

Inhaled Corticosteroids/Long Acting β_2 -agonists as Relievers: The SMART Approach

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Disclosures 2013 - 2021

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Lectures: AstraZeneca, ALK, Boehringer Ingelheim, Chiesi, Menarini, Novartis, Orion, Regeneron, Sanofi Aventis

Consultancy or Advisory Boards: ALK, AstraZeneca, Novartis, Regeneron, Sanofi Aventis

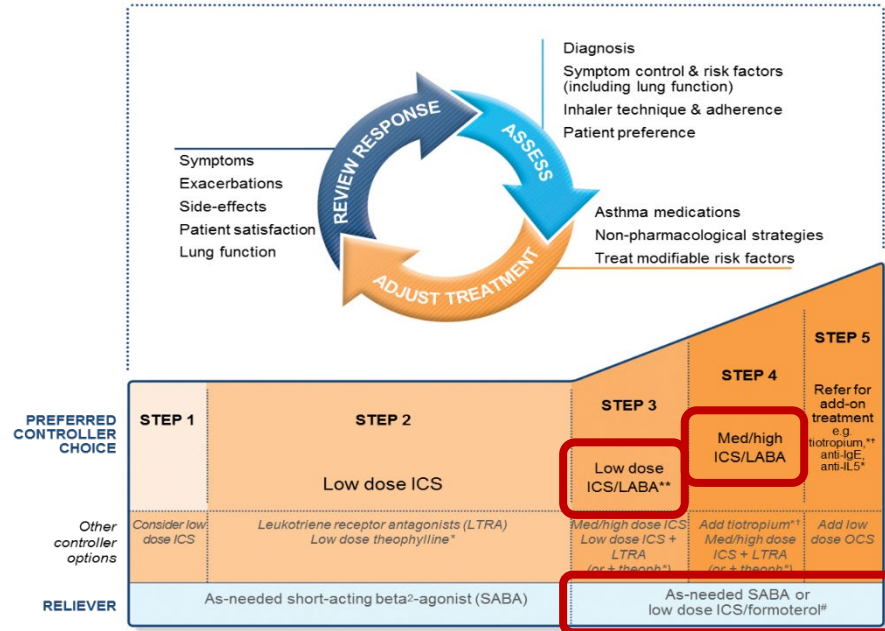
Educational programmes: Global Initiative for Asthma, BOLD Board

2006
2006 revision



If a combination inhaler containing formoterol and budesonide 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 treatment¹⁵⁴⁻¹⁵⁷ (Evidence A). Whether this approach can be employed with other combinations of controller and reliever requires further study.

2014



MART = Maintenance And Reliever Therapy

or

SMART = Single Inhaler for Maintenance and Relief Therapy



ASSESS:

Confirmation of diagnosis
Symptom control & modifiable risk factors (including lung function)

Comorbidities
Inhaler technique & adherence
Patient preferences and goals

MART = Maintenance And Reliever Therapy

START HERE IF:

AIR = Anti-Inflammatory Reliever Therapy

PREFERRED CONTROLLER
to prevent exacerbations and control symptoms

STEP 1
As-needed low dose ICS-formoterol *

STEP 2
Daily low dose inhaled corticosteroid (ICS) or as-needed low dose ICS-formoterol *

STEP 3
Low dose ICS-LABA

STEP 4
Medium dose ICS-LABA

STEP 5
High dose ICS-LABA

Other controller options

Low dose ICS taken whenever SABA taken †

Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †

Medium dose ICS, or low dose ICS+LABA #

High dose ICS, or low dose tiotropium, or add-on LTRA #

Add-on high dose OCS, or combination of OCS with controller side effects

PREFERRED RELIEVER

As-needed low dose ICS-formoterol *
As-needed low dose ICS-formoterol for patients prescribed maintenance and reliever therapy ‡
As-needed short-acting β_2 -agonist (SABA)

Other reliever option

* Data only with budesonide-formoterol (bud-form)
† Separate or combination ICS and SABA inhalers

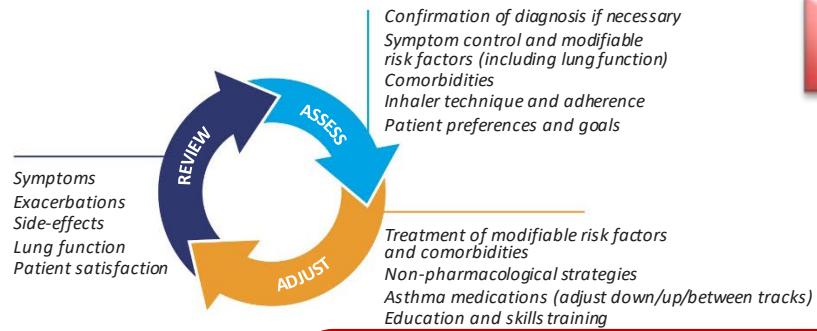
‡ Low-dose ICS-form is the reliever only for patients prescribed bud-form or BDP-form maintenance and reliever therapy
Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 >70% predicted

Adults and adolescents 12+ years

Personalized asthma management

Assess, Adjust, Review
for individual patient needs

2021



Track 1
Controller and preferred reliever (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1–2
As-needed low dose ICS-formoterol

STEP 3
Low-dose maintenance ICS-formoterol

STEP 4
Medium-dose maintenance ICS-formoterol

STEP 5
Add-on LAMA
Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R
Consider high-dose ICS-formoterol

RELIEVER: As-needed low-dose ICS-formoterol

Track 2
Controller and

STEP 2

STEP 3
Low-dose

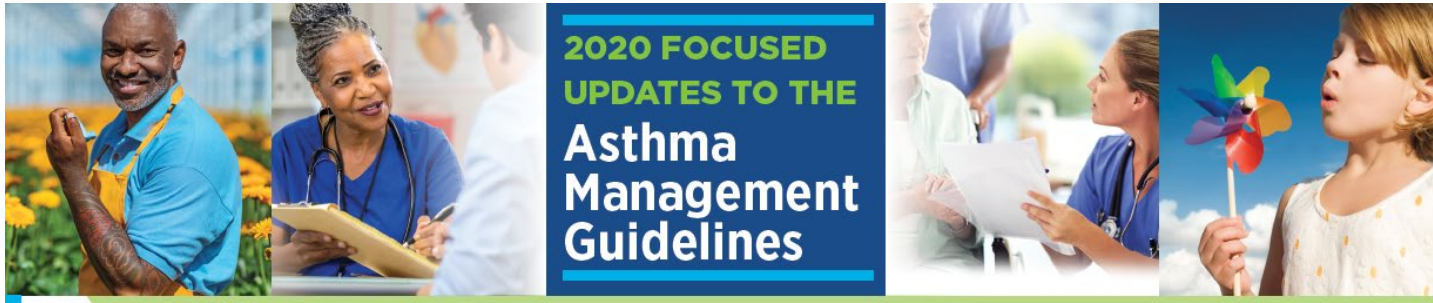
STEP 4
Medium-/high-dose maintenance ICS-LABA

STEP 5
Add-on LAMA
Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R

Maintenance treatment for day-to-day symptom control and prevention of exacerbations PLUS Immediate relief of symptoms and additional prevention of exacerbations

Other controller options for either track	SABA taken, or daily LTRA, or add HDM SLIT	add LTRA, or add HDM SLIT	switch to high-dose ICS	LTRA; add low-dose OCS, but consider side-effects
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GINA: Global Initiative for Asthma; HDM SLIT: house dust mite sublingual immunotherapy; ICS: inhaled corticosteroid; Ig: immunoglobulin; IL: interleukin; LABA: long-acting β₂-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; SABA: short-acting β₂ agonist.



