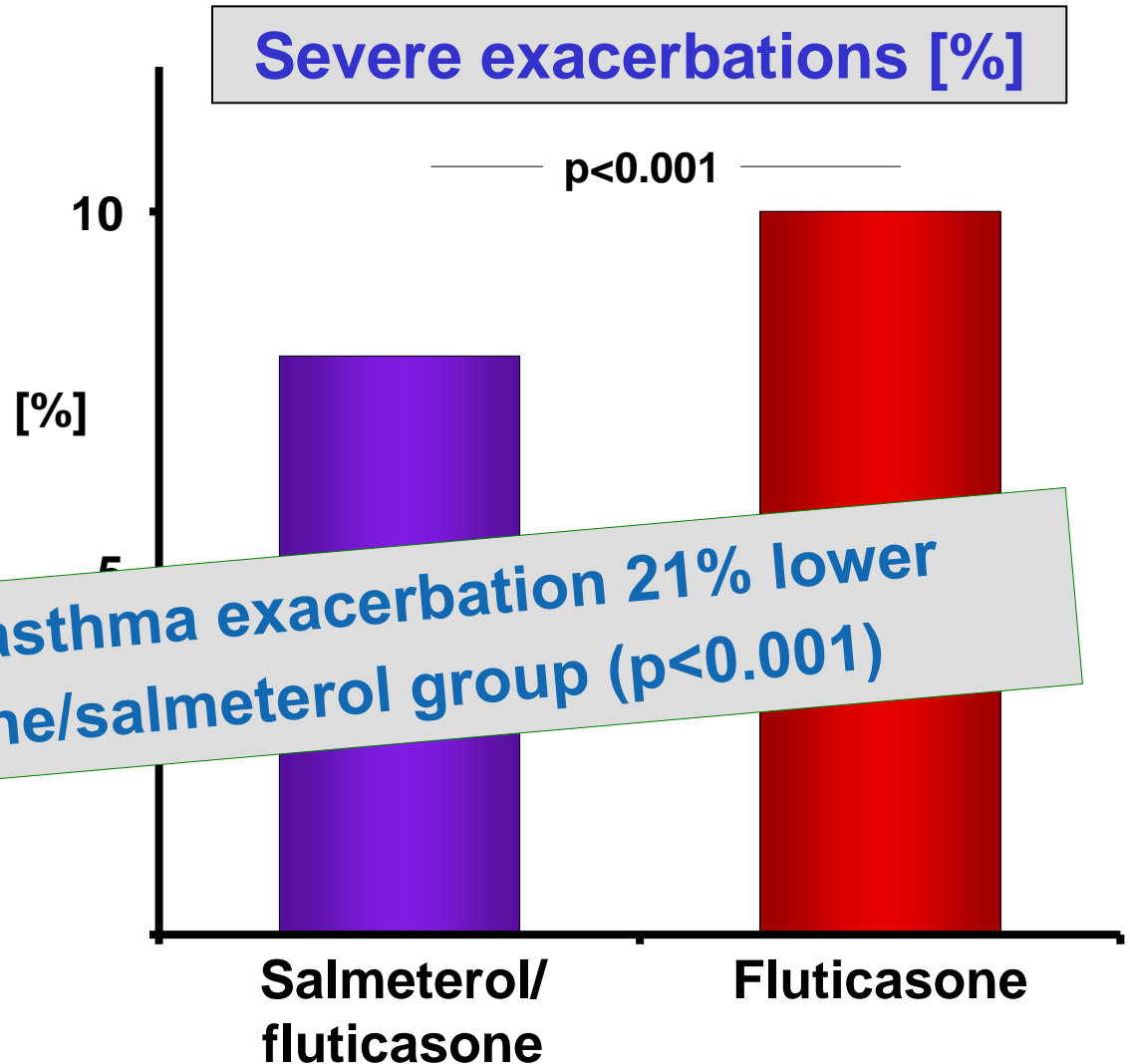
# Serious asthma events with fluticasone plus salmeterol versus fluticasone alone

11679 asthma patients  
≥ 1 exacerbation  
in previous year

- Salm/FP bid  
50/125 µg, 50/250 µg or 50/500 µg
- Fluticasone bid  
125 µg, 250 µg or 500 µg

• Risk of severe asthma exacerbation 21% lower  
in the fluticasone/salmeterol group ( $p < 0.001$ )

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



# Asthma

- **What's new in GINA 2016 ?**
- **LABA safety**
- **FeNO-driven strategies for asthma control**
- **Severe asthma**
  - **Definition**

# Definition of severe asthma

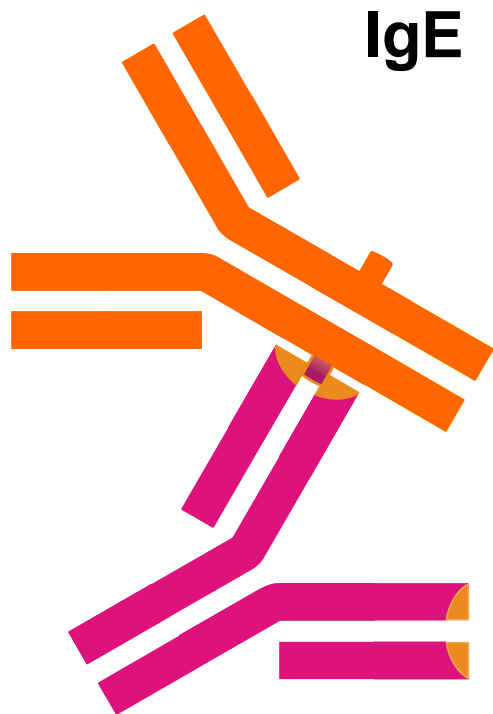
**Asthma which requires treatment with high dose ICS and LABA  $\pm$  systemic CS for  $\geq 50\%$  of the previous year to prevent it from becoming uncontrolled or is uncontrolled despite this therapy**

- **Poor symptom control:** ACQ  $> 1.5$ , ACT  $< 20$   
(or “not well controlled” by NAEPP/GINA guidelines)
- **Frequent severe exacerbations:**  $\geq 2$  bursts of systemic CS  
( $> 3$  days each) in the previous year
- **Serious exacerbations:**  $\geq 1$  hospitalisation, ICU stay  
or mechanical ventilation in the previous year
- **Airflow limitation:** FEV1  $< 80\%$  after appropriate  
bronchodilator withhold, FEV1/FVC  $<$  lower limit of normal
- **Controlled asthma that worsens on tapering of treatment**

# Asthma

- **What's new in GINA 2016 ?**
- **LABA safety**
- **FeNO-driven strategies for asthma control**
- **Severe asthma**
  - **Definition**
  - **Nebulized ICS**
  - **Biologics**

# Biologics in asthma



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

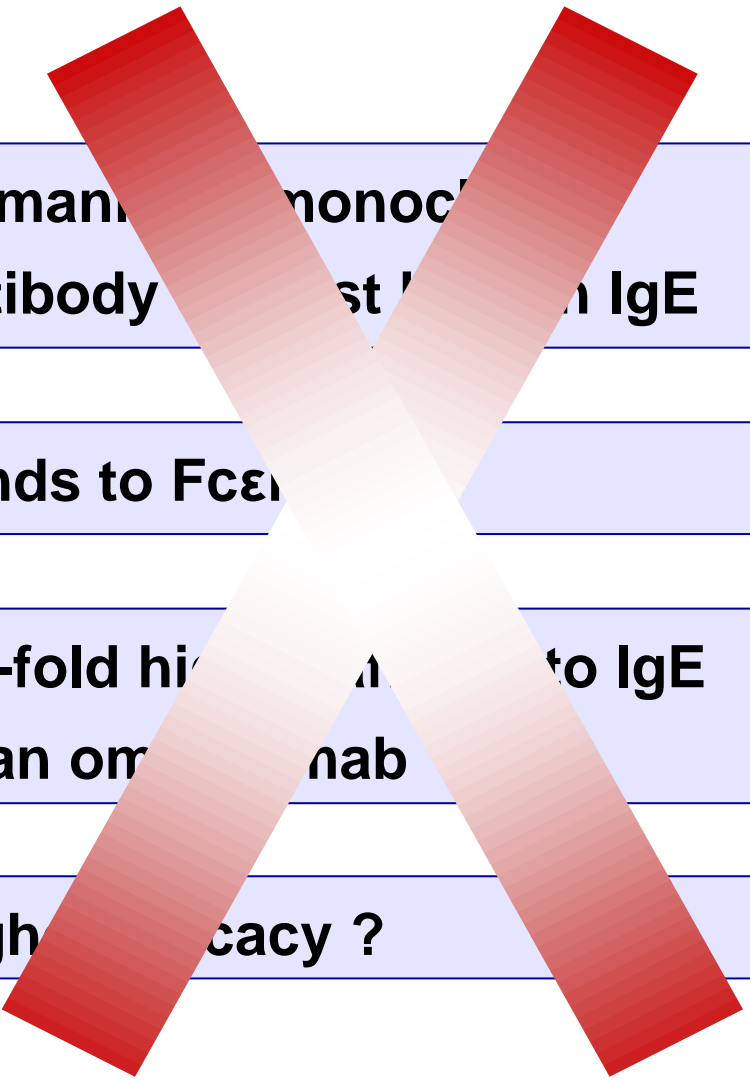
**Anti - IgE**

# QGE031 – the next anti - IgE

- Humanised, monoclonal antibody against human IgE
- Binds to FcεRI
- 50-fold higher affinity to IgE than omalizumab
- Higher efficacy ?



# QGE031 – the next anti - IgE

- 
- Human monoclonal antibody that binds to IgE
  - Binds to FcεR1
  - 50-fold higher affinity to IgE than omalizumab
  - High efficacy ?

