ΒΡΟΓΧΙΚΟ ΑΣΘΜΑ

ΠΕΤΡΟΣ ΜΠΑΚΑΚΟΣ
Αναπλ. Καθηγητής Πνευμονολογίας ΕΚΠΑ
ΝΝΘΑ «Σωτηρία»
14-3-2018

GINA 2017

The burden of asthma

GINA Global Strategy for Asthma Management and Prevention 2015

This slide set is restricted for academic and educational purposes only. Use of the slide set, or of individual slides, for commercial or promotional purposes requires approval from GINA.

© Global Initiative for Asthma

GINA Global Strategy for Asthma Management and Prevention

- Not a guideline, but a practical approach to managing asthma in clinical practice
- A global strategy, relevant to both low and high resource countries
- Evidence-based and clinically-oriented
- Provides clinical tools and measurable outcomes

Εκτίμηση του άσθματος

1. Έλεγχος άσθματος – 2 domains
   - Εκτίμησε τον έλεγχο των συμπτωμάτων τις 4 τελευταίες εβδομάδες
   - Εκτίμησε παράγοντες κινδύνου για φτωχές εκβάσεις, συμπεριλαμβανομένης της χαμηλής πνευμονικής λειτουργίας
2. Ζητήματα θεραπείας
   - Έλεγξε την τεχνική εισπνοών και τη συμμόρφωση
   - Ρώτησε για ανεπιθύμητες ενέργειες
   - Έχει ο ασθενής ένα γραπτό πλάνο δράσης?
   - Ποιά είναι η στάση του ασθενούς και οι στόχοι της θεραπείας για το άσθμα του?
3. Συνοσηρότητες
   - Σκέψου για ρινίτιδα/παραρινοκολπίτιδα, παχυσαρκία, ΓΟΠ, ΣΑΥ, κατάθλιψη, αγχώδεις διαταραχές
   - Οι συνοσηρότητες συμβάλουν στα συμπτώματα και την φτωχή ποιότητα ζωής των ασθματικών

GINA assessment of symptom control

A. Symptom control

In the past 4 weeks, has the patient had:		Level of asthma symptom control: Well-controlled	Partly controlled	Uncontrolled
• Daytime asthma symptoms more than twice a week?	Yes ❑ No ❑	None of these	1-2 of these	3-4 of these
• Any night waking due to asthma?	Yes ❑ No ❑			
• Reliever needed for symptoms* more than twice a week?	Yes ❑ No ❑			
• Any activity limitation due to asthma?	Yes ❑ No ❑			

B. Risk factors for poor asthma outcomes

- Assess risk factors at diagnosis and periodically
- Measure FEV_1 at start of treatment, after 3 to 6 months of treatment to record the patient's personal best, then periodically for ongoing risk assessment

ASSESS PATIENT'S RISKS FOR:

- Exacerbations
- Fixed airflow limitation
- Medication side-effects

© Global Initiative for Asthma

Assessment of risk factors for poor asthma outcomes

Independent* risk factors for exacerbations include:

- Ever intubated for asthma
- Uncontrolled asthma symptoms
- Having ≥1 exacerbation in last 12 months
- Low FEV_1 (measure lung function at start of treatment, at 3-6 months to assess personal best, and periodically thereafter)
- Incorrect inhaler technique and/or poor adherence
- Smoking
- Elevated FeNO in adults with allergic asthma
- Obesity, pregnancy, blood eosinophilia

UPDATED 2017

* Independent of the level of symptom control

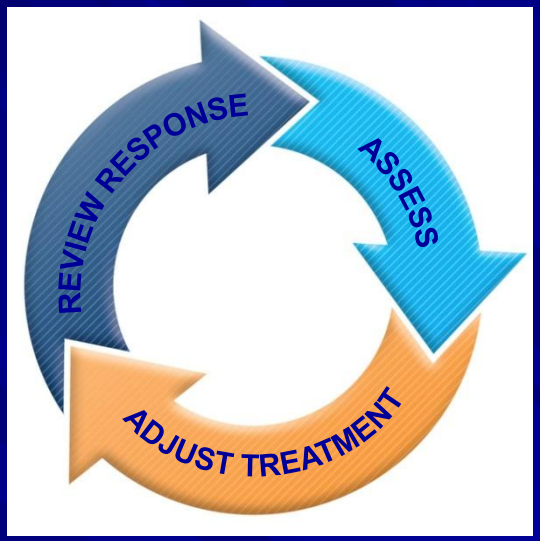
© Global Initiative for Asthma

ΒΑΡΥΤΗΤΑ ΑΣΘΜΑΤΟΣ

- Πώς?
  - Η βαρύτητα εκτιμάται **αναδρομικά** από το επίπεδο θεραπείας που απαιτείται για να ελέγχονται τα συμπτώματα και να αποφεύγονται οι παροξύνσεις
- Πότε?
  - Μετά από αρκετούς μήνες θεραπείας με ρυθμιστικά φάρμακα
  - Η βαρύτητα δεν είναι στατική – μεταβάλλεται στο χρόνο ή καθώς διαφορετικές θεραπείες γίνονται διαθέσιμες
- Κατηγορίες βαρύτητας άσθματος
  - *Mild asthma:* well-controlled with Steps 1 or 2 (as-needed SABA or low dose ICS)
  - *Moderate asthma:* well-controlled with Step 3 (low-dose ICS/LABA)
  - *Severe asthma:* requires Step 4/5 (moderate or high dose ICS/LABA ± add-on), or remains uncontrolled despite this treatment

Treating to control symptoms and minimize risk

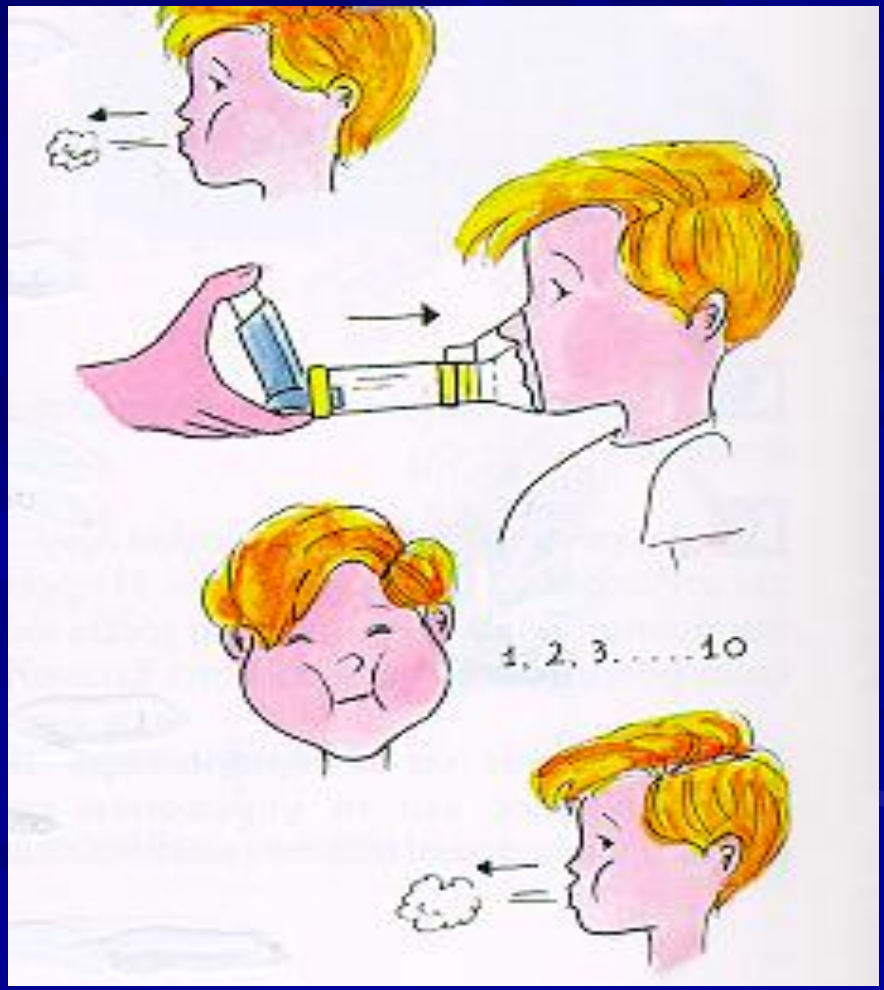
- Establish a patient-doctor partnership
- Manage asthma in a continuous cycle:
  - **Assess**
  - **Adjust** treatment (pharmacological and non-pharmacological)
  - **Review** the response
- Teach and reinforce essential skills
  - Inhaler skills
  - Adherence
  - Guided self-management education
    - Written asthma action plan
    - Self-monitoring
    - Regular medical review



Εκπαίδευση στην τεχνική εισπνοών

Εκπαίδευσε τον ασθενή

Επανέλαβε και έλεγξε σε <u>κάθε επίσκεψη</u>



Example Of Contents Of An Action Plan To Maintain Asthma Control

Your Regular Treatment:

1. Each day take _____
2. Before exercise, take _____

WHEN TO INCREASE TREATMENT

Assess your level of Asthma Control

In the past week have you had:

Daytime asthma symptoms more than 2 times ?	No	Yes
Activity or exercise limited by asthma?	No	Yes
Waking at night because of asthma?	No	Yes
The need to use your [rescue medication] more than 2 times?	No	Yes
If you are monitoring peak flow, peak flow less than_____?	No	Yes

If you answered YES to three or more of these questions, your asthma is uncontrolled and you may need to step up your treatment.

HOW TO INCREASE TREATMENT

STEP-UP your treatment as follows and assess improvement every day:

_____ [Write in next treatment step here]

Maintain this treatment for _____ days [specify number]

WHEN TO CALL THE DOCTOR/CLINIC.

Call your doctor/clinic: _____ [provide phone numbers]

If you don't respond in _____ days [specify number]

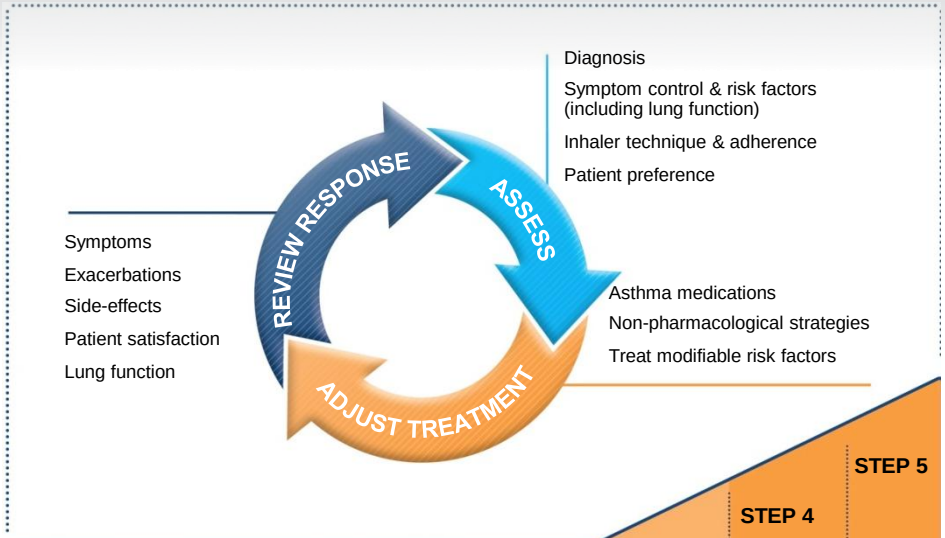
_____ [optional lines for additional instruction]

EMERGENCY/SEVERE LOSS OF CONTROL

- ✓If you have severe shortness of breath, and can only speak in short sentences,
- ✓If you are having a severe attack of asthma and are frightened,
- ✓If you need your reliever medication more than every 4 hours and are not improving.

1. Take 2 to 4 puffs _____ [reliever medication]
2. Take ____mg of _____ [oral glucocorticosteroid]
3. Seek medical help: Go to _____; Address_____
   Phone: _____
4. Continue to use your _____[reliever medication] until you are able to get medical help.

Stepwise approach to control asthma symptoms and reduce risk



	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER CHOICE		Low dose ICS	Low dose ICS/LABA**	Med/high ICS/LABA	Refer for add-on treatment e.g. tiotropium,*† anti-IgE, anti-IL5*
Other controller options	*Consider low dose ICS*	*Leukotriene receptor antagonists (LTRA) Low dose theophylline**	*Med/high dose ICS Low dose ICS+LTRA (or + theoph*)*	*Add tiotropium*† High dose ICS + LTRA (or + theoph*)*	*Add low dose OCS*
RELIEVER	As-needed short-acting beta$_2$-agonist (SABA)		As-needed SABA or low dose ICS/formoterol#		

REMEMBER TO...

- Provide guided self-management education (self-monitoring + written action plan + regular review)
- Treat modifiable risk factors and comorbidities, e.g. smoking, obesity, anxiety
- Advise about non-pharmacological therapies and strategies, e.g. physical activity, weight loss, avoidance of sensitizers where appropriate
- Consider stepping up if … uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is >70% predicted
- Consider stepping down if … symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.

SLIT added as an option

© Global Initiative for Asthma

Stepwise management, SLIT as an add-on option for some patients

REMEMBER TO...

- Provide guided self-management education
- Treat modifiable risk factors and comorbidities
- Advise about non-pharmacological therapies and strategies
- Consider stepping up if … uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV_1 is 70% predicted
- Consider stepping down if … symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.

SLIT: sublingual immunotherapy

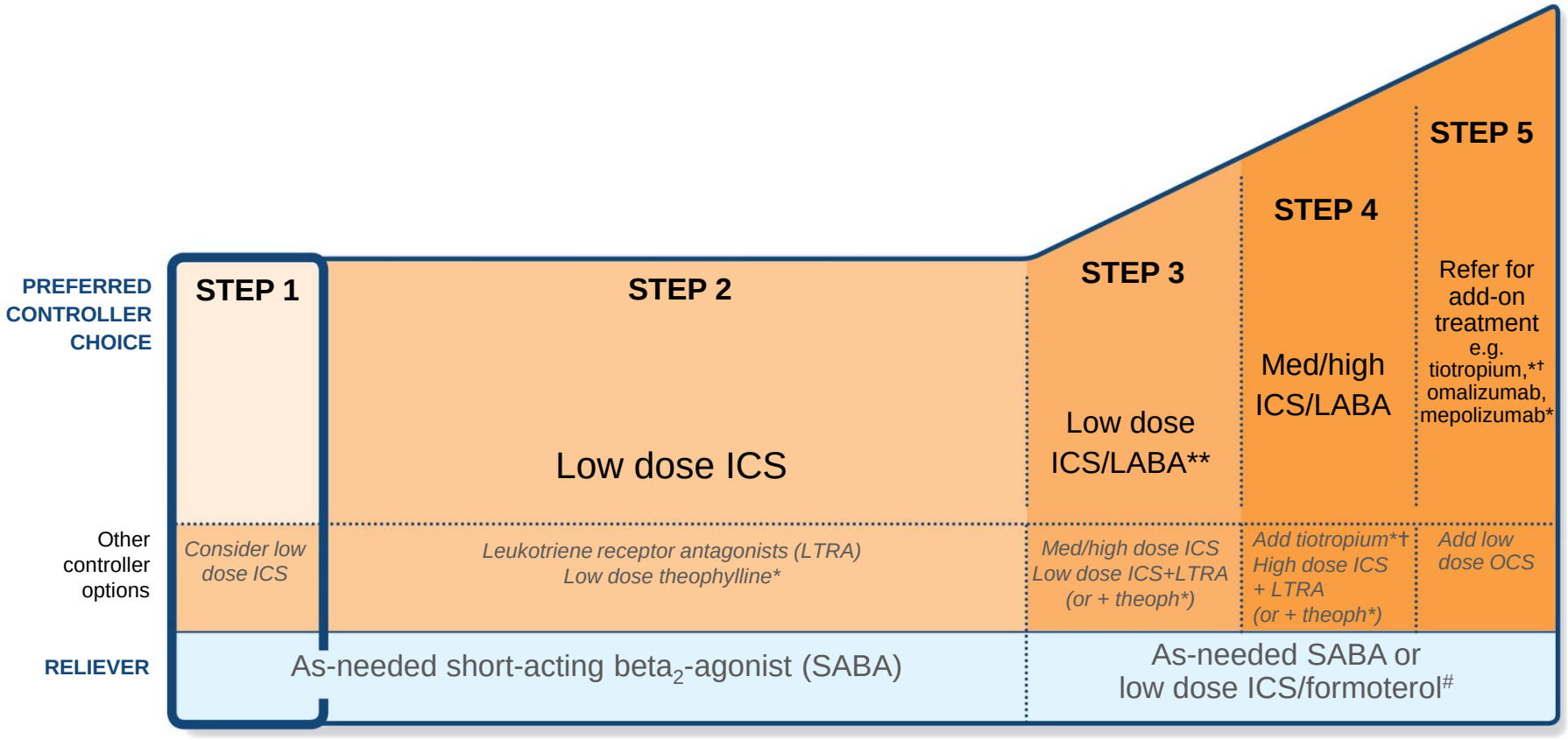
© Global Initiative for Asthma

Treatment – other changes in 2017

- Step 5 treatment for severe asthma
  - Anti-IL5: reslizumab (IV) added to mepolizumab (SC) for ≥18 years
- Step-down from low-dose ICS (Box 3-7)
  - Add-on LTRA may help
  - Insufficient evidence for step-down to as-needed ICS with SABA
- Side-effects of oral corticosteroids
  - When prescribing short-term OCS, remember to advise patients about common side-effects (sleep disturbance, increased appetite, reflux, mood changes); references added
- Vitamin D
  - To date, no good quality evidence that Vitamin D supplementation leads to improved asthma control or fewer exacerbations
- Chronic sinonasal disease
  - Treatment with nasal corticosteroids improves sinonasal symptoms but not asthma outcomes

© Global Initiative for Asthma

Step 1 – as-needed inhaled short-acting beta$_2$-agonist (SABA)

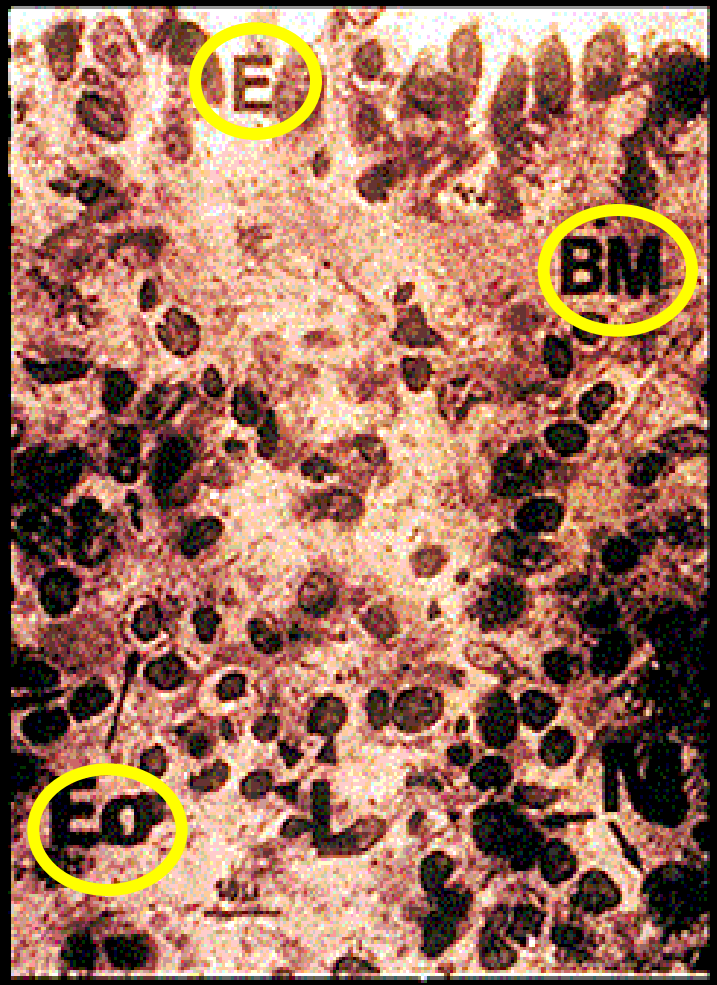


*Not for children <12 years
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

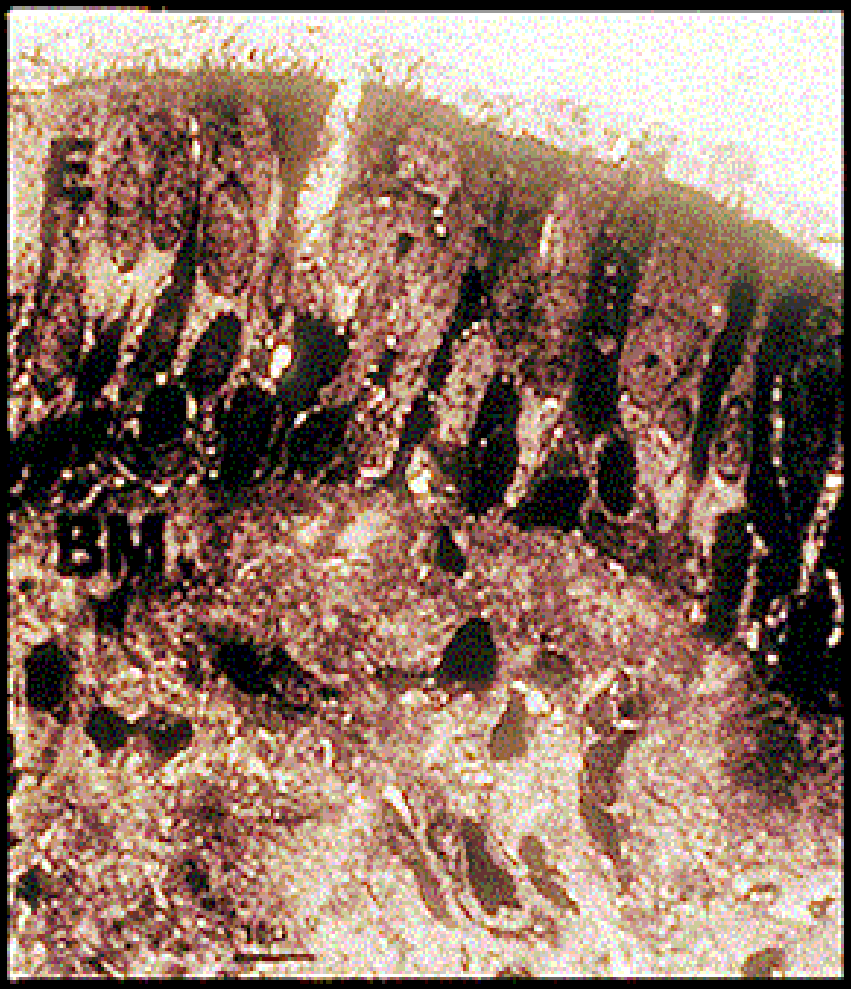
© Global Initiative for Asthma

Step 1 – as-needed reliever inhaler

- Preferred option: as-needed inhaled short-acting beta$_2$-agonist (SABA)
  - SABAs are highly effective for relief of asthma symptoms
  - However …. there is insufficient evidence about the safety of treating asthma with SABA alone
  - This option should be reserved for patients with infrequent symptoms (less than twice a month) of short duration, and with no risk factors for exacerbations
- Other options
  - Consider adding regular low dose inhaled corticosteroid (ICS) for patients at risk of exacerbations



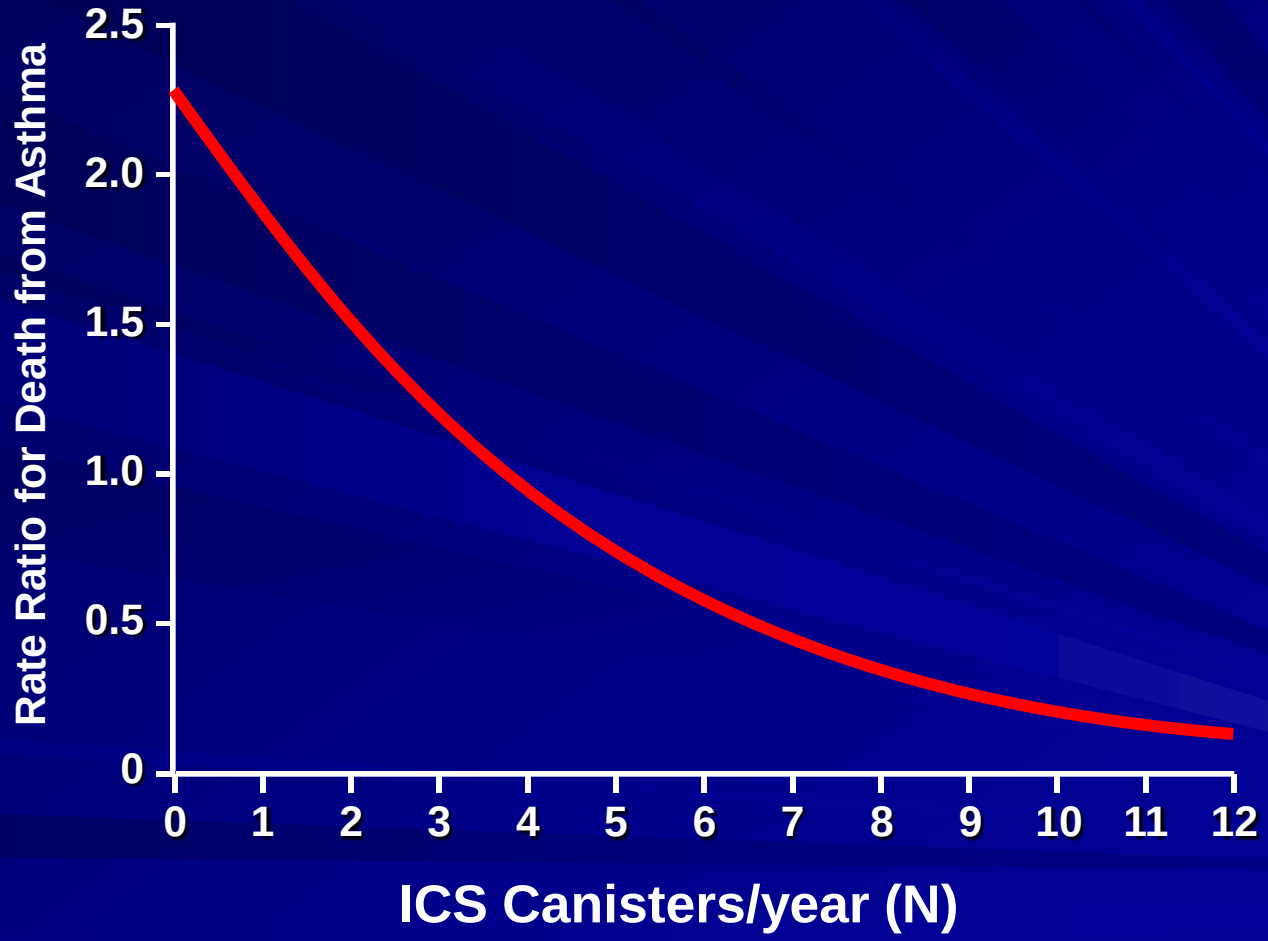
Asthmatic



Steroid-treated asthmatic

Laitinen LA et al, J Allergy Clin Immunol 1992

Effects of ICS on asthma mortality: Saskatchewan Health data



Suissa S, N Engl J Med 2000

Low, medium and high dose inhaled corticosteroids

UPDATED!

