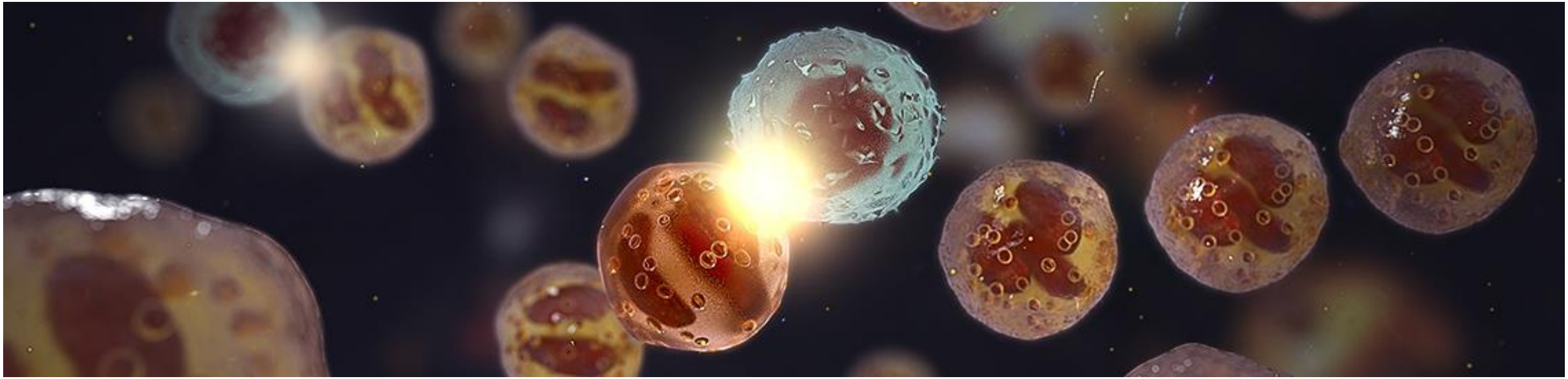
Efficacy When It Matters
Asthma

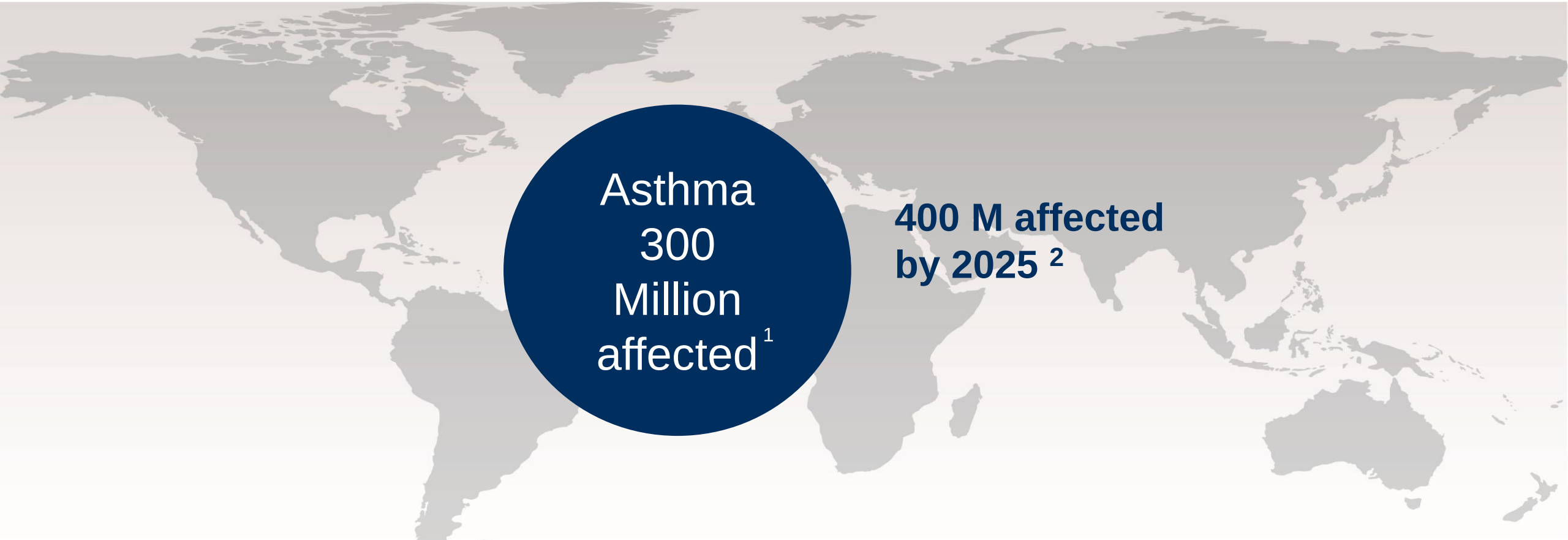
Symbicort
budesonide/formoterol

Hossein Esmaeilzadeh
Associate Prof. of Allergy and Clinical Immunology. SUMS



SYM-401-SK-0122-0124-IRN

Global Asthma Burden



400 M affected by 2025 [2]

Many Asthmatic patients are struggling to breathe…

1. Global Initiative for Asthma. Available at: http://ginasthma.org/2019-pocket-guide-for-asthma-management-and-prevention Last accessed December 2019 2. Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy2004;59:469-78

Asthma control in adults in the Middle East and North Africa: Results from the ESMAA study

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

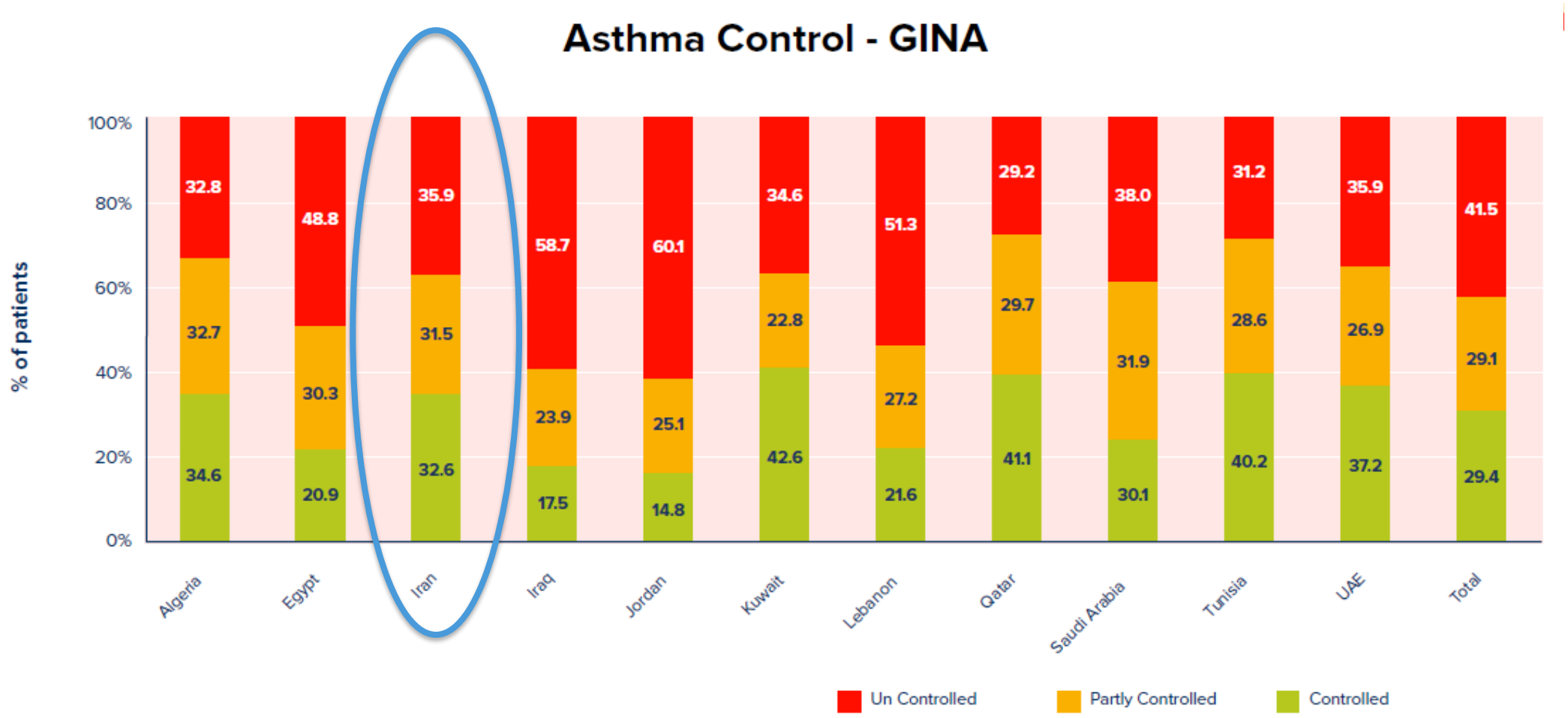
Asthma control in adults in the Middle East and North Africa: Results from the ESMAA study

Hesham Tarraf[a,*], Hamdan Al-Jahdali[b], Abdul Hameed Al Qaseer[c], Anamarija Gjurovic[d], Houria Haouichat[e], Basheer Khassawneh[f], Bassam Mahboub[g], Roozbeh Naghshin[h], François Montestruc[i], Naser Behbehani[j]

Tarraf H, Al-Jahdali H, Al Qaseer AH, Gjurovic A, Haouichat H, Khassawneh B, Mahboub B, Naghshin R, Montestruc F, Behbehani N. Asthma control in adults in the Middle East and North Africa: Results from the ESMAA study. Respiratory medicine. 2018 May 1;138:64-73.