**2020 FOCUSED
UPDATES TO THE
Asthma
Management
Guidelines**

**Management of Persistent Asthma in Individuals
Ages 5 – 11 ≥12 years**

Preferred

Alternative

	STEP 3	STEP 4
Preferred	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲
Alternative	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LTRA,* or daily low-dose ICS + Theophylline,* and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA or Daily medium-dose ICS + LTRA* or daily medium-dose ICS + Theophylline,* and PRN SABA

	STEP 3	STEP 4
Preferred	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲
Alternative	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA or Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲ or Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA

Strength of evidence

- Ages 4-11 yrs – moderate
- Ages ≥12 yrs - high

Recommendation - strong

“All patients would want and should be offered”

Inhaled corticosteroids/long acting β_2 -agonists as relievers

Outline

- Reasons for the change
- Summary of the evidence in mild and moderate-to-severe asthma
- Potential mechanisms of action
- Some practical considerations

Why the change?

- **Epidemiology**

- Improvements in morbidity and mortality have stalled¹

- **Pharmacology**

- Regular SABA use is associated with worsening asthma²
- ICS improve asthma outcomes even in the mildest disease²

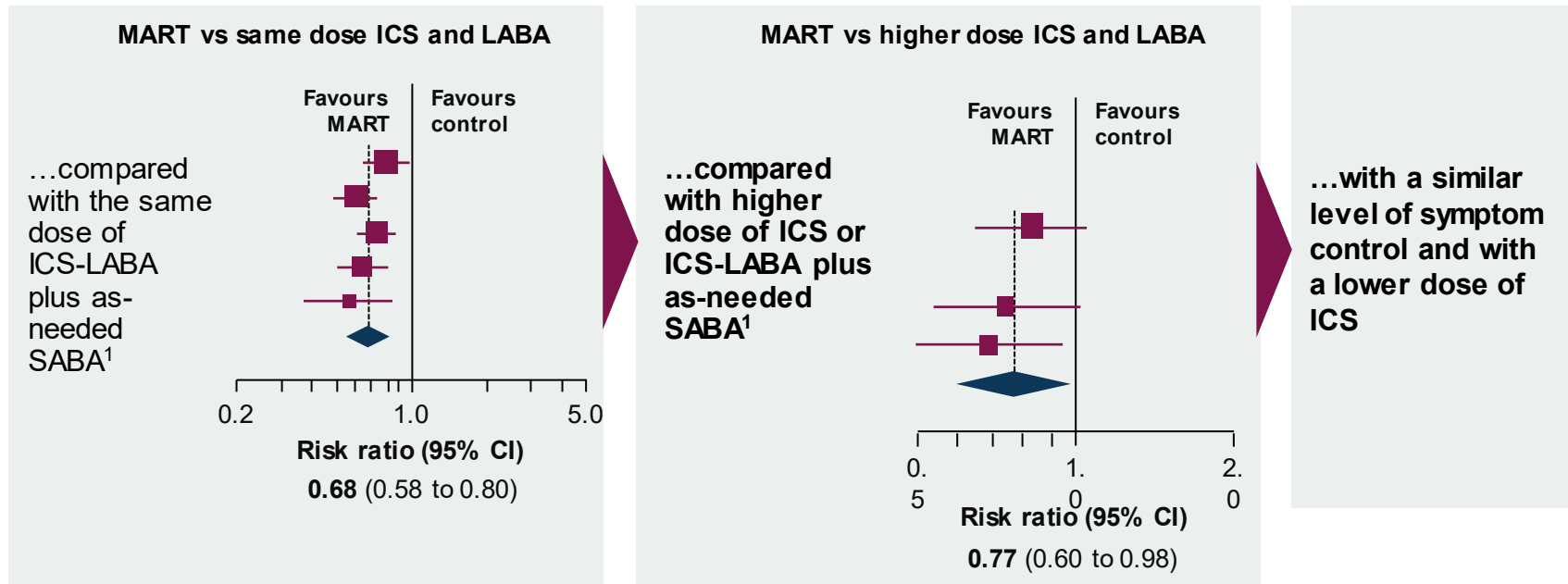
- **Patient behaviour**

- Patient reliance on and overuse of SABAs is a global issue²

- **Anti-inflammatory reliever therapy** is the most effective treatment for worsening asthma²

GRADE analysis of benefits of MART vs conventional therapy with as-needed SABA (NAEPP USA)

- In patients (n=22,748) at increased risk of exacerbations, maintenance and reliever therapy (MART) with low-dose ICS-formoterol reduces severe exacerbations



CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; ICS, inhaled corticosteroid(s); LABA, long-acting β_2 -agonist; NAEPP, National Asthma Education and Prevention Program; SABA, short-acting β_2 -agonist

1. Sobieraj DM, *et al.* *JAMA* 2018;319:1485-1496; 2. NAEPPCC.

Steps 3–4: SMART versus Current Best Practice + SABA for adults and adolescents

	Patients compared with current best practice (not selected for previous exacerbations)
Evidence	<ul style="list-style-type: none">• Meta-analysis of 6 studies in 2009¹<ul style="list-style-type: none">• Fewer severe exacerbations: 0.20 vs 0.24/year $p < 0.02$; no difference in time to first exacerbation• Better symptom control: OR for ACQ remaining < 0.75: 1.29 $p < 0.01$ OR for ACQ remaining ≥ 1.5: 0.81, $p < 0.01$• Cochrane meta-analysis in 2013, 9 open-label RCTs²<ul style="list-style-type: none">• Fewer severe exacerbations: OR 0.83 (0.70 to 0.98)• Lower ICS dose: 107 vs 385 $\mu\text{g}/\text{day}$• Adverse events: no difference in SAEs• Patients with low lung function, and smoking history, benefitted more from higher maintenance MART dose, i.e. Step 4³
	<ul style="list-style-type: none">• ¹Demoly P, et al. <i>Respir Med</i> 2009;103:1623-32.• ²Cates CJ, Karner C. <i>Cochrane Database Syst. Rev</i> 2013 (Apr 30);(4):CD007313. doi:10.1002/14651858.• ³Aubier M, et al. <i>Eur Respir J</i> 2010;36(3):524-530.



ORIGINAL ARTICLE

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.

O'Byrne PM, *et al. N Engl J Med*, 2018; 378:1865-76.

ORIGINAL ARTICLE

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.

Bateman ED, *et al. N Engl J Med*, 2018; 378:1877-87.

