

# Asthma Year in Review

Sandy Khurana, MD, FCCP  
Director, Mary Parkes Asthma Center  
University of Rochester, NY



# Disclosures

Grant support – GSK

I will not be discussing off-label use for any drugs or devices

# Objectives

- Review findings from, and strengths/limitations of recent significant publications in asthma
- Discuss how these findings may impact daily clinical practice when caring for patients with asthma

# Outline

- Are LABAs safe in asthma?
- Is as-needed ICS/LABA an effective strategy in mild asthma?
- Can escalation of ICS dose early in ‘yellow zone’ of asthma action plan abort exacerbations?
- New treatment for severe asthma

# Background: LABA safety concerns

## 1993: Serevent nationwide surveillance study (SNS)

- A 16-week RCT in the UK, evaluating Salmeterol vs. Salbutamol in ~ 25,000 participants, found a small, not statistically significant, increase in asthma-related deaths in Salmeterol group

## 2006: Salmeterol Multicenter Asthma Research Trial (SMART)

- 28-week RCT in ~ 26,000 participants evaluated Salmeterol vs. placebo added-on to usual therapy
- Interim analysis revealed a small but statistically significant increase in serious asthma related events in African American subjects

# Background

- 2005: FDA required black-box warning regarding increased asthma related deaths for all LABAs
- 2011-2016: FDA mandated LABA safety studies
- 2016: 4 parallel trials with 41,297 patients (3 studies > age 12, & 1 age 4-11)
  - No significant increase in risk of serious asthma events with LABA used in combination with ICS (Hazard ratio 1.10; 95% CI 0.85-1.44)
  - Significant reduction in exacerbations (Hazard ratio 0.79-0.89)
- 2017: ‘black box warning’ removed!

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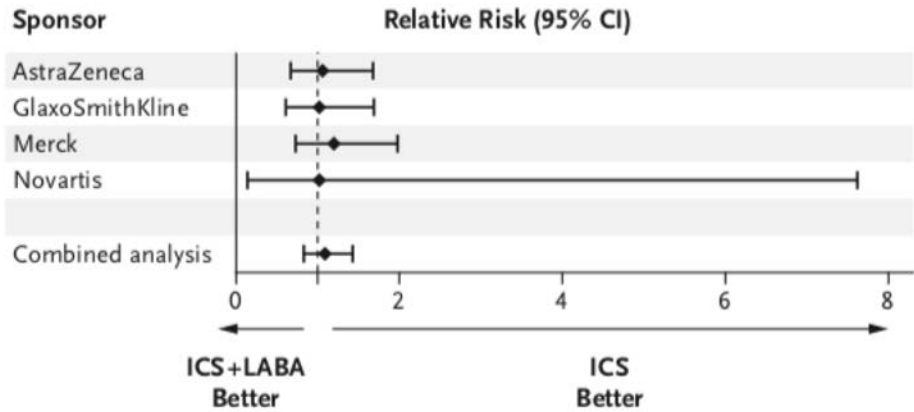
ORIGINAL ARTICLE

# Combined Analysis of Asthma Safety Trials of Long-Acting $\beta_2$ -Agonists

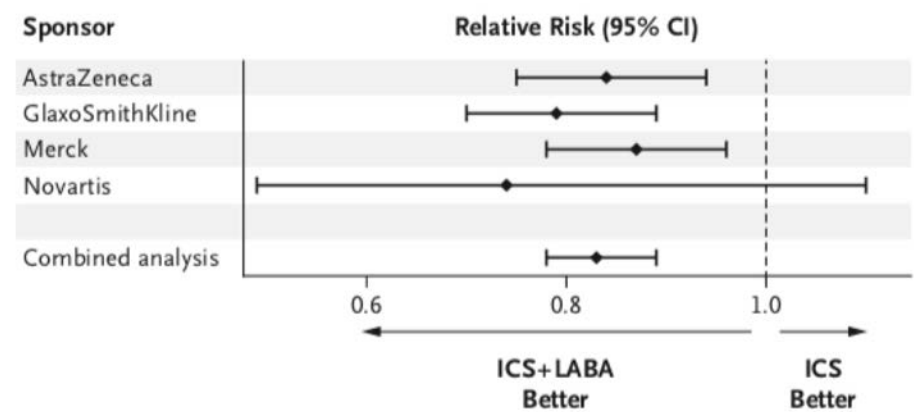
William W. Busse, M.D., Eric D. Bateman, M.B., Ch.B., M.D.,  
Arthur L. Caplan, Ph.D., H. William Kelly, Pharm.D., Paul M. O'Byrne, M.B.,  
Klaus F. Rabe, M.D., Ph.D., and Vernon M. Chinchilli, Ph.D.