Asthma control in adults in the Middle East and North Africa: Results from the ESMAA study

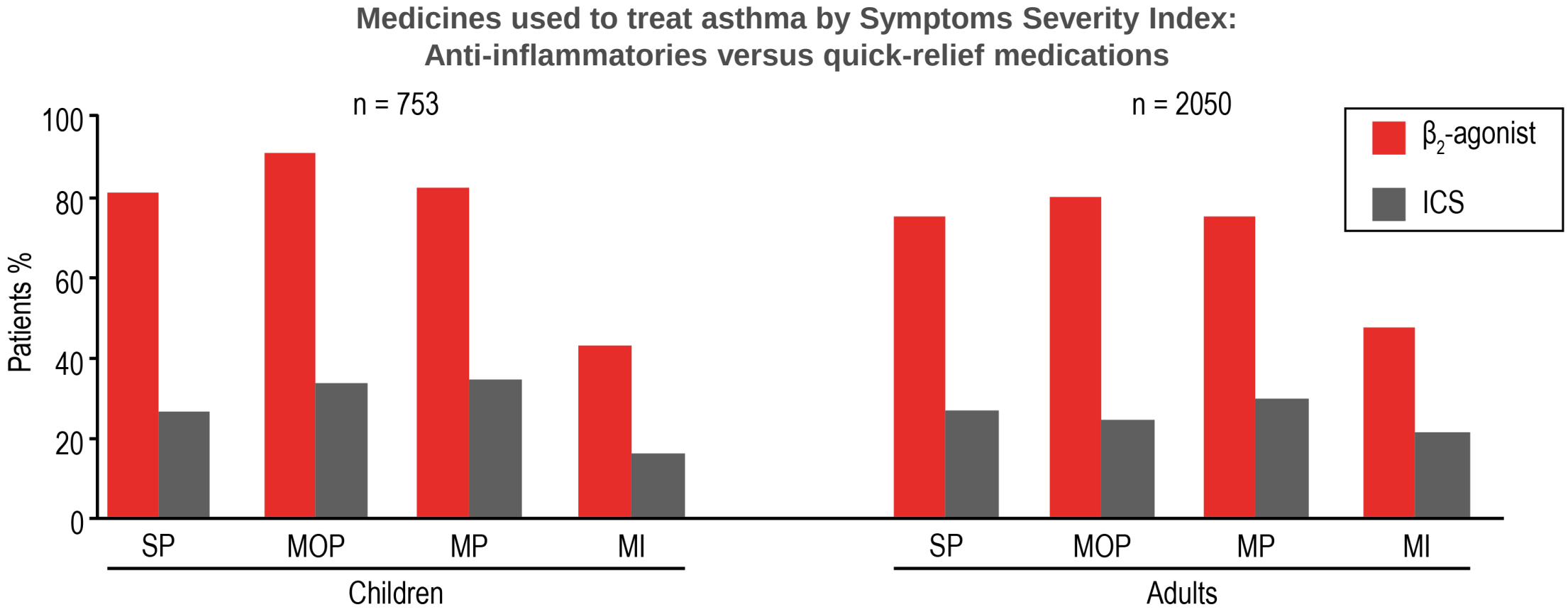
- Overall **7236** eligible patients were included in **577** sites between June 2014 and December 2015 (median 10 patients/site).



Tarraf H, Al-Jahdali H, Al Qaseer AH, Gjurovic A, Haouichat H, Khassawneh B, Mahboub B, Naghshin R, Montestruc F, Behbehani N. Asthma control in adults in the Middle East and North Africa: Results from the ESMAA study. Respiratory medicine. 2018 May 1;138:64-73.

Over-reliance on SABA occurs in children and adults and is irrespective of asthma severity

- In the AIRE survey, ~3 times as many patients were using rescue medication (SABA) than their maintenance inhaler (ICS) over a 4-week period



ICS, inhaled corticosteroid; MI, mild intermittent; MP, mild persistent; MOP, moderate persistent; SABA, short-acting β_2-agonist; SP, severe persistent.

Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. European Respiratory Journal. 2000 Nov 1;16(5):802-7.

NRAD report reveals excessive prescribing of SABAs and under-prescribing of preventer medication

- The NRAD report was an investigation of recent asthma deaths in the UK by the Royal College of Physicians

Evidence of excessive prescribing of reliever medication

39% of patients who were on short-acting relievers at the time of death had been prescribed more than

12 short-acting reliever inhalers in the year before they died

4% had been prescribed more than

50 reliever inhalers

Evidence of under-prescribing of preventer medication

To comply with recommendations, most patients would usually need at least

12 preventer prescriptions per year

38% of patients on preventer inhalers* received fewer than

4 inhalers in the year leading up to their death…

and **80%** received fewer than 12 preventer inhalers

*Of those patients for which the number of prescriptions was known. Among 189 patients who were on short-acting relievers at the time of death, the number of prescriptions was known for 165. Among 168 patients on preventer inhalers at the time of death, either as stand-alone or in combination, the number of prescriptions was known for 128.

NRAD, National Review of Asthma Deaths; SABA, short-acting β_2-agonist

Royal College of Physicians. *Why Asthma Still Kills? The National Review of Asthma Deaths (NRAD)* [online] 2014. Available from: https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills [Last accessed: December, 2019].

SABINA Programme: To establish global patterns of SABA and maintenance therapy use in asthma, and their relation to asthma outcomes

Largest real-world data analysis on SABA and maintenance therapy globally

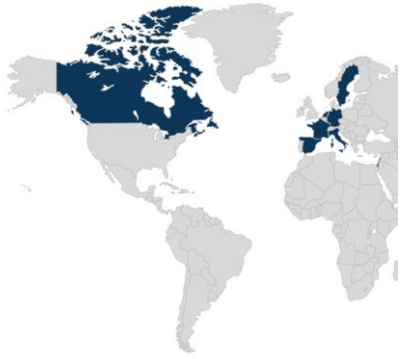
Flexible framework with one core protocol and core requirements across pillars to ensure scientific alignment[1]

SABINA I

Retrospective, observational database studies

UK

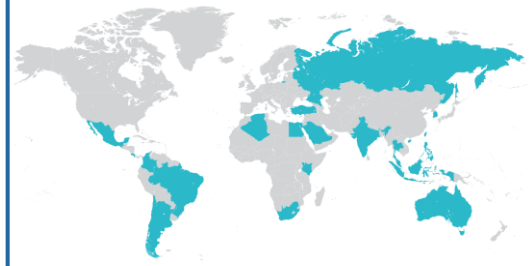
SABINA II



Retrospective, observational database studies

6 EU countries plus Canada, Israel

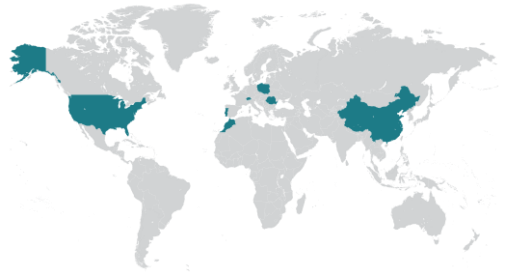
SABINA III



Cross-sectional study

24 countries across 5 continents

SABINA +



Multi-design studies

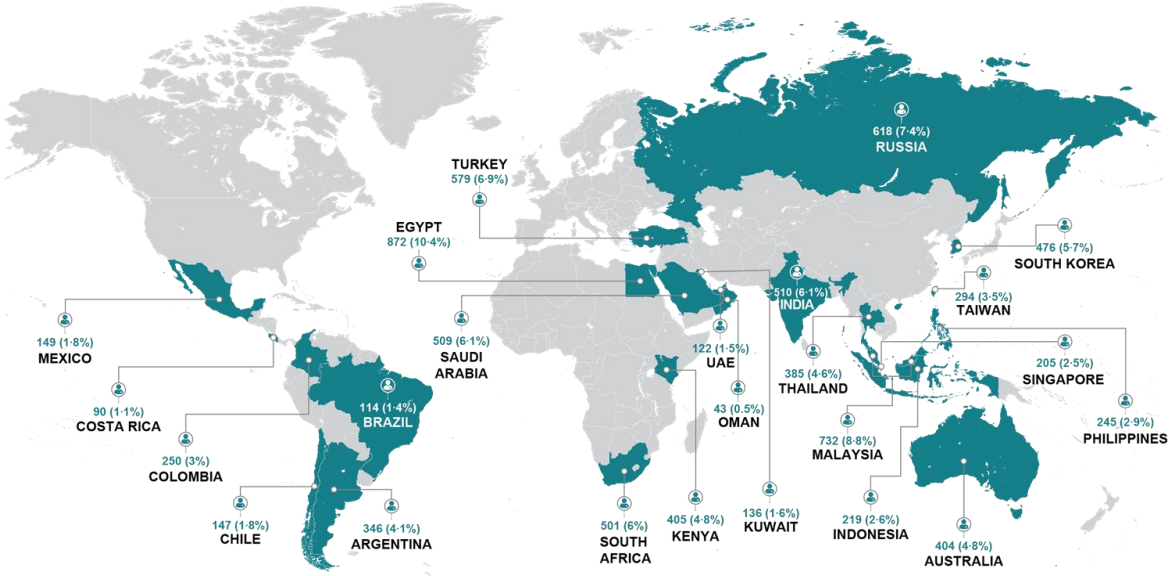
China, Hong Kong, Morocco, Poland, Portugal, Romania, Switzerland, US; more to enroll soon

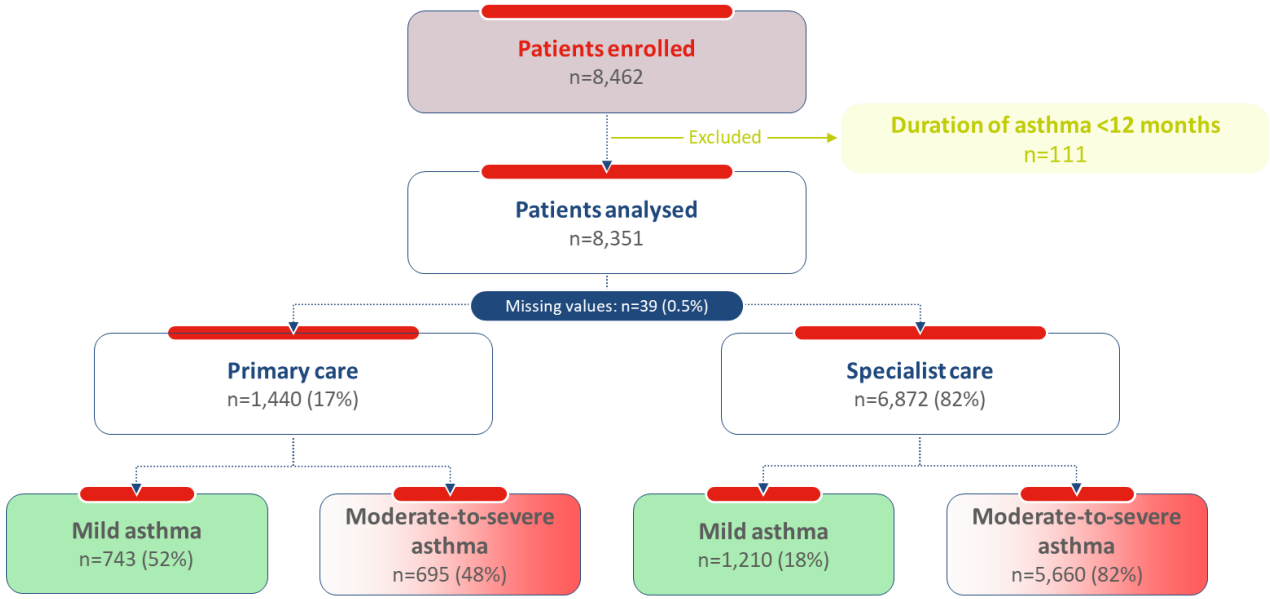
EU, European Union; SABA, short-acting β_2-agonists; SABINA, SABA use IN Asthma; UK, United Kingdom; US, United States.

