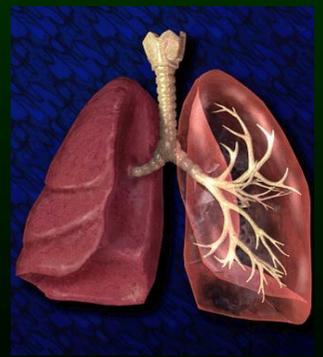




As needed ICS/LABA in mild asthma: pro and con

Shih-Lung Cheng MD, PhD

Division for Pulmonary Medicine
Department of Internal Medicine
Center of Evidence-Based Medicine
Center of Clinical Trial
Far Eastern Memorial Hospital



GINA 2019 Update

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed Low dose ICS-formoterol ⁺	Daily low dose inhaled corticosteroid (ICS) or as-needed low dose ICS-formoterol ⁺	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g.tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	Low dose ICS taken whenever SABA is taken	Leukotriene receptor antagonist (LTRA), or Low dose ICS taken whenever SABA taken [#]	Medium dose ICS, or low dose ICS+LTRA	High dose ICS, add-on tiotropium, or add-on LTRA ^{**}	Add low dose OCS, but consider side effect
PREFERRED RELIEVER	As-needed low dose ICS-formoterol ⁺		As-needed low dose ICS-formoterol [*]		
Other reliever options	As needed short-acting β ₂ -agonist (SABA)		As needed SABA		

<p>+ Off-label: Data only with Budesonide-formoterol (Bud-Form)</p> <p># Off-label: separate or combination ICS and SABA inhalers</p>	<p>* Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy.</p> <p>** Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV₁>70% predicted.</p>
---	---

GINA 2019: a fundamental change in asthma management

Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

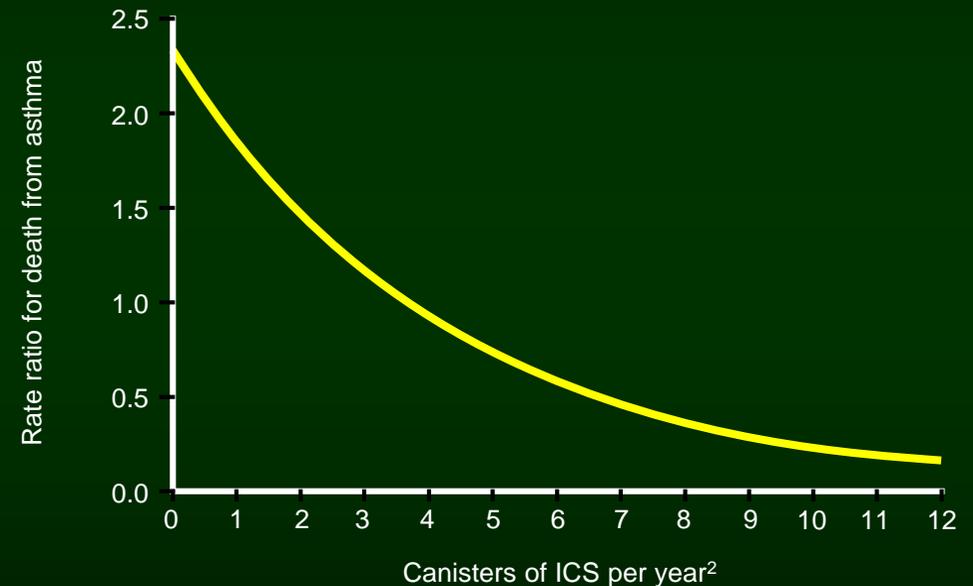
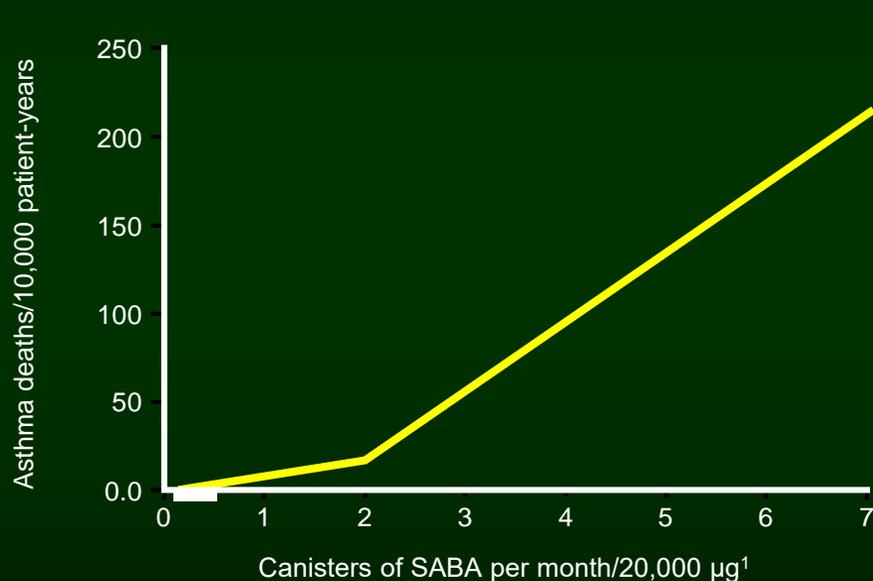
considered the most fundamental change in asthma management in 30 years.

GINA no longer recommends treating adults/adolescents with asthma with short-acting bronchodilators alone. Instead, they should receive symptom-driven (in mild asthma) or a daily corticosteroid-containing inhaler, to reduce risk of severe exacerbations. <http://bit.ly/310LLzE>

Reddel HK, et al. Eur Respir J 2019; 53:1901046

Relationship between mortality rates and SABA or ICS use

- Over-reliance on SABA at the expense of ICS controller therapy was associated with an increased risk of asthma-related death
- Episodes of high reliever use (>6 inhalations/day on at least 1 day) were predictive of an increased risk of exacerbations³



ICS, inhaled corticosteroid; SABA, short-acting β_2 -agonist.

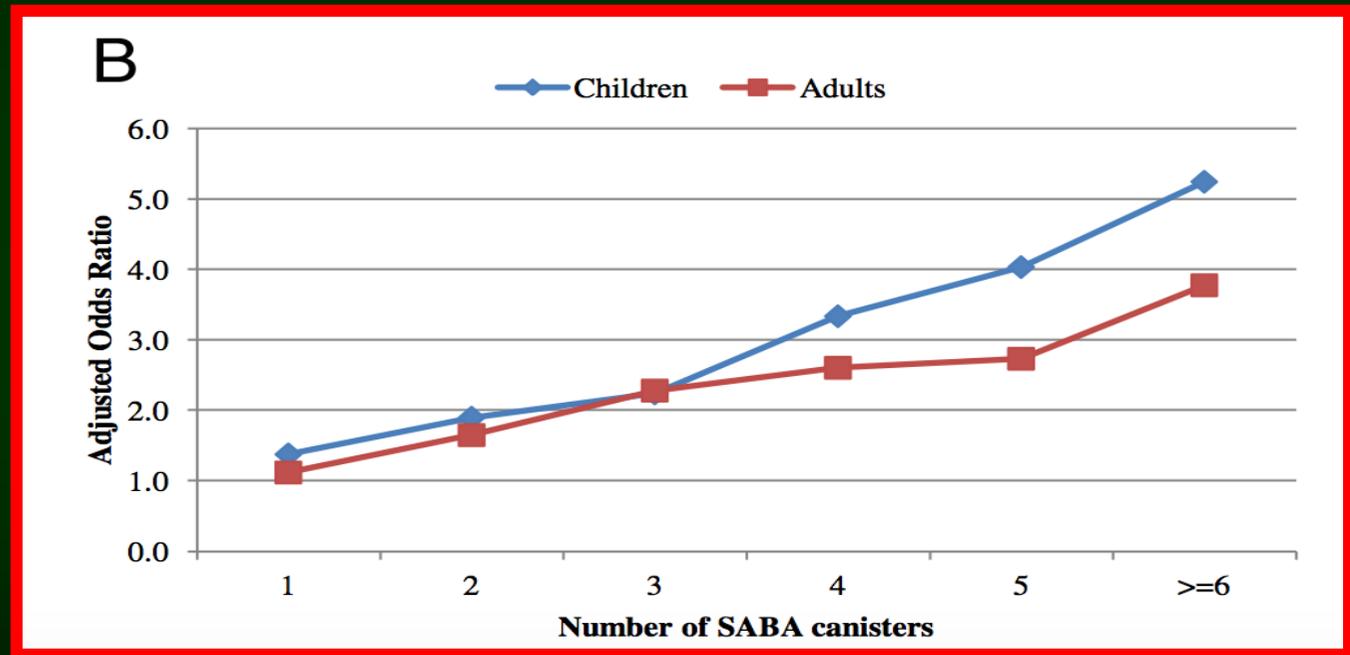
1. Suissa S, et al. Am J Respir Crit Care Med 1994;149:604–10; 2. Suissa S, et al. N Engl J Med 2000;343:332–6; 3. Buhl R, et al. Respir Res 2012;13:59.

3 or more SABA canisters/year is an indicator of increased risk of severe attack



Children n = 41,753
Adults n = 59,684

Risk of severe attack increase >2-fold at 3 or more SABAs/year¹

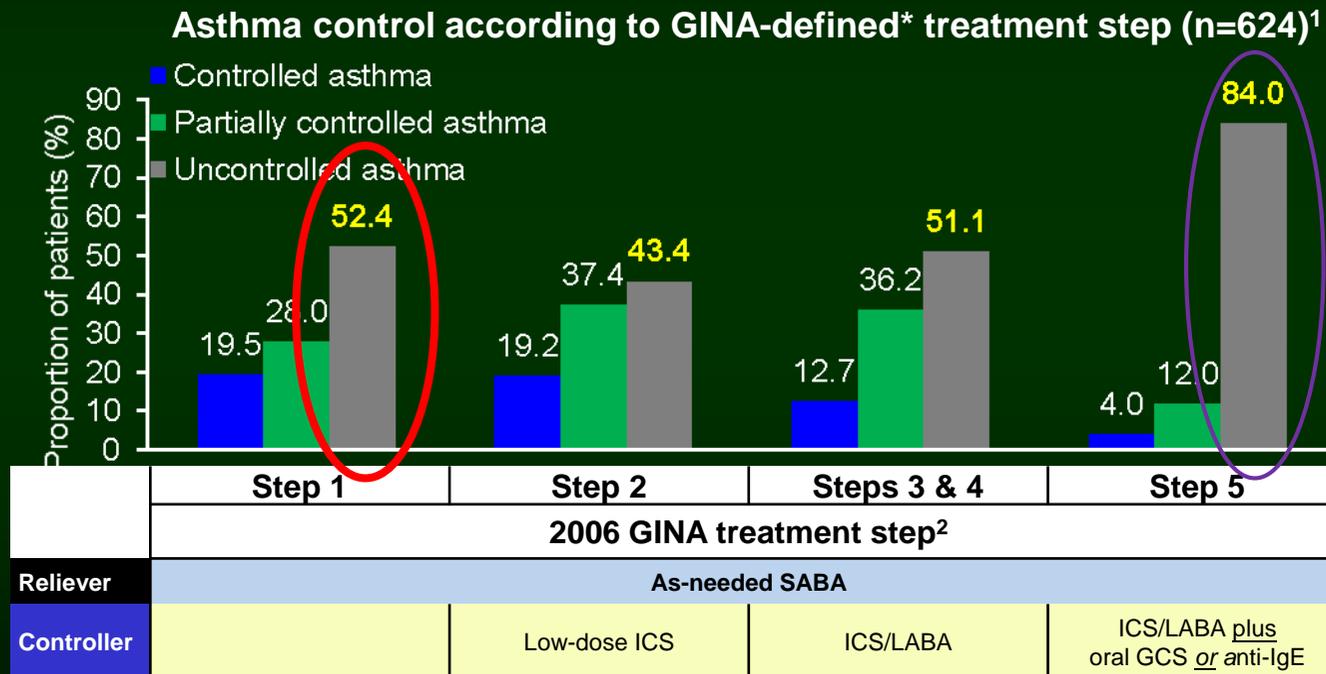


1. Stanford R, et al.. Ann Allergy Asthma Immunol 109 (2012)
2. Silver HS. J Asthma. 2010; 47(6): 660-6.
CE: Canister equivalent

Critical thresholds for risk¹:
Children: 3 SABA canisters in 12 months
Adults: 2 SABA canisters in 6 months

Asthma control is poor for many patients at all levels of severity

- In the MAGIC study of patients with physician-diagnosed asthma (n=1,286), the incidence of uncontrolled asthma increased with increasing GINA* Steps 2–5¹
- Asthma control was poor, even at GINA Step 1¹



An epidemiological descriptive study with prospective data collection, and population (n=1,286) split into development (2/3) and validation (1/3).