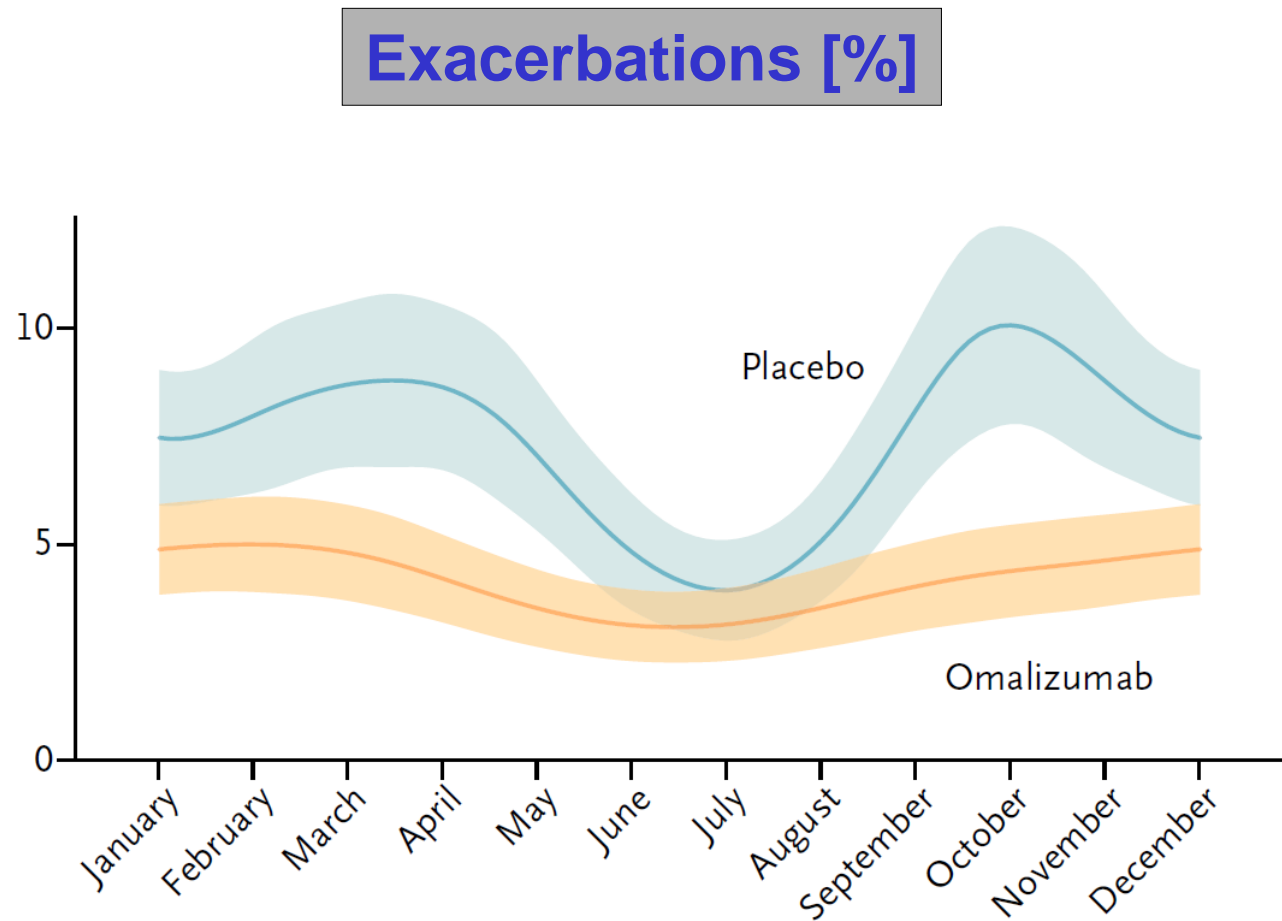
# Omalizumab for asthma in inner-city children

419 asthma patients  
10.8 (8-14) years  
FEV1 92±17%  
73% moderate or severe disease

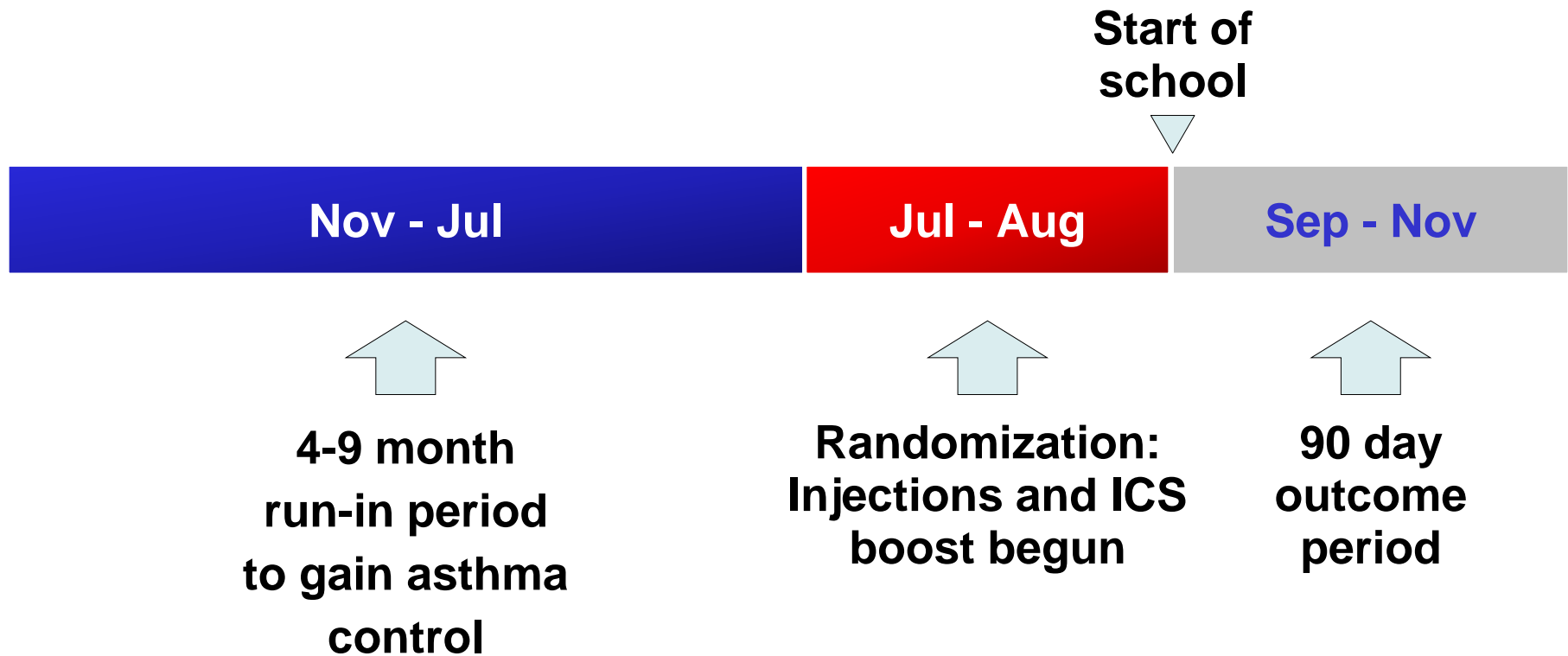
- Omalizumab  
75-375 mg  
q 2 - 4 weeks
- Placebo