1. Cabrera CS, Nan C, Lindarck N, Beekman MJ, Arnetorp S, van der Valk RJ. SABINA: global programme to evaluate prescriptions and clinical outcomes related to short-acting β2-agonist use in asthma. European Respiratory Journal. 2020 Feb 1;55(2).

SABINA III – An observational, cross-sectional study carried out in 24 countries[1]

- Aim: To assess SABA prescriptions and associated outcomes in countries most of which lacked national healthcare databases
- Real-world primary data was collected in local health care settings through eCRFs
- Unlike in database studies, this enabled assessment of additional parameters, such as asthma control and SABA purchase without a prescription





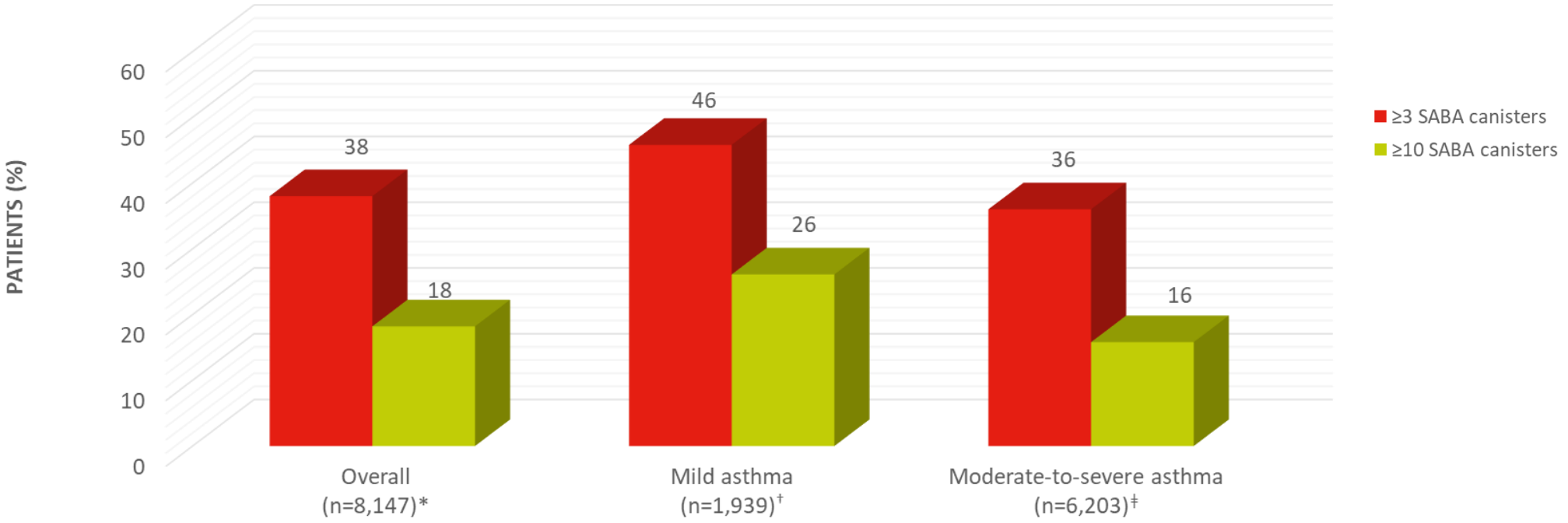
Of the patients included, 37% were from Asia, 21% from Africa, 17% from the Middle East, 13% from Latin America, 7% from Russia and 5% from Australia

Bateman ED, Price DB, Wang HC, Khattab A, Schonffeldt P, Catanzariti A, van der Valk RJ, Beekman MJ. Short-acting β2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. European Respiratory Journal. 2021 Jan 1.

SABINA III – An observational, cross-sectional study carried out in 24 countries[1]

- 63% of patients were prescribed SABA, either as monotherapy or in addition to maintenance therapy
- Overall, 38% of patients had SABA over-prescriptions in the previous year and almost one-fifth were prescribed ≥10 SABA canisters

61% of the patients who were prescribed SABA had used more than 3 canister per year (overuse)



Bateman ED, Price DB, Wang HC, Khattab A, Schonffeldt P, Catanzariti A, van der Valk RJ, Beekman MJ. Short-acting β2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. European Respiratory Journal. 2021 Jan 1.

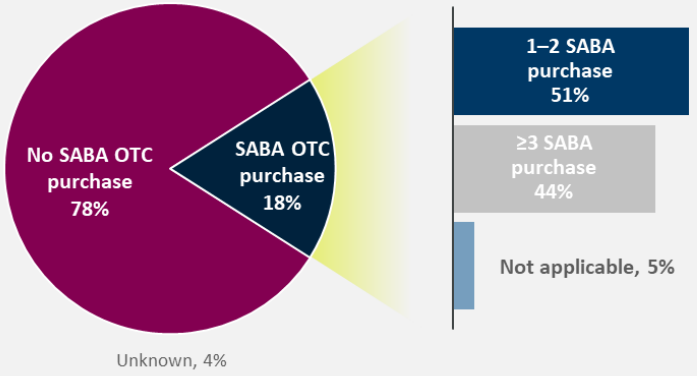
SABINA III – An observational, cross-sectional study carried out in 24 countries[1]

SABA purchase over the counter

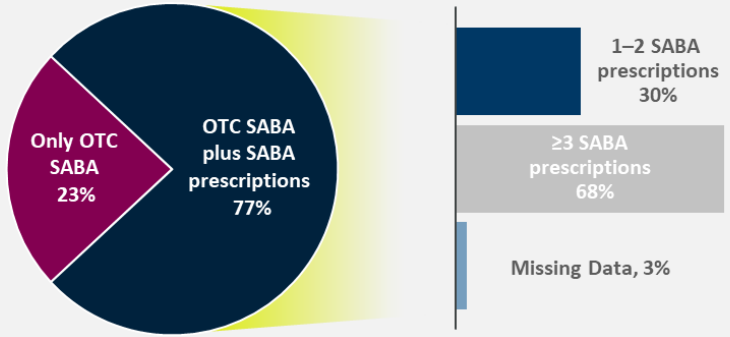
18% of patients purchased SABA OTC, 77% also received SABA prescriptions and of these, 68% had ≥3 SABA canister prescriptions

44% of patients who buy SABA as OTC, overuse SABA

- **18%** of patients **purchased SABA OTC**
  - Of these patients, **44% purchased ≥3 SABA canisters**



- **77%** of patients who **purchased SABA OTC also received SABA** prescriptions
  - **68%** of these patients received **prescriptions for ≥3 SABA canisters**



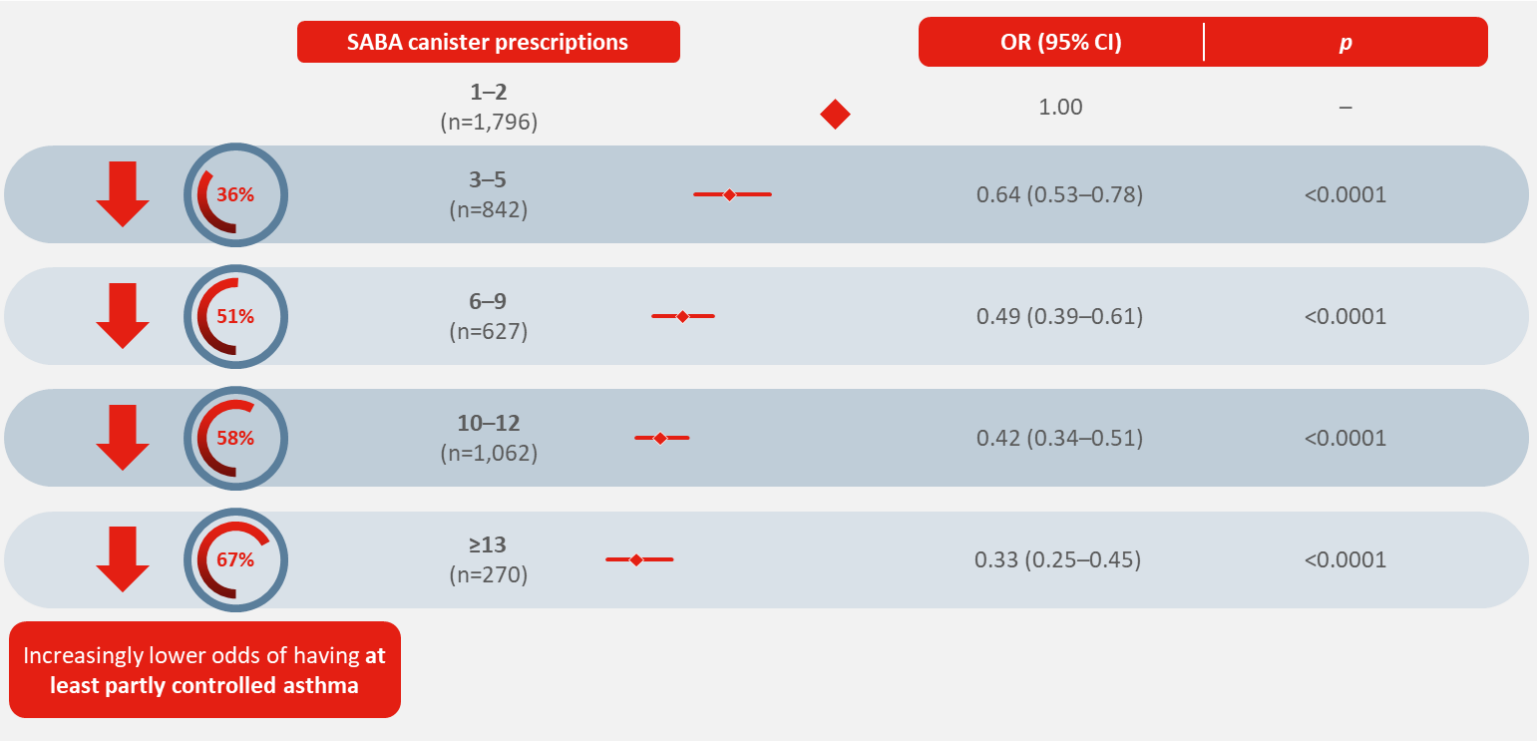
Bateman ED, Price DB, Wang HC, Khattab A, Schonffeldt P, Catanzariti A, van der Valk RJ, Beekman MJ. Short-acting β2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. European Respiratory Journal. 2021 Jan 1.