*Based on 2006 GINA guidelines².

GCS, glucocorticoids; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting β_2 -agonist; SABA, short-acting β_2 -agonist.

1. Olaguibel JM, et al. *Respir Res* 2012;13:50; 2. Bateman ED, et al. *Eur Respir J* 2008;31:143–78.

Asthma – definition, diagnosis and pathophysiology

- Asthma is a chronic disease characterized by inflammation and episodes of increased symptoms and exacerbations associated with worsening inflammation^{1,2}
- Asthma is diagnosed from lung function and a history of respiratory symptoms such as wheeze, cough, chest tightness and expiration difficulty from airway inflammation and smooth muscle constriction)³
- Asthma is categorised by symptoms and their severity, but not the underlying pathophysiology⁴

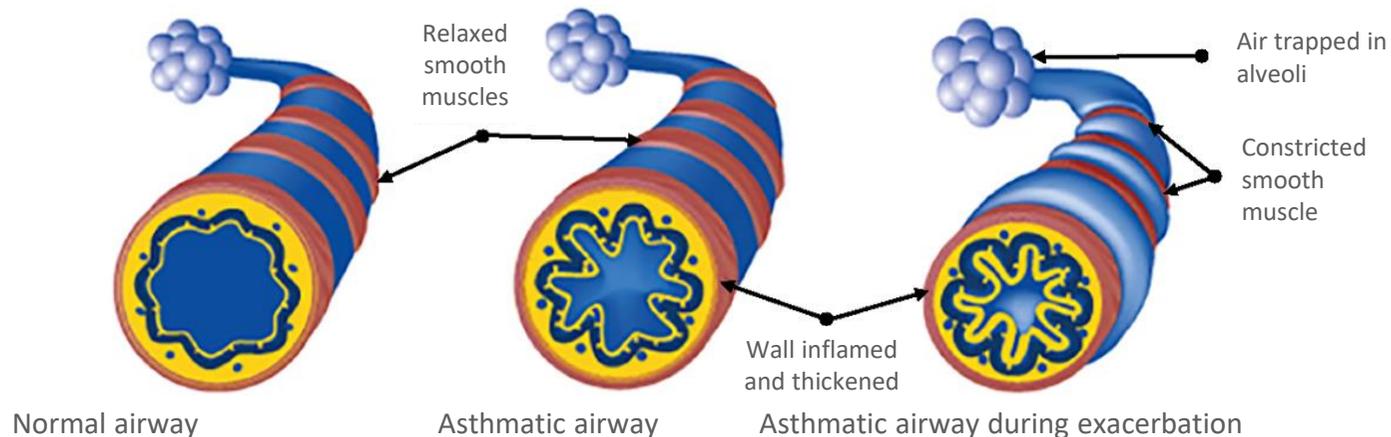
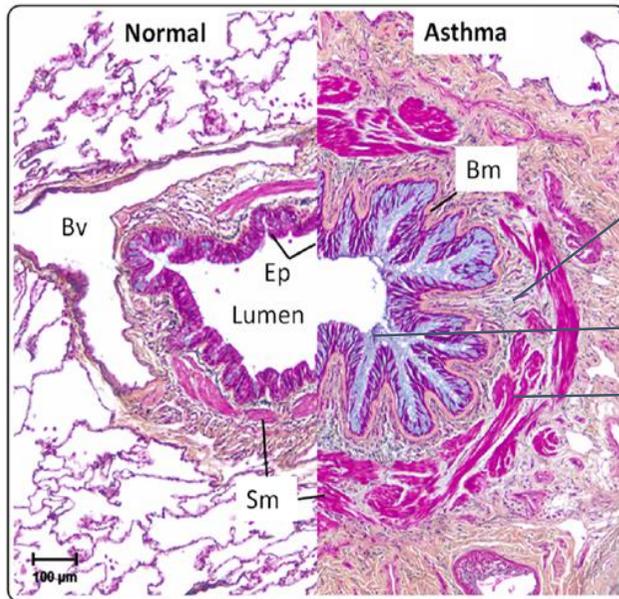


Figure adapted from Reference 4.

1. O'Byrne P, et al Eur Respir J 2017;50. pii:1701103; 2. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2017. Available from: <http://www.ginasthma.org> [Last accessed: September 2017]; 3. Doeing DC, Solway J. J Appl Physiol 2013;114:834–43; 4. Ishmael F, et al. J Am Osteopath Assoc 2011;111:S11–7.

Inflammation is central to symptoms and exacerbations¹

Healthy versus severe asthmatic airway²

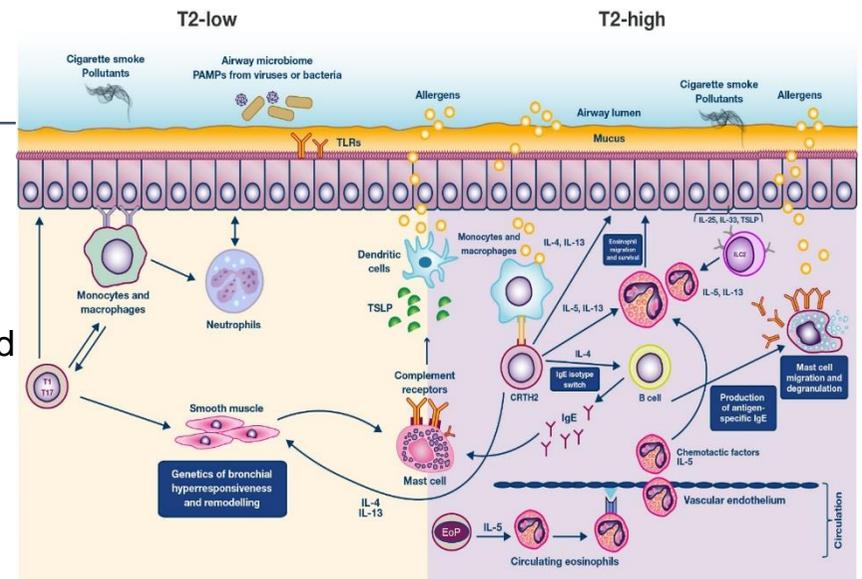


INFLAMMATION



Mucus hypersecretion
Smooth muscle thickened

Key inflammatory pathways in asthma³⁻⁵

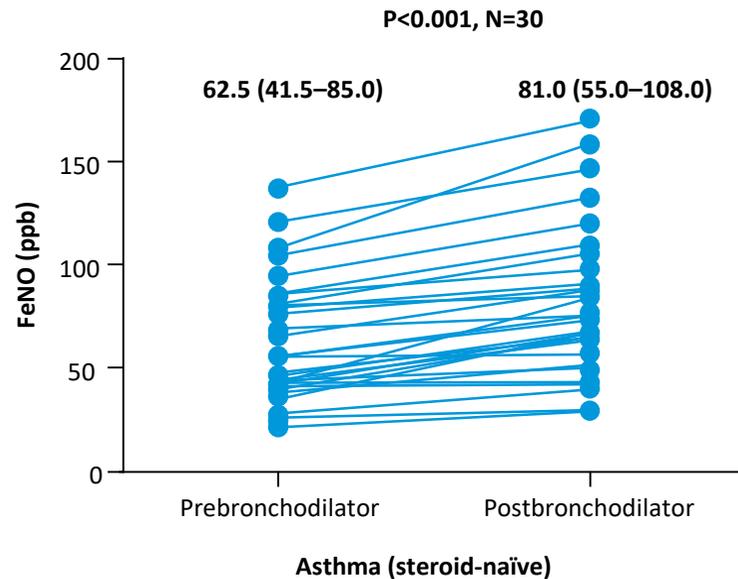


Bm = basement membrane; Bv = blood vessel; CRTH2 = chemoattractant receptor-homologous molecule expressed on Th2 cells; EoP = eosinophilopoiesis; Ep = epithelium; IgE = immunoglobulin E; IL = interleukin; ILC2 = type 2 innate lymphoid cells; SM = smooth muscle; T1 = Type 1 cell; T2 = Type 2 cell; T17 = Type 17 cell; TLR = toll-like receptor; TSLP = thymic stromal lymphopoietin.

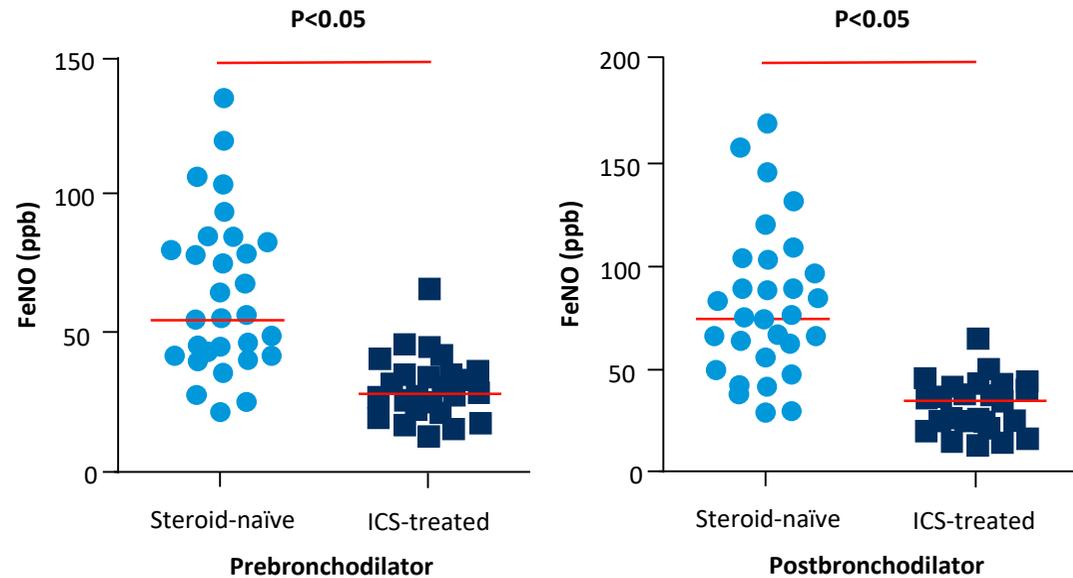
1. Global Initiative for Asthma. 2019 GINA Report, Global Strategy for Asthma Management and Prevention. <http://www.ginasthma.org>. Accessed 12 June 2019; 2. Holgate ST, et al. *Nat Rev Dis Primers*. 2015;1:15025; 3. Wenzel SE. *Nat Med*. 2012;18:716-725; 4. Peters SP, et al. *J Allergy Clin Immunol Pract*. 2017;5:S15-S24; 5. Mukherjee M, et al. *World Allergy Organ J*. 2014;7:32.

SABA has no anti-inflammation effect only an anti-Inflammatory has an anti- inflammation effect!

Salbutamol can not lower airway
inflammation response¹



ICS lower airway inflammation response
(β agonist has no effect)¹



1. Zhao et al. Clin Respir J 2017;11:328-336.

Clinical Programme Investigating Budesonide/Formoterol as an Anti-inflammatory Reliever in Mild Asthma

START Study Analysis: Mild patients benefit from early introduction and long-term ICS (budesonide)¹



Novel START:
As-needed budesonide/formoterol
in mild asthma³

PRACTICAL:^a
An independent study
As-needed budesonide/formoterol^{4,5}

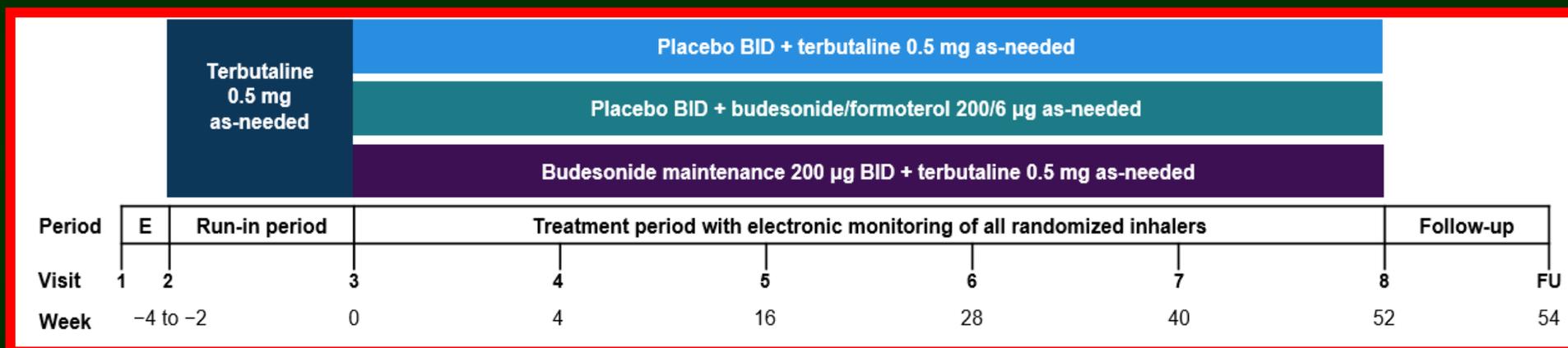
^aPRACTICAL is not an AstraZeneca study.

