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KATRD 제135차 춘계학술대회 오찬 특강

How to Reduce Exacerbation in Asthma: Focused on Anti-Inflammatory Reliever

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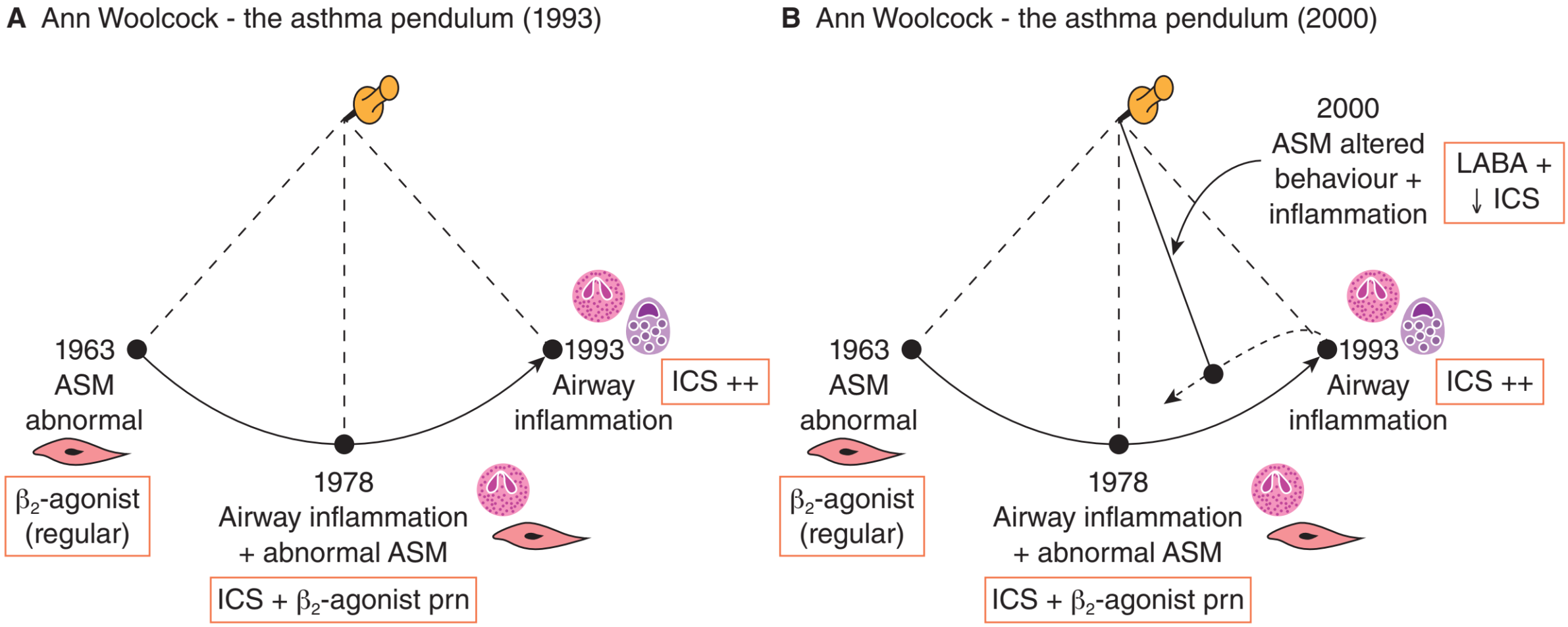
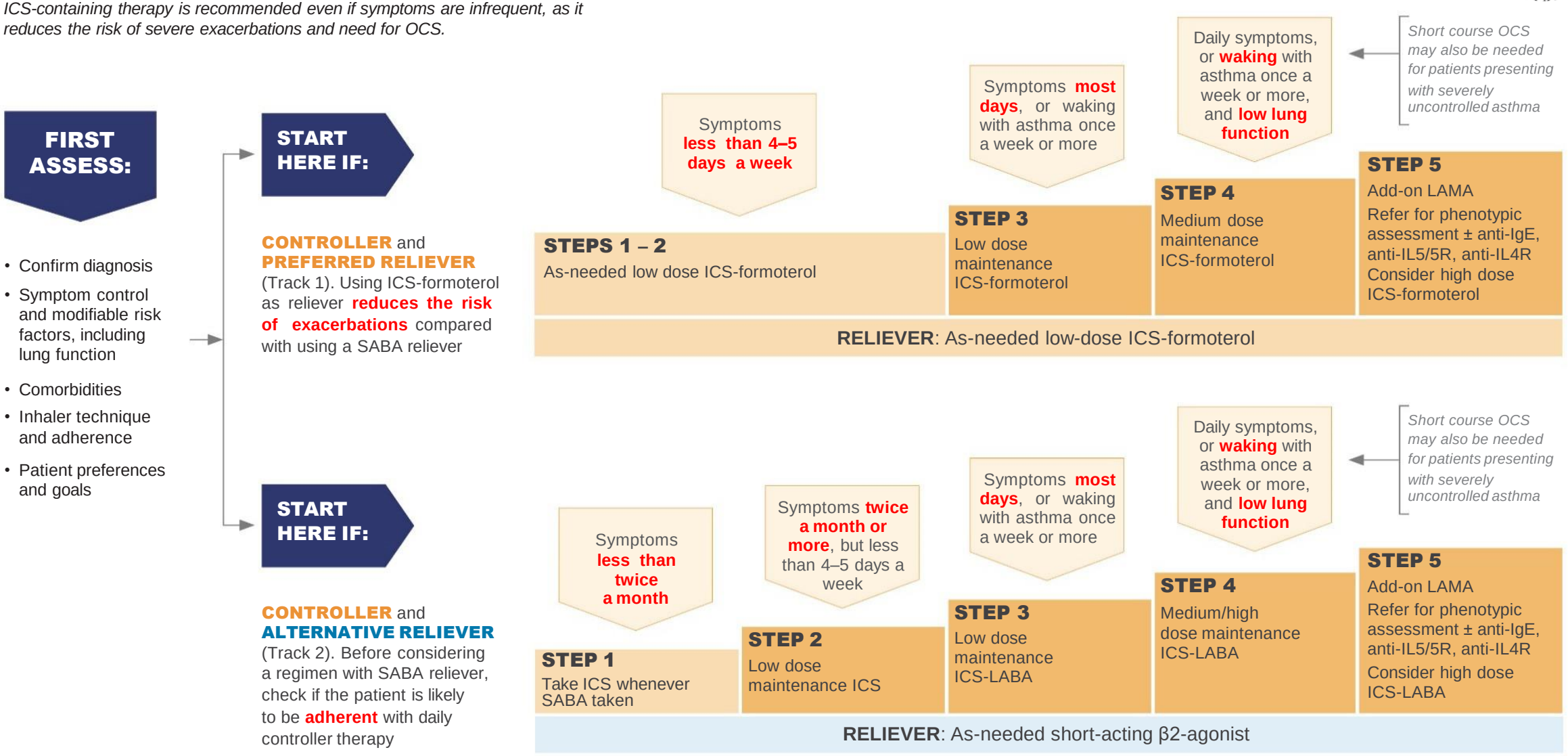


Reddel HK BRN Rev 2019;5:4-18

STARTING TREATMENT

in adults and adolescents with a diagnosis of asthma

Track 1 is preferred if the patient is likely to be poorly adherent with daily controller ICS-containing therapy is recommended even if symptoms are infrequent, as it reduces the risk of severe exacerbations and need for OCS.



Box 3-6. Low, medium and high daily metered doses of inhaled corticosteroids (alone or with LABA)

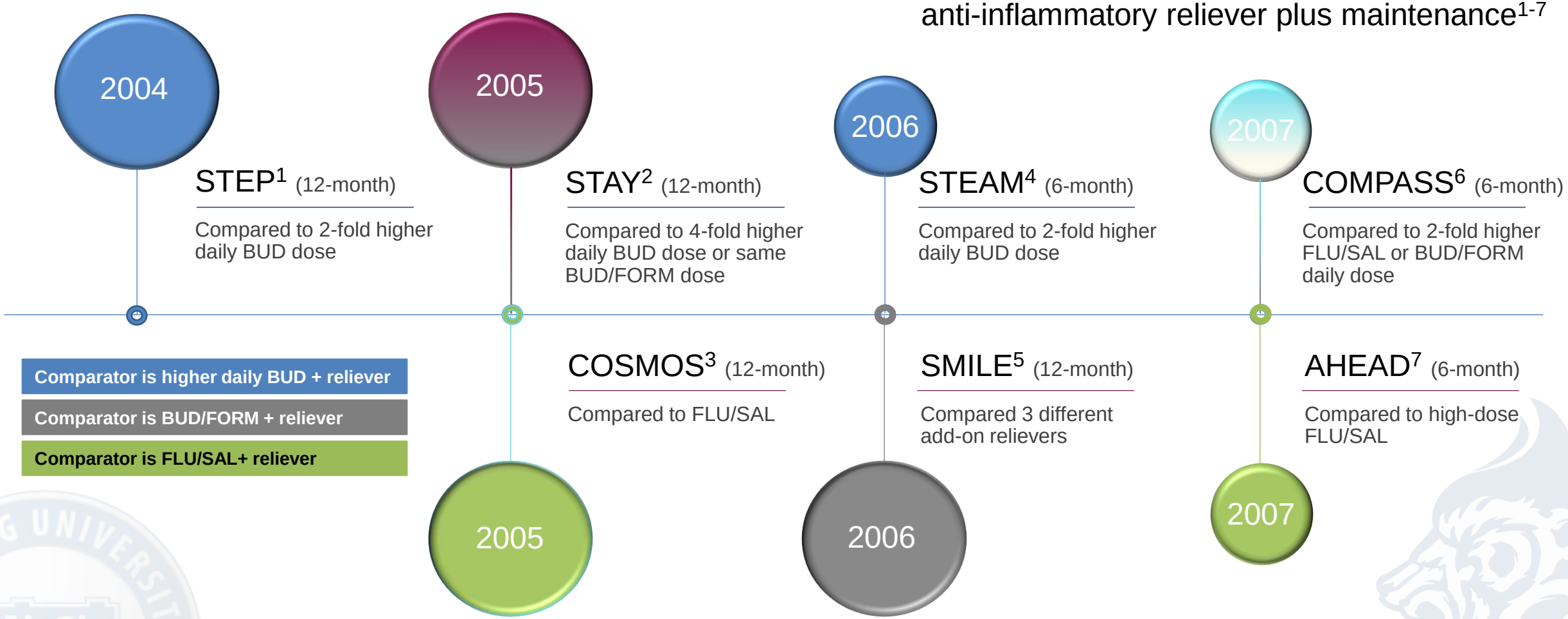
◆ Few data are available for comparative potency, so this table does **NOT imply potency equivalence**

Adults and adolescents (12 years and older)

Inhaled corticosteroid	Total daily ICS dose (mcg) – see notes above		
	Low	Medium	High
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400

Budesonide/Formoterol Anti-inflammatory Reliever Plus Maintenance Program:
>16,500 patients across 7 clinical trials[1-7]

>6600 patients received budesonide/formoterol anti-inflammatory reliever plus maintenance[1-7]

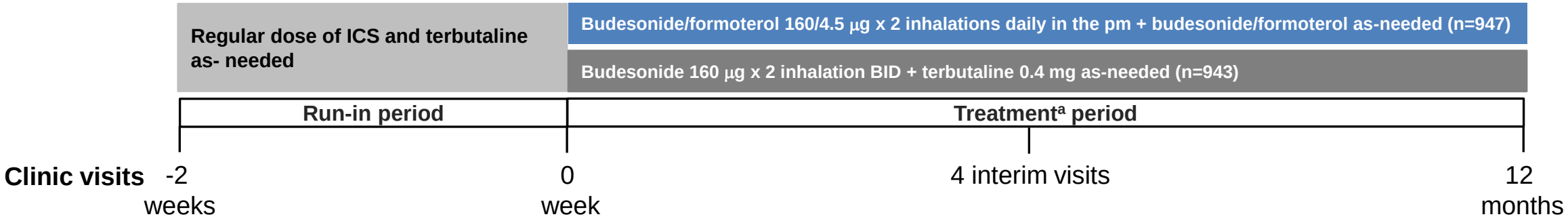


BUD = budesonide; FLU = fluticasone; FORM = formoterol; SAL = salmeterol.

1. Scicchitano R et al. *Curr Med Res Opin.* 2004;20:1403-1418; 2. O'Byrne PM et al. *Am J Respir Crit Care Med.* 2005;171:129-136; 3. Vogelmeier C et al. *Eur Respir J.* 2005; 26:819-828;
4. Rabe KF et al. *Chest.* 2006;129:246-256; 5. Rabe KF et al. *Lancet.* 2006;368:744-753; 6. Kuna P et al. *Int J Clin Pract.* 2007;61:725-736; 7. Bousquet J et al. *Resp Med.* 2007;101:2437-2446.

STEP: Study Design

12-month, randomized, double-blind, double-dummy, parallel-group, multicenter study (N=1890)
to determine if budesonide/formoterol anti-inflammatory reliever plus maintenance is more effective than **2x higher ICS** + SABA in patients with moderate to severe, persistent asthma



Primary efficacy endpoint: Time to first severe exacerbation defined as deterioration in asthma resulting in hospitalization or ED treatment, the need for OCS, or a decrease from baseline in morning PEF on 2 consecutive days

Secondary endpoints:[a] Risk of severe exacerbation, as-needed medication use, lung function (PEF), asthma symptoms and control

Safety data: Adverse events

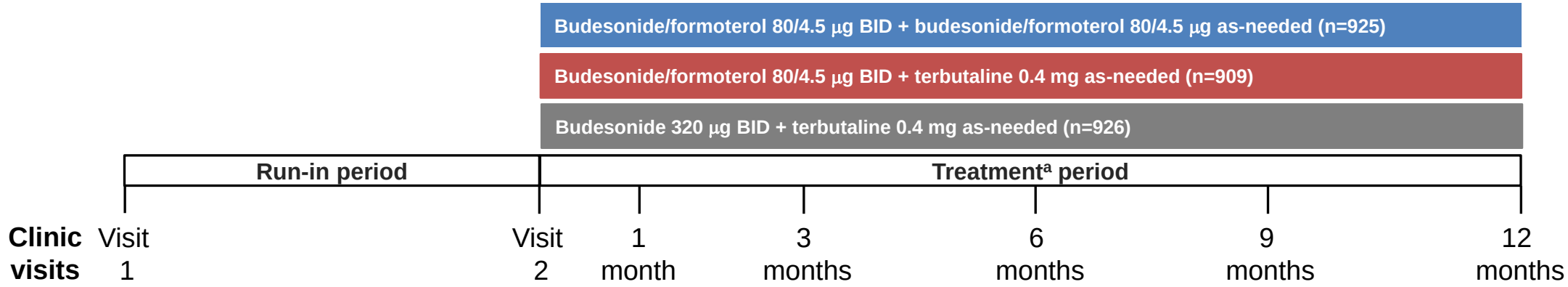
[a]Select secondary endpoints.

ED = emergency department; ICS = inhaled corticosteroids; OCS = oral corticosteroids; PEF = peak expiratory flow; SABA = short-acting β_2-agonist.

Scicchitano R et al. *Curr Med Res Opin.* 2004;20:1403-1418.

STAY: Study Design

12-month, randomized, double-blind, parallel-group, multicenter study (N=2760)
to determine if budesonide/formoterol anti-inflammatory reliever plus maintenance is more effective than **fixed-dose ICS/LABA** + SABA or a **4x higher dose of ICS** + SABA in patients with moderate to severe, persistent asthma



Primary efficacy endpoint:	Time to first severe exacerbation defined as deterioration in asthma resulting in hospitalization/ED treatment, OCS (or increase in ICS or other treatment for children), or PEF ≤70% of baseline on 2 consecutive days
Secondary endpoints:[b]	Rates of severe exacerbation, as-needed medication use, lung function (PEF and FEV_1), asthma symptoms and control, ICS load
Safety data:	Adverse events

[a]Treatment stratification: 8 adults: 1 child. Children <12 years received half the maintenance dose once daily at night; children <12 years represented 11–13% of the study population in each treatment group. [b]Select secondary endpoints.

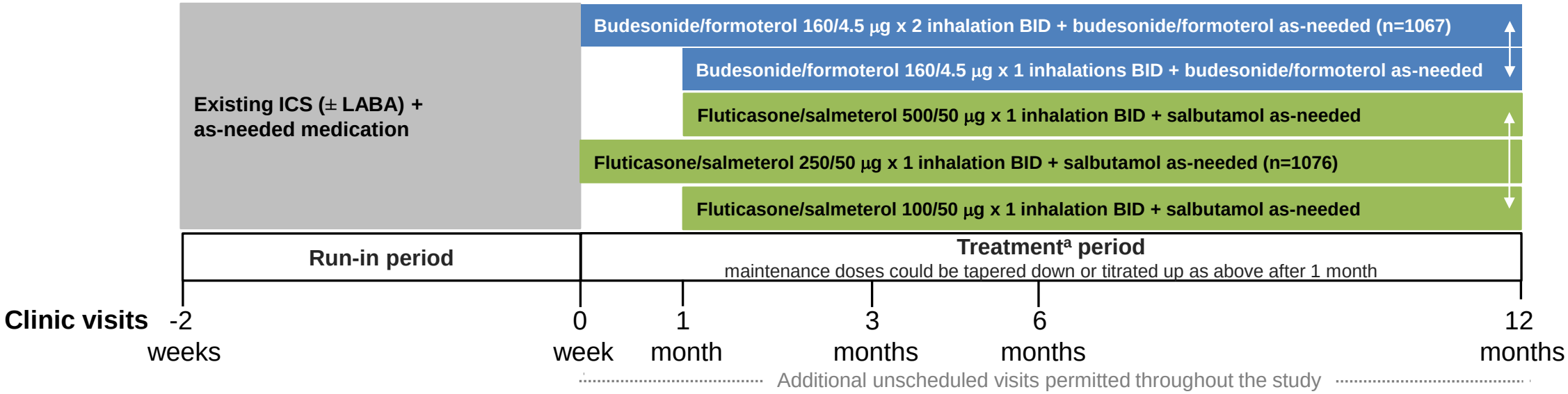
Budesonide/formoterol anti-inflammatory reliever plus maintenance is not licensed for children aged <12 years.

ED = emergency department; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; OCS = oral corticosteroids; PEF = peak expiratory flow; SABA = short-acting β_2-agonist.

O'Byrne PM et al. *Am J Respir Crit Care Med.* 2005;171:129-136.

COSMOS: Study Design

12-month, randomized, **open-label**, dose-titration, parallel-group, multicenter study (N=2143)
to determine if budesonide/formoterol anti-inflammatory reliever plus maintenance is more effective than another ICS/LABA in the **real world** in patients with moderate to severe, persistent asthma



Primary efficacy endpoint: Time to first severe exacerbation defined as deterioration in asthma resulting in hospitalization or ED treatment, the need for OCS for ≥3 days, or an unscheduled visit leading to treatment change

Secondary endpoints:[a] Rate of severe exacerbation, OCS/ICS use, as-needed medication use, FEV_1, asthma symptoms and control

Safety data: Adverse events

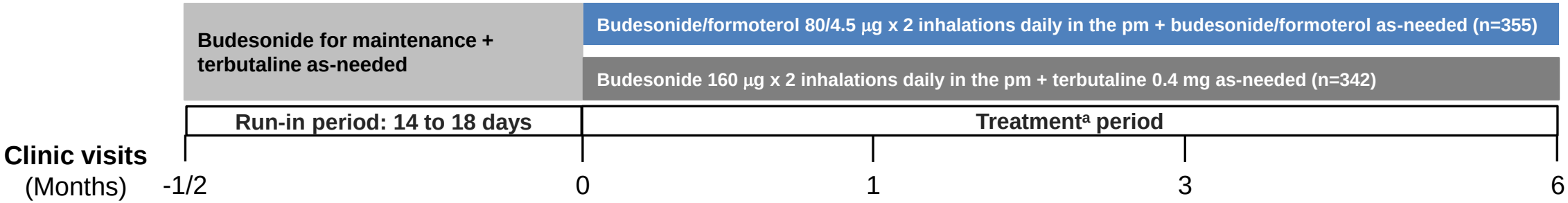
[a]Select secondary endpoints.

ED = emergency department; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; OCS = oral corticosteroids.

Vogelmeier C et al. *Eur Respir J.* 2005;26:819-828.

STEAM: Study Design

6-month, randomized, multicenter, double-blind, parallel-group, multicenter study (N=697)
to determine if budesonide/formoterol anti-inflammatory reliever plus maintenance is more effective than **2x higher ICS** + SABA in patients with mild to moderate, persistent asthma



Primary efficacy endpoint:	**Morning PEF**
Secondary endpoints:[a] need for OCS, or a ≥30%	Time to first and rate of severe exacerbations defined as deterioration in asthma resulting in hospitalization or ED treatment, the decrease from baseline in morning PEF on 2 consecutive days; as-needed medication use; lung function (PEF and FEV1); asthma symptoms and control
Safety data:	Adverse events

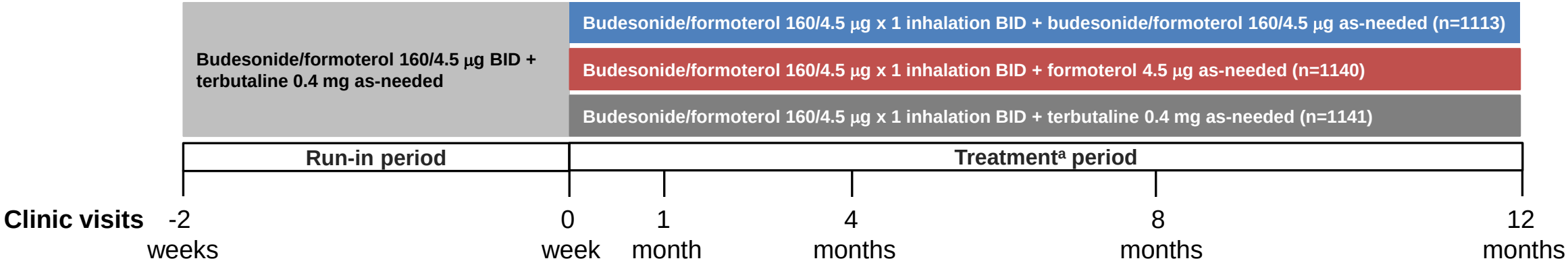
[a]Select secondary endpoints.

ED = emergency department; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; OCS = oral corticosteroids; PEF = peak expiratory flow; SABA = short-acting β_2-agonist.

Rabe KF et al. *Chest*. 2006;129:246-256.

SMILE: Study Design

12-month, randomized, double-blind, parallel-group, multicenter study (N=3394) to assess the comparative contribution of different relievers (anti-inflammatory reliever vs. fast-acting LABA vs. SABA) to maintenance therapy in patients with moderate to severe, persistent asthma



Primary efficacy endpoint: Time to first severe exacerbation defined as deterioration in asthma resulting in hospitalization or ED treatment, or the need for OCS for ≥3 days

Secondary endpoints:[a] Rates of severe exacerbation, as-needed medication use, lung function (PEF and FEV_1), asthma symptoms and control

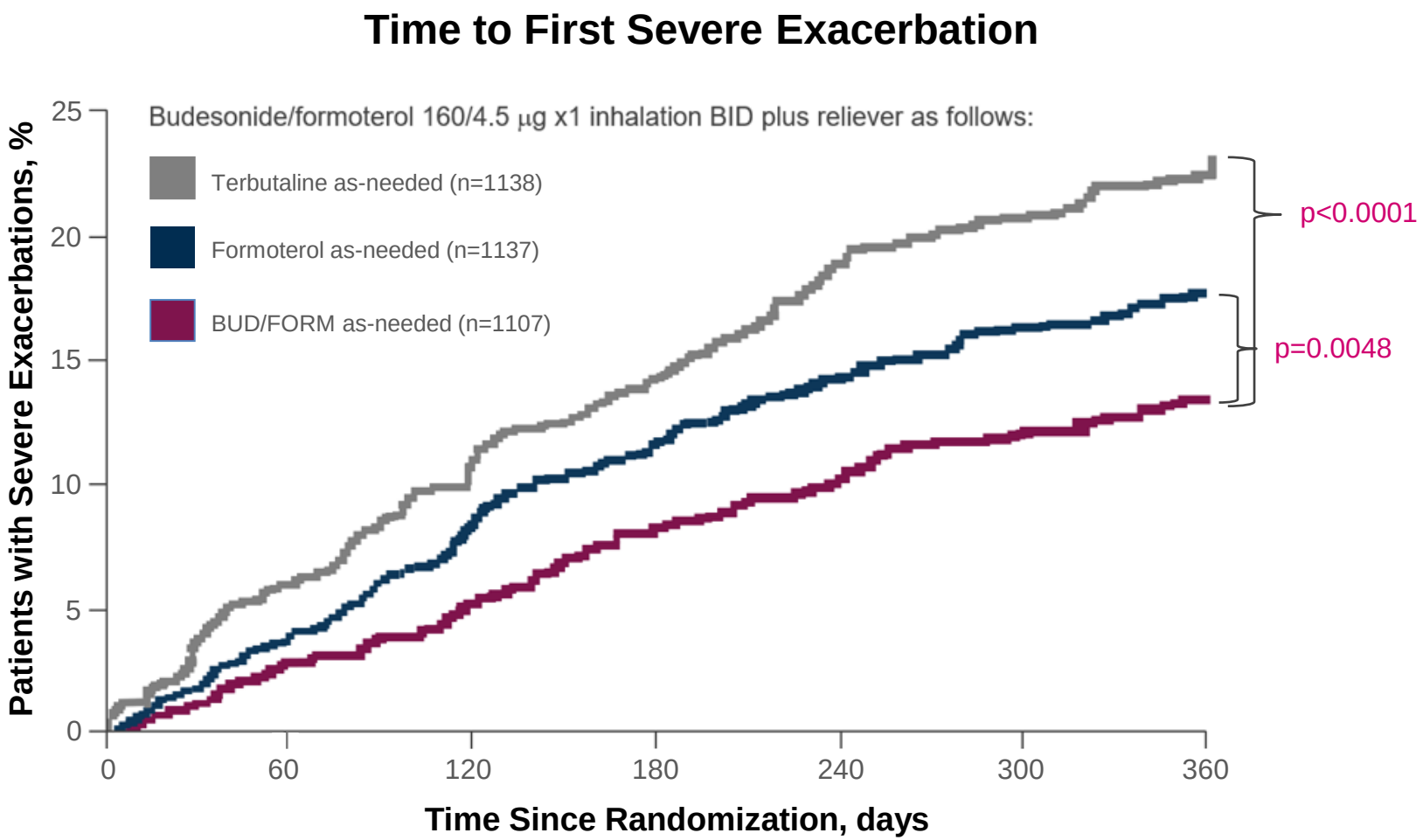
Safety data: Adverse events

[a]Select secondary endpoints.