ORIGINAL ARTICLE

Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma

Richard Beasley, D.Sc., Mark Holliday, B.Sc., Helen K. Reddel, Ph.D.,
Irene Braithwaite, Ph.D., Stefan Ebmeier, B.M., B.Ch., Robert J. Hancox, M.D.,
Tim Harrison, M.D., Claire Houghton, B.M., B.S., Karen Oldfield, M.B., Ch.B.,
Alberto Papi, M.D., Ian D. Pavord, F.Med.Sci., Mathew Williams, Dip.Ex.Sci.,
and Mark Weatherall, F.R.A.C.P., for the Novel START Study Team*

Beasley R, *et al. N Engl J Med*, 2019;380:2020-2030.

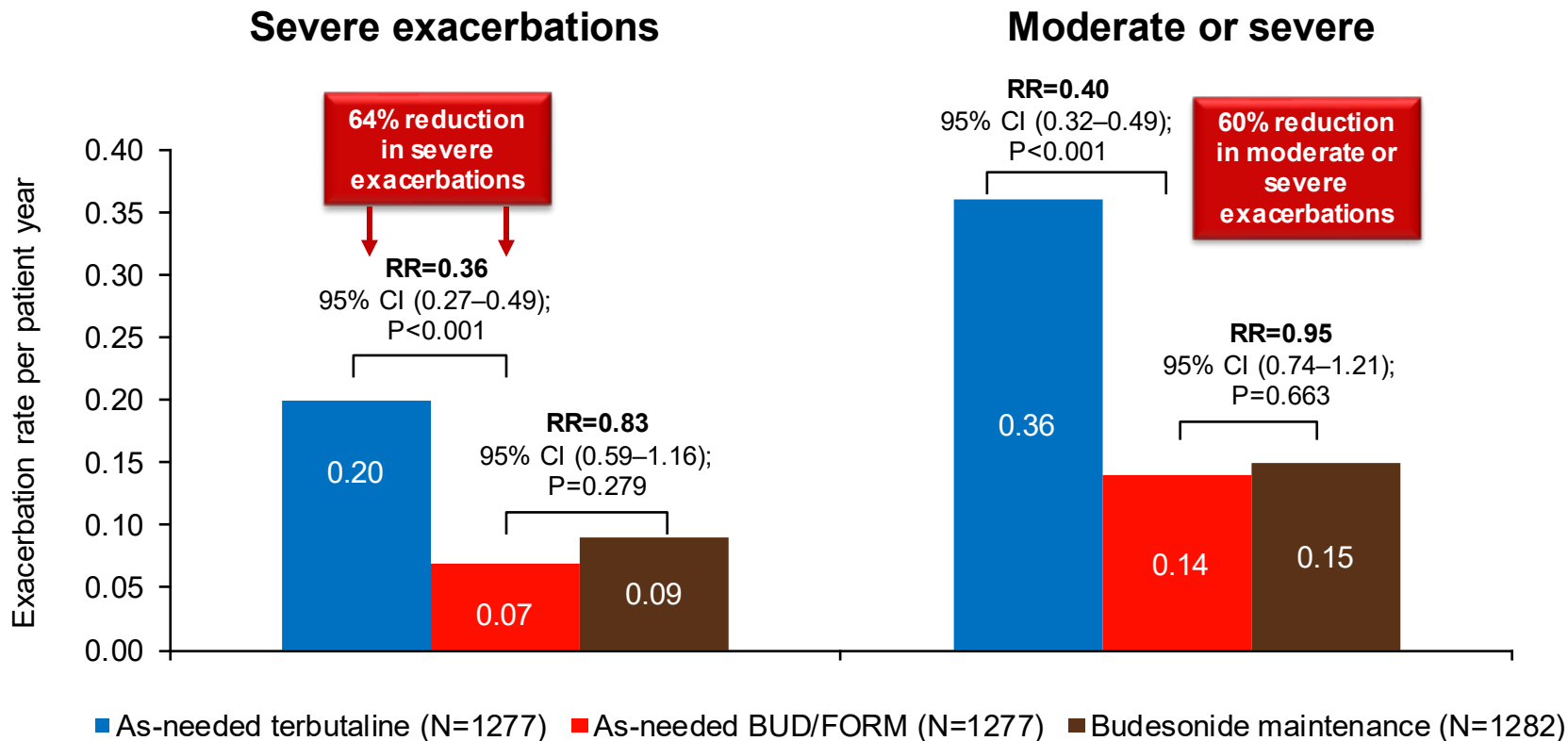
PRACTICAL^a:

Independent, pragmatic, real-world study
As-needed budesonide/formoterol⁴

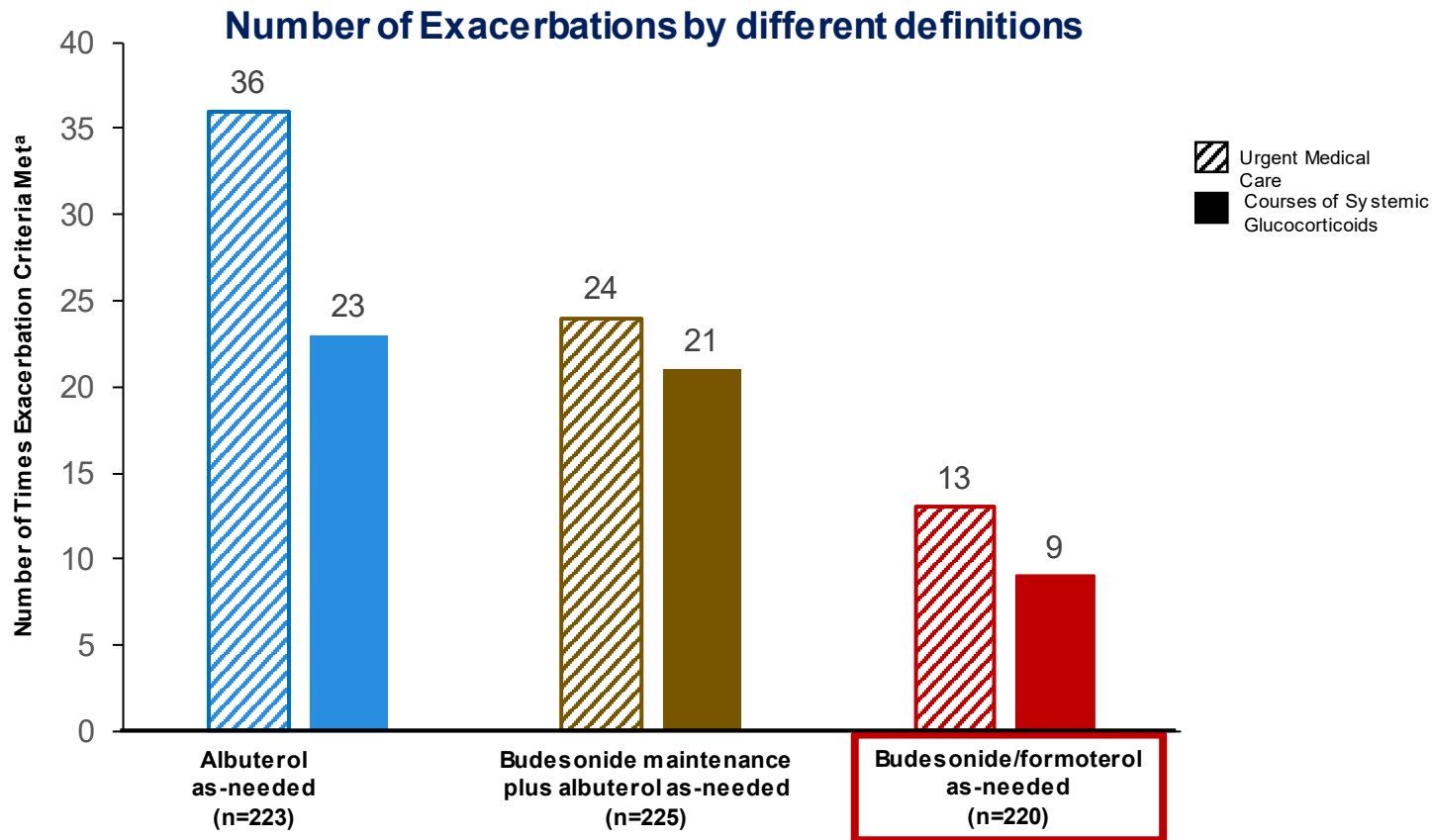
Open-label trial of as-needed budesonide/formoterol
in adults with mild to moderate asthma previously
treated with as-needed SABA only or ICS with SABA
as-needed