SABINA III – An observational, cross-sectional study carried out in 24 countries[1]

Association of SABA prescriptions with asthma symptom control (n=4,597)

The odds of having at least partly-controlled asthma were significantly lowered with increasing SABA canister prescriptions (vs. 1–2 canisters)

SABA prescriptions and asthma symptom control | SABA prescriptions and rate of severe exacerbations



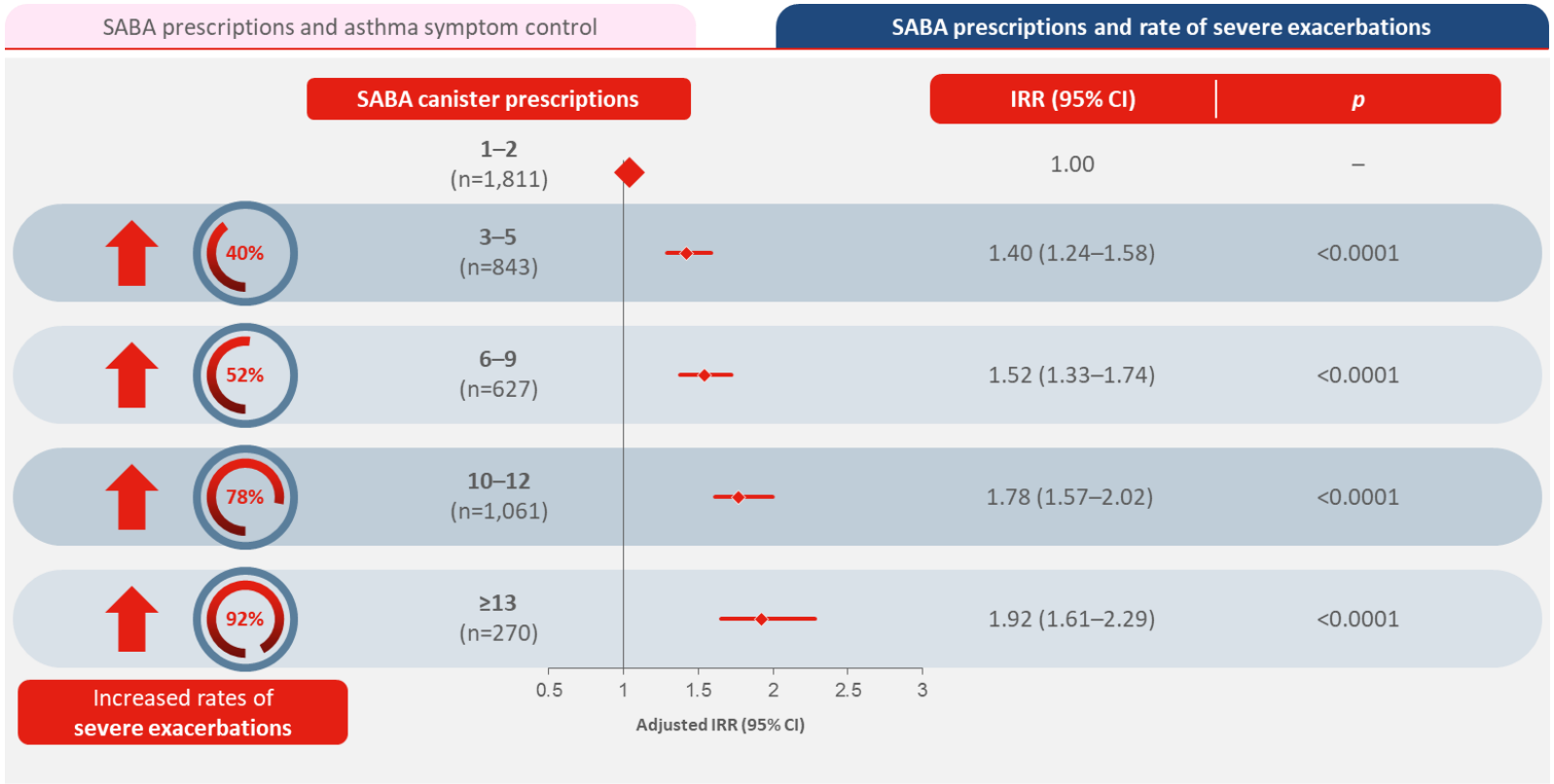
Analyses were adjusted for the following covariates: country, age, sex, BMI, asthma duration, smoking history, comorbidity, GINA step, and education level. Asthma symptom control was assessed as per 2017 GINA Assessment of Asthma Symptom Control.
BMI, body mass index; GINA, Global Initiative for Asthma; OR, odds ratio; SABA, short-acting β_2-agonists.

Bateman ED, Price DB, Wang HC, Khattab A, Schonffeldt P, Catanzariti A, van der Valk RJ, Beekman MJ. Short-acting β2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. European Respiratory Journal. 2021 Jan 1.

SABINA III − An observational, cross-sectional study carried out in 24 countries[1]

Association of SABA prescriptions with severe exacerbations (n=4,612)

The rate of severe exacerbations significantly increased with the number of SABA prescriptions (vs. 1–2 SABA prescriptions)



Analyses were adjusted for the following covariates: country, age, sex, BMI, smoking history, GINA step, and education level. Severe exacerbations were defined as per American Thoracic Society/European Respiratory Society recommendations.
BMI, body mass index; GINA, Global Initiative for Asthma; IRR, incidence rate ratio; SABA, short-acting β_2-agonists.

Bateman ED, Price DB, Wang HC, Khattab A, Schonffeldt P, Catanzariti A, van der Valk RJ, Beekman MJ. Short-acting β2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. European Respiratory Journal. 2021 Jan 1.

Asthma guidelines have moved towards earlier ICS use

EDITORIAL
GINA 2019

GINA 2019: a fundamental change in asthma management

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

Helen K. Reddel[1], J. Mark FitzGerald[2], Eric D. Bateman[3], Leonard B. Bacharier[4], Allan Becker[5], Guy Brusselle[6], Roland Buhl[7], Alvaro A. Cruz[8], Louise Fleming[9], Hiromasa Inoue[10], Fanny Wai-san Ko[11], Jerry A. Krishnan[12], Mark L. Levy[13], Jiangtao Lin[14], Søren E. Pedersen[15], Aziz Sheikh[16], Arzu Yorgancioglu[17] and Louis-Philippe Boulet[18]

Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, Buhl R, Cruz AA, Fleming L, Inoue H, Wai-san Ko F. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents.

GINA – landmark changes in asthma management

- For safety, GINA no longer recommends SABA-only treatment for Step 1 in adults and adolescents
  - This decision was based on evidence that SABA-only treatment increases the risk of severe exacerbations, and that adding any ICS significantly reduces the risk
- GINA now recommends that all adults and adolescents with asthma should receive ICS-containing controller treatment, to reduce the risk of serious exacerbations
  - The ICS can be delivered by regular daily treatment or, in mild asthma, by as-needed low dose ICS-formoterol
- This is a population-level risk reduction strategy
  - Other examples: statins, anti-hypertensives
  - The aim is to reduce the probability of serious adverse outcomes at a population level
  - Individual patients may not necessarily experience (or be aware of) short-term clinical benefit

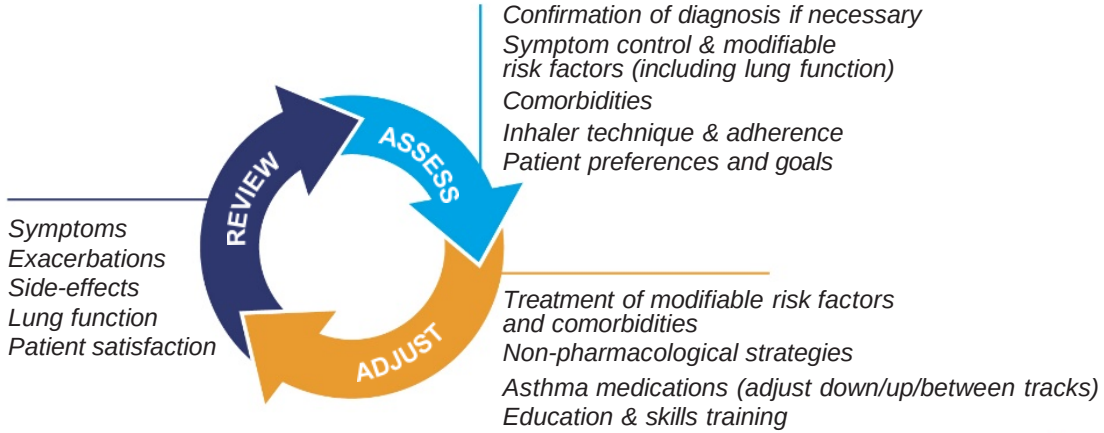
ICS: inhaled corticosteroids; SABA: short-acting beta2-agonist

Global Initiative For Asthma (GINA), Global strategy for asthma management and prevention, http://ginasthma.org. Last accessed May 2021.,

GINA 2021

Adults & adolescents 12+ years

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



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 phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-formoterol
RELIEVER: As-needed low-dose ICS-formoterol			

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 phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA
RELIEVER: As-needed short-acting β2-agonist				

Other controller options for either track

	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; add low dose OCS but consider side-effects*

Global Initiative For Asthma (GINA), Global strategy for asthma management and prevention, http://ginasthma.org. Last accessed May 2021.

