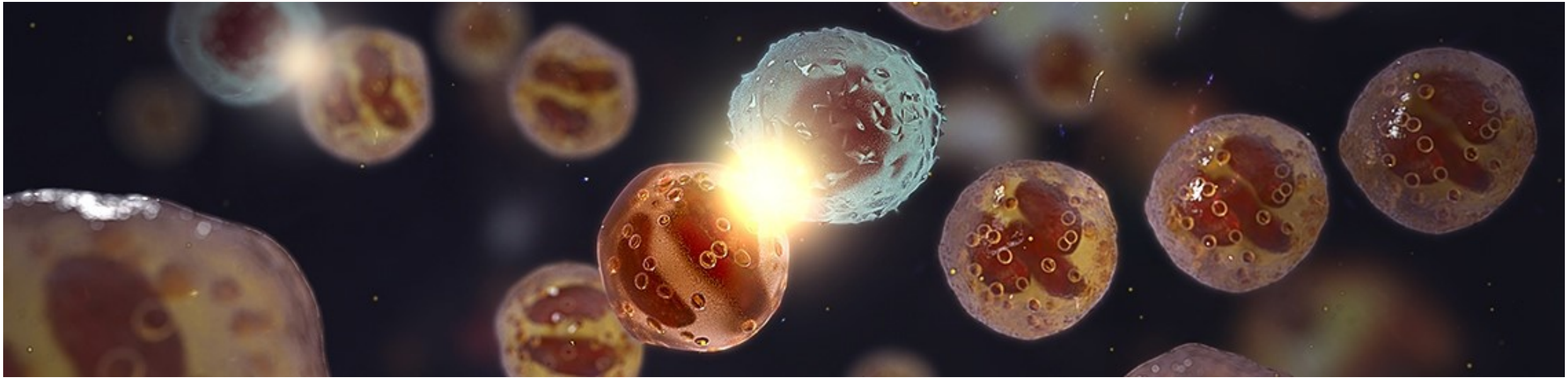
AstraZeneca

Symbicort
budesonide/formoterol

Efficacy When It Matters
Asthma

Dr. M. Hadi Alakkad

SYM-67-SK-0222-0224-NE



Titles

- Asthma and its Global Burden
- Why Symbicort® Turbuhaler® is different?
  - Efficacy
    - Efficacy Data: Exacerbations
    - Efficacy data: Symptoms and asthma control
    - Safety and tolerability profile

  - The role of Turbuhaler®

Asthma Definition

- Asthma is a heterogeneous disease, usually characterized by **chronic airway inflammation**
- It is defined by history of respiratory symptoms such as:
  - Wheeze
  - Shortness of breath
  - Chest tightness
  - Cough

  that vary over time and in intensity, together with **variable expiratory airflow limitation**

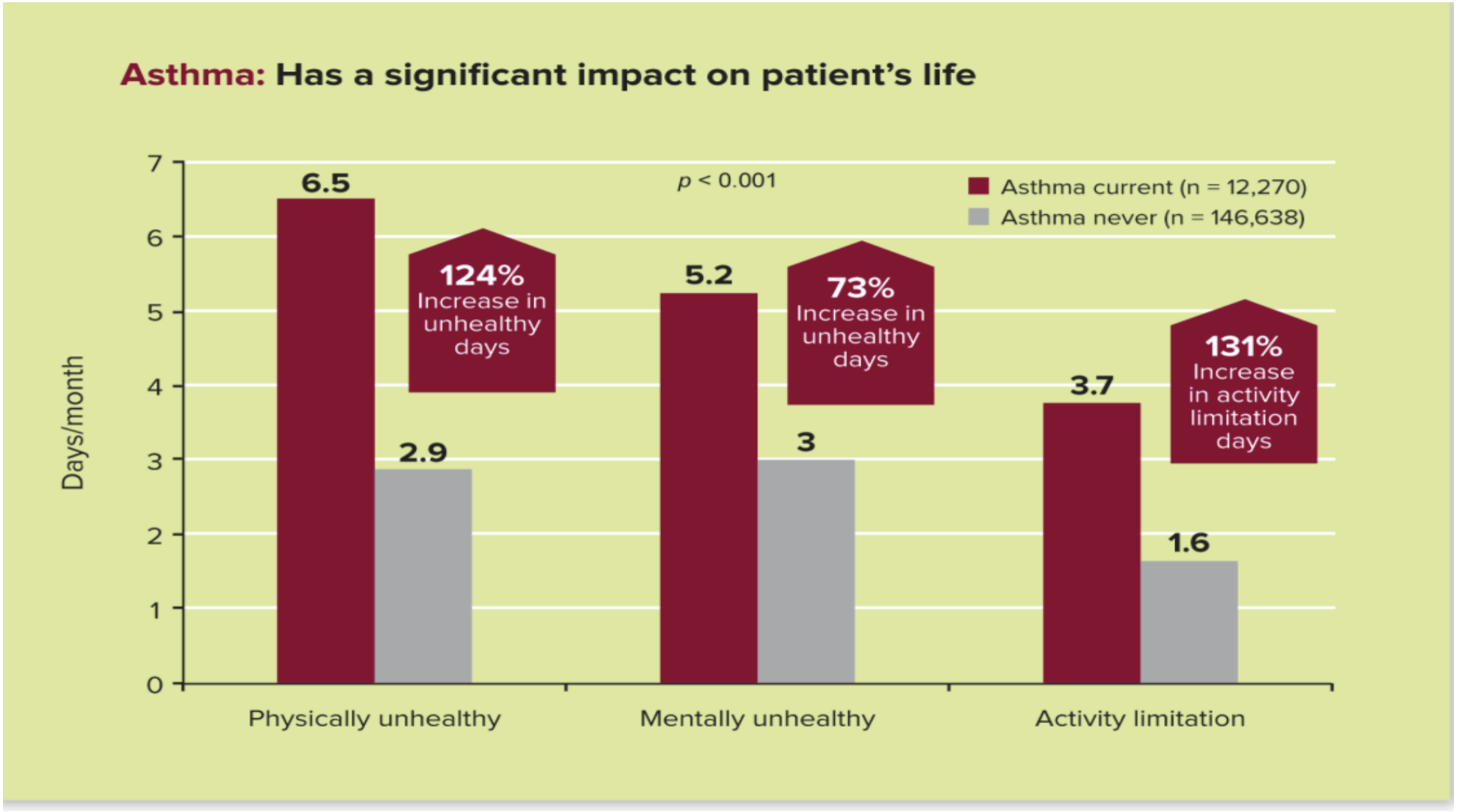
- Asthma is usually associated with airway **hyperresponsiveness** and **airway inflammation**, these are **not necessary or sufficient to make the diagnosis.**

- People with asthma often have periods of worsening symptoms and worsening airway obstruction, called **exacerbations** (also called attacks or flare-ups), that **can be fatal**.

- Most of the **morbidity and mortality** associated with asthma is **preventable**, particularly with use of **inhaled corticosteroids**.

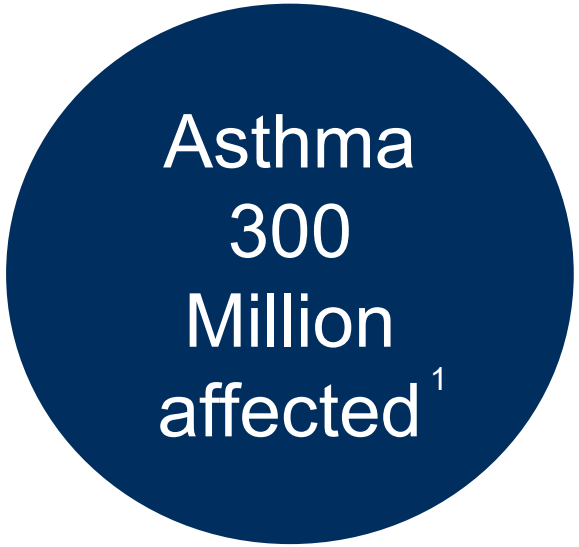
Global Initiative for Asthma. Available at: http://ginasthma.org/2019-pocket-guide-for-asthma-management-and-prevention Last accessed December 2019

Asthma is a real restriction to life



Adapted from Ford ES, Mannino DM, Homa DM, Gwynn C, Redd SC, Moriarty DG, Mokdad AH. Self-reported asthma and health-related quality of life: findings from the behavioral risk factor surveillance system. Chest. 2003 Jan 1;123(1):119-27.