Hardy J, *et al. Lancet*. 2019. [http://dx.doi.org/10.1016/S0140-6736\(19\)31948-8](http://dx.doi.org/10.1016/S0140-6736(19)31948-8).

SYGMA 1 in MILD Asthma: Asthma exacerbations



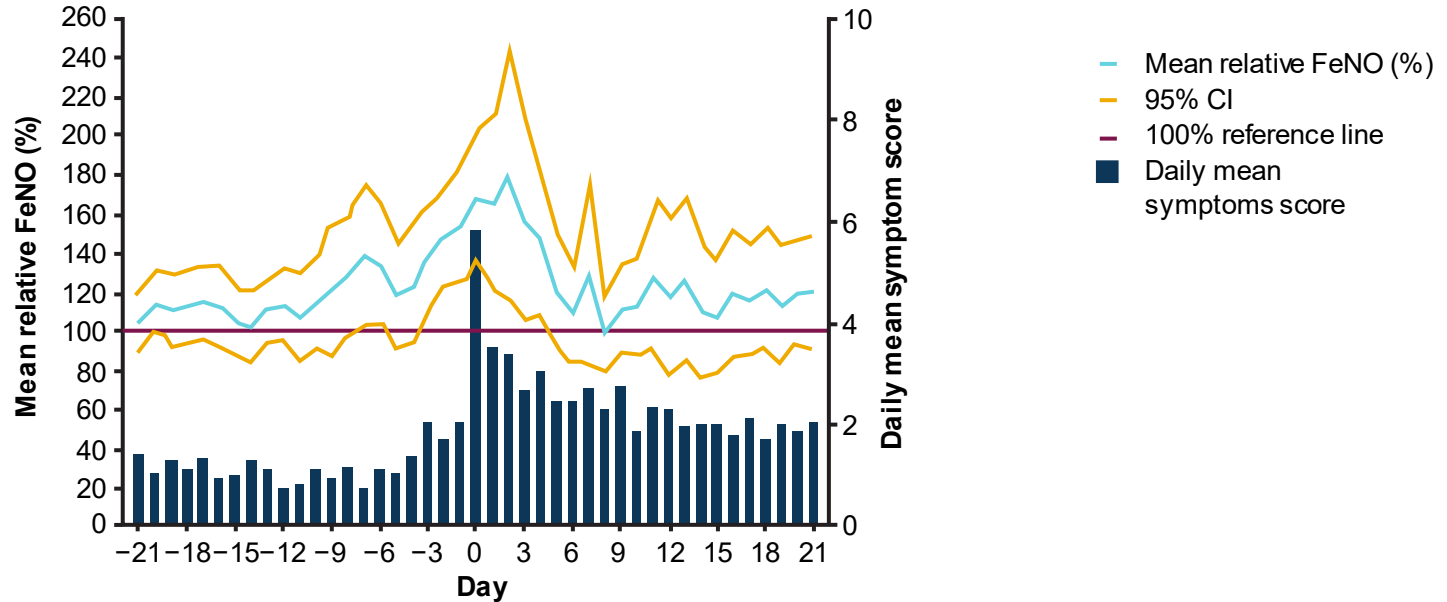
Mild asthma: Open-label trial of as-needed BUD/FORM in adults previously treated with as-needed SABA only



^aSecondary endpoints were not adjusted for multiplicity.

Asthma worsening is associated with increased airway inflammation

FeNO levels in children



Post-hoc analysis of FeNO data from 77 children with asthma;

A descriptive study of 425 severe exacerbations; exacerbations were defined as the need for a course of OCS or a reduction in morning PEF of >30% on 2 consecutive days.

Markers of airway inflammation during asthma exacerbations

1. Viral exacerbations are associated with increase in sputum eosinophils¹
2. Exacerbations may also be associated with increased airway neutrophils and their mediators²⁻⁵
3. Return of symptoms after ICS withdrawal is associated with increase in sputum (and blood?) eosinophils and in release of eosinophilic granules^{5,6}

1. Busse WW, *et al. Lancet* 2010;376:826-834.

2. Persson CG, *et al. Thorax* 1997;52:569-574.

3. Fahy JV, *et al. J Allergy Clin Immunol.* 1995;95:843-852.

4. Lamblin C, *et al. Amer J Respir Crit Care Med* 1998;157:394-402.

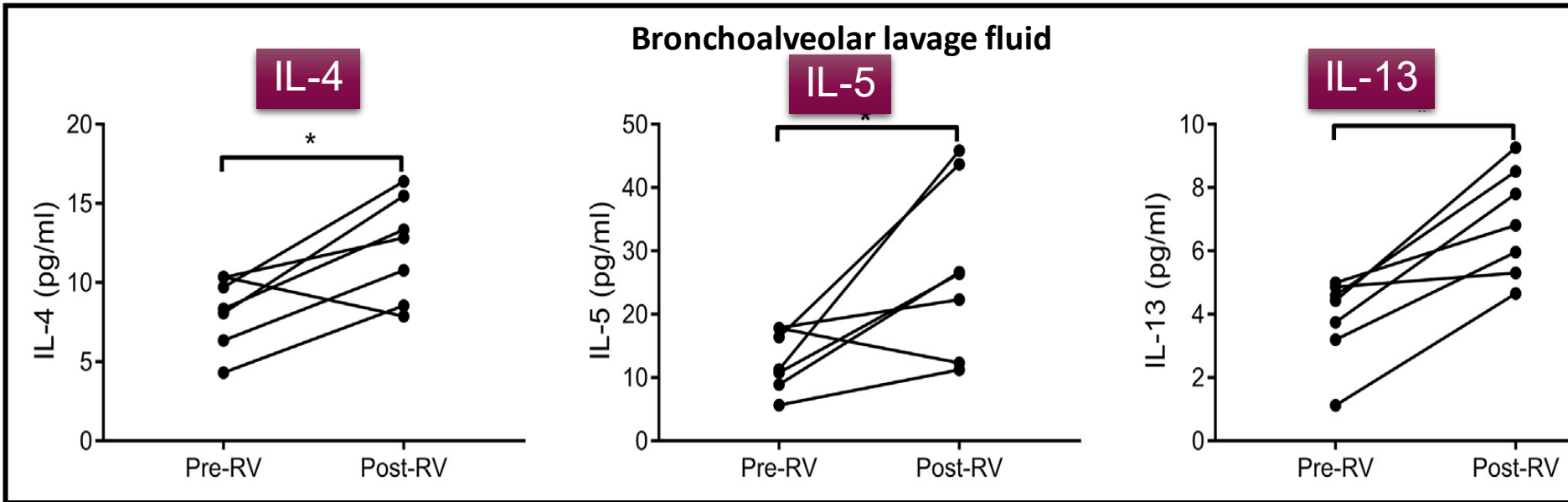
5. Maneechotesuwan K, *et al. Chest.* 2007;132:98-105.