The GINA 2021 treatment figure for adults and adolescents

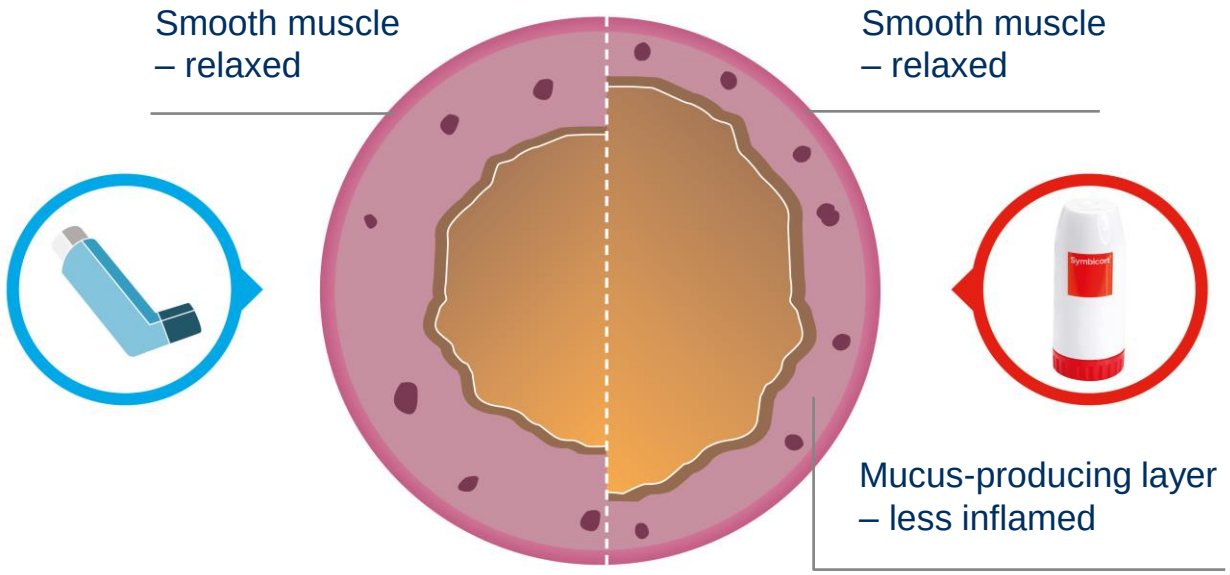
- For clarity, the GINA treatment figure now shows two ‘tracks’, based on evidence about outcomes with the two reliever choices across asthma severity
- **Track 1, with low dose ICS-formoterol as the reliever, is the preferred approach**
  - Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever, with similar symptom control and similar lung function
- **Track 2, with SABA as the reliever, is an alternative approach**
  - Use this if Track 1 is not possible, or is not preferred by a patient with no exacerbations on their current controller therapy
  - Before considering a regimen with SABA reliever, consider whether the patient is likely to be adherent with daily controller – if not, they will be exposed to the risks of SABA-only treatment
- Treatment may be stepped up or down within a track using the same reliever at each step, or switched between tracks, according to the patient’s needs and preferences

Global Initiative For Asthma (GINA), Global strategy for asthma management and prevention, http://ginasthma.org. Last accessed May 2021.

Symbicort®* – anti-inflammatory relief from a single inhaler to reduce exacerbations[1,2] and provide 24-hour symptom control[3]

Worsening symptoms are due to bronchoconstriction and inflammation[3]

SABAs provide only bronchodilation, without inflammatory control[3]



When Symbicort®* is used as an anti-inflammatory reliever as needed on top of maintenance therapy it provides:

bronchodilation and additional **inflammatory control**

to reduce exacerbations[1,2] and provide 24-hour symptom control[3]

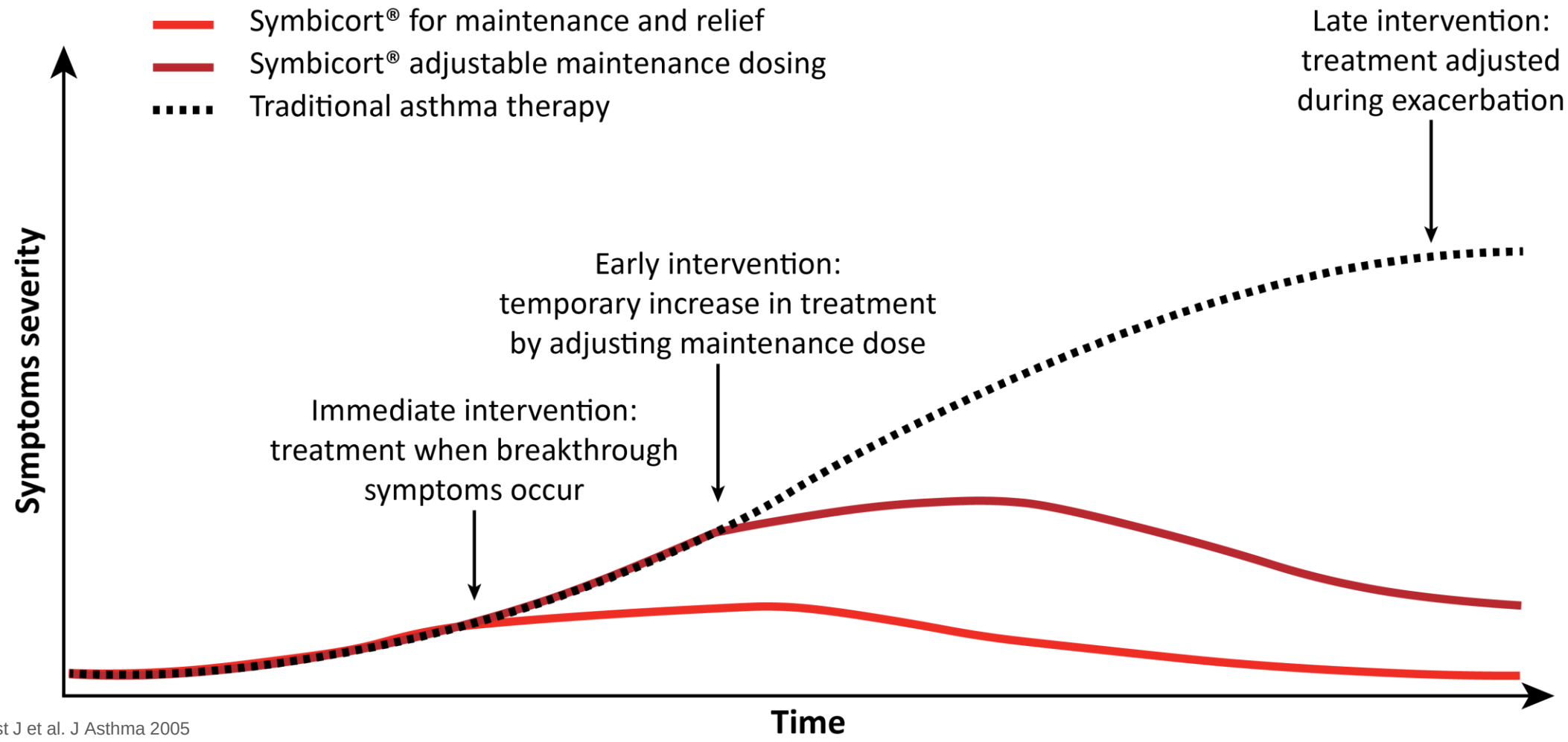
*Symbicort® Maintenance and Reliever

Ref 3: Randomized, double-blind 6-month study of 3335 symptomatic adult and adolescent asthma patients (mean FEV1 73% predicted, mean inhaled corticosteroid dose 745 µg/day). Symbicort® Maintenance and Reliever 160/4.5 µg one inhalation bd + additional inhalations as needed. Symbicort® Maintenance and Reliever prolonged the time to first severe exacerbation requiring hospitalisation, emergency room treatment or oral steroids (primary variable) vs fixed-dose salmeterol/fluticasone and budesonide/formoterol (p=0.0034 and p=0.023 respectively). Symbicort had 7x more asthma control days (defined as no day-time symptoms, no night-time symptoms, no night awakenings caused by asthma, no as-needed medication use) vs baseline: Baseline 5.8% vs Treatment 41.3%. Study results also showed salmeterol/fluticasone 25/125 µg two inhalations bd + terbutaline as needed has similar asthma control days results: Baseline 5.7% vs Treatment 43.7%.

1. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, Buhl R. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. International journal of clinical practice. 2007 May;61(5):725-36. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, Boulet LP. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC public health. 2012 Dec;12(1):204. 2. Selroos O. A smarter way to manage asthma with a combination of a long-acting β2-agonist and inhaled corticosteroid. Therapeutics and clinical risk management. 2007 Jun;3(2):349. 3. Shahidi N, FitzGerald JM. Current recommendations for the treatment of mild asthma. Journal of asthma and allergy. 2010;3:169.