60 weeks

- Exacerbations

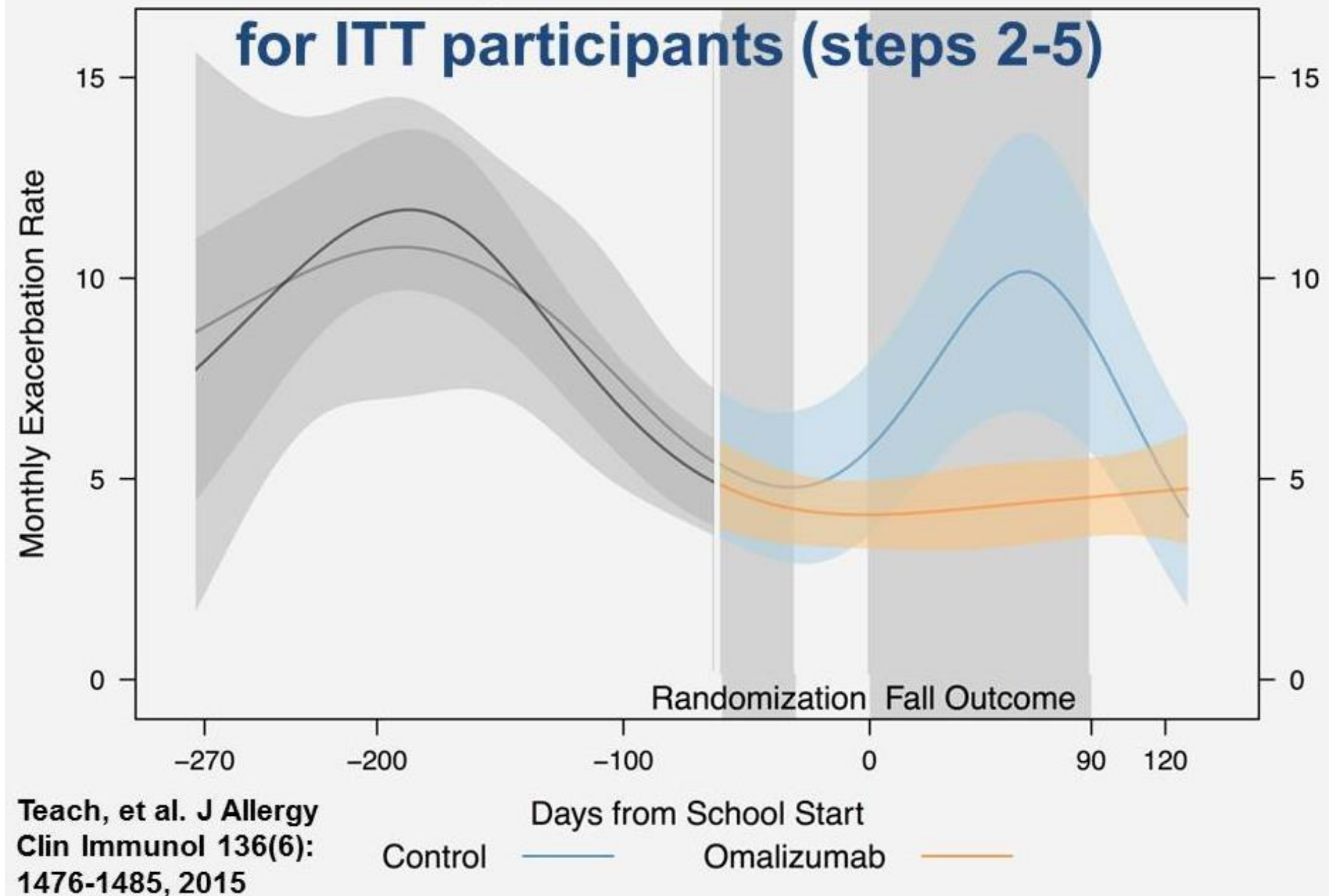


# **PR**eventative **O**malizumab or **S**tep-up Therapy for Severe Fall **E**xacerbations (PROSE)

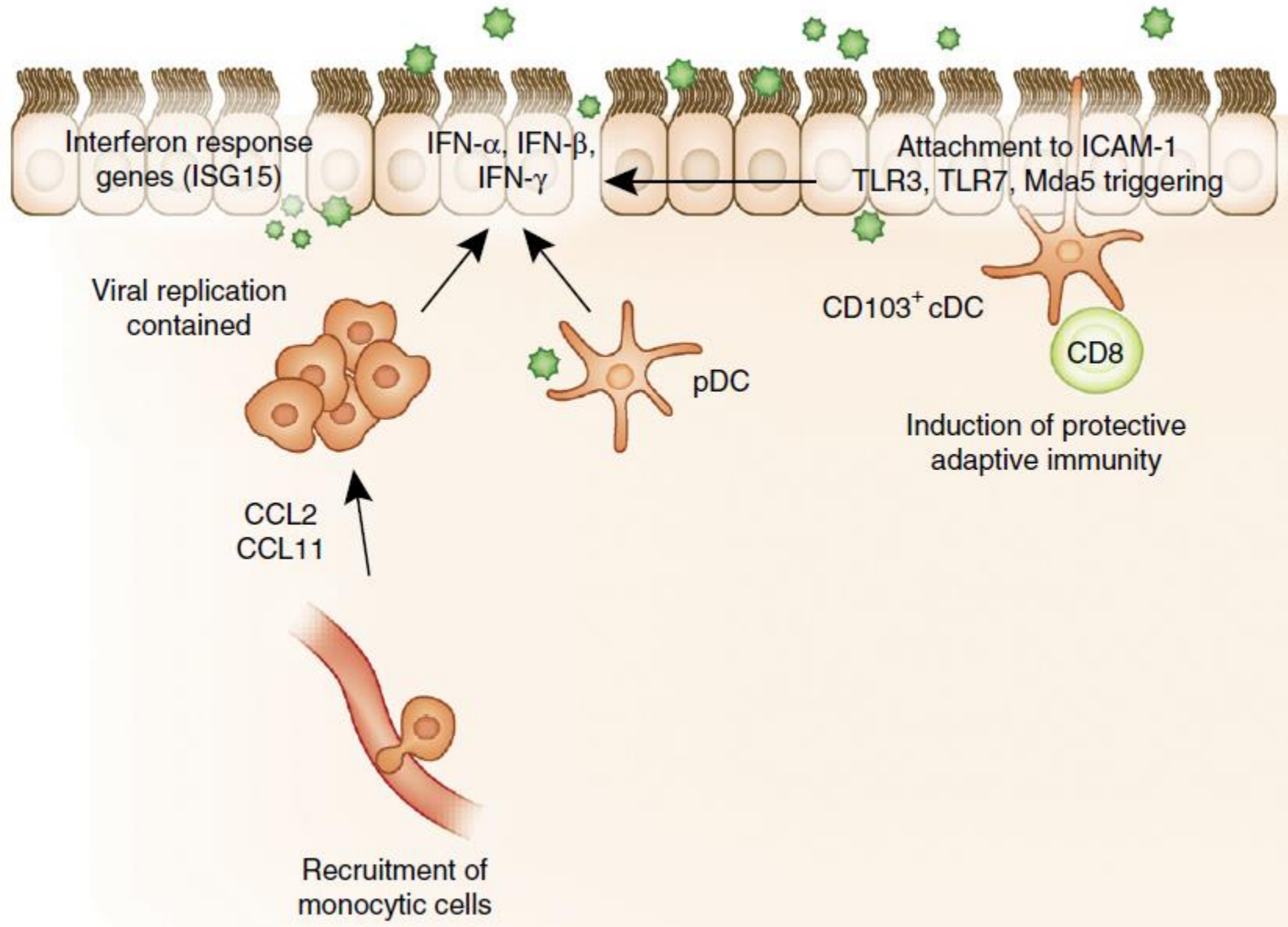


Teach, et al. J Allergy Clin Immunol 136(6):1476-1485, 2015

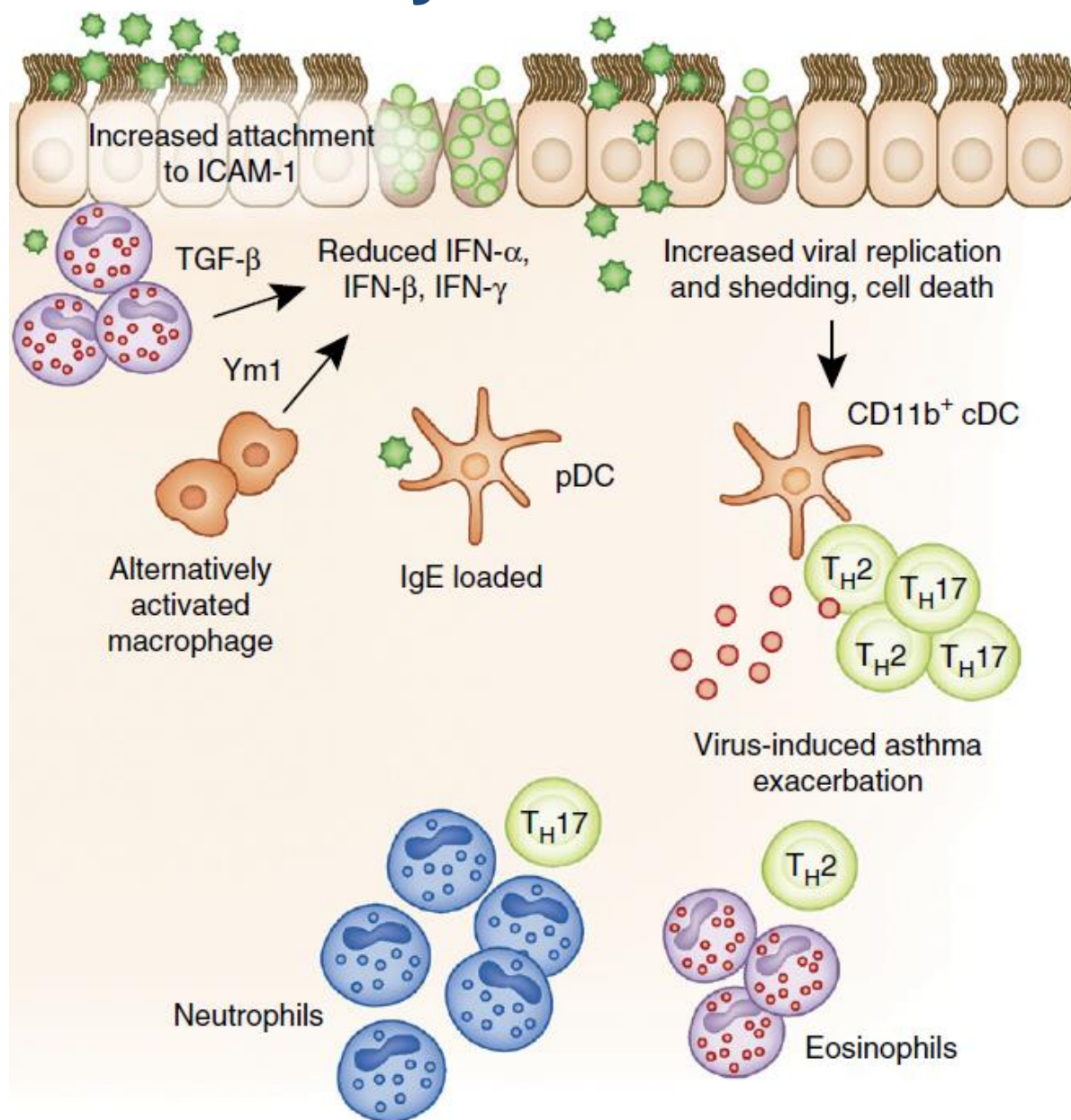
# Monthly exacerbation rates for ITT participants (steps 2-5)



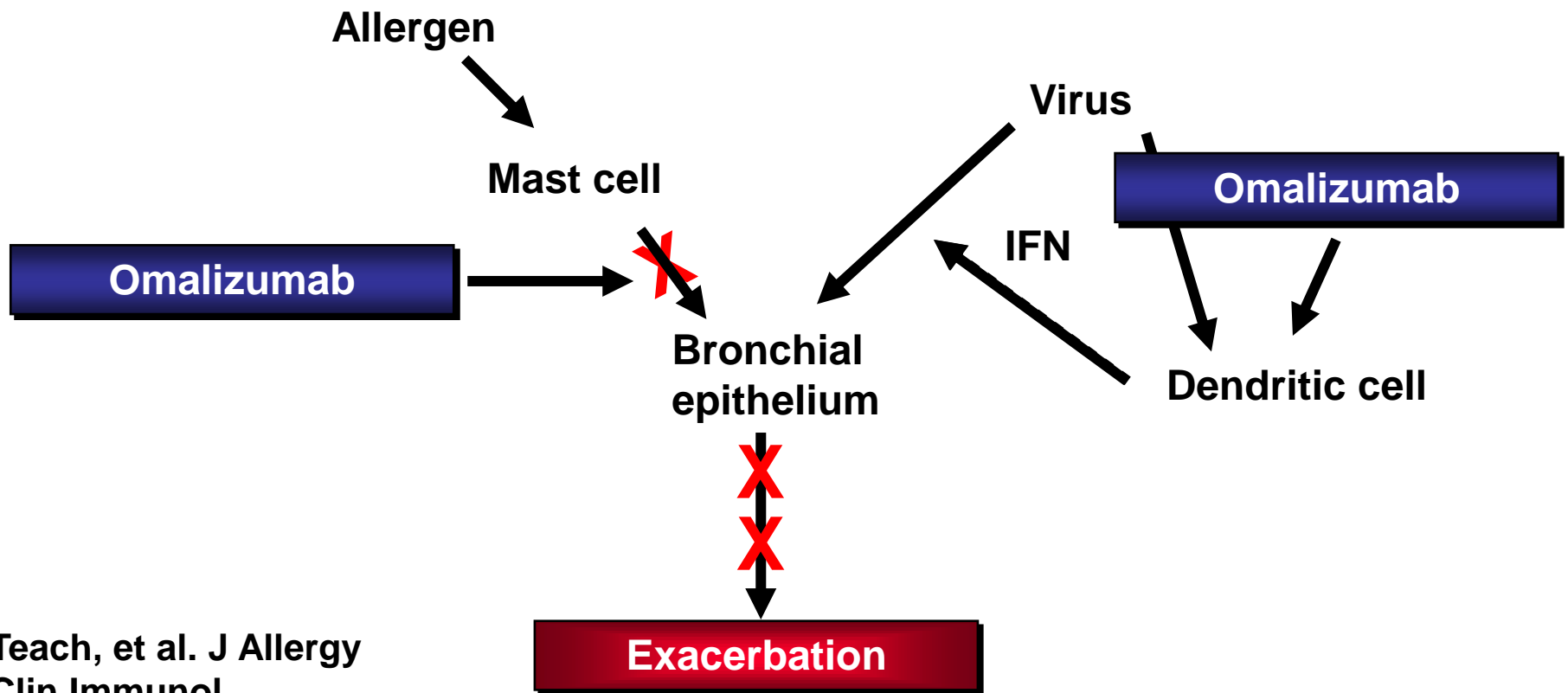
# Normal antiviral immunity to rhinovirus