ICS = inhaled corticosteroid; Novel START = Symbicort Turbuhaler Asthma Reliever Therapy; PRACTICAL = PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist; START = Steroid Treatment As Regular Therapy; SYGMA = SYmbicort Given as needed in Mild Asthma.

1. Reddel HK et al. *Lancet*. 2017;389:157-166; 2. O'Byrne PM et al. *Trials*. 2017;18:12. <https://doi.org/10.1186/s13063-016-1731-4>. Accessed March 4, 2019; 3. Beasley R et al. *Eur Respir J*. 2016;47:981-984; 4. Study ACTRN12616000377437. Australian New Zealand Clinical Trials Registry website. <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370122>. Accessed March 4, 2019; 5. Fingleton J et al. *BMJ Open Resp Res*. 2017;4:e000217. <https://bmjopenrespres.bmj.com/content/4/1/e000217>. Accessed March 7, 2019.

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 + 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 + terbutaline as-needed), severe asthma exacerbation rate, FEV₁, ACQ-5, AQLQ, ICS use, use of as-needed inhalations

Safety: Adverse events

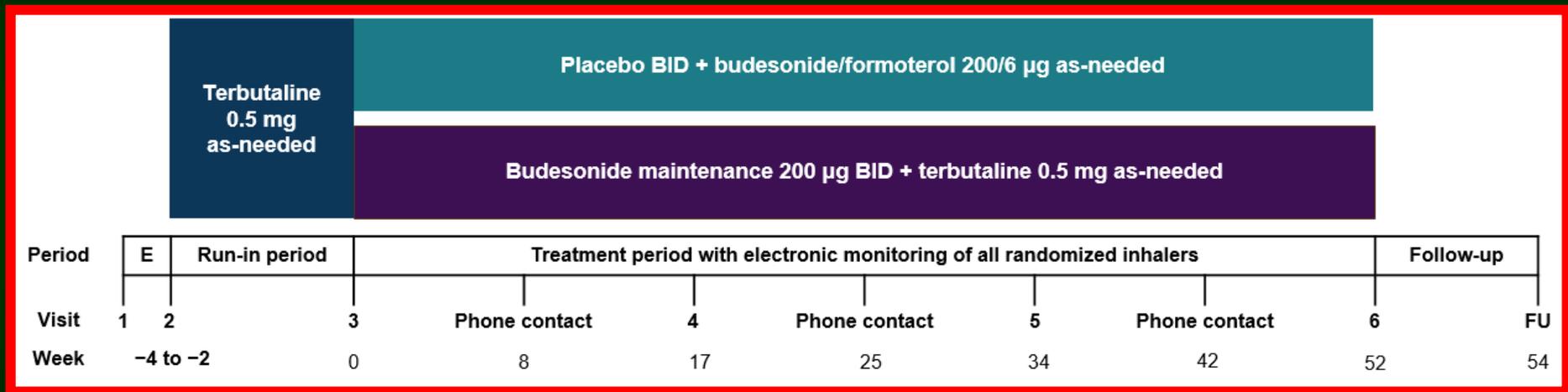
^aAnalysis was based on the full analysis set according to the intention-to-treat principle set forth by the International Conference on Harmonization E9 Working group.³

ACQ-5 = Asthma Control Questionnaire-5; AQLQ = Asthma Quality of Life Questionnaire; E = enrolment; FEV₁ = forced expiratory volume in 1 second; FU = follow-up phone contact; ICS = inhaled corticosteroid; SABA = short-acting β₂-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 March 4, 2019; 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 + 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: FEV₁, ACQ-5, AQLQ, ICS use, use of as-needed inhalations

Safety: Adverse events

^aAnalysis 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; FEV₁ = 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.

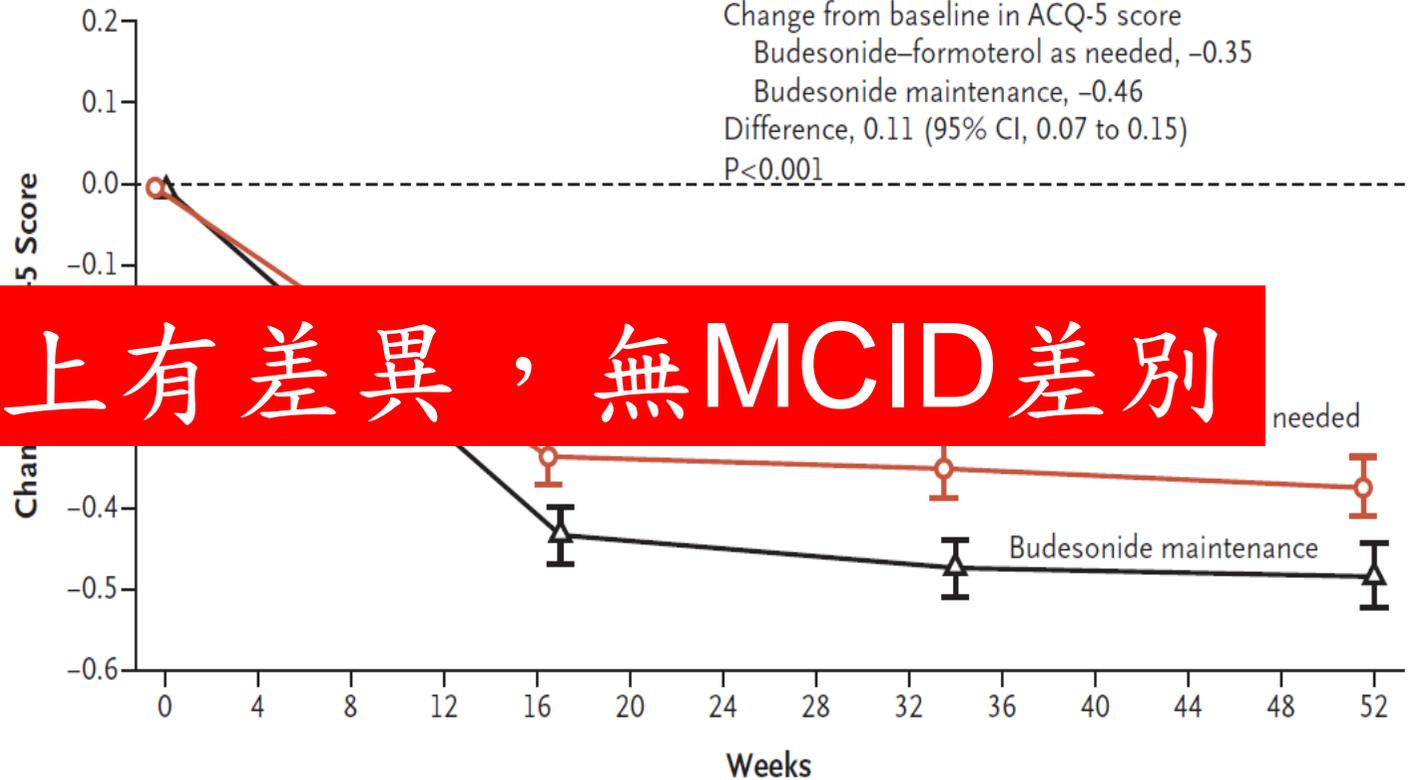
1. O'Byrne PM et al. *Trials*. 2017;18:12. <https://doi.org/10.1186/s13063-016-1731-4>. Accessed March 4, 2019; 2. Bateman ED et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1877-1887; 3. International Conference on Harmonization Steering Committee. Statistical principles for clinical trials. ICH harmonized tripartite guideline. February 5, 1998.

ICS/LABA as needed vs ICS

A Change in Prebronchodilator FEV₁ from Baseline

Change in Prebronchodilator FEV₁ (ml)

B Change in ACQ-5 Score from Baseline



統計上有差異，無MCID差別

No. of Patients

Budesonide-formoterol as needed
 Budesonide maintenance

No. of Patients

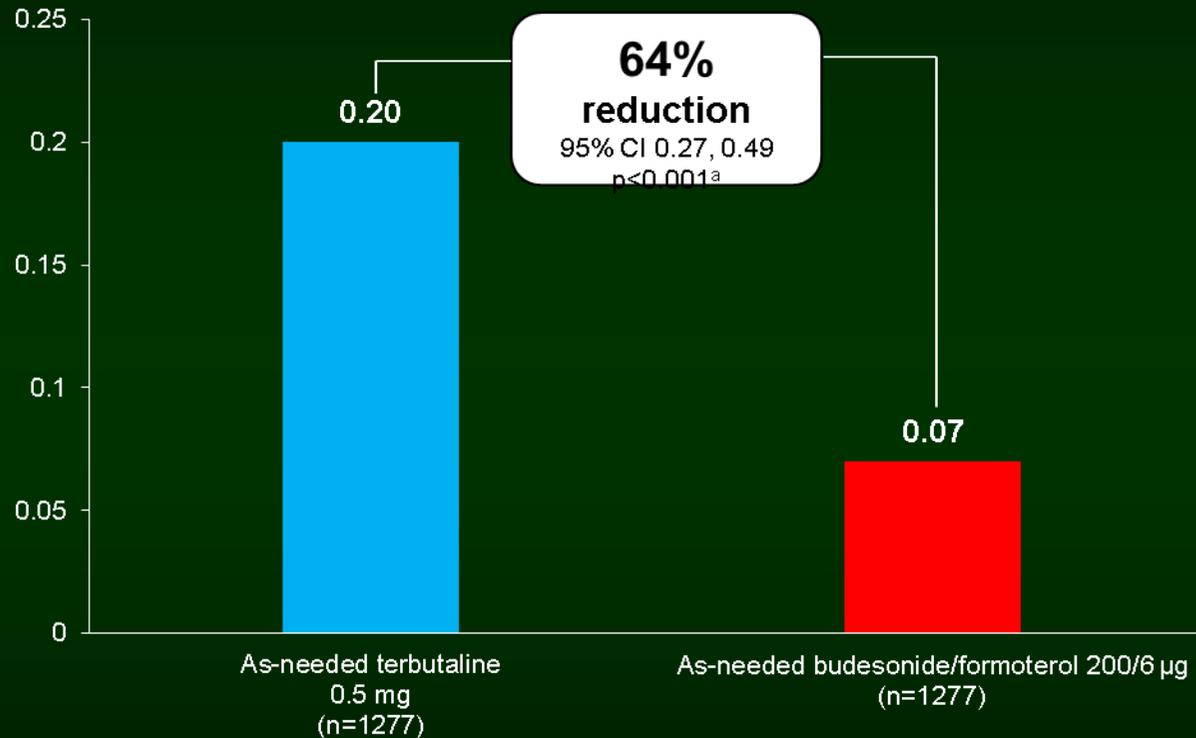
Budesonide-formoterol as needed
 Budesonide maintenance