6. De G, *et al. Chest Sept* 2019; doi. 10.1016/j.chest.2019.09.27.

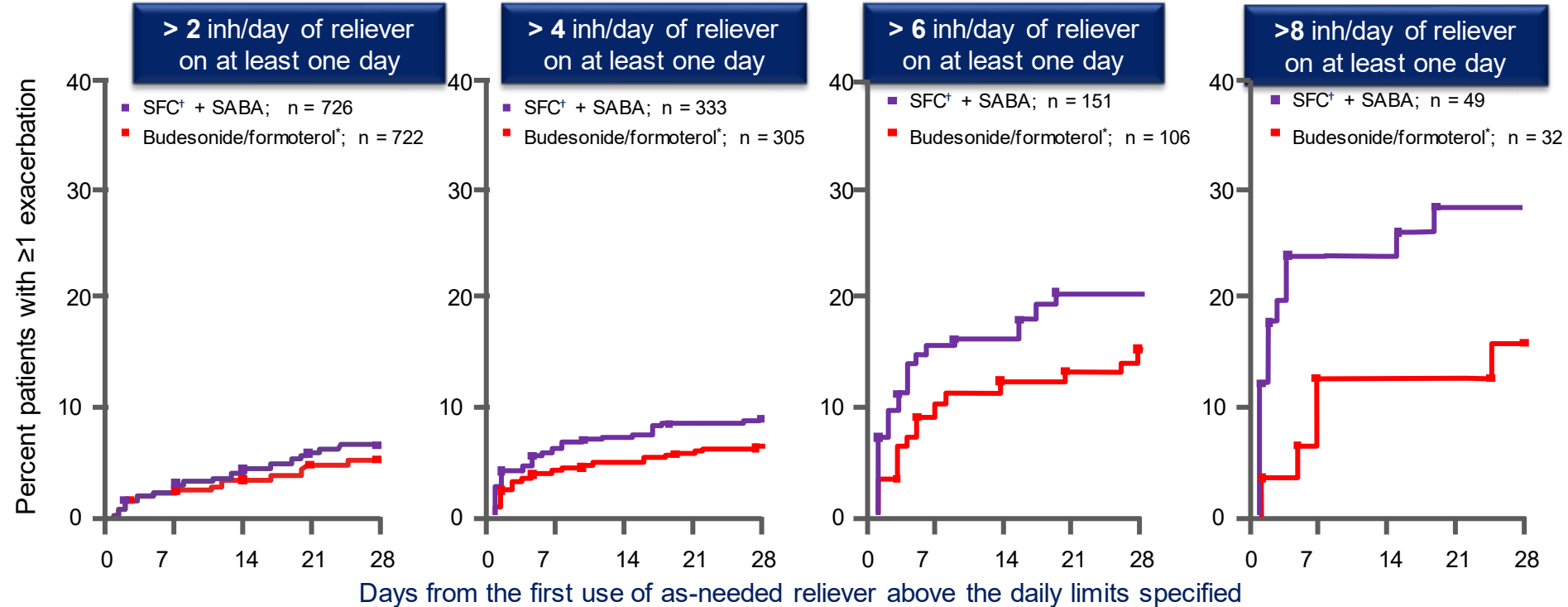
Type 2 inflammation after rhinovirus infection in moderate asthma

Experimental infection of 11 adult patients with rhinovirus.

Peak symptoms of cold at 5 days, worsening asthma 7 days. Interferons α , β , γ , δ and CXCL10 and CXCL11 increased



Proportion of patients with severe exacerbation within 28 days of the first day of as-needed reliever use: (AHEAD study*)



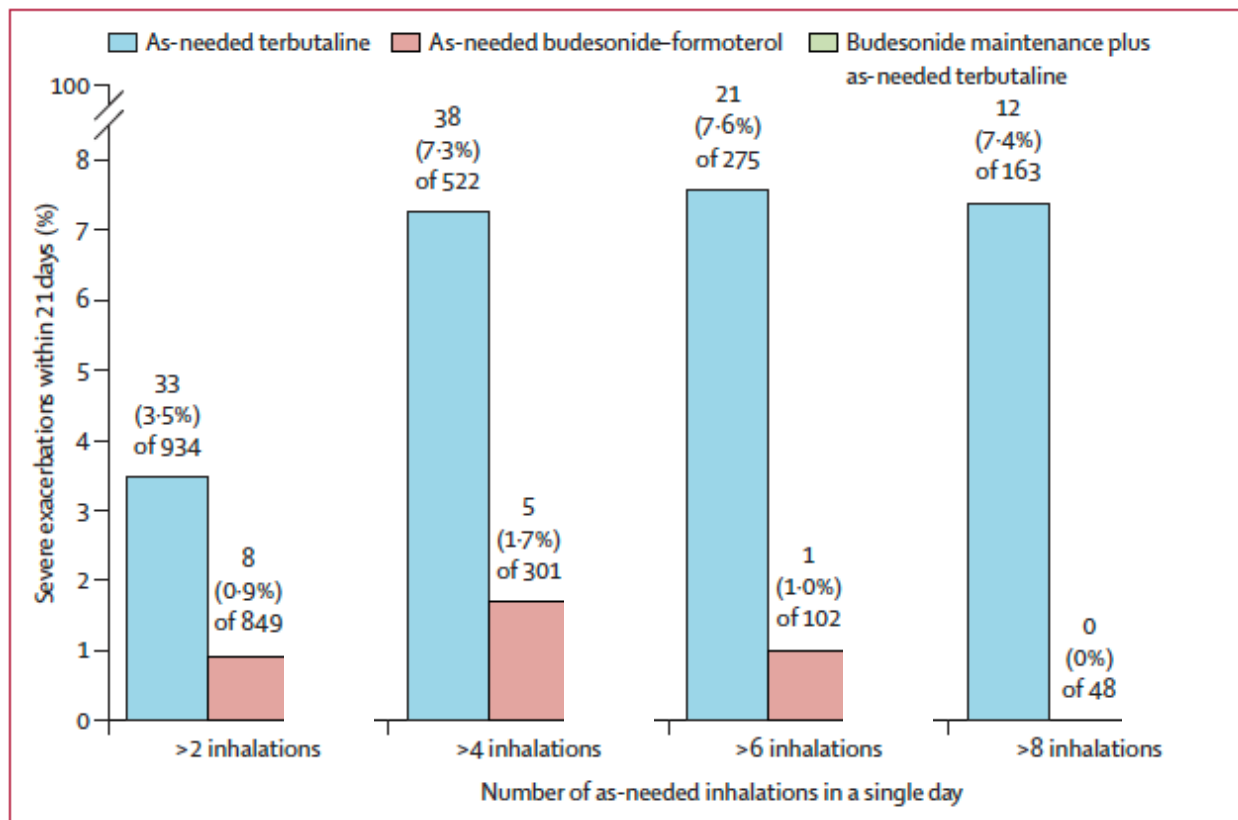
* This study did not achieve its primary endpoint (time to first severe exacerbation); *Severe exacerbations were defined as deterioration in asthma leading to hospitalisation/ emergency room treatment and/or oral corticosteroid treatment for at least 3 days