Inhaled corticosteroid	Total daily dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (CFC)	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate (DPI or HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

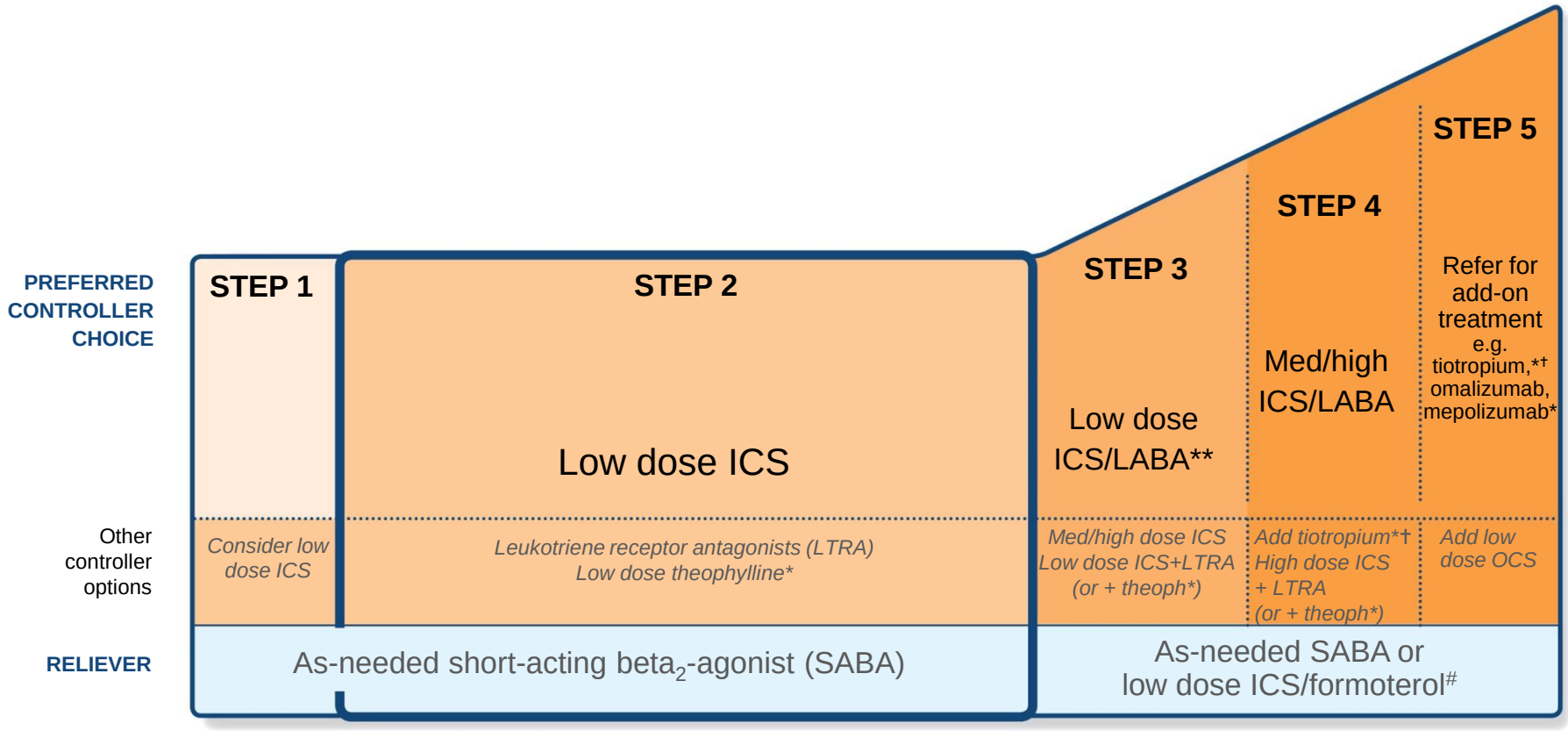
– This is not a table of equivalence, but of estimated clinical comparability

– Most of the clinical benefit from ICS is seen at low doses

– High doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects

GINA 2016, Box 3-6 (1/2)

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

© Global Initiative for Asthma

Step 2 – Low dose controller + as-needed SABA

- Preferred option: regular low dose ICS with as-needed inhaled SABA
  - Low dose ICS reduces symptoms and reduces risk of exacerbations and asthma-related hospitalization and death
- Other options
  - Leukotriene receptor antagonists (LTRA) with as-needed SABA
    - Less effective than low dose ICS
    - May be used for some patients with both asthma and allergic rhinitis, or if patient will not use ICS
  - Combination low dose ICS/long-acting beta2-agonist (LABA) with as-needed SABA
    - Reduces symptoms and increases lung function compared with ICS
    - More expensive, and does not further reduce exacerbations
  - Intermittent ICS with as-needed SABA for purely seasonal allergic asthma with no interval symptoms
    - Start ICS immediately symptoms commence, and continue for 4 weeks after pollen season ends

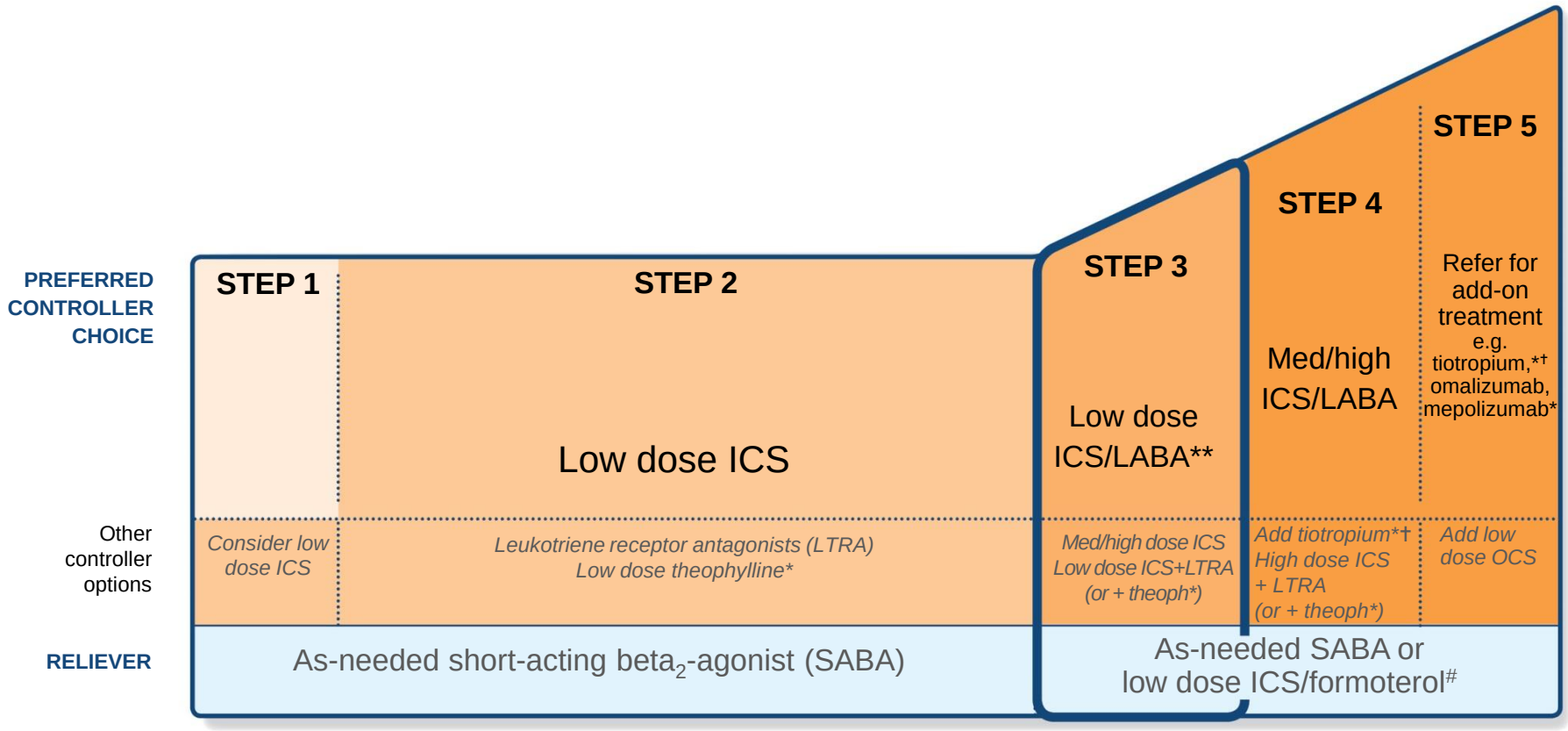
© Global Initiative for Asthma

The Cochrane Library Evidence for healthcare decision-making

- As monotherapy, ICS display superior efficacy to LTRA in adults and children with persistent asthma ; the superiority is particularly marked in patients with moderate airway obstruction. On the basis of efficacy, the results support the current guidelines‘ recommendation that inhaled corticosteroids are the preferred monotherapy.

Chauhan BF, *et al*. Cochrane Database Syst Rev 2012

Step 3 – one or two controllers + as-needed inhaled reliever



*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

© Global Initiative for Asthma

Step 3 – one or two controllers + as-needed inhaled reliever

- Before considering step-up
  - Check inhaler technique and adherence, confirm diagnosis
- Adults/adolescents: preferred options are either combination low dose ICS/LABA maintenance with as-needed SABA, OR combination low dose ICS/formoterol maintenance and reliever regimen*
  - Adding LABA reduces symptoms and exacerbations and increases FEV_1, while allowing lower dose of ICS
  - In at-risk patients, maintenance and reliever regimen significantly reduces exacerbations with similar level of symptom control and lower ICS doses compared with other regimens
- Children 6-11 years: preferred option is medium dose ICS with as-needed SABA
- Other options
  - Adults/adolescents: Increase ICS dose or add LTRA or theophylline (less effective than ICS/LABA)
  - Adults: consider adding SLIT (see Non-pharmacological interventions)
  - Children 6-11 years – add LABA (similar effect as increasing ICS)

UPDATED 2017

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

© Global Initiative for Asthma

The Cochrane Library Evidence for healthcare decision-making

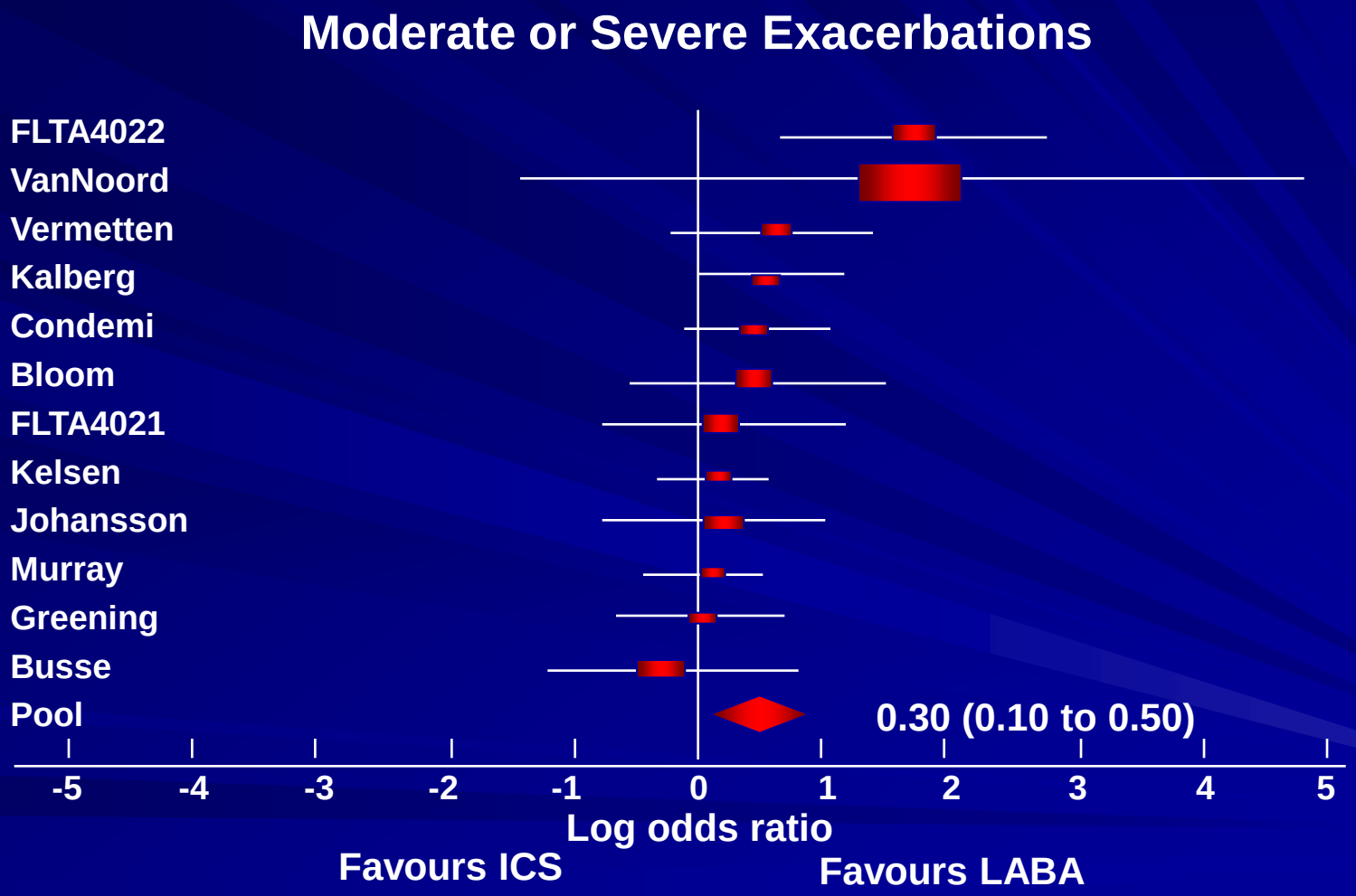
- «……In asthmatic adults inadequately controlled on low doses of inhaled steroids, the addition of LABA is superior to LTRA in reducing oral steroid treated exacerbations.
- Differences favouring LABA in lung function, functional status and quality of life scores are generally modest.»

Ducharme FM, *et al*. Cochrane Database Syst Rev 2011

- LABAs are more effective than theophylline in improving morning and evening PEF, but are not significantly different in their effect on FEV_1. There is evidence of decreased SABA requirement with salmeterol. Fewer adverse events occurred with LABAs (salmeterol and formoterol) compared to theophylline.

Tee AK, *et al*. Cochrane Database Syst Rev 2007

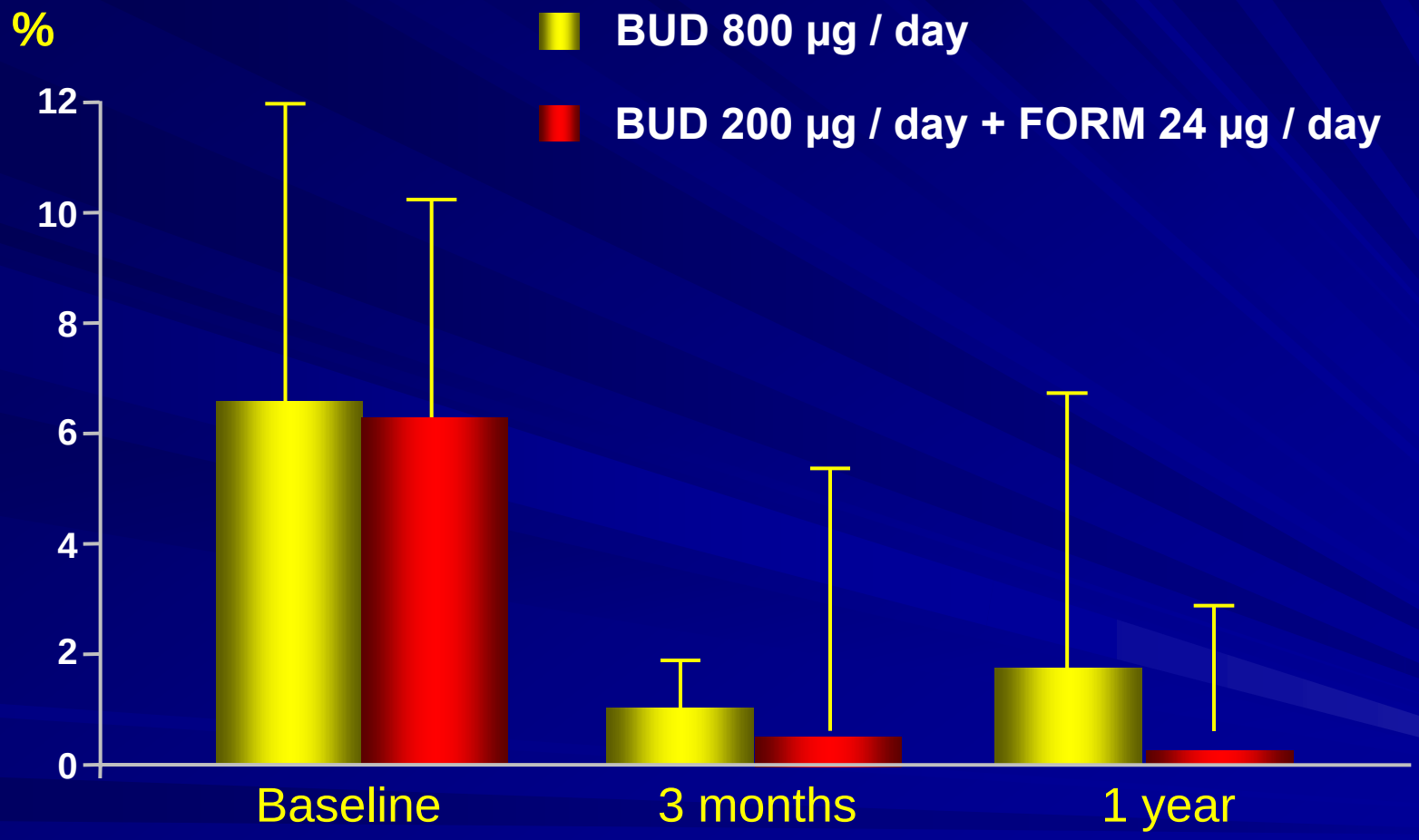
Adding Salmeterol vs. >2x Dose of ICS



PLUS: **less withdrawals due to asthma, greater FEV_1, morning and evening PEF, and less use of reliever in the SALM group**

Masoli M, Thorax 2005

ICS + LABA : Better control of inflammation (Sputum eosinophils)

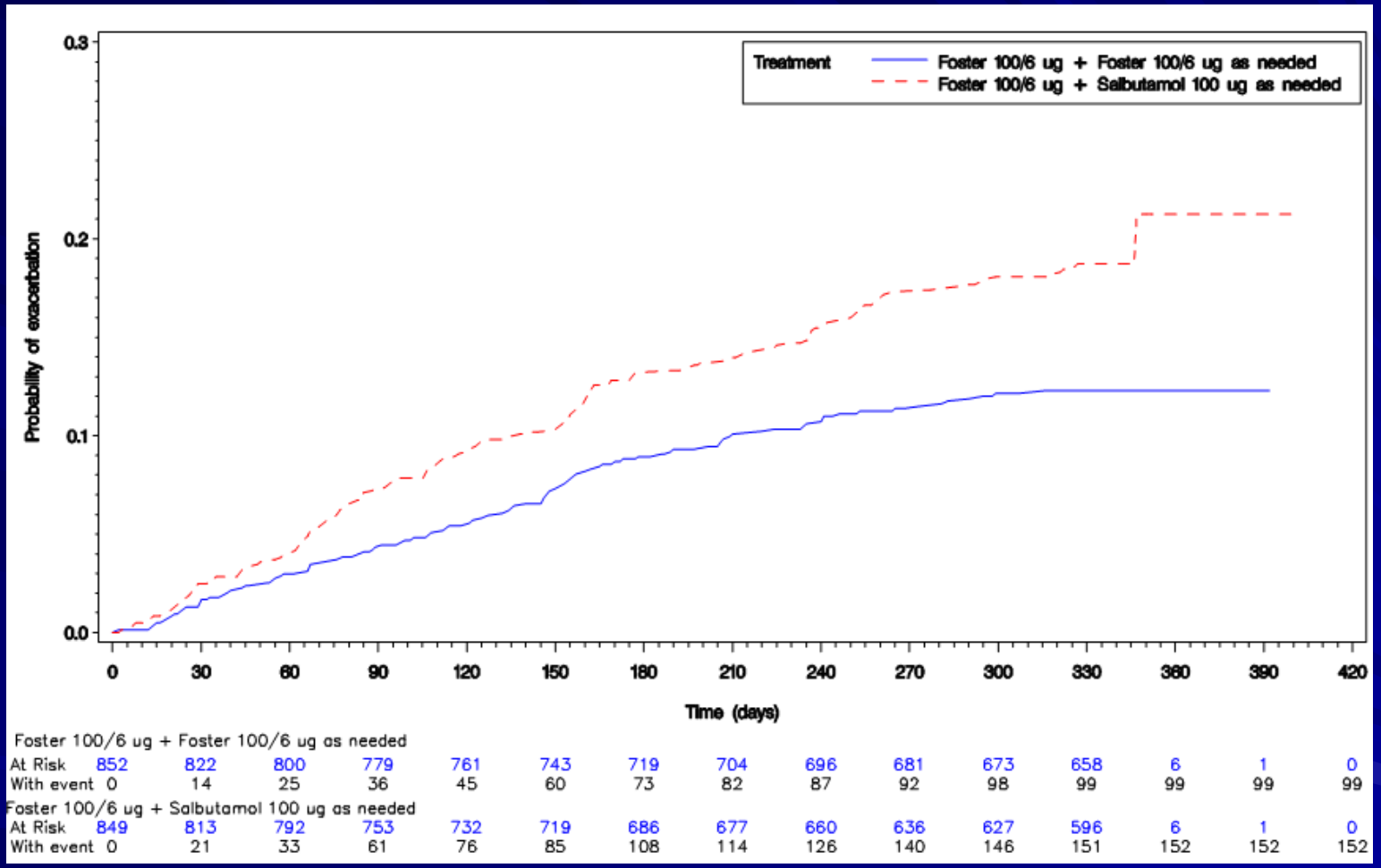


Kips et al. AJRCCM 2000

SMART strategy for an ICS/LABA combination including formoterol

« If a combination inhaler containing formoterol and budesonide or formoterol and beclomethasone is selected, it may be used for both rescue and maintenance. This approach has been shown to result in reductions in exacerbations and improvements in asthma control in adults and adolescents at relatively low doses of treatment (Evidence A) »