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 is a global health concern

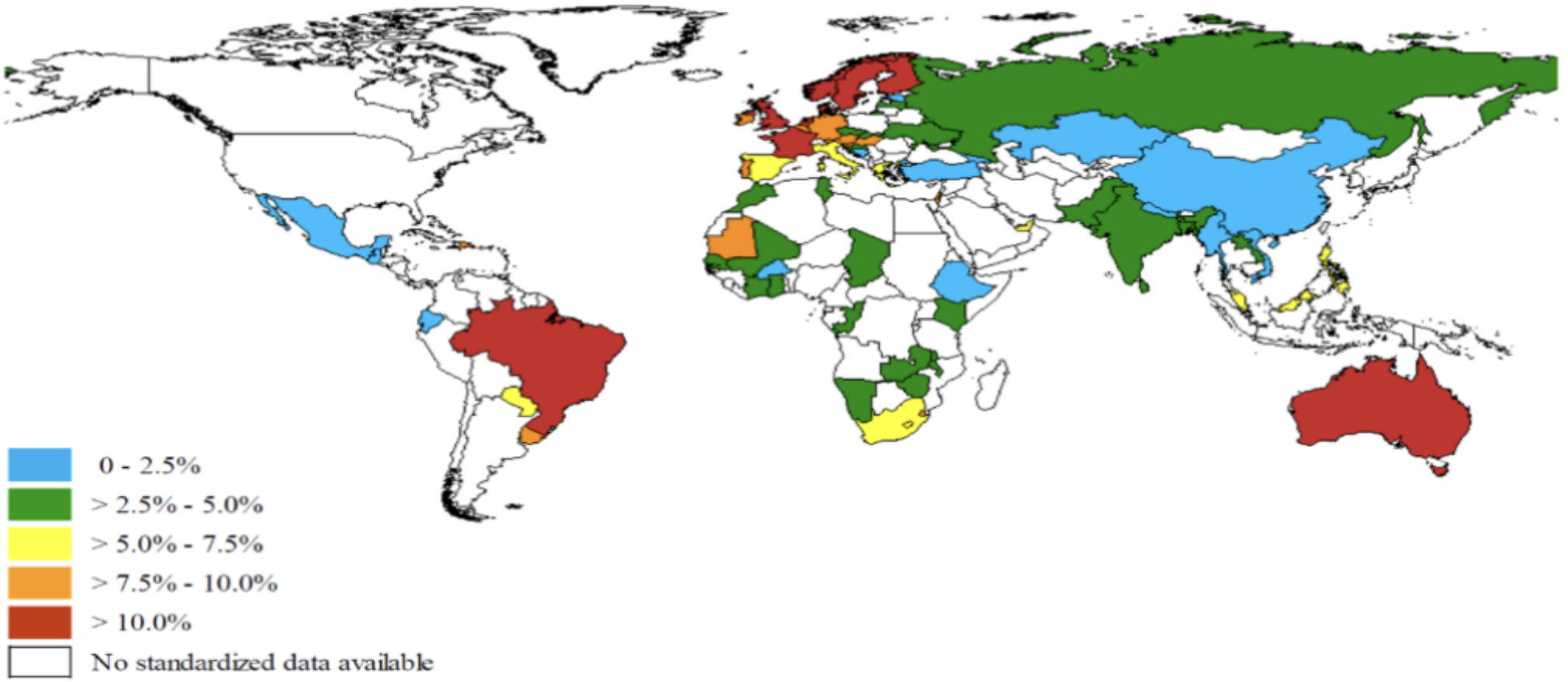


Figure source: To T et al. 2012

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.

Figure source: To T et al. 2012

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.

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

ELSEVIER

Contents lists available at ScienceDirect

Respiratory Medicine

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

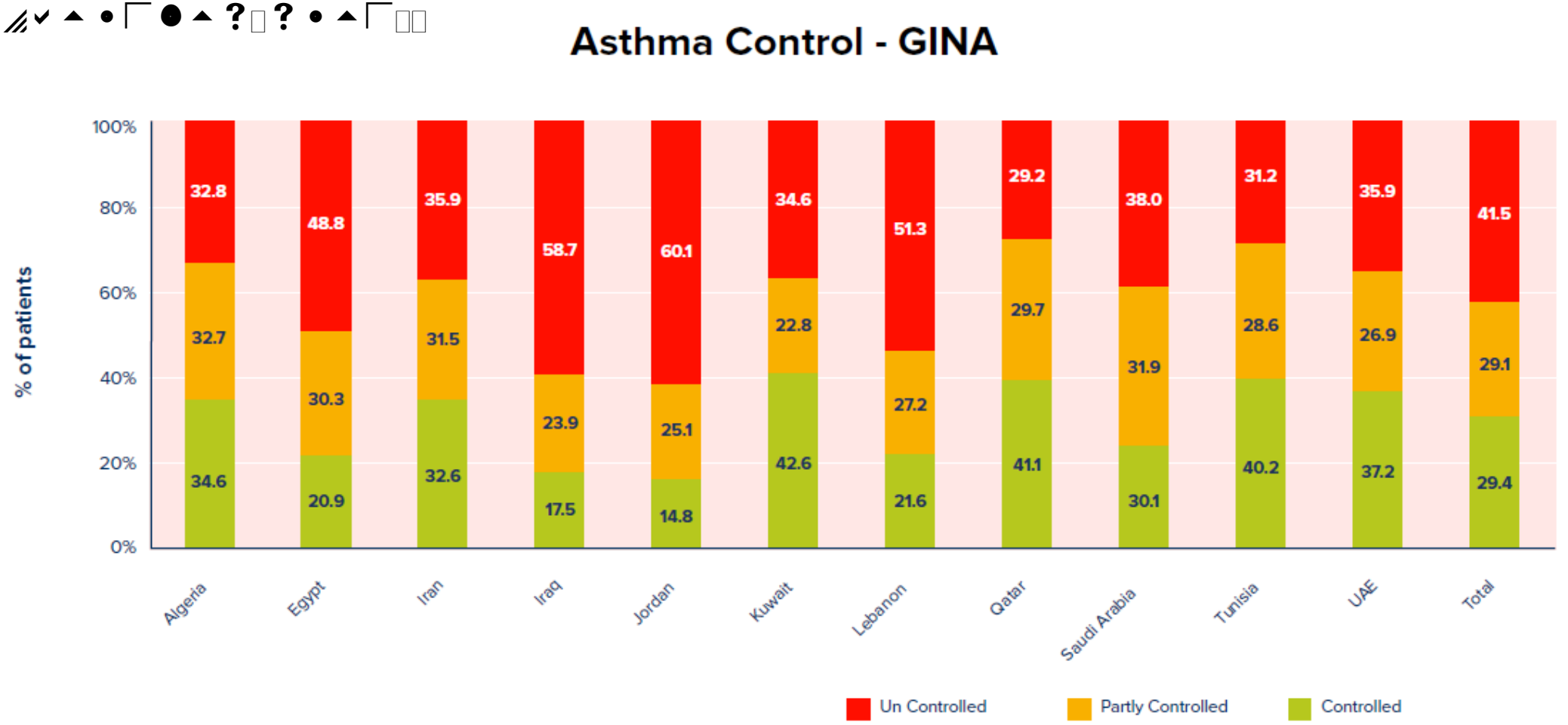
Asthma control in adults in the Middle East and North Africa: Results from the ESMAA study

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.