** Budesonide/formoterol 320/4.5µg bid via Turbuhaler

[†]SFC, salmeterol-fluticasone 50/500µg bid via Discus™

Adapted from Bousquet J, *et al. Respir Med* 2007;101:2437–2446

Mild Asthma: Proportion of patients with a severe exacerbation within 21 days of the first day with extra reliever use



10 Practical considerations

1. Explain that ICS-formoterol replaces SABA completely. Effect of LABA lasts longer
2. Profile each patients' exacerbation risk and explain how SMART works
3. Emphasize need to have inhaler on hand at all times
4. Total daily limit (including maintenance) 12 puffs for adults, 8 for children
5. Emphasize planned maintenance dosing and that it will be reviewed regularly
6. Explain when to seek urgent medical care
7. Address concerns and emphasize safety. Address reluctance with “two pocket” approach
8. Mouth rinsing unnecessary
9. Address issues relating to supply of inhaler

What SMART is NOT!

1. A license for intermittent or no maintenance treatment
2. Encouraging worse symptom control
3. Reducing the need for follow-up
4. Reducing the need for interval objective assessments of lung function and other risk factors and co-morbidities

Additional Standards of Care

1. Tailor the discussion about SMART to the patient's individual goals, preferences and concerns
2. Instruct and check inhaler technique
3. Provide a customized written action plan

My Asthma Action Plan

Maintenance
And Reliever Therapy

Name: _____

Date: _____

GP: _____

Usual best PEF: _____ L/min

GP phone: _____

Normal mode

MY _____ ASTHMA TREATMENT IS:

- _____
- _____

MY REGULAR TREATMENT EVERY DAY:

Take _____ inhalation(s) in the morning
and _____ inhalation(s) in the evening, every day

RELIEVER:

Use 1 inhalation of _____ whenever needed
for relief of my asthma symptoms

I should always carry my _____

MY ASTHMA IS STABLE IF:

- I can take part in normal physical activity without asthma symptoms
- AND
- I do not wake up at night or in the morning because of asthma

OTHER INSTRUCTIONS:

Asthma flare-up

IF OVER A PERIOD OF 2–3 DAYS:

- My asthma symptoms are getting worse OR not improving **OR**
- I am using more than _____ reliever inhalations a day, _____

I should:

- Continue to use my regular everyday treatment PLUS 1 inhalation of _____ whenever needed to relieve symptoms
- Start a course of prednisolone
- Contact my doctor

COURSE OF PREDNISOLONE TABLETS:

Take _____ mg prednisolone
tablets per day for _____ days OR

IF I NEED MORE THAN _____ INHALATIONS (TOTAL) IN ANY DAY,

I must see my doctor or go to hospital
the same day

Asthma emergency

SIGNS OF AN ASTHMA EMERGENCY:

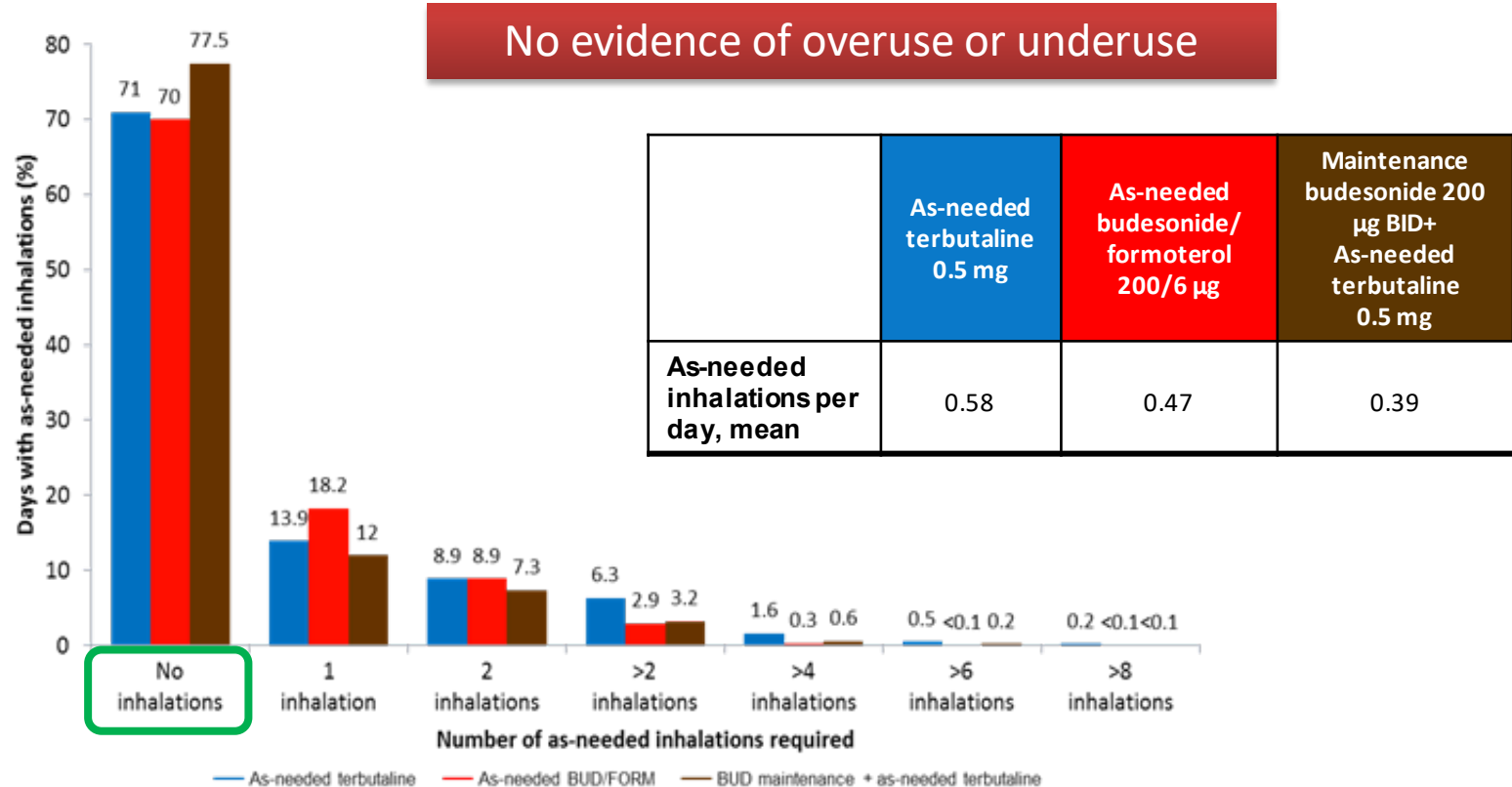
- Symptoms getting worse quickly
- Extreme difficulty breathing or speaking
- Little or no improvement from _____
reliever inhalations