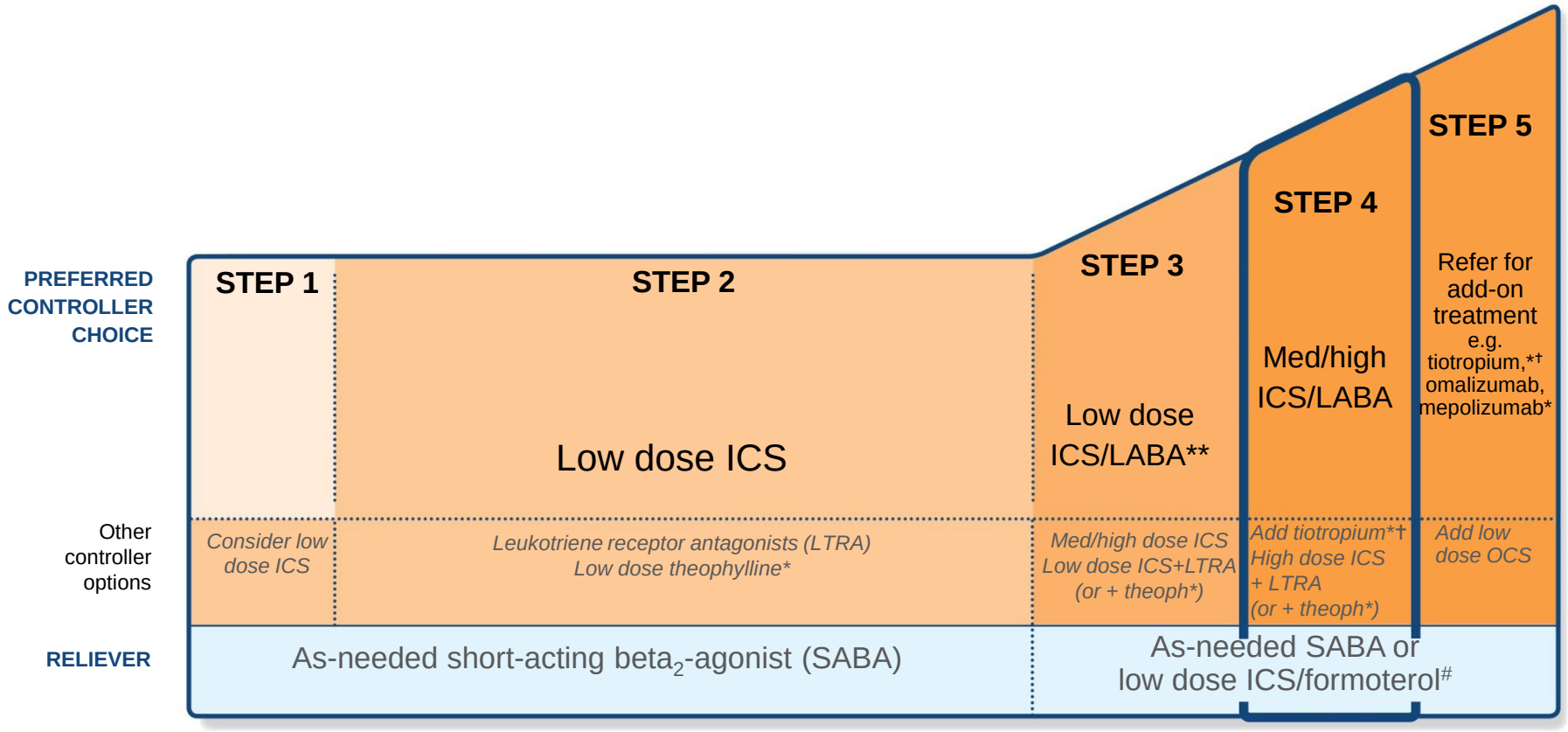
MART2 study: time to first severe exacerbation BECLOMETHASONE/FORMOTEROL



	FOSTER + FOSTER N=852	*FOSTER + SALBUTAMOL N=849*	*LOG RANK CHI SQUARE*	*P- VALUE*	*HAZARD RATIO (95% CI)*
***PATIENTS WITH EVENTS* (251)**	**99**	**152**	13.002	**<0.001**	**0.64 (0.49-0.82)**

Papi A et al, Lancet Respir Med 2013

Step 4 – two or more controllers + as-needed inhaled reliever



*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

© Global Initiative for Asthma

Step 4 – two or more controllers + as-needed inhaled reliever

- Before considering step-up
  - Check inhaler technique and adherence
- Adults or adolescents: preferred option is combination low dose ICS/formoterol as maintenance and reliever regimen*, OR combination medium dose ICS/LABA with as-needed SABA
- Children 6–11 years: preferred option is to refer for expert advice
- Other options (adults or adolescents)
  - Tiotropium by mist inhaler may be used as add-on therapy for patients aged ≥12 years with a history of exacerbations
  - Adults: consider adding SLIT (see Non-pharmacological therapy)
  - Trial of high dose combination ICS/LABA, but little extra benefit and increased risk of side-effects
  - Increase dosing frequency (for budesonide-containing inhalers)
  - Add-on LTRA or low dose theophylline

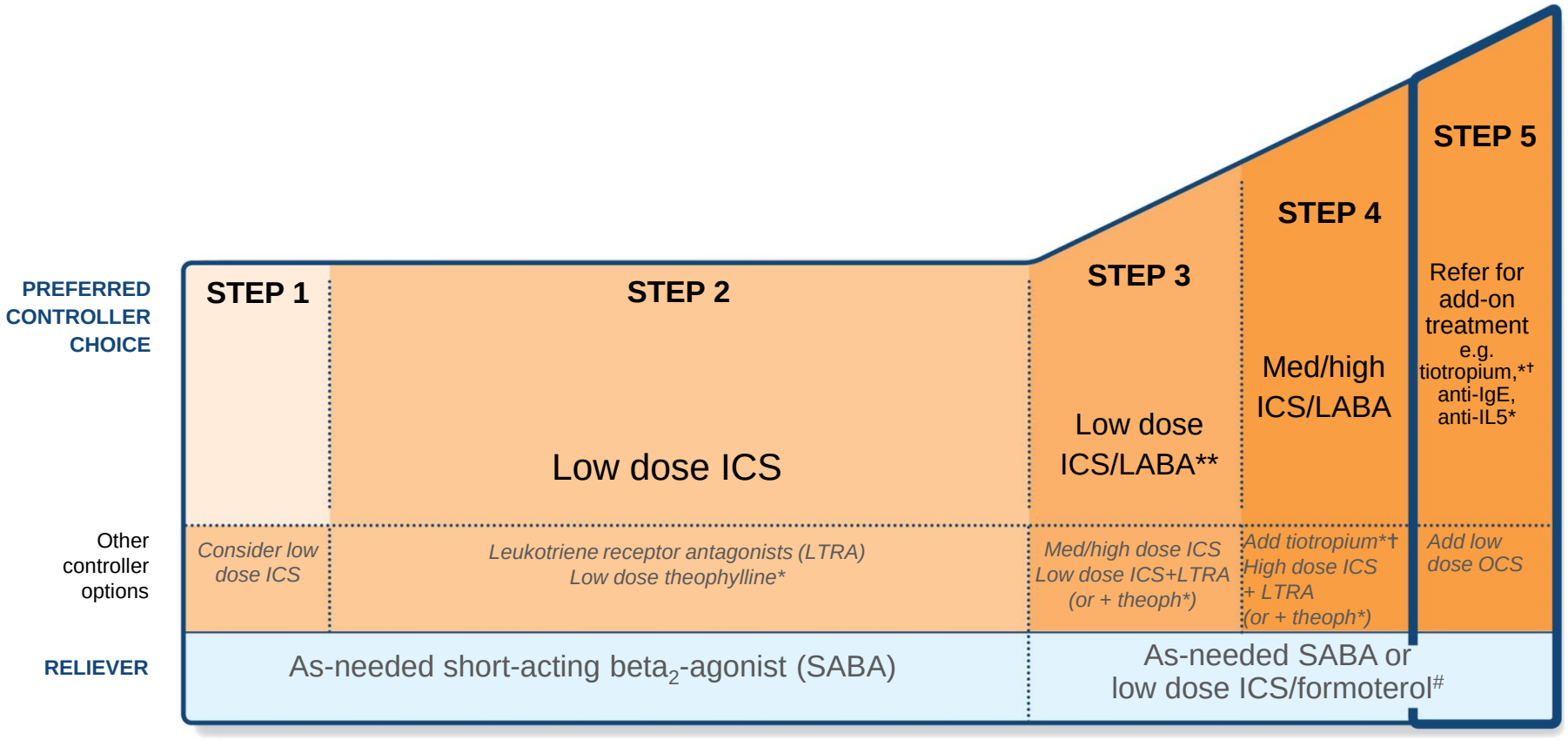
UPDATED 2017

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

© Global Initiative for Asthma

Step 5 – higher level care and/or add-on treatment

UPDATED 2017



*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

© Global Initiative for Asthma

Step 5 – higher level care and/or add-on treatment

- Preferred option is referral for specialist investigation and consideration of add-on treatment
  - If symptoms uncontrolled or exacerbations persist despite Step 4 treatment, check inhaler technique and adherence before referring
  - Add-on tiotropium for patients ≥12 years with history of exacerbations
  - Add-on anti-IgE (omalizumab) for patients with severe allergic asthma
  - Add-on anti-IL5 (mepolizumab (SC) or reslizumab (IV)) for severe eosinophilic asthma (≥12 yrs)
- Other add-on treatment options at Step 5 include:
  - Sputum-guided treatment: this is available in specialized centers; reduces exacerbations and/or corticosteroid dose
  - Add-on low dose oral corticosteroids (≤7.5mg/day prednisone equivalent): this may benefit some patients, but has significant systemic side-effects. Assess and monitor for osteoporosis
  - See ERS/ATS Severe Asthma Guidelines (Chung et al, ERJ 2014) for more detail

© Global Initiative for Asthma

ΑΝΟΣΟΘΕΡΑΠΕΙΑ

- Μεγαλύτερο όφελος σε αλλεργική ρινίτιδα
- Περιορισμένος ρόλος στο άσθμα
- Πιο επιτυχής σε ασθενείς με ευαισθησία σε 1 αλλεργιογόνο
- "GINA: *Specific immunotherapy should be considered only after strict environmental avoidance and pharmacologic intervention, including inhaled glucocorticosteroids, have failed to control a patient's asthma"*

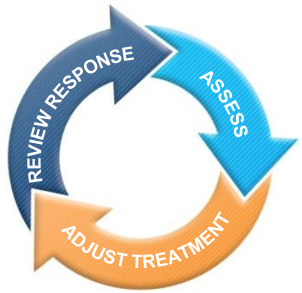
Μη φαρμακολογικές παρεμβάσεις

- Αποφυγή έκθεσης σε καπνό τσιγάρου
  - Provide advice and resources at every visit; advise against exposure of children to environmental tobacco smoke (house, car)
- Φυσική δραστηριότητα
  - Encouraged because of its general health benefits. Provide advice about exercise-induced bronchoconstriction
- Επαγγελματικό άσθμα
  - Ask patients with adult-onset asthma about work history. Remove sensitizers as soon as possible. Refer for expert advice, if available
- Αποφυγή φαρμάκων
  - Always ask about asthma before prescribing NSAIDs or beta-blockers
- (Αποφυγή αλλεργιογόνων)
  - (Not recommended as a general strategy for asthma)

This slide shows examples of interventions with high quality evidence

GINA 2015, Box 3-9

Αξιολογώντας την απάντηση και προσαρμόζοντας τη θεραπεία



- Πόσο συχνά επανεκτιμάται ο ασθενής?
  - 1-3 μήνες μετά την έναρξη της θεραπείας, μετά κάθε 3-12 μήνες
  - Κατά τη διάρκεια της κύησης κάθε 4-6 εβδομάδες
  - Μετά από παρόξυνση εντός 1 εβδομάδας
- Stepping up της θεραπείας
  - *Sustained step-up*, για τουλάχιστον 2-3 μήνες αν είναι πτωχά ελεγχόμενο
    - Σημαντικό: πρώτα έλεγξε για συνήθη αίτια (συμπτώματα μη οφειλόμενα στο άσθμα, λανθασμένη τεχνική εισπνοής, πτωχή συμμόρφωση)
  - *Short-term step-up*, για 1-2 εβδομάδες π.χ με ιογενή λοίμωξη ή έκθεση σε αλλεργιογόνο
    - Μπορεί να γίνει από τον ίδιο τον ασθενή με βάση το γραπτό πλάνο δράσης
  - *Day-to-day adjustment*
    - Για ασθενείς που λαμβάνουν low-dose ICS/formoterol ως θεραπεία συντήρησης και ανακουφιστική θεραπεία*
- Stepping down της θεραπείας
  - Σκέψου τη μετά από καλό έλεγχο που διατηρείται για 3 μήνες
  - Βρες για κάθε ασθενή την ελάχιστη δραστική δόση που ελέγχει τα συμπτώματα και τις παροξύνσεις

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

© Global Initiative for Asthma

Stepping down σε ελεγχόμενο άσθμα

Ελεγχόμενο μόνο με ICS

- **Όταν ελέγχεται μόνο με μέτρια-υψηλή δόση ICS** ελάττωσε τη δόση του ICS κατά 50% **ανά 3 μήνες** (Evidence B)**.**
- **Εάν ο έλεγχος διατηρείται σε χαμηλή δόση ICS μόνο, στους περισσότερους ασθενείς η θεραπεία θα αλλάξει σε once-daily dosing (**Evidence A**).**

Stepping down σε ελεγχόμενο άσθμα

- Όταν ελέγχεται με συνδυασμό ICS/LABA, η προτεινόμενη προσέγγιση είναι να μειωθεί η δόση του ICS κατά 50% ενώ συνεχίζεται η χορήγηση του LABA (Evidence B)
- Εφόσον ο έλεγχος διατηρείται, μείωσε τα ICS σε χαμηλή δόση και σταμάτησε τον LABA (Evidence D)
- Εναλλακτικά, μπορεί να διακοπεί ο LABA σε πρωιμότερο στάδιο και να συνεχιστούν τα ICS στην ίδια δοσολογία που περιέχεται στο συνδυασμό. Ωστόσο, αυτό συνδυάζεται με συχνότερη απώλεια του ελέγχου του άσθματος (Evidence B).

Stepping down σε ελεγχόμενο άσθμα

Ελεγχόμενο με ICS + άλλο ρυθμιστικό (όχι LABA)

- **Όταν το άσθμα ελέγχεται με ICS+ άλλο ρυθμιστικό φάρμακο (όχι LABA),** μείωσε τη δόση του ICS κατά 50% **μέχρι να φτάσεις σε χαμηλή δόση και αν ο έλεγχος διατηρείται διέκοψε το άλλο ρυθμιστικό φάρμακο** (Evidence D)**.**

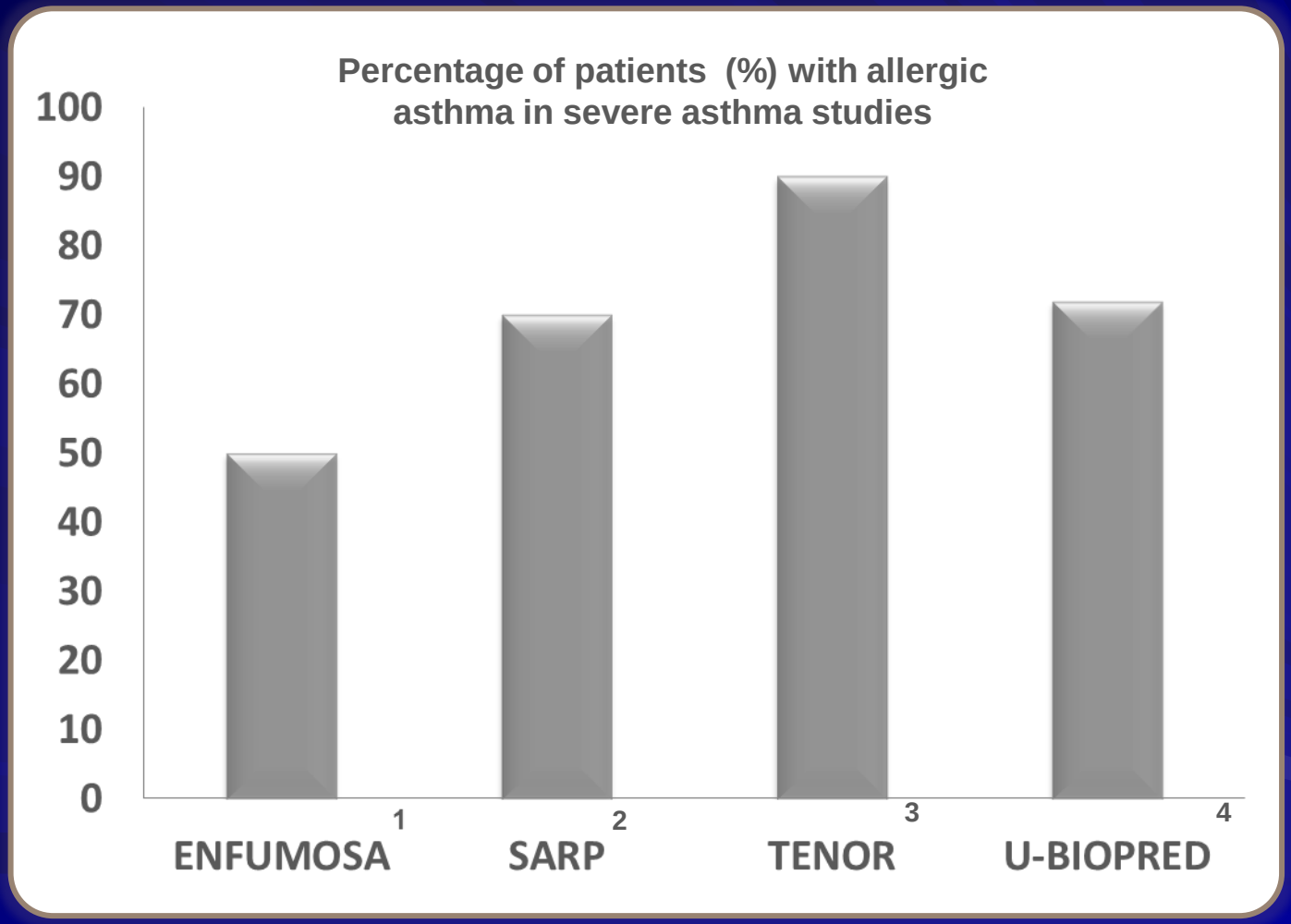
Stepping down σε ελεγχόμενο άσθμα

- **Η ρυθμιστική θεραπεία μπορεί να σταματήσει όταν ο ασθενής παραμένει ελεγχόμενος στη χαμηλότερη δόση ρυθμιστικού φαρμάκου και δεν υπάρχουν συμπτώματα για 1 χρόνο** (Evidence D)**.**

Anti-IgE in asthma

- ONLY in severe ALLERGIC asthma not controlled by high-dose ICS and/or requires per os steroids
- (+) SPT in at least 1 perennial aeroallergen
- Subcutaneous administration once or twice / month
- How long ?