ED = emergency department; FEV_1 = forced expiratory volume in 1 second; LABA = long-acting β_2-agonist; OCS = oral corticosteroids; PEF = peak expiratory flow; SABA = short-acting β_2-agonist.

Rabe KF et al. *Lancet.* 2006;368:744-753.

SMILE: Reduced Risk of First Severe Exacerbation



As-needed budesonide/formoterol reduced the risk of a severe exacerbation by:[1]

- 27% vs. formoterol as needed (p=0.0038)[a,b]
  - Events/100 patients/year: 19 BUD/FORM as needed vs. 29 FORM as needed
- 45% vs. terbutaline as needed (p<0.0001)[a,c]
  - Events/100 patients/year: 19 BUD/FORM as needed vs. 37 Terbutaline as needed

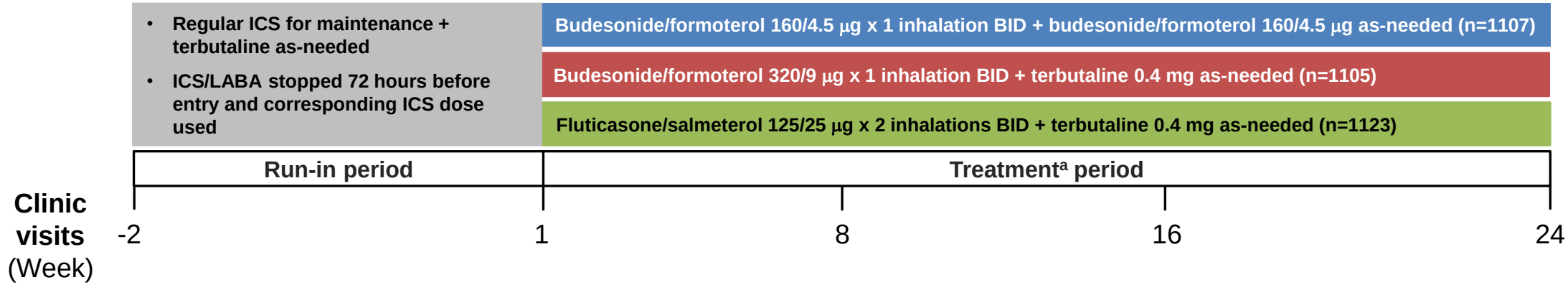
[a]Patients with event, n (%): budesonide/formoterol as-needed, 143 (13%); formoterol as-needed, 195 (17%), terbutaline as-needed, 245 (22%);
[b]Hazard ratio, 0.73 (95% CI, 0.59-0.90); [c]Hazard ratio, 0.55 (95% CI, 0.45-0.68).

BUD = budesonide; FORM = formoterol.

Rabe KF et al. *Lancet.* 2006;368:744-753.

COMPASS: Study Design

6-month, randomized, double-blind, double-dummy, parallel-group, multicenter study (N=3335)
to determine if budesonide/formoterol anti-inflammatory reliever plus maintenance is more effective than **doubling the dose of different ICS/LABA** + SABA in patients with moderate to severe, persistent asthma



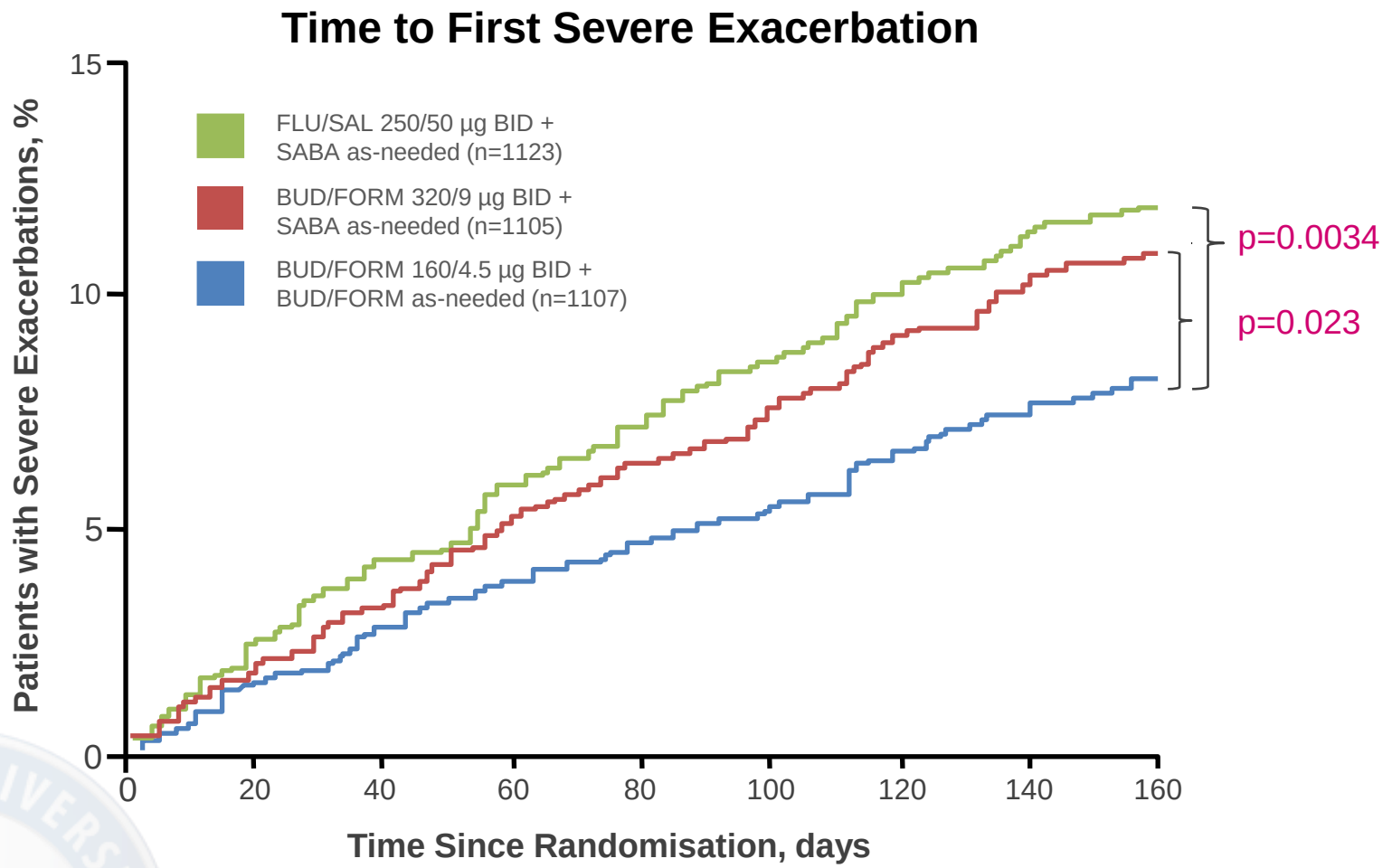
Primary efficacy endpoint:	Time to first severe exacerbation defined as deterioration in asthma resulting in hospitalization or ED treatment, or the need for OCS for ≥3 days
Secondary endpoints:[a]	Rates of severe exacerbation, as-needed medication use, lung function (PEF and FEV_1), asthma symptoms and control
Safety data:	Adverse events

[a]Select secondary endpoints.

ED = emergency department; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; OCS = oral corticosteroids;
PEF = peak expiratory flow; SABA = short-acting β_2-agonist.

Kuna P et al. *Int J Clin Pract.* 2007;61:725-736.

COMPASS: Reduced Risk of First Severe Exacerbation



Budesonide/formoterol anti-inflammatory reliever plus maintenance reduced the risk of a severe exacerbation by:

- 33% vs. FLU/SAL + SABA (p=0.003)[a,b]
  - Events/100 patients/6 months: 12 BUD/FORM reliever plus maintenance vs. 19 FLU/SAL + SABA
- 26% vs. BUD/FORM + SABA (p=0.026)[a,c]
  - Events/ 100 patients/6 months: 12 BUD/FORM reliever plus maintenance vs. 16 BUD/FORM + SABA

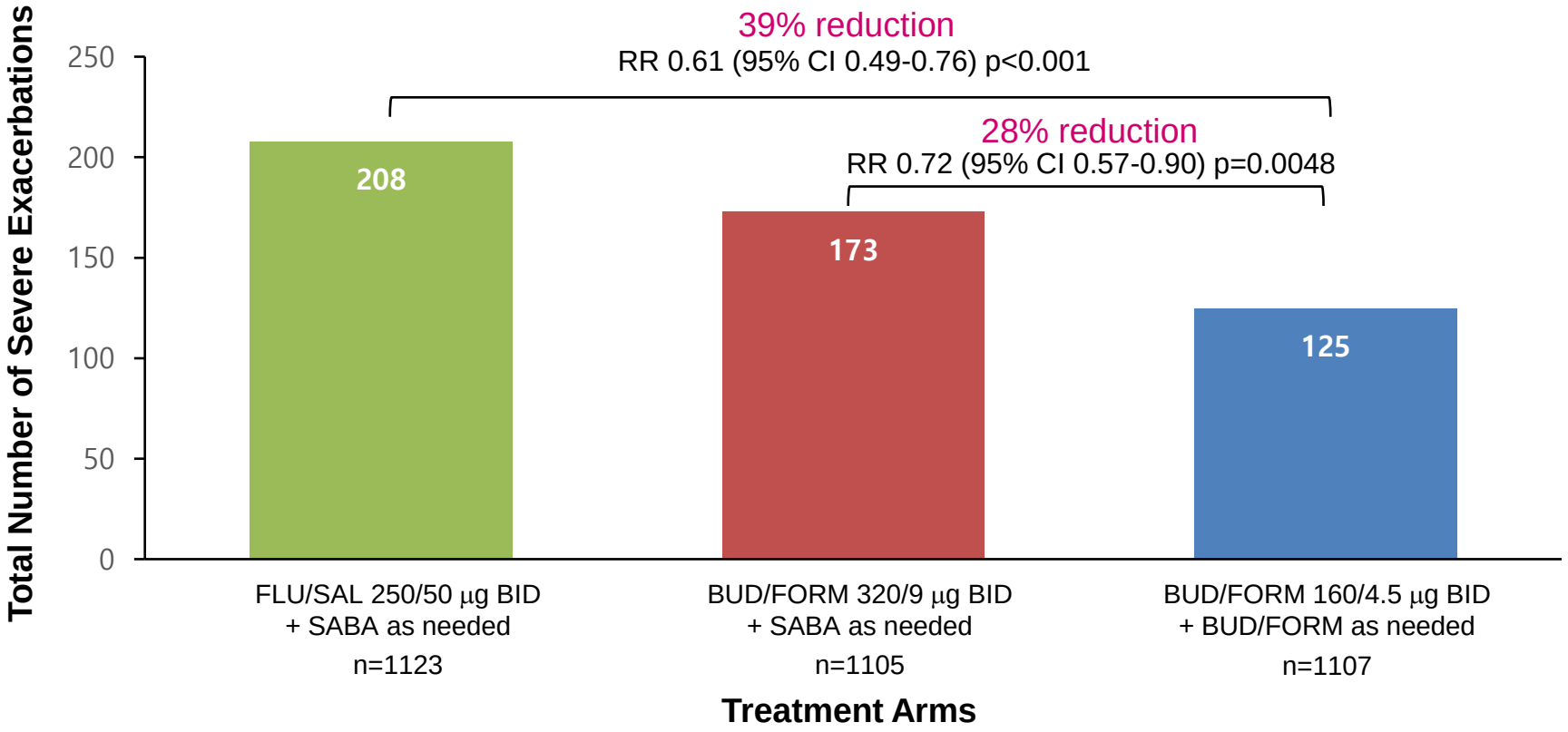
[a]Patients having ≥1 exacerbation, n (%): BUD/FORM BID + BUD/FORM as-needed, 94 (9%); BUD/FORM + SABA, 126 (11%), FLU/SAL + SABA, 138 (12%);
[b]Hazard ratio, 0.67 (95% CI, 0.52-0.87); [c]Hazard ratio, 0.74 (95% CI, 0.56-0.96).

BUD = budesonide; FLU = fluticasone; FORM = formoterol; SABA = short-acting β_2-agonist; SAL = salmeterol.

Kuna P et al. *Int J Clin Pract.* 2007;61:725-736.

COMPASS: Exacerbation Rate Reduction

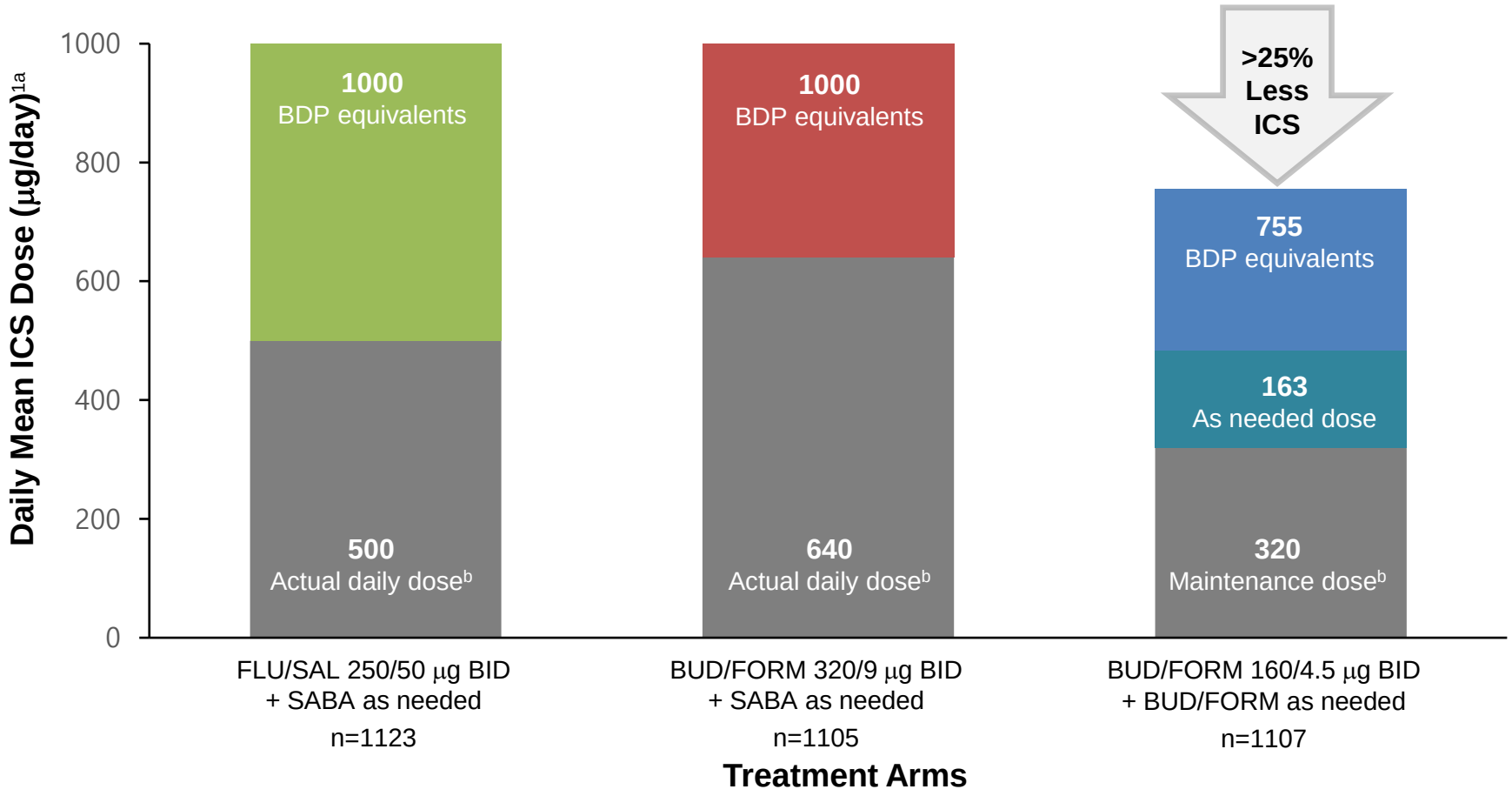
In addition to meeting its primary endpoint (time to first severe exacerbation), budesonide/formoterol anti-inflammatory reliever plus maintenance reduced the number of severe exacerbations over 6 months



BUD = budesonide; FLU = fluticasone; FORM = formoterol; SABA = short-acting β_2-agonist; SAL = salmeterol.

Kuna P et al. *Int J Clin Pract.* 2007;61:725-736.

COMPASS: Lower Mean Daily ICS Dose

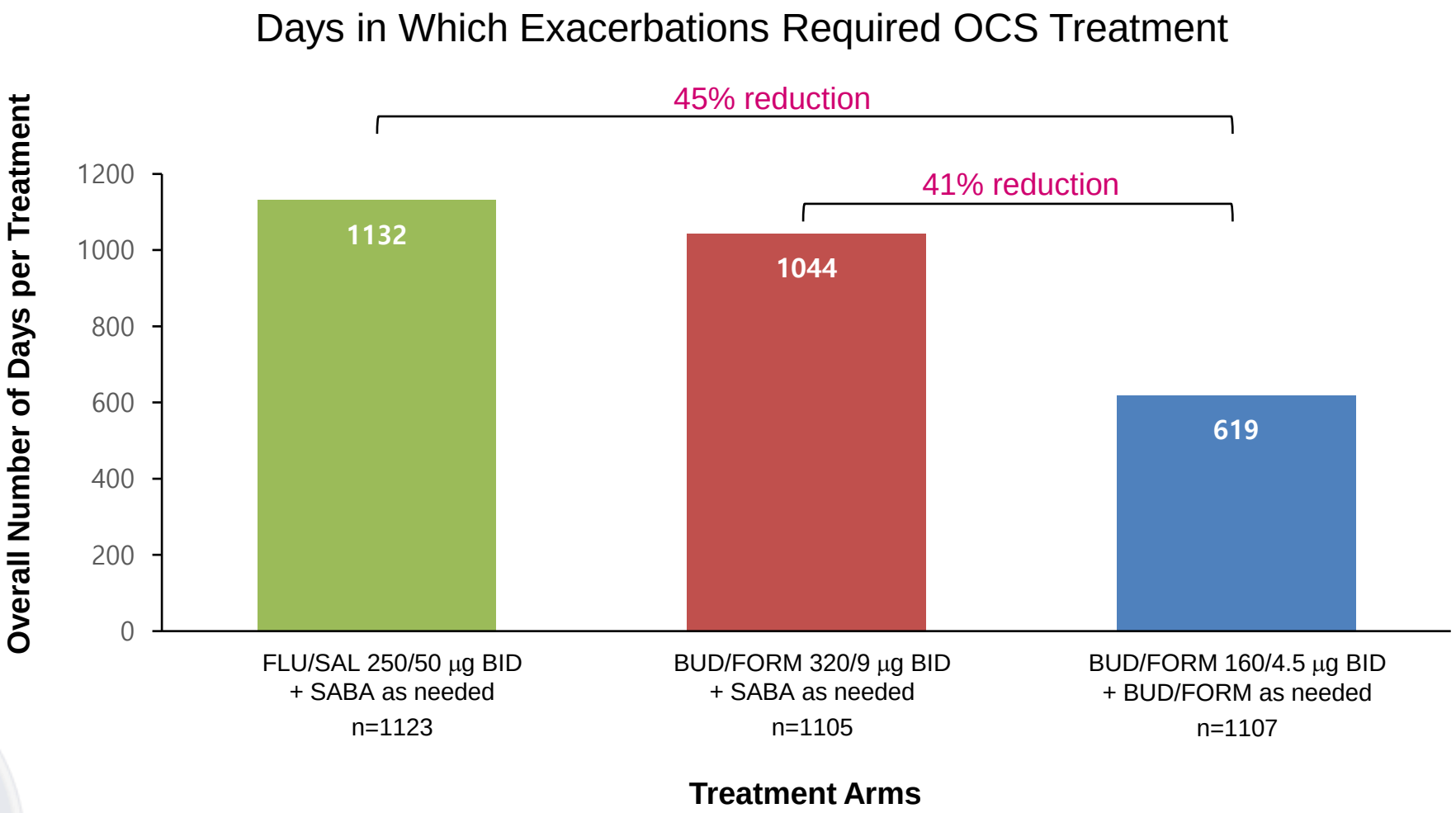


[a]Descriptive analysis; [b]actual dose = dose prescribed at randomisation. Calculations based on GINA estimates of comparable ICS doses (FLU presented as metered dose and BUD presented as delivered doses in above bar graphs).[1]

BDP = beclomethasone dipropionate; BUD = budesonide; FLU = fluticasone; FORM = formoterol; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; SABA = short-acting β_2-agonist; SAL = salmeterol

1. Kuna P et al. *Int J Clin Pract.* 2007;61:725-736.

COMPASS: Fewer OCS Treatment Days for Exacerbations



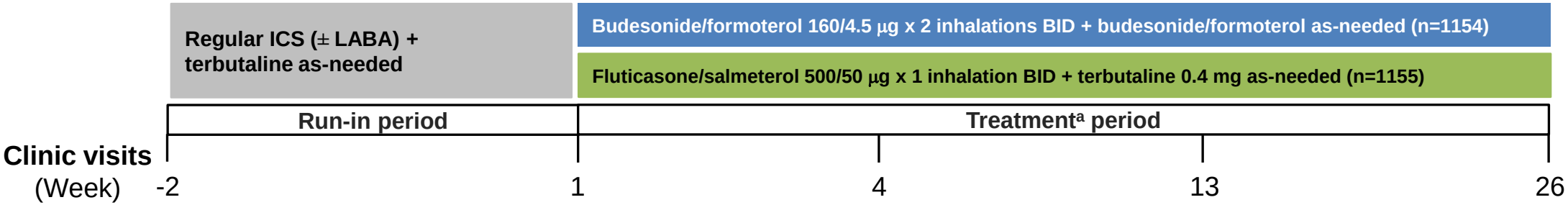
Note: Descriptive analysis.

BUD = budesonide; FLU = fluticasone; FORM = formoterol; OCS = oral corticosteroid; SABA = short-acting β_2-agonist; SAL = salmeterol.

Kuna P et al. *Int J Clin Pract.* 2007;61:725-736

AHEAD: Study Design

6-month, randomized, double-blind, double-dummy, parallel-group, multicenter study (N=2309) to determine if budesonide/formoterol anti-inflammatory reliever plus maintenance is more effective than a **different fixed-dose, maximum-dose ICS/LABA**+ SABA in patients with moderate to severe, persistent asthma



Primary efficacy endpoint:	Time to first severe exacerbation defined as deterioration in asthma resulting in hospitalization or ED treatment, or the need for OCS for ≥3 days
Secondary endpoints:[a]	Rates of severe exacerbation, time to first hospitalization or ED visit, as-needed medication use, lung function (PEF and FEV_1), asthma symptoms and control, ICS load
Safety data:	Adverse events

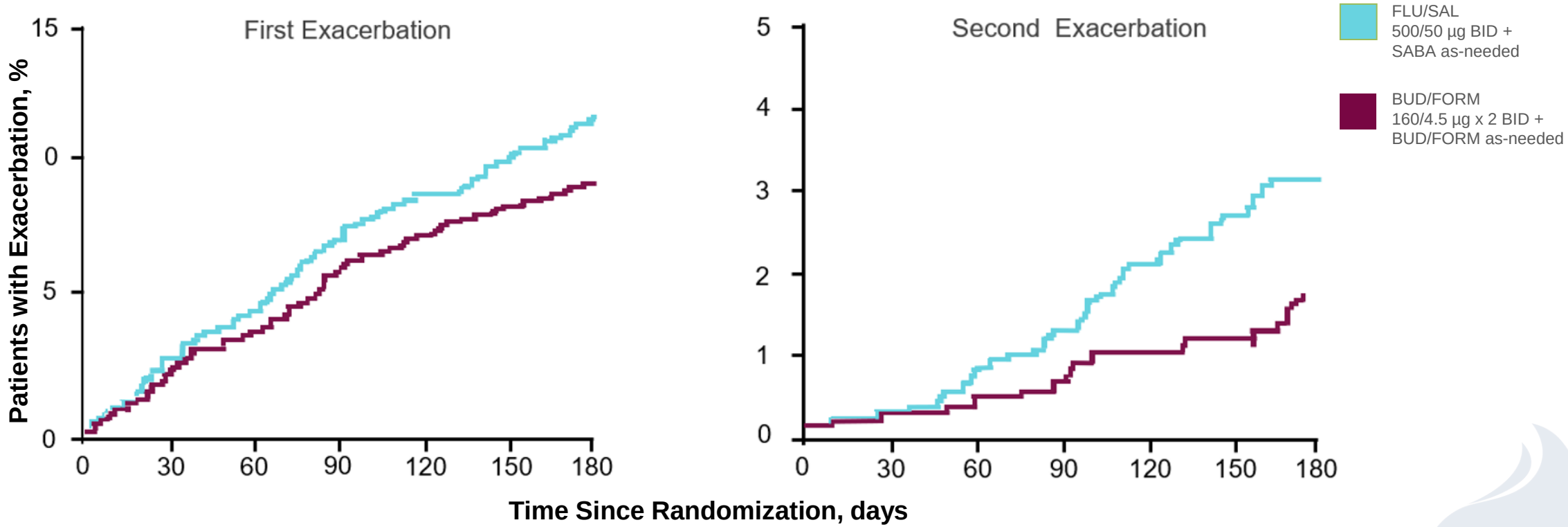
Time to first severe exacerbation, the pre-specified primary outcome, was not significantly prolonged (risk ratio 0.82; 95% confidence interval 0.63, 1.05).

[a]Select secondary endpoints.

ED = emergency department; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; OCS = oral corticosteroids; PEF = peak expiratory flow; SABA = short-acting β_2-agonist.

Bousquet J et al. *Respir Med.* 2007;101:2437-2446.