1941
 1919

1898
 1887

1862
 1840

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

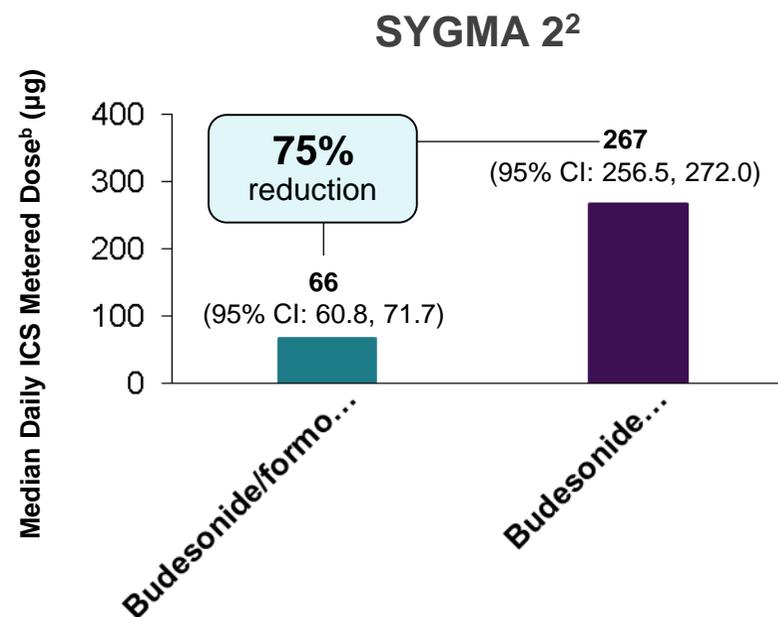
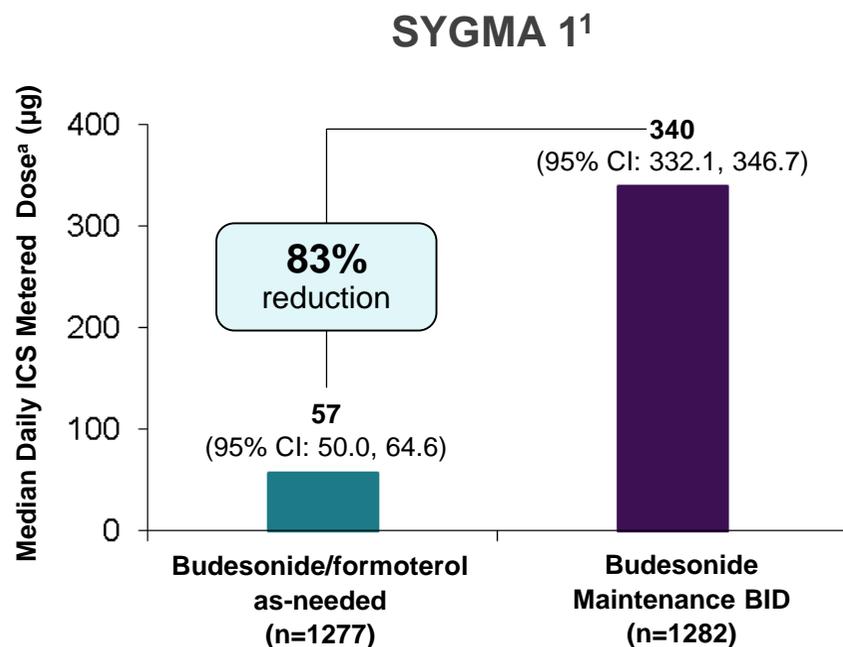
Note: Severe asthma exacerbation rates were analysed by a negative binomial regression model with randomized treatment, pre-study treatment, region, and number of severe exacerbations in the 12 months prior to screening (0 or ≥ 1) as factors.

^ap-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: Comparable Risk of Severe Exacerbations With $\geq 75\%$ Lower Corticosteroid Load



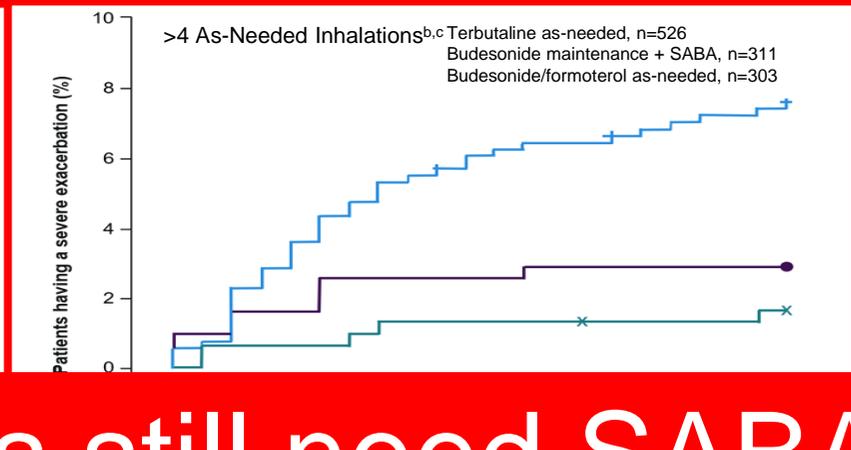
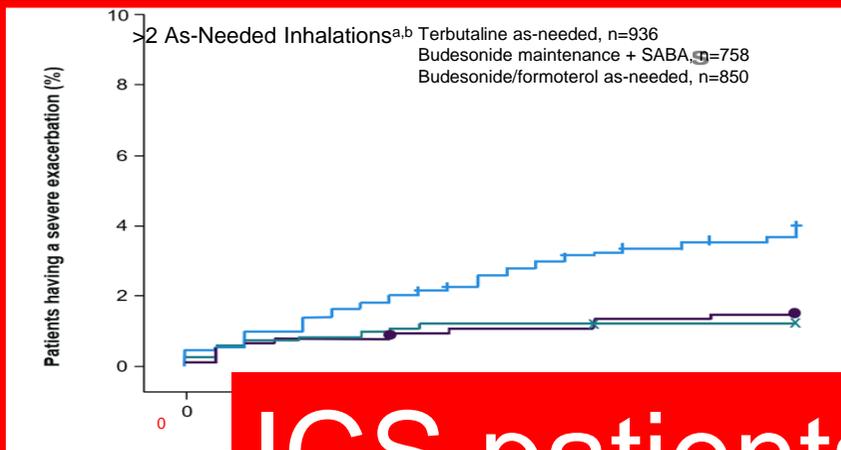
^aIncluding open-label glucocorticoid prescribed for moderate or severe exacerbations or for long-term poor asthma control; ^bIncluding non-blinded ICS use prescribed during severe exacerbations. BID = twice daily; CI = confidence interval; ICS = inhaled corticosteroid; SYGMA = SYmbicort Given as needed 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.

TW-8719-SYM-29/04/2019 For medical reactive use only

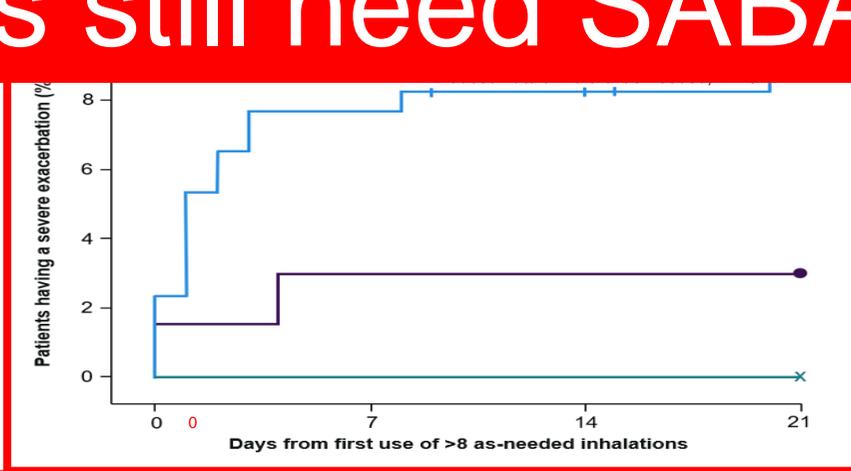
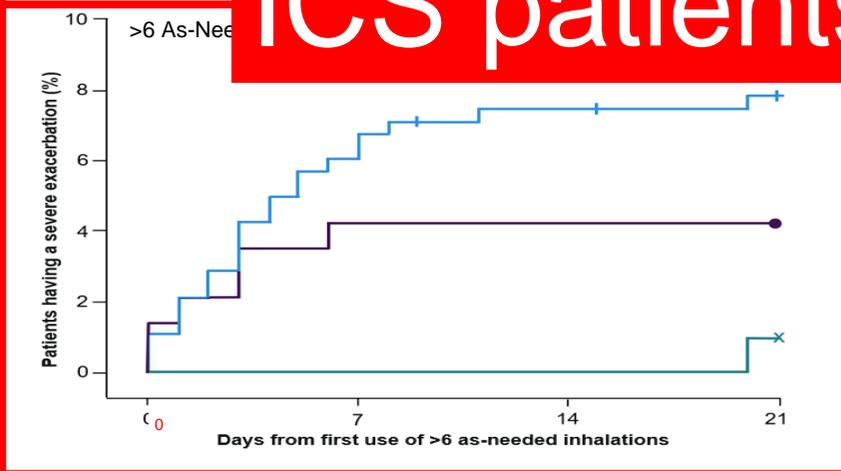
SYGMA 1 Post Hoc Analysis: Severe Exacerbations Within 21 Days of First Day of High Reliever Use (Day 0)

Patients Having a Severe Exacerbation (%)



— Terbutaline as-needed (n=1225)
 — Budesonide maintenance + terbutaline as-needed (n=1237)
 — Budesonide/formoterol as-needed (n=1241)

ICS patients still need SABA use



Days From First Use (Day 0) of As-Needed Inhalations

^aBudesonide/formoterol as-needed vs. terbutaline as-needed, p=0.001; ^bBudesonide/formoterol as-needed vs. budesonide maintenance plus terbutaline as-needed, not significant; ^cBudesonide/formoterol as-needed vs. terbutaline as-needed, p=0.002; ^dHazard ratios not calculated owing to low event rates. SABA = short-acting β_2 -agonist; SYGMA = SYmbicort Given as needed in Mild Asthma.

SYGMA 1 & 2 Conclusions

In patients with mild asthma, budesonide/formoterol as-needed:

- Increased the odds of a well-controlled asthma week compared to terbutaline as-needed (OR 1.14) but not compared to budesonide maintenance¹
- Reduced the rate of severe exacerbations by 64% compared to terbutaline as-needed¹
- Resulted in a comparable rate of severe exacerbations as maintenance budesonide + terbutaline as-needed^{1,2}
- Demonstrated efficacy with a $\geq 75\%$ lower steroid load than the budesonide maintenance arm^{1,2}
- Resulted in fewer days with high reliever use
- Reduced the short-term (21-day) risk of exacerbation versus as-needed terbutaline following a day of high reliever use³

OR = odds 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; 3. O'Byrne P et al. *Eur Respir J.* 2018;52(suppl 62). Abs 1680.

© 2018 AstraZeneca. For medical review use only.

Clinical Programs Investigating Budesonide/Formoterol as an Anti-inflammatory Reliever in Mild Asthma

START Study Analysis: Mild patients benefit from early introduction and long-term ICS (budesonide)¹



Novel START:
As-needed budesonide/formoterol
in mild asthma³

To investigate if an open-label, clinical trial of as-needed budesonide/formoterol in adults previously treated with as-needed SABA only could extend the results from SYGMA to a real world setting

PRACTICAL:^a
An independent study
As-needed budesonide/formoterol^{4,5}

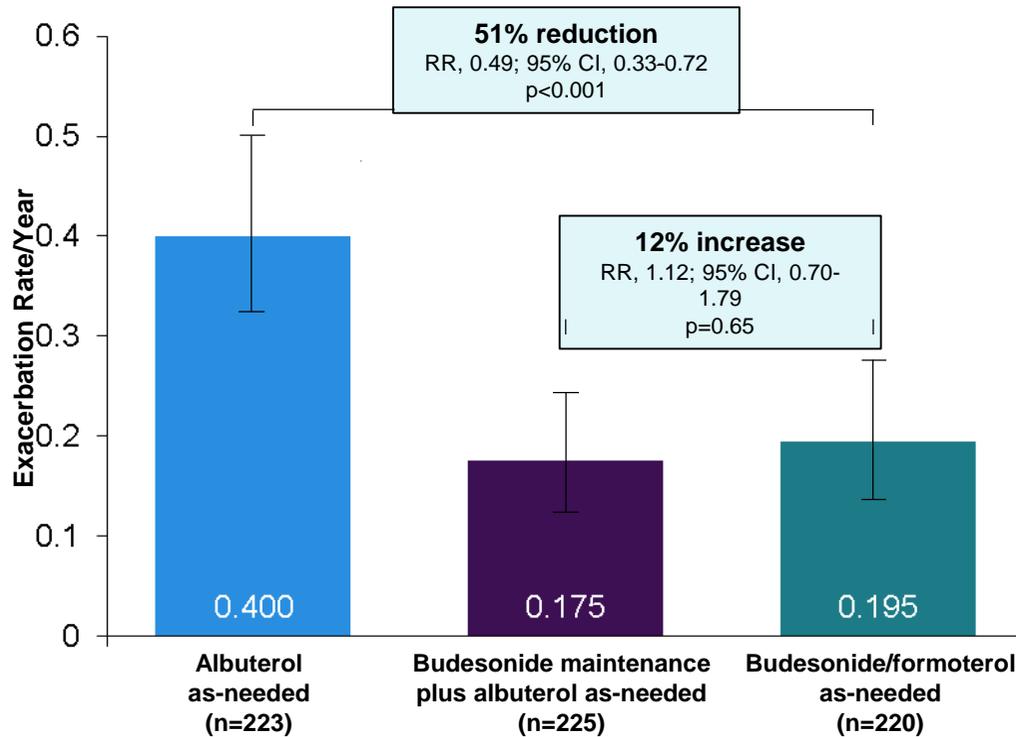
^aPRACTICAL is not an AstraZeneca study.