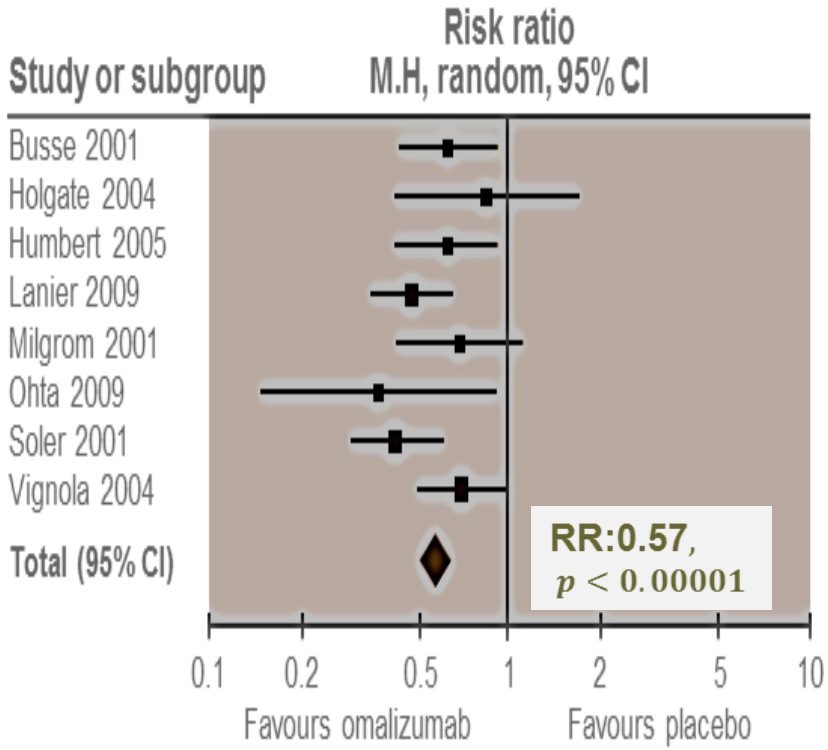
ALLERGIC ASTHMA IS THE MOST FREQUENT PHENOTYPE OF SEVERE ASTHMA



1. ENFUMOSA. Eur Respir J 2003; 2. Moore WC, et al. J Allergy Clin Immunol 2007; 3. Haselkorn T, et al. J Asthma 2006; 4. U-BIOPRED Study Group ERJ 2015

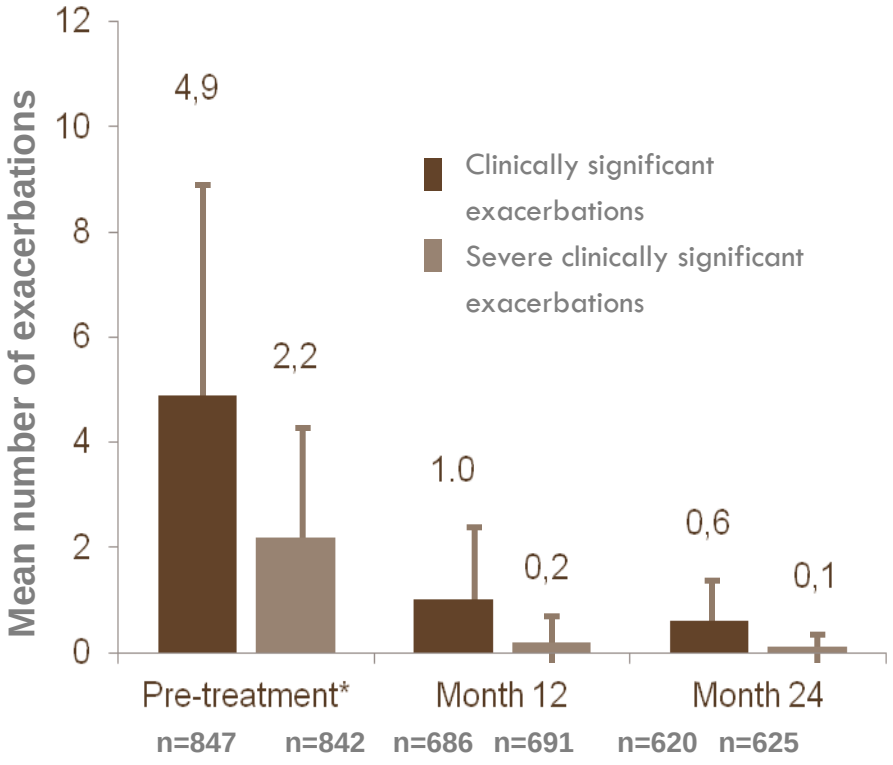
REDUCTION OF EXACERBATIONS

Evidence from RCTs



Rodrigo GJ, et,al. Chest 2011

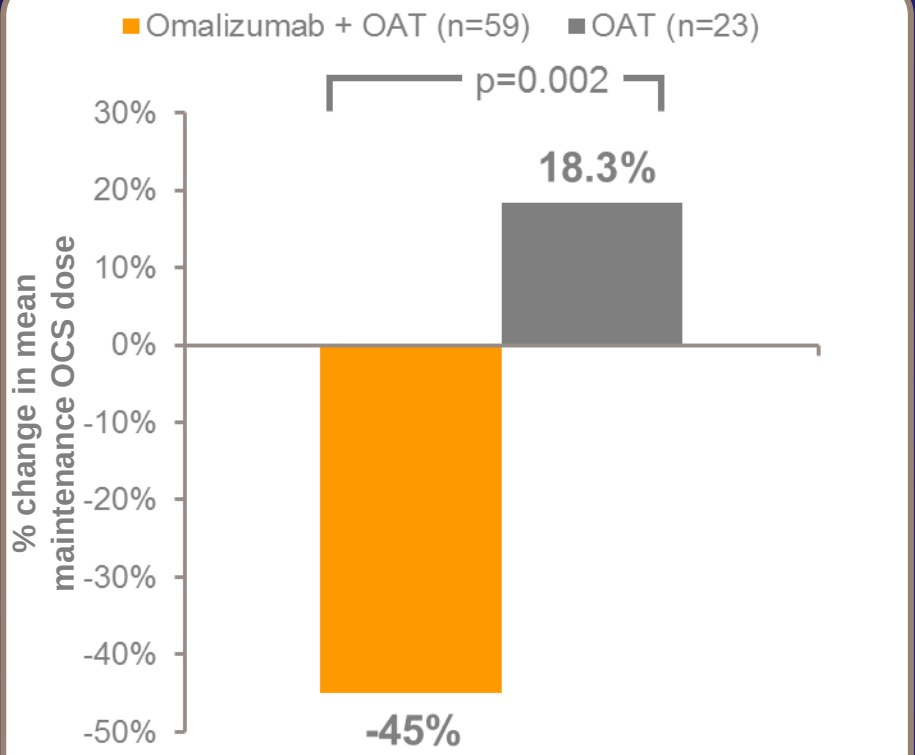
Evidence from Real-Life studies



Braunstahl G-J, et al. Respir Med 2013

REDUCED OCS USE

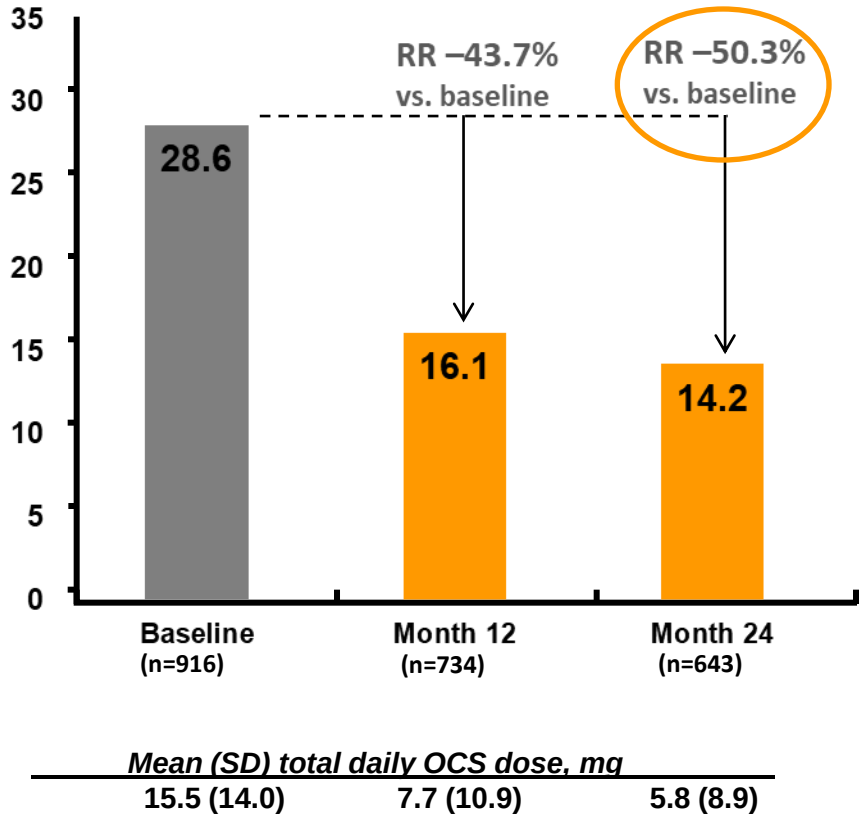
Evidence from RCTs



*OAT = optimized asthma therapy (i.e. high-dose inhaled corticosteroids plus long-acting β_2-agonist ± controller).

Siergiejko Z, et al. Cur. Med. Research & Opinion 2011

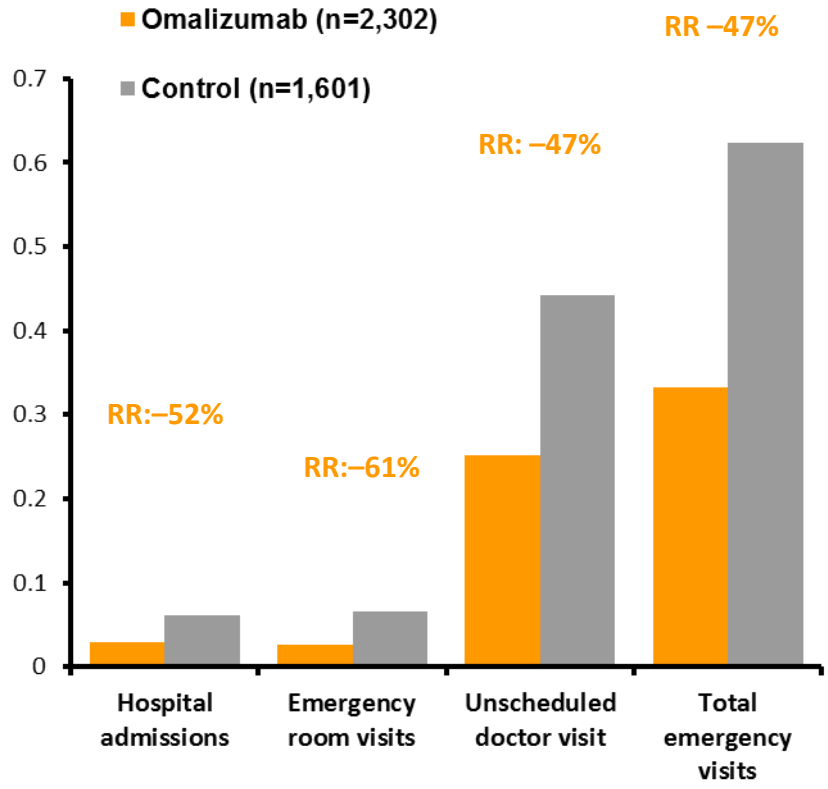
Evidence from Real-Life studies



Braunstahl G-J, et al. Respir Med 2013

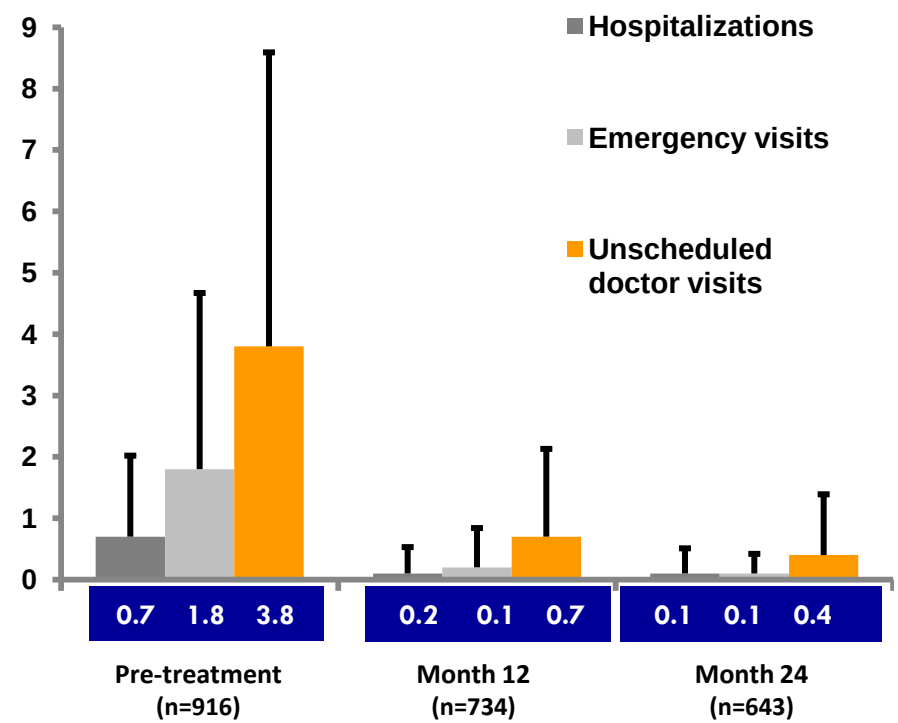
REDUCED HCU SOURCE

Evidence from RCTs



Bousquet J, et al. Allergy 2005

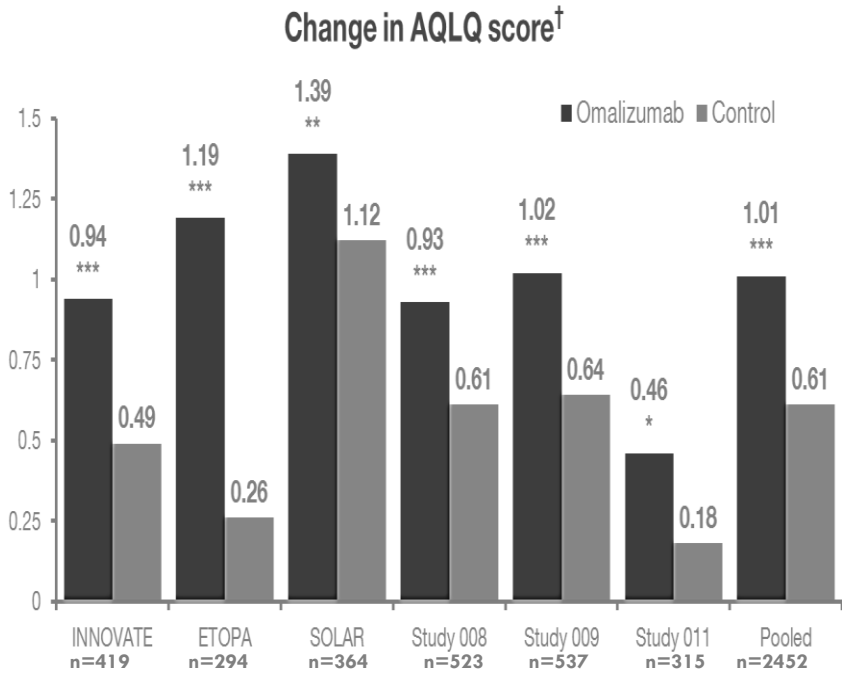
Evidence from Real-Life studies



Braunstahl G-J, et al. Respir Med 2013

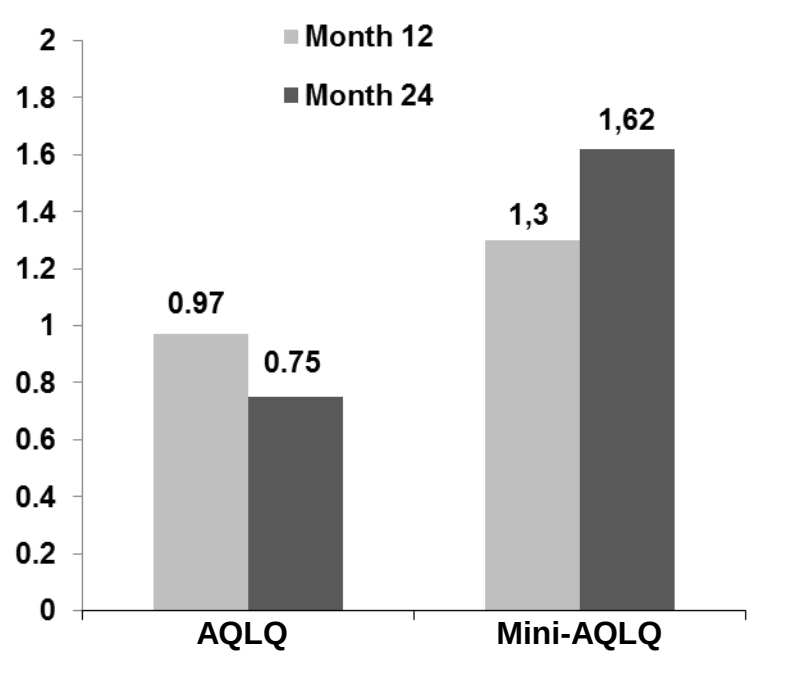
QOL IMPROVEMENT

Evidence from RCTs



Chipps B, et al. Curr Med Res Opin 2006

Evidence from Real-Life studies



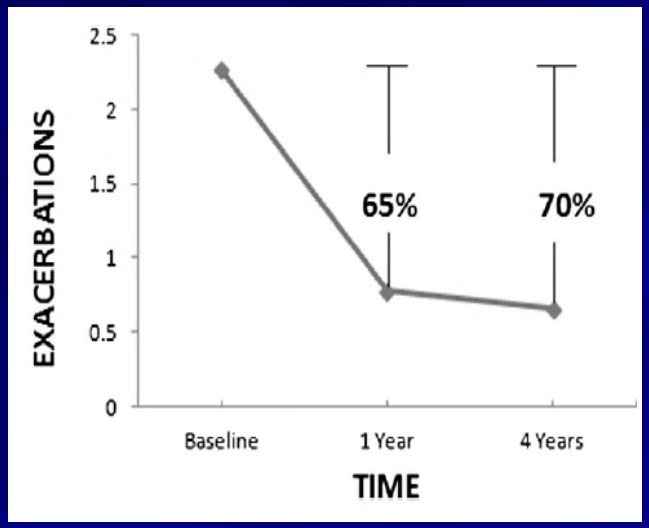
Braunstahl G-J, et al. Respir Med 2013

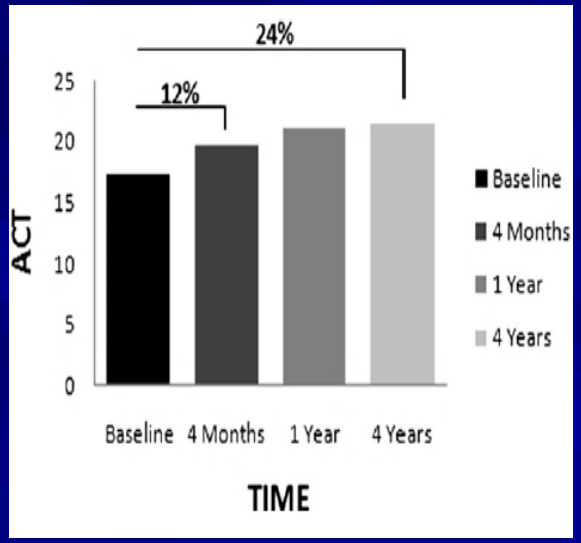
CONCERNS REGARDING OMALIZUMAB

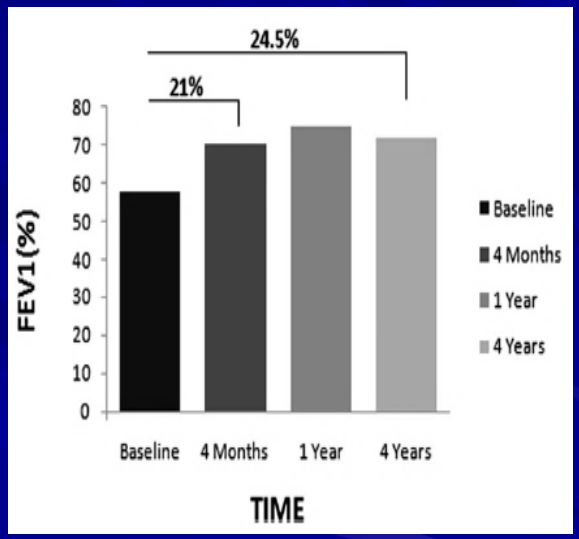
- Dosage
- Allergy to a perennial allergen
- No biomarker for response or duration of treatment
- Safety (however few concerns)

Omalizumab duration of treatment

4 years





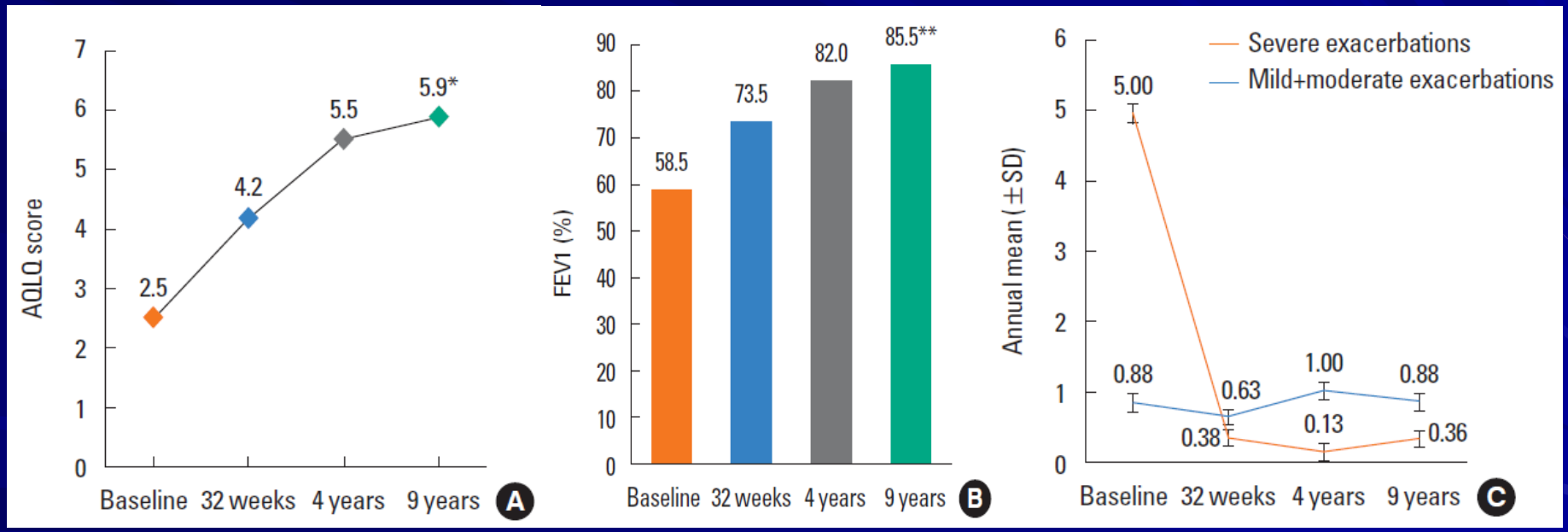


Tzortzaki, et al. Pulm Pharmacol & Ther 25 (2015); 77-82

Real-life Efficacy of Omalizumab After 9 Years of Follow-up

Francesco Menzella,[1*] Carla Galeone,[1] Debora Formisano,[2] Claudia Castagnetti,[1] Patrizia Ruggiero,[1] Anna Simonazzi,[1] Luigi Zucchi[1]

[1]*Department of Cardio-Thoracic-Vascular and Intensive Care Medicine, Pneumology Unit, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy*
[2]*Scientific Directorate, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy*



Menzella F et. al, Allergy Asthma Immunol Res. 2017

Anti-IL-5 and prednisone sparing effect

- Randomized double-blind parallel-group trial
- Asthmatic patients with persistent sputum eosinophilia and symptoms despite prednisone treatment
- 20 pts (9 pts 5 infusions of anti-IL-5 750mg IV and 11 pts placebo)
- Primary outcome: Proportion of pts with exacerbations and mean reduction in prednisone dose

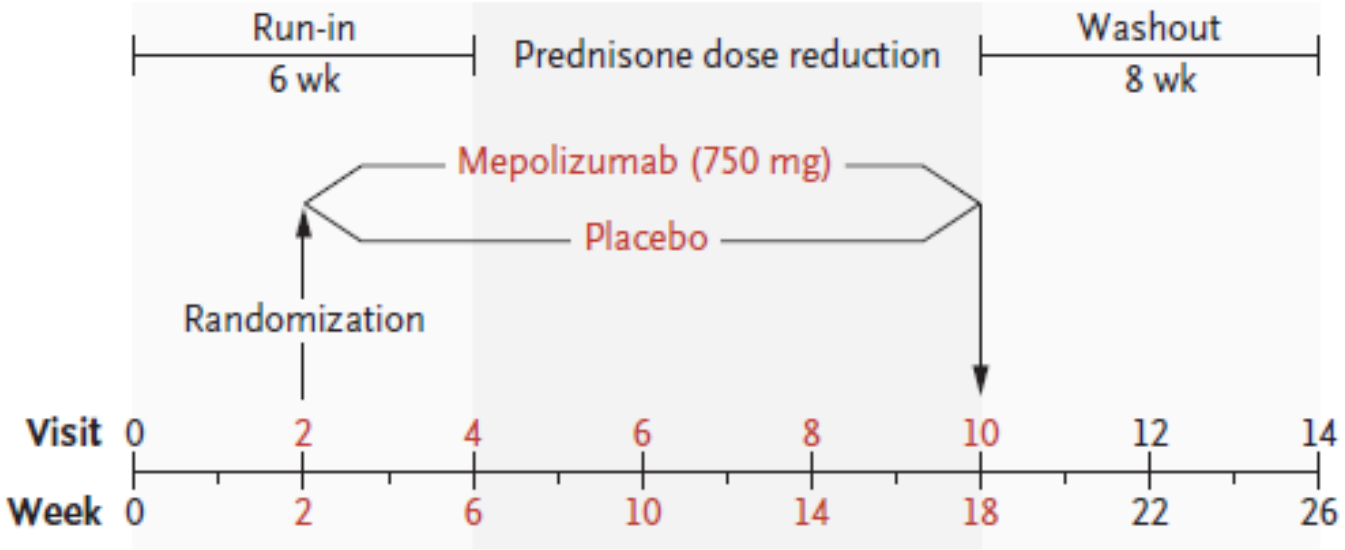
Nair et al, N Engl J Med 2009

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Mepolizumab (N=9)	Placebo (N=11)
Age (yr)	56.4±10.9	58.2±7.1
Male sex (no. of patients)	4	8
Height (cm)	166.2±14.5	168.6±9.9
Weight (kg)	85.8±16.7	89.5±14.9
Duration of symptoms (yr)	13.3±10.3	12.5±9.5
FEV_1		
Previous minimum†		
Value (liters)	1.4±0.6	1.6±0.5
% of predicted value	48±17	52±13
Previous maximum†		
Improvement with bronchodilation (%)	28.4±12.03	24.6±10.6
Decrease during exacerbation (%)	42.0±16.9	45.5±13.7
Current postbronchodilation		
% of predicted value	66.6±18.3	74.3±17.9
Ratio of FEV_1 to vital capacity (%)	63.8±16.2	65.9±13.1
Sputum eosinophils (%)		
Median	16.6	4.0
Range	1.6–54.3	0–35.3
Prednisone (mg/day)		
Median	10.0	10.0
Range	5.0–25.0	2.5–20.0
Duration of daily use of prednisone (yr)	9.3±7.6	8.9±8.5
Inhaled corticosteroids (μg/day)‡		
Median	1000	1000
Range	600–2000	1000–2000
Short-acting β-agonist (no. of puffs/wk)	10±6	9±8
Long-acting β-agonist (no. of patients)	9	9
Leukotriene-receptor antagonists (no. of patients)	2	1
Atopy (no. of patients)	3	4
Nasal polyp (no. of patients)	3	5
Smoking history of >10 pack-years (no. of patients)	2	3