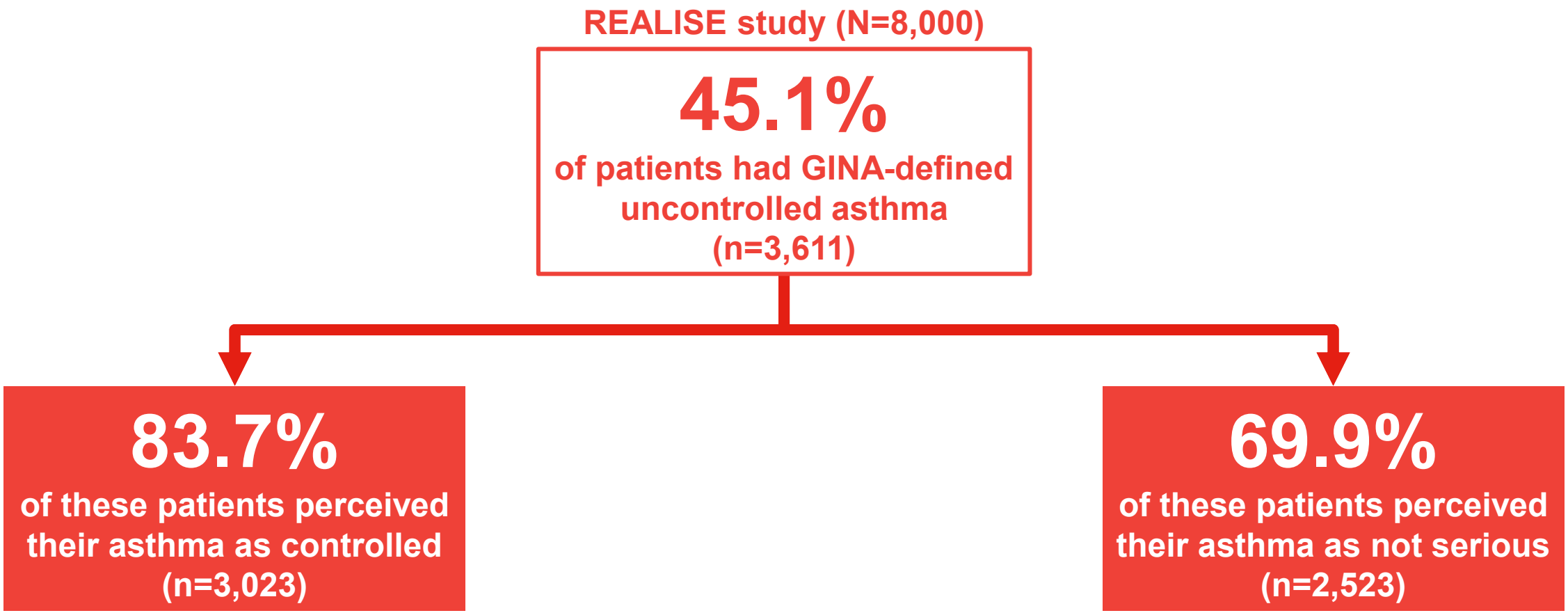
Asthma control in adults in the Middle East and North Africa: Results from the ESMAA study

- [illegible]



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.

There is an unmet need for improved understanding and attainment of asthma control

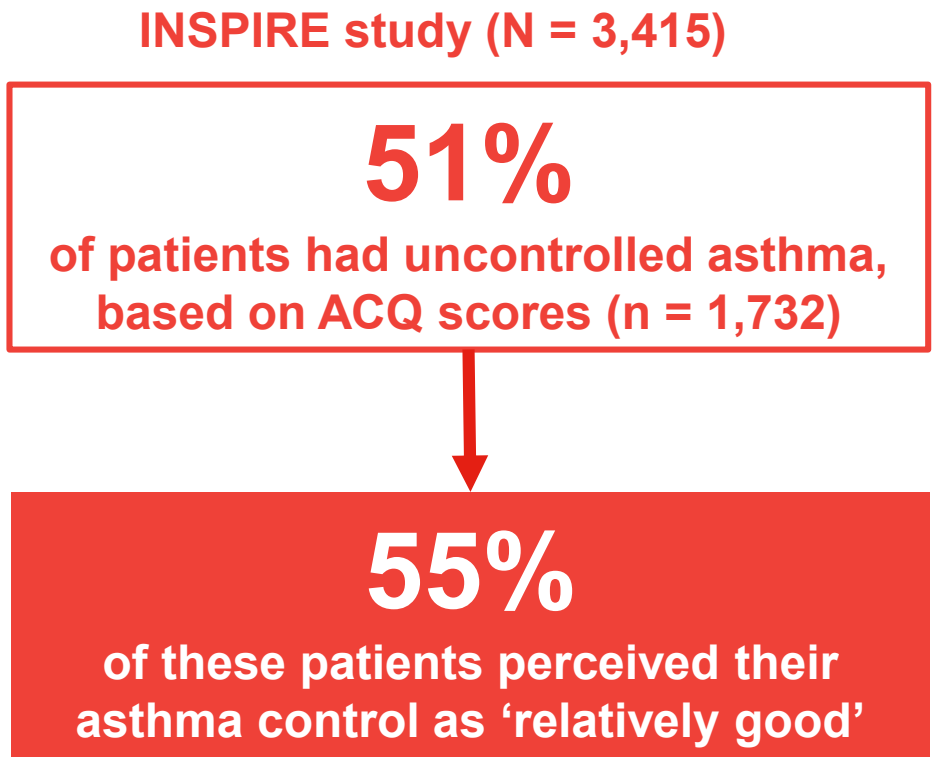


- The REALISE study demonstrated a **large gap** between patients' perception of asthma control, and the clinical reality of asthma control

The REALISE survey was conducted in patients aged 18–50 years who were active on social media.

Price D, Fletcher M, Van Der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. NPJ primary care respiratory medicine. 2014 Jun 12;24:14009.

Patients' perception of asthma control does not match the reality



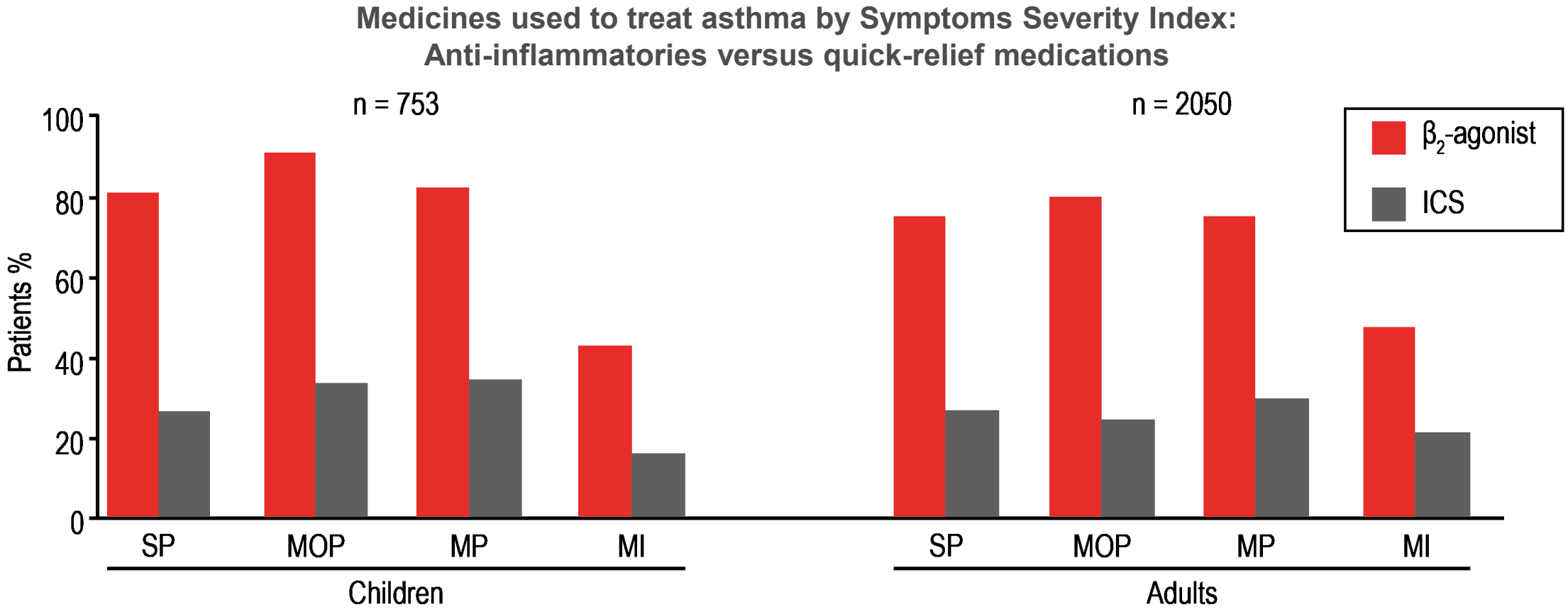
- Levels of asthma **control were poor** in the INSPIRE study
- However**, most patients** with poorly controlled asthma **were unaware of their asthma control status**
- In addition, **74% of patients** used ≥1 **SABA** inhalation every day in the previous 7 days

ACQ, Asthma Control Questionnaire

Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. BMC pulmonary medicine. 2006 Dec;6(1):13.