ICS = inhaled corticosteroid; Novel START = Novel Symbicort Turbuhaler Asthma Reliever Therapy; PRACTICAL = PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist; SABA = short-acting beta₂-agonist; START = Steroid Treatment As Regular Therapy; SYGMA = SYmbicort Given as needed in Mild Asthma.

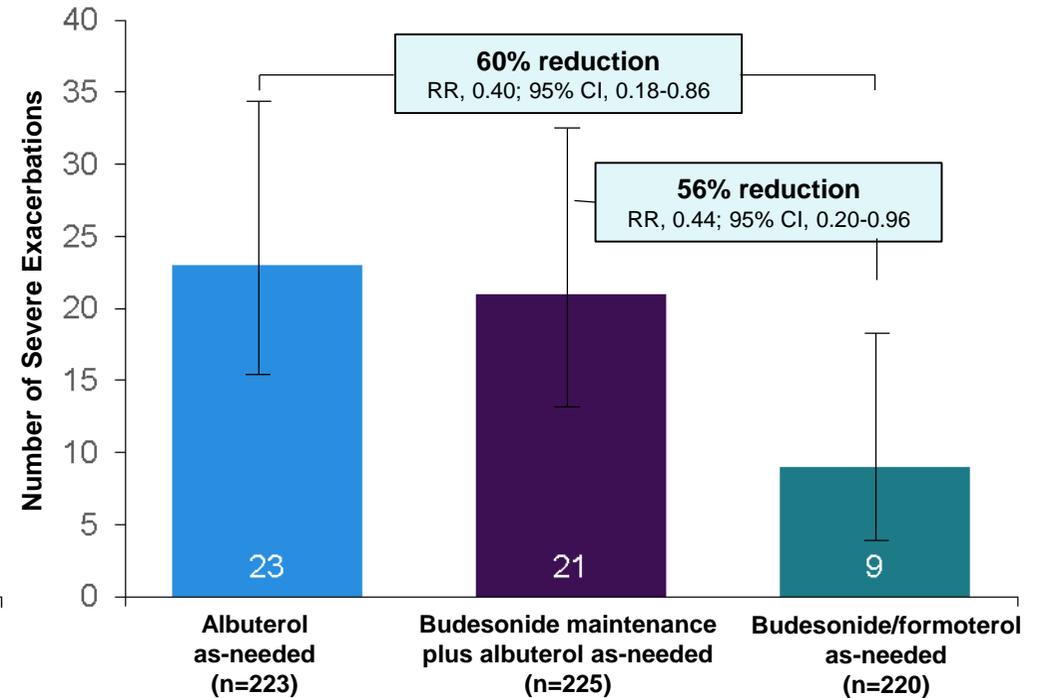
1. Reddel HK et al. *Lancet*. 2017;389:157-166; 2. O'Byrne PM et al. *Trials*. 2017;18:12. <https://doi.org/10.1186/s13063-016-1731-4>. Accessed March 4, 2019; 3. 2. Beasley R et al. *Eur Respir J*. 2016;47:981-984.; 4. Study ACTRN12616000377437. Australian New Zealand Clinical Trials Registry website. <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370122>. Accessed March 4, 2019; 5. Fingleton J et al. *BMJ Open Resp Res*. 2017;4:e000217. <https://bmjopenrespres.bmj.com/content/4/1/e000217>. Accessed March 7, 2019.

Exacerbation Outcomes

Annualized Exacerbation Rate¹
(Primary Outcome)



Number of Severe^a Exacerbations
(Secondary Outcome)^{1b}

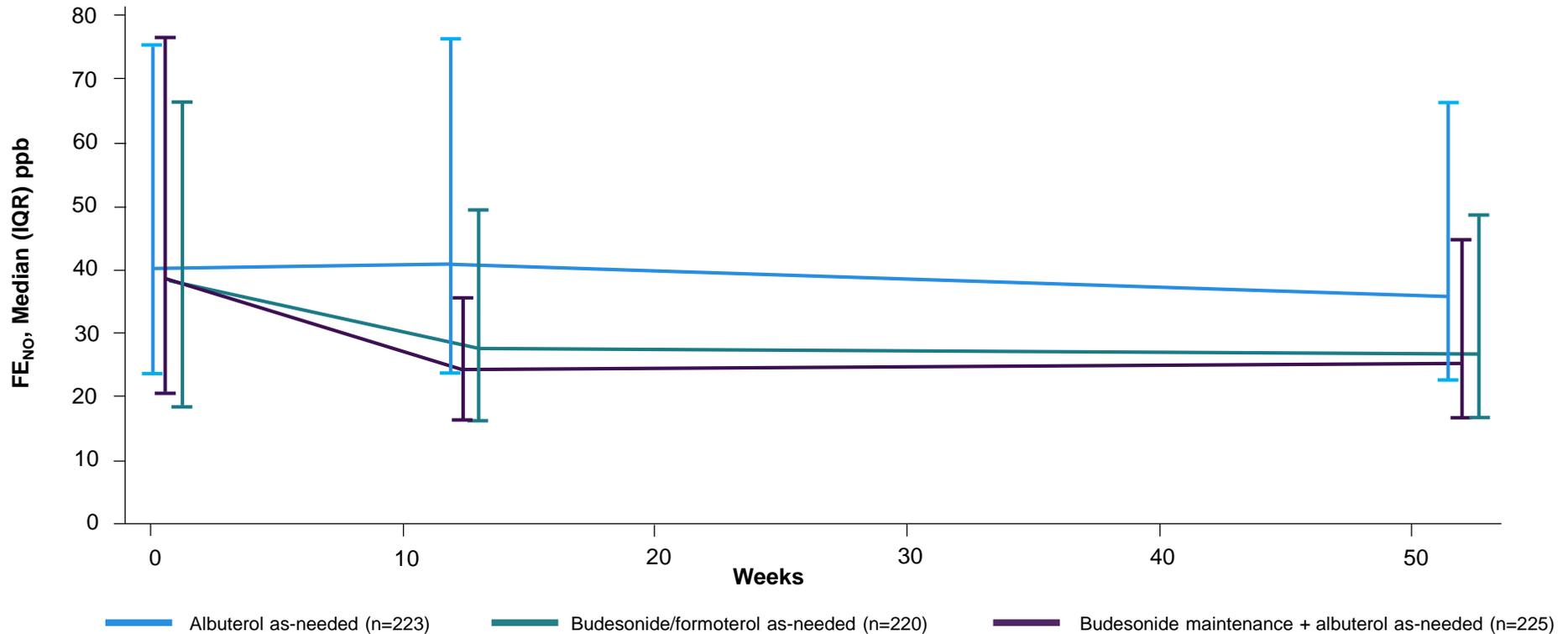


^aFor severe exacerbations, the *relative risk* was estimated as opposed to the *relative rate*, as participants could only have 1 severe exacerbation after which they were withdrawn from the study;² ^bSecondary endpoints were not adjusted for multiplicity. RR = relative rate (left graph); RR = relative risk (right graph).

1. Beasley R et al. *N Engl J Med*. 2019. <http://dx.doi.org/10.1056/NEJMoa1901963>. Accessed 19 May, 2019 ; 2. Beasley R et al. Supplementary appendix. *N Engl J Med*. 2019.

https://www.nejm.org/doi/suppl/10.1056/NEJMoa1901963/suppl_file/nejm1901963_appendix.pdf. Accessed 19 May, 2019. For medical reactive use only. AstraZeneca does not, under any circumstances, promote its products for off-label or unapproved uses

Fraction of Exhaled Nitric Oxide



Ratio of Geometric Mean FE_{NO} at 52 weeks:^a BUD/FORM as-needed vs. albuterol as-needed, 0.83 (95% CI, 0.75-0.91); BUD/FORM as-needed vs. BUD maintenance, 1.13 (95% CI, 1.02-1.25)

^aSecondary endpoints were not adjusted for multiplicity. BUD = budesonide; FE_{NO} = fraction of exhaled nitric oxide; FORM = formoterol; IQR = interquartile range; ppb = parts per billion.

Beasley R et al. *N Engl J Med.* 2019. <http://dx.doi.org/10.1056/NEJMoa1901963>. Accessed 19 May, 2019.

For medical reactive use only. AstraZeneca does not, under any circumstances, promote its products for off-label or unapproved uses

Novel START: Conclusions

In an open-label study of patients with mild asthma who were previously treated with SABA as-needed, treatment with budesonide/formoterol as-needed resulted in the following:

- Compared to albuterol as-needed:
 - Reduced rate of any exacerbation by 51%
 - Reduced rate of severe exacerbations by 60%
- Compared to maintenance budesonide:
 - Comparable rate of any exacerbation
 - Reduced rate of severe exacerbations by 56% at a 52% lower steroid load
 - FeNO reduction is equal (have the same anti-inflammatory effects)

SABA = short-acting β_2 -agonist.

Beasley R et al. *N Engl J Med*. 2019. <http://dx.doi.org/10.1056/NEJMoa1901963> Accessed 19 May, 2019

Clinical Studies Investigating Budesonide/Formoterol as an Anti-inflammatory Reliever Offer a Breadth of Data in Mild Asthma

START Study Analysis: Patients with mild asthma benefit from early introduction and long-term ICS (budesonide)¹



SYGMA 1 and 2 were 52-week, Phase III, multicenter, randomized, double-blind, placebo-controlled studies that evaluated as-needed budesonide/formoterol dry powder inhaler as an anti-inflammatory reliever in patients with mild asthma²

Novel START:

Pragmatic, real-world study
As-needed budesonide/formoterol³

Investigate if an open-label, clinical trial of as-needed budesonide/formoterol in adults previously treated with as-needed SABA only could extend the results from SYGMA to a real world setting

PRACTICAL:^a

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

Open-label trial that investigated if as-needed budesonide/formoterol in adults with mild to moderate asthma previously treated with as-needed SABA only or ICS with SABA as-needed could extend to a real world setting

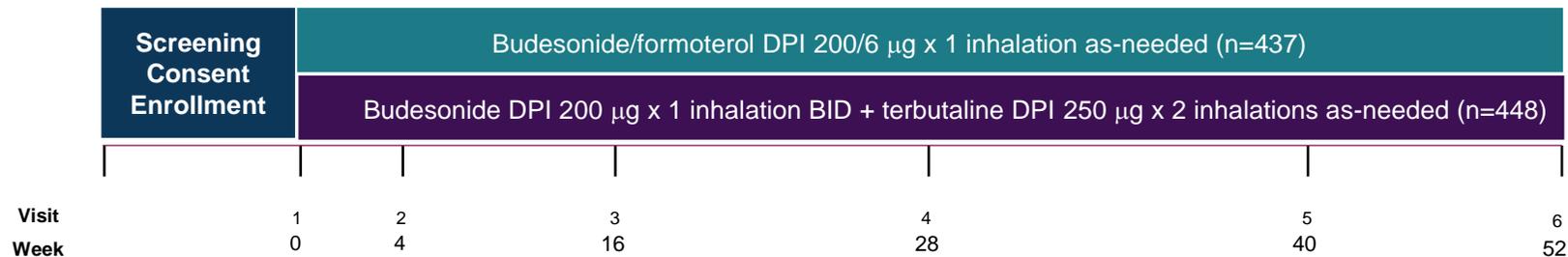
^aPRACTICAL was an independent study funded by the Health Research Council of New Zealand.

ICS = inhaled corticosteroid; Novel START = Novel Symbicort Turbuhaler Asthma Reliever Therapy; PRACTICAL = PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist; SABA = short-acting β_2 -agonist; START = Steroid Treatment As Regular Therapy; SYGMA = SYmbicort Given as needed in Mild Asthma

1. Reddel HK et al. *Lancet*. 2017;389:157-166; 2. O'Byrne PM, et al. *Trials*. 2017;18:12. <https://doi.org/10.1186/s13063-016-1731-4>. Accessed August 26, 2019.; 3. Beasley R et al. *Eur Respir J*. 2016;47:981-984.; 4. 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). Accessed August 26, 2019.