AHEAD: Time to First and Second Severe Exacerbation



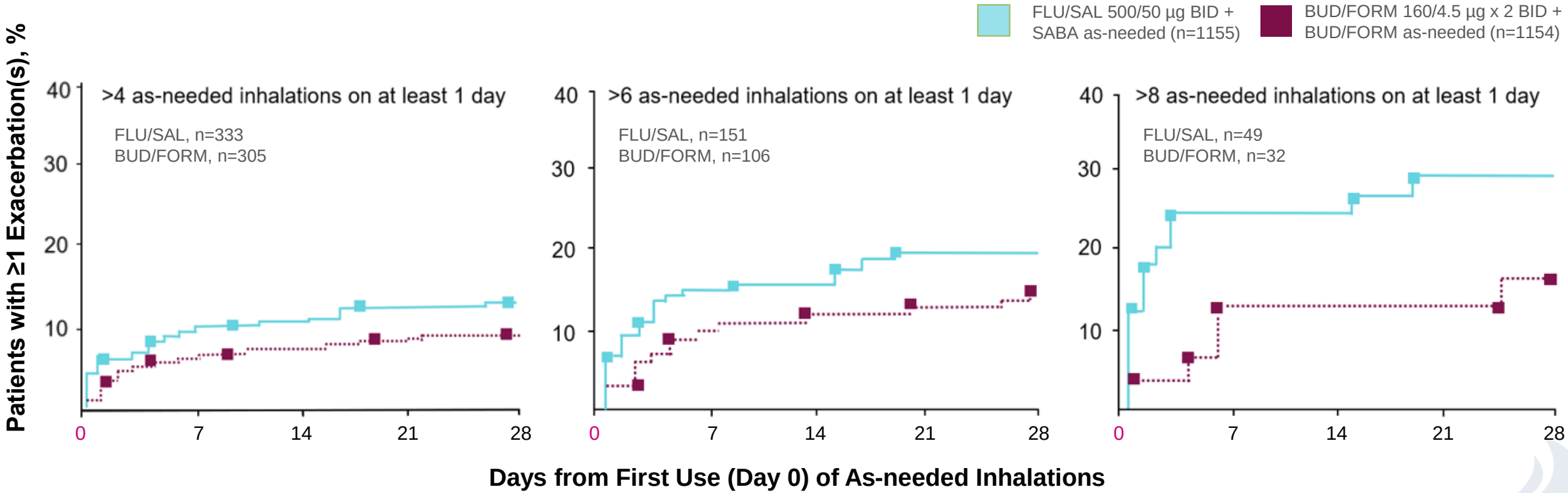
Time to first severe exacerbation was prolonged by 18% but did not significantly differ between groups (primary endpoint: hazard ratio, 0.82; p=0.12)

Budesonide/formoterol anti-inflammatory reliever plus maintenance tended to prolong time to repeat exacerbations compared to fluticasone/salmeterol

Time to first severe exacerbation, the pre-specified primary outcome, was not significantly prolonged (risk ratio 0.82; 95% confidence interval 0.63, 1.05).
BUD = budesonide; FLU = fluticasone; FORM = formoterol; SABA = short-acting β_2-agonist; SAL = salmeterol.

Bousquet J et al. *Respir Med.* 2007;101:2437-2446.

AHEAD Post Hoc Analysis: Severe Exacerbations Within 28 Days of First Day of Higher Reliever Use (Day 0)



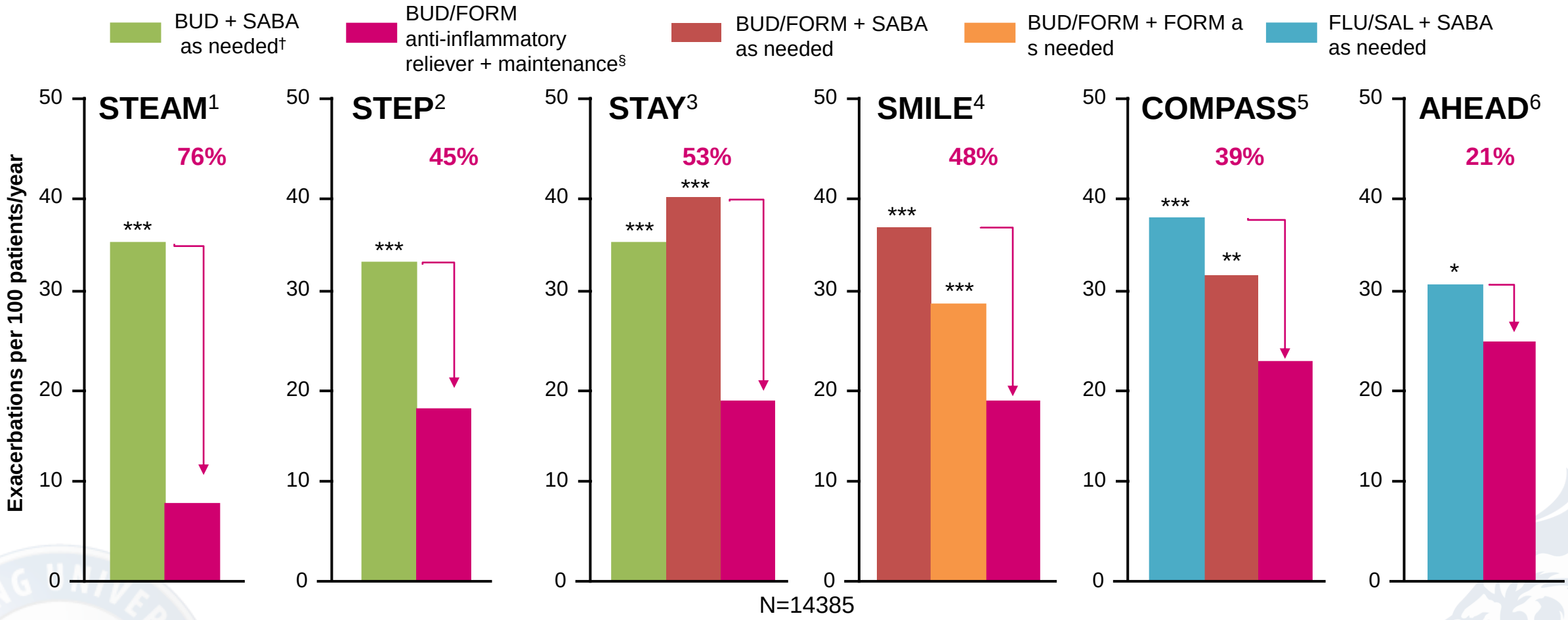
- Time to first severe exacerbation did not significantly differ between groups (primary endpoint: hazard ratio, 0.82; p=0.12)
- A smaller percentage of patients on budesonide/formoterol anti-inflammatory reliever plus maintenance experienced a severe exacerbation in the month following higher reliever use than patients on fluticasone/salmeterol plus SABA as-needed

Time to first severe exacerbation, the pre-specified primary outcome, was not significantly prolonged (risk ratio 0.82; 95% confidence interval 0.63, 1.05).

BUD = budesonide; FLU = fluticasone; FORM = formoterol; SABA = short-acting β_2-agonist; SAL = salmeterol.

Bousquet J et al. *Respir Med.* 2007;101:2437-2446.

BUD/FORM anti-inflammatory reliever + maintenance reduced exacerbations versus same, higher and highest dose ICS/LABA + SABA



*P=0.039 versus BUD/FORM anti-inflammatory reliever + maintenance. **P=0.0048 versus BUD/FORM anti-inflammatory reliever + maintenance. ***P<0.001 versus BUD/FORM anti-inflammatory reliever + maintenance.
†BUD maintenance dose in each study was either one inhalation of 320 µg BID or two inhalations of 160 µg QD
§BUD/FORM was delivered via Turbuhaler in all studies apart from STEAM; in STEAM BUD/FORM was delivered via DPI
BID = twice daily; BUD = budesonide; DPI = dry powder inhaler; FLU = fluticasone; FORM = formoterol; ICS = inhaled corticosteroid(s); LABA = long-acting β_2-agonist; QD = once daily; SABA = short-acting β_2-agonist; SAL = salmeterol.

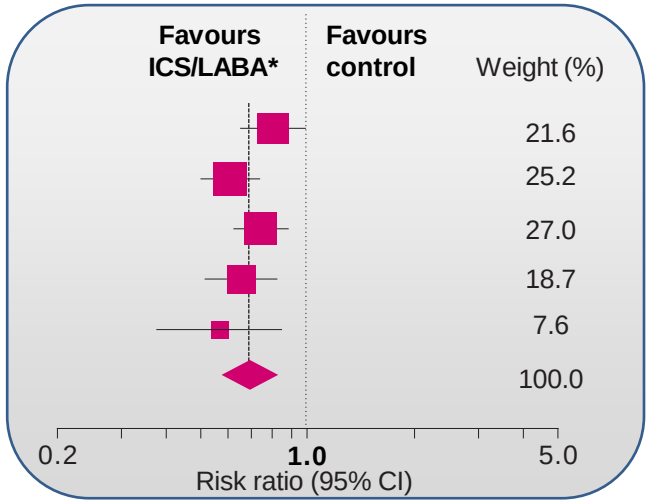
1. Rabe KF, et al. *Chest.* 2006;129:246-256; 2. Scicchitano R, et al. *Curr Med Res Opin.* 2004;20:1403-1418; 3. O'Byrne PM, et al. *Am J Respir Crit Care Med.* 2005;171:129-136; 4. Rabe KF, et al. *Lancet.* 2006;368:744-753; 5. Kuna P, et al. *Int J Clin Pract.* 2007;61:725-736; 6. Bousquet J, et al. *Respir Med.* 2007;101:2437-2446.

In Moderate to Severe Asthma, Anti-inflammatory Reliever Plus Maintenance Reduced Exacerbations vs. Same, Higher and Highest Dose ICS/LABA + SABA as Needed

Risk of Exacerbations of Anti-inflammatory Reliever Plus Maintenance vs Same Dose ICS and LABA Maintenance

Meta-analysis Source	ICS/LABA*		Control		Absolute risk difference (95% CI), %	Risk ratio (95% CI)
	Total No. of Participants	No. with event	Total No. of Participants	No. with event		
Vogelmeier et al, 2012	1067	132	1076	167	−3.1 (−6.1, −0.2)	0.80 (0.64 , 0.99)
Rabe et al, 2006	1107	143	1138	245	−8.6 (−11.7, −5.5)	0.60 (0.50 , 0.72)
Atienza et al, 2013	1049	170	1042	229	−5.8 (−9.1, −2.4)	0.74 (0.62 , 0.88)
Papi et al, 2013	852	99	849	152	−6.3 (−9.6, −2.9)	0.65 (0.51, 0.82)
Patel et al, 2013	151	28	152	50	–14.4 (–24.1 , −4.6)	0.56 (0.38, 0.84)
Overall (random-effects model)	4226	572	4257	843	−6.4 (−10.2, −2.6)	0.68 (0.58 , 0.80)

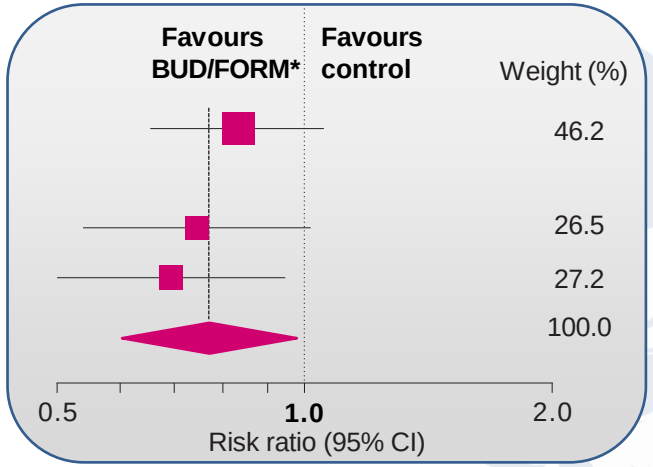
Heterogeneity: I^2=29%, P=0.23; test for overall effect: t_4=−6.44, P<0.001



Risk of Exacerbations of BUD/FORM Anti-inflammatory Reliever Plus Maintenance vs Higher Dose ICS and LABA Maintenance

Meta-analysis Source	BUD/FORM*		Control		Absolute risk difference (95% CI), %	Risk ratio (95% CI)
	Total No. of Participants	No. with event	Total No. of Participants	No. with event		
Bousquet et al, 2007	1151	108	1153	130	−2.7 (−5.2, 0.6)	0.83 (0.65, 1.06)
Kuna et al, 2007						
vs. BUD/FORM+SABA	552	47	1099	126	−2.9 (−5.9, 0.1)	0.74 (0.54, 1.02)
vs. FLU/SAL+SABA	552	47	1119	138	−3.8 (−6.8, −0.8)	0.69 (0.50, 0.95)
Overall (random-effects model)	2254	202	3371	394	−2.7 (−5.2, −0.3)	0.77 (0.60, 0.98)

Heterogeneity: I^2=0%, p=0.64; test for overall effect: t_4=−4.71, P=0.04

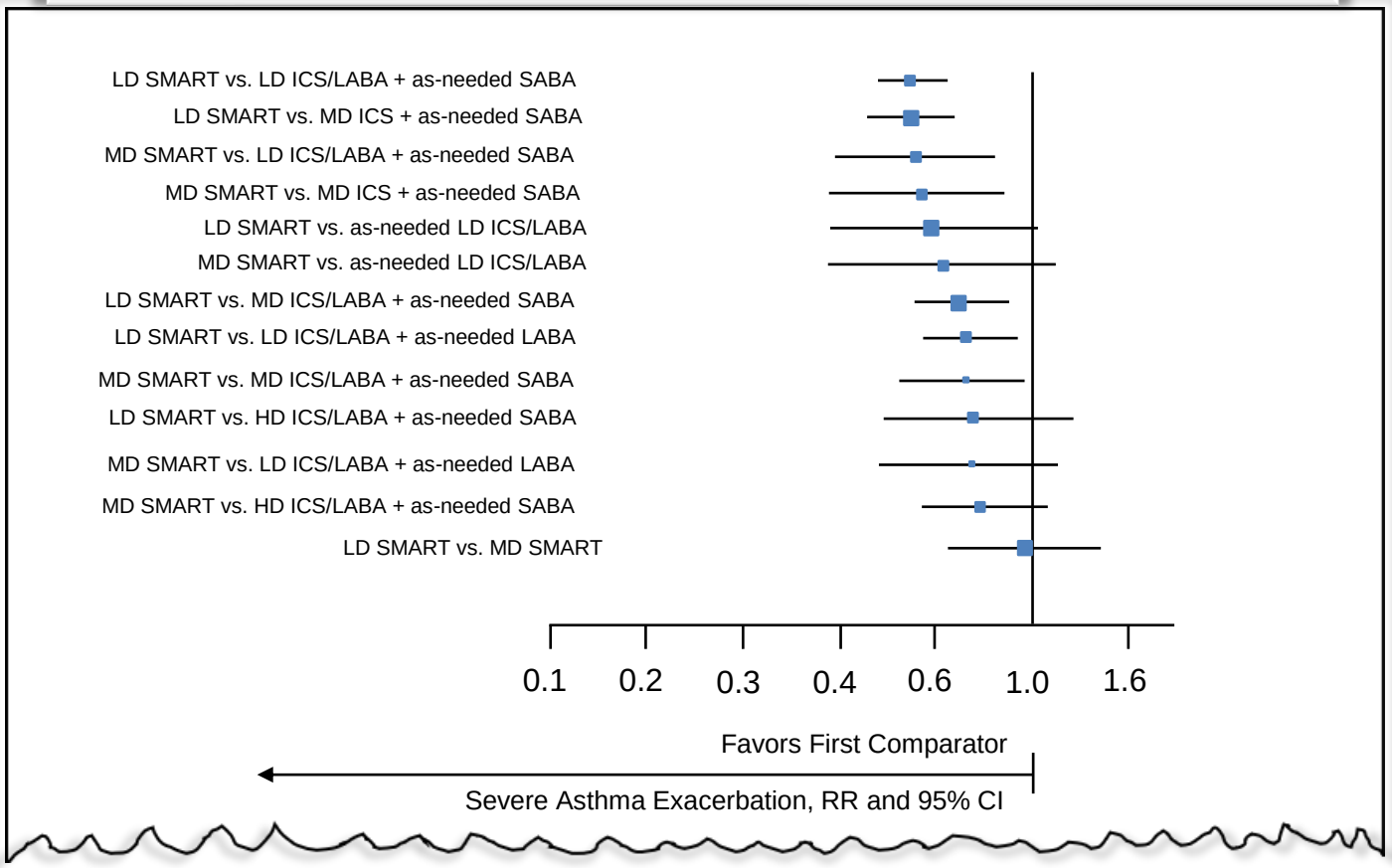


*ICS/LABA anti-inflammatory reliver plus maintenance.

BUD = budesonide; FLU = fluticasone; FORM = formoterol; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; SABA = short-acting β_2-agonist; SAL = salmeterol. Sobieraj DM, et al. *JAMA.* 2018;319:1485–1496.

As-needed anti-inflammatory reliever with maintenance was preferred to reduce risk of severe exacerbation in a RCT meta-analysis of moderate to severe asthma

Low-to-Medium Dose Anti-inflammatory Reliever with Maintenance in the Subset of **Moderate to Severe Asthma**



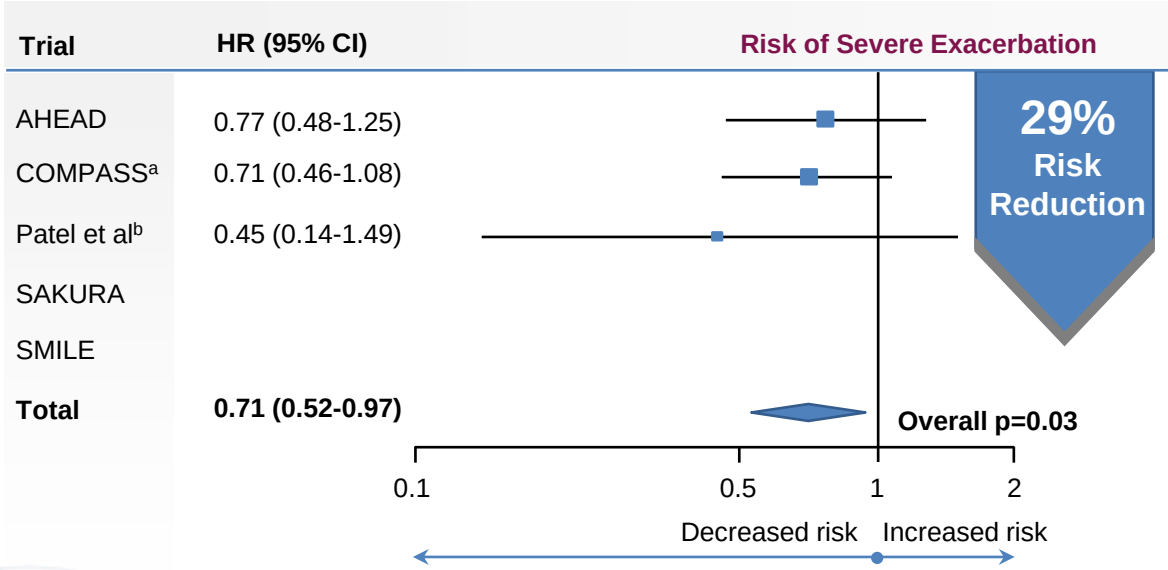
Notes: A network meta-analysis of 21 Phase III RCTs, 6 to 12 months in duration (4 in mild asthma, 3 in moderate asthma, 4 in mild to moderate asthma, 10 in moderate to severe asthma) including at least 1 anti-inflammatory reliever plus maintenance arm with data from 32,096 patients with mild to severe asthma; Only treatment arms containing anti-inflammatory reliever with maintenance are included on this slide. ICS = inhaled corticosteroids; RR = relative risk; LABA = long-acting β_2-agonist; LD = low dose; MD = medium dose; RCT = randomized, controlled trial; SABA = short-acting β_2-agonist; SMART = single maintenance and reliever therapy.

Rogliani P, et al. Article and supplementary material. *Eur Respir J.* 2020;56. https://doi.org.10.1183/13993003.00625-2020. Accessed 26 January 2022.

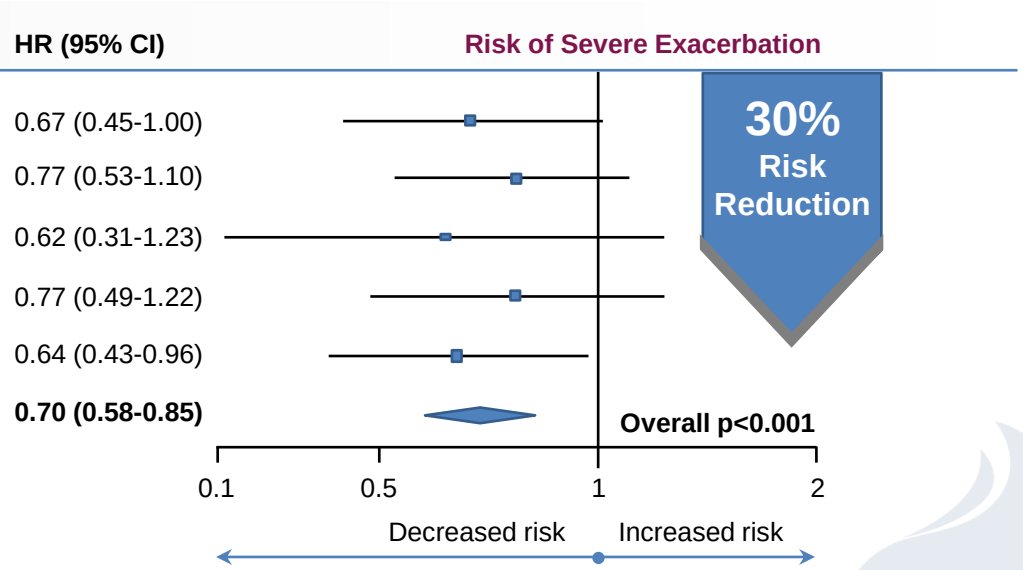
In a meta-analysis of poorly controlled asthma, switching to BUD/FORM as needed plus maintenance reduced risk of exacerbations by ~30%

In patients with GINA 3 or 4 uncontrolled asthma, **switching to anti-inflammatory reliever plus maintenance was preferrable** to stepping up or continuing GINA treatment with ICS/LABA + SABA

Anti-inflammatory Reliever plus Maintenance vs Step Up to GINA 4



Anti-inflammatory Reliever plus Maintenance vs Same Step GINA 3



There was also a **greater improvement in asthma control when switching to anti-inflammatory reliever plus maintenance** compared to stepping up (ACQ-5 difference, -0.10; 95% CI, -0.19 to -0.01) or continuing (ACQ-5 difference, -0.12; 95% CI, -0.20 to -0.05) GINA treatment

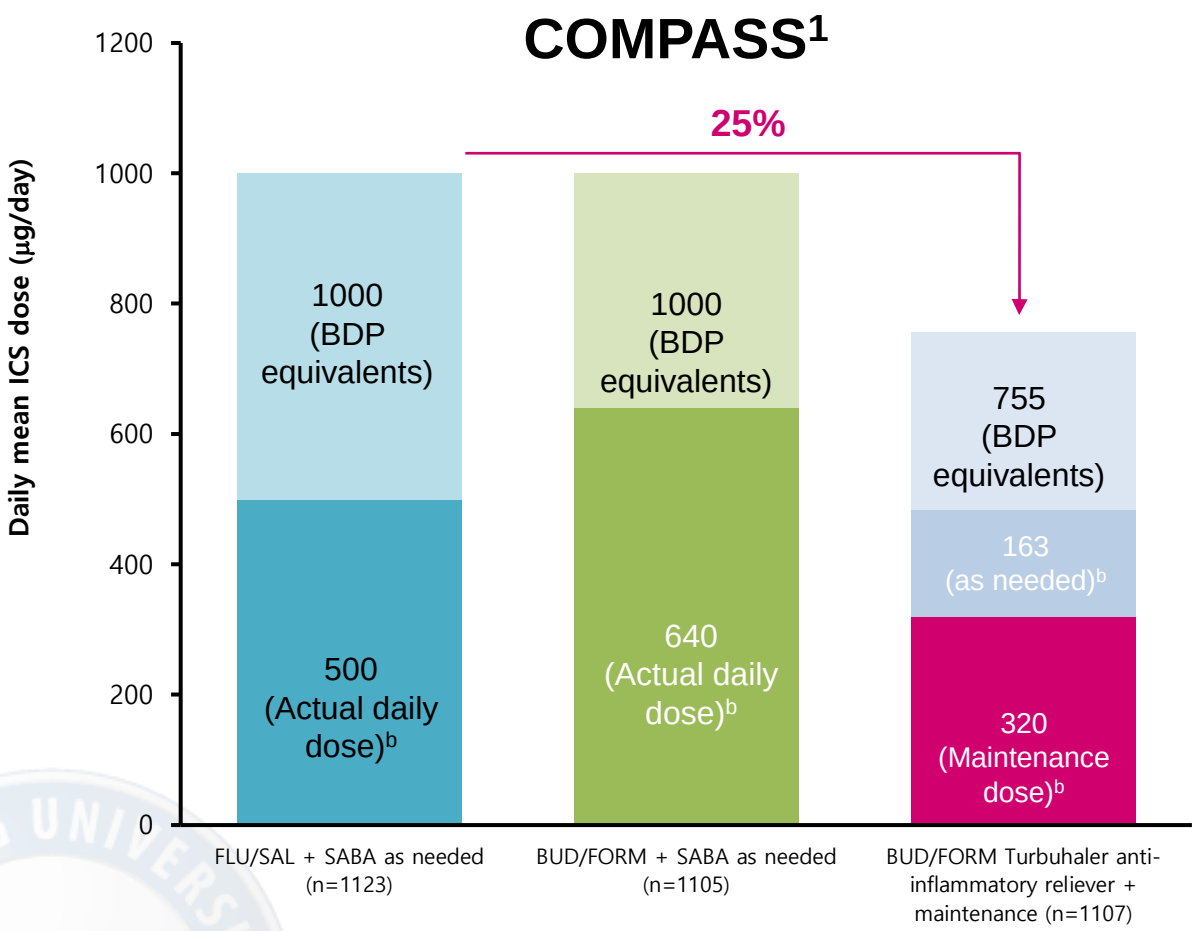
Notes: A meta-analysis of 5 BUD-FORM RCTs with baseline data on asthma control (ACQ ≥1.5 required), baseline data on **GINA step 3&4**, ≥24-week treatment period, and access to individual patient data with a total of 4863 participants. **Primary endpoint was time to first severe exacerbation**.