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

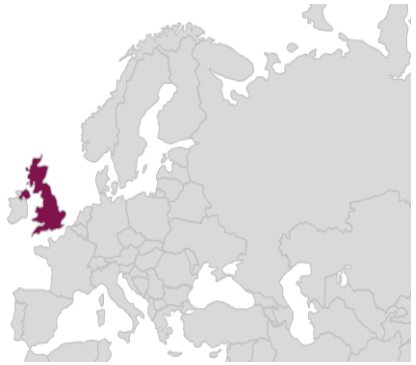
Royal College of Physicians. *Why Asthma Still Kills? The National Review of Asthma Deaths (NRAD)* [online] 2014. Available from: https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills [Last accessed: December, 2019].

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]

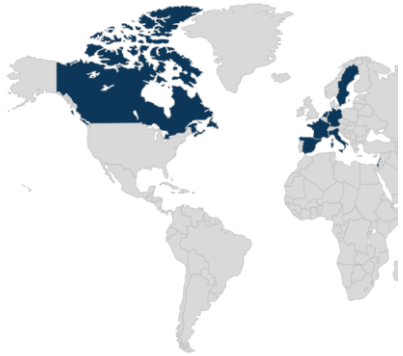
SABINA I



Retrospective, observational database studies

UK

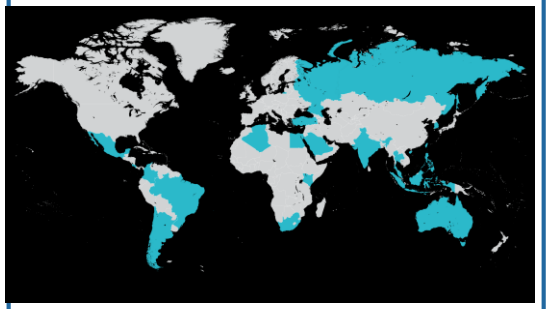
SABINA II



Retrospective, observational database studies

6 EU countries plus Canada, Israel

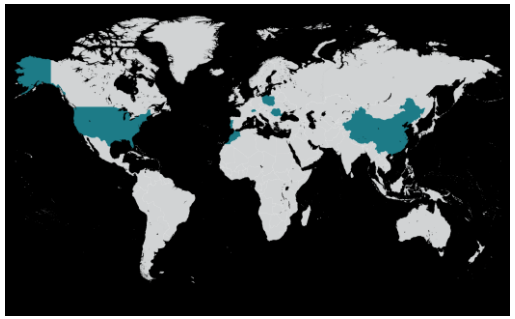
SABINA III



Cross-sectional study

24 countries across 5 continents

SABINA +



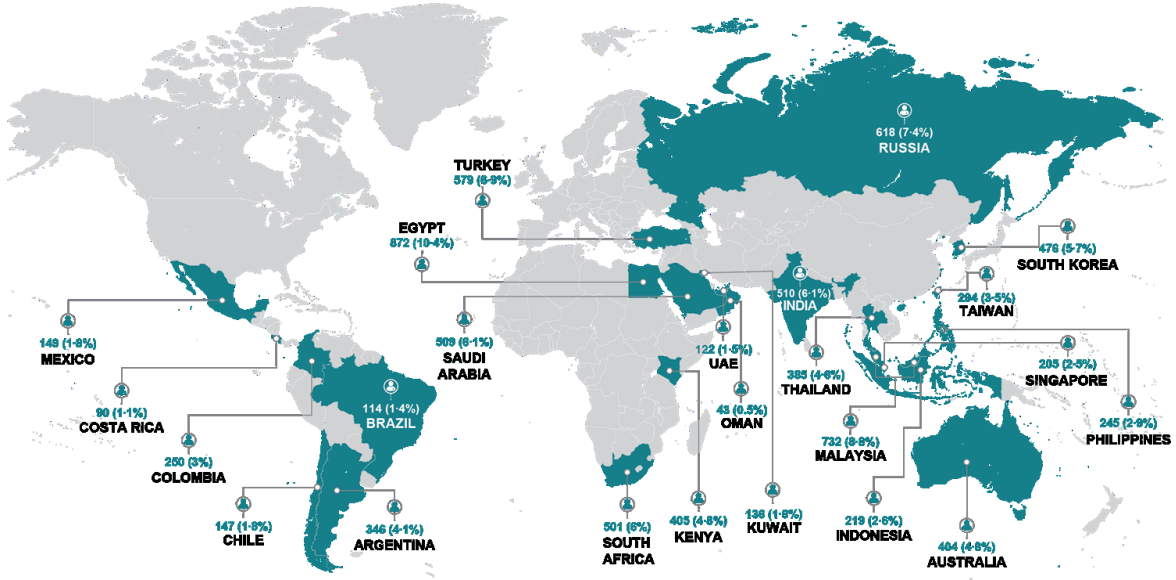
Multi-design studies

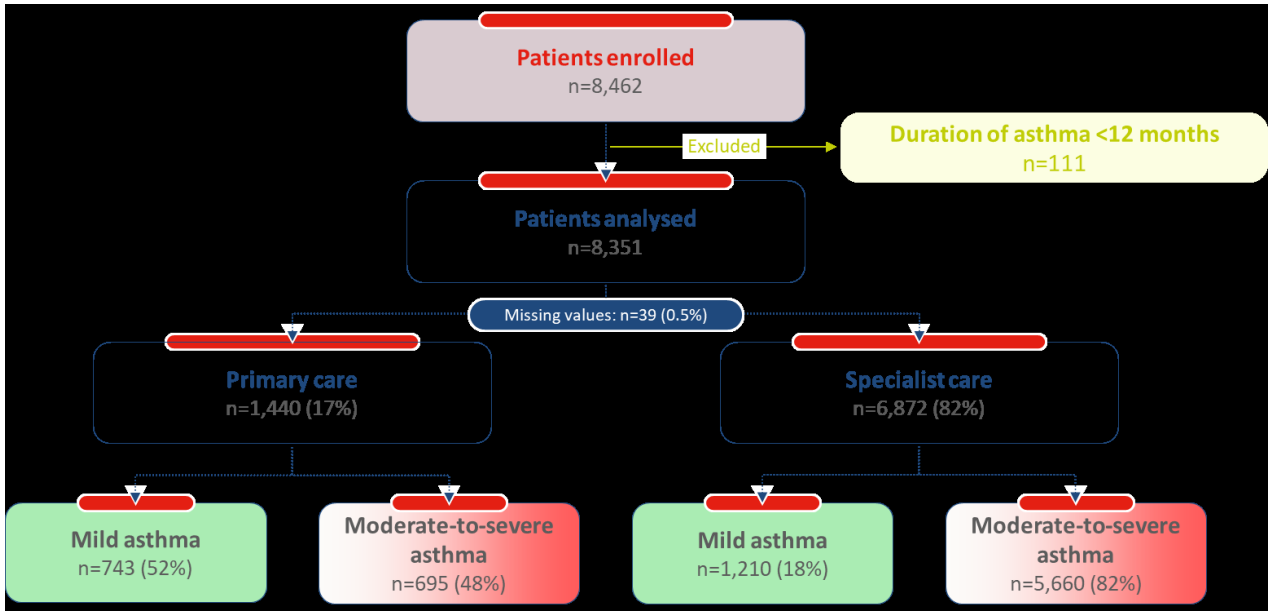
China, Hong Kong, Morocco, Poland, Portugal, Romania, Switzerland, US; more to enroll soon

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).