A Pragmatic, Real-World Study Design^{1,2}

52-week, **pragmatic**, randomized, controlled, open-label, parallel-group, multicenter study (N=890) to compare the long-term efficacy and safety of budesonide/formoterol anti-inflammatory reliever therapy compared with maintenance budesonide plus as-needed SABA in patients with mild to moderate asthma **previously treated with SABA alone or SABA plus ICS**



Definition of severe exacerbation was based on ATS/ERS criteria:

Worsening asthma resulting in ≥ 1 of the following:

- Use of systemic corticosteroids for at least 3 days due to asthma or
- Hospitalization or ED visit for asthma requiring systemic corticosteroids

Primary efficacy endpoint^a: Annualized severe exacerbation rate

Key secondary endpoints^a: Number of severe exacerbations; time to first severe asthma exacerbation; number of moderate to severe exacerbation rate; time to first moderate or severe exacerbation; FeNO (parts per billion); ACQ-5

Safety: Adverse events and serious adverse events

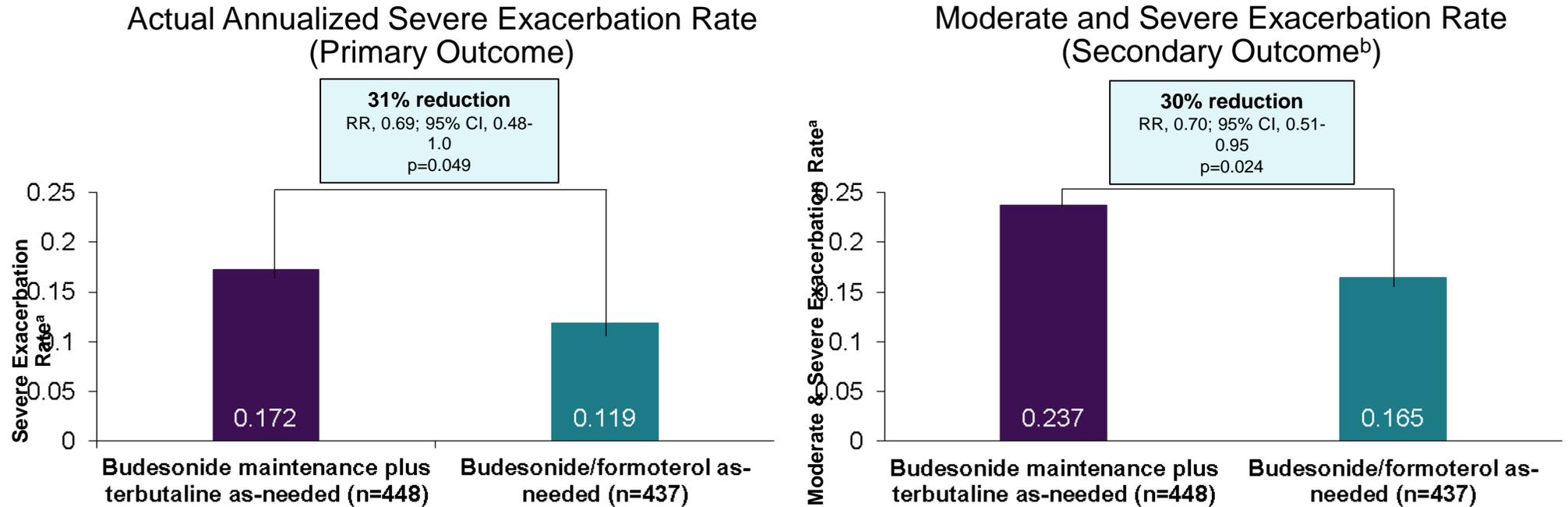
^aAnalyses were intention-to-treat.

ACQ-5 = Asthma Control Questionnaire-5; ATS = American Thoracic Society; DPI = dry powder inhaler; ED = emergency department; ERS = European Respiratory Society; FeNO = fraction of exhaled nitric oxide; ICS = inhaled corticosteroid; SABA = short-acting β_2 -agonist.

1. Fingleton J, et al. *BMJ Open Resp Res*. 2017;4:e000217. <https://bmjopenrespres.bmj.com/content/4/1/e000217>. Accessed August 26, 2019. 2. 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). Accessed August 26, 2019.

Budesonide/Formoterol As-Needed Reduced Exacerbation Rates



Prespecified subgroup analyses did not identify any effect modification for any variable with respect to severe exacerbation

^aper patient per year; ^bSecondary endpoints were not adjusted for multiplicity.

RR = relative rate.

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). Accessed August 26, 2019.

Symptom Control was Similar between Budesonide/Formoterol As-Needed and Budesonide Maintenance plus SABA

ACQ-5 Scores

Across all time points, ACQ-5 score^{a,b} was similar between treatment groups (mean difference, 0.06; 95% CI, -0.005 to 0.12, $p=0.07$)¹

MCID

Across all time points, the mean change in ACQ-5 score was smaller than the MCID of 0.5 unit.²

Subgroup Analyses

Prespecified subgroup analyses found consistent treatment effect on ACQ-5 for all variables studied except for the highest quartile of baseline blood eosinophils^c which favored-maintenance budesonide, but did not meet the minimal clinically important difference^d.¹

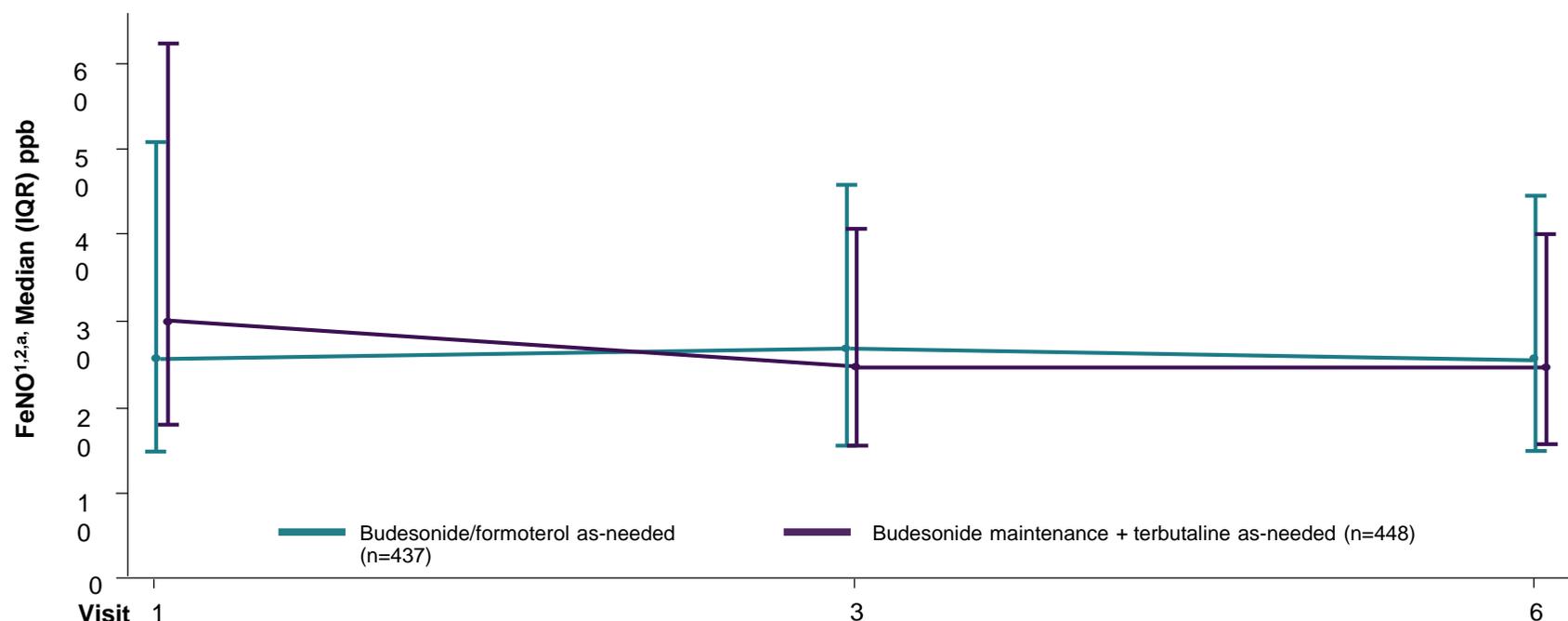
ACQ-5 = Asthma Control Questionnaire; MCID = minimal clinically important difference; SABA = short-acting β_2 -agonist.

^aThe mean of 5 questions about asthma symptoms during the previous week, each scored on a 7 point scale between 0 (no impairment) and 6 (maximum impairment); ^bSecondary endpoints were not adjusted for multiplicity; ^c $\geq 0.4 \times 10^9/L$; ^d ≥ 0.5 unit change.

1. 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). Accessed August 26, 2019; 2. Hardy J, et al. Supplemental content. *Lancet*. 2019. [http://dx.doi.org/10.1016/S0140-6736\(19\)31994-4](http://dx.doi.org/10.1016/S0140-6736(19)31994-4). Accessed August 26, 2019.

No Clinically Relevant Difference in Fraction of Exhaled Nitric Oxide was Observed at Month 12

No clinically relevant difference in FeNO was observed between budesonide/formoterol as-needed (26 ppb) and maintenance budesonide (25 ppb) at Month 12^{1,a}



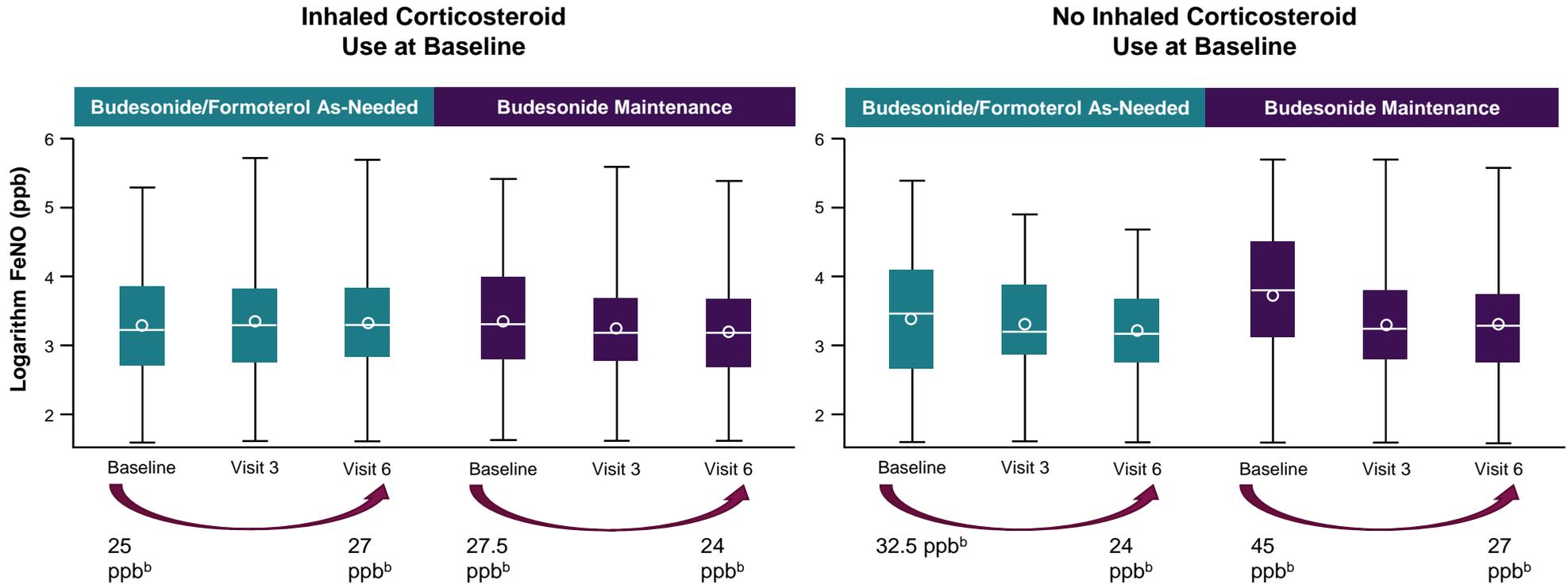
Ratio of Geometric Mean FeNO Across Time Points¹: BUD/FORM as-needed vs. BUD maintenance, 1.13 (95% CI, 1.07-1.21), $p < 0.001^a$

^aSecondary endpoints were not adjusted for multiplicity.

BUD = budesonide; FeNO = fraction of exhaled nitric oxide; FORM = formoterol; IQR = interquartile range; ppb = parts per billion.

1. 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). Accessed August 26, 2019; 2. Hardy J, et al. Supplemental content. *Lancet*. 2019. [http://dx.doi.org/10.1016/S0140-6736\(19\)31994-4](http://dx.doi.org/10.1016/S0140-6736(19)31994-4). Accessed August 26, 2019.