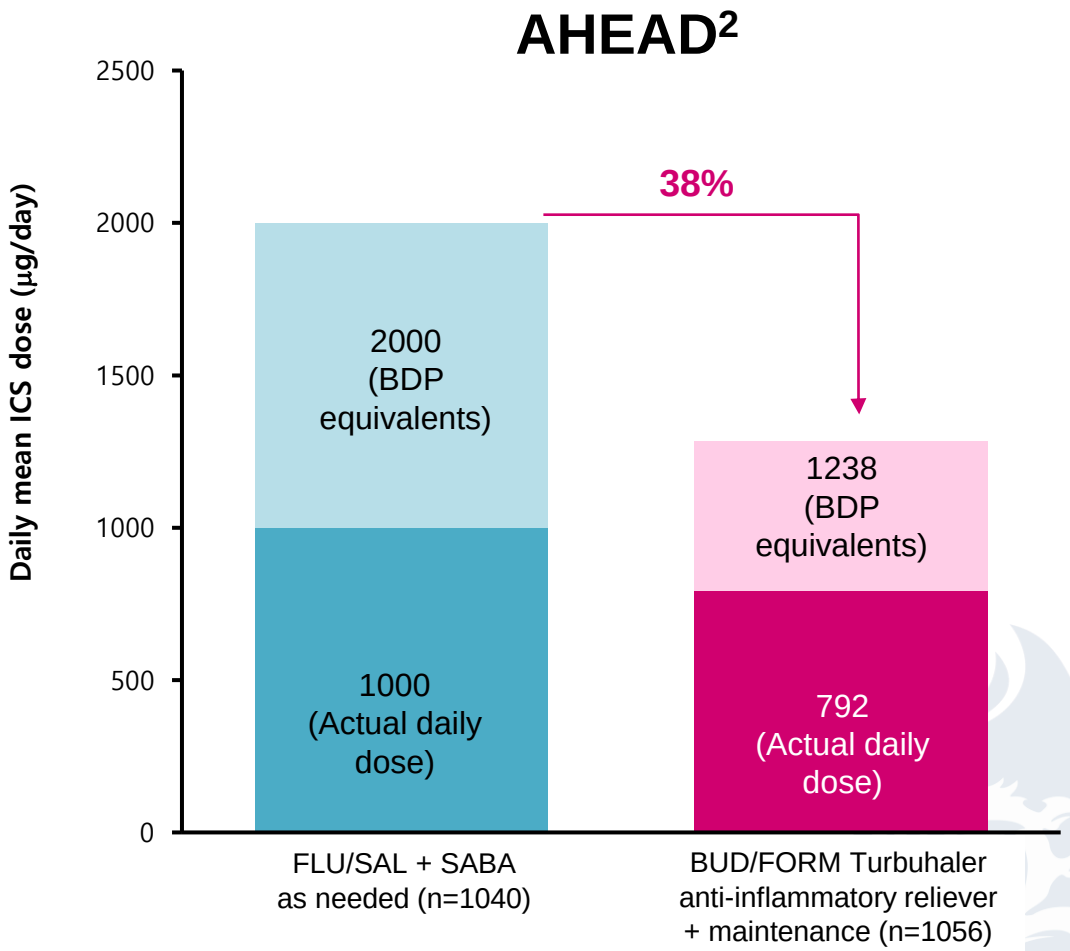
[a]2 comparator arms were pooled into 1 fixed ICS-LABA arm; [b]open-label study with BUD/FORM pressurized metered-dose inhaler vs. the other studies which were double-blinded with BUD/FORM dry powder inhaler.

ACQ = Asthma Control Questionnaire; BUD = budesonide; FORM = formoterol; GINA = Global Initiative for Asthma; HR = hazard ratio; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; SABA = short-acting β_2-agonist.

Beasley R, et al. *JAMA Netw Open*. 2022;5:e220615.doi:10.1001/jamanetworkopen.2022.0615.

BUD/FORM Turbuhaler anti-inflammatory reliever + maintenance has a lower ICS load than other maintenance therapies



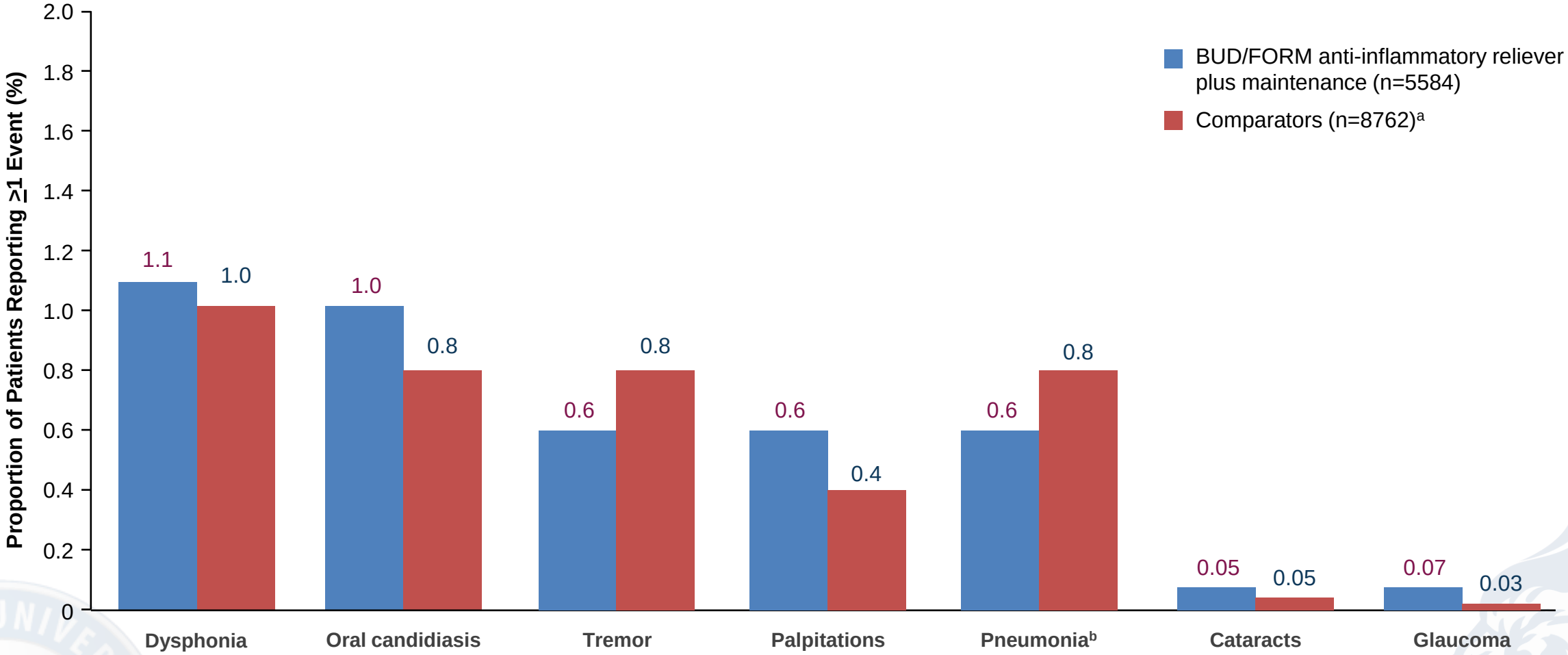


In both studies, overall ICS treatment load was compared between groups by converting ICS doses to BDP-equivalent doses. Calculations were based on the GINA estimates of equipotence (fluticasone 500 µg = budesonide 800 µg = beclomethasone 1000 µg).

BDP = beclomethasone dipropionate; BID = twice daily; BUD = budesonide; FLU = fluticasone; FORM = formoterol; ICS = inhaled corticosteroid(s); SAL = salmeterol

1. Kuna P, et al. *Int J Clin Pract.* 2007;61:725-736; 2. Bousquet J, et al. *Respir Med.* 2007;101:2437-2446.

Safety of BUD/FORM anti-inflammatory reliever + maintenance has been well studied in moderate-to-severe asthma

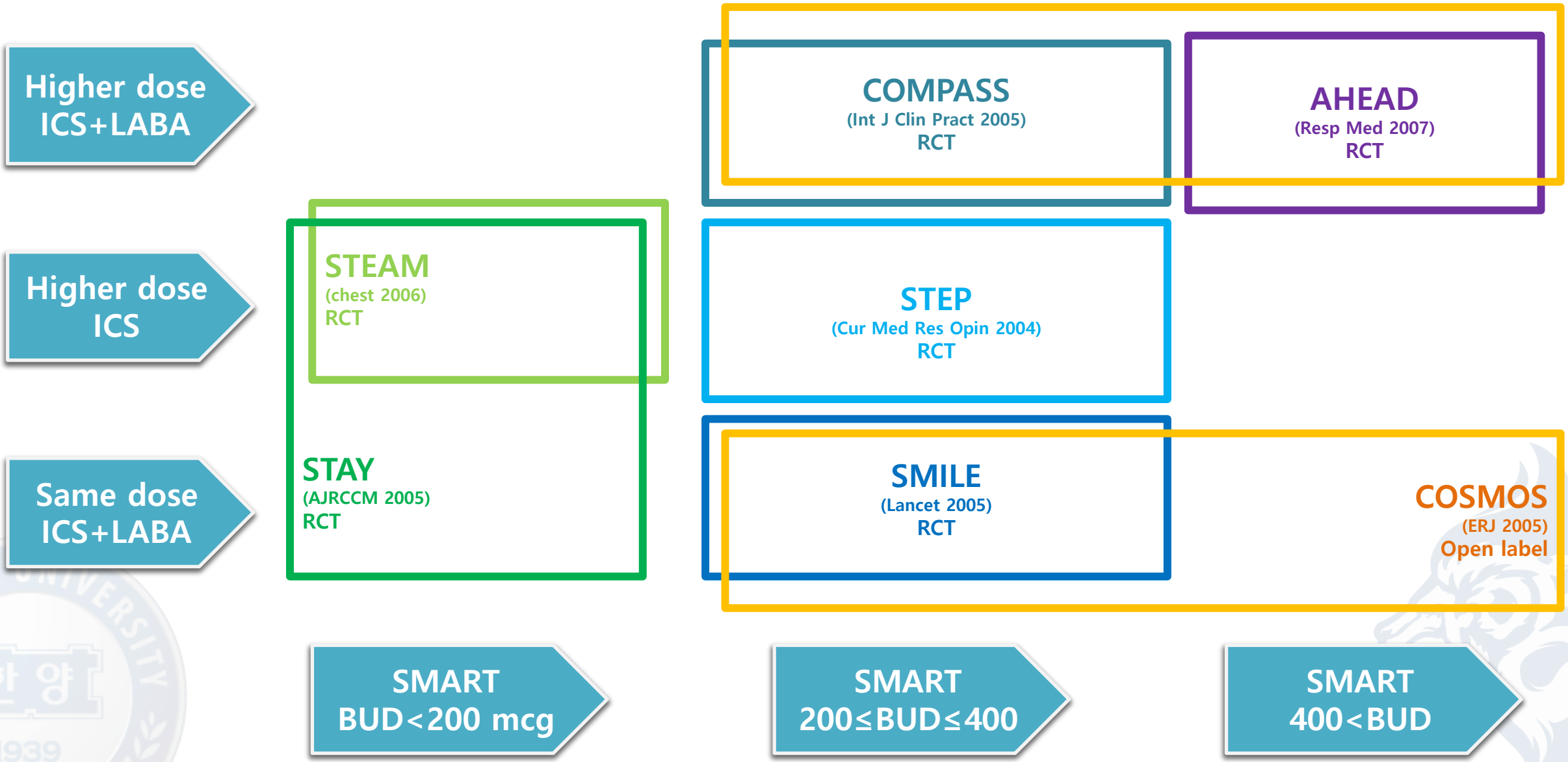


[a]As there were multiple arms in some of the clinical trials, the number of patients in the comparator groups exceed those in the BUD/FORM maintenance and reliever therapy groups;
[b]Pneumonia was included for completeness owing to the current debate on the relationship between ICS use and pneumonia risk in chronic obstructive pulmonary disease.

BUD = budesonide; ICS = inhaled corticosteroids; FORM = formoterol.

Sears MR et al. *Respir Med.* 2009;103:1960-1968.

Summary of Clinical Trials for Moderate to Severe Asthma



CHEST Clinical Commentary

Rescue Treatment in Asthma*

More Than As-Needed Bronchodilation

Alberto Papi, MD; Gaetano Caramori, MD, PhD; Ian M. Adcock, PhD; and Peter J. Barnes, MD, FCCP

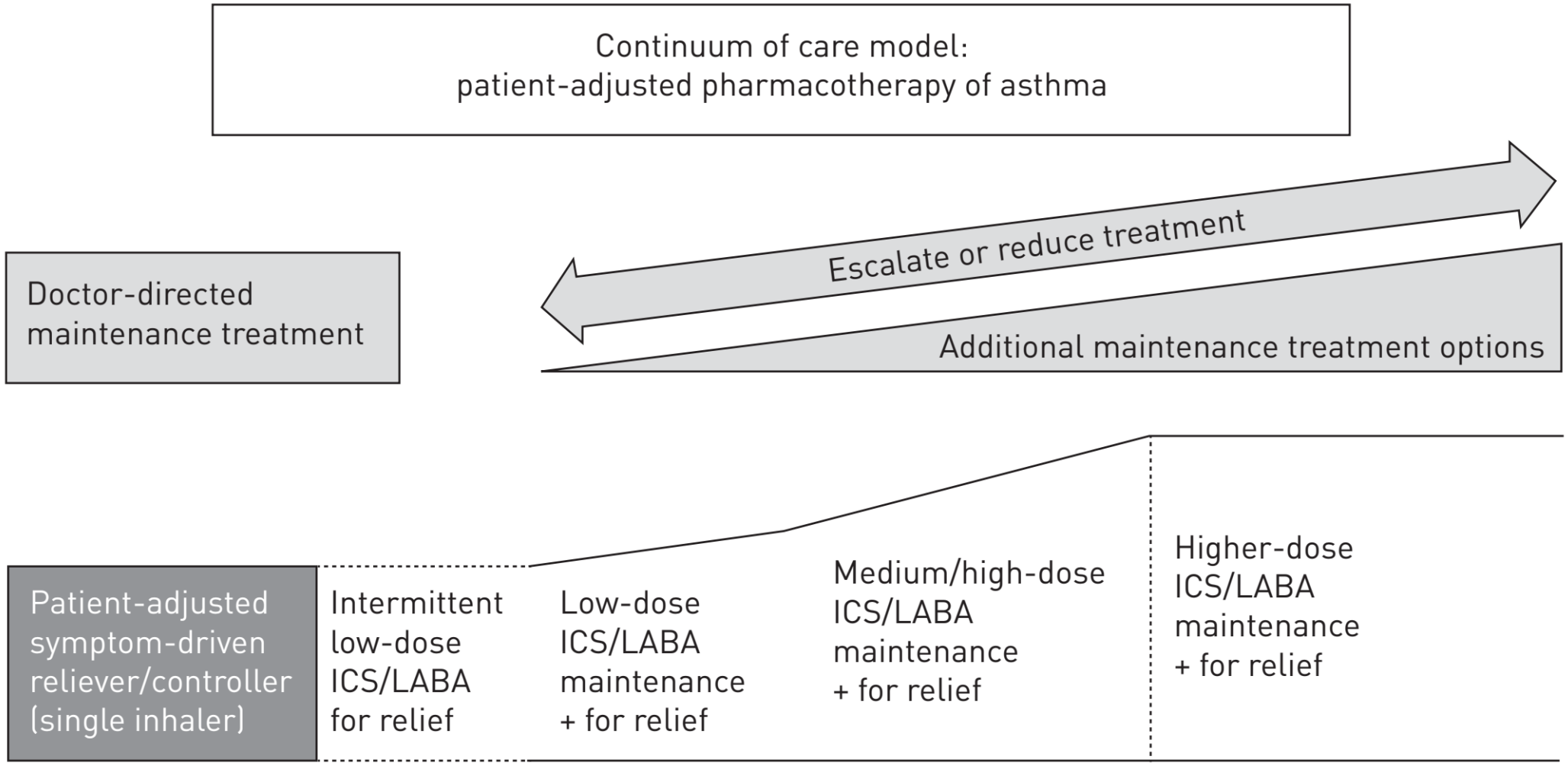
- Asthma symptoms are associated not only with **bronchoconstriction** but also with increased **airway inflammation**.
  - **Inhaled beta2-agonists** have a rapid onset of **bronchodilator** action
  - **Inhaled corticosteroids** also have rapid clinical effects that can **suppress** lower airway **inflammation**
- On the basis of this emerging evidence, we propose that the current rescue use of **rapid-onset inhaled beta2-agonists** alone should now be **replaced by an inhaled rapid-acting beta2-agonist combined with a corticosteroid** as preferred PRN strategy.

- In the future it might even be **possible to control asthma entirely with PRN combination inhalers** without maintenance therapy, **at least in patients with less severe disease**.

Papi A et al. Chest 2009;135:1628-33 [PMID 19497897]

Continuum of Care

Patient-adjusted Plus Physician-directed Step-wedge Approach to Pharmacotherapy in Asthma



O'Byrne PM, Eur Respir J 2017;50.

Contents

The Single combination budesonide–formoterol inhaler Maintenance And Reliever Therapy (SMART)

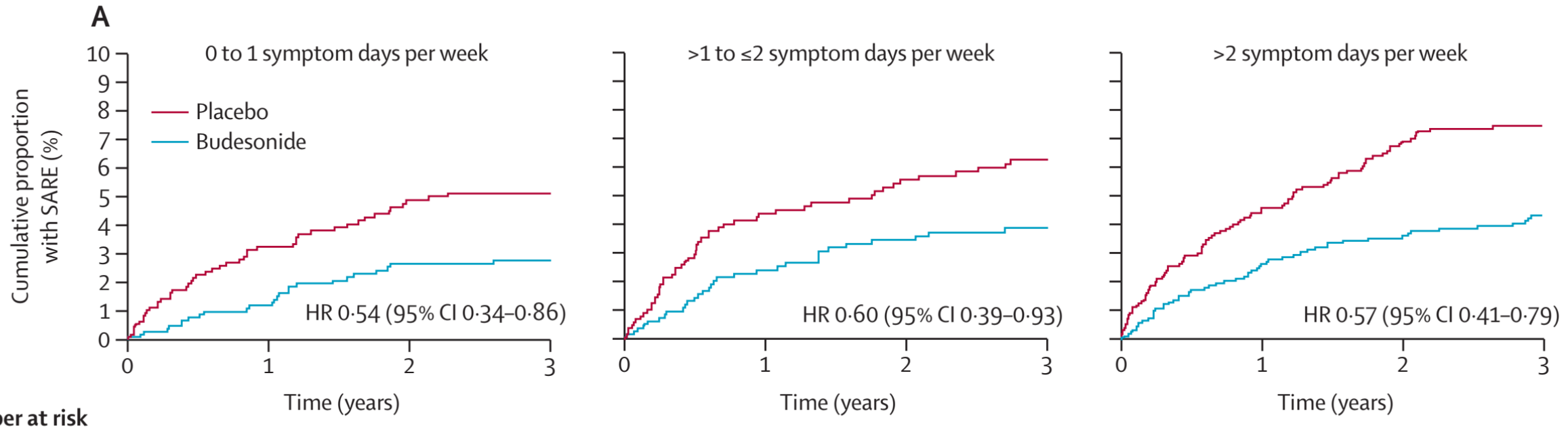
Anti-Inflammatory Reliver (AIR)

Guidelines of Asthma Treatment

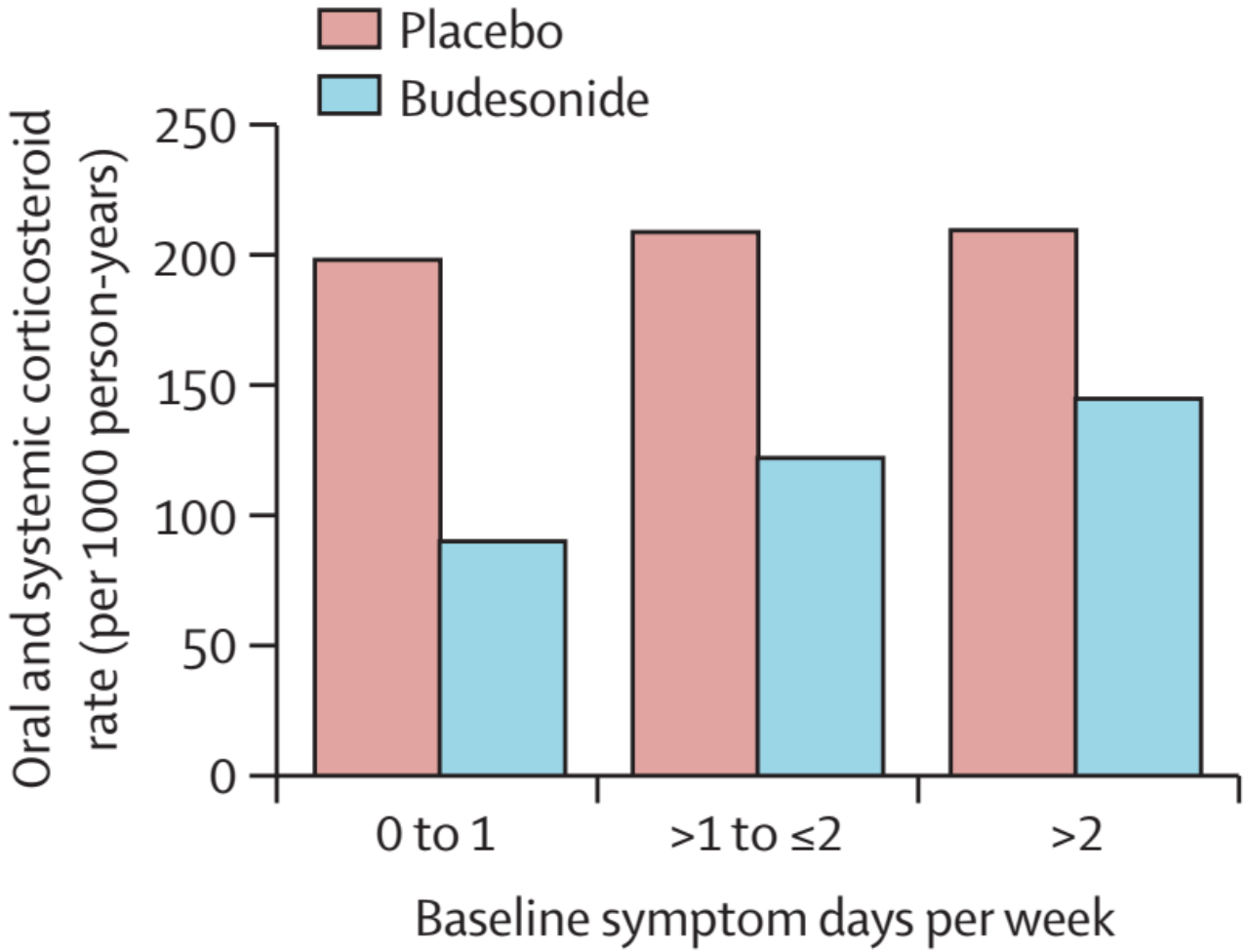
Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study

Helen K Reddel, William W Busse, Søren Pedersen, Wan C Tan, Yu-Zhi Chen, Carin Jorup, Dan Lythgoe, Paul M O'Byrne

Reddel HK et al. Lancet 2017;389:157-66 [PMID 27912982]



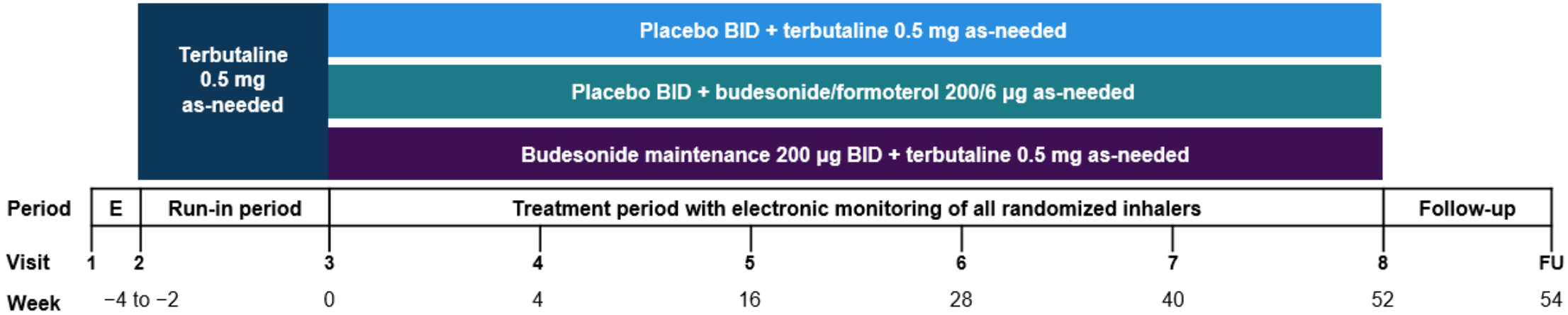
Reddel HK et al. Lancet 2017;389:157-66 [PMID 27912982]



Reddel HK et al. Lancet 2017;389:157-66 [PMID 27912982]

SYGMA 1: Study design[a]

12-month, randomized, double-blind, parallel-group, multicenter study (N=**3849**) to assess the long-term efficacy and safety of budesonide/formoterol anti-inflammatory reliever in comparison to SABA as-needed or ICS maintenance plus SABA as-needed in patients with **mild asthma**[1,2]



Primary efficacy endpoint: **WCAW** (superiority vs. terbutaline as-needed)

Secondary endpoints: WCAW (non-inferiority vs. budesonide maintenance plus terbutaline as-needed), severe asthma exacerbation rate, FEV_1, ACQ-5, AQLQ, ICS use, use of as-needed inhalations

Safety: Adverse events

[a]Analysis was based on the full analysis set according to the intention-to-treat principle set forth by the International Conference on Harmonization E9 Working group.[3]

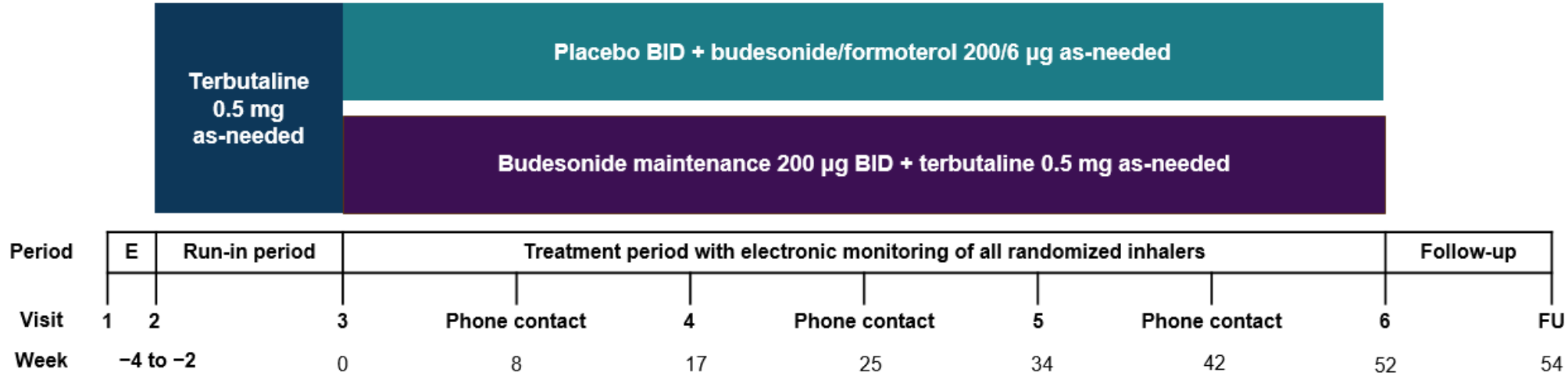
ACQ-5 = Asthma Control Questionnaire-5; AQLQ = Asthma Quality of Life Questionnaire; E = enrolment; FEV_1 = forced expiratory volume in 1 second; FU = follow-up phone contact; ICS = inhaled corticosteroid; SABA = short-acting β_2-agonist; SYGMA = SYmbicort Given as needed in Mild Asthma; **WCAW = well-controlled asthma week.**

1. O'Byrne PM et al. *Trials*. 2017;18:12. https://doi.org/10.1186/s13063-016-1731-4. Accessed 10 May 2021; 2. O'Byrne PM et al. *N Engl J Med*. 2018;378:1865-1876;

3. International Conference on Harmonization Steering Committee. Statistical principles for clinical trials. ICH harmonized tripartite guideline. February 5, 1998.