# Antiviral immunity to rhinovirus in asthma



# IgE and allergic sensitization in virally induced asthma exacerbations



Teach, et al. J Allergy  
Clin Immunol  
136(6):1476-1485, 2015



# Biologics in asthma

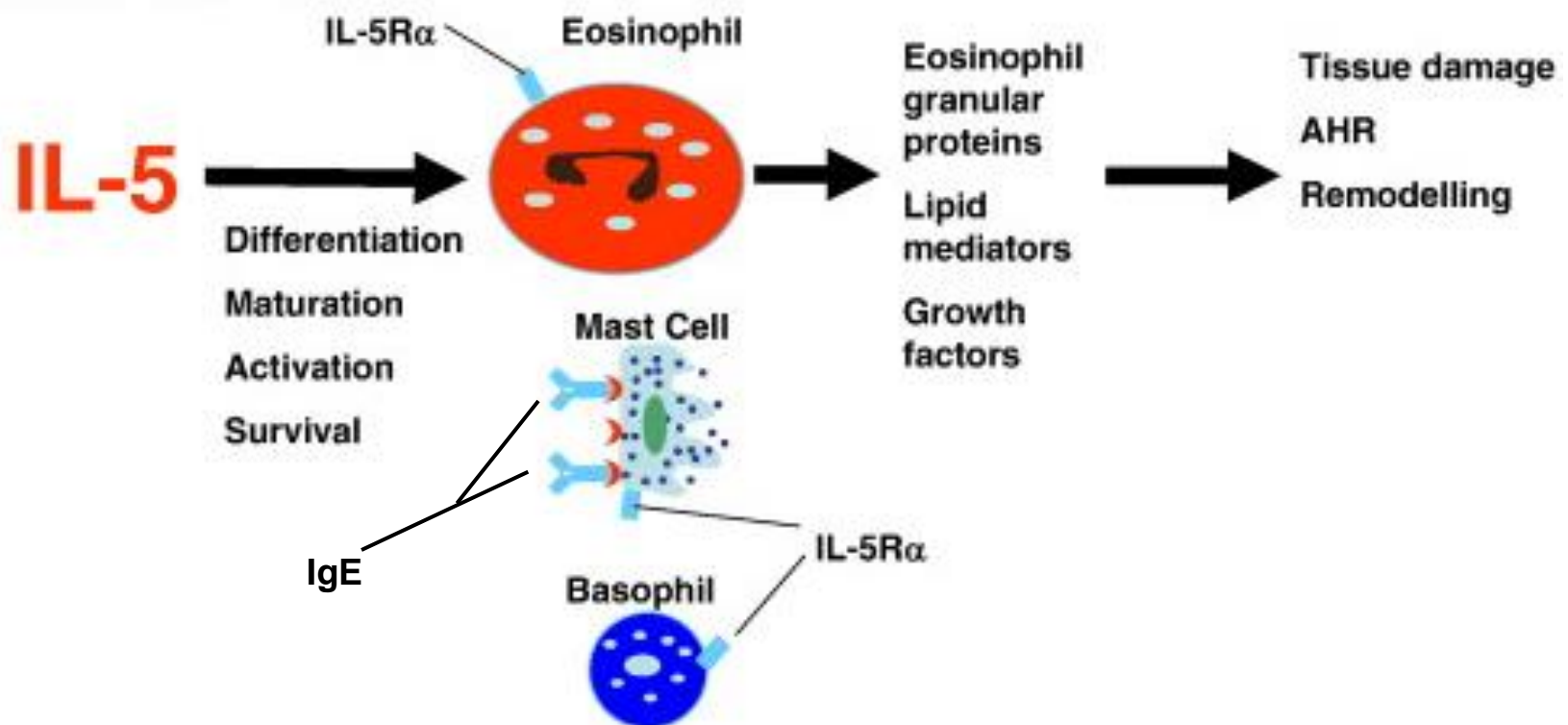
- **Anti - IgE**
  - **Omalizumab**

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



# IL-5 is a central modulator of eosinophilic asthma

- IL-5 is a 60-kDa glycoprotein produced by a large number of cell types including activated CD4<sup>+</sup> Th2 lymphocytes, eosinophils, basophils, CD34<sup>+</sup> progenitor cells, and NKT cells



# Blood eosinophils & asthma disease burden

130 248 UK  
asthma pts.  
12-80 years

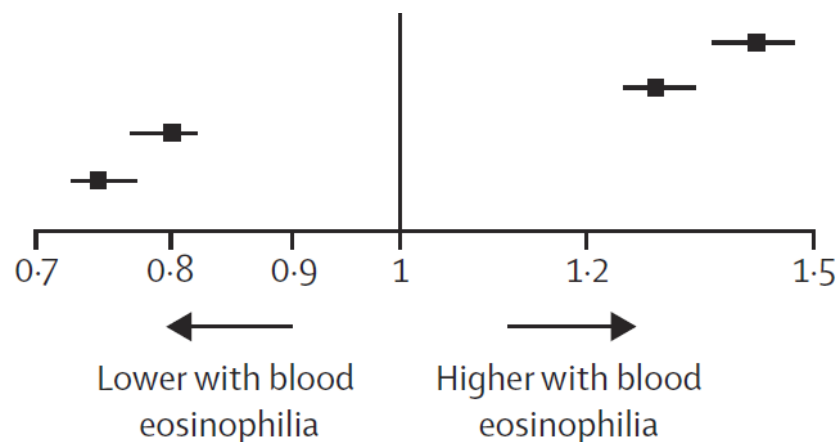
• Blood  
eosinophils  
> vs.  $\leq$  400 / $\mu$ L

- Severe exacerbations
- Acute respiratory events
- Asthma control

- 20 929 (16%) patients had  
> 400 blood eosinophils per  $\mu$ L

RR / OR with blood eosinophils > 400 /  $\mu$ L

Severe exacerbations  
Acute respiratory events  
Risk-domain asthma control  
Overall asthma control



Severe exacerbations	RR 1.42 (1.36–1.47)*
Acute respiratory events	RR 1.28 (1.24–1.33)*
Risk-domain asthma control	OR 0.78 (0.75–0.80)*
Overall asthma control	OR 0.74 (0.72–0.77)*

# Mepolizumab indication in the US

- **Mepolizumab for use with other asthma medicines for the maintenance treatment of asthma in patients age 12 years and older**
- **Patients who have a history of severe asthma exacerbations despite receiving their current asthma medicines**
- **Mepolizumab is administered once every four weeks by subcutaneous injection**

# Mepolizumab indication in the EU

- Mepolizumab ... as an add-on treatment for severe refractory eosinophilic asthma in adult patients for use with other asthma medicines
- Mepolizumab (100 mg) is administered once every four weeks by subcutaneous injection

• Patients & biomarkers ?

# **‘Eosinophilic’ asthma**

- **Late onset of disease**
- **Symptoms ↑, exacerbations ↑**
- **Eosinophilia in blood** ( $\pm$  sputum)
  - $\geq 300$  eosinophils/ $\mu$ l blood
  - $\geq 150$  eosinophils/ $\mu$ l blood if OCS therapy
- **$\pm$  FeNO > 50 ppb**
- **No *clinically relevant* allergy**
- **$\pm$  Nasal polyposis**
  - smell ↓ & taste ↓
- **Response to (oral) glucocorticoids and anti - IL-5**

# Severe asthma

Blood  
eosinophils (/μl)

## Non-allergic asthma

- Mepolizumab
- Omalizumab (POC\*)

## Allergic asthma with eosinophilia

- Mepolizumab
- Omalizumab

300

Type 2 low  
asthma

?