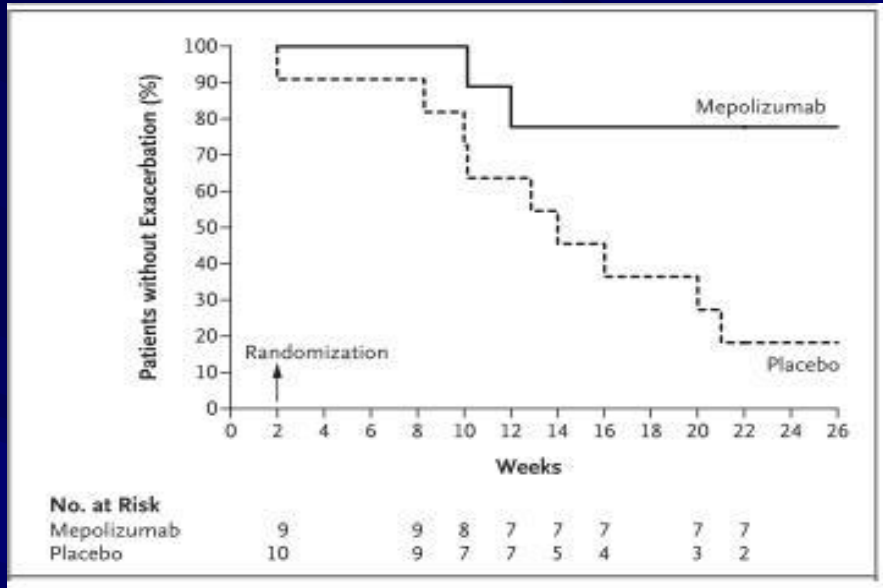
Nair et al, N Engl J Med 2009

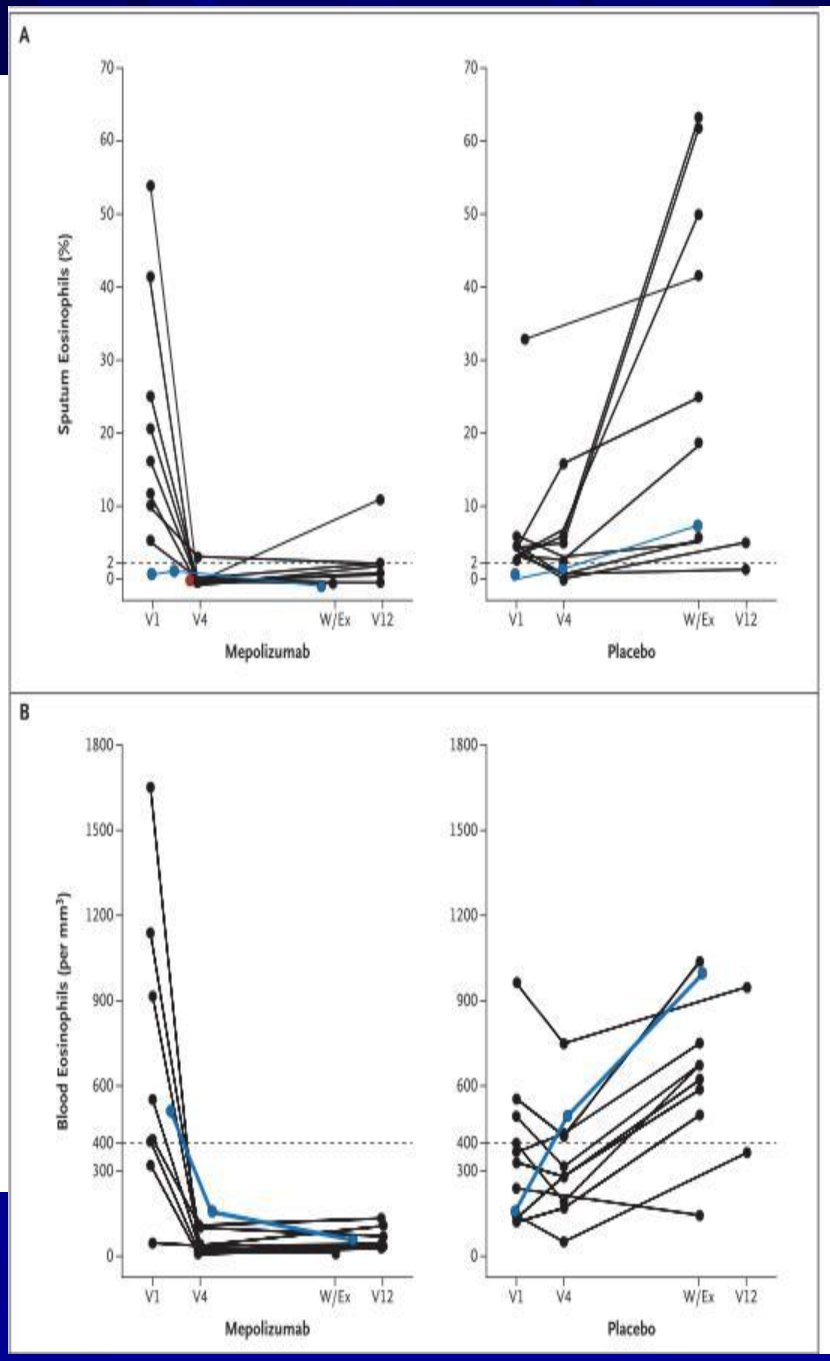
Protocol for reduction in the dose of prednisone



Starting Doses of Prednisone					
25.0	20.0	15.0	10.0	7.5	5.0
20.0	15.0	10.0	7.5	5.0	5.0
17.5	12.5	7.5	5.0	5.0	5.0
15.0	10.0	7.5	5.0	5.0	5.0
12.5	7.5	5.0	2.5	2.5	2.5
10.0	7.5	5.0	2.5	2.5	2.5
7.5	5.0	2.5	0.0	0.0	0.0
5.0	2.5	0.0	0.0	0.0	0.0

Nair et al, N Engl J Med 2009





Nair et al, N Engl J Med 2009

Anti-IL-5 and exacerbations of refractory eosinophilic asthma

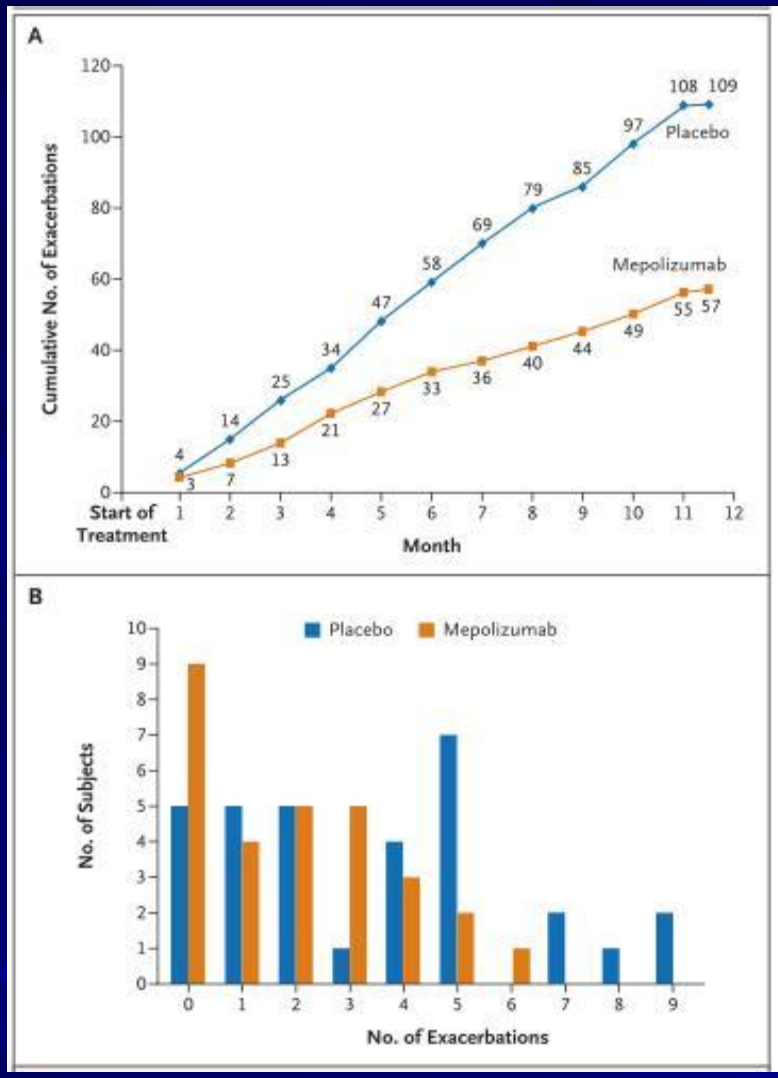
- Randomized double-blind placebo-controlled, parallel-group study
- 61 pts with refractory asthma and eosinophilic airway inflammation and recurrent exacerbations despite treatment with high doses of corticosteroids
- 29 pts mepolizumab - 32 pts placebo for 12 months
- Number of exacerbations per subject
- Symptoms, QOL/AQLQ, FEV1, BHR, blood and sputum eosinophils, airway structure (CT)

Haldar et al, N Engl J Med 2009

Table 1. Baseline Characteristics of Subjects in the Intention-to-Treat Population.*

Characteristic	Mepolizumab (N=29)	Placebo (N=32)	P Value†
Sex (no. of subjects)			0.80
Male	14	18	
Female	15	14	
Age (yr)			0.34
Mean	48	50	
Range	21–63	24–72	
Age at onset of symptoms (yr)			0.99
Mean	26	26	
Range	2–53	2–57	
Body-mass index‡	29.4±7.3	29.2±5.9	0.92
Positive atopic status (% of subjects)§	67.9	68.8	0.78
Total IgE (U/ml)¶	177.8±2.47	195±2.64	0.75
Presence of nasal polyps (% of subjects)	34.4	31.2	0.59
Severe exacerbations per subject in previous year (no.)‖	5.5	5	0.71
Previous admission to the intensive care unit for asthma (% of subjects)	27.5	31.3	0.78
PC_{20} (mg/ml)¶	0.6±1.24 (N=16)	1.1±1.1 (N=18)	0.38
FEV_1 after bronchodilator use (% of predicted value)	78.1±20.9	77.6±24.1	0.93
FEV_1:FVC ratio (%)	72.2±9.6	67.7±13.5	0.15
Improvement in FEV_1 after bronchodilator use (%)	9.1±14.2	7.0±13.1	0.57
Eosinophil count in sputum (%)¶‖	6.84±0.64	5.46±0.75	0.60
Eosinophil count in blood ($\times 10^{-9}$/liter)¶	0.32±0.38	0.35±0.30	0.57
F_{ENO} (ppb)¶**	44.4±0.40	35.5±0.40	0.31
Score on modified Juniper Asthma Control Questionnaire	1.98±1.07	2.38±1.35	0.28
Score on Asthma Quality of Life Questionnaire	4.72±1.26	4.84±1.13	0.71
Dose of inhaled corticosteroid — beclomethasone dipropionate–equivalent (μg)††			0.03
Daily dose	2038	1711	
Range	1000–4000	1000–4000	
Use of long-acting beta-agonists (% of subjects)	92.9	90.6	0.99
Use of oral prednisolone‖			
Regular use (% of subjects)	57.1	53.1	0.80
Daily maintenance dose (mg)			0.72
Mean	9	10	
Range	5–20	2–40	
Use of montelukast (% of subjects)	21.4	25	0.76
Use of methotrexate for asthma (no. of subjects)	0	2	0.49

Haldar et al. N Engl J Med 2009



The mean number of severe exacerbations per subject was 2.0 in the mepolizumab group, as compared with 3.4 in the placebo group (relative risk, 0.57; 95% confidence interval [CI], 0.32 to 0.92; **P = 0.02**).

3 hospital admissions for exacerbations of asthma in the mepolizumab group, as compared with 11 admissions in the placebo group (**P = 0.07**).

Haldar et al, N Engl J Med 2009

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

Ian D Pavord, Stephanie Korn, Peter Howarth, Eugene R Bleecker, Roland Buhl, Oliver N Keene, Hector Ortega, Pascal Chanez

- Multicentre, double-blind, placebo-controlled trial, 81 centres, 13 countries
- 621 pts randomized
- History of ≥ 2 exacerbations requiring systemic corticosteroids in the previous year
- Eosinophilic inflammation: sputum eos >3% OR FeNO>50ppb OR blod eos >300/μL OR asthma control deterioration after 25% or less reduction in regular maintenance inhaled or oral steroids
- Randomization 1:1:1:1 (75, 150, 750mg IV, placebo)
- 13 infusions at 4-week intervals

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

Ian D Pavord, Stephanie Korn, Peter Howarth, Eugene R Bleecker, Roland Buhl, Oliver N Keene, Hector Ortega, Pascal Chanez

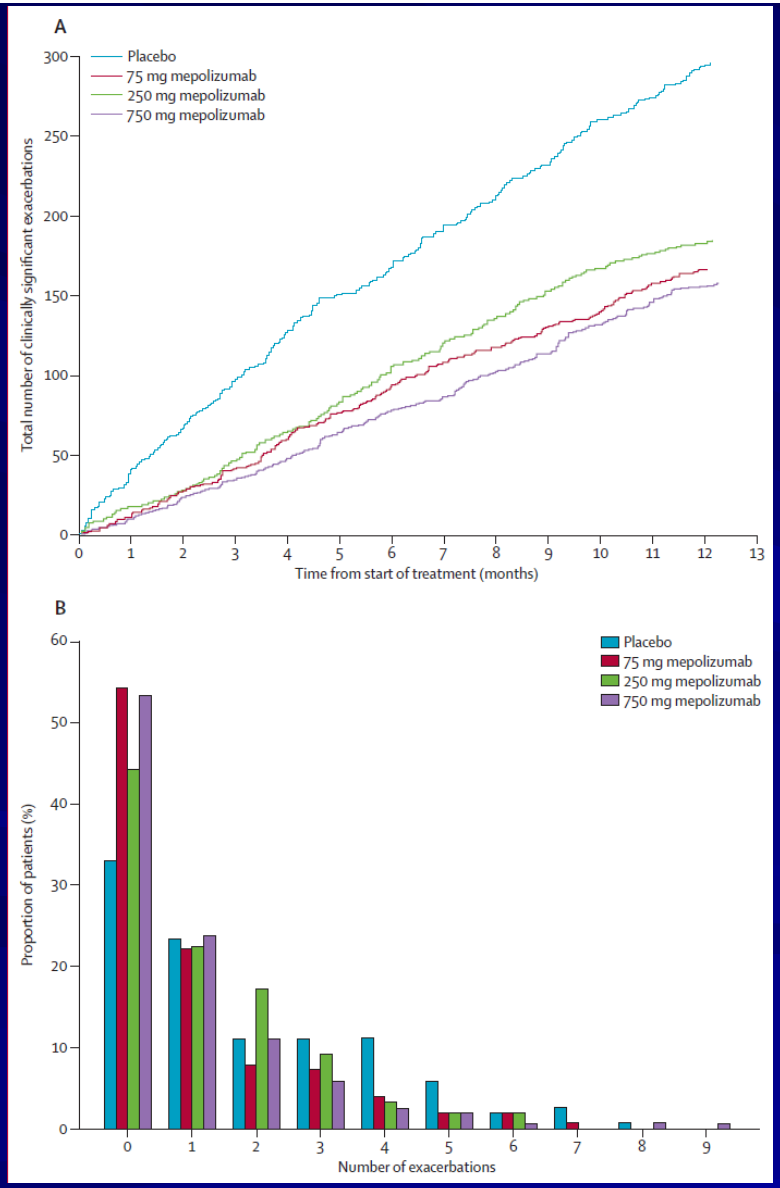
	Placebo group (n=155)	75 mg mepolizumab group (n=153)	250 mg mepolizumab group (n=152)	750 mg mepolizumab group (n=156)
Women	97 (63%)	104 (68%)	93 (61%)	93 (60%)
Age (years)	46·4 (11·3)	50·2 (10·8)	49·4 (11·6)	48·6 (11·1)
White ethnic origin	140 (90%)	139 (91%)	135 (89%)	140 (90%)
Body-mass index (kg/m^2)	28·3 (6·1)	28·4 (6·0)	28·3 (5·9)	28·9 (5·8)
Former smoker	34 (22%)	31 (20%)	31 (20%)	37 (24%)
Duration of asthma (years)	17·9 (13·7)	19·0 (14·1)	20·4 (13·9)	19·1 (15·3)
Use of longacting β-agonists	150 (97%)	143 (93%)	145 (95%)	151 (97%)
Maintenance use of oral corticosteroids	45 (29%)	46 (30%)	50 (33%)	47 (30%)
Daily dose (mg)*	10 (10–20)	10 (10–20)	10 (8–20)	13 (10–20)
Nasal polyps†	16 (10%)	11 (7%)	22 (14%)	13 (8%)
Atopy‡	81 (52%)	78 (51%)	76 (50%)	76 (49%)
Prebronchodilator FEV_1 (mL)	1900 (653)	1810 (637)	1850 (672)	1950 (670)
Postbronchodilator FEV_1 (mL)	2290 (773)	2150 (695)	2220 (732)	2260 (784)
Percentage of predicted prebronchodilator FEV_1	59% (15)	60% (16)	59% (17)	61% (16)
Postbronchodilator FEV_1/FVC	67% (12)	68% (12)	66% (13)	68% (20)
Score on asthma control questionnaire	2·5 (1·1)	2·2 (1·1)	2·4 (1·1)	2·3 (1·2)
Score on asthma quality of life questionnaire	4·1 (1·2)	4·2 (1·2)	4·2 (1·2)	4·2 (1·2)
Blood eosinophil count (×10^9/L)§¶	0·28 (1·01)	0·25 (0·95)	0·23 (1·20)	0·25 (0·93)
Sputum eosinophil count (%)§¶	6·8% (2·01); n=24	13·9% (1·47); n=18	8·1% (1·79); n=23	5·8% (2·15); n=21
FE_{NO} (ppb)§¶	33·7 (0·79)	29·2 (0·76)	31·4 (0·80)	31·6 (0·81)
Severe exacerbations in previous year	3·7 (3·8)	3·7 (3·1)	3·4 (2·4)	3·5 (2·8)
Exacerbations requiring admission in previous year	40 (26%)	35 (23%)	36 (24%)	39 (25%)

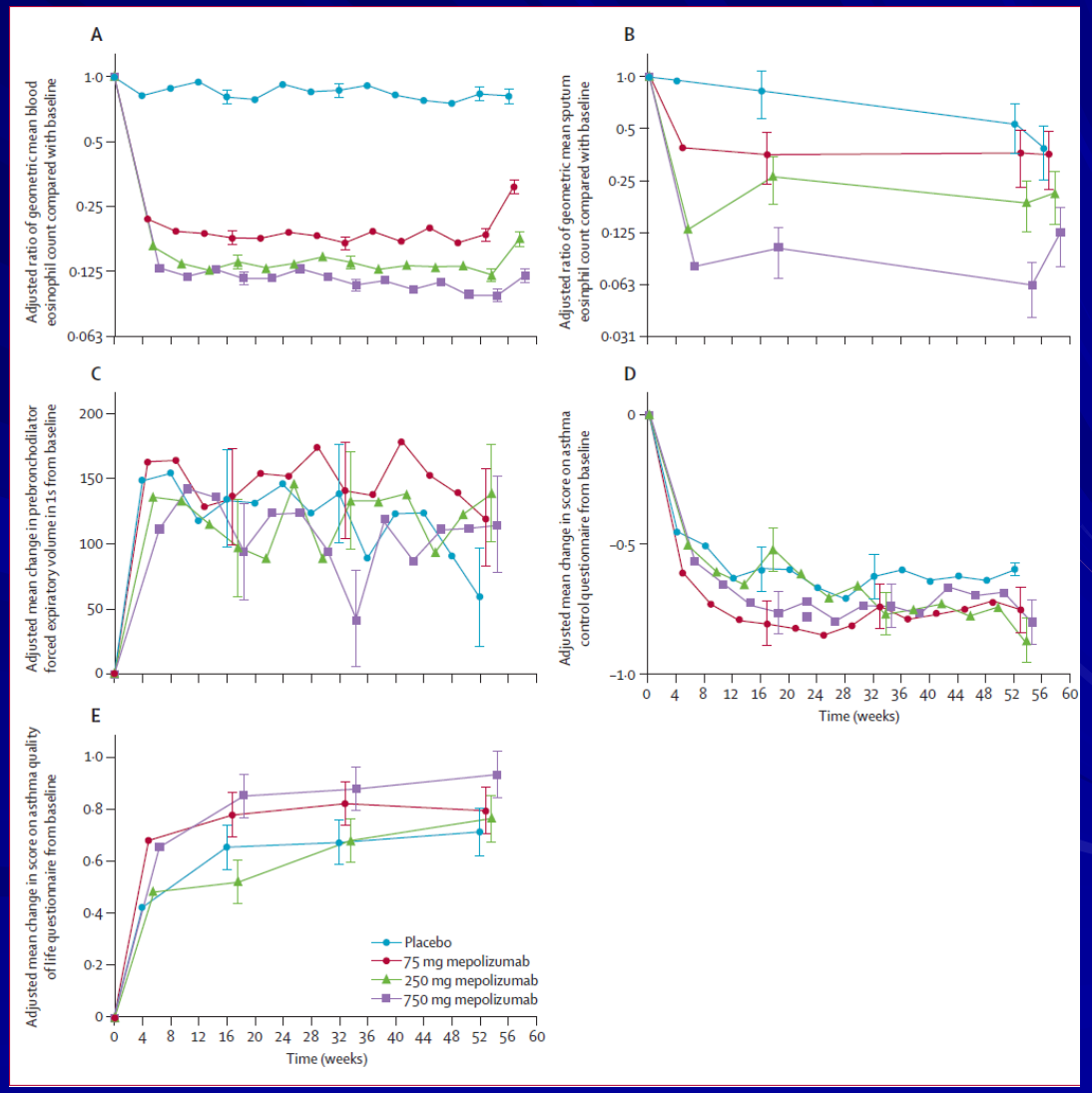
Data are n (%), mean (SD), or median (IQR), unless otherwise stated. *Prednisolone equivalent. †Self reported. ‡Positive atopic status was defined as a positive radioallergosorbent test for any of four specified aeroallergens. §Values below lower limit of quantification were replaced by half the lower limit of quantification. ¶Geometric mean on $\log_e$ scale.