**IF I HAVE ANY OF THE ABOVE DANGER SIGNS,
I SHOULD DIAL _____ FOR AN AMBULANCE AND
SAY I AM HAVING A SEVERE ASTHMA ATTACK.**

WHILE I AM WAITING FOR THE AMBULANCE START MY ASTHMA FIRST AID PLAN:

- Sit upright and stay calm
- Take 1 inhalation of _____ . Wait 1–3 minutes.
If there is no improvement take another inhalation
of _____ (up to a maximum of 6 inhalations)
- If only _____ is available, take 4 puffs as
often as needed until help arrives
- Start a course of prednisolone tablets (as
directed) while waiting for the ambulance
- Even if my symptoms appear to settle quickly,
I should see my doctor immediately after a
serious asthma attack

Mild asthma: Percentage days with as-needed inhalations (SYGMA 1)

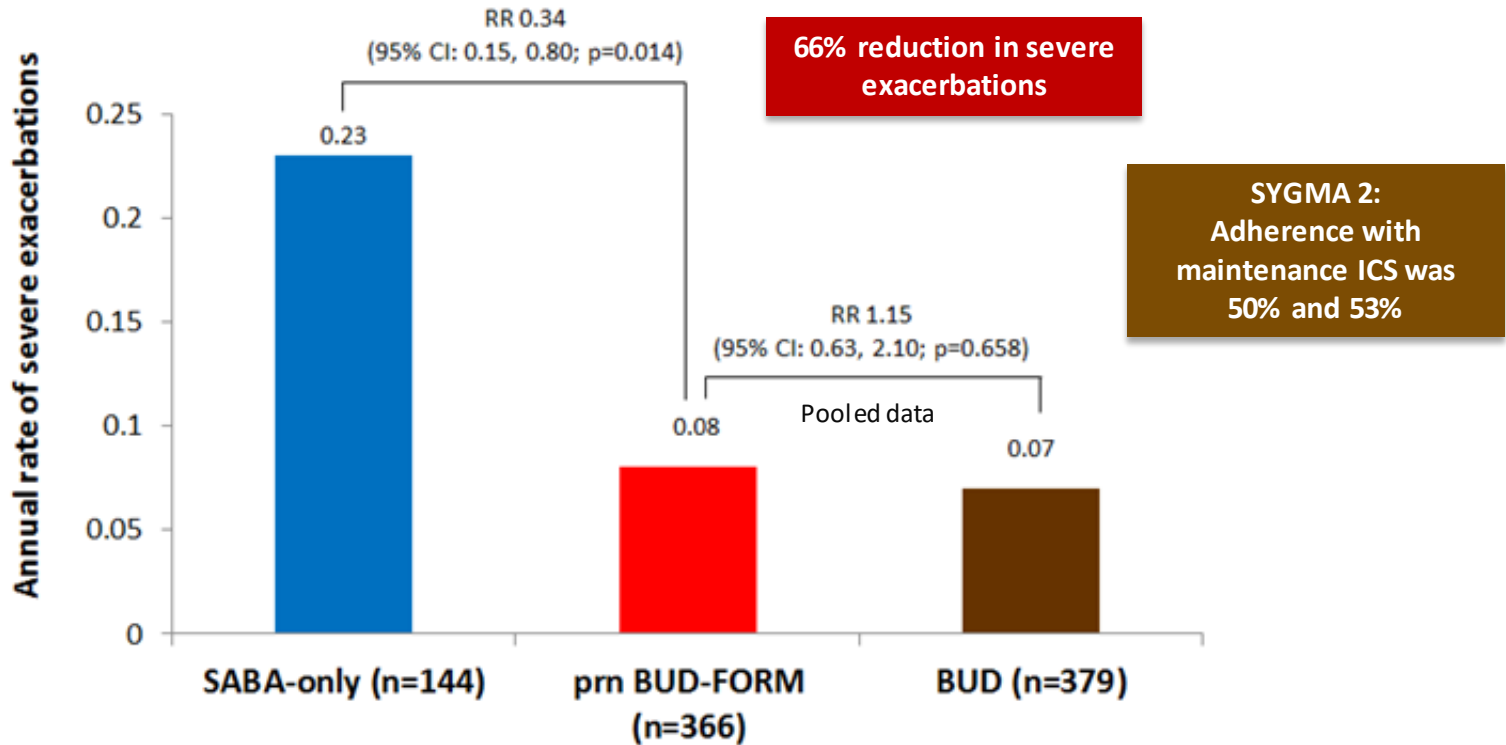


Self-titration of ICS-LABA in mild asthma in the PRACTICAL study

Use of BUD (alone or as BUD-FORM)	BUD-FORM n=55	Maintenance BUD n=55	
Mean actuations/day	0.9 (0.7)	1.5 (0.4)*	
Daily ICS use (μg)	176 (143)	302 (85)	P=0.001
Days with <u>no</u> ICS use	182 (109)	46 (65)	P=0.001
Longest period without ICS (days)	40	9	
Maximum ICS actuations in a single day	6	4	
Mean days with ≥ 6 ICS actuations	3	0.4	

*Mean adherence in BUD maintenance group=76%

Efficacy of as-needed BUD-FORM in adolescents with mild asthma (SYGMA 1 and 2)



Severe exacerbations: use of oral corticosteroids for ≥ 3 days, or emergency department presentation or hospitalization plus systemic corticosteroid.
BUD: budesonide; FORM: formoterol; RR: relative risk; SABA: short-acting β_2 -agonist; SYGMA: Symbiaort Given as Needed in Mild Asthma.

Patient experiences of as-needed budesonide-formoterol in mild asthma: a qualitative study (NOVEL-Start)

35 patients after 10 months of treatment (66% female, mean age 43.5 years)

- **Efficacy:**

- Majority described effectiveness
 - *I just need one puff, and after a few minutes it works*
 - *I think my asthma has been way better controlled*
 - *I'm less nervous about doing physical stuff ... I'm getting out more, and I can walk a decent amount.*
- Prior treatment: those not previously on the controller tended to report being better, and those on the controller were the same (not worse).