Early intervention with Symbicort® as part of a reliever regimen can prevent exacerbations[1,2]

Potential outcomes with different asthma treatment regimens in response to worsening symptoms[1]



Adapted from Ankerst J et al. J Asthma 2005

1. Ankerst J. Combination inhalers containing inhaled corticosteroids and long-acting β2-agonists: improved clinical efficacy and dosing options in patients with asthma. Journal of Asthma. 2005 Jan 1;42(9):715-24. **2.** Global Initiative For Asthma (GINA), Global strategy for asthma management and prevention, http://ginasthma.org. Last accessed Dec 2019

Recommended doses for Adults (18 years & older)*

- ✓ The recommended maintenance dose is 2 inhalations per day (160/4.5), given either as one inhalation in the morning or evening. For some patients a maintenance dose of 2 inhalations twice daily may be appropriate.

- ✓ Patients should take one additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken.

- ✓ **Not more than 6 inhalations should be taken on any single occasion.**

- ✓ **A total daily dose of more than 8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations could be used for a limited period.**

*Symbicort Prescribing Information, last reviewed 2017

As-needed budesonide/formoterol use in a real-life observational study of budesonide/formoterol as-needed on top of maintenance therapy

- As-needed medication was generally low for the majority of the 12-month follow-up (mean 61–66% of reliever-free days)
- High as-needed use (>4 inhalations) was observed for a mean of 1–3% of days
- Budesonide/formoterol as-needed on top of maintenance therapy provided appropriate levels of asthma control in normal clinical practice

Mean percentage of days with budesonide/formoterol as-needed inhalation use

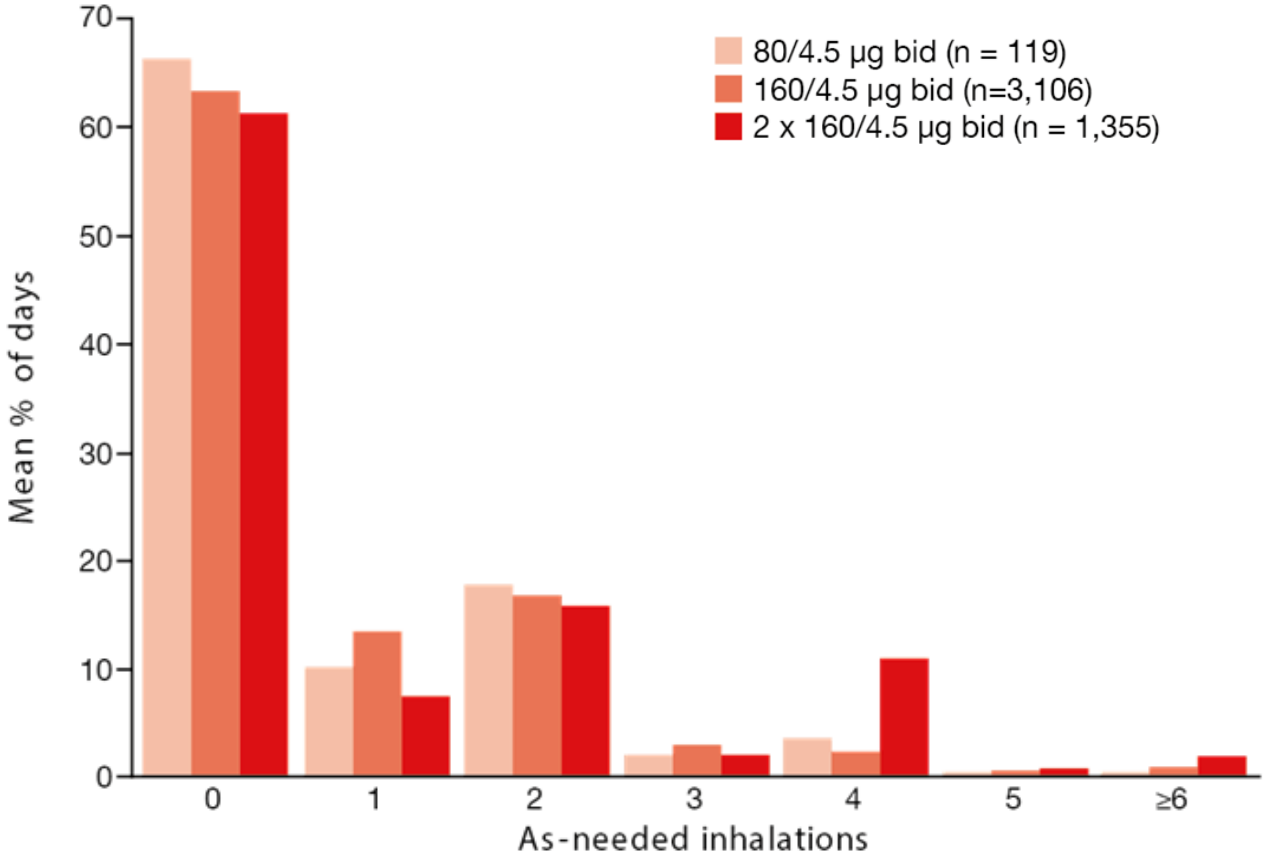


Figure adapted from Stahlberg et al, 2015.

bid, twice per day.

Ställberg B, Naya I, Ekelund J, Eckerwall G. Real-life use of budesonide/formoterol in clinical practice: a 12-month follow-up assessment in a multi-national study of asthma patients established on single-inhaler maintenance and reliever therapy. International journal of clinical pharmacology and therapeutics. 2015 Jun;53(6):447..

GINA Recommendation For Maintenance And Reliever Therapy *

1

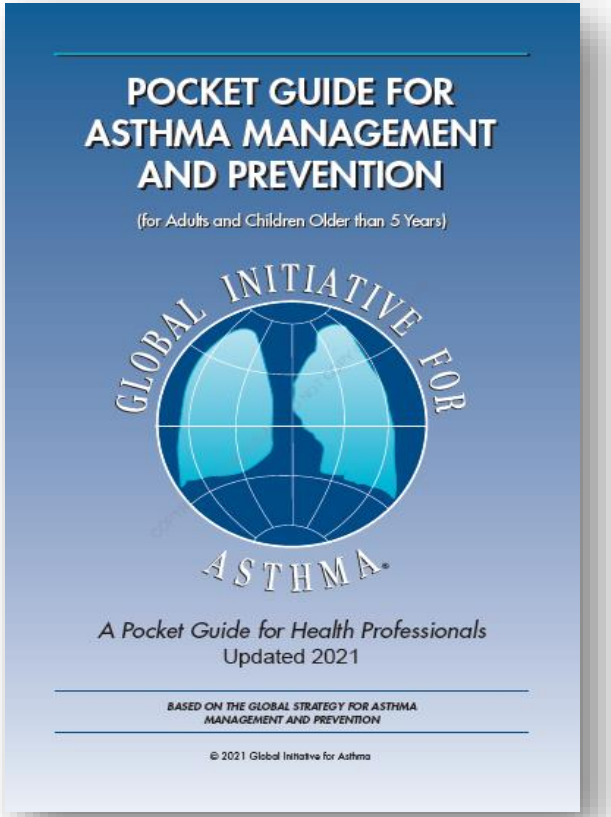
Track 1: **The reliever is as-needed low dose ICS-formoterol.**
This is the preferred approach recommended by GINA for adults and adolescents. Using low dose ICS-formoterol as reliever reduces the risk of severe exacerbations compared with regimens with SABA as reliever, with similar symptom control. With this approach:

- When a patient at any treatment step has asthma symptoms, they use low dose ICS-formoterol in a single inhaler for symptom relief.
- In Steps 3–5, patients also take ICS-formoterol as their regular daily treatment. This is called 'maintenance and reliever therapy' (MART).

2

ICS-formoterol should not be used as the reliever by patients taking any other ICS-LABA.

Track 2: **The reliever is as-needed SABA.** This is an alternative approach when Track 1 is not possible or is not preferred by a patient who has no exacerbations on their current therapy.

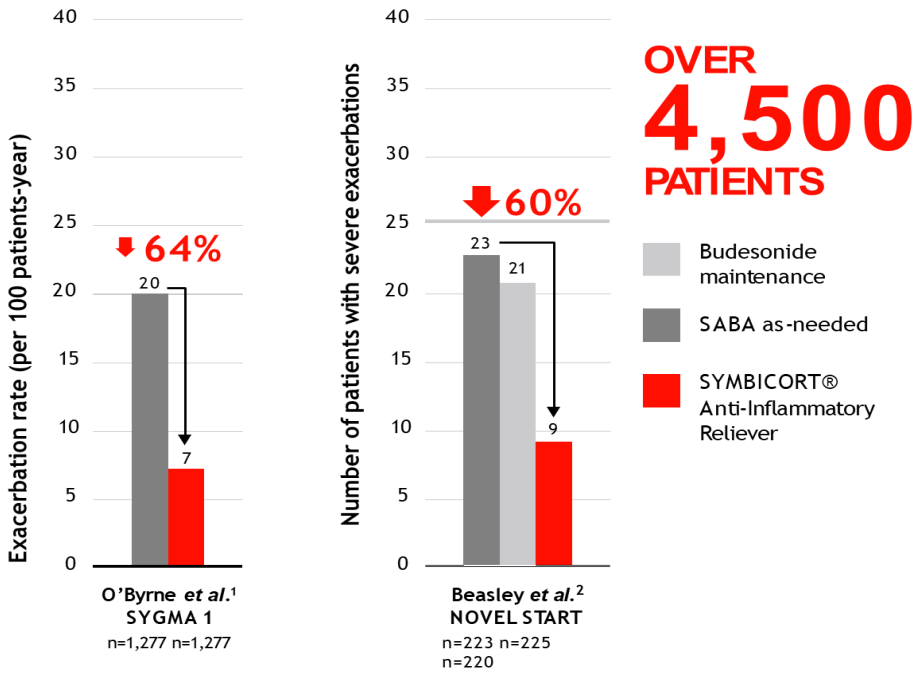


ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist;.