## Allergic asthma

- Omalizumab

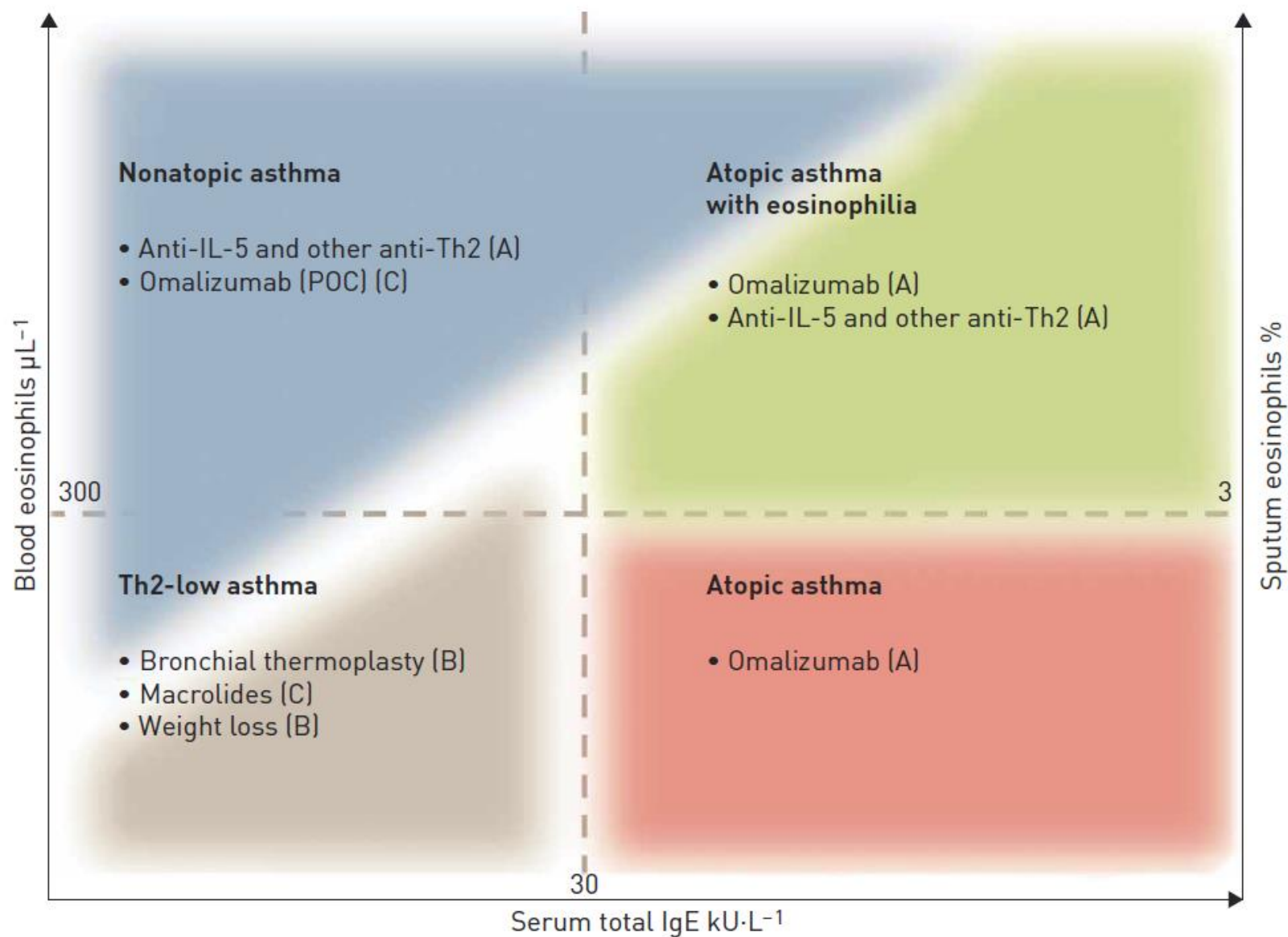
\*off label

30

Total serum IgE (KU/l)

1500

# Severe asthma



# Morbidity associated with oral corticosteroids in severe asthma

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

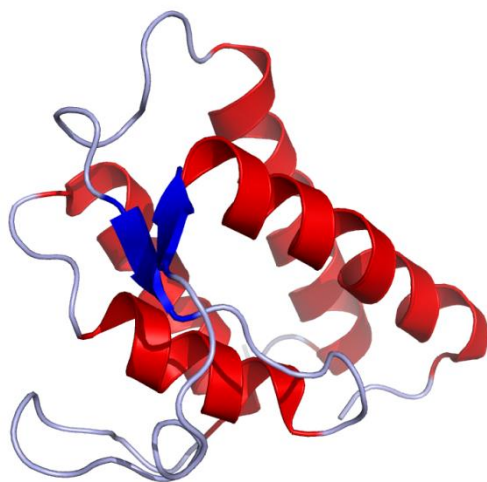
## Compared with mild/moderate asthma

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

Lefebvre, et al. JACI 2016  
Choo & Pavord. Thorax 2016



# Biologics in asthma



Human  
interleukin-13

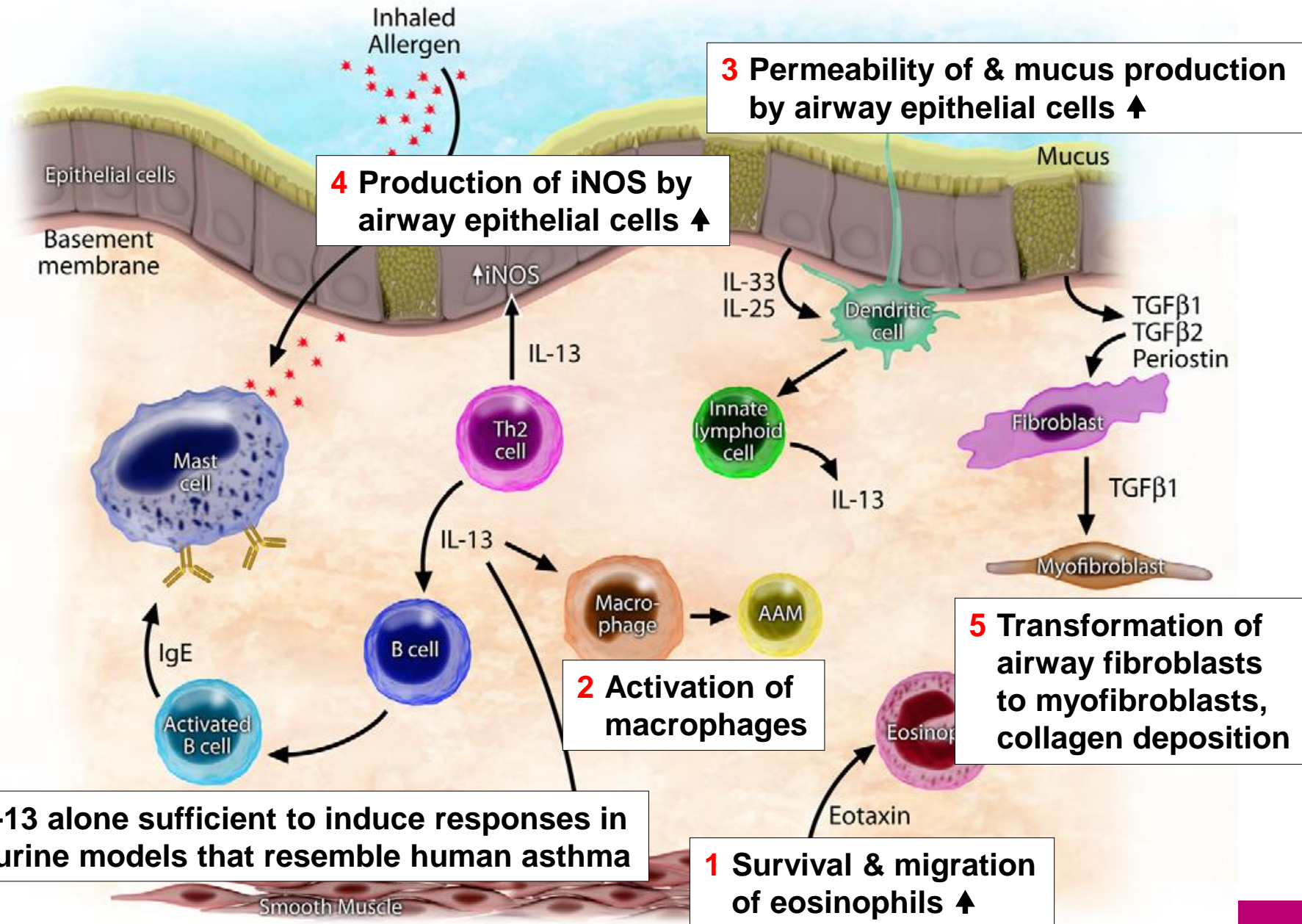
- **Anti - IgE**
  - Omalizumab
- **Anti - IL-5**
  - Mepolizumab
  - Reslizumab
  - Benralizumab (anti-IL-5 - receptor)
- **Anti - IL-13**
  - Lebrikizumab
  - Tralokinumab

Roche Media Release  
LAVOLTA, 29.2. 2016

<http://www.meretciel.com/goods.php?id=201>

# IL-13 and the asthmatic airway

Ingram & Kraft JACI 2012 130(4):829-842, 2012



# Efficacy of tralokinumab in patients with severe uncontrolled asthma

452 asthma patients  
MD-HD ICS + LABA  
≥ 2 exacerbations  
in previous year

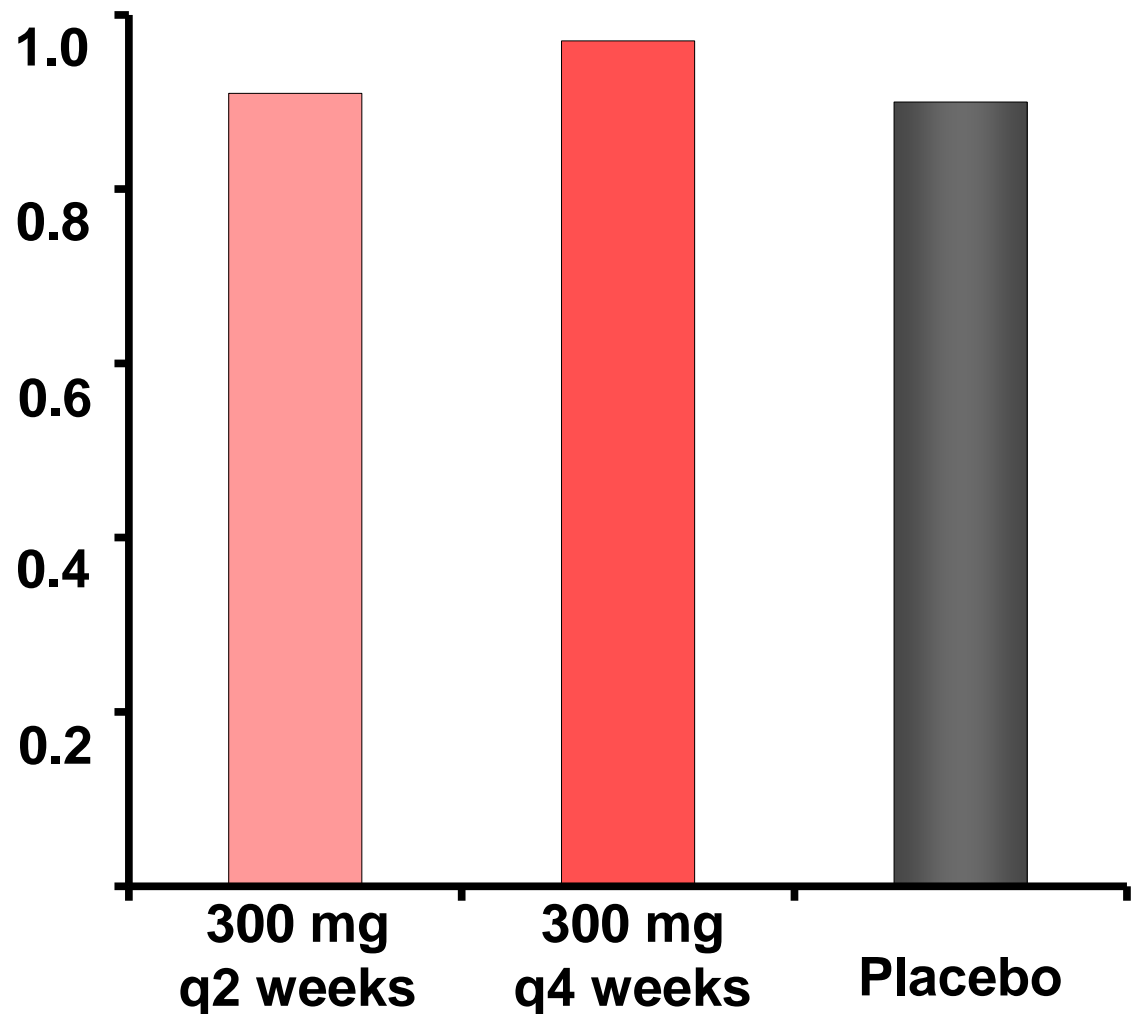
- Tralokinumab  
300 mg s.c. every  
2 weeks, or every  
2 weeks for 12 weeks  
then every 4 weeks
- Placebo