- **Lifestyle:**

- Fitted well into their lifestyle: convenience of single inhaler and removed disincentive to ICS therapy
 - *Part of it is laziness and having other things to do in my life*
 - *With my [previous medication] I just forgot. [Now] it doesn't matter whether I forget ... I just take it when I absolutely need to ...*
 - One patient preferred using it daily ... *"It's part of your 'getting up routine' in the morning"*
- Cost – *could be a potential barrier.*

Patient experiences of as-needed budesonide-formoterol in mild asthma: a qualitative study (NOVEL-Start)

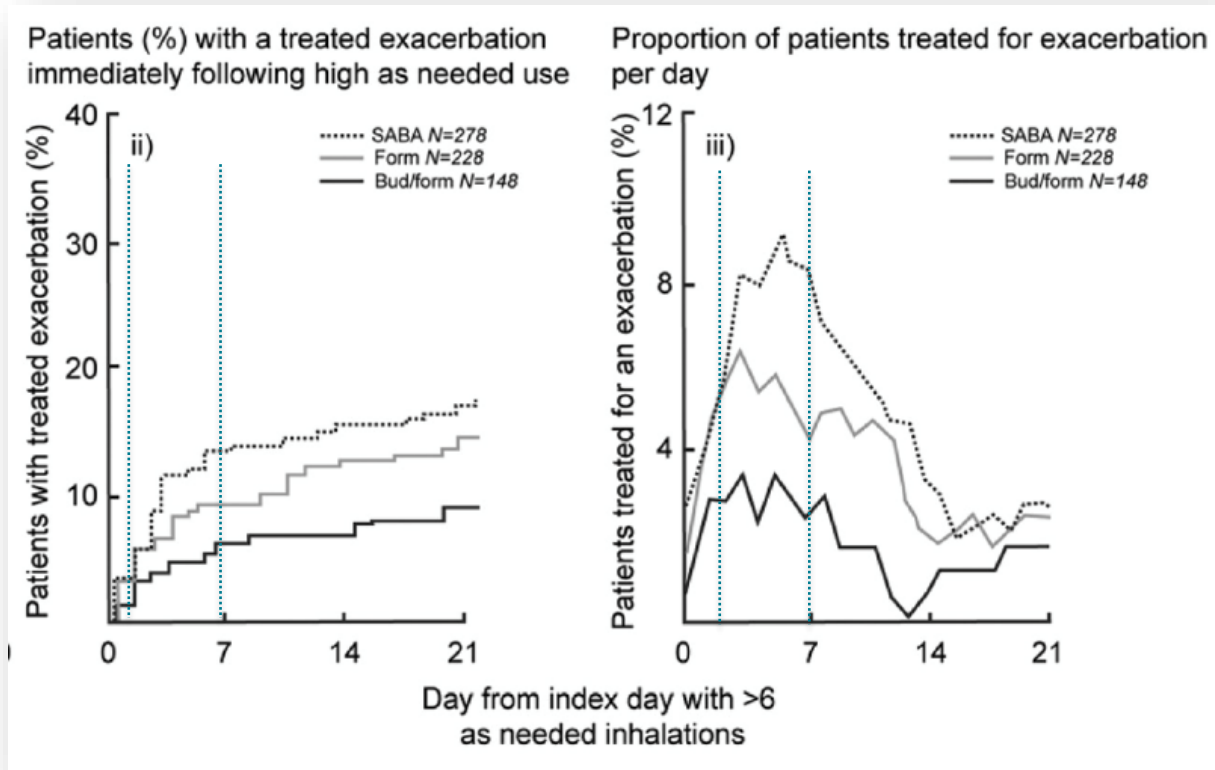
- **Attitudes toward medication use and safety:**
 - Some reported strong faith in short-acting β_2 agonists (SABA) and limited confidence in budesonide/formoterol; recognized that this requires time
 - Some questioned the necessity of a controller inside their reliever
 - There was little concern about safety of long-term use
 - Side effects were similar to past experience with inhalers.
- **Doctor–patient relationship:**
 - Most agreed to future use
 - Trusted doctors' decision
 - Working though patients' personal barriers appeared key to ongoing use.

Patient preferences for symptom-driven or regular preventer treatment in mild to moderate asthma: PRACTICAL real life study

- At final study visit (12 months) patients tended to favour the treatment they had received
- Preference for as-needed BUD/FORM approach:
 - Among as-needed BUD/FORM users **90%** (95% CI 85.2-94.8%)
 - Among Twice-daily ICS + SABA users **40%** (95% CI 32.7-48.1%)

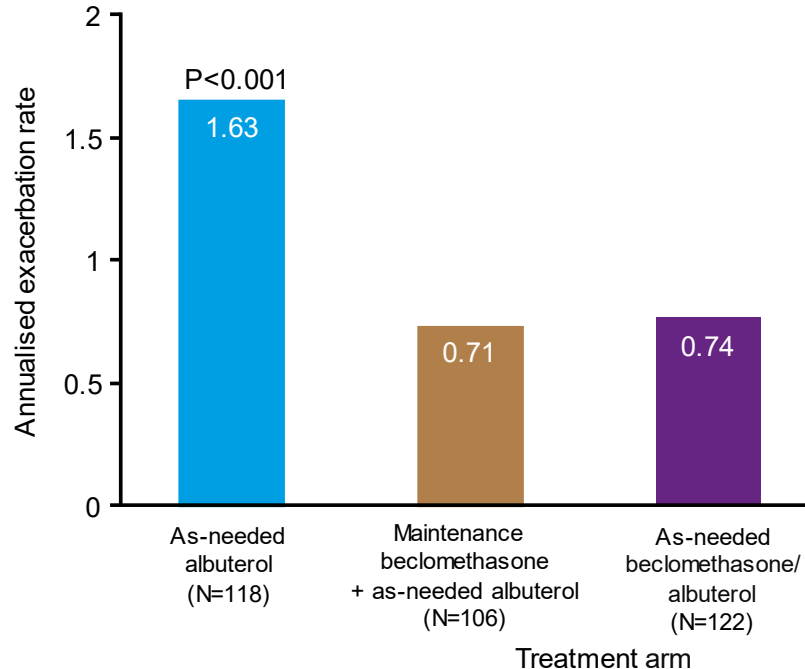
92% of BUD-FORM as-needed users were confident to use BUD/FORM as a reliever

Effect of SMART on risk of severe exacerbations following one day of high reliever use (6 doses in a day)



BEST study: As-needed beclomethasone and albuterol combination inhaler in mild-moderate asthma

Annualised exacerbation rates (composite¹)



¹Severe exacerbation defined as one requiring treatment with oral glucocorticoids, as judged by the investigator, or a decrease in the morning peak expiratory flow to >30% below the baseline value on two consecutive days

Inhaled corticosteroids/long acting β_2 -agonists as relievers

Conclusions

- There is a sound rationale and scientific basis for using an ICS-containing rapid-onset reliever across the spectrum of asthma severities
- Well-established approach globally
- SMART targets exacerbations and provides a better "safety net" when attacks threaten
- Both the ICS and formoterol contribute to the effectiveness of SMART
- SMART leverages normal patient behavior in the face of increasing symptoms
- The general principles of physician supervision and review remain