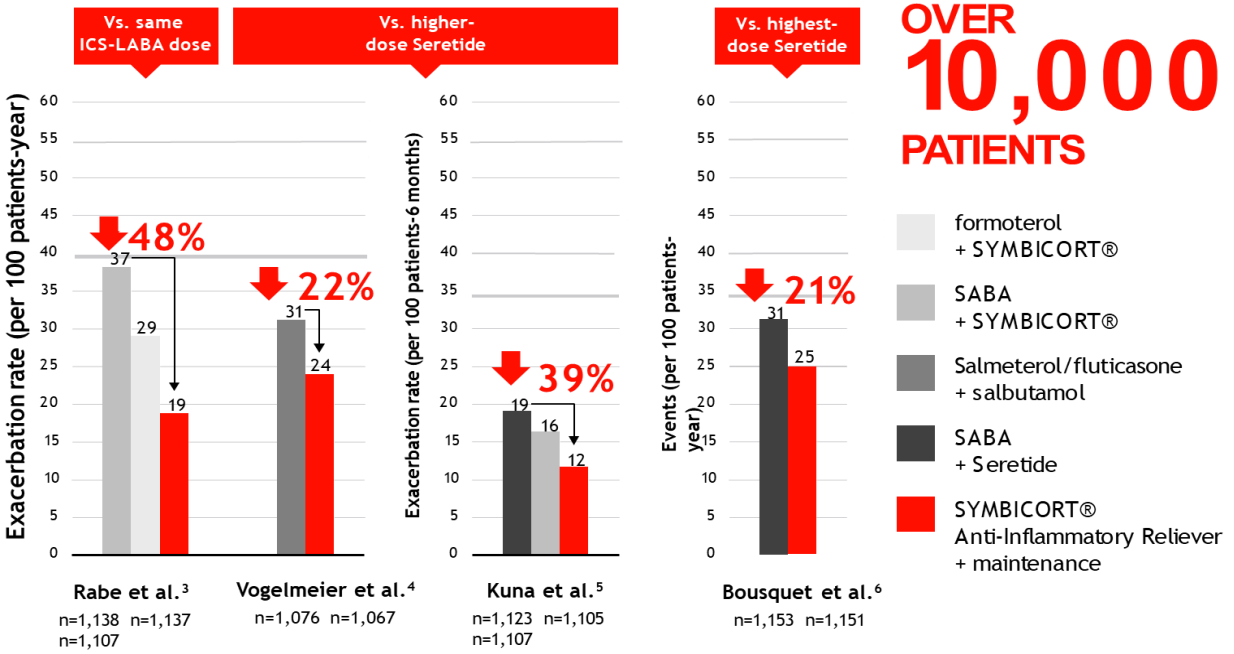
* Global Initiative For Asthma (GINA), Global strategy for asthma management and prevention, http://ginasthma.org. Last accessed May 2021.

Across All Severities, Symbicort® Anti-inflammatory Reliever Is Superior In Reducing Exacerbations Vs Saba

In **mild asthma**, SYMBICORT® Anti-Inflammatory Reliever reduced the rate of severe exacerbations by 60 to 64% vs SABA[1,2]



In **moderate-to-severe asthma**, SYMBICORT® reduced severe exacerbation rates by 21 to 48% vs ICS-LABA maintenance[3-6]

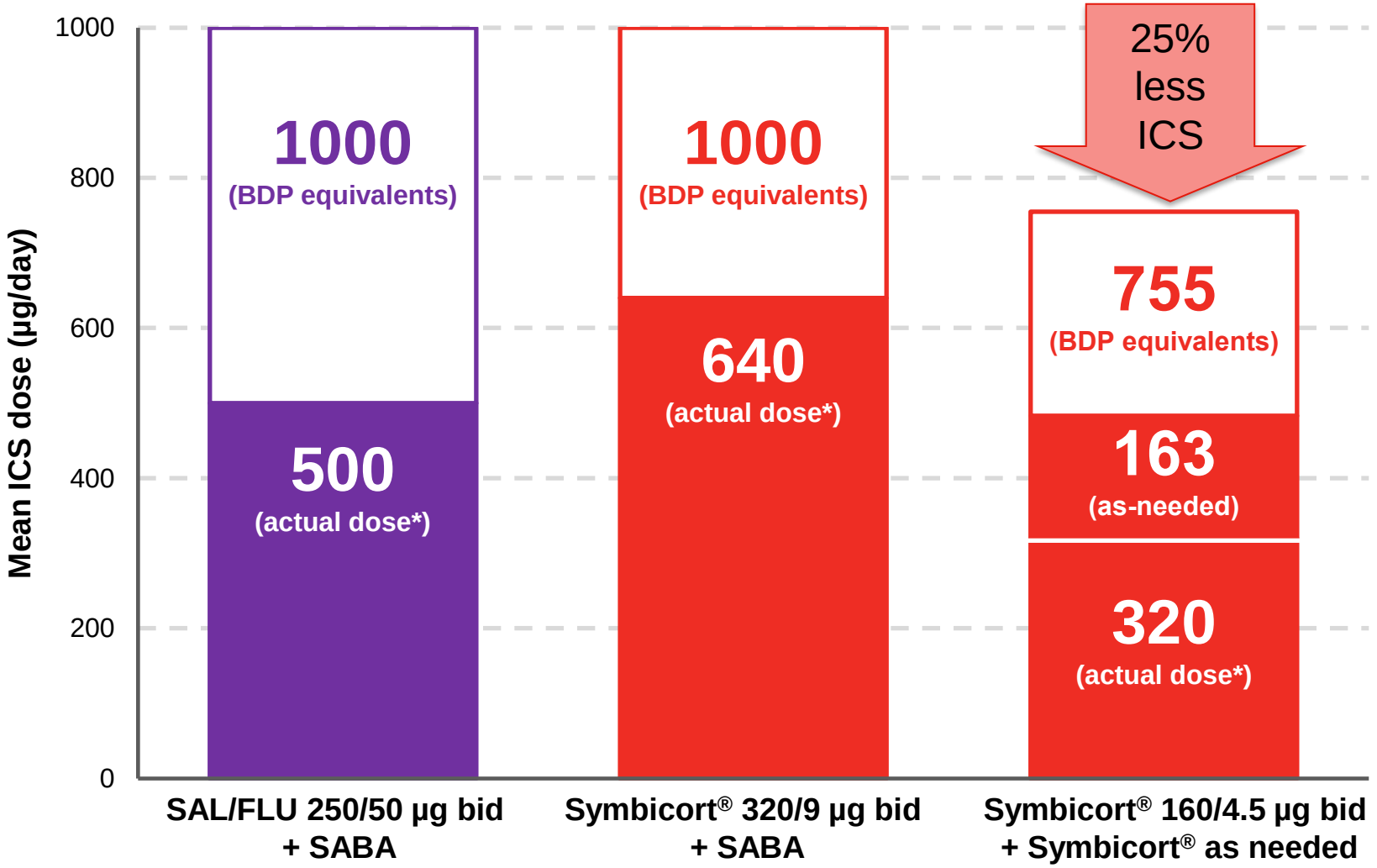


Reliever choice changes lives: as-needed low-dose ICS-formoterol is now the preferred reliever in mild, moderate and severe patients

ICS = inhaled corticosteroids, LABA = long-acting beta-agonists, SABA = short-acting beta-agonists.

1. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Ivanov S, Reddel HK. Inhaled combined budesonide-formoterol as needed in mild asthma. New England Journal of Medicine. 2018 May 17;378(20):1865-76. 2.Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, Harrison T, Houghton C, Oldfield K, Papi A, Pavord ID. Controlled trial of budesonide-formoterol as needed for mild asthma. New England Journal of Medicine. 2019 May 23;380(21):2020-30. 3. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. The Lancet. 2006 Aug 26;368(9537):744-53. 4. Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S, Naya I, Price D. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option?. European Respiratory Journal. 2005 Nov 1;26(5):819-28. 5. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, Buhl R. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. International journal of clinical practice. 2007 May;61(5):725-36. 6. Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, Carlsheimer Å. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respiratory medicine. 2007 Dec 1;101(12):2437-46.

Symbicort® provides similar symptom control to salmeterol/fluticasone at a lower BDP equivalent ICS dose

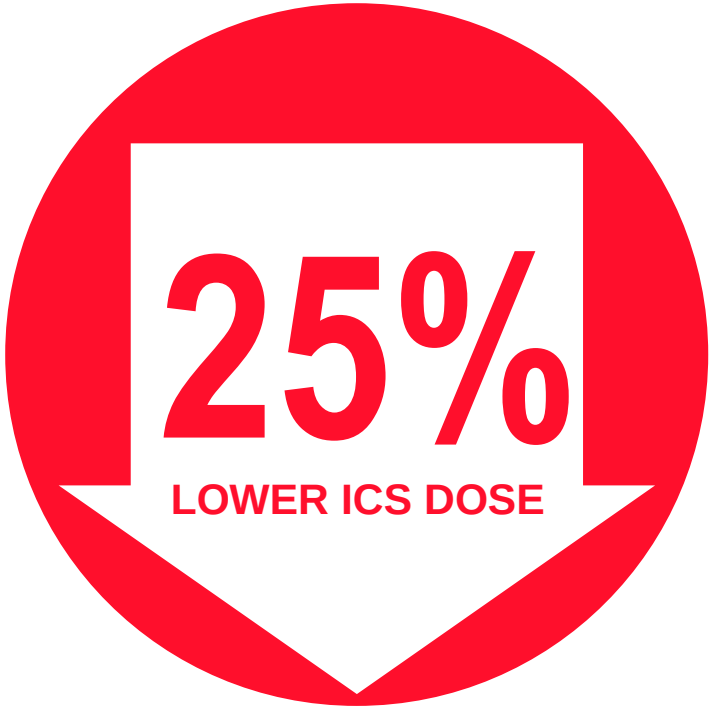


*Actual dose = dose prescribed at randomisation

bid, twice per day; BDP, beclomethasone dipropionate; ICS, inhaled corticosteroid; SABA, short-acting β_2-agonist; SAL/FLU, salmeterol/fluticasone

Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, Buhl R. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. International journal of clinical practice. 2007 May;61(5):725-36.