52 weeks

- Exacerbation rate

Brightling, et al. Lancet Respir  
Med 3(9):692-701, 2015

Exacerbations / year



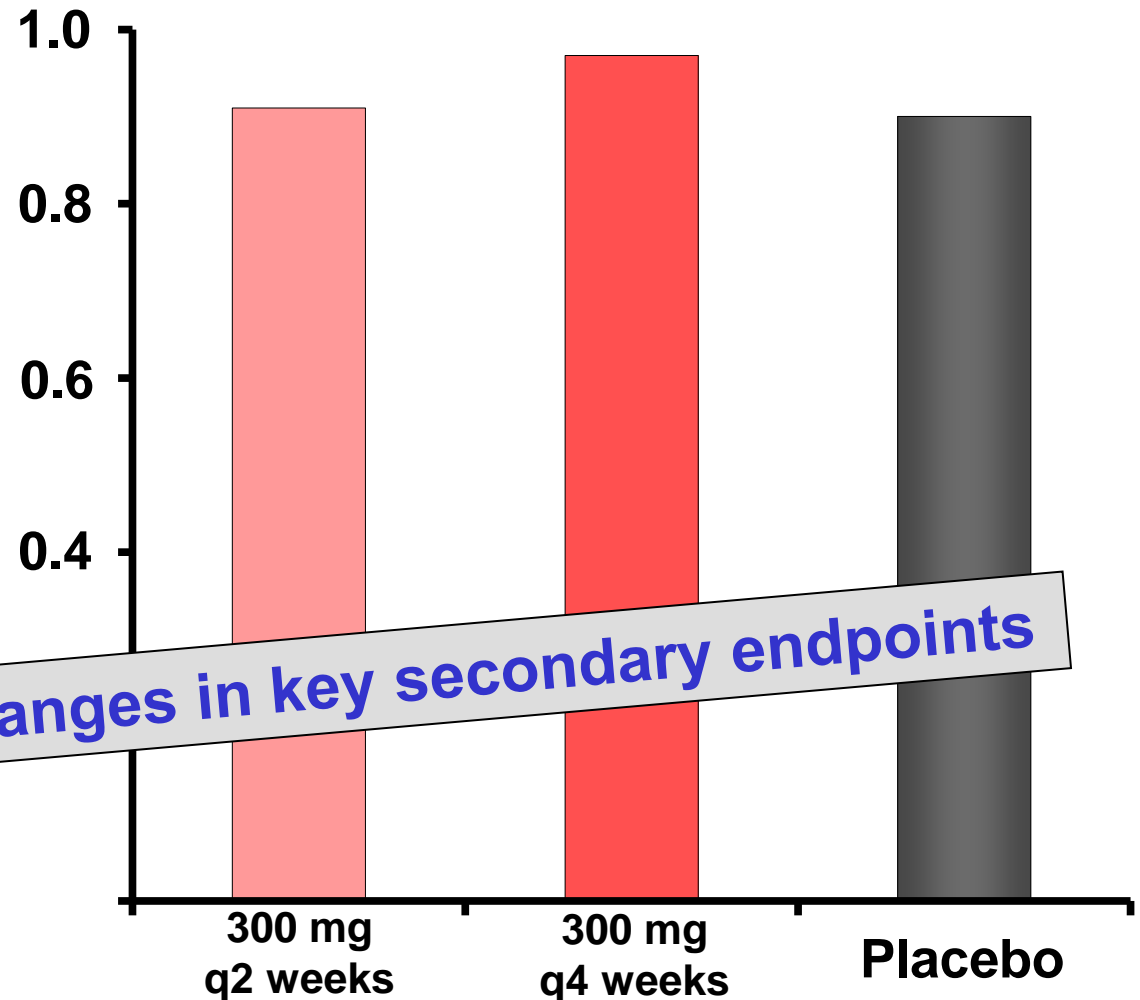
# Efficacy of tralokinumab in patients with severe uncontrolled asthma

452 asthma patients  
MD-HD ICS + LABA  
≥ 2 exacerbations  
in previous year

Exacerbations / year

- Tralokinumab  
300 mg s.c. every  
2 weeks, or every  
2 weeks for 12 weeks  
then every 4 weeks
- Placebo

52 weeks



• No significant changes in key secondary endpoints

- Exacerbation rate

Brightling, et al. Lancet Respir  
Med 3(9):692-701, 2015

# Efficacy of tralokinumab in patients with severe uncontrolled asthma

452 asthma patients  
MD-HD ICS + LABA  
≥ 2 exacerbations  
in previous year

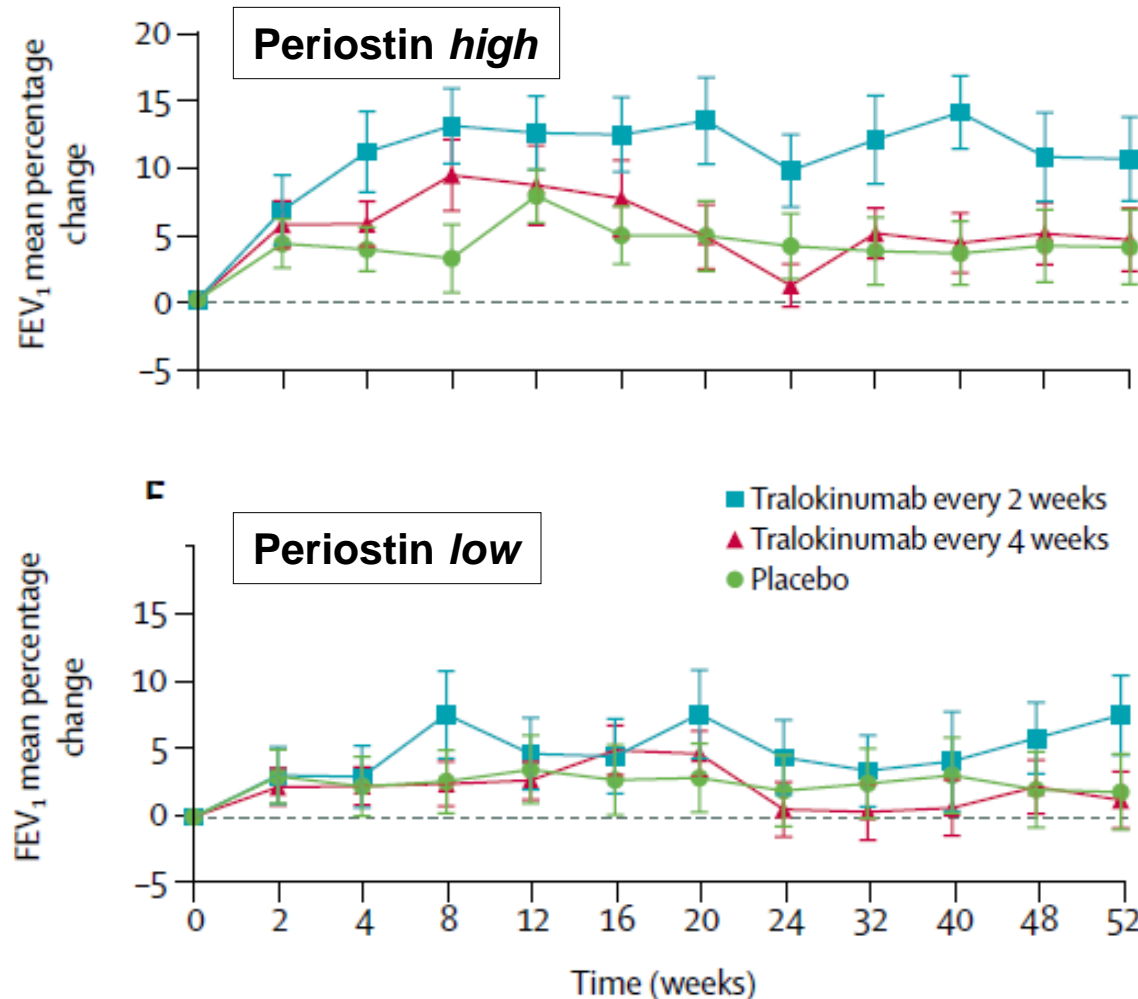
- Tralokinumab 300 mg s.c. every 2 weeks, or every 2 weeks for 12 weeks then every 4 weeks
- Placebo

52 weeks

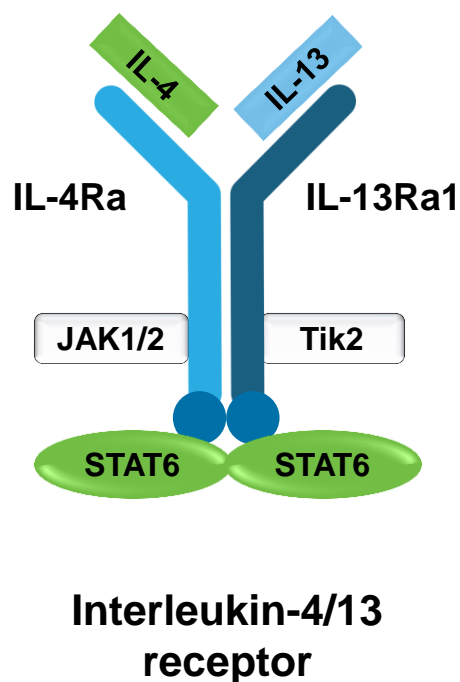
•  $\Delta$  FEV<sub>1</sub>

Brightling, et al. Lancet Respir Med 3(9):692-701, 2015

$\Delta$  FEV<sub>1</sub> [ml]