- 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



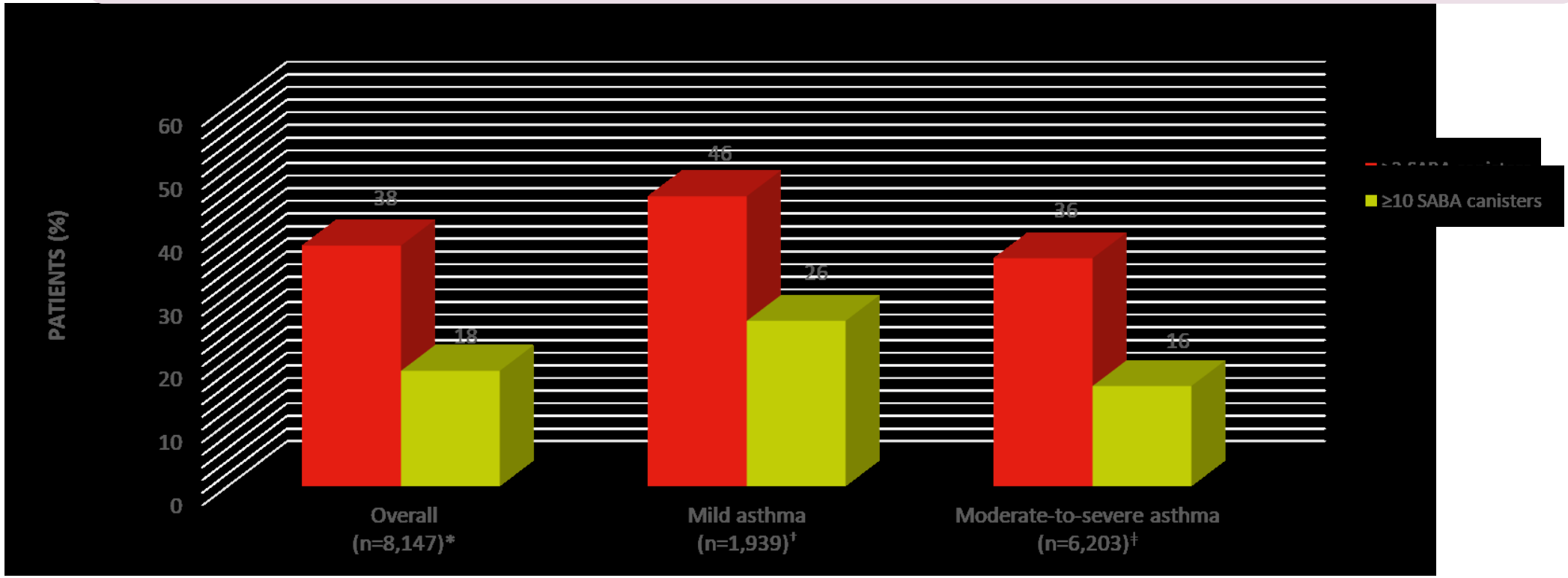


Of the patients included, 37% were from Asia, 21% from Africa, 17% from the Middle East, 13% from Latin America, 7% from Russia and 5% from Australia

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.

- 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

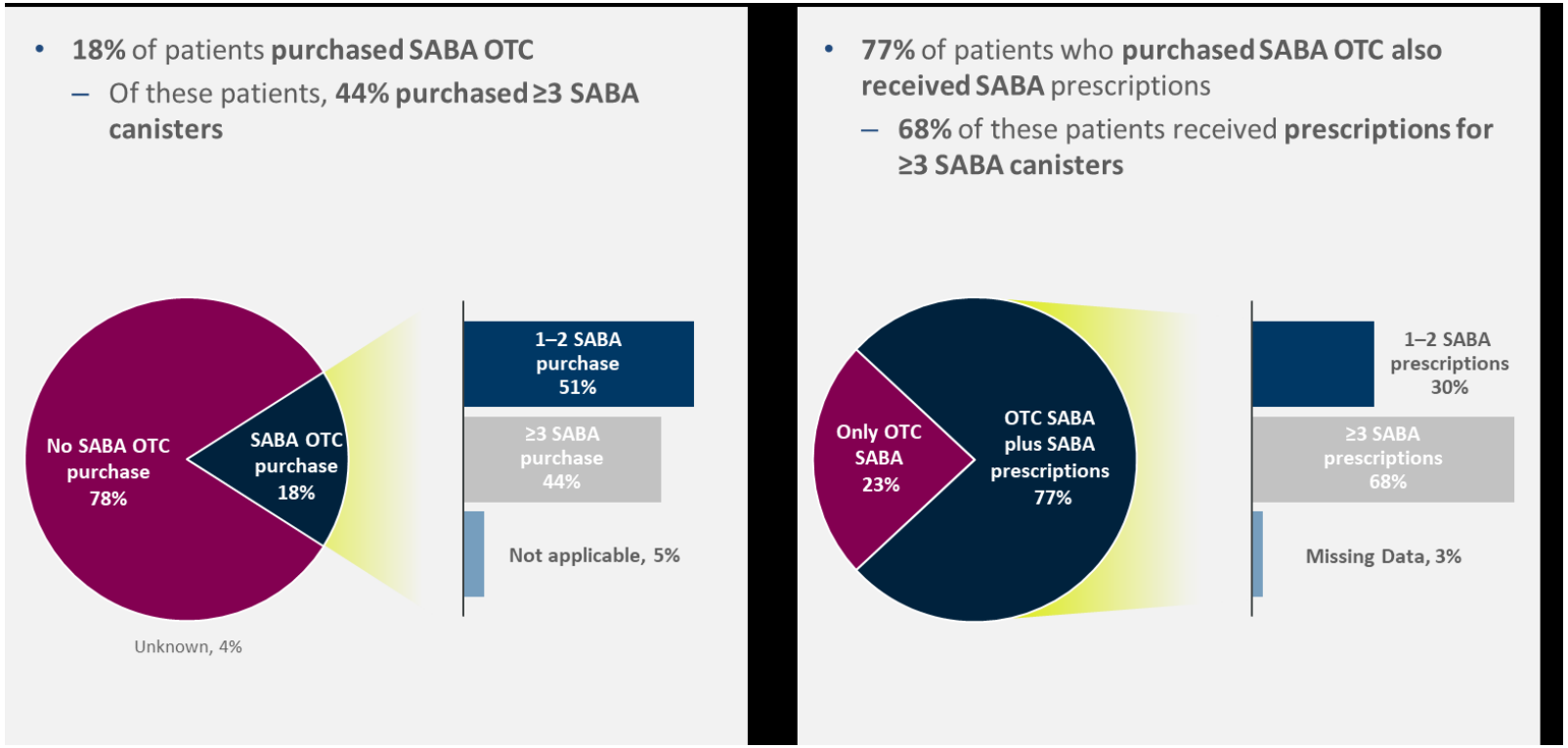
61% of the patients who were prescribed SABA had used more than 3 canister per year (overuse)



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.

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

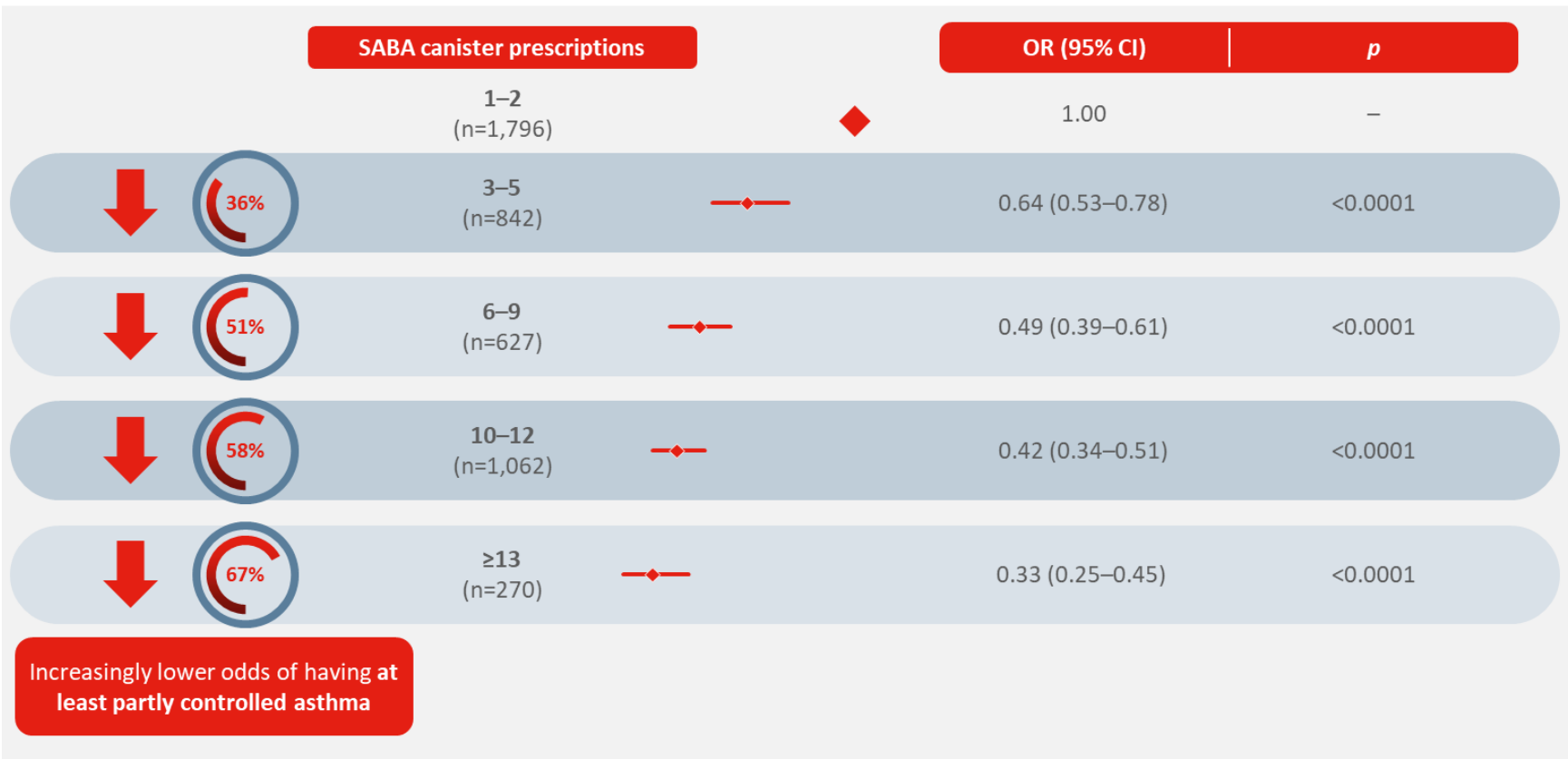
44% of patients who buy SABA as OTC, over use SABA