Table 1: **Baseline characteristics of the intention-to-treat population**

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

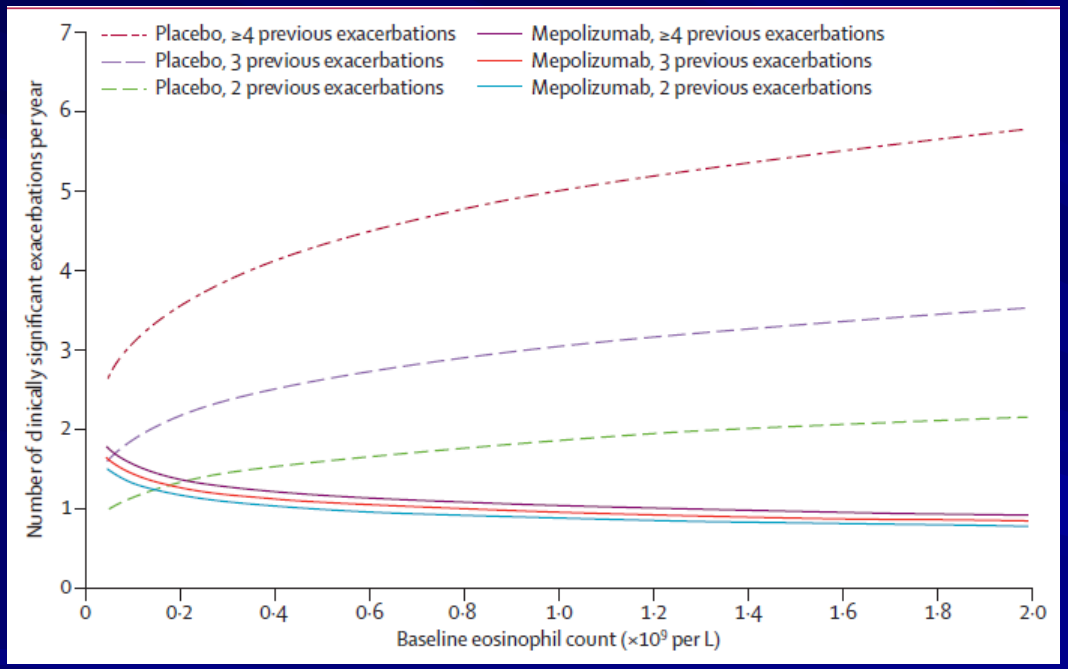
Ian D Pavord, Stephanie Korn, Peter Howarth, Eugene R Bleecker, Roland Buhl, Oliver N Keene, Hector Ortega, Pascal Chanez





Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

Ian D Pavord, Stephanie Korn, Peter Howarth, Eugene R Bleecker, Roland Buhl, Oliver N Keene, Hector Ortega, Pascal Chanez



	Placebo group (n=155)	75 mg mepolizumab group (n=153)	250 mg mepolizumab group (n=152)	750 mg mepolizumab group (n=156)
Adverse events leading to withdrawal	6 (4%)	5 (3%)	8 (5%)	9 (6%)
Fatal adverse events	0	0	2 (1%)	1 (<1%)
Any on-treatment serious adverse events*	25 (16%)	20 (13%)	24 (16%)	19 (12%)
Respiratory, thoracic, and mediastinal disorders	17 (11%)	11 (7%)	16 (11%)	10 (6%)
Infections	5 (3%)	7 (5%)	3 (2%)	5 (3%)
Cardiac disorders	1 (<1%)	2 (1%)	1 (<1%)	4 (3%)
Injury, poisoning, and procedural complications	2 (1%)	1 (<1%)	2 (1%)	1 (<1%)
Gastrointestinal disorders	1 (<1%)	0	2 (1%)	1 (<1%)
Nervous system disorders	3 (2%)	0	0	1 (<1%)
Renal and urinary disorders	2 (1%)	0	2 (1%)	0
Vascular disorders	0	2 (1%)	1 (<1%)	1 (<1%)

*Patients can have more than one event; events shown are those reported in four or more patients across all groups.

Table 3: Adverse events

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez M.D., Ph.D., for the MENSA Investigators*

- Randomized, double-blind, double-dummy study
- 576 pts with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high doses of ICS
- 3 study groups: mepolizumab 75mg IV, mepolizumab 100mg SC, placebo for 32 weeks (every 4 weeks)
- Primary outcome: Annualized rate of exacerbations
- Secondary outcomes: FEV1, SGRQ, ACQ-5, safety
- At least 2 asthma exacerbations in the previous year treated with systemic glucocorticoids, while on >880µg fluticasone and an additional controller (for 3 m)
- Blood eosinophil count >150/µL or >300 at some time the previous year

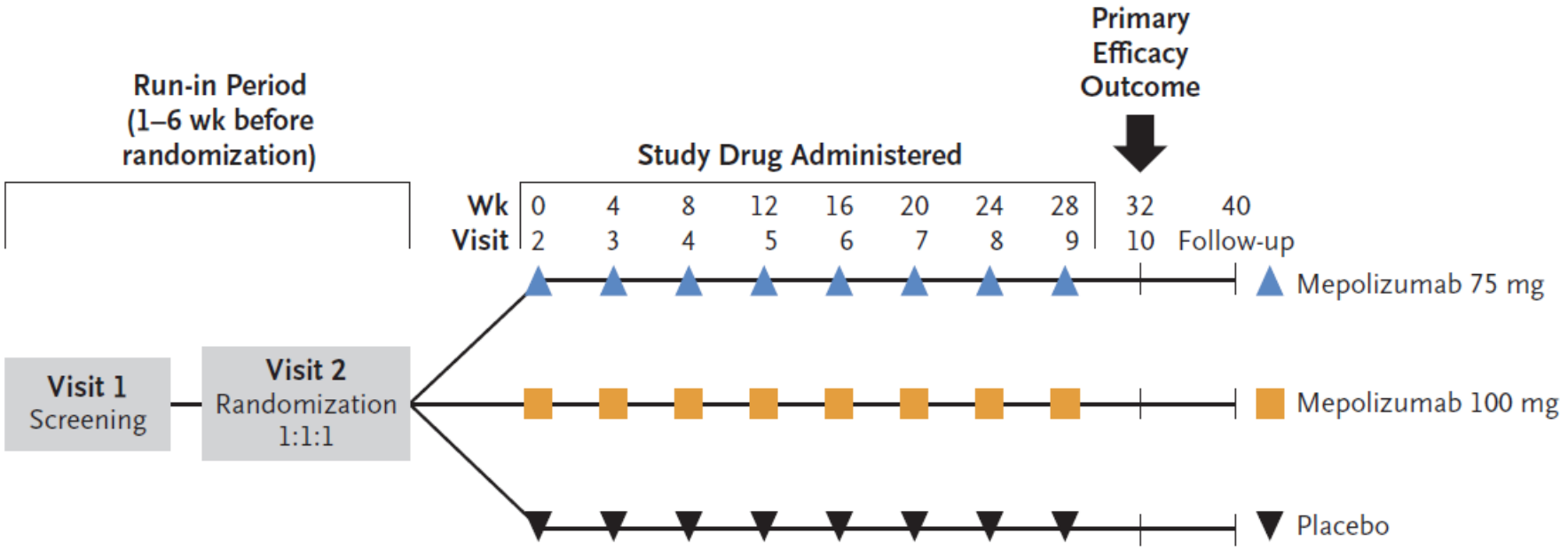
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez M.D., Ph.D., for the MENSA Investigators*

A



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez M.D., Ph.D., for the MENSA Investigators*

Table 1. Characteristics of the Patients at Baseline in the Intention-to-Treat Population.*

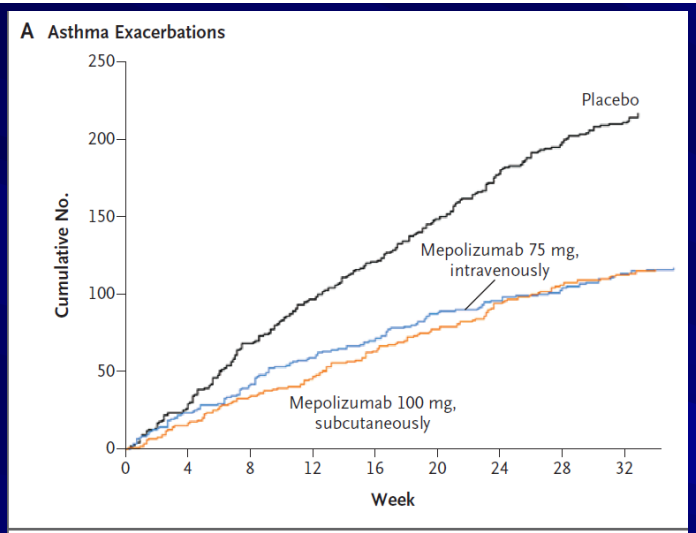
Characteristic	Placebo (N=191)	Mepolizumab	
		Intravenous (N=191)	Subcutaneous (N=194)
Mean age (range) — yr	49 (12–76)	50 (13–82)	51 (12–81)
Female sex — no. (%)	107 (56)	106 (55)	116 (60)
Body-mass index†	28.0±5.6	27.7±5.7	27.6±6.2
Former smoker — no. (%)	57 (30)	52 (27)	50 (26)
Duration of asthma — yr	19.5±14.6	19.8±14.0	20.5±12.9
Use of oral glucocorticoids			
Maintenance use — no. (%)	44 (23)	48 (25)	52 (27)
Mean daily dose (range) — mg‡	15.1 (5–80)	12.0 (1–40)	12.6 (2–50)
Allergic rhinitis — no. (%)	95 (50)	91 (48)	95 (49)
FEV_1			
Before bronchodilation — liters§	1.86±0.63	1.86±0.70	1.73±0.66
Percent of predicted value before bronchodilation¶	62.4±18.1	61.4±18.3	59.3±17.5
Reversibility — %	27.4±20.8	25.4±19.6	27.9±24.0
FEV_1:FVC ratio — %‖	64±13	64±13	63±13
Morning peak expiratory flow — liters/min	277±106	269±112	255±108
Score on Asthma Control Questionnaire**	2.28±1.19	2.12±1.13	2.26±1.27
Score on St. George's Respiratory Questionnaire††	46.9±19.8	44.4±19.4	47.9±19.4
Geometric mean IgE on $\log_e$ scale — U/ml	150±1.5	180±1.5	150±1.5
Geometric mean blood eosinophil count on $\log_e$ scale — cells/μl‡‡	320±938	280±987	290±1050
Asthma exacerbations			
Severe episodes in previous year — no./patient	3.6±2.8	3.5±2.2	3.8±2.7
Necessitating hospitalization in previous year — no. (%)	35 (18)	41 (21)	33 (17)
History of asthma-related intubation — no. (%)	3 (2)	10 (5)	8 (4)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez M.D., Ph.D., for the MENSA Investigators*



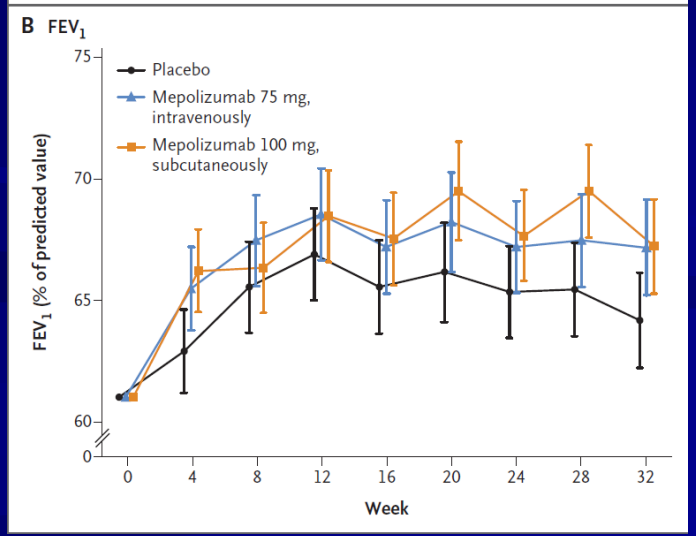


Table 2. Summary of Efficacy Outcomes.*

Outcome	Placebo (N=191)	Intravenous Mepolizumab (N=191)	Difference from Placebo (95% CI)	P Value	Subcutaneous Mepolizumab (N=194)	Difference from Placebo (95% CI)	P Value
Mean rate of clinically significant exacerbations	1.74	0.93	47 (28 to 60)†	<0.001	0.83	53 (36 to 65)†	<0.001
Mean rate of exacerbations requiring hospitalization or emergency department visit	0.20	0.14	32 (−41 to 67)†	0.30	0.08	61 (17 to 82)†	0.02
Mean rate of exacerbations requiring hospitalization	0.10	0.06	39 (−66 to 77)†	0.33	0.03	69 (9 to 89)†	0.03
Change from baseline in FEV_1 — ml							
Before bronchodilation	86±31	186±32	100 (13 to 187)	0.02	183±31	98 (11 to 184)	0.03
After bronchodilation	30±34	176±34	146 (50 to 242)	0.003	167±33	138 (43 to 232)	0.004
Change from baseline in score on Asthma Control Questionnaire	−0.50±0.07	−0.92±0.07	−0.42 (−0.61 to −0.23)	<0.001	−0.94±0.07	−0.44 (−0.63 to −0.25)	<0.001
Change from baseline in score on St. George's Respiratory Questionnaire	−9.0±1.2	−15.4±1.2	−6.4 (−9.7 to −3.2)	<0.001	−16.0±1.1	−7.0 (−10.2 to −3.8)	<0.001

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2014 VOL. 371 NO. 13

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

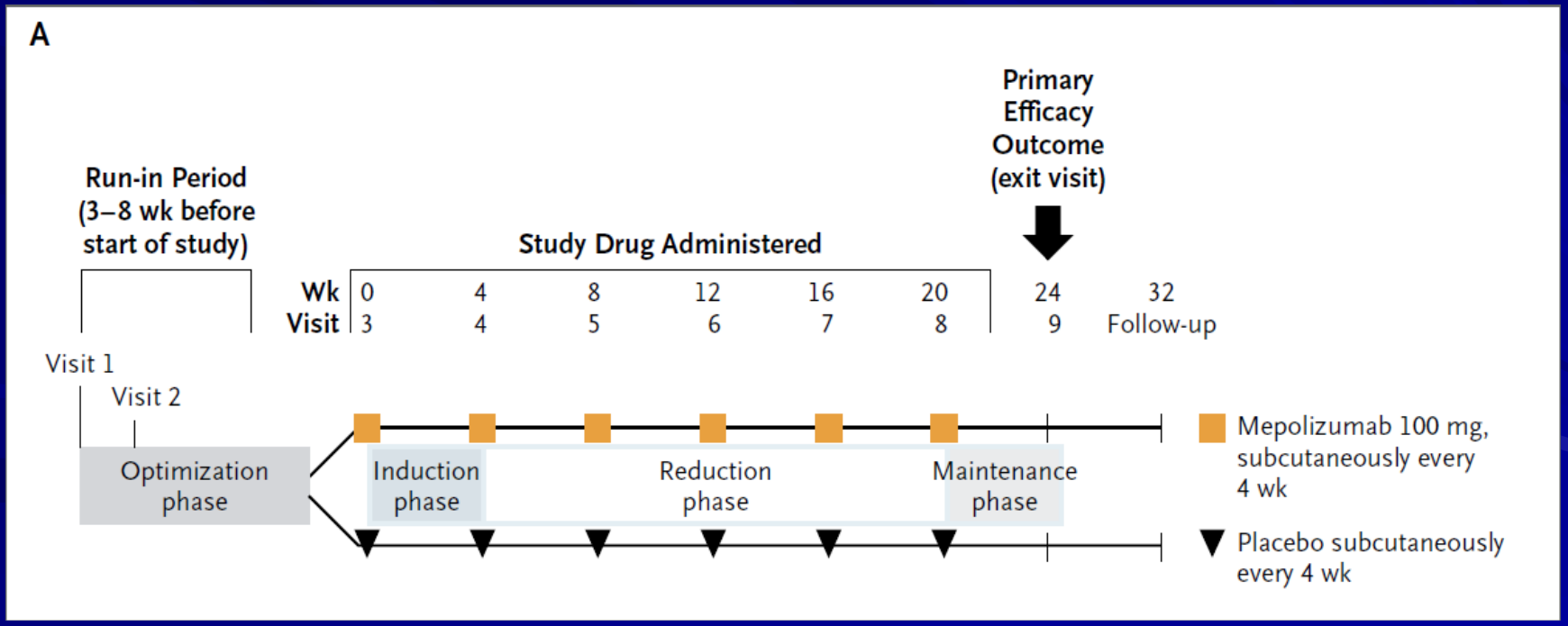
- Randomized double-blind trial
- 135 pts, 100mg mepolizumab SC vs. placebo, every 4 weeks for 20 weeks
- Primary outcome: percentage reduction in the daily glucocorticoid dose (90-100% reduction, 75-<90%, 50-<75%, >0-<50%, no decrease, lack of asthma control at weeks 20-24)
- Other outcomes: rate of asthma exacerbations, asthma control, safety
- 4 phases: optimization of oral steroid regimen, induction, reduction in the oral steroid dose and maintenance
- At least 6m of treatment with oral steroids plus eosinophilic inflammation (blood eosinophils > 150cells/μL or >300 the past 12m)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2014 VOL. 371 NO. 13

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2014 VOL. 371 NO. 13

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Placebo (N=66)	Mepolizumab (N=69)
Mean age (range) — yr	50 (28–70)	50 (16–74)
Female sex — no. (%)	30 (45)	44 (64)
Body-mass index†	29.5±6.0	27.8±5.9
Former smoker — no. (%)	25 (38)	28 (41)
Duration of asthma — yr	20.1±14.4	17.4±11.8
Median daily oral glucocorticoid dose — mg‡		
At screening	15.0	12.5
During optimization phase	12.5	10.0
Duration of oral glucocorticoid use ≥5 yr — no. (%)	31 (47)	34 (49)
FEV_1 before bronchodilation		
Mean — liters	2.00±0.82	1.90±0.66
Percent of predicted value	57.8±18.5	59.6±17.0
FEV_1:FVC ratio before bronchodilation — %§	61±11.7	63±12.4
Percent reversibility of FEV_1	24.8±18.1	27.3±17.4
ACQ-5 score¶	2.0±1.2	2.2±1.3
SGRQ score‖	45±18	50±18
Geometric mean IgE on $\log_e$ scale — U/ml	114±1	117±1
Geometric mean blood eosinophil count on $\log_e$ scale — cells/μl**	230±1001	250±1245
Severe exacerbations in previous year — no./patient	2.9±2.8	3.3±3.4
Exacerbations in the previous year requiring hospitalization — no. (%)	9 (14)	14 (20)
History of asthma-related intubation — no. (%)	3 (5)	2 (3)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2014 VOL. 371 NO. 13

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

Table 2. Primary and Secondary Outcomes.

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

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2014 VOL. 371 NO. 13

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

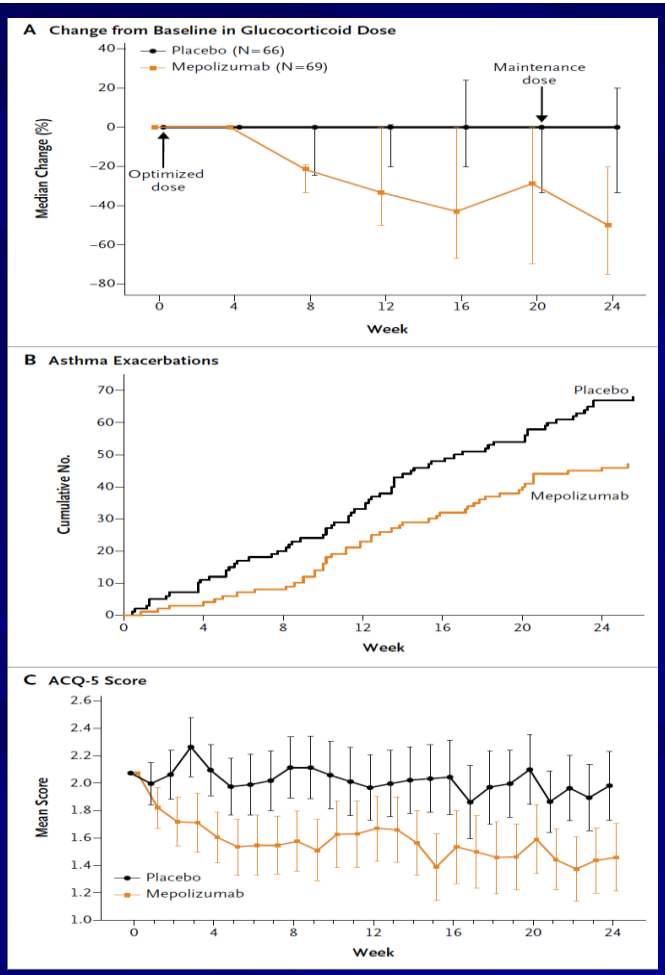


Table 3. Summary of Adverse Events.