# Biologics in asthma



- **Anti - IgE**

- Omalizumab

- **Anti - IL-5**

- Mepolizumab

- Reslizumab

- Benralizumab (anti-IL-5 - receptor)

- **Anti - IL-13**

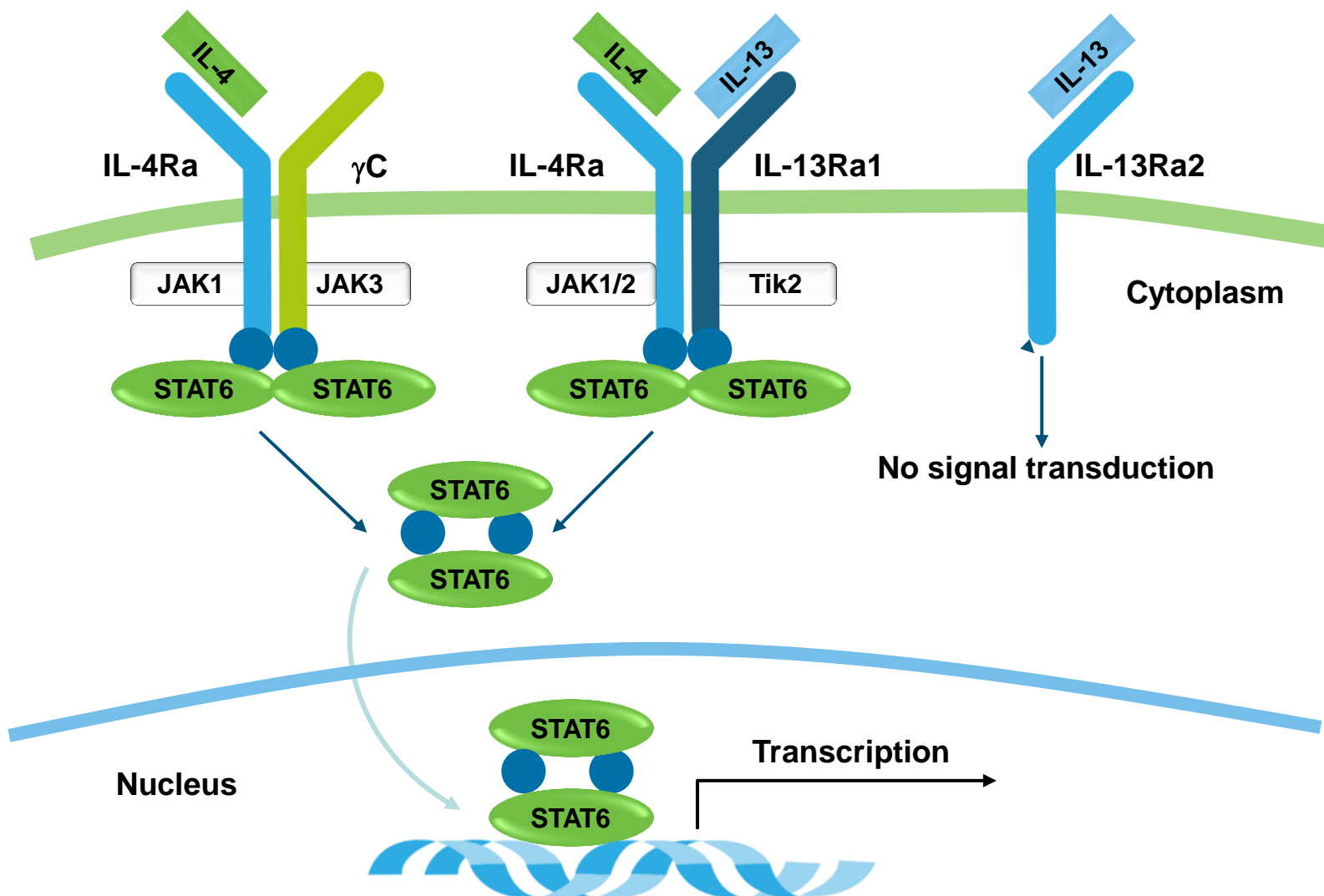
- Lebrikizumab

- Tralokinumab

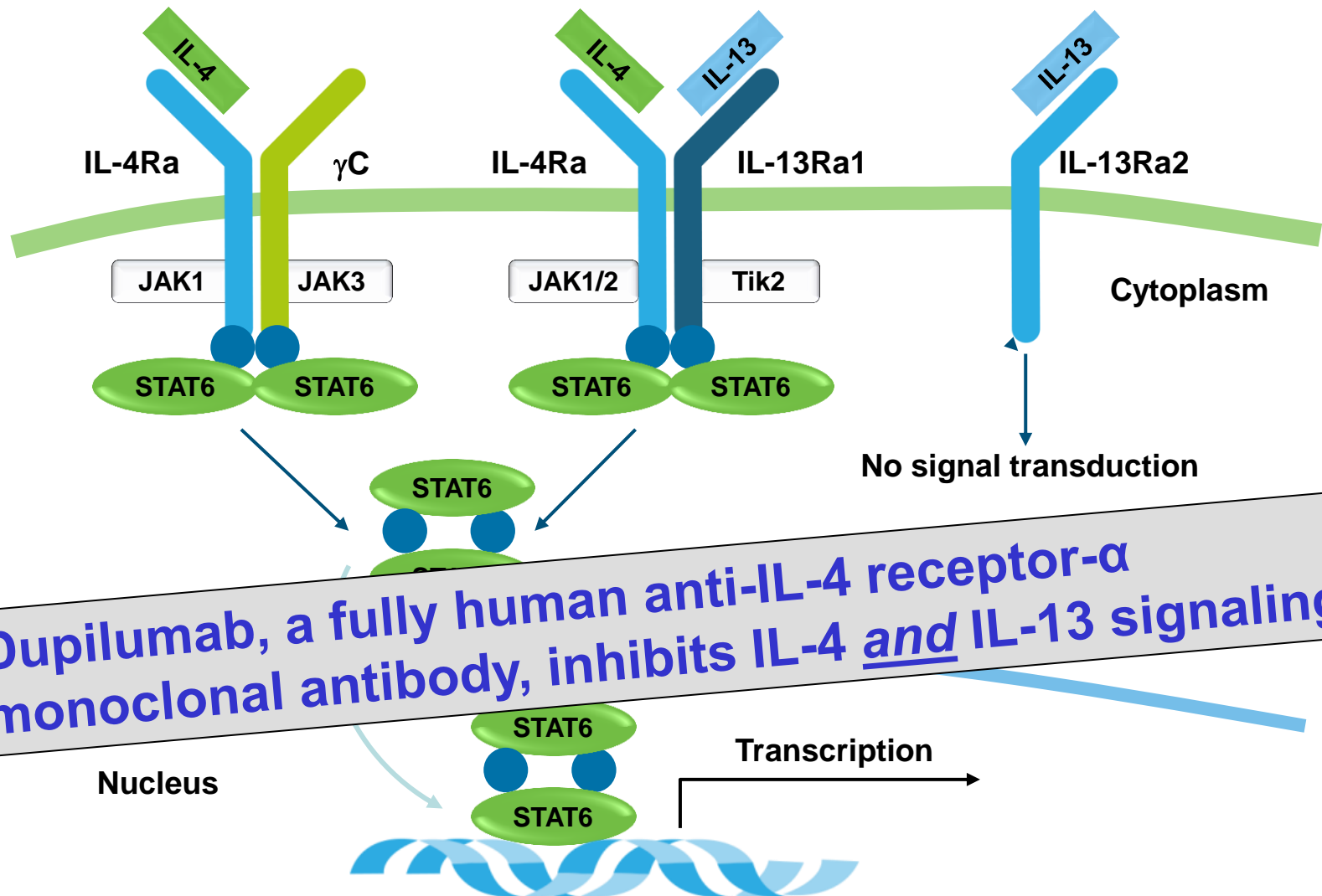
- **Anti - IL-4 / IL-13**

- Dupilumab (anti-IL-4/IL-13 - receptor)

# IL-4 and IL-13 receptors



# IL-4 and IL-13 receptors





# Dupilumab in uncontrolled asthma despite ICS + LABA

776 asthma patients  
MD-HD ICS + LABA  
≥ 1 exacerbations  
in previous year

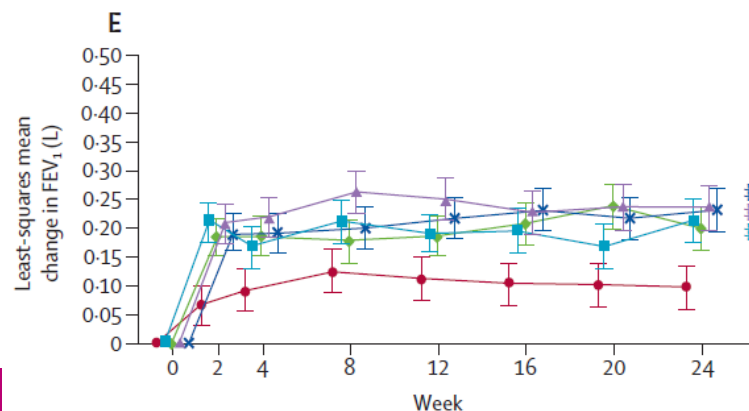
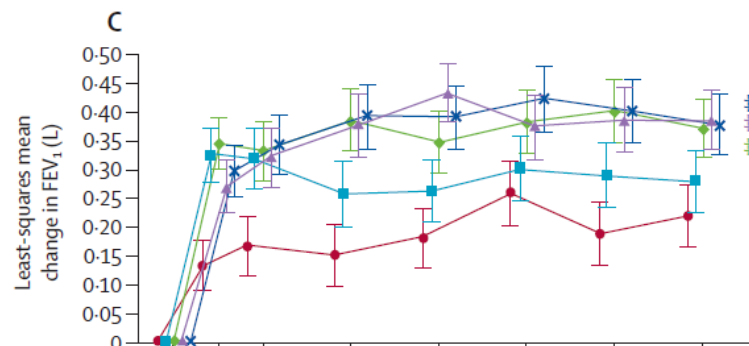
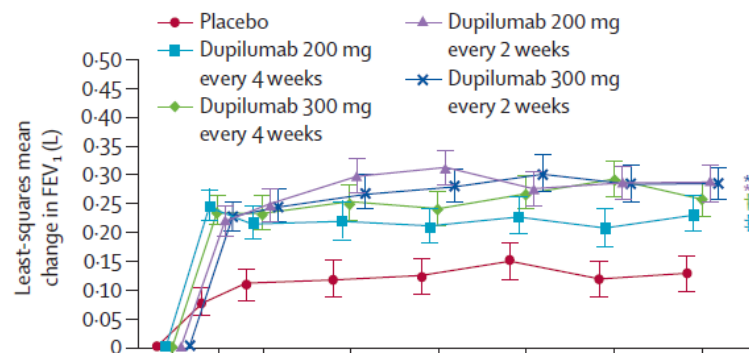
- Dupilumab 200 or 300 mg s.c. every 2 or 4 weeks
- Placebo