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.

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

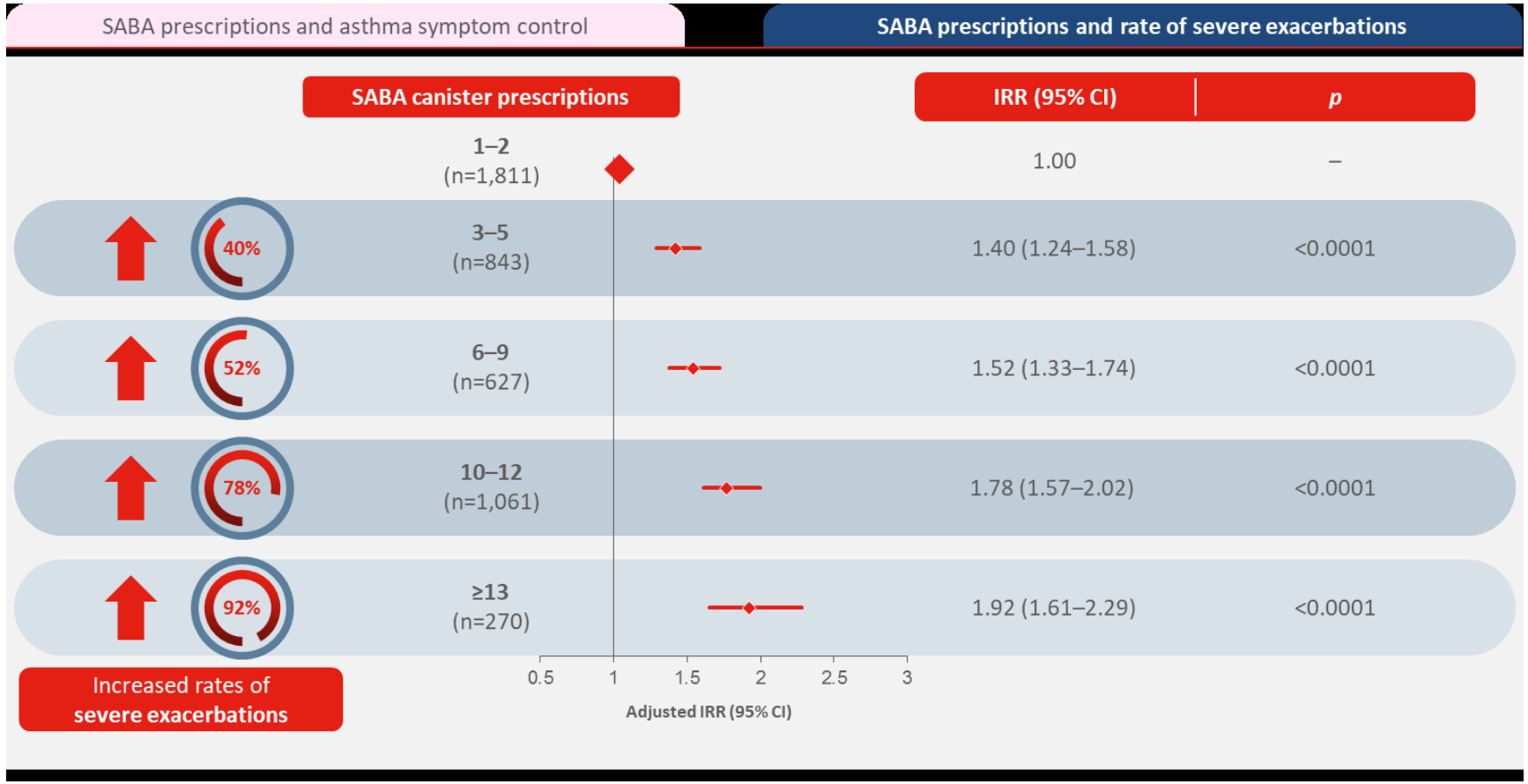
SABA prescriptions and asthma symptom control | SABA prescriptions and rate of severe exacerbations



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.

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

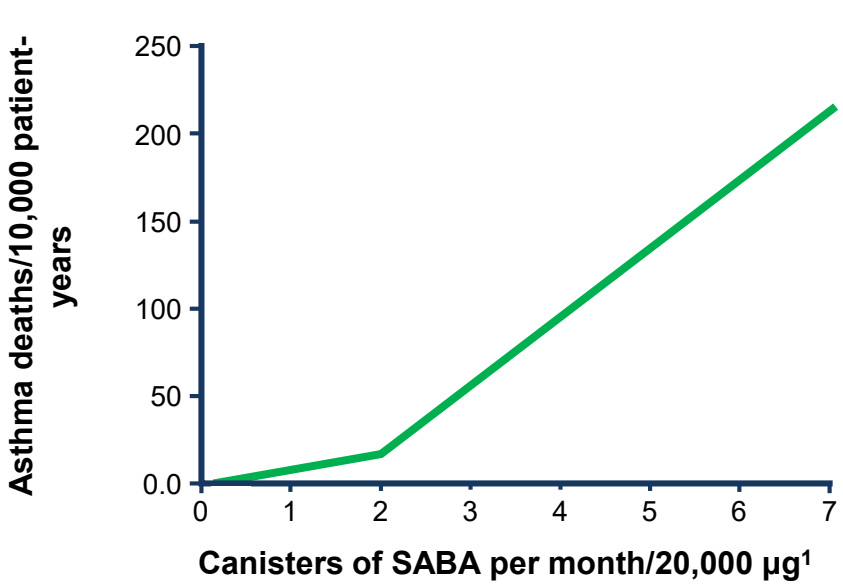


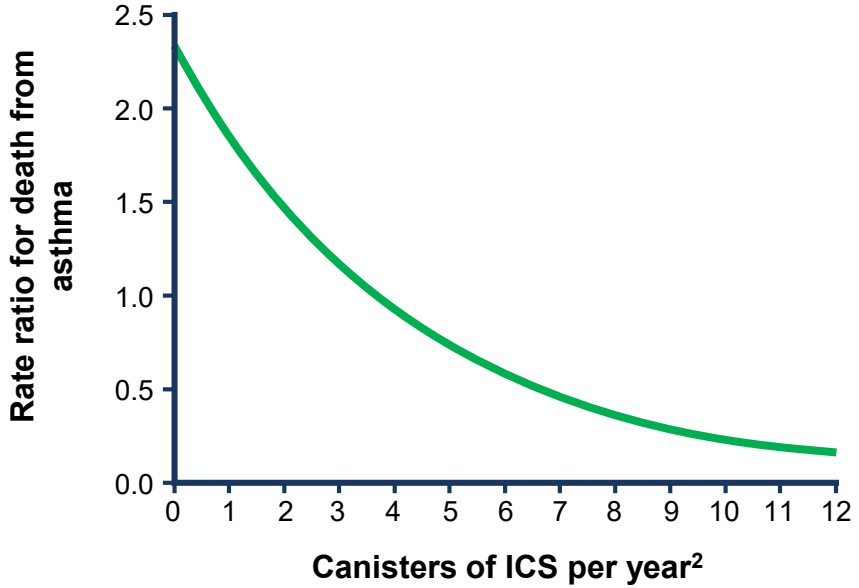
Analyses were adjusted for the following covariates: country, age, sex, BMI, smoking history, GINA step, and education level. Severe exacerbations were defined as per American Thoracic Society/European Respiratory Society recommendations.
BMI, body mass index; GINA, Global Initiative for Asthma; IRR,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