Anti-Inflammatory Effects of Budesonide/Formoterol As-Needed Confirmed in Steroid Naïve^a Patients



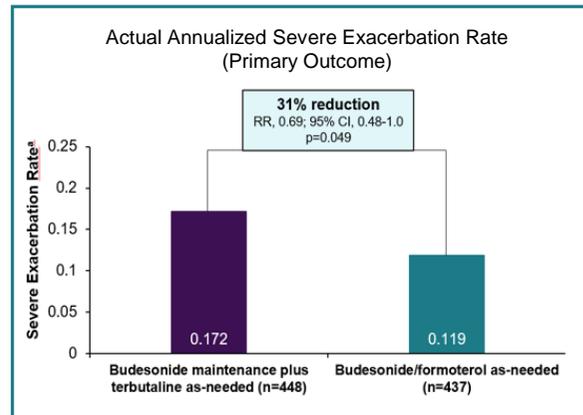
^asteroid naïve at baseline; ^bmedian FeNO

FeNO = fraction of exhaled nitric oxide; ppb = parts per billion.

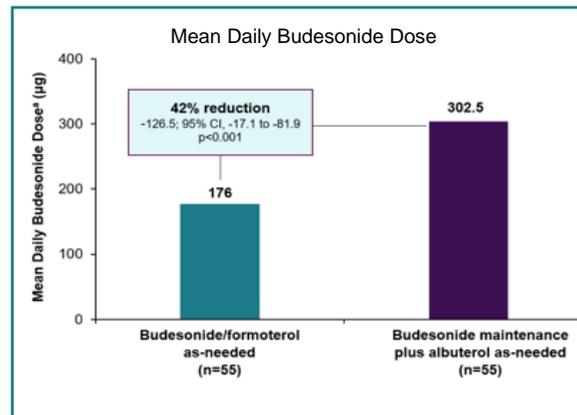
Hardy J, et al. Supplemental content. *Lancet*. 2019. [http://dx.doi.org/10.1016/S0140-6736\(19\)31994-4](http://dx.doi.org/10.1016/S0140-6736(19)31994-4). Accessed August 26, 2019.

Summary – Budesonide/Formoterol As-Needed Reduced Severe Exacerbations with Similar Symptom Control in a More Real-World Setting

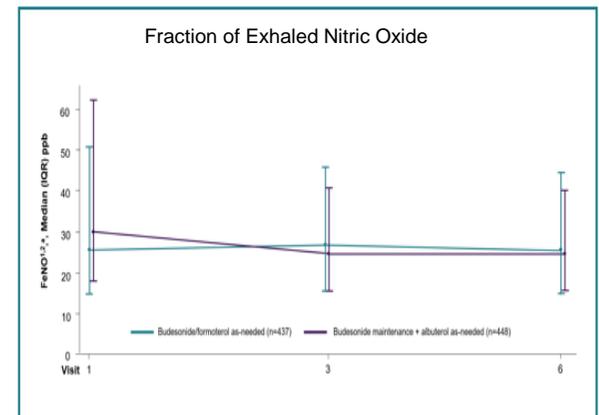
In a 52-week, open-label, **pragmatic study** of patients with mild to moderate asthma previously treated with SABA as-needed \pm maintenance ICS, Budesonide/Formoterol As needed:



Decreased severe and moderate and severe exacerbation rates with similar asthma control per ACQ-5 scores between groups



42% lower mean daily steroid load



No clinically significant difference in FeNO between groups

ACQ-5 = Asthma Control Questionnaire; FeNO = fraction of exhaled nitric oxide; ICS = inhaled corticosteroid; SABA = short-acting β_2 -agonist.

Hardy J, et al. *Lancet*. 2019. <http://dx.doi.org/10.1016/>

As needed ICS/LABA in mild asthma: Pro

- Decreased SABA use, decreased SABA-related adverse effects
- Decreased A.E. rate, exp. severe exacerbation
- Decreased ICS consumption in asthma patients
- Still have anti-inflammatory effects in airway
- **Limitation: step 2 mild asthma patients enrolled in three trials (indirect evidence in step 1)**

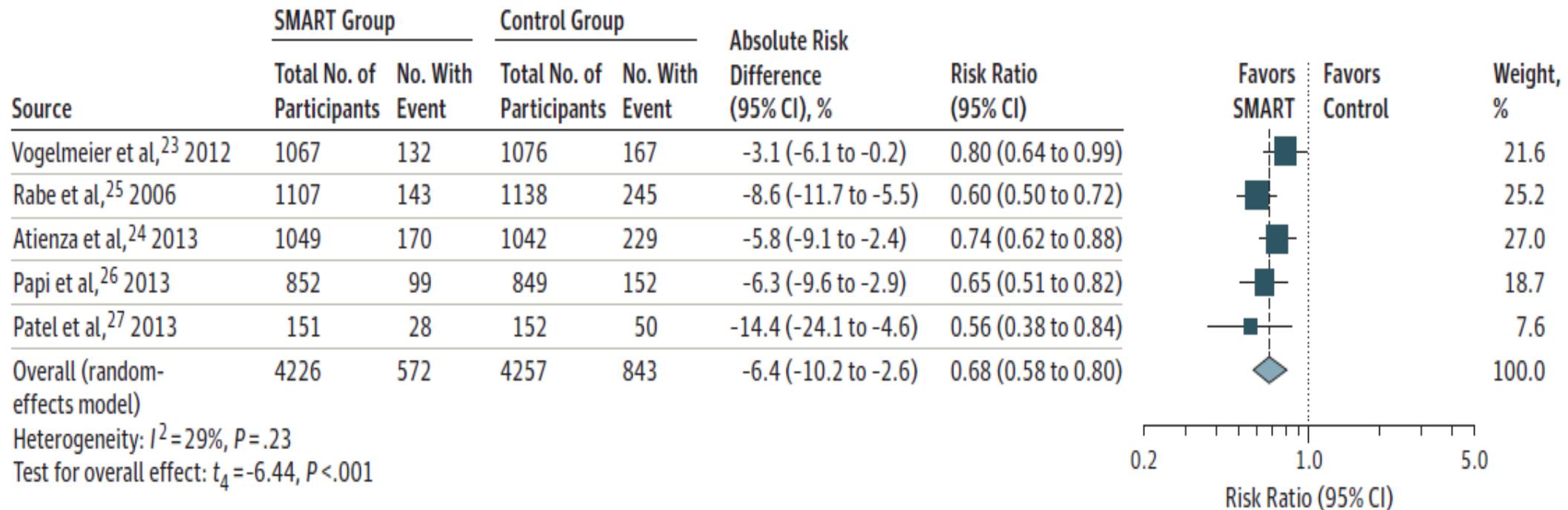
These findings suggest that titrating the dose of inhaled corticosteroids through as-needed use of a combination inhaler which also delivers a fast-onset LABA is more effective for prevention of severe exacerbations than maintenance inhaled corticosteroids with as-needed SABA in patients with mild to moderate asthma. The timing of inhaled corticosteroid administration is probably a more important determinant of efficacy than the total dose, and a symptom-driven increase in the dose of inhaled corticosteroid in worsening asthma might lead to resolution of an exacerbation before it becomes severe enough for the patient to seek medical review. The co-administration of LABA rather than SABA reliever therapy would also contribute to a reduction in severe exacerbation risk in worsening asthma¹⁷

Treatment Outcomes: SMART vs. Conventional Best Practice (N=1538)

	SMART vs. CBP
ER visits or hospitalizations	↓ 41%
As-needed inhalations	↓ 15%
Asthma medication cost	↓ 28%
Asthma total cost	↓ 23%

SMART for Asthma Exacerbation

Figure 2. Association of SMART With Exacerbations Requiring Systemic Corticosteroids, Hospitalization, or ED Visits Among Patients Aged 12 Years or Older vs the Same Dose of Inhaled Corticosteroids and LABA Controller Therapy



POOR ASTHMA CONTROL ↑ RISK OF AE

Pooled analysis of 5 SMART studies

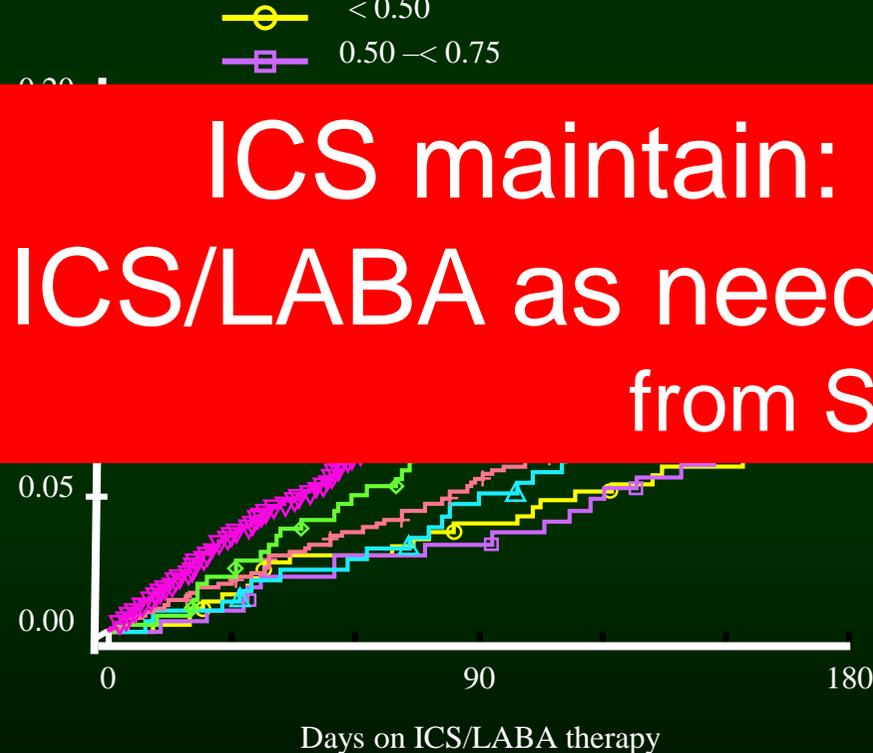
ACQ-5: asthma control questionnaire

ACQ-5 cut-points:

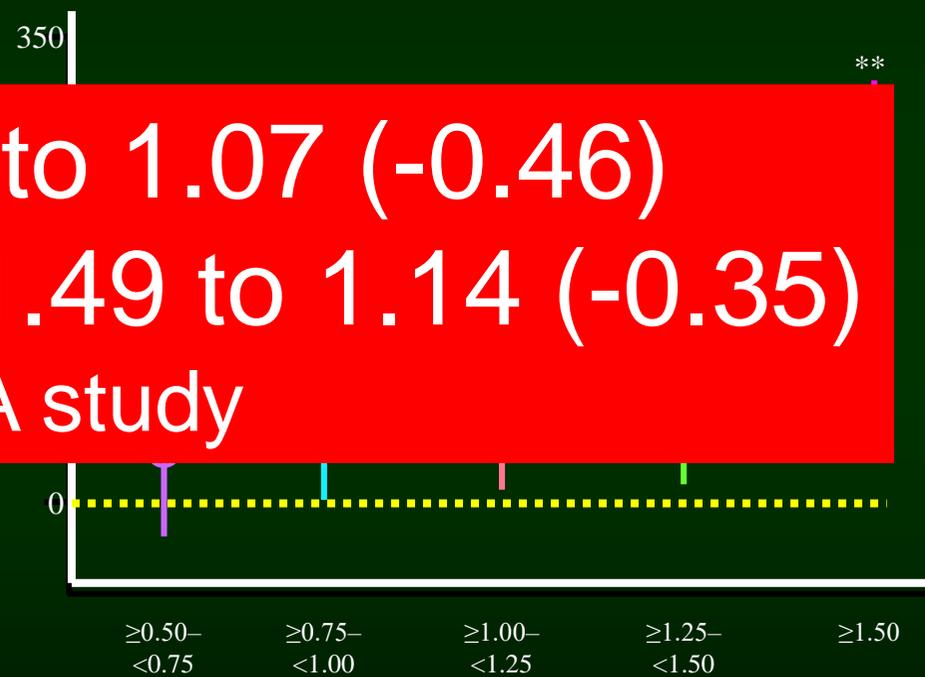
- < 0.50
- 0.50 – < 0.75

↑ Exacerbation rate vs ACQ < 0.5

Exacerbations/patient



Exacerbation rate (%)