24 weeks

- Lung function
- Exacerbations

Wenzel, et al. Lancet 2016  
[epub ahead of print]

Pneumo Update Europe 2016



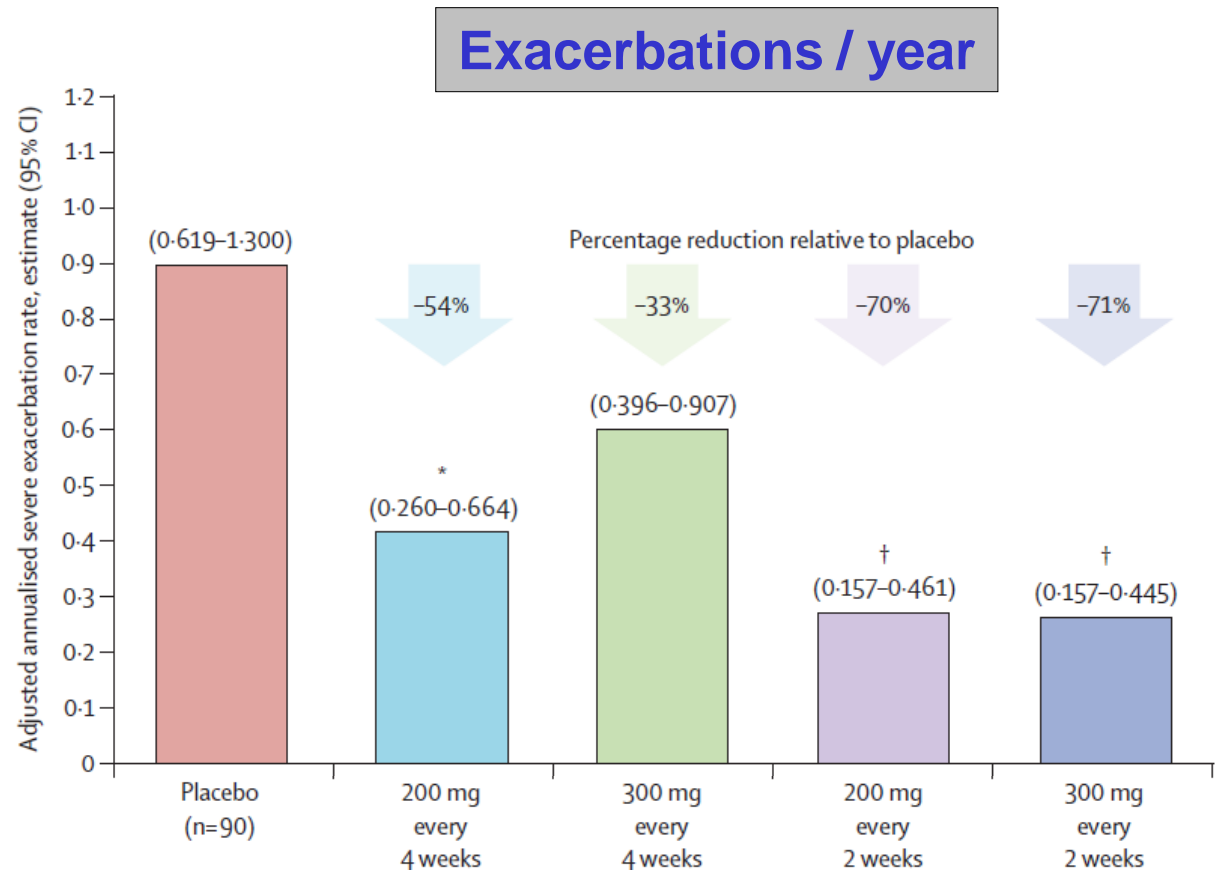
# Dupilumab in uncontrolled asthma despite ICS + LABA

776 asthma patients  
MD-HD ICS + LABA  
≥ 1 exacerbations  
in previous year

- Dupilumab  
200 or 300 mg s.c.  
every 2 or 4 weeks
- Placebo

24 weeks

- Lung function
- Exacerbations



# Effect of dupilumab on nasal polyps

60 patients with nasal polyposis refractory to intranasal corticosteroids

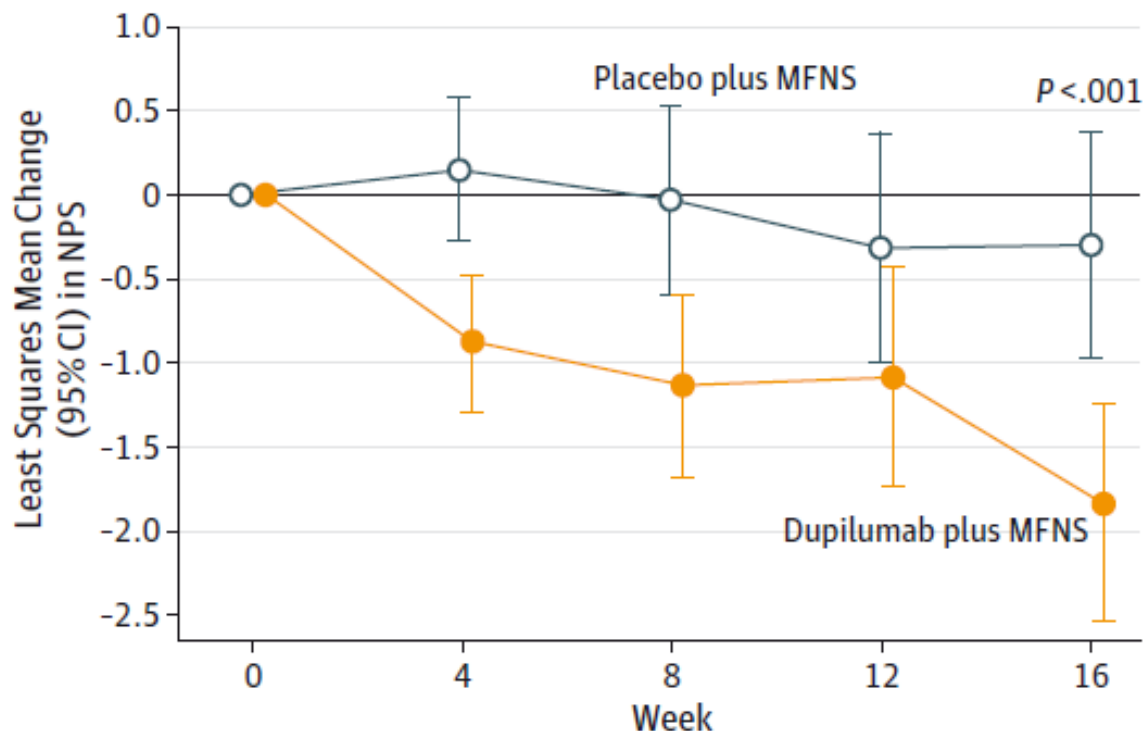
Mometasone nasal spray *plus*

- Dupilumab 300 mg s.c. weekly
- Placebo

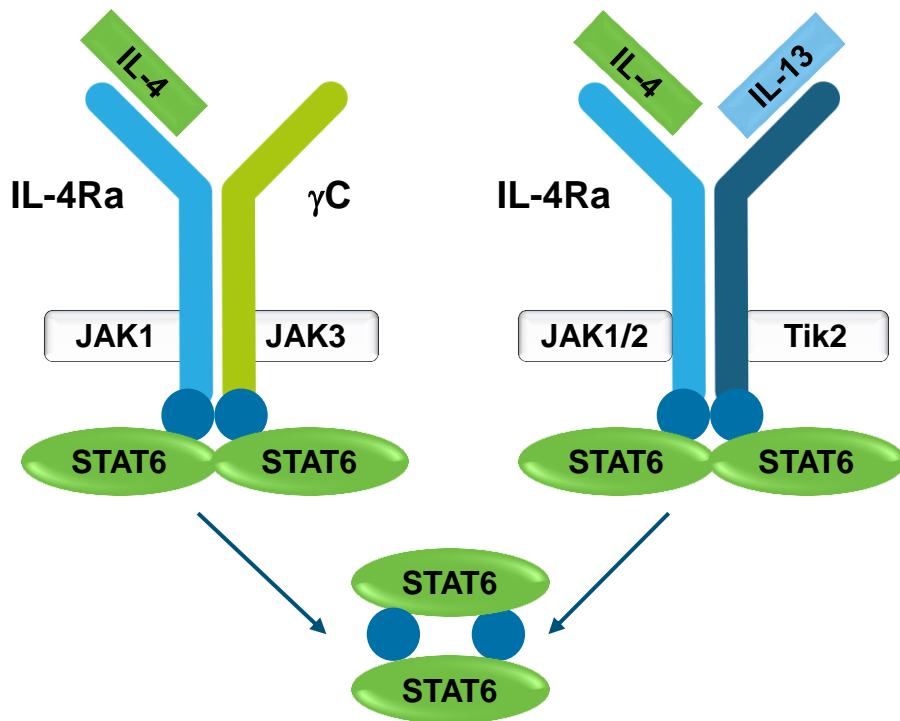
16 weeks

- Endoscopic nasal polyp score

## Endoscopic nasal polyp score



# 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

# Biologics in 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**
  - **AMG 157**

# Asthma

- **What's new in GINA 2016 ?**
- **LABA safety**
- **FeNO-driven strategies for asthma control**
- **Severe asthma**
  - **Definition**
  - **Nebulized ICS**
  - **Biologics**

# References

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