Event	Placebo (N = 66)	Mepolizumab (N = 69)
	no. of patients (%)	
Adverse event		
Any	61 (92)	57 (83)
Nonasthma	60 (91)	57 (83)
Worsening of asthma	8 (12)	2 (3)
Related to study drug*	12 (18)	21 (30)
Leading to discontinuation of study drug or withdrawal from the study	3 (5)	3 (4)
Serious adverse event		
During treatment	12 (18)	1 (1)
Fatal	1 (2)	0

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

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

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

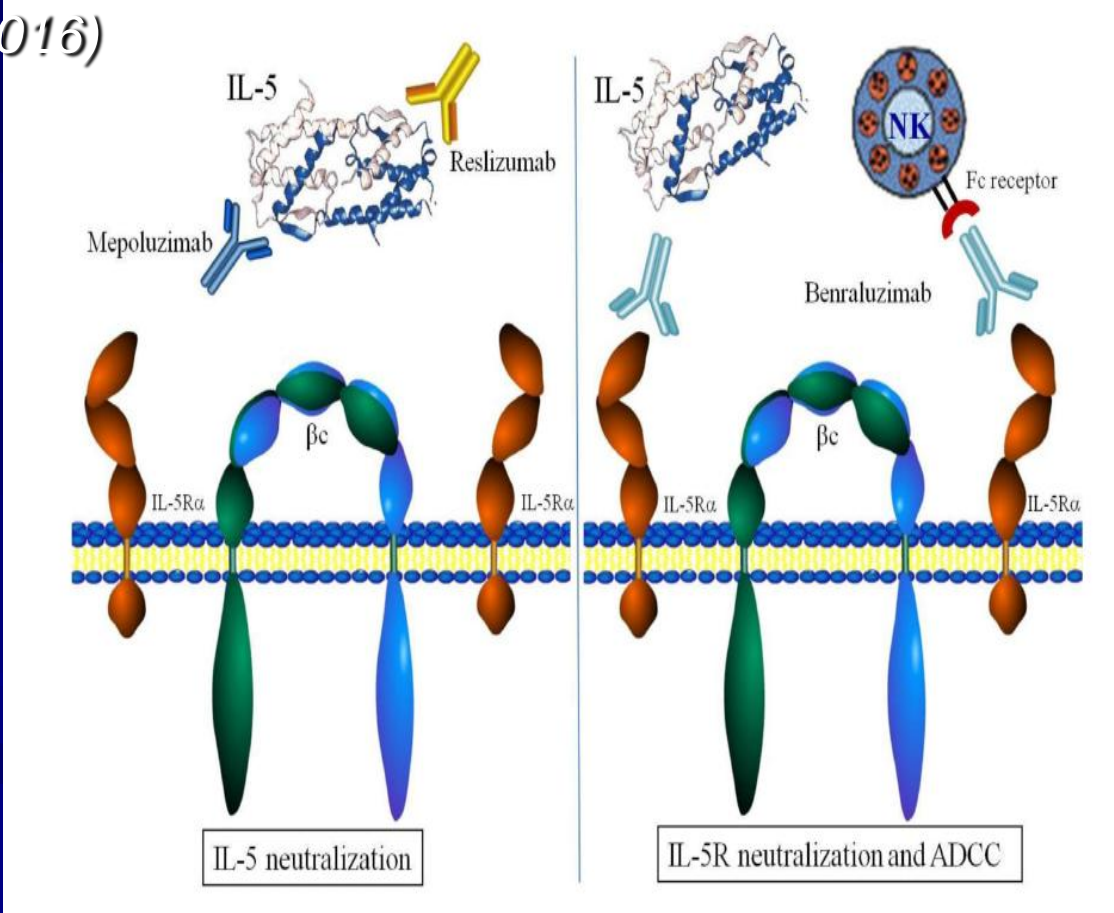
Lancet Respir Med 2016; 4: 549–56

OTHER ANTI-IL-5 Abs

Reslizumab:

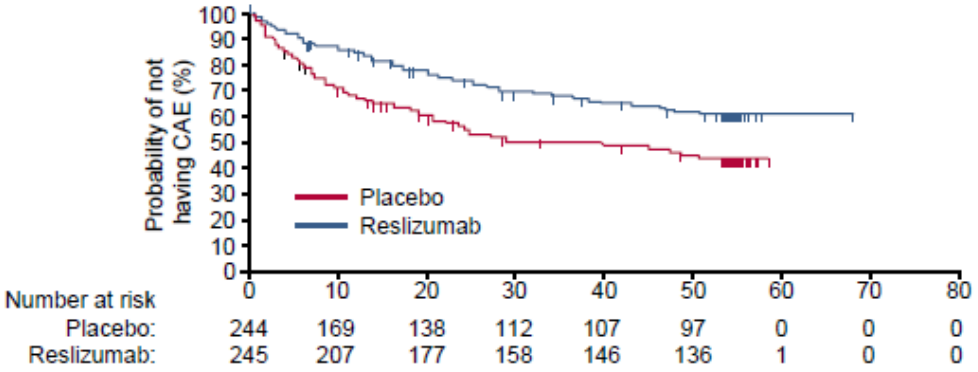
Humanized IgG4 Ab against IL-5 (FDA approval 23/3/2016)

***Benralizumab**: Humanized Ab against a chain of IL-5R*

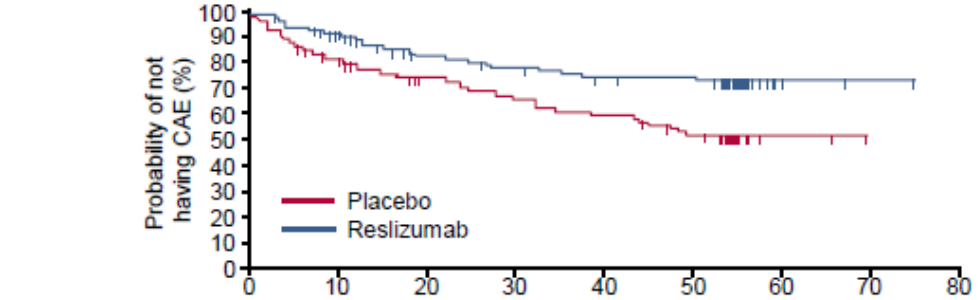


Amini-Vaughan ZJ et al, Curr Allergy Asthma Rep 2012

Reslizumab significantly improved outcomes for patients with inadequately controlled asthma and elevated blood eosinophil counts



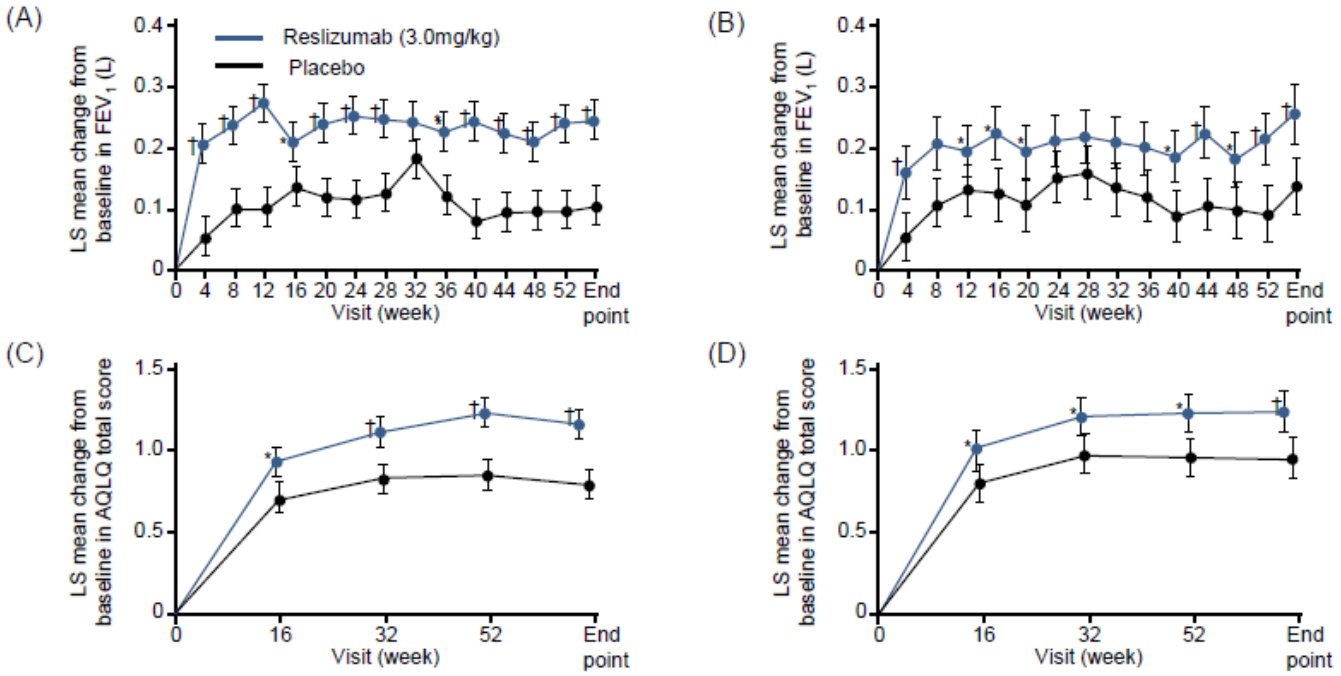
Placebo; n=244
Reslizumab; 3.0 mg/kg; n=245
HR 0.575 (95% CI 0.44–0.75)
p<0.0001



Placebo; n=232
Reslizumab; 3.0 mg/kg; n=232
HR 0.486 (95% CI 0.353–0.75)
p<0.0001

Castro M, et al. Lancet Respir Med 2015;3:355-66

Changes in FEV_1 and AQLQ over 52 weeks



Changes in FEV_1 (A) and AQLQ (C) for Study 1 and FEV_1 (B) and AQLQ (D) for study 2. In both studies FEV_1 improved by week 4 and this was maintained until the end of the study. AQLQ score was improved compared to baseline (week 0) at the first measured timepoint (week 16) and this improvement was maintained until week 52.

LS, least-squares; FEV_1, forced expiratory volume in 1s; AQLQ, asthma quality of life questionnaire.
*p<0.05, †p<0.01

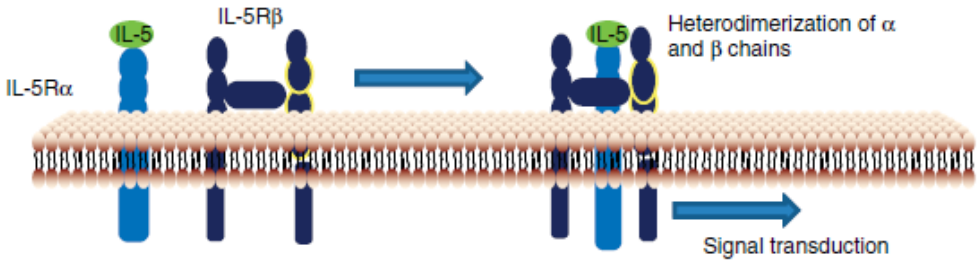
Castro M, et al. Lancet Respir Med 2015;3:355-66

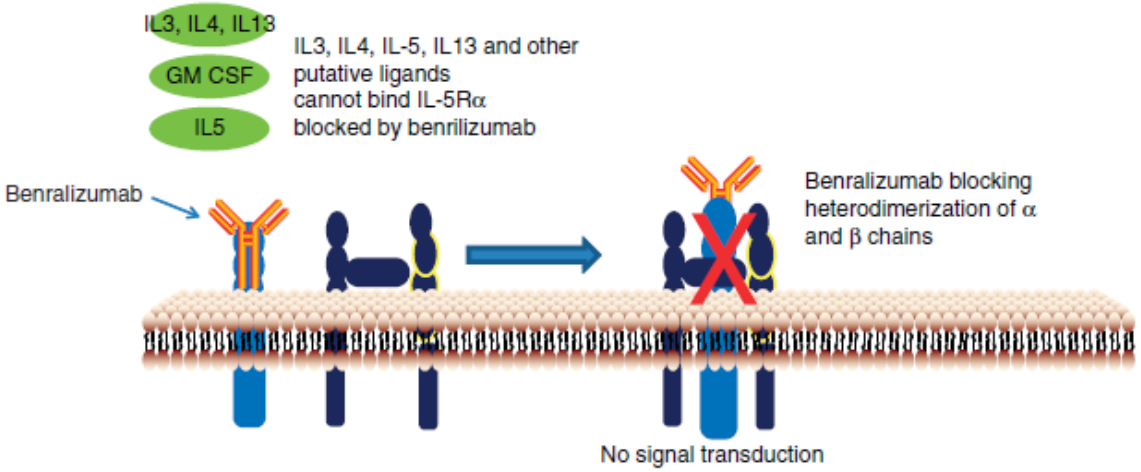
Expert Opinion

1. Introduction
2. Expert opinion and conclusions

Benralizumab – a humanized mAb to IL-5Rα with enhanced antibody-dependent cell-mediated cytotoxicity – a novel approach for the treatment of asthma

Aasia Ghazi, Anita Trikha & William J Calhoun†





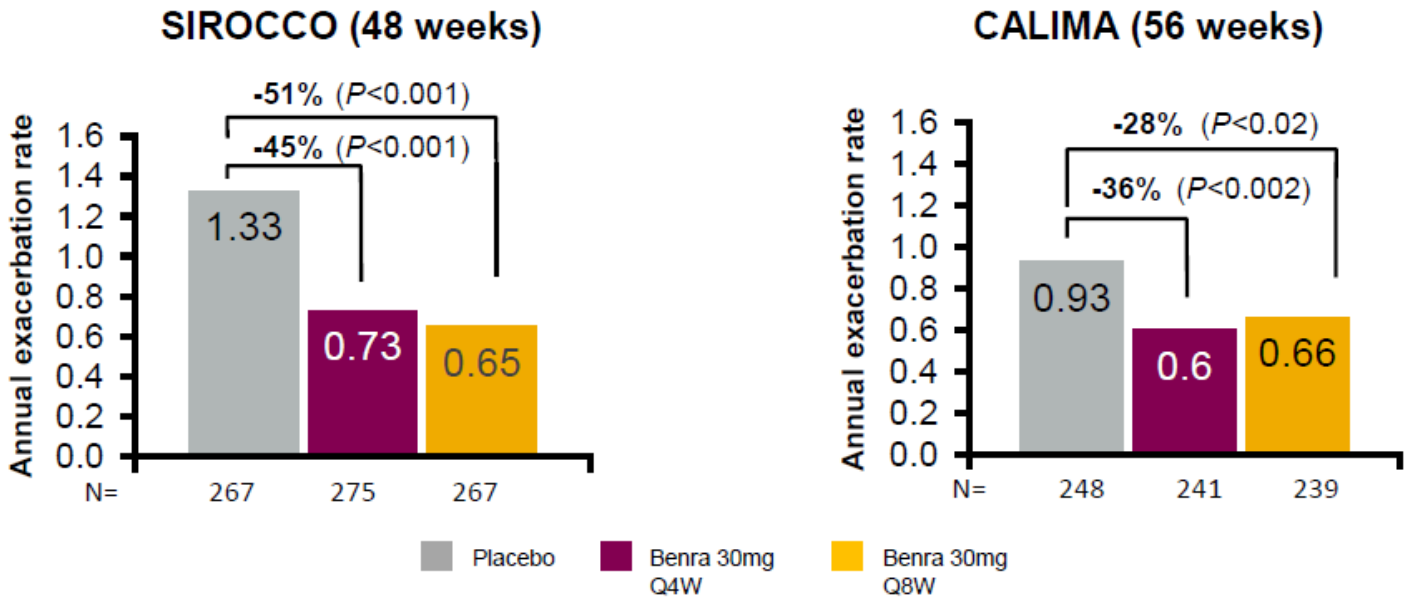
BENRALIZUMAB

SIROCCO – CALIMA

- Same study design
- Benralizumab 30mg Q4W, Q8W (first 3 doses every 4 weeks) or placebo
- > or < 300 eosinophils per µL
- SIROCCO: 48 weeks - 407 placebo, 400 Q4W, 398 Q8W
- CALIMA: 56 weeks – 440 placebo, 425 Q4W, 441 Q8W
- Stratification 2:1

BENRALIZUMAB

Primary effficacy: both benralizumab dosing schedules significantly reduced AER Compared to placebo (FAS, eos ≥300 cells/µL, high-dosage ICS)

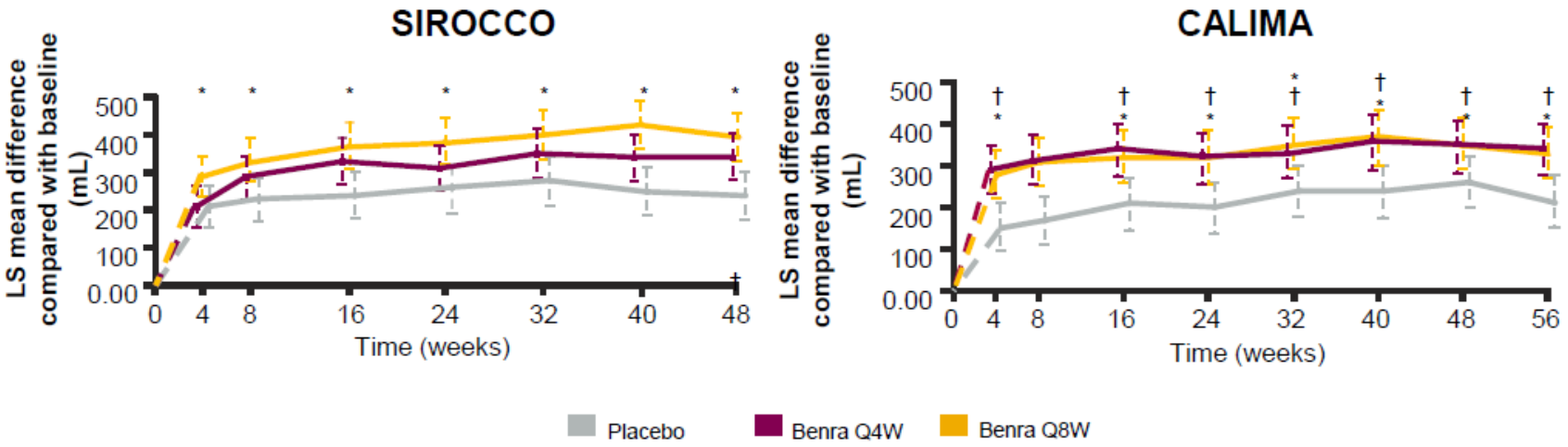


AER, annual asthma exacerbation rate, EOS, eosinophil; FAS, full analysis set; ICS, inhaled corticosteroids

Bleecker et al.Lancet 2016; 6736: 31324-1; FitzGerald et al.. Lancet 2016 6736:31332-8

BENRALIZUMAB

Both benralizumab dosing schedules significantly increased pre-bronchodilator FEV_1



Bleecker et al.Lancet 2016; 6736: 31324-1; FitzGerald et al.. Lancet 2016 6736:31332-8

Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies

	Placebo	Benralizumab Q4W	Benralizumab Q8W
Annual exacerbation rate			
<150 cells per µL			
Number of patients analysed	122	101	105
Rate estimate (95% CI)	1·26 (0·98 to 1·61)	0·97 (0·72 to 1·30)	0·91 (0·67 to 1·22)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·29 (−0·71 to 0·13)	−0·35 (−0·76 to 0·06)
Rate ratio *vs* placebo (95% CI)	..	0·77 (0·52 to 1·13)	0·72 (0·49 to 1·06)
p value *vs* placebo	..	0·18	0·10
150–299 cells per µL			
Number of patients analysed	137	136	147
Rate estimate (95% CI)	1·22 (0·96 to 1·54)	0·78 (0·60 to 1·02)	0·94 (0·73 to 1·21)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·43 (−0·79 to −0·08)	−0·27 (−0·65 to 0·10)
Rate ratio *vs* placebo (95% CI)	..	0·64 (0·45 to 0·92)	0·77 (0·55 to 1·09)
p value *vs* placebo	..	0·0152	0·15
300–449 cells per µL			
Number of patients analysed	205	216	201
Rate estimate (95% CI)	1·03 (0·85 to 1·26)	0·62 (0·50 to 0·78)	0·72 (0·57 to 0·90)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·41 (−0·66 to −0·17)	−0·32 (−0·58 to −0·05)
Rate ratio *vs* placebo (95% CI)	..	0·60 (0·44 to 0·81)	0·69 (0·51 to 0·94)
p value *vs* placebo	..	0·0008	0·0178
≥450 cells per µL			
Number of patients analysed	306	295	298
Rate estimate (95% CI)	1·16 (1·00 to 1·36)	0·69 (0·58 to 0·83)	0·58 (0·48 to 0·70)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·47 (−0·69 to −0·25)	−0·59 (−0·80 to −0·37)
Rate ratio *vs* placebo (95% CI)	..	0·59 (0·47 to 0·75)	0·50 (0·39 to 0·64)
p value *vs* placebo	..	<0·0001	<0·0001

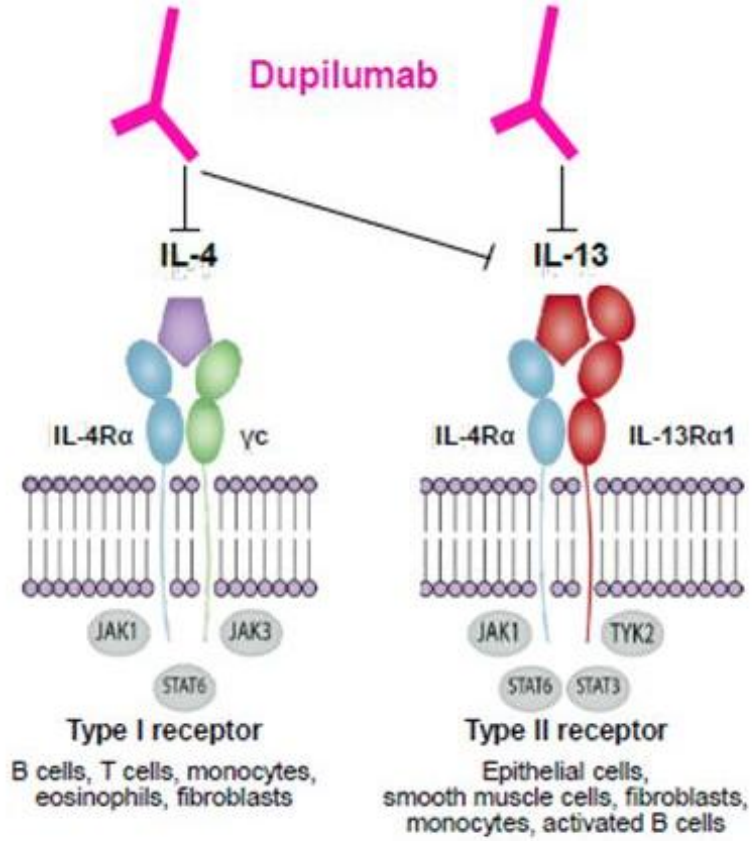
BENRALIZUMAB

Potential advantages over other anti-IL-5 Abs are:

- different mechanism of action
- less frequent dosing and
- a potential to reduce exacerbations irrespective of the blood eosinophil count.

Dupilumab:
An IL-4/IL-13 monoclonal antibody, targeting type 2/Th2 pathway

- IL-4 and IL-13 are type 2/Th2 cytokines that are thought to mediate many features of AD
- Dupilumab is a fully human monoclonal antibody directed against the IL-4Rα subunit of the IL-4 and IL-13 receptors
- Dupilumab is currently under clinical development, and its safety and efficacy have not been fully evaluated by any regulatory authority.



ANTI-IL-4R IN PERSISTENT EOSINOPHILIC ASTHMA

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 27, 2013 VOL. 368 NO. 26

Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

Sally Wenzel, M.D., Linda Ford, M.D., David Pearlman, M.D., Sheldon Spector, M.D., Lawrence Sher, M.D., Franck Skobieranda, M.D., Lin Wang, Ph.D., Stephane Kirkesseli, M.D., Ross Rocklin, M.D., Brian Bock, D.O., Jennifer Hamilton, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Graham, M.D., and Gianluca Pirozzi, M.D., Ph.D.

ABSTRACT

BACKGROUND

Moderate-to-severe asthma remains poorly treated. We evaluated the efficacy and safety of dupilumab (SAR231893/REGN668), a fully human monoclonal antibody to the alpha subunit of the interleukin-4 receptor, in patients with persistent, moderate-to-severe asthma and elevated eosinophil levels.