SYGMA 2: Study design[a]

12-month, randomized, double-blind, parallel-group, multicenter study (N=**4215**) to assess the long-term efficacy and safety of budesonide/formoterol anti-inflammatory reliever in comparison to ICS maintenance plus SABA as-needed in a pragmatic trial of patients with **mild asthma**[1,2]



Primary efficacy endpoint: **Annualized severe asthma exacerbation rate** (non-inferiority) defined as systemic corticosteroids for ≥3 days or hospitalization or ED visit due to asthma requiring systemic corticosteroids

Secondary endpoints: FEV_1, ACQ-5, AQLQ, ICS use, use of as-needed inhalations

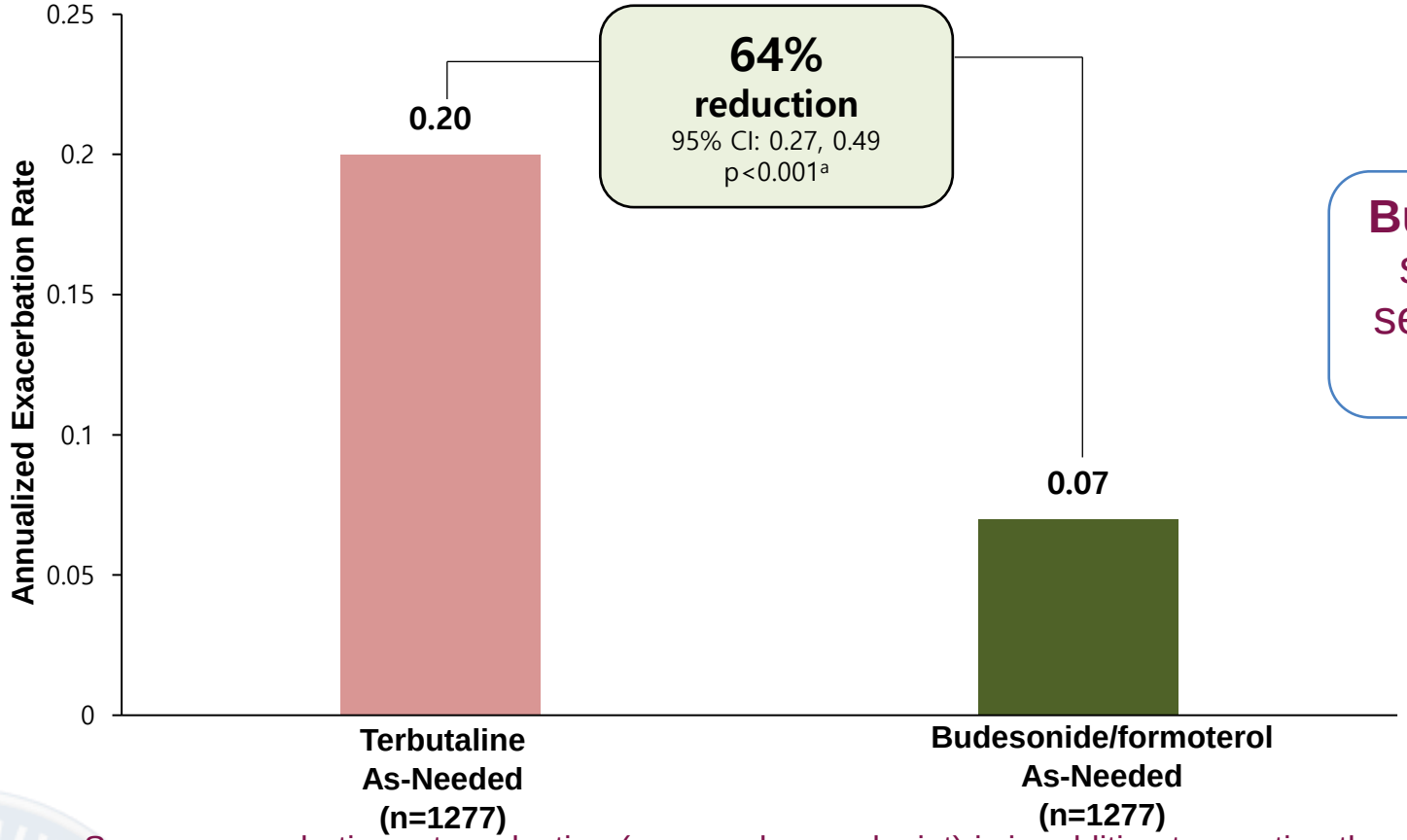
Safety: Adverse events

[a]Analysis was based on the full analysis set according to the intention-to-treat principle set forth by the International Conference on Harmonization E9 Working group.[3]

ACQ-5 = Asthma Control Questionnaire-5; AQLQ = Asthma Quality of Life Questionnaire; E = enrolment; ED = emergency department; FEV_1 = forced expiratory volume in 1 second; FU = follow-up phone contact; ICS = inhaled corticosteroid; SABA = short-acting β_2-agonist; SYGMA = SYmbicort Given as needed in Mild Asthma.

1. O'Byrne PM et al. *Trials*. 2017;18:12. https://doi.org/10.1186/s13063-016-1731-4. Accessed 10 May 2021; 2. Bateman ED et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1877-1887; 3. International Conference on Harmonization Steering Committee. Statistical principles for clinical trials. ICH harmonized tripartite guideline. February 5, 1998.

SYGMA 1: Lower severe exacerbation rate



Budesonide/formoterol as-needed significantly decreased the rate of severe exacerbations in comparison to terbutaline as-needed

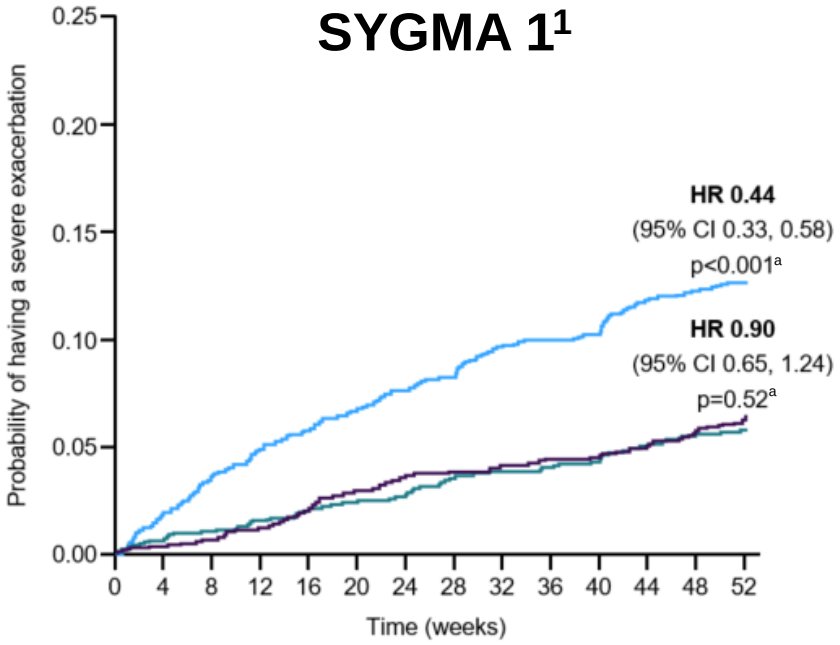
Severe exacerbation rate reduction (a secondary endpoint) is in addition to meeting the primary endpoint of increased odds of a WCAW (OR: 1.14; 95% CI: 1.00, 1.30; p=0.046)

Notes: Severe asthma exacerbation rates were analysed by a negative binomial regression model with randomized treatment, pre-study treatment, region, and number of severe exacerbations in the 12 months prior to screening (0 or ≥1) as factors. Severe exacerbations defined as worsening of asthma that is associated with a medical intervention, requiring either the use of systemic glucocorticoids for ≥3 days (or an injection of depot corticosteroids), or inpatient hospitalization or an emergency department visit (or other urgent, unscheduled health care visit) due to asthma that required systemic glucocorticoids. [a]p-values not controlled for multiplicity.CI = confidence interval; OR = odds ratio; SYGMA = SYmbicort Given as needed in Mild Asthma; WCAW = well-controlled asthma week.

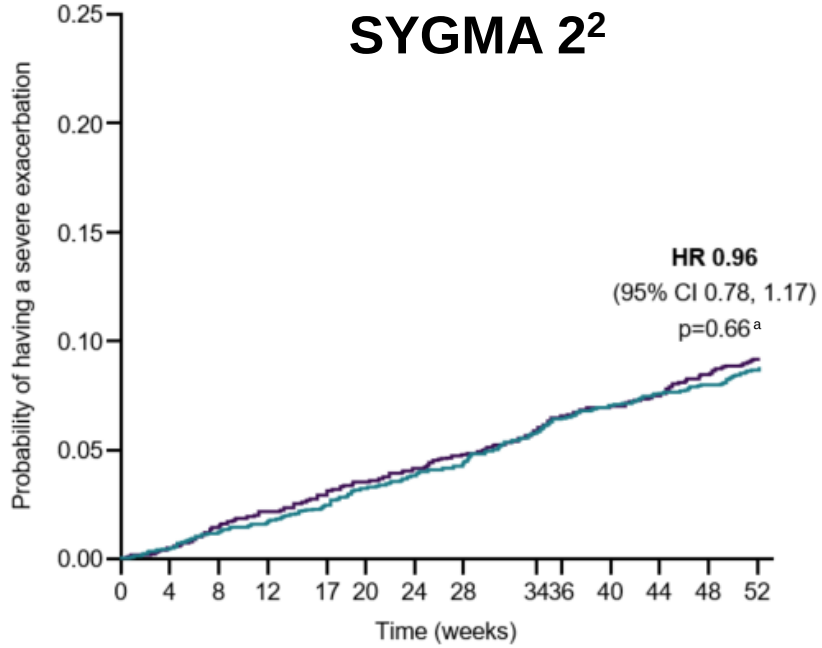
O'Byrne PM et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1865-1876.

SYGMA 1 & 2: Time to first severe exacerbation

SYGMA 1[1]



SYGMA 2[2]



Terbutaline As-Needed | Budesonide/formoterol As-Needed | Budesonide Maintenance + Terbutaline As-Needed

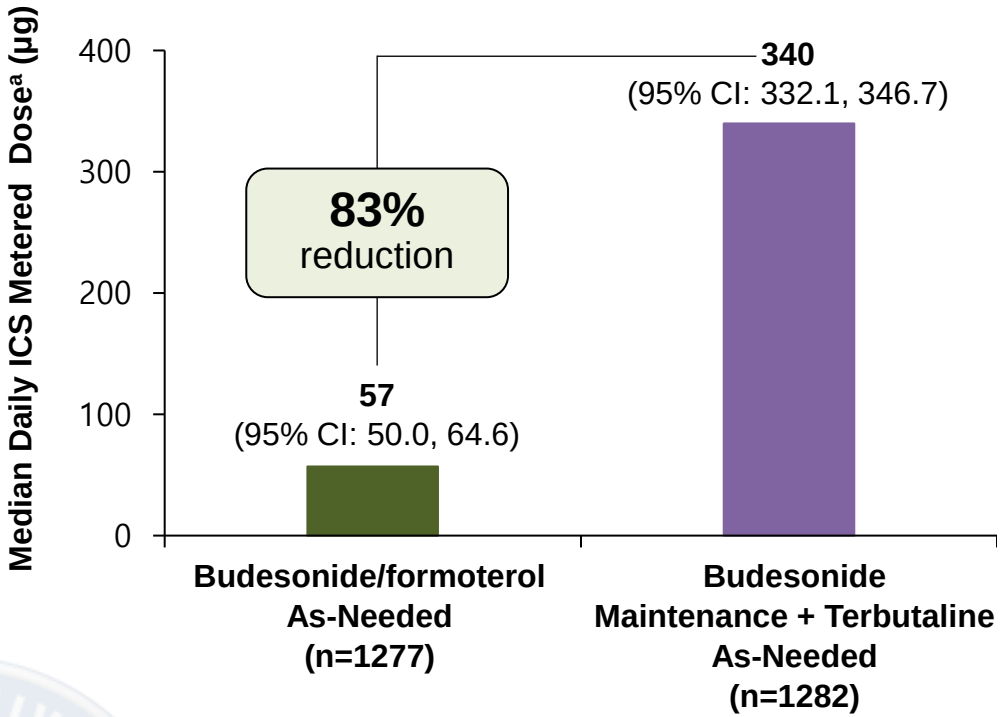
Budesonide/formoterol as-needed was not significantly different from budesonide maintenance plus terbutaline as-needed and was superior to terbutaline as-needed in prolonging time to first severe exacerbation[1,2]

Note: Severe exacerbations defined as worsening of asthma that is associated with a medical intervention, requiring either the use of systemic glucocorticoids for ≥3 days (or an injection of depot corticosteroids), or inpatient hospitalization or an emergency department visit (or other urgent, unscheduled health care visit) due to asthma that required systemic glucocorticoids.[1,2] [a]p-values not controlled for multiplicity.CI = confidence interval; HR = hazard ratio; SYGMA = SYmbicort Given as needed in Mild Asthma.

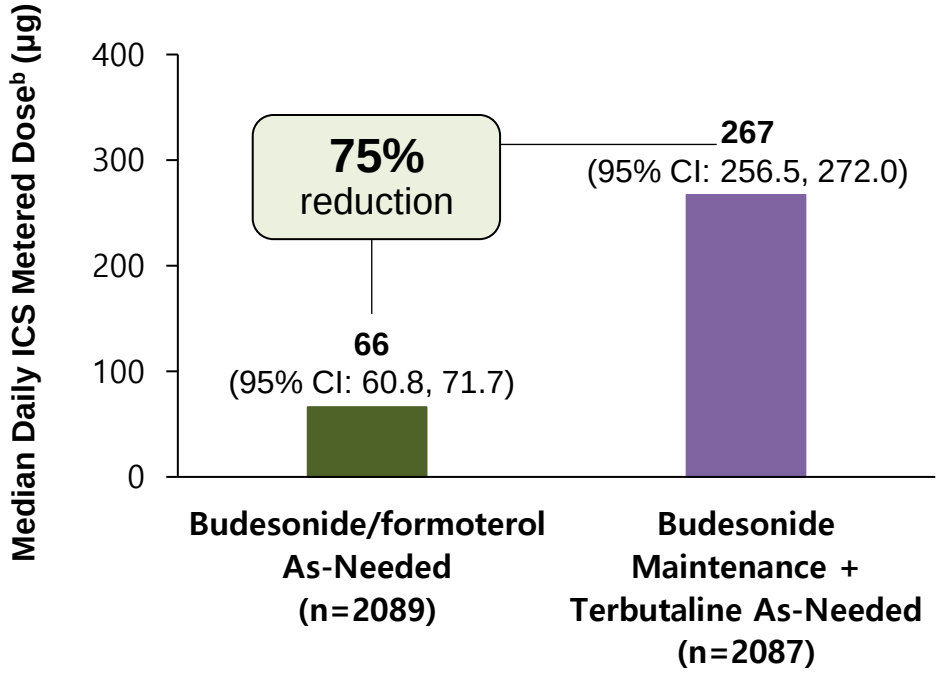
1. O'Byrne PM et al. *N Engl J Med*. 2018;378:1865-1876; 2. Bateman ED et al. *N Engl J Med*. 2018;378:1877-1887.

SYGMA 1 & 2: Comparable risk of severe exacerbations with ≥75% lower corticosteroid load

SYGMA 1[1]



SYGMA 2[2]



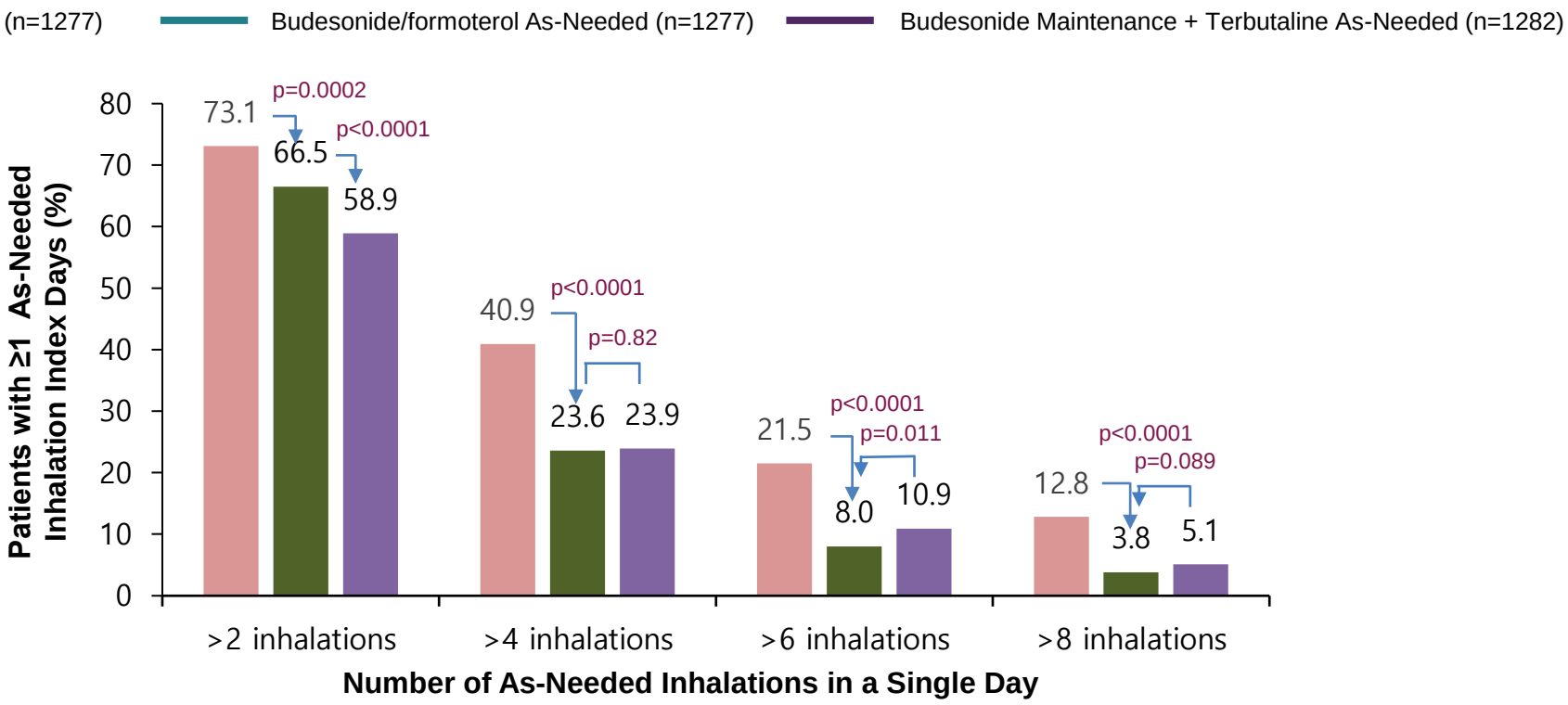
Note: Severe exacerbations defined as worsening of asthma that is associated with a medical intervention, requiring either the use of systemic glucocorticoids for ≥3 days (or an injection of depot corticosteroids), or inpatient hospitalization or an emergency department visit (or other urgent, unscheduled health care visit) due to asthma that required systemic glucocorticoids.[1,2]

[a]Including open-label glucocorticoid prescribed for moderate or severe exacerbations or for long-term poor asthma control; [b]Including non-blinded ICS use prescribed during severe exacerbations.

BID = twice daily; CI = confidence interval; ICS = inhaled corticosteroid; SYGMA = SYmbicort Given as needed in Mild Asthma.

1. O'Byrne PM et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1865-1876; 2. Bateman ED et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1877-1887.

SYGMA 1 post hoc analysis: Proportion of patients with a single day of increased as-needed inhalations lower with BUD/FORM as-needed than SABA



Fewer patients in the budesonide/formoterol as-needed group required increased as-needed inhalations:

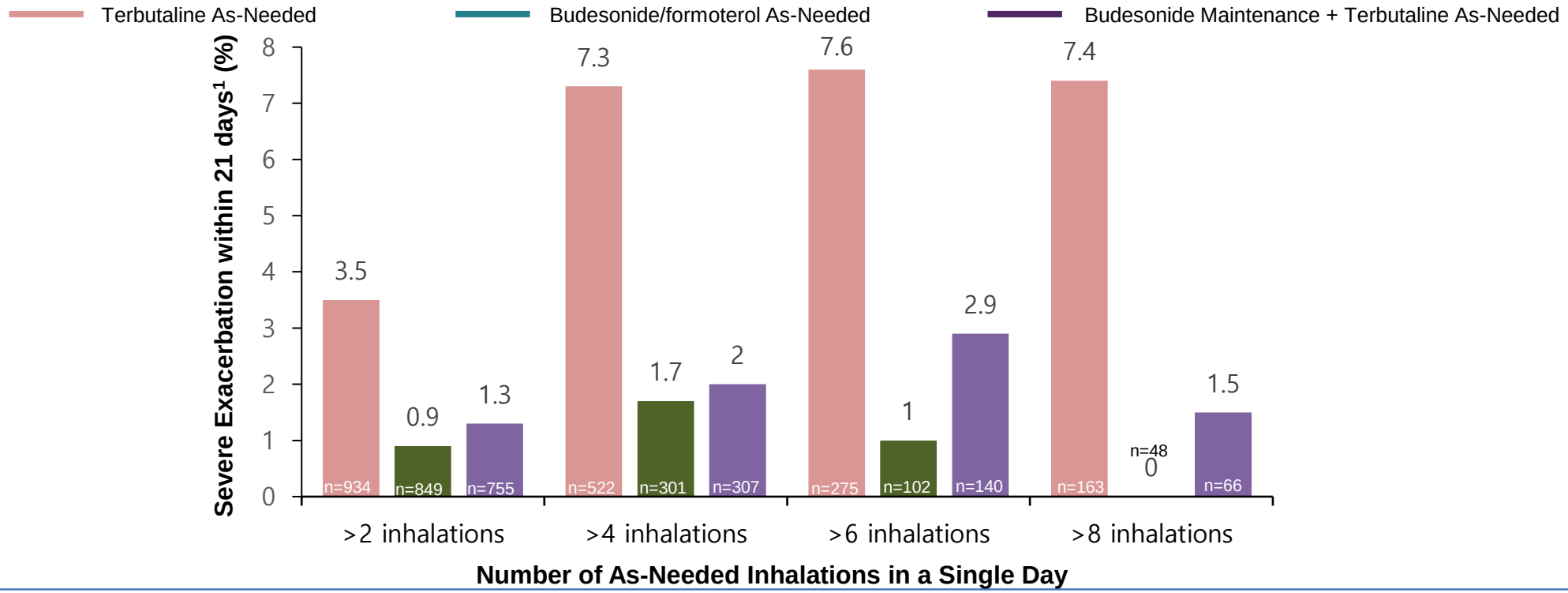
- Across all as-needed inhalation use thresholds compared to the terbutaline as-needed group
- Compared to the budesonide maintenance plus terbutaline as-needed group in patients who received >6 and >8 inhalations

Note: As-needed inhalation days were not counted if a severe exacerbation was ongoing and for an additional 6 days, per American Thoracic Society and European Respiratory Society criteria for separate exacerbations.

BUD = budesonide; FORM = formoterol; SABA = short-acting β_2-agonist.

O'Byrne PM et al. *Lancet Respir Med.* 2020. https://doi.org/10.1016/S2213-2600(20)30416-1. Accessed 10 May 2021.