*June 2018*

**A Serious Asthma-Related Events, According to Sponsored Study**

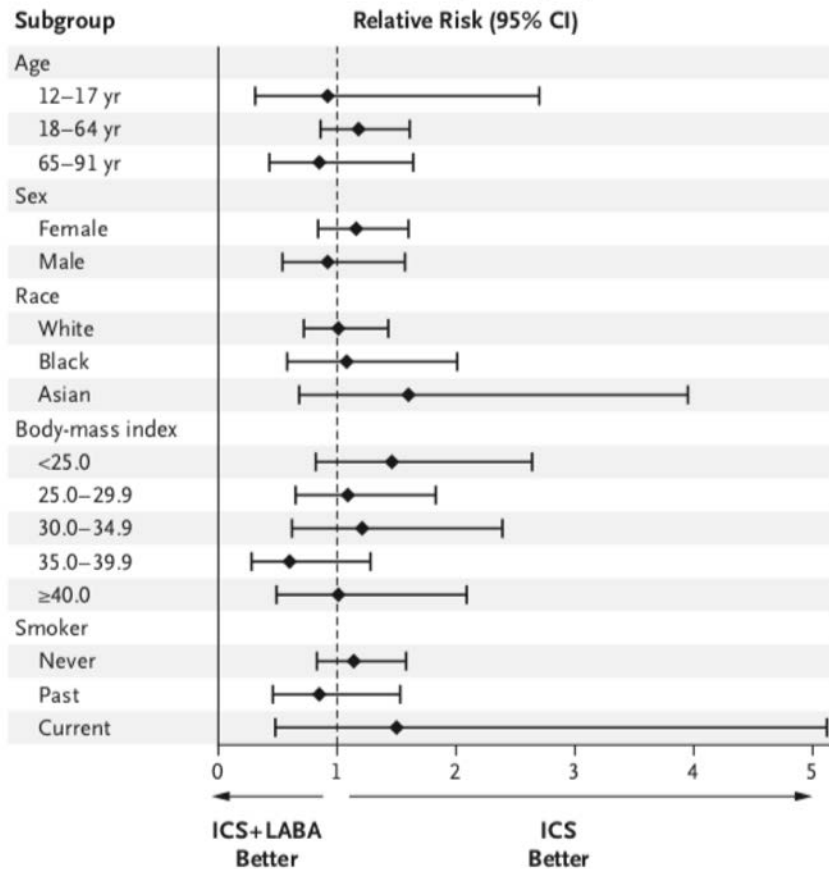


**A Asthma Exacerbations, According to Sponsored Trial**

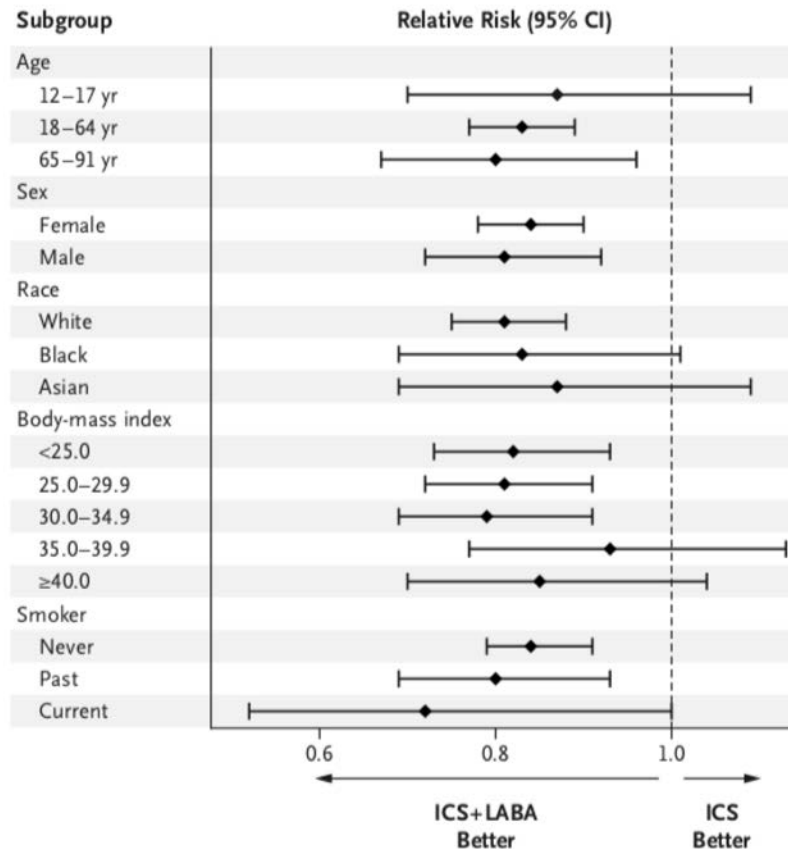




### B Serious Asthma-Related Events, According to Subgroup



### B Asthma Exacerbations, According to Subgroup



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Inhaled Combined Budesonide–Formoterol as Needed  
in Mild Asthma

Paul M. O'Byrne, M.B., J. Mark FitzGerald, M.D., Eric D. Bateman, M.D., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D.,  
Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Stefan Ivanov, M.D., Ph.D., and Helen K. Reddel, M.B., B.S., Ph.D.