From the Division of Pulmonary Allergy and Critical Care Medicine, University of Pittsburgh, Pittsburgh (S.W.); Asthma and Allergy Center, Bellevue, NE (L.F.); Colorado Allergy and Asthma Centers, Denver (D.P.); California Allergy and Asth-

The NEW ENGLAND JOURNAL of MEDICINE

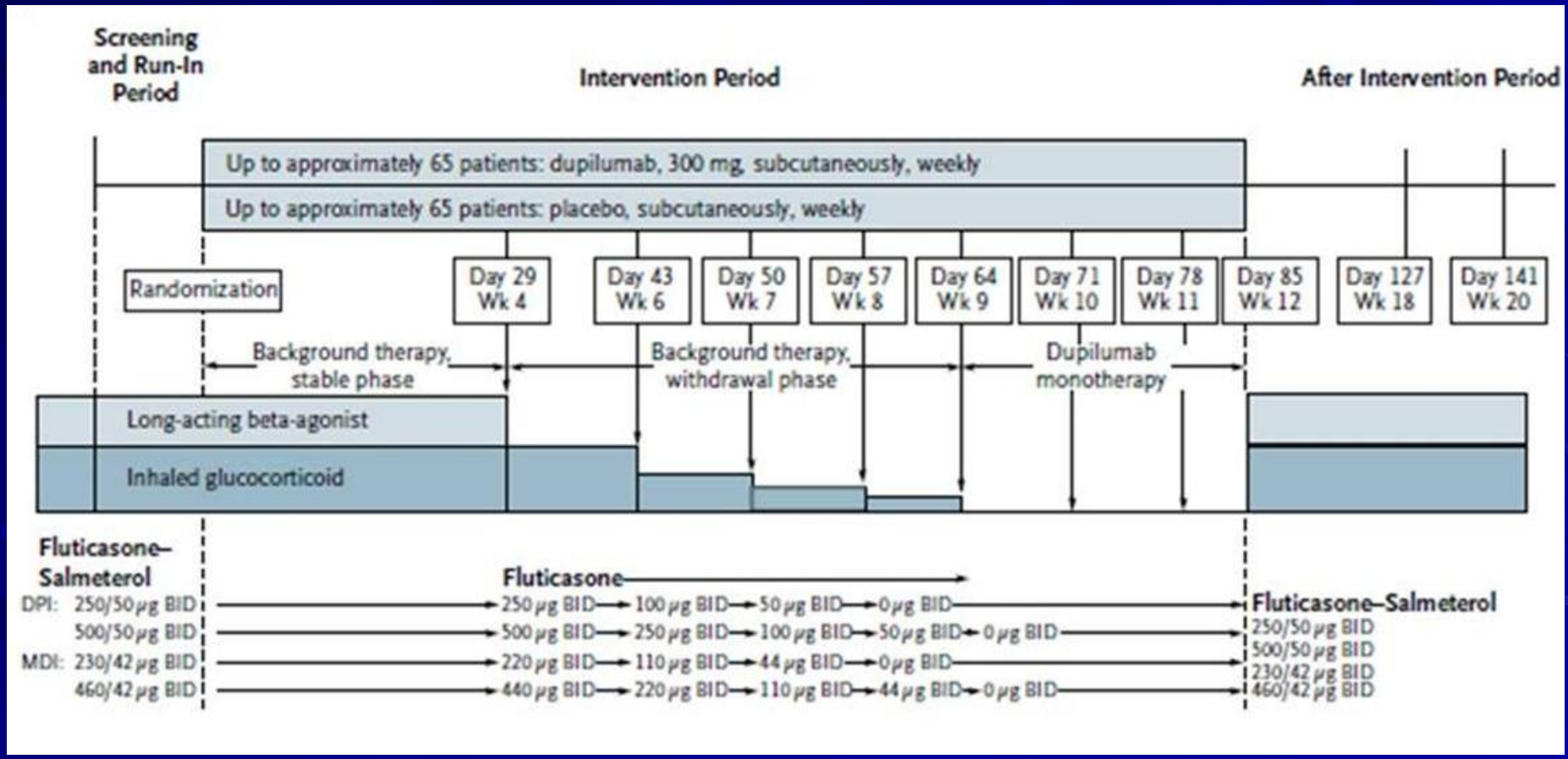
ESTABLISHED IN 1812 JUNE 27, 2013 VOL. 368 NO. 26

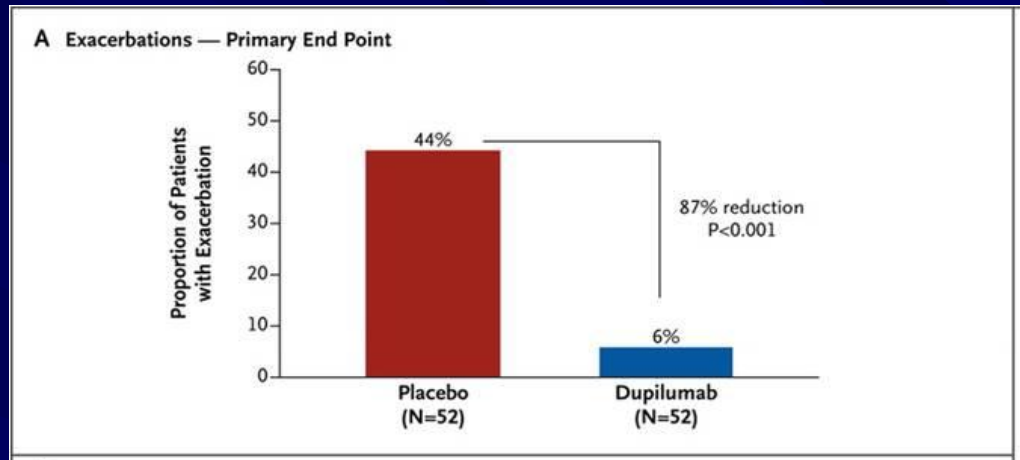
Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

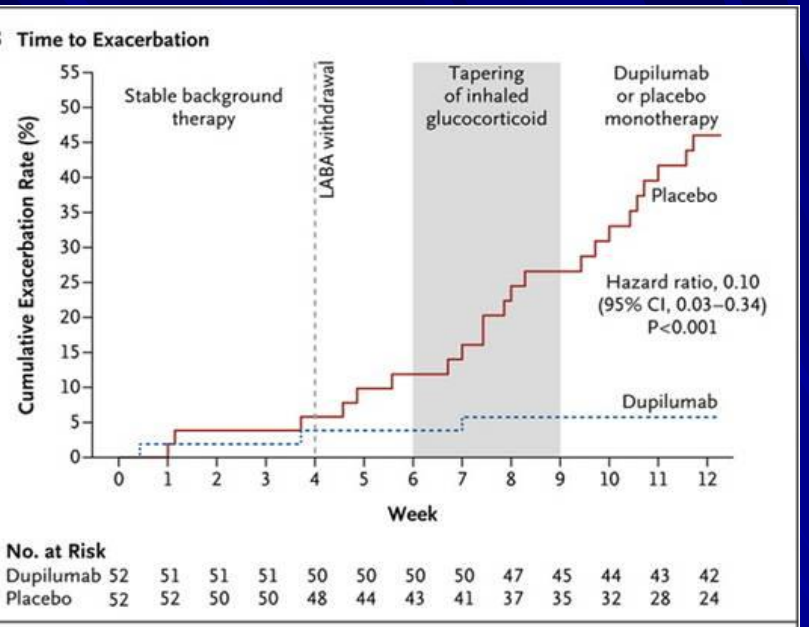
Sally Wenzel, M.D., Linda Ford, M.D., David Pearlman, M.D., Sheldon Spector, M.D., Lawrence Sher, M.D., Franck Skobieranda, M.D., Lin Wang, Ph.D., Stephane Kirkesseli, M.D., Ross Rocklin, M.D., Brian Bock, D.O., Jennifer Hamilton, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Graham, M.D., and Gianluca Pirozzi, M.D., Ph.D.

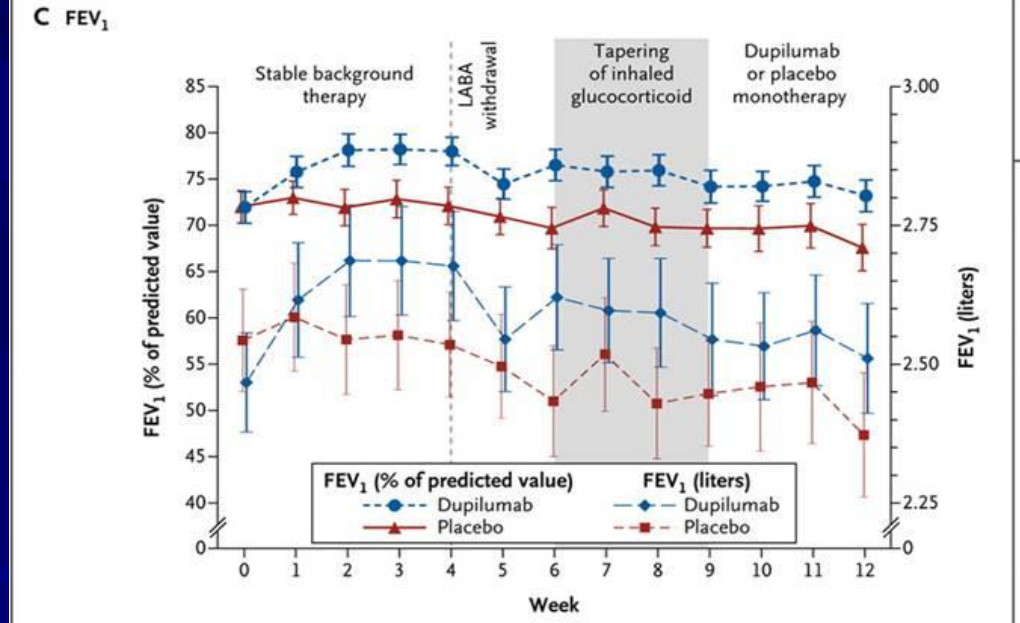
Study design

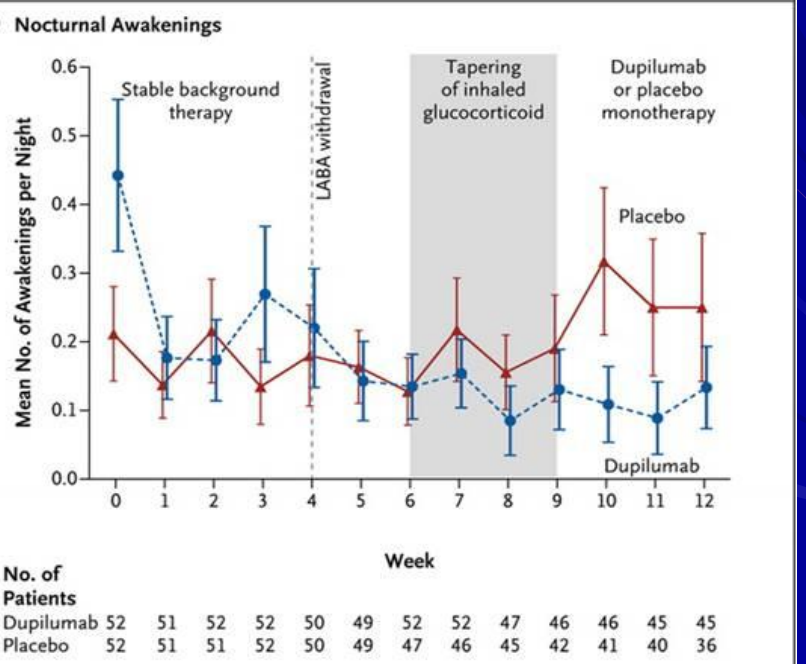
12 weeks or until first exacerbation











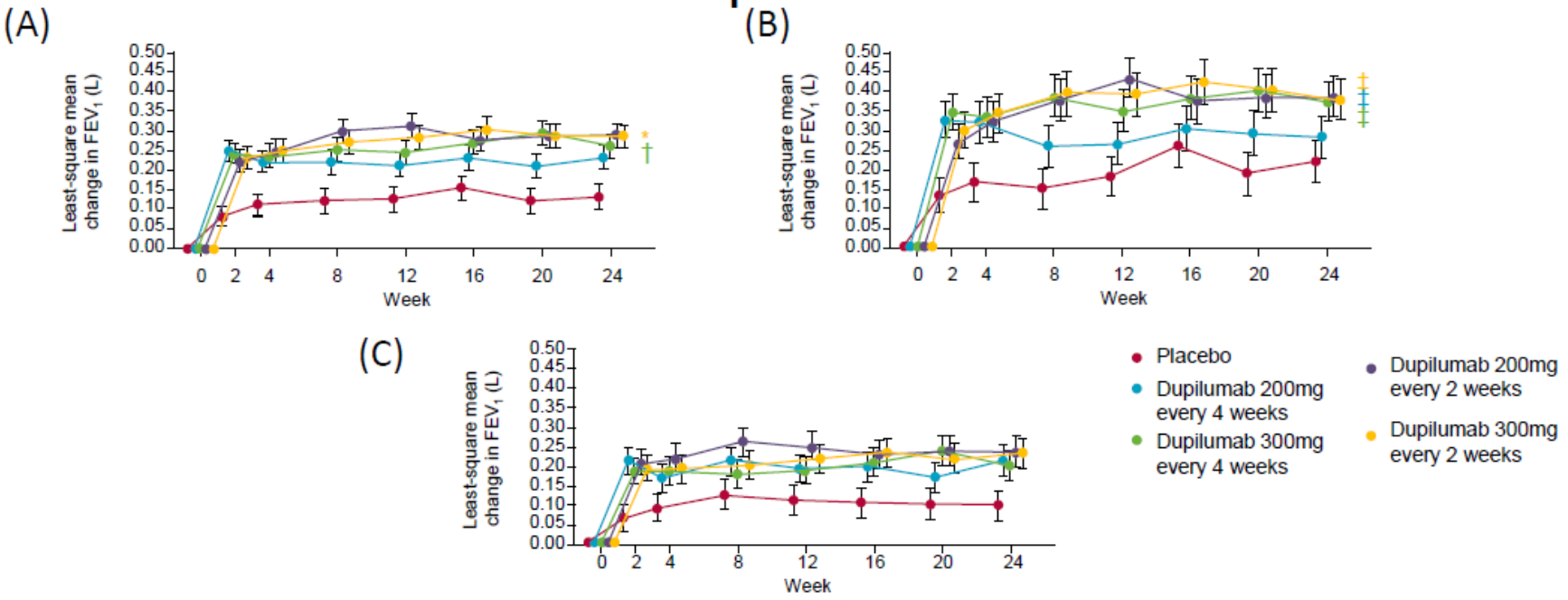
Wenzel S et al, NEJM 2013

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

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

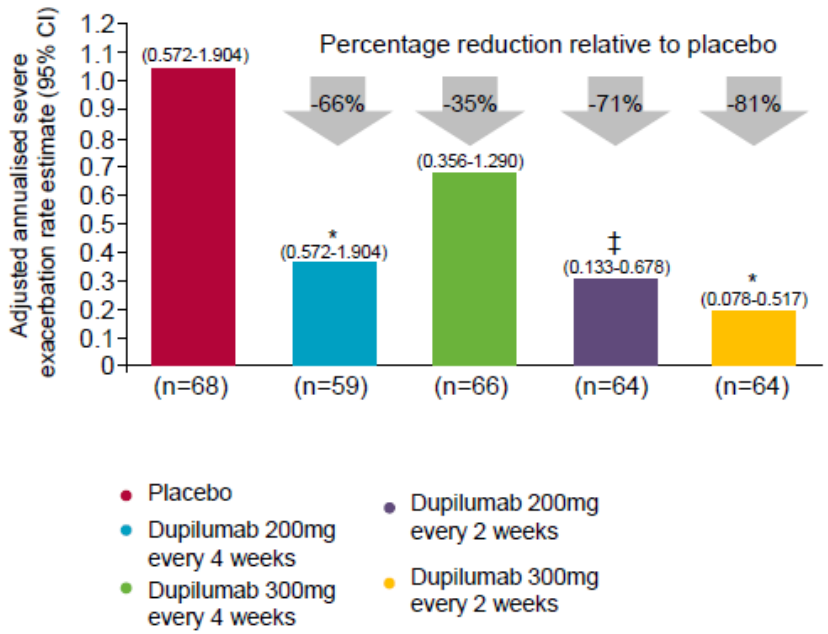
Wenzel et al Lancet 2016; 388:31-44

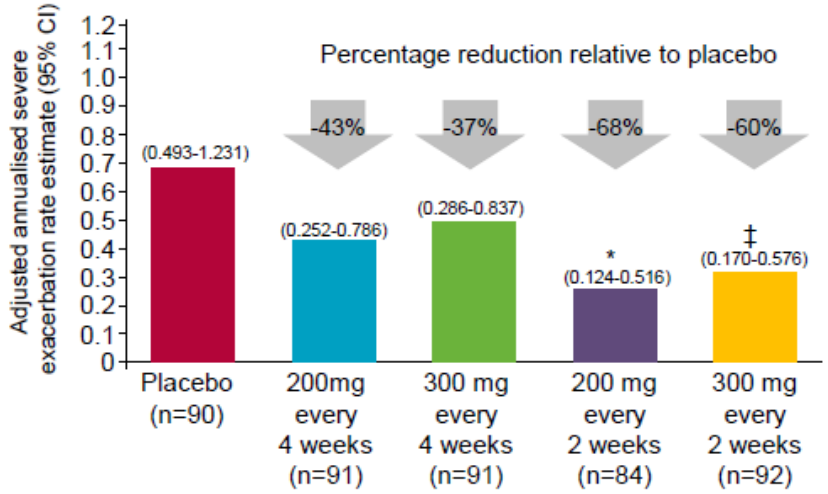
Dupliumab increases lung function in patients with uncontrolled persistent asthma



Wenzel et al Lancet 2016; 388:31-44

Dupliumab reduces the annual exacerbation rate in patients with uncontrolled persistent asthma





Wenzel et al Lancet 2016; 388:31-44

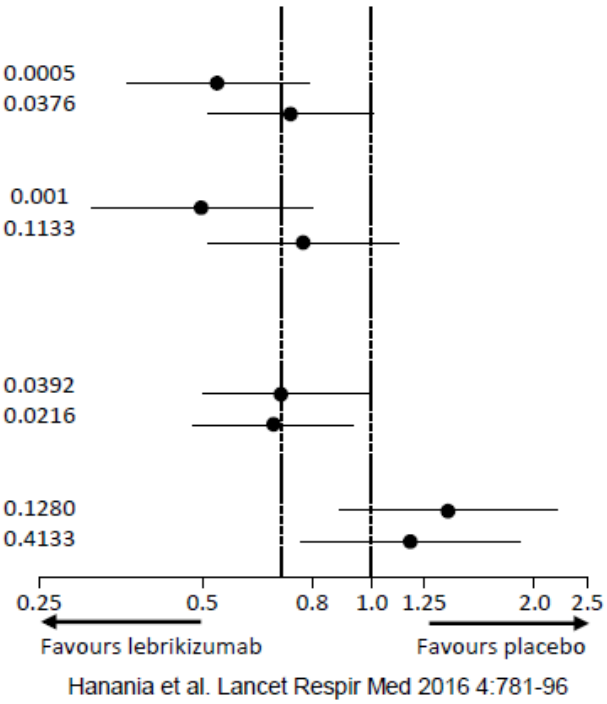
≥ 300 eosinophils/ µL

< 300 eosinophils/ µL

Anti-IL-13

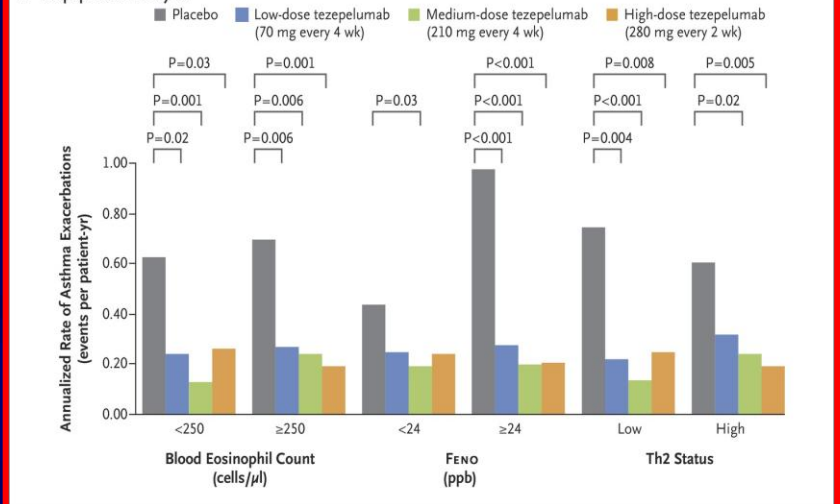
LAVOLTA I and LAVOLTA II :Efficacy and safety of lebrikizumab in patients with uncontrolled asthma

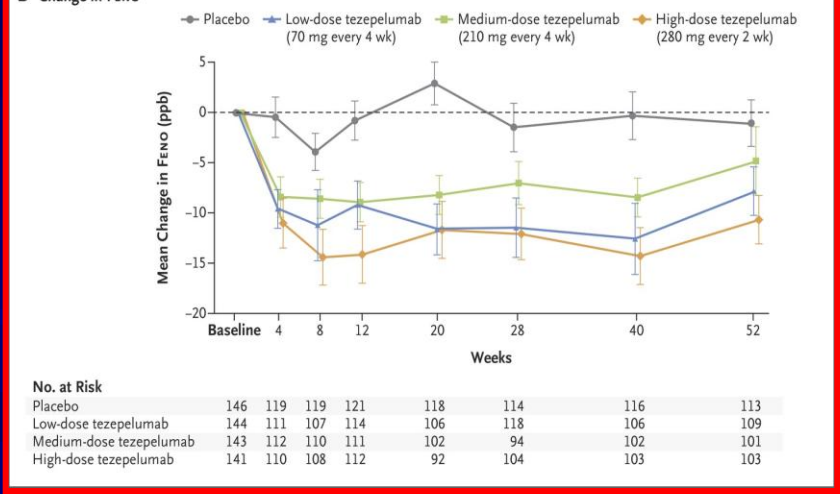
	N	Adjusted exacerbation rate (per patient per year)	Rate difference (lebrikizumab-placebo)	Rate reduction (%)	Rate ratio (lebrikizumab vs placebo, 95% CI)	p value
LAVTOLA I						
Periostin high						
Placebo	220	0.95				
Lebrikizumab 37.5 mg	211	0.48	-0.46	49	0.51 (0.35–0.74)	0.0005
Lebrikizumab 125 mg	221	0.66	-0.29	31	0.69 (0.49–0.98)	0.0376
Periostin low						
Placebo	142	0.68				
Lebrikizumab 125 mg	149	0.32	-0.36	53	0.47 (0.30–0.74)	0.001
Lebrikizumab 37.5 mg	138	0.50	-0.19	27	0.73 (0.49–1.08)	0.1133
LAVOLTA II						
Periostin high						
Placebo	214	0.77				
Lebrikizumab 37.5 mg	218	0.54	-0.23	30	0.70 (0.50–0.98)	0.0392
Lebrikizumab 125 mg	220	0.52	-0.25	32	0.68 (0.48–0.94)	0.0216
Periostin low						
Placebo	140	0.35				
Lebrikizumab 125 mg	138	0.50	0.15	-43	1.43 (0.90–2.26)	0.1280
Lebrikizumab 37.5 mg	137	0.43	0.08	-22	1.22 (0.76–1.96)	0.4133



Hanania et al. Lancet Respir Med 2016 4:781-96

Anti-TSLP





No. at Risk

Placebo	146	119	119	121	118	114	116	113
Low-dose tezepelumab	144	111	107	114	106	118	106	109
Medium-dose tezepelumab	143	112	110	111	102	94	102	101
High-dose tezepelumab	141	110	108	112	92	104	103	103

Table 2. Annualized Rate of Asthma Exacerbations and Change from Baseline in FEV_1, ACQ-6 Score, and AQLQ(S)+12 Score in the Intention-to-Treat Population.

Variable	Placebo (N=148)	Low-Dose Tezepelumab (N=145)	Medium-Dose Tezepelumab (N=145)	High-Dose Tezepelumab (N=146)
Annualized rate of asthma exacerbations through wk 52 — events per patient-yr (90% CI)	0.67 (0.57 to 0.80)	0.26 (0.19 to 0.34)	0.19 (0.13 to 0.27)	0.22 (0.16 to 0.30)
Relative reduction vs. placebo — % (90% CI)	—	61 (39 to 75)	71 (53 to 82)	66 (47 to 79)
P value	—	<0.001	<0.001	<0.001
FEV_1 before bronchodilation				
No. of patients evaluated	141	137	128	125
Least-squares mean change from baseline at wk 52 — % of predicted value	−0.99	7.11	7.27	9.37
Difference vs. placebo (95% CI)	—	8.11 (2.39 to 13.82)	8.26 (2.50 to 14.03)	10.36 (4.60 to 16.13)
P value*	—	0.006	0.005	<0.001
Least-squares mean change from baseline at wk 52 — liters	−0.05	0.07	0.06	0.11
Difference vs. placebo (95% CI)	—	0.12 (0.02 to 0.21)	0.11 (0.02 to 0.20)	0.15 (0.06 to 0.25)
P value*	—	0.01	0.02	0.002
ACQ-6 score†				
No. of patients evaluated	53	53	44	49
Least-squares mean change from baseline at wk 52	−0.89	−1.13	−1.16	−1.22
Difference vs. placebo (95% CI)	—	−0.24 (−0.50 to 0.02)	−0.27 (−0.54 to 0.00)	−0.33 (−0.60 to −0.07)
P value*	—	0.07	0.046	0.01
AQLQ(S)+12 score‡				
No. of patients evaluated	47	52	41	49
Least-squares mean change from baseline at wk 52	0.95	1.07	1.13	1.33
Difference vs. placebo (95% CI)	—	0.12 (−0.15 to 0.39)	0.18 (−0.10 to 0.47)	0.38 (0.10 to 0.65)
P value*	—	0.39	0.21	0.008

* P values are nominal and were not adjusted for multiplicity.
† ACQ-6 scores range from 0 to 6, with lower scores indicating better disease control. The minimal clinically important difference is 0.5 points.
‡ AQLQ(S)+12 scores range from 1 to 7, with higher scores indicating better asthma-related quality of life. The minimal clinically important difference is 0.5 points.

Corren J et al. N Engl J Med 2017

The NEW ENGLAND JOURNAL of MEDICINE

ΣΥΜΠΕΡΑΣΜΑΤΙΚΑ

- Το άσθμα είναι ένα σοβαρό παγκόσμιο πρόβλημα υγείας
- Η πλειονότητα των ασθματικών ασθενών πρέπει να λαμβάνει καθημερινή θεραπεία ελέγχου
- Τα εισπνεόμενα κορτικοειδή αποτελούν τον ακρογωνιαίο λίθο της αντιασθματικής θεραπείας
- Νέες (πιο στοχευμένες) θεραπείες αναμένονται για υποομάδες ασθματικών ασθενών με σοβαρό ανθεκτικό στη θεραπεία άσθμα

ΕΥΧΑΡΙΣΤΩ