SYGMA 1 post hoc analysis: Fewer patients with short-term, severe exacerbation after a single day of higher as-needed use with BUD/FORM as-needed than SABA



After a single day of increased use of as-needed inhalations, budesonide/formoterol as-needed was associated with a:

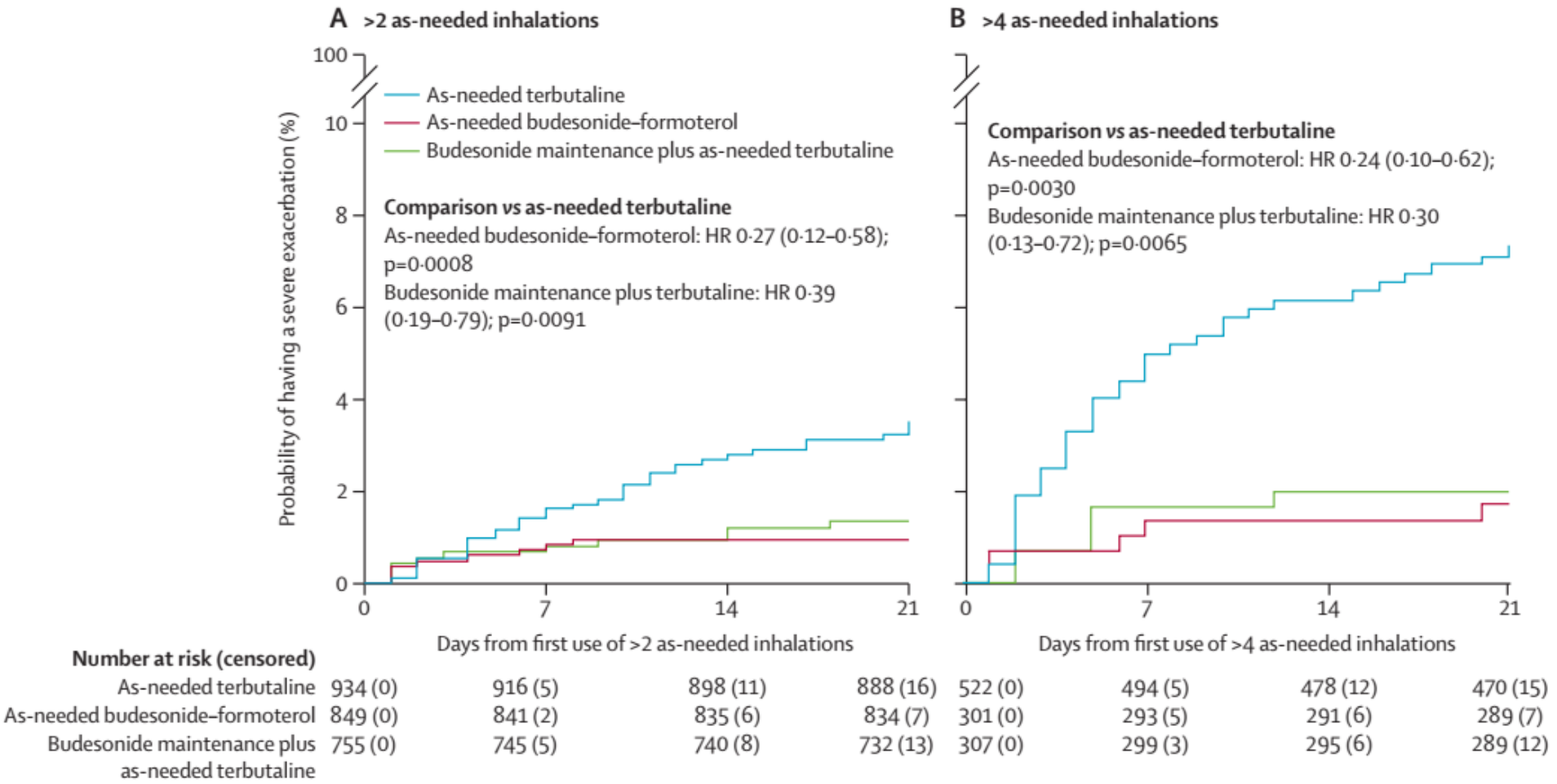
- **Lower proportion of patients with short-term, severe exacerbation** than terbutaline as-needed across all as-needed inhalation use thresholds[1]
- **Similar proportion of patients with short-term, severe exacerbation** to high adherence[a] with budesonide maintenance plus terbutaline as-needed[1,2]

Notes: Includes the first as-needed inhalations index day for each patient; as-needed inhalation days were not counted if a severe exacerbation was ongoing and for an additional 6 days, per American Thoracic Society and European Respiratory Society criteria for separate exacerbations.

[a]In SYGMA 1, adherence to budesonide maintenance plus terbutaline as-needed was 78.9%.

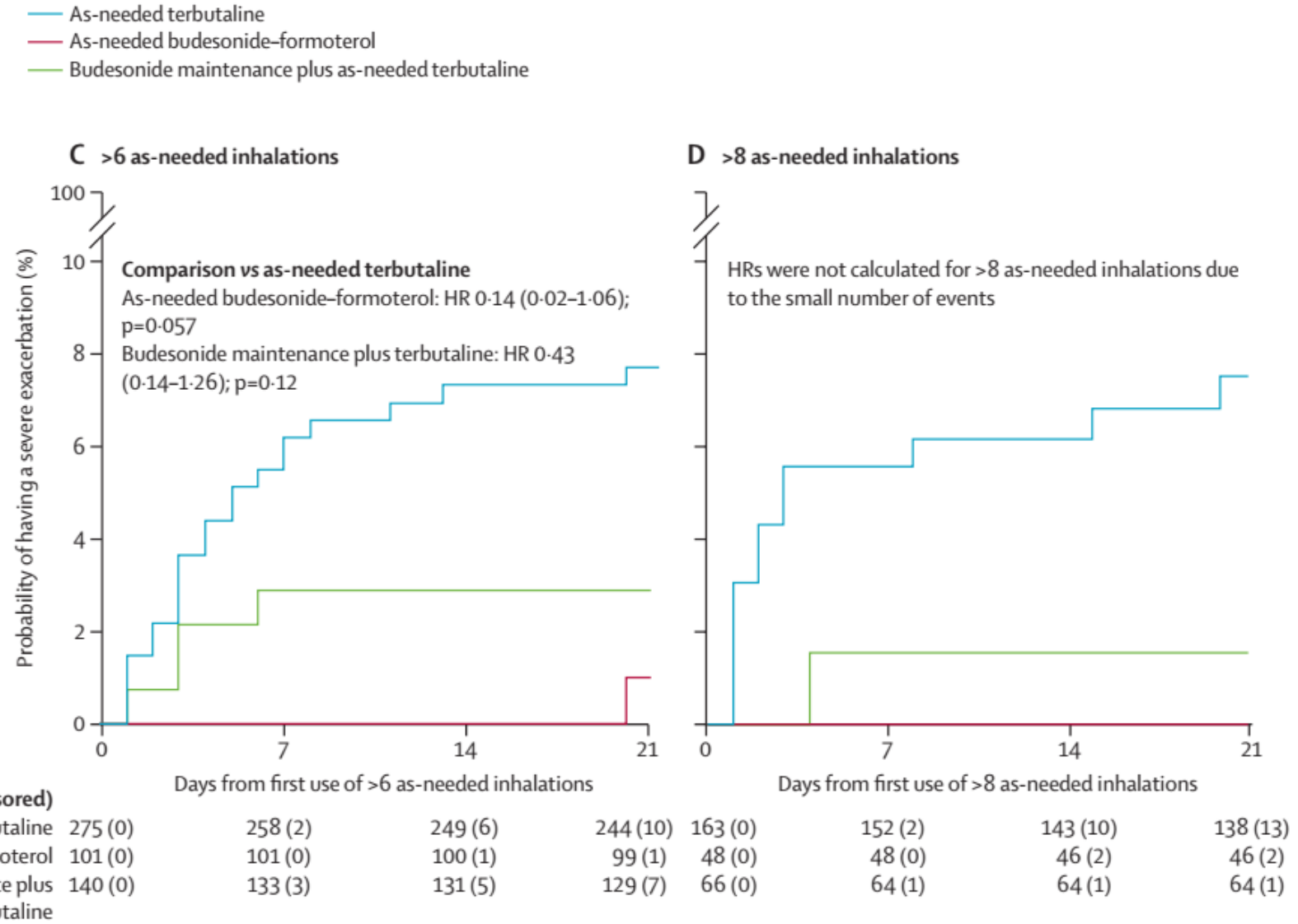
BUD = budesonide; FORM = formoterol; SABA = short-acting β_2-agonist.

1. O'Byrne PM et al. *Lancet Respir Med.* 2020. https://doi.org/10.1016/S2213-2600(20)30416-1. Accessed 10 May 2021; 2. O'Byrne PM et al. *N Engl J Med.* 2018;378:1865-1876.



Number at risk (censored)								
As-needed terbutaline	934 (0)	916 (5)	898 (11)	888 (16)	522 (0)	494 (5)	478 (12)	470 (15)
As-needed budesonide–formoterol	849 (0)	841 (2)	835 (6)	834 (7)	301 (0)	293 (5)	291 (6)	289 (7)
Budesonide maintenance plus as-needed terbutaline	755 (0)	745 (5)	740 (8)	732 (13)	307 (0)	299 (3)	295 (6)	289 (12)

O'Byrne PM, Lancet Respir Med 2020.



- **the greater the risk of severe exacerbation** (as suggested by increased reliever use), **the greater the benefit of as-needed budesonide–formoterol**.

O'Byrne PM, Lancet Respir Med 2020.

Novel START

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, N Engl J Med 2019;380:2020-30.

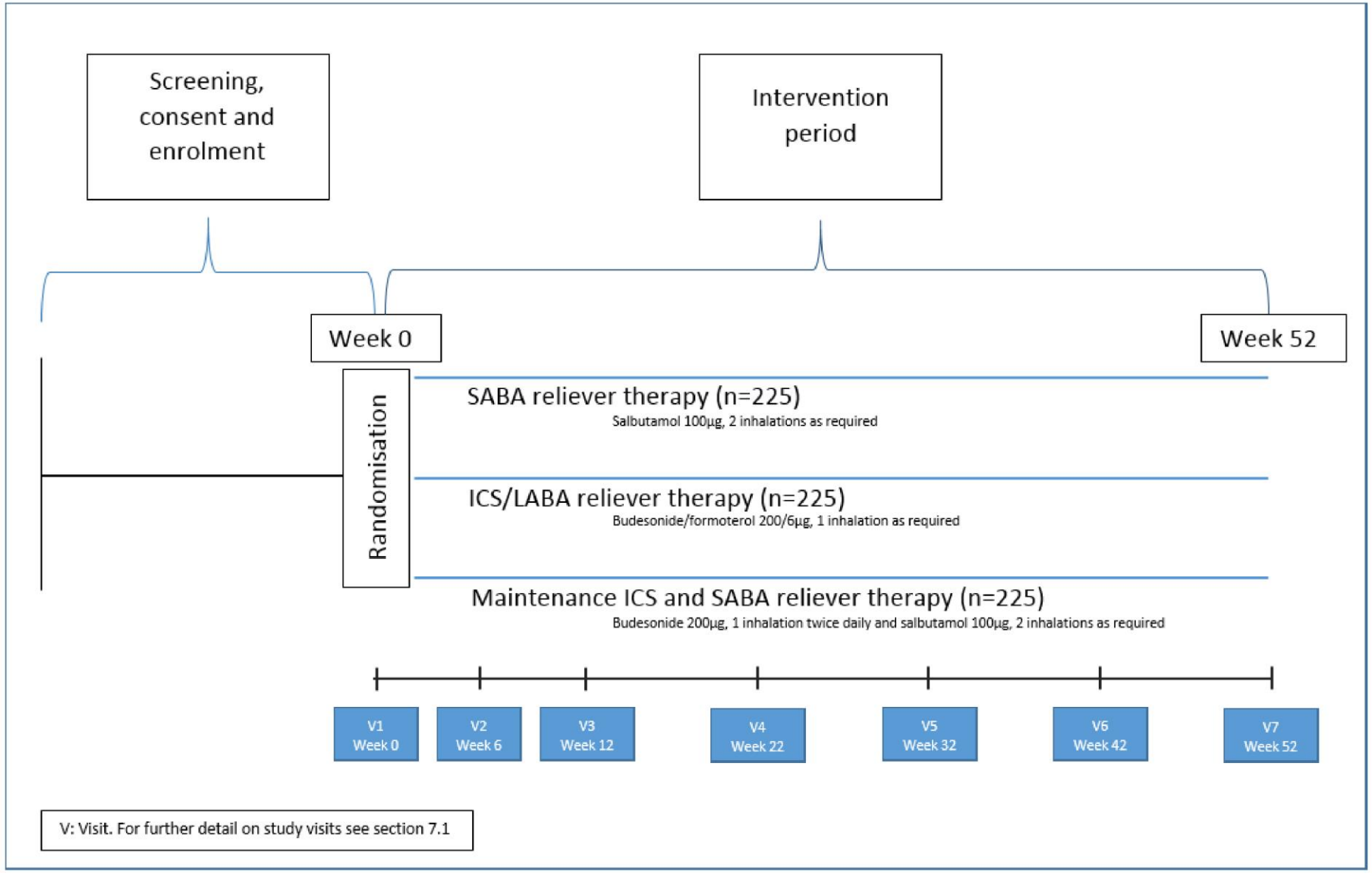
- Novel START -

- patients with **mild intermittent** asthma as well as patients with **mild persistent** asthma.
- 12-month, pragmatic, randomized, open-label, parallel-group, multicenter study(N=675)
- adults were randomly assigned to one of three treatments.
  - **albuterol** as needed for relief of asthma symptoms
  - **budesonide**, 200 μg twice daily, as maintenance therapy plus as needed albuterol
  - **budesonide–formoterol** as needed for relief of symptoms

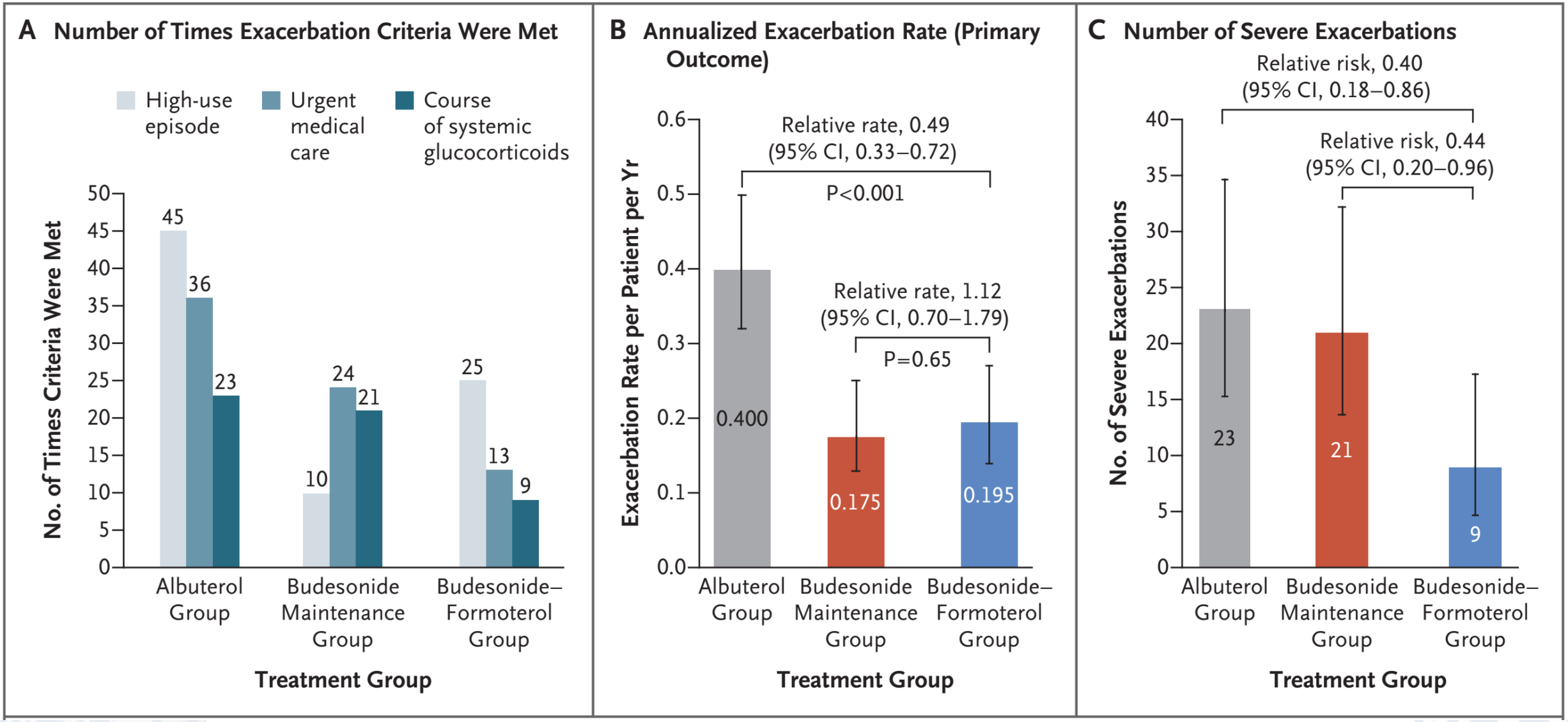
- **Primary outcome** : **Annualized rate of asthma exacerbations**
- Secondary outcome : Score on the Asthma Control Questionnaire–5, the on treatment FEV1, the fraction of exhaled nitric oxide, the number of severe exacerbations
- **Exacerbation** defined as worsening asthma that resulted in an episode of **high β2-agonist inhaler use**, in an **urgent medical care** consultation, or in a course of **systemic glucocorticoids**

Beasley R, N Engl J Med 2019;380:2020-30.

Novel START: Study Design



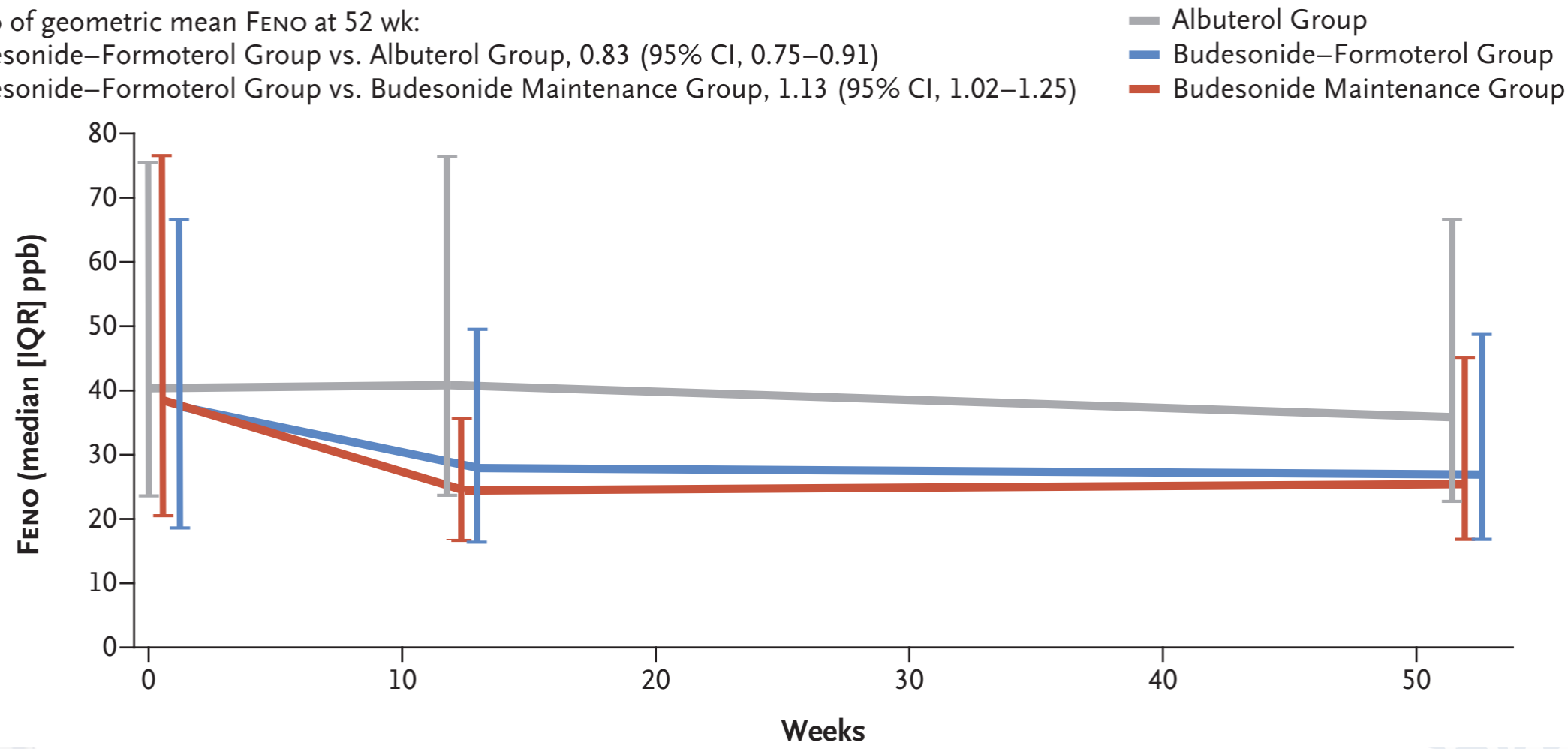
Beasley R, N Engl J Med 2019;380:2020-30.



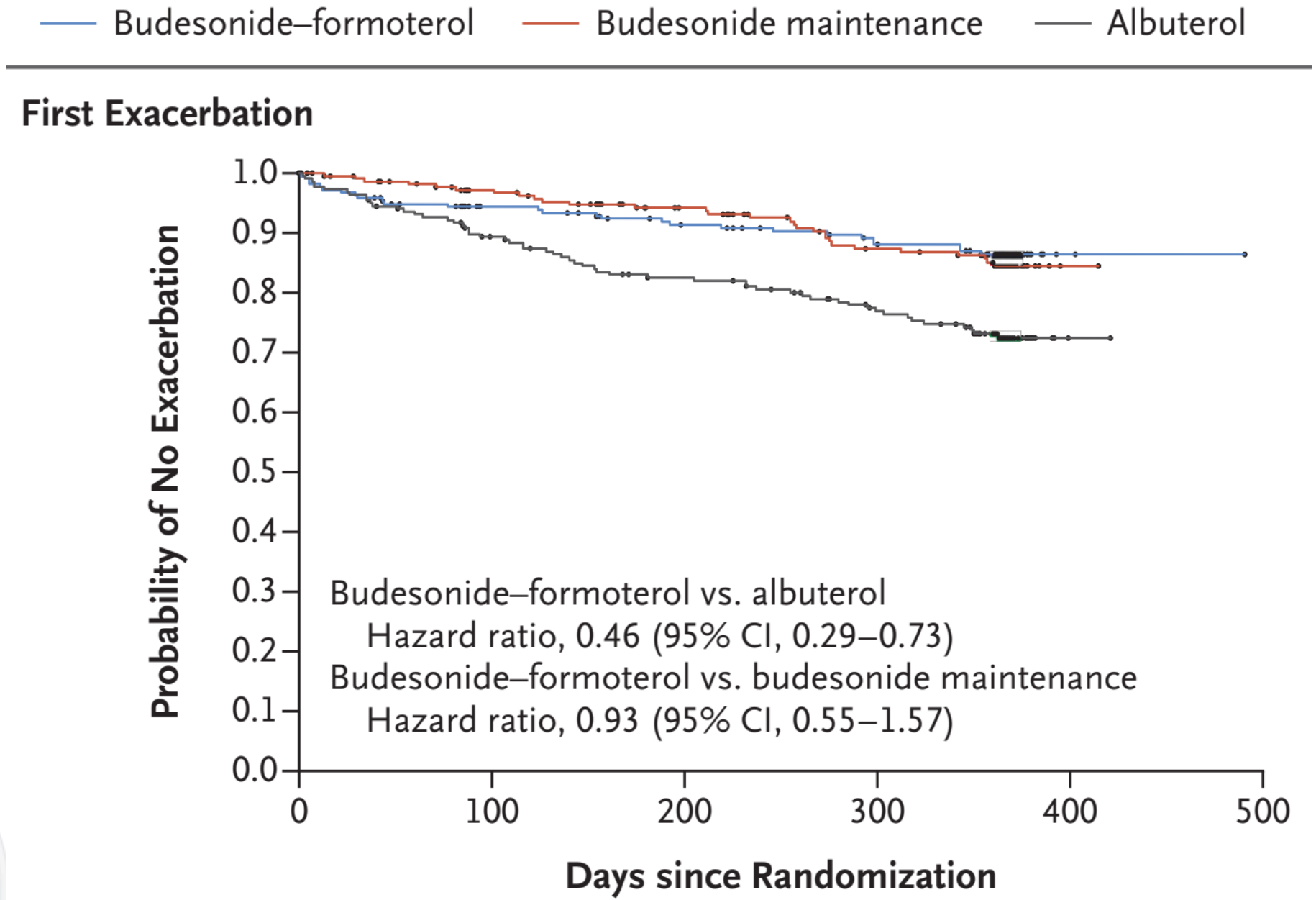
Beasley R, N Engl J Med 2019;380:2020-30.