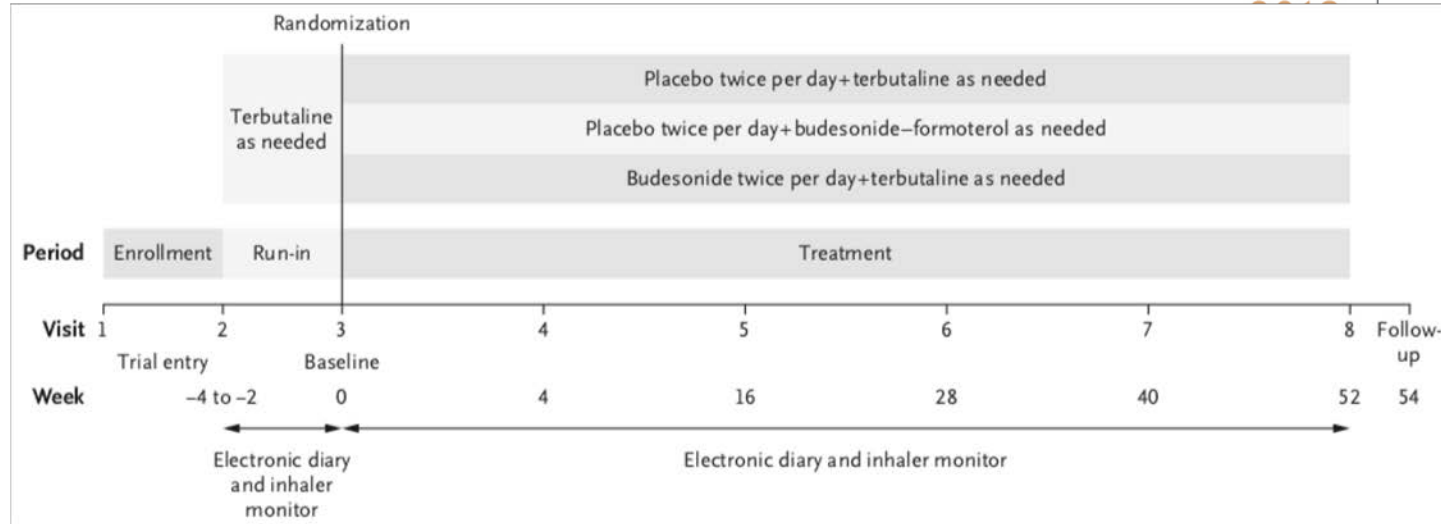
As-Needed Budesonide–Formoterol versus  
Maintenance Budesonide in Mild Asthma

Eric D. Bateman, M.D., Helen K. Reddel, M.B., B.S., Ph.D.,  
Paul M. O'Byrne, M.B., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D.,  
Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D.,  
Agnieszka Siwek-Posluszna, M.D., and J. Mark FitzGerald, M.D.

# Background

- Mild asthma occurs in 50-75% of patients with asthma
- Symptoms may not be burdensome but airway inflammation is often present
- These patients are at risk of exacerbations and event asthma related death
- Guidelines recommend regular use of inhaled steroids as maintenance but poor adherence is a major problem, leading to undertreatment of airway inflammation
- At the same time, patients rely heavily on SABAs for symptom relief.

# SYGMA 1: Budesonide/Formoterol given as needed in mild asthma



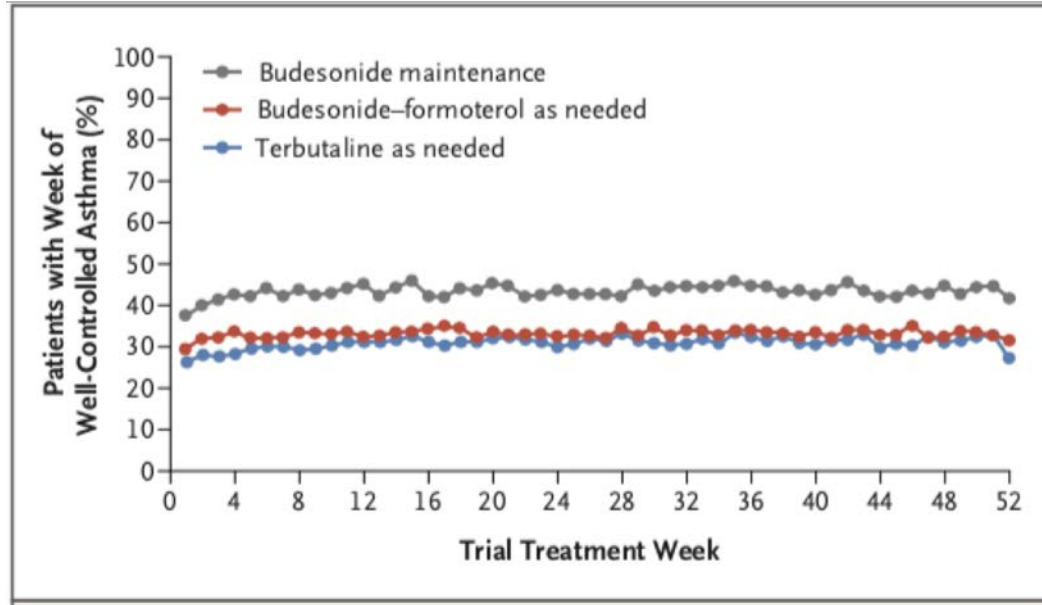
52 week double blind RCT, age > 12 years

GINA Step 2 (either uncontrolled on SABA alone, or controlled on Step 2)

Primary outcome: electronically recorded weeks with well controlled asthma (electronic diary and digital inhaler) with as needed ICS/Formoterol compared to terbutaline alone

Secondary outcome: non inferiority of ICS/Formoterol to fixed dose ICS

# SYGMA 1: Budesonide/Formoterol given as needed in mild asthma



In terms of weeks of well controlled asthma, budesonide-formoterol was:

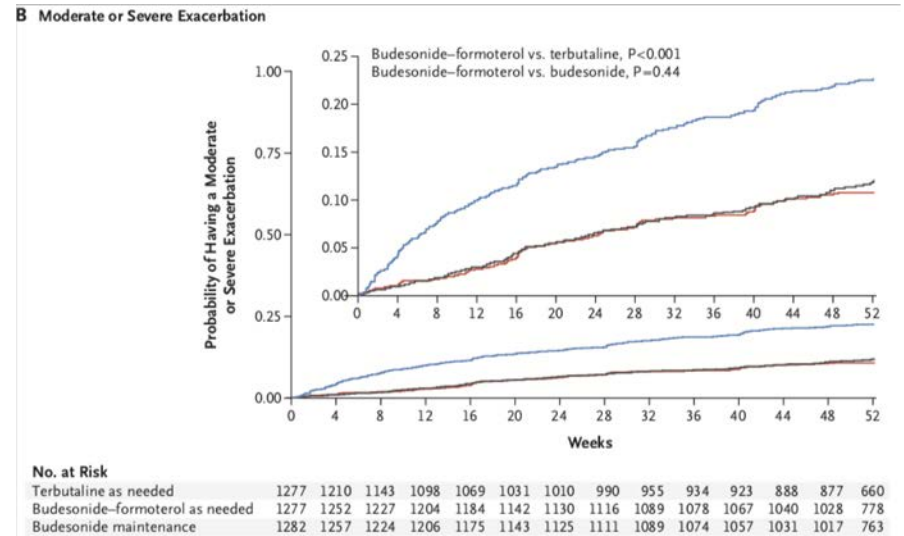
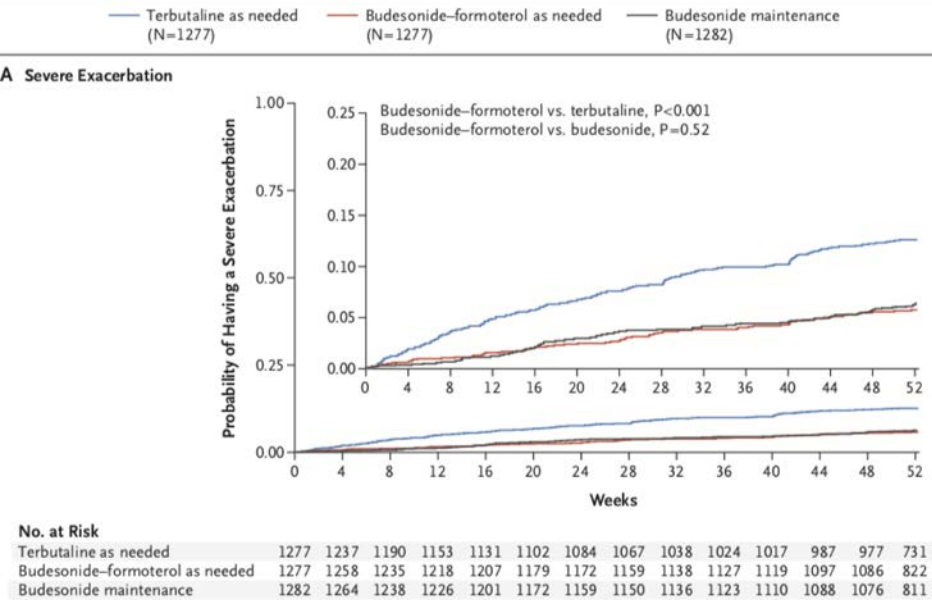
Superior to as needed terbutaline

Inferior to Budesonide maintenance

# SYGMA 1: Budesonide/Formoterol given as needed in mild asthma

## Time to First Exacerbation.

P values were not controlled for multiple comparisons. Insets show the same data on an enlarged y axis.



In terms of exacerbations:  
As-needed budesonide/formoterol was non-inferior to maintenance ICS with 1/5<sup>th</sup> of the ICS dose (57 ug vs. 340 ug)

# SYGMA 2: Budesonide/Formoterol given as needed in mild asthma

Parallel study to SYGMA 1 but Pragmatic design:

no daily reminders to use maintenance inhalers

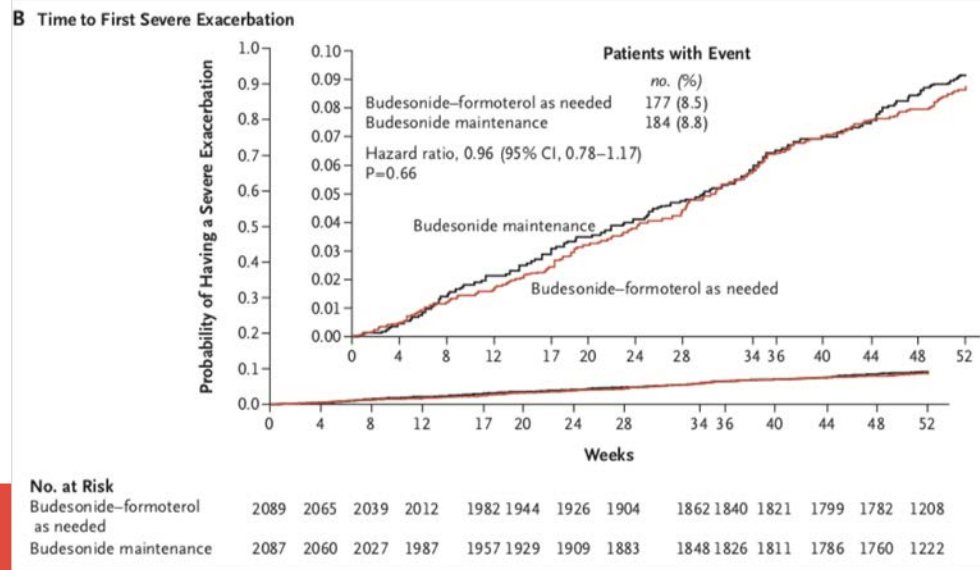
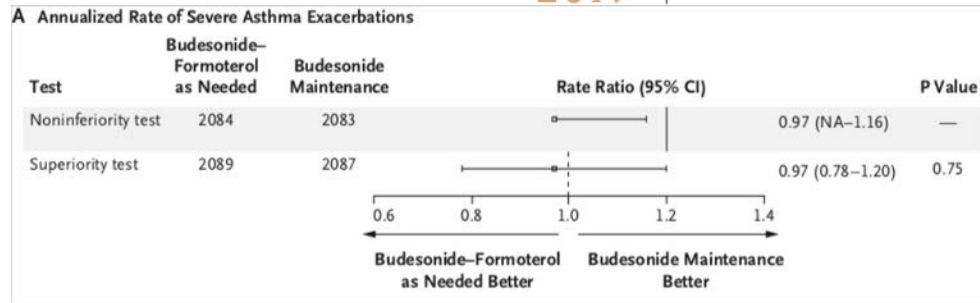
only 2 mid-trial visits

no diary, no PEF monitoring

Remote digital monitoring of inhaler use

BFC non-inferior to fixed dose ICS and ICS lower similar to SYGMA 1

Higher than anticipated adherence



# Can exacerbations be prevented with early escalation in ICS dose?

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### Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations

Tricia McKeever, Ph.D., Kevin Mortimer, Ph.D., Andrew Wilson, M.D., Samantha Walker, Ph.D., Christopher Brightling, Ph.D., Andrew Skeggs, B.Sc., Ian Pavord, F.Med.Sci., David Price, F.R.C.G.P., Lelia Duley, M.D., Mike Thomas, Ph.D., Lucy Bradshaw, M.Sc., Bernard Higgins, Ph.D., Rebecca Haydock, B.Sc., Eleanor Mitchell, B.A., Graham Devereux, Ph.D., and Timothy Harrison, M.D.

### Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations

D.J. Jackson, L.B. Bacharier, D.T. Mauger, S. Boehmer, A. Beigelman, J.F. Chmiel, A.M. Fitzpatrick, J.M. Gaffin, W.J. Morgan, S.P. Peters, W. Phipatanakul, W.J. Sheehan, M.D. Cabana, F. Holguin, F.D. Martinez, J.A. Pongratic, S.N. Baxi, M. Benson, K. Blake, R. Covar, D.A. Gentile, E. Israel, J.A. Krishnan, H.V. Kumar, J.E. Lang, S.C. Lazarus, J.J. Lima, D. Long, N. Ly, J. Marbin, J.N. Moy, R.E. Myers, J.T. Olin, H.H. Raissy, R.G. Robison, K. Ross, C.A. Sorkness, and R.F. Lemanske, Jr., for the National Heart, Lung, and Blood Institute AsthmaNet\*



# Background

Acute exacerbations of asthma cause considerable illness and costs related to asthma

Asthma action plans have been shown to improve asthma control

Limited guidance for change in asthma medications for early loss of asthma control 'yellow zone' = Zone 2

2016 Cochrane review concluded that doubling ICS dose not efficacious

Quadrupling the dose of ICS identified as potentially efficacious in a single study previously



# Quadrupling ICS dose to abort exacerbations

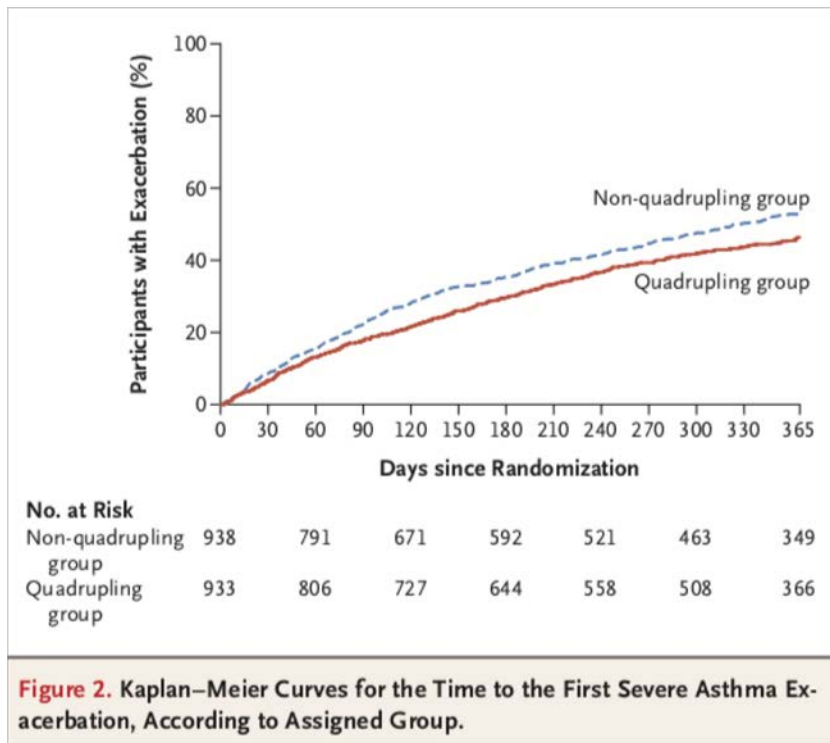
Pragmatic unblinded randomized trial in adults and adolescents

N = 1922, age > 16, > 1 exacerbation in past 12 months

Primary outcome: Time to first severe exacerbation (OCS or urgent medical visit)

Quadrupling Group	Non-Quadrupling Group
<b>Indication of deteriorating asthma control (one or more)</b>	<b>Indication of deteriorating asthma control (one or more)</b>
You need your reliever inhaler more than usual.	You need your reliever inhaler more than usual.
You have more difficulty sleeping because of your asthma.	You have more difficulty sleeping because of your asthma.
Your peak flow is below [80% of your normal level].	Your peak flow is below [80% of your normal level].
<b>Action</b>	<b>Action</b>
Use your reliever inhaler to relieve your symptoms and quadruple your inhaled glucocorticoid dose as described.	Use your reliever inhaler to relieve your symptoms and continue your inhaled glucocorticoid medication at your normal dose.
Once your symptoms or peak flow have returned to normal or after a maximum of 14 days, return to your normal treatment.	
If your symptoms get worse, follow Zone 3 instructions.	If your symptoms get worse, follow Zone 3 instructions.
Start to record your morning peak flow, symptoms, and medication in the trial diary.	Start to record your morning peak flow, symptoms, and medication in the trial diary.
Telephone your research nurse to arrange a trial visit.	Telephone your research nurse to arrange a trial visit.