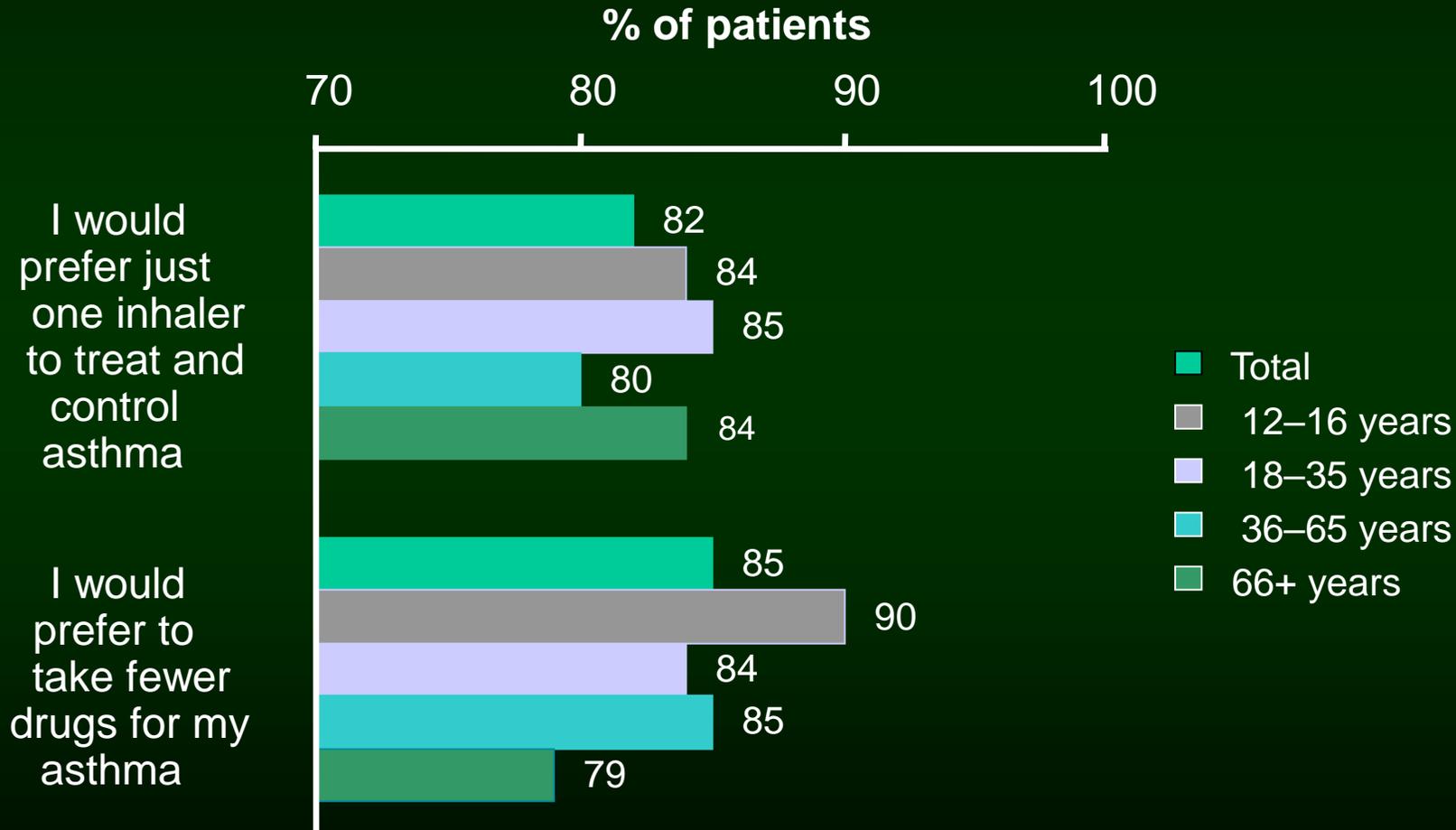


ICS maintain: 1.53 to 1.07 (-0.46)
ICS/LABA as needed: 1.49 to 1.14 (-0.35)
from SYGMA study

ACQ-5 score in run-in as a guide to exacerbation rate compared with patients with ACQ-5 score < 0.5

Share-Decision Making (SDM)

Patients would prefer a single inhaler to treat and control their asthma



SDM:

你為何未遵照醫師指示用藥？

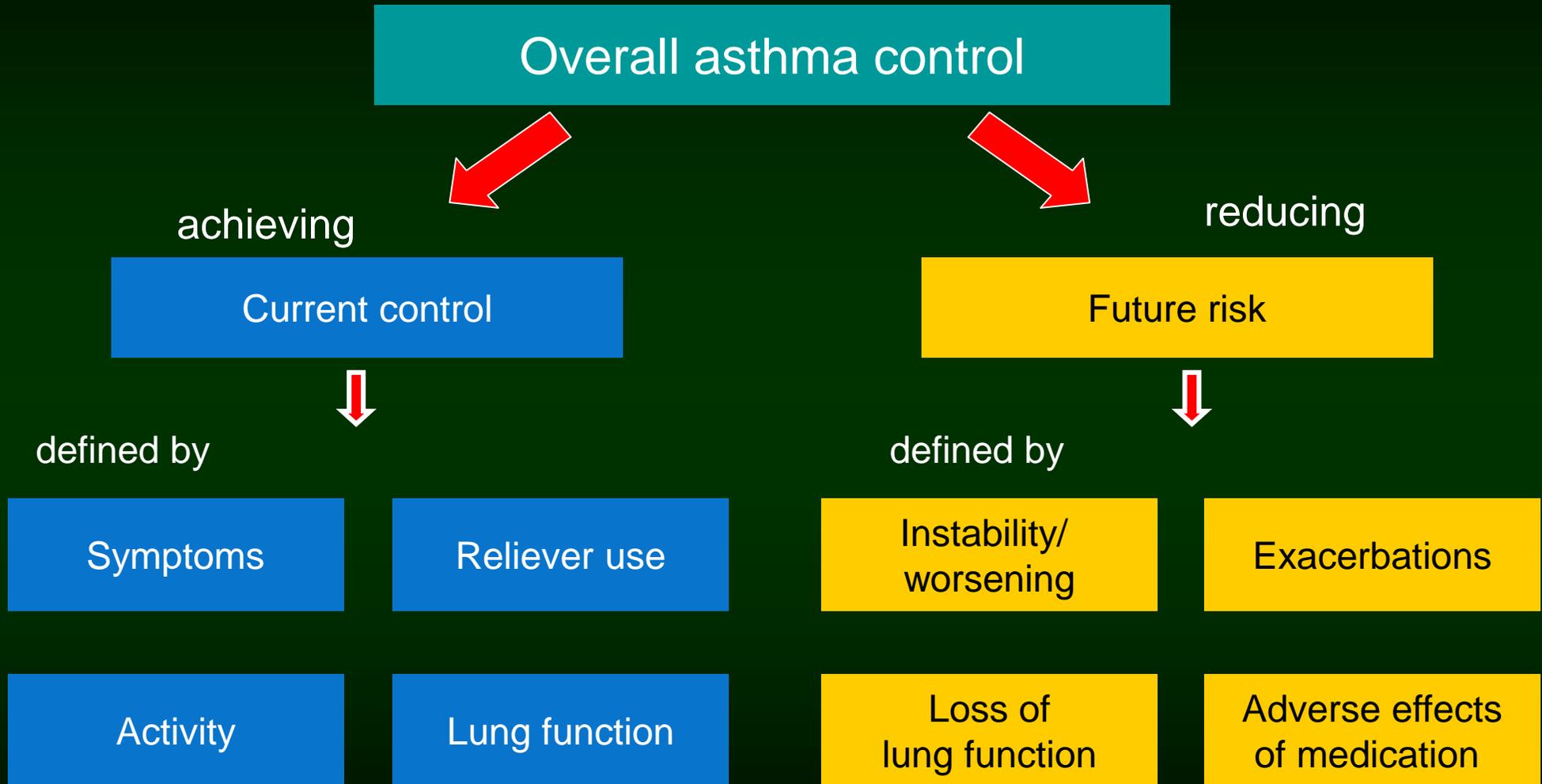
- 擔心藥物副作用 97%

As needed ICS/LABA

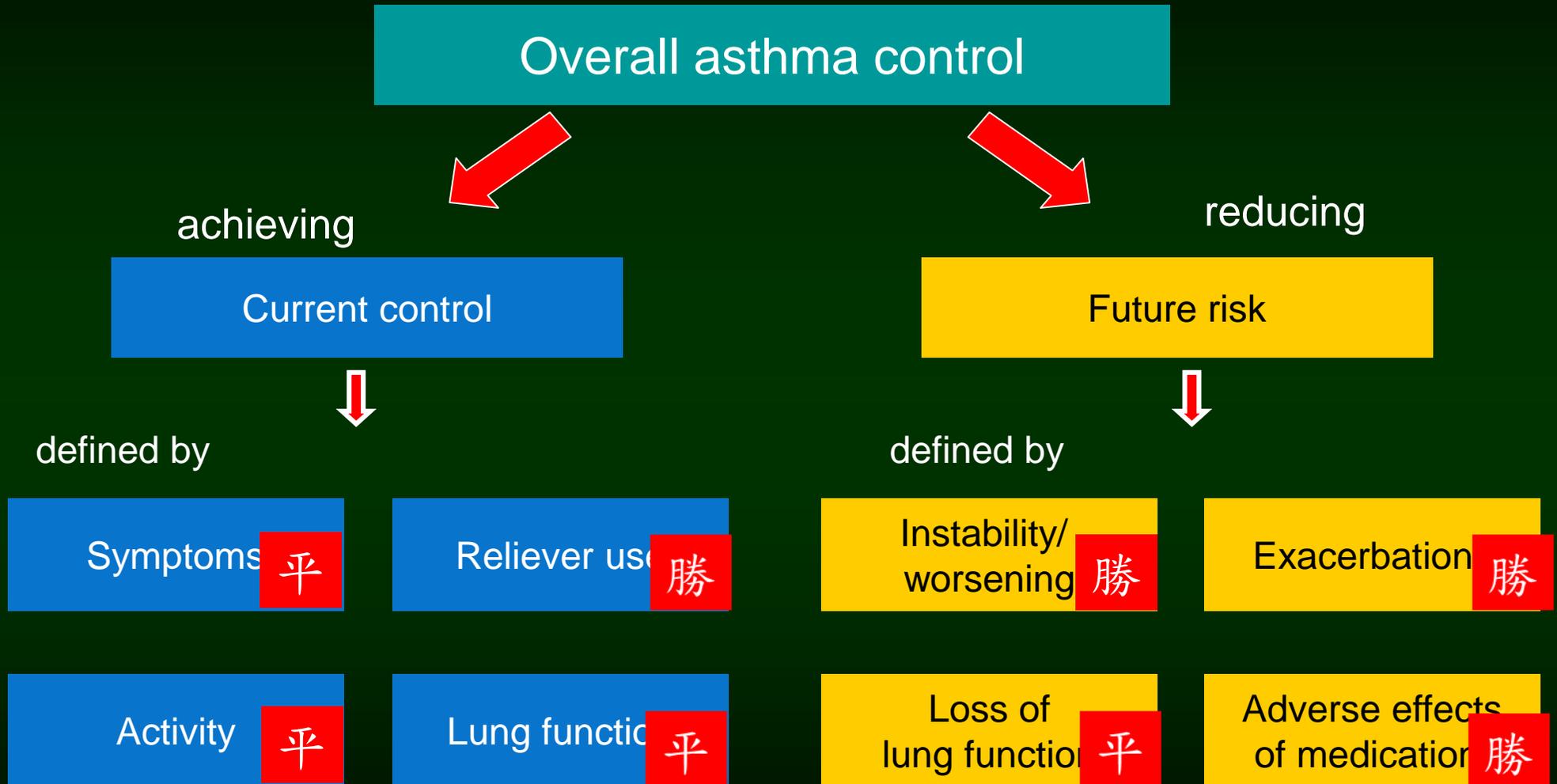
在mild asthma較符合臨床病患感受

- 不知道用藥的重要性 72%
- 沒有症狀就不用藥 68%

The goal of asthma management



As needed ICS/LABA vs. ICS



NAEPP. Expert Panel Report 3. 2007.

Taylor DR, et al. Eur Respir J 2008; 32(3):545-554

Conclusion:

As needed ICS/LABA in mild asthma: Pro

- Decreased SABA use, decreased SABA-related adverse effects
- Decreased A.E. rate, esp. severe exacerbation
- Decreased ICS consumption in asthma patients
- Still have anti-inflammatory effects in airway
- Symptoms, lung function: no MCID, have same effects
- Share-decision making: Patient conception and improve adherence
- **Step 2 patients have the benefits, then step 1 patients have more efficacy**

Thanks for Your Attention !