Fraction of Exhaled Nitric Oxide

Ratio of geometric mean FENO at 52 wk:
Budesonide–Formoterol Group vs. Albuterol Group, 0.83 (95% CI, 0.75–0.91)
Budesonide–Formoterol Group vs. Budesonide Maintenance Group, 1.13 (95% CI, 1.02–1.25)

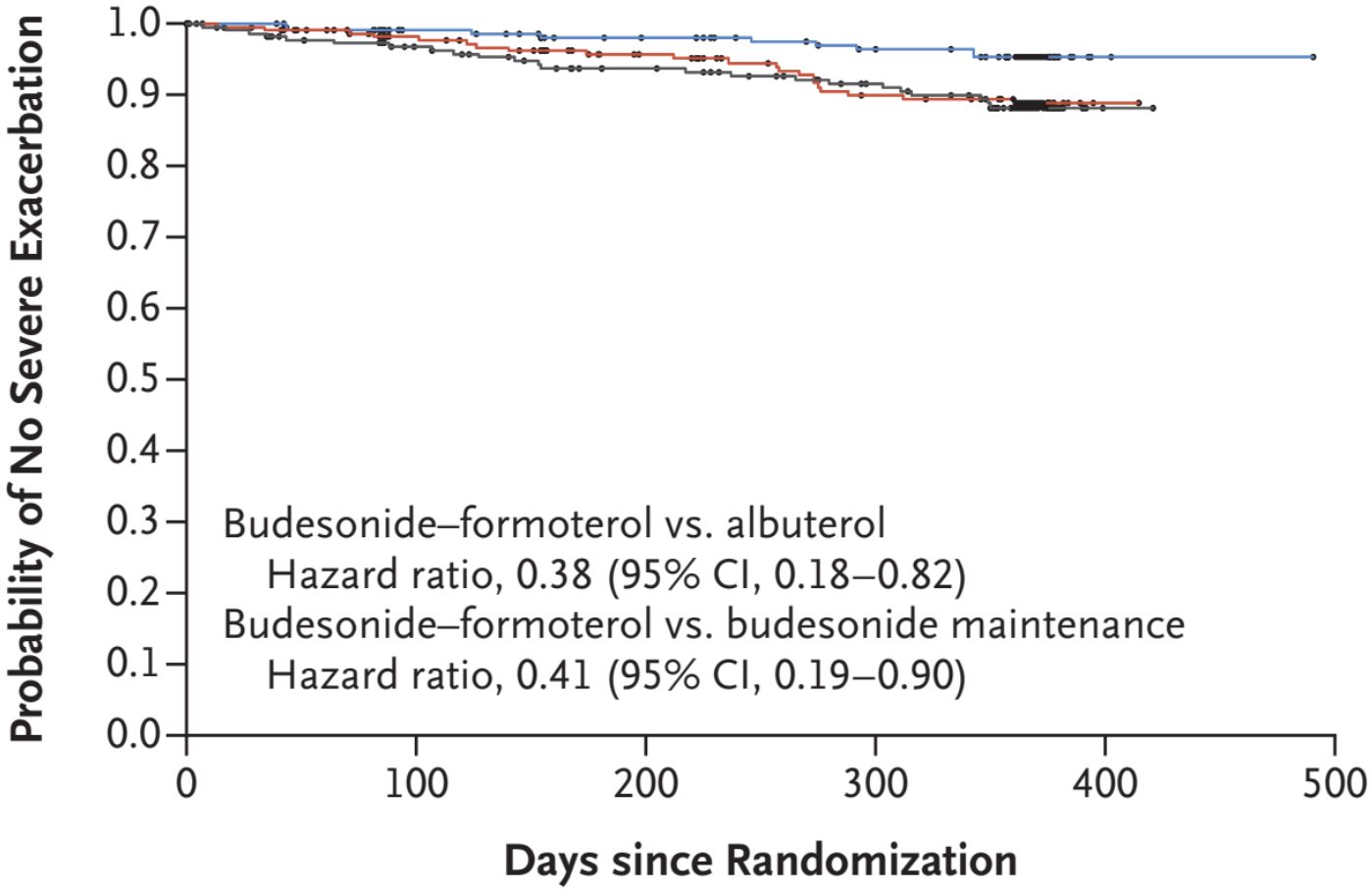


Beasley R, N Engl J Med 2019;380:2020-30.



Beasley R, N Engl J Med 2019;380:2020-30.

First Severe Exacerbation



No. at Risk

Budesonide–formoterol	220	197	184	172	2
Budesonide maintenance	225	199	176	157	1
Albuterol	223	197	180	164	1

Beasley R, N Engl J Med 2019;380:2020-30.

Research letter

Budesonide-formoterol reliever therapy in intermittent *versus* mild persistent asthma

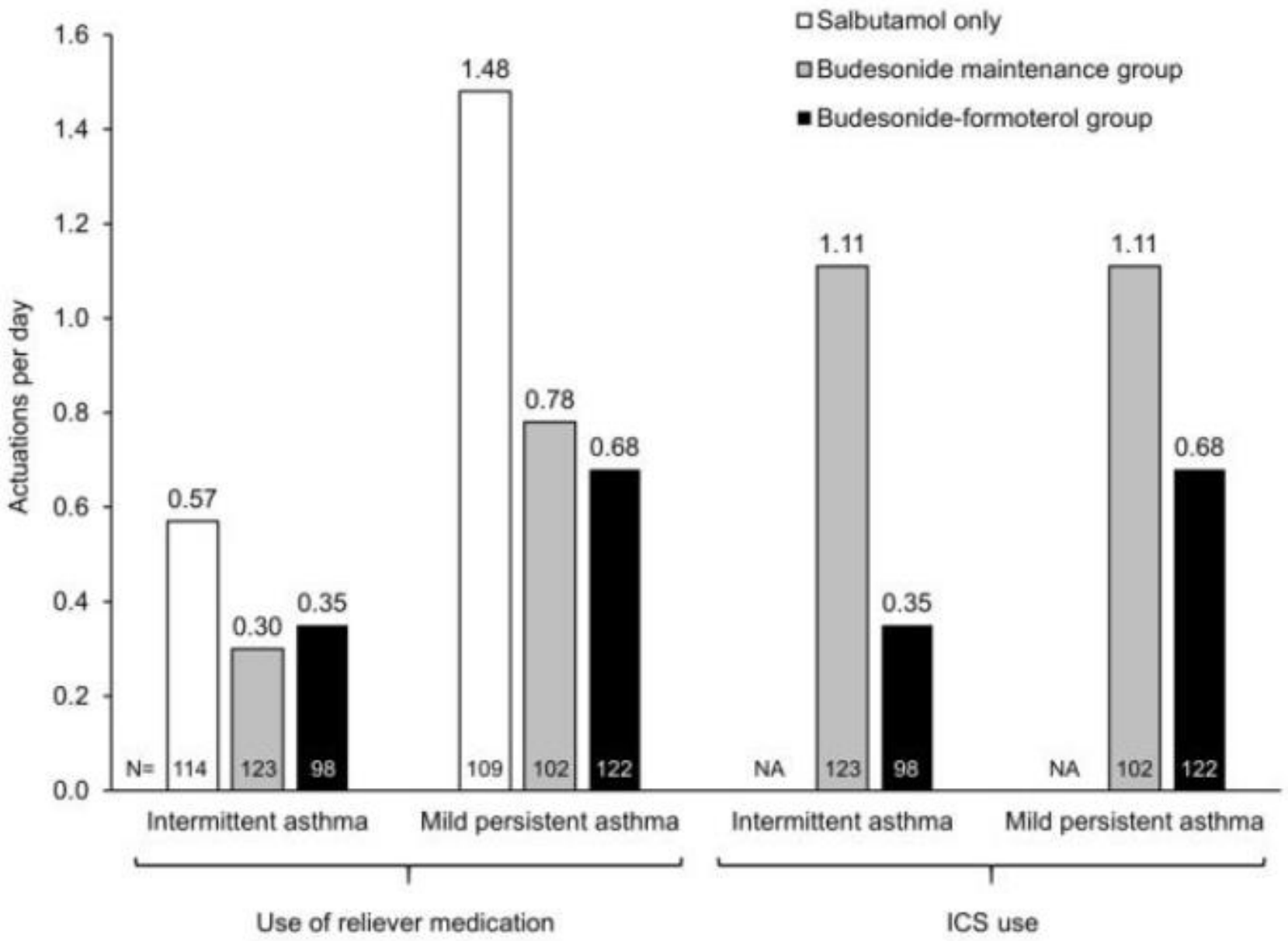
Alberto Papi, Irene Braithwaite, Stefan Ebmeier, B. Hancox, Tim Harrison, Mark Holliday, Claire Houghton, Luca Morandi, Karen Oldfield, Ian D. Pavord, Helen K. Reddel, Mathew Williams, Mark Weatherall, Richard Beasley

- **post-hoc analyses** of the **Novel START** study
- "**intermittent asthma**" defined as use of SABA-alone on **≤2 occasions/week** in the four weeks before entry, and with no severe exacerbation in the previous year.
- "**mild persistent asthma**", using SABA-alone on **>2 occasions/week** (but less than twice-daily) in the previous four weeks, and/or ≥1 severe exacerbation in the previous year

- A total of 668 participants were included, 335 (**50.1%**) with **intermittent asthma.**

Papi A, Eur Respir J 2020.

D



Papi A, Eur Respir J 2020.

- PRACTICAL -

Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial

Jo Hardy, Christina Baggott*, James Fingleton, Helen K Reddel, Robert J Hancox, Matire Harwood, Andrew Corin, Jenny Sparks, Daniela Hall, Doñah Sabbagh, Saras Mane, Alexandra Vohlidkova, John Martindale, Mathew Williams, Philippa Shirtcliffe, Mark Holliday, Mark Weatherall, Richard Beasley, on behalf of the PRACTICAL study team†*

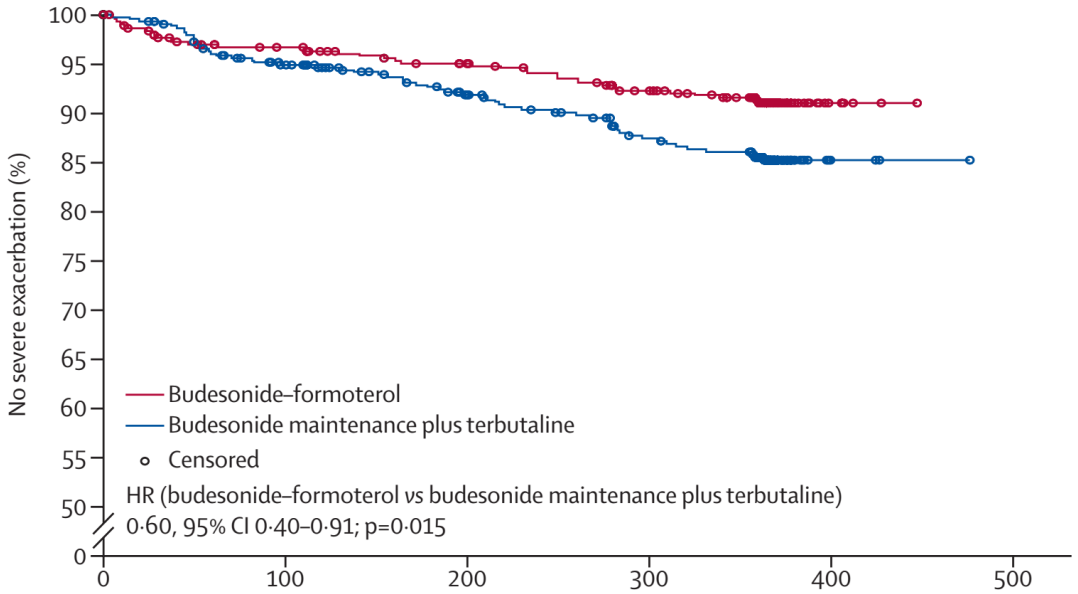
- **a 52-week, open-label**, parallel-group, multicentre, superiority, randomised controlled trial (N=**885**)
- adults aged 18–75 years with a self-reported doctor's diagnosis of asthma who were **using SABA for symptom relief** with or without maintenance **low to moderate doses of inhaled corticosteroids** in the previous 12 weeks (=**asthma patients in GINA Step 1 to 3**)
- (1:1) to either
  reliever therapy with budesonide 200 µg–formoterol 6 µg Turbuhaler (one inhalation as needed for relief of symptoms) or
  maintenance budesonide 200 µg Turbuhaler (one inhalation twice daily) plus **terbutaline 250 µg Turbuhaler** (two inhalations as needed)

- Primary outcome : **the number of severe exacerbations per patient per year**

Hardy J, Lancet 2019;394:919-28.

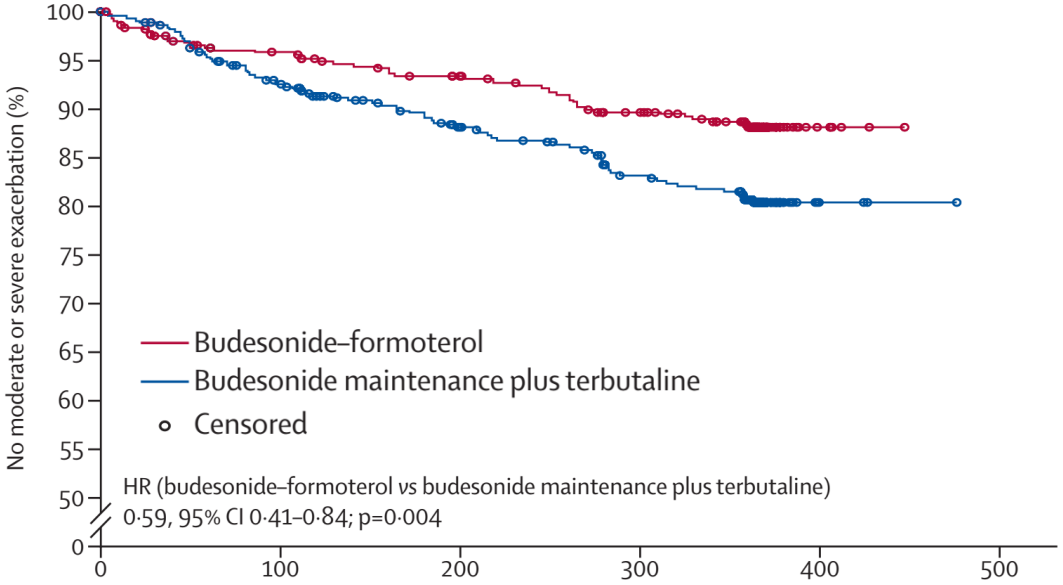
Time to First Severe AE

HR (budesonide–formoterol vs budesonide maintenance plus terbutaline)
0·60, 95% CI 0·40–0·91; p=0·015



Time to First Moderate or Severe AE

HR (budesonide–formoterol vs budesonide maintenance plus terbutaline)
0·59, 95% CI 0·41–0·84; p=0·004



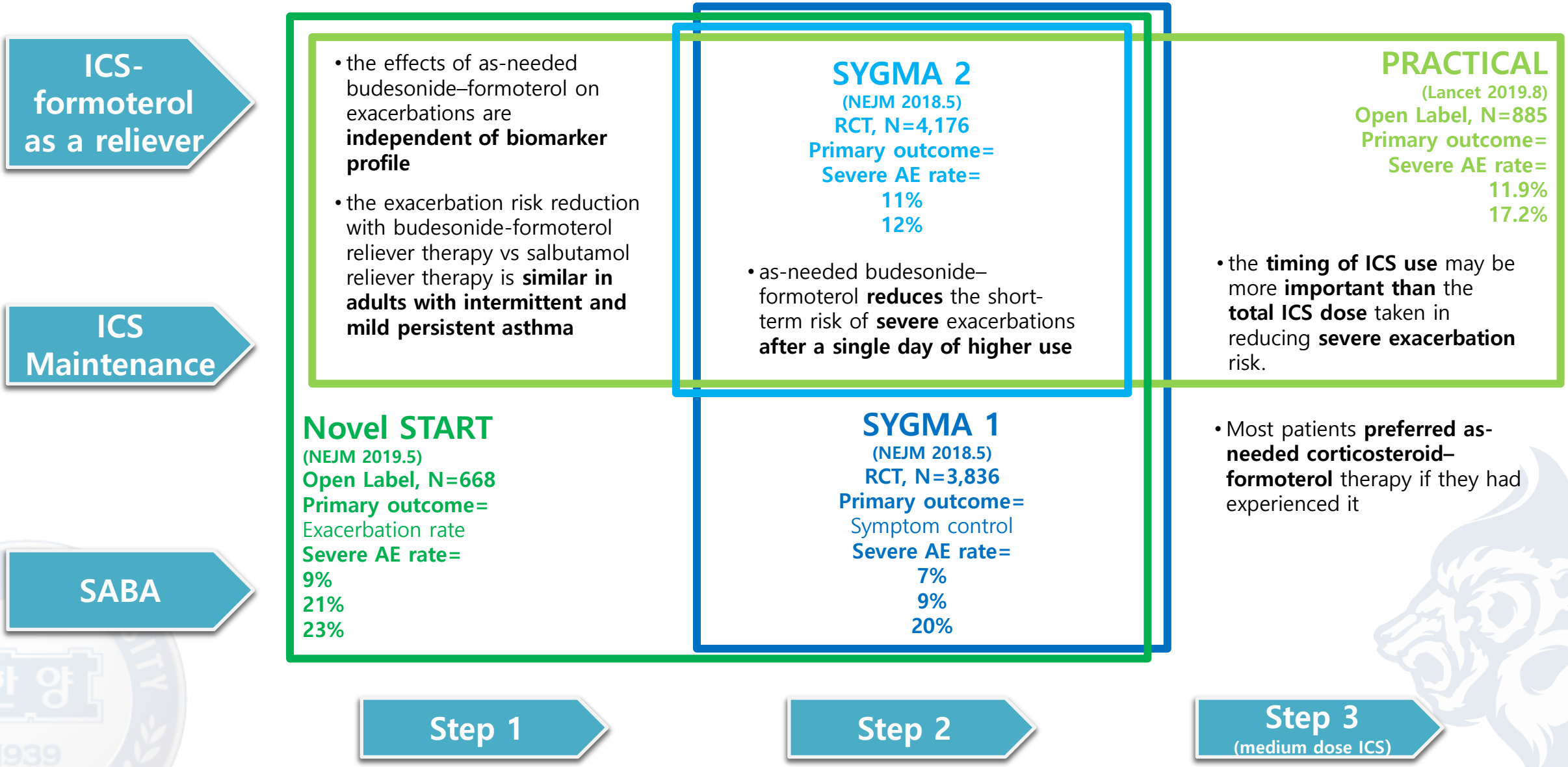
Hardy J, Lancet 2019;394:919-28.

Medication Outcomes in Electronic Monitoring Subgroups

	Budesonide–formoterol as needed (n=55)	Budesonide maintenance plus terbutaline as needed (n=55)
Inhaled corticosteroid use		
Number of budesonide-containing actuations per day		
Mean (SD)	0·9 (0·7)	1·5 (0·4)
Median (IQR)	0·8 (0·4–1·3)	1·6 (1·2–1·8)
Range†	0·0–3·4	0·1–2·3
Daily budesonide dose (µg)		
Mean (SD)	176·0 (143·0)	302·5 (84·8)
Median (IQR)	164·3 (74·0–251·7)	328·3 (245·8–364)
Range‡	6·7–682·5	26·8–458·1
β_2-agonist use		
Number of β_2-agonist-containing actuations per day		
Mean (SD)	0·9 (0·7)	0·5 (0·6)
Median (IQR)	0·8 (0·4–1·3)	0·3 (0·1–0·6)
Range†	0·0–3·4	0·0–2·7

Hardy J, Lancet 2019;394:919-28.

Summary of Clinical Trials for Mild Asthma



Contents

The Single combination budesonide–formoterol inhaler Maintenance And Reliever Therapy (SMART)

Anti-Inflammatory Reliver (AIR)

Guidelines of Asthma Treatment

Timeline of US National Asthma Guidelines

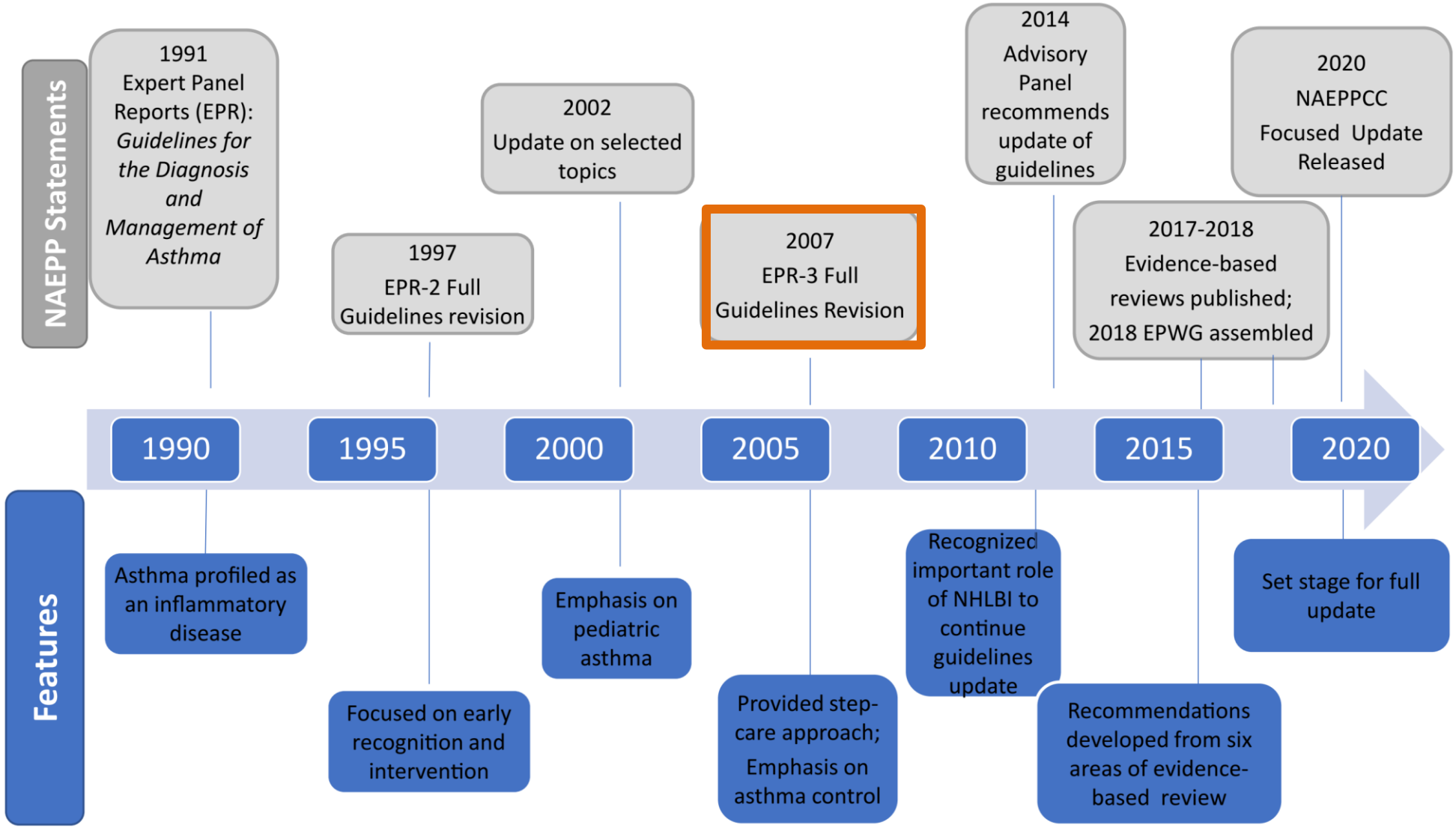


FIG 1. Time line for the development of US national guidelines through EPRs with oversight from the NAEPP, and recently, through an EPWG with oversight from the NAEPPCC.

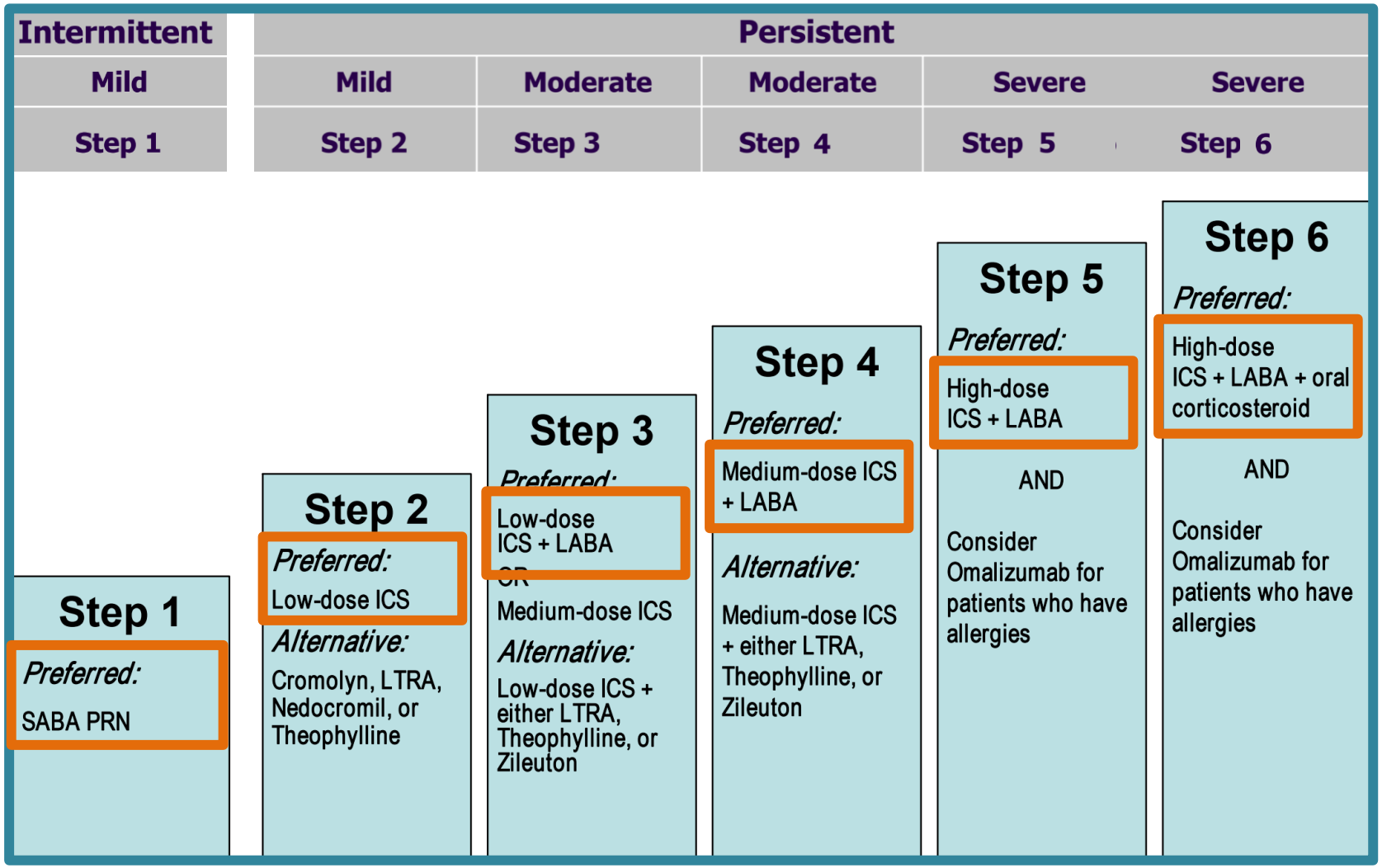
Szefler SJ, J Allergy Clin Immunol 2020;146:1275-80 [PMID 32004522]

Classifying Severity For Patients Who Are Not Currently Taking Long-term Control Medications (EPR 3)