# Quadrupling ICS dose to abort exacerbations



58% of participants had a zone 2 event

45% in intervention vs. 52% in control group

RR 0.81

Increased laryngeal adverse effects

# Quintupling ICS dose to prevent exacerbation in children

Run-in Phase: 4 Wk	Treatment Phase: 48 Wk		
	Randomized treatment group	Daily <i>except</i> during 7-day yellow zone	Daily <i>only</i> during 7-day yellow zone
Fluticasone 44 µg/inhalation, 2 inhalations twice daily	Low dose	Fluticasone 44 µg/inhalation, 2 inhalations twice daily	Fluticasone 44 µg/inhalation, 2 inhalations twice daily
	High dose	Fluticasone 44 µg/inhalation, 2 inhalations twice daily	Fluticasone 220 µg/inhalation, 2 inhalations twice daily

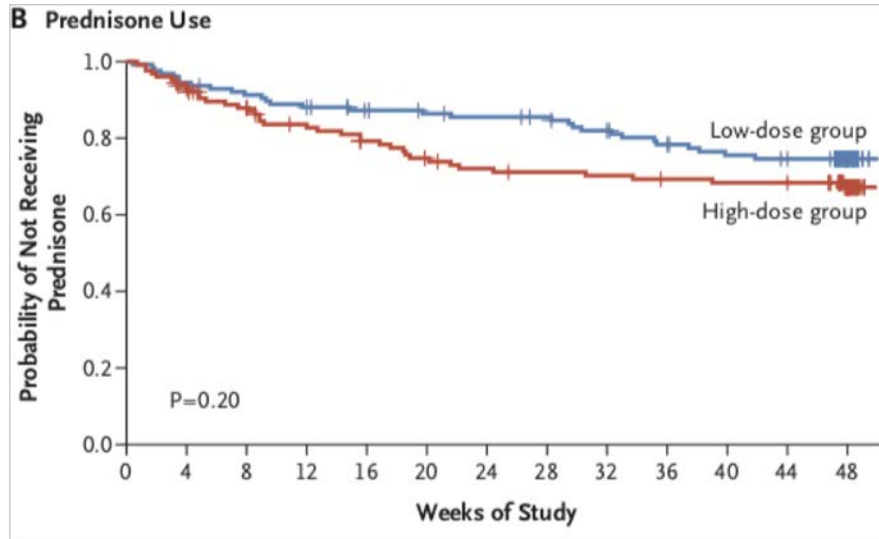
Randomized, blinded study

Children ages 5-11 years

Mild-to-moderate doctor diagnosed asthma

Step 2 therapy of NAEPP-EPR3

# Quintupling ICS dose to prevent exacerbation in children



No difference in number of exacerbations, ED visits, hospitalization, treatment failure

Systemic levels of steroids in high dose group and possible decreased linear growth in children < 7

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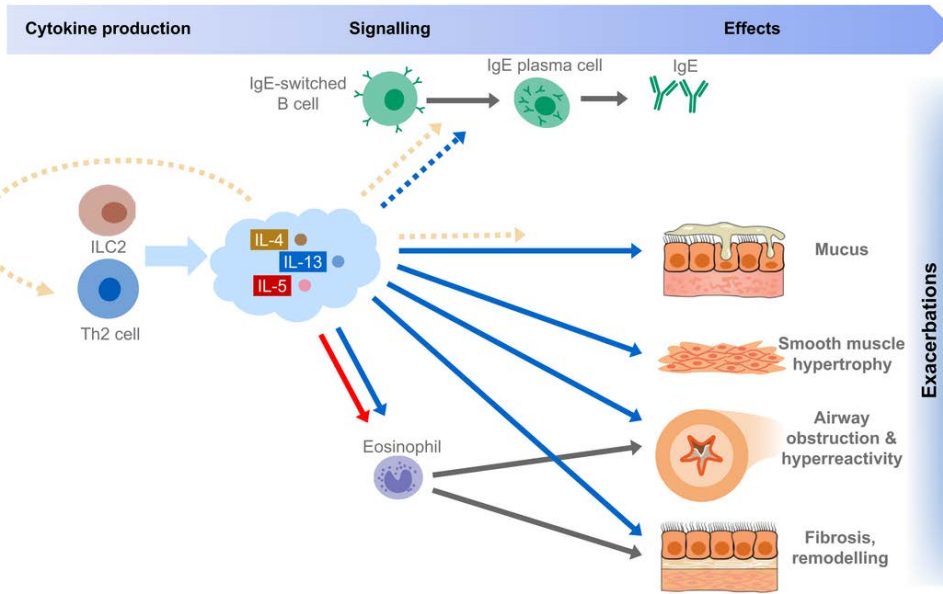
## Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher, J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B. Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl, G.D. Yancopoulos, and A. Teper