Over-reliance on SABA and under-use of ICS are both associated with an increase in mortality

- Over-reliance on SABA at the expense of ICS controller therapy is associated with an increased risk of asthma-related death, as a result of under-treatment of inflammation[1-2]

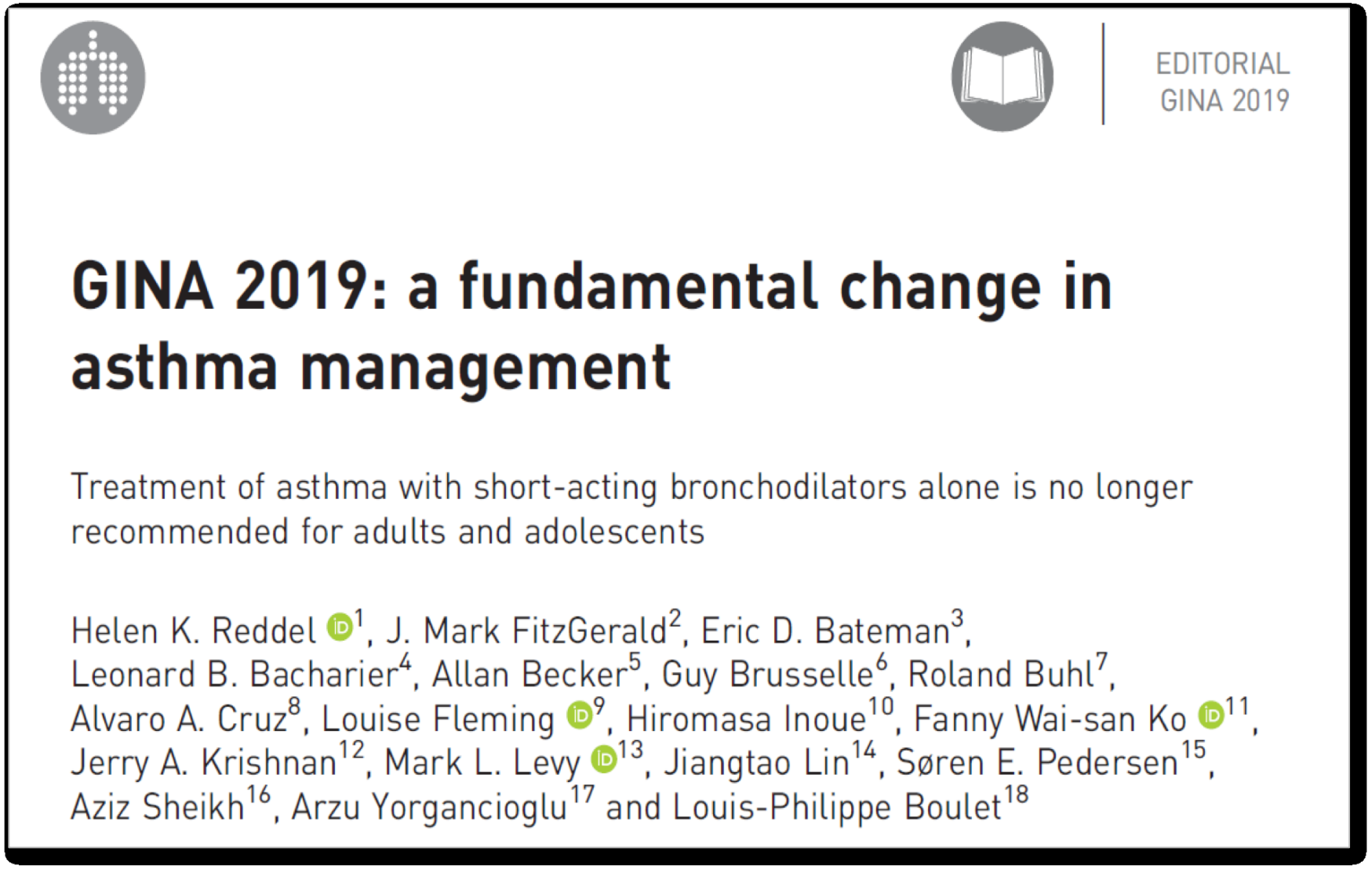




- Episodes of high reliever use (>6 inhalations/day on at least one day) are also predictive of an increased risk of exacerbations[3]

1. Suissa S, Ernst P, Boivin JF, Horwitz RI, Habbick BR, Cockroft D, Blais L, McNutt M, Buist AS, Spitzer WO. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. American journal of respiratory and critical care medicine. 1994 Mar;149(3):604-10. 2. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. New England Journal of Medicine. 2000 Aug 3;343(5):332-6. 3. Buhl R, Kuna P, Peters MJ, Andersson TL, Naya IP, Peterson S, Rabe KF. The effect of budesonide/formoterol maintenance and reliever therapy on the risk of severe asthma exacerbations following episodes of high reliever use: an exploratory analysis of two randomised, controlled studies with comparisons to standard therapy. Respiratory research. 2012 Dec;13(1):59.

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.

Personalized asthma management

CONTROLLER
PREFERRED RELIEVER

STEPS 1 – 2

STEP 3

STEP 4

STEP 5

CONTROLLER
ALTERNATIVE RELIEVER

STEP 1

STEP 2

STEP 3

STEP 4

STEP 5

	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*

Disclaimer : (Budesonide/Formoterol is indicated only in management of Moderate to Severe Asthma (GINA Stage 3 to 5) as per label in Jordan , Iraq, Syria ,Sudan & Libya

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

Why Symbicort® Turbuhaler® is different?