Symbicort®* – efficacy with a lower mean ICS dose than salmeterol/fluticasone + SABA[1]



Symbicort®* 160/4.5 µg bd + additional inhalations as needed delivers 39% fewer severe exacerbations** and similar asthma control*** at a

lower mean ICS dose†

compared with salmeterol/fluticasone 50/250 µg bd + SABA as needed[1]

- Total number of severe exacerbations = 208 vs 125 for salmeterol/fluticasone + SABA and Symbicort®*, respectively[1]

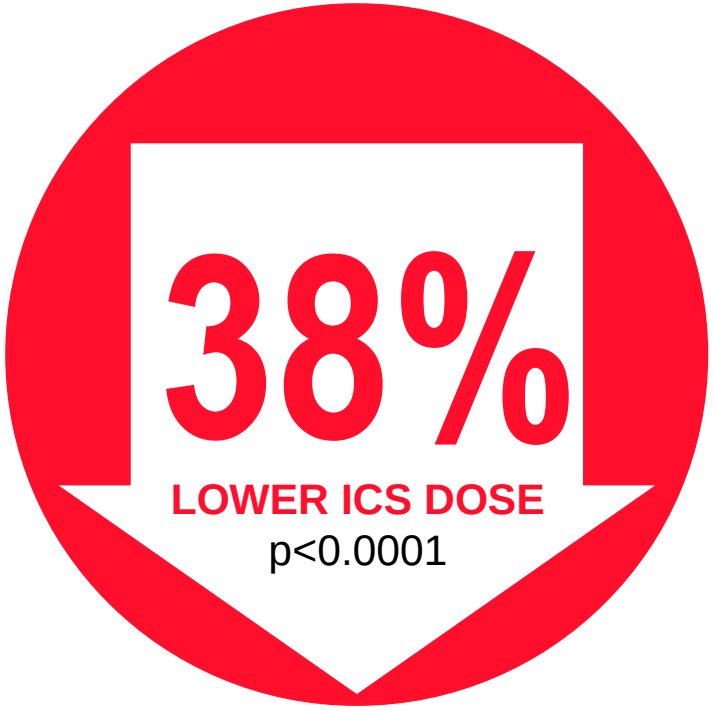
*Symbicort® Maintenance and Reliever

**Severe exacerbations defined as deterioration in asthma requiring hospitalization or ER treatment, or the need for oral steroids for ≥3 days (as judged by the investigator). ***Asthma control days defined as a day with no symptoms (day or night), no awakenings caused by asthma and no as-needed medication use. †Mean overall daily ICS dose in BDP equivalents was approximately 750 µg in the Symbicort® ® Maintenance and Reliever group vs 1000 µg in the salmeterol/fluticasone + SABA group. Randomized, double-blind 6-month study of 3335 symptomatic adult and adolescent asthma patients (mean FEV_1 73% predicted, mean inhaled corticosteroid dose 745 µg/day). Symbicort® Maintenance and Reliever prolonged the time to first severe exacerbation requiring hospitalisation, emergency room treatment or oral steroids (primary variable) vs fixed-dose salmeterol/fluticasone (p=0.0034).[1]

1. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, Buhl R. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. International journal of clinical practice. 2007 May;61(5):725-36.

AHEAD study: Symbicort®* – efficacy with a lower mean ICS dose than salmeterol/fluticasone + SABA[1†]

In a trial that did not achieve its primary endpoint (time to first severe exacerbation), secondary and additional endpoints suggested that:



Symbicort®* 320/9 µg bd + additional inhalations as needed delivers 21% fewer severe exacerbations** and similar asthma control*** at a

lower mean ICS dose†

vs highest licensed dose of salmeterol/fluticasone (50/500 µg bd) + SABA[1]

- Total number of severe exacerbations = 173 vs 137 for salmeterol/fluticasone + SABA and Symbicort®*, respectively[1]

*Symbicort® Maintenance and Reliever

**Severe exacerbations defined as deterioration in asthma leading to hospitalisation/emergency room (ER) treatment and/or oral corticosteroid treatment for at least 3 days. Patients should not be initiated on Symbicort® during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.2,3 ***Asthma control defined as a day and night with no asthma symptoms, no night awakenings and no as-needed medication use. †Mean overall daily ICS dose in BDP equivalents was 1238 µg in the Symbicort® group vs 2000 µg in the salmeterol/fluticasone + SABA group. 6-month, randomized, double-blind, parallel-group study of 2309 patients aged >12 years with symptomatic asthma (FEV1 >50% predicted) who had experienced an asthma exacerbation in the previous year. Study results showed 21% fewer severe exacerbations for Symbicort®* vs salmeterol/fluticasone (95% CI, 1-37, p=0.039) and similar asthma control days: Symbicort®*: Baseline 6.3% vs Treatment 44.0%.; salmeterol/fluticasone: Baseline 5.8% vs Treatment 44.9%.[1]

†This study did not achieve its primary endpoint (time to first severe exacerbation)[1]

1. Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, Carlsheimer Å. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respiratory medicine. 2007 Dec 1;101(12):2437-46. ; 2. Symbicort® Turbohaler 100/6, Inhalation powder. Summary of Product Characteristics; 3. Symbicort® Turbohaler 200/6, Inhalation powder. Summary of Product Characteristics

Symbicort Prescribing Information

Abbreviated Prescribing Information: Symbicort Turbuhaler, 4.5 /160 µg /dose budesonide/formoterol inhalation powder. **Composition:** budesonide 160 micrograms/inhalation and formoterol fumarate dihydrate 4.5 micrograms/inhalation. **Excipient:** Lactose monohydrate 730 micrograms per dose. **Therapeutic indications:** Asthma: Symbicort is indicated in the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting beta-agonist) is appropriate. COPD: symptomatic treatment of patients with severe COPD (FEV≥50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators. **Posology and method of administration:** Asthma: Symbicort is not intended for the initial management of asthma. The dosage of the components of Symbicort is individual and should be adjusted to the severity of the disease. This should be considered not only when treatment with combination products is initiated but also when the maintenance dose is adjusted. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. **For Symbicort there are two treatment approaches:** A. Symbicort maintenance therapy: Adults (18 years and older): 1-2 inhalations twice daily. Some patients may require up to a maximum of 4 inhalations twice daily. Adolescents (12 -17 years): 1-2 inhalations twice daily. Children (6 years and older): A lower strength is available for children 6-11 years. B. Symbicort maintenance and reliever therapy (only Symbicort 80 µg & 160 µg): Adults (18 years and older): The recommended maintenance dose is 2 inhalations per day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or evening. Children and adolescents under 18 years: Symbicort maintenance and reliever therapy is not recommended for children and adolescents. General information: An increased exposure can be expected in patients with severe liver cirrhosis. **COPD Recommended doses: Adults:** 1 inhalation twice daily. **Contraindications:** Hypersensitivity (allergy) to budesonide, formoterol, or lactose (which contains small amounts of milk proteins). **Special warnings and precautions for use:** It is recommended that the dose is tapered when the treatment is discontinued and should not be stopped abruptly. If patients find the treatment ineffective, or exceed the highest recommended dose of Symbicort, medical attention must be sought. Sudden and progressive deterioration in control of asthma or COPD is potentially life threatening and the patient should undergo urgent medical assessment. Long acting β2 adrenergic agonist (Formoterol) products: Increase risk of life-threatening asthma episodes or asthma related deaths in patients taking these products. Patients should always be advised to have their rescue inhaler available. Patients should not be initiated on Symbicort during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma. Serious asthma-related adverse events and exacerbations may occur during treatment with Symbicort. As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. Concomitant treatment with itraconazole, ritonavir or other potent CYP3A4 inhibitors should be avoided. Symbicort should be administered with caution in patients with thyrotoxicosis, pheochromocytoma, diabetes mellitus, untreated hypokalemia, hypertrophic obstructive cardiomyopathy, idiopathic sub valvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischemic heart disease, tachyarrhythmias or severe heart failure. Caution should be observed when treating patients with prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval. The need for, and dose of inhaled corticosteroids should be re-evaluated in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways. Concomitant treatment of β2 agonists with drugs which can induce hypokalemia or potentiate a hypokalemic effect, e.g. xanthine-derivatives, steroids and diuretics, may add to a possible hypokalemic effect of the β2 agonist. As for all β2 agonist, additional blood glucose controls should be considered in diabetic patients. Symbicort Turbuhaler contains lactose (<1 mg/inhalation). This amount does not normally cause problems in lactose intolerant people. *Pneumonia in patients with COPD:* An increase in the incidence of pneumonia, including pneumonia requiring hospitalization, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patient with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Interactions: Beta-adrenergic blockers can weaken or inhibit the effect of formoterol. Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias. In addition, L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards β2 - sympathomimetics. Concomitant treatment with monoamine oxidase inhibitors including agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions. There is an elevated risk of arrhythmias in patients receiving concomitant anesthesia with halogenated hydrocarbons. Concomitant use of other beta-adrenergic drugs can have a potentially additive effect. Hypokalemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides. Budesonide and formoterol have not been observed to interact with any other drugs used in the treatment of asthma. **Pregnancy and lactation:** During pregnancy, Symbicort should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used. Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the nursing child are anticipated. It is not known whether formoterol passes into human breast milk. **Undesirable effects:** The most common drug related adverse reactions are pharmacologically predictable side-effects of β2 agonist therapy, such as tremor and palpitations. Systemic effects of inhaled corticosteroids may occur particularly at high doses prescribed for prolonged periods. **Infections and infestations:** Common: Candida infections in the oropharynx. Nervous system disorders: Common: Headache, tremor. Respiratory, thoracic and mediastinal disorders: Common: Mild irritation in the throat, coughing, hoarseness. Treatment with β2 agonist may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies. **Pharmacodynamic properties:** Formoterol: The bronchodilation effect is dose dependent, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose. **Special precautions for storage:** Do not store above 30°C. Keep the container tightly closed. Doc ID-000306983 vs 8.0 Date of revision of text: Sep 2020. API updated on 18 Aug 2021.

Full prescribing information is available on request from AstraZeneca

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For any adverse event report, product quality complaint or medical information request related to AZ products, you can complete the web-based form accessible 24/7 via the URL: http://contactazmedical.astrazeneca.com
For medical information requests, you can alternatively send to: medinfo-ne@astrazeneca.com
For adverse events reporting, you can alternatively send directly to: Patientsafety.ne@astrazeneca.com
Or Contact our office on Tel: +96265827580 or +9611385534

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