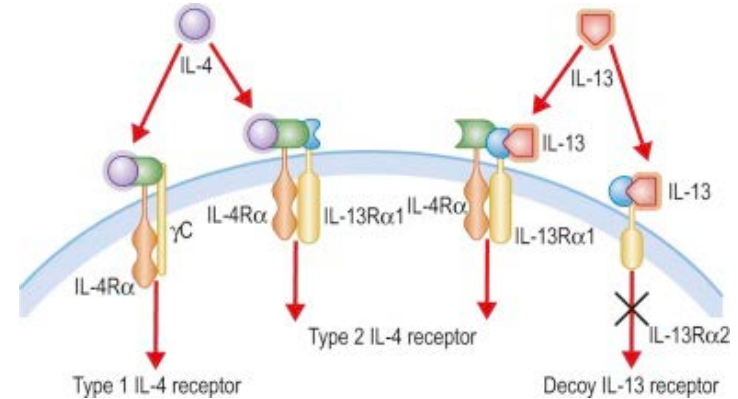
## Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

Klaus F. Rabe, M.D., Ph.D., Parameswaran Nair, M.D., Ph.D.,  
Guy Brusselle, M.D., Ph.D., Jorge F. Maspero, M.D., Mario Castro, M.D.,  
Lawrence Sher, M.D., Hongjie Zhu, Ph.D., Jennifer D. Hamilton, Ph.D.,  
Brian N. Swanson, Ph.D., Asif Khan, M.B., B.S., M.P.H., Jingdong Chao, Ph.D.,  
Heribert Staudinger, M.D., Ph.D., Gianluca Pirozzi, M.D., Ph.D.,  
Christian Antoni, M.D., Ph.D., Nikhil Amin, M.D., Marcella Ruddy, M.D.,  
Bolanle Akinlade, M.D., Neil M.H. Graham, M.B., B.S., M.D., Neil Stahl, Ph.D.,  
George D. Yancopoulos, M.D., Ph.D., and Ariel Teper, M.D.

# Background - Dupilumab

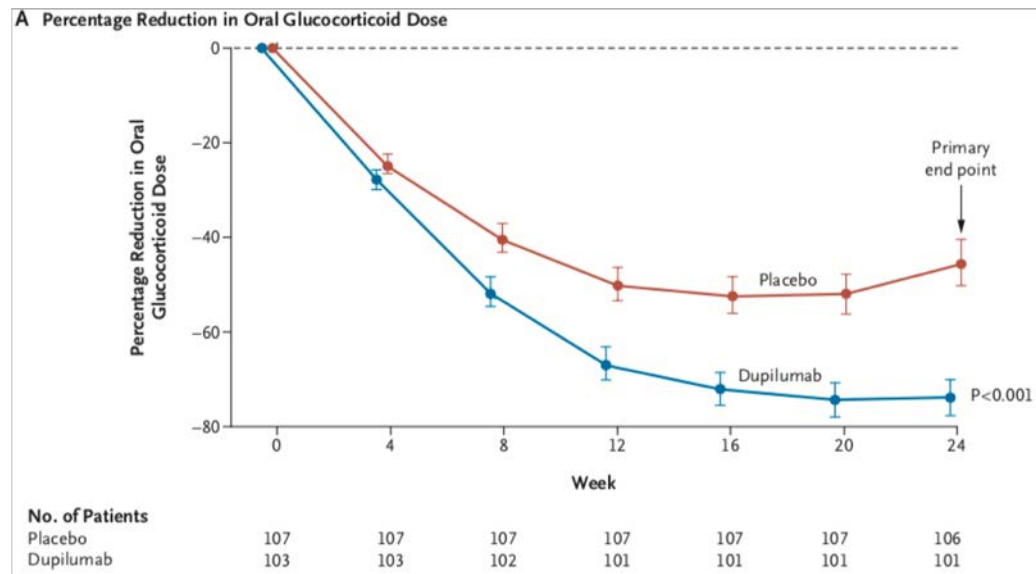


- IL-4 and IL-13 bind to a shared subunit, IL-4R $\alpha$
- Dupilumab, a human monoclonal IgG4 antibody, binds to IL-4R $\alpha$ , blocking both IL-4 and IL-13 signaling
- IL-4 and IL-13 pathways have unique and overlapping function



# Dupilumab & OCS-dependent Asthma

- 210 patients with OCS dependent asthma
- Dupilumab vs. placebo after an OCS optimization run-in period
- Tapering week 4-20 then stable for 4 weeks
- Primary endpoint: % reduction in OCS at week 24





**Table 2. Overview of Adverse Events during 24-Week Intervention Period and Injection-Site Reactions (Safety Population).\***

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

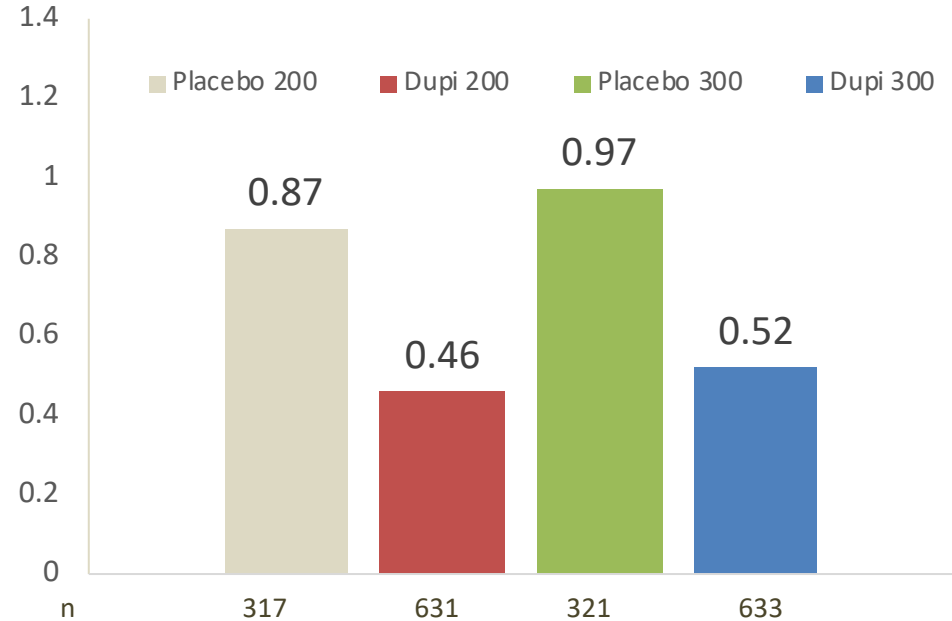
# Dupilumab & mod-severe uncontrolled asthma