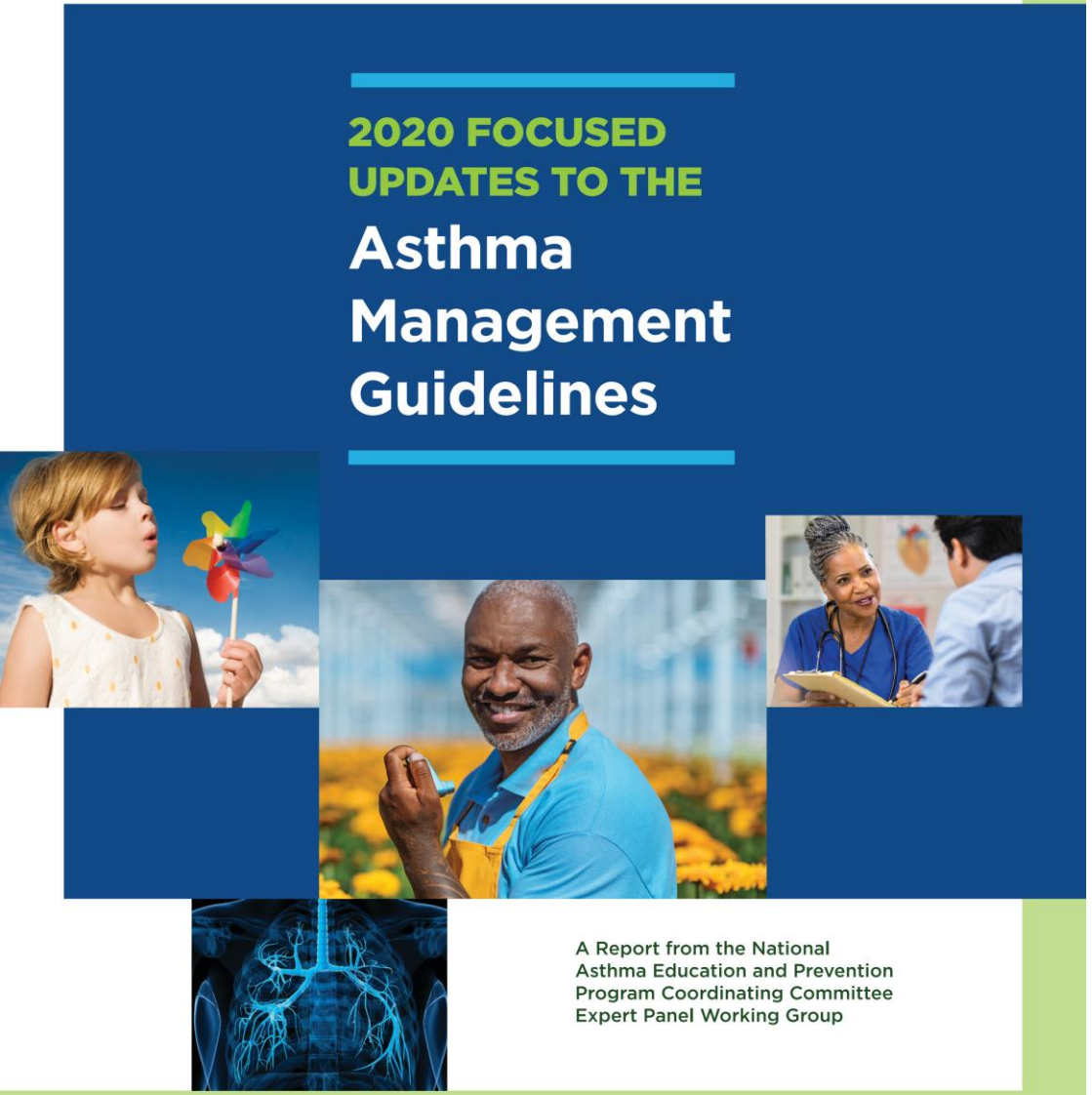
Components of Severity		Classification of Asthma Severity (Youths ≥12 years of age and adults)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment **Normal FEV_1/FVC:** **8–19 yr 85%** **20–39 yr 80%** **40–59 yr 75%** **60–80 yr 70%**	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 ≥80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1			

Expert Panel Report 3 (EPR 3) J Allergy Clin Immunol 2007:120;S94-138

Classifying Severity In Patients After Asthma Becomes Well Controlled, by Lowest Level Of Treatment Required To Maintain Control (EPR 3)



Expert Panel Report 3 (EPR 3) J Allergy Clin Immunol 2007:120;S94-138



JAMA | Special Communication

Managing Asthma in Adolescents and Adults

2020 Asthma Guideline Update From the National Asthma Education and Prevention Program

Michelle M. Cloutier, MD; Anne E. Dixon, MA, BM, BCh; Jerry A. Krishnan, MD, PhD; Robert F. Lemanske Jr, MD; Wilson Pace, MD; Michael Schatz, MD, MS

IMPORTANCE Asthma is a major public health problem worldwide and is associated with excess morbidity, mortality, and economic costs associated with lost productivity. The National Asthma Education and Prevention Program has released the 2020 Asthma Guideline Update with updated evidence-based recommendations for treatment of patients with asthma.

OBJECTIVE To report updated recommendations for 6 topics for clinical management of adolescents and adults with asthma: (1) intermittent inhaled corticosteroids (ICSs); (2) add-on long-acting muscarinic antagonists; (3) fractional exhaled nitric oxide; (4) indoor allergen mitigation; (5) immunotherapy; and (6) bronchial thermoplasty.

EVIDENCE REVIEW The National Heart, Lung, and Blood Advisory Council chose 6 topics to update the 2007 asthma guidelines based on results from a 2014 needs assessment. The Agency for Healthcare Research and Quality conducted systematic reviews of these 6 topics based on literature searches up to March-April 2017. Reviews were updated through October 2018 and used by an expert panel (n = 19) that included asthma content experts, primary care clinicians, dissemination and implementation experts, and health policy experts to develop 19 new recommendations using the GRADE method. The 17 recommendations for individuals aged 12 years or older are reported in this Special Communication.

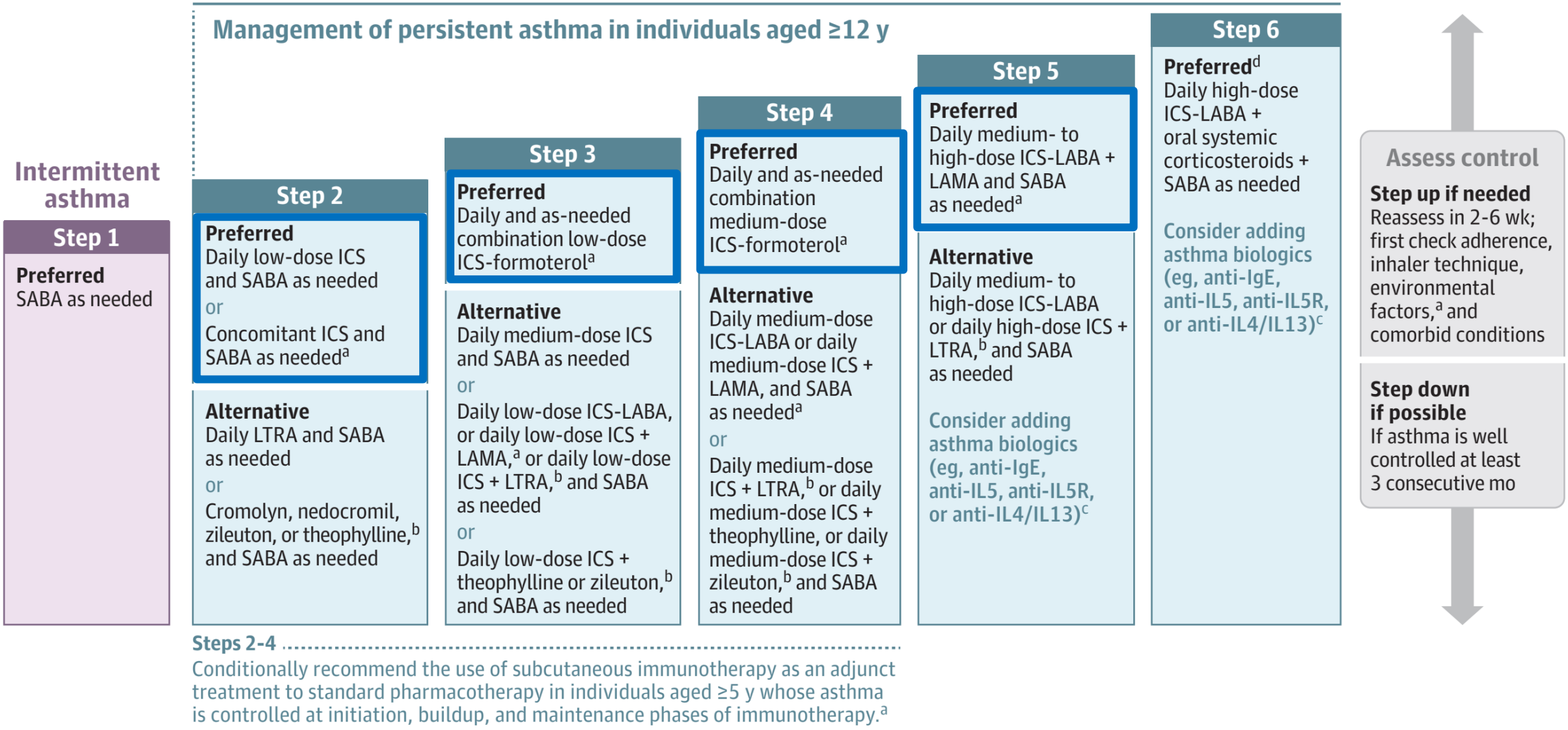
FINDINGS From 20 572 identified references, 475 were included in the 6 systematic reviews to form the evidence basis for these recommendations. Compared with the 2007 guideline, there was no recommended change in step 1 (intermittent asthma) therapy (as-needed short-acting β_2-agonists [SABAs] for rescue therapy). In step 2 (mild persistent asthma), either daily low-dose ICS plus as-needed SABA therapy or as-needed concomitant ICS and SABA therapy are recommended. Formoterol in combination with an ICS in a single inhaler (single maintenance and reliever therapy) is recommended as the preferred therapy for moderate persistent asthma in step 3 (low-dose ICS-formoterol therapy) and step 4 (medium-dose ICS-formoterol therapy) for both daily and as-needed therapy. A short-term increase in the ICS dose alone for worsening of asthma symptoms is not recommended. Add-on long-acting muscarinic antagonists are recommended in individuals whose asthma is not controlled by ICS-formoterol therapy for step 5 (moderate-severe persistent asthma).

Editorial
Supplemental content
CME Quiz at jamacmelookup.com

TABLE IA. Systematic review key questions

Topic	Key question
FENO	What is the diagnostic accuracy of FENO measurement(s) for making the diagnosis of asthma in individuals aged 5 y and older?
	What is the clinical utility of FENO measurements in monitoring disease activity and asthma outcomes in individuals with asthma aged 5 y and older?
	What is the clinical utility of FENO measurements to select medication options (including steroids) for individuals aged 5 y and older?
	What is the clinical utility of FENO measurements to monitor response to treatment in individuals aged 5 y and older?
	In children aged 0-4 years with recurrent wheezing, how accurate is FENO testing in predicting the future development of asthma at age 5 y and above?
Allergen mitigation	Among individuals with asthma, what is the effectiveness of interventions to reduce or remove exposures to indoor inhalant allergens on asthma control, exacerbations, quality of life, and other relevant outcomes?
ICS	What is the comparative effectiveness of intermittent ICS compared to no treatment, pharmacologic therapy, or nonpharmacologic therapy in children aged 0-4 y with recurrent wheezing?
	What is the comparative effectiveness of intermittent ICS compared to ICS controller therapy in individuals 5 y and older with persistent asthma?
	What is the comparative effectiveness of ICS with LABA used as both controller and quick-relief therapy compared to ICS with or without LABA used as controller therapy in individuals 5 y and older with persistent asthma?
LAMA	What is the comparative effectiveness of LAMA compared to other controller therapy as add-on to ICS in individuals aged 12 y and older with uncontrolled, persistent asthma?
	What is the comparative effectiveness of LAMA as add-on to ICS controller therapy compared to placebo or increased ICS dose in individuals aged 12 y and older with uncontrolled, persistent asthma?
	What is the comparative effectiveness of LAMA as add-on to ICS-LABA compared to ICS-LABA as controller therapy in individuals aged 12 y and older with uncontrolled, persistent asthma?
Immunotherapy	What is the evidence for the efficacy of SCIT in the treatment of asthma?
	What is the evidence for the safety of SCIT in the treatment of asthma?
	What is the evidence for the efficacy of SLIT, in tablet and aqueous form, for the treatment of asthma?
	What is the evidence for the safety of SLIT, in tablet and aqueous form, for the treatment of asthma?
BT	What are the benefits and harms of using BT in addition to standard treatment for the treatment of individuals aged 18 y and older with asthma?

Figure. Stepwise Approach for Management of Asthma in Individuals Aged 12 Years or Older



Cloutier MM, JAMA 2020;324:2301-17 [PMID 33270095]

NAEPP 2020 Update of the Expert Panel Report 3
Step Therapy Diagram for individuals 12 years of age and older

Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12 Years and Older				
Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Preferred: prn SABA	*Preferred:* Daily low-dose ICS and prn SABA ***OR*** **prn concomitant low-dose ICS and prn SABA** *Alternative:* Daily LTRA and prn SABA	*Preferred:* **Daily and prn low-dose ICS-formoterol (SMART)** *Alternative:* Daily medium-dose ICS and prn SABA *OR* Daily low-dose ICS + LABA or LTRA **or LAMA** and prn SABA	*Preferred:* **Daily and prn medium-dose ICS-formoterol (SMART)** *Alternative:* Daily medium-dose ICS + LABA **or LAMA** or LTRA and prn SABA	*Preferred:* **Daily medium-dose ICS + LABA + LAMA and prn SABA** *Alternative:* Daily high-dose ICS + LABA and prn SABA *OR* Daily high-dose ICS + LTRA and prn SABA	Not in material reviewed by the Expert Panel

Chipps BE et al. J Allergy Clin Immunol Pract 2022;10:S19-S30 [PMID 34718214]

2020 NAEPP Guidelines Update and GINA 2021—Asthma Care Differences, Overlap, and Challenges

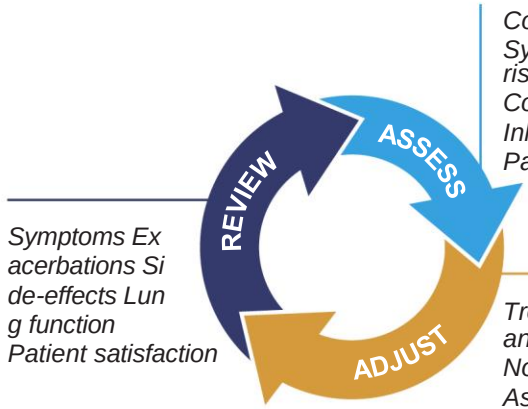
Bradley E. Chipps, MD[a], Kevin R. Murphy, MD[b], and John Oppenheimer, MD[c] *Sacramento, Calif; Boystown, Neb; and Newark, NJ*

- The studies by O'Byrne et al (SYGMA 1) and Bateman et al (SYGMA 2) of as-needed budesonide-formoterol, although published in May 2018, were not reviewed by NAEPP because the question about **intermittent ICS therapy** that was decided upon in 2015 was **interpreted as excluding ICS-long-acting beta-agonist (LABA)** combination therapy

Chipps BE et al. J Allergy Clin Immunol Pract 2022;10:S19-S30 [PMID 34718214]

Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Symptoms Exacerbations Side-effects Lung function Patient satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications (adjust down/up/between tracks)
Education & skills training

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	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol

See GINA severe asthma guide

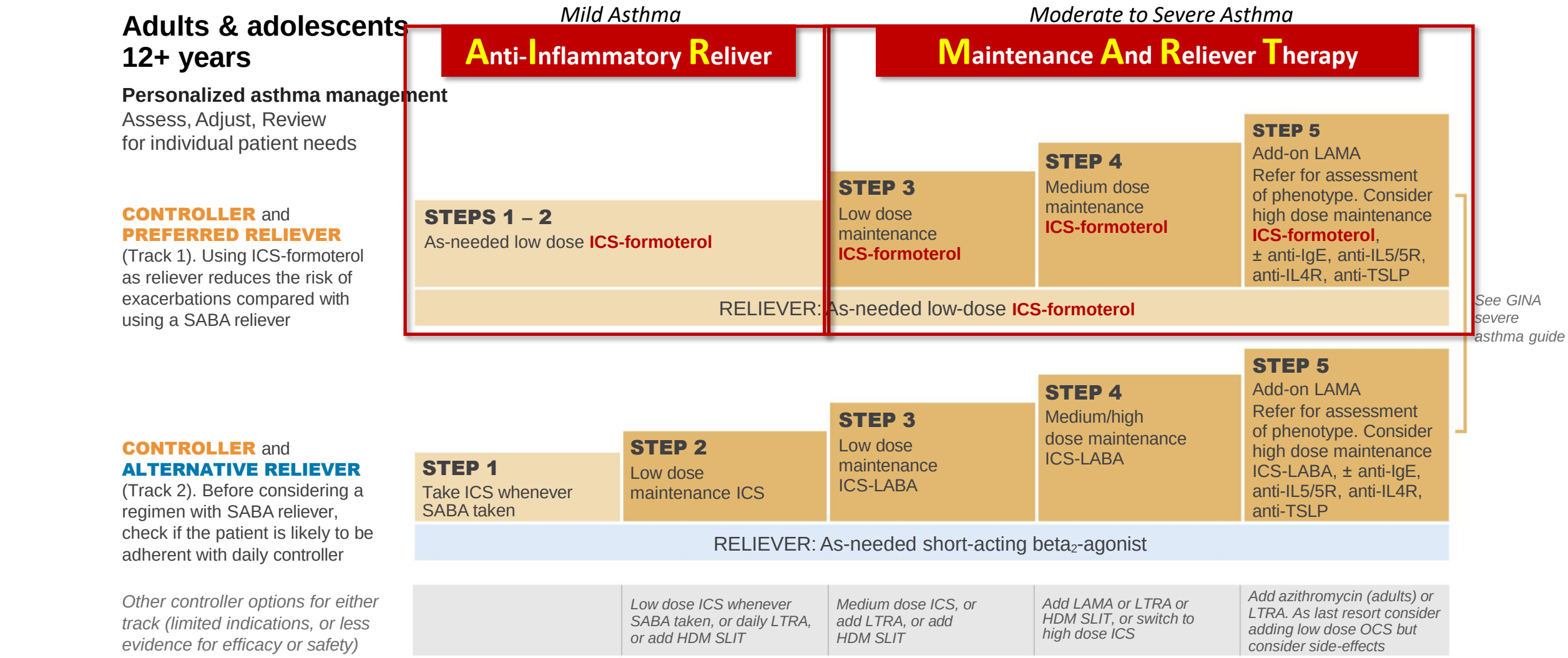
CONTROLLER and **ALTERNATIVE RELIEVER** (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP

RELIEVER: As-needed short-acting beta$_2$-agonist

Other controller options for either track (limited indications, or less evidence for efficacy or safety)				
	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

"AIR" & "MART"



Benefit of Single Device Considering Patient Adherence

- 천식 치료시 Same device 사용 군이 Mixed devices 사용 군 보다 더 나은 천식 증상 조절, 중증 악화 감소 효과를 보였습니다.[2]
- 따라서 환자에게 **한 가지 흡입기**의 올바른 사용법을 교육하여 **적절한 천식 치료 시작**하는 것이 다양한 흡입기를 사용하는 것보다 **효과적**입니다.

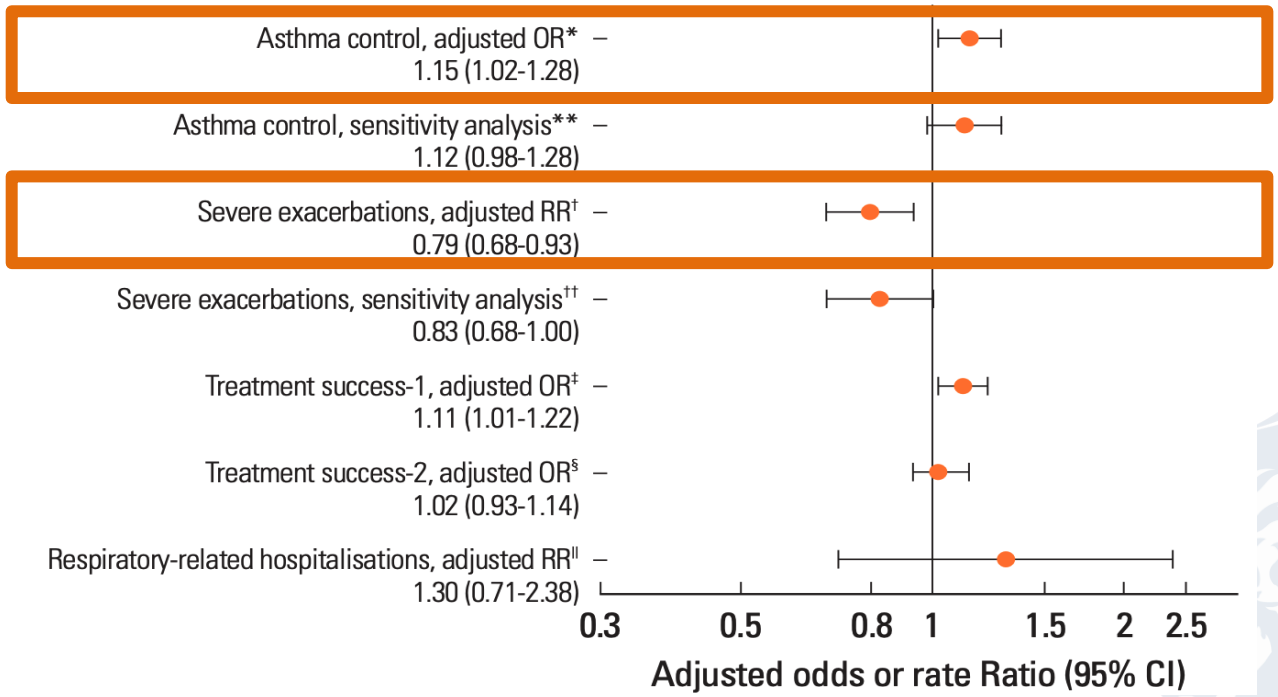
Poor medication adherence in asthma[1]

Factors contributing to poor adherence

Medication/regimen factors
- Difficulties using inhaler device (e.g. arthritis)
- Burdensome regimen (e.g. multiple times per day)
- Multiple different inhalers

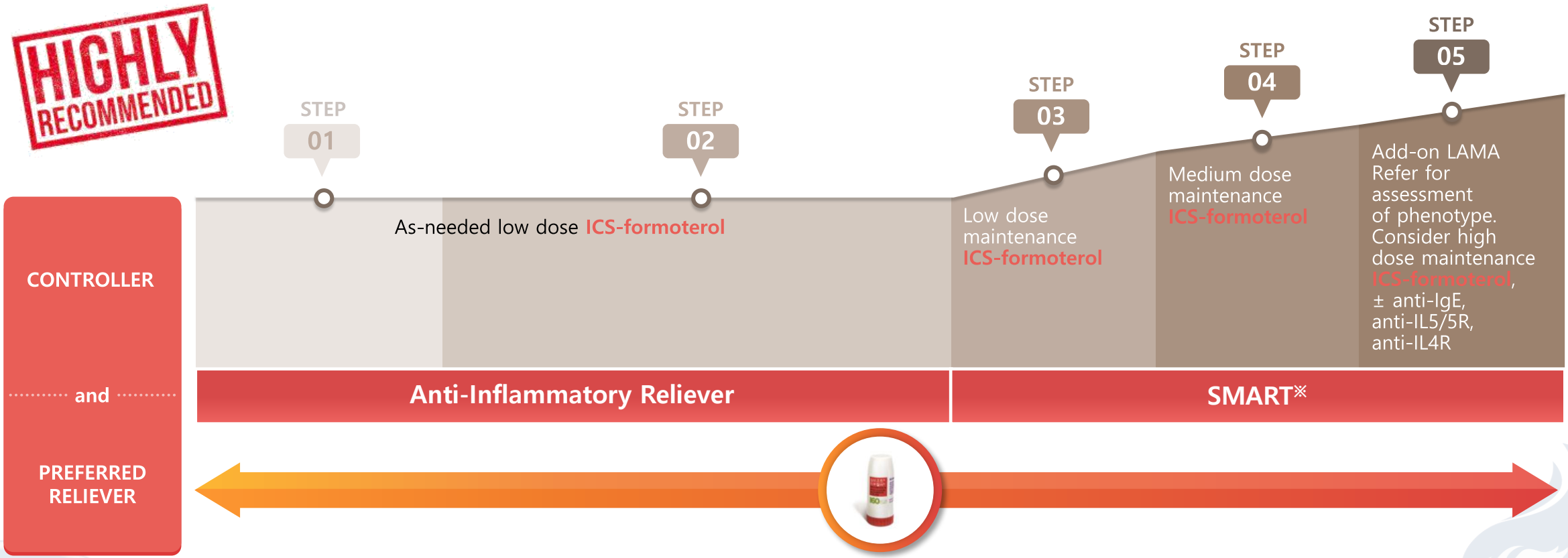
Unintentional poor adherence
- Misunderstanding about instructions
- Forgetfulness
- Absence of a daily routine
- Cost

Mixed devices vs. Same device[2]



1. Global Initiative for Asthma. Main report 2020. 2. David Price et al, Effectiveness of same versus mixed asthma inhaler devices: a retrospective observational study in primary care Allergy Asthma Immunol Res. 2012 July;4(4):184-191.

One Device for All Steps, Symbicort!



국내에서는 심비코트 터부헬러® 160/4.5 μg 및 심비코트 라피헬러® 흡입제 80/2.25 μg이 경증 천식 환자의 항염증 증상완화요법으로 허가를 받았습니다.

*2022 GINA table의 경우 국내 허가사항에 맞게 일부 조정하였음을 밝힙니다.

1.O'Byrne PM, FitzGerald JM, Bateman ED, *et al.* Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. *N Engl J Med.* 2018;378(20):1865-1876. 2. Bateman ED, Reddel HK, O'Byrne PM, *et al.* As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma. *N Engl J Med.* 2018;378(20):1877-1887. 3. Beasley R, Holliday M, Reddel HK, *et al.* Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. *N Engl J Med.* 2019;380(21):2020-2030. 4. Kuna P, Peters MJ, Manjra AI, *et al.* Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract.* 2007;61(5):725-736. 5. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2022. Available at: www.ginasthma.org. Accessed on 11May2022.