1902 patients

Adolescents & adults

200 vs 300 mg dupilumab SC q 2 weeks

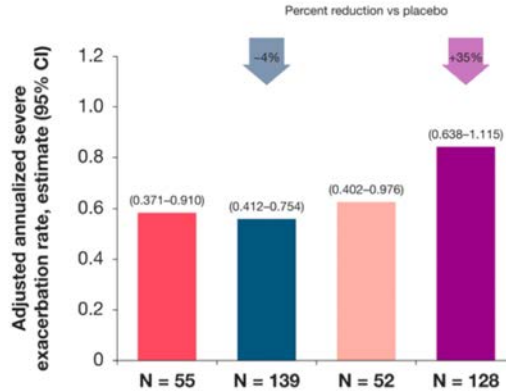
Adjusted Annual Severe Exacerbation Rate over 52 weeks



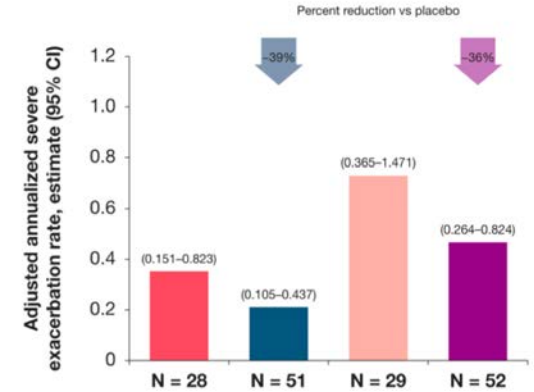
# Effect of dupilumab by baseline Eos and FeNO

A

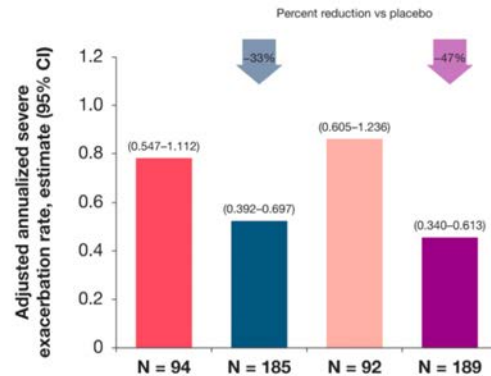
FE<sub>NO</sub> <25 ppb and eosinophils <150 cells/ $\mu$ L  
(19.9% of ITT population)



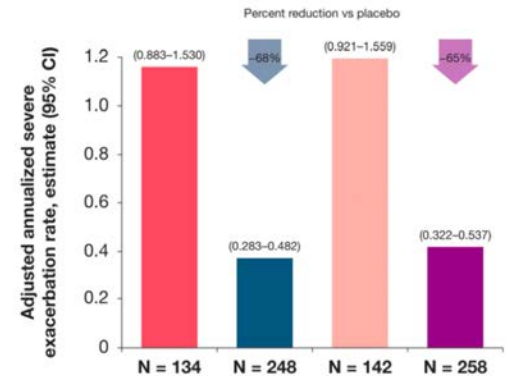
FE<sub>NO</sub>  $\geq$ 25 ppb and eosinophils <150 cells/ $\mu$ L  
(8.5% of ITT population)



FE<sub>NO</sub> <25 ppb and eosinophils  $\geq$ 150 cells/ $\mu$ L  
(29.9% of ITT population)



FE<sub>NO</sub>  $\geq$ 25 ppb and eosinophils  $\geq$ 150 cells/ $\mu$ L  
(41.7% of ITT population)



# Summary

- Reassuring data on safety of LABA in asthma when used in combination with ICS
- More evidence for formoterol containing ICS/LABA as ‘SMART’ strategy
- Escalation of ICS dose during ‘yellow’ zone
  - Not effective in children
  - Small benefit in adults
- New class of biologic – dupilumab – effective in reducing exacerbation and OCS dependence. Effect size larger in patients with elevated FeNO or blood eos

# Honorable mentions

- Inadequate assessment of adherence to maintenance medication leads to loss of power and increased costs in trials of severe asthma therapy. Results from a systematic literature review and modelling study. *European Respiratory Journal* 2019; DOI: 10.1183/13993003.02161-2018
- Refractory airway type 2 inflammation in a large subgroup of asthmatic patients treated with inhaled corticosteroids. *JACI* 2019; 143: 104.
- Managing Asthma in Pregnancy (MAP) trial: FENO levels and childhood asthma. *JACI* 2018; 142: 1765
- Asthma Is a Risk Factor for Respiratory Exacerbations Without Increased Rate of Lung Function Decline. *CHEST* 2018; 153: 368
- Associations of Asthma and Asthma Control With Atrial Fibrillation Risk. Results From the Nord-Trøndelag Health Study (HUNT). *JAMA* 2018; 3: 721
- Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med.* 2019; 7: 46.
- Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *JACI* 2018. doi: 10.1016/j.jaci.2018.09.033.