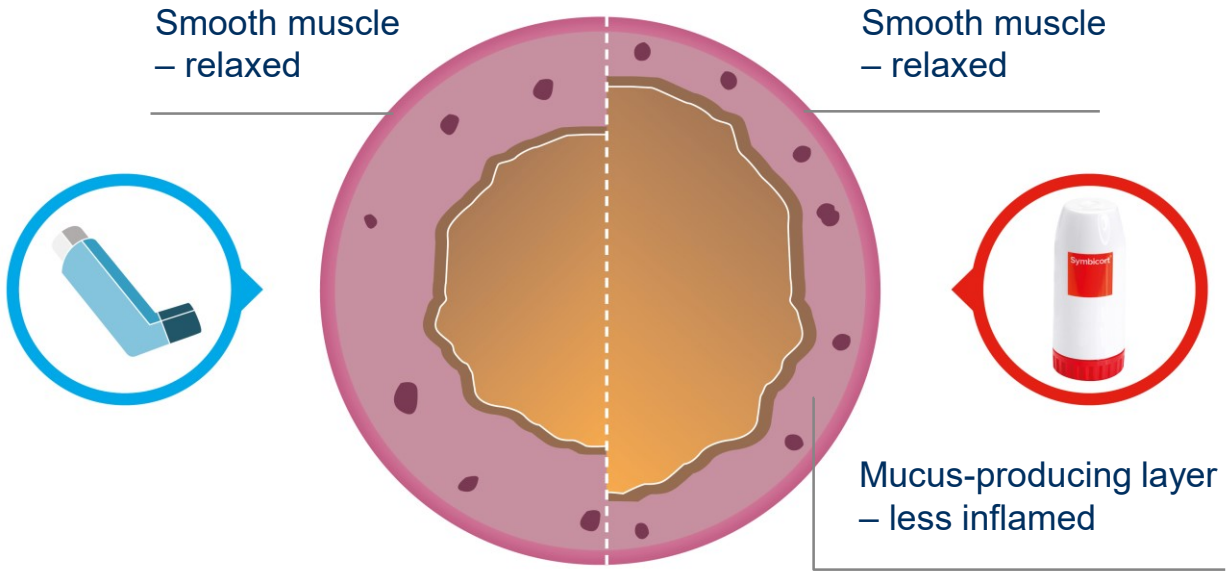
Symbicort®
budesonide/formoterol

Symbicort® – Efficacy Data: Exacerbations

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**

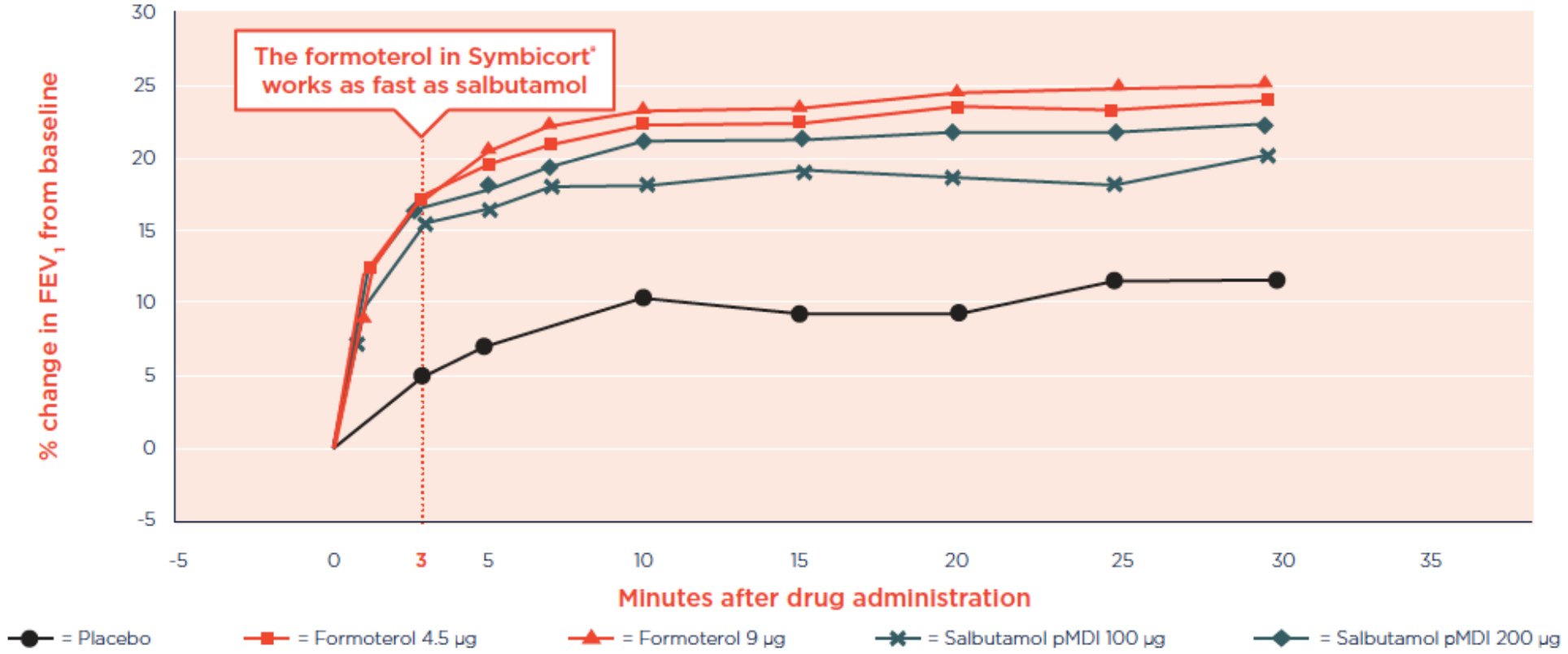
to reduce exacerbations[1,2] and provide 24-hour symptom control[3]

*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.

- Improvement in FEV_1 is as rapid and effective with formoterol 4.5 or 9 µg as with salbutamol 100 or 200 µg



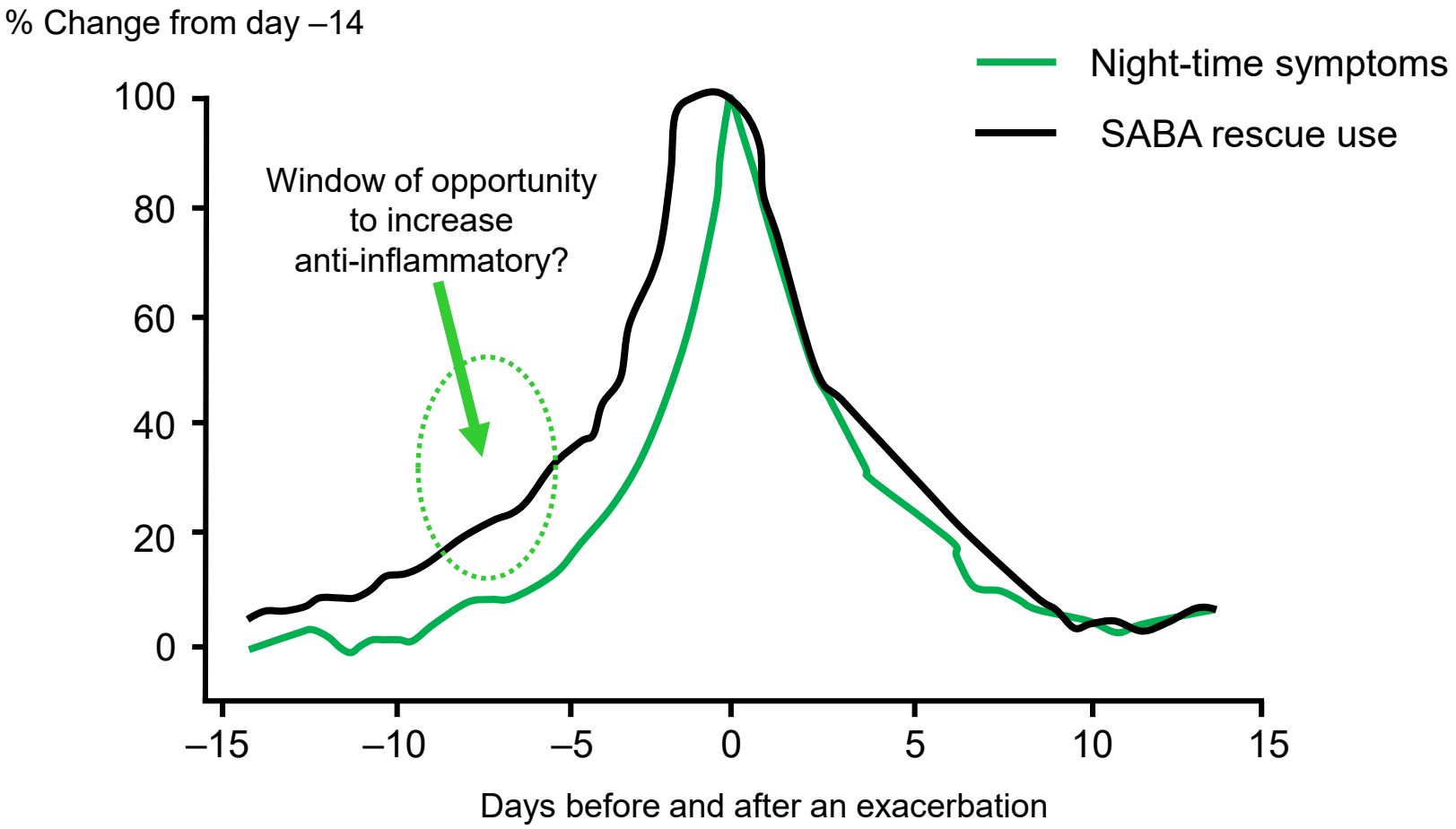
N = 36

Figure source: Seberová E and Andersson A. 2000

FEV_1, forced expiratory volume in 1 second; pMDI, pressurised metered dose inhaler

Seberová E, Andersson A. Oxis®(formoterol given by Turbuhaler®) showed as rapid an onset of action as salbutamol given by a pMDI. Respiratory medicine. 2000 Jun 1;94(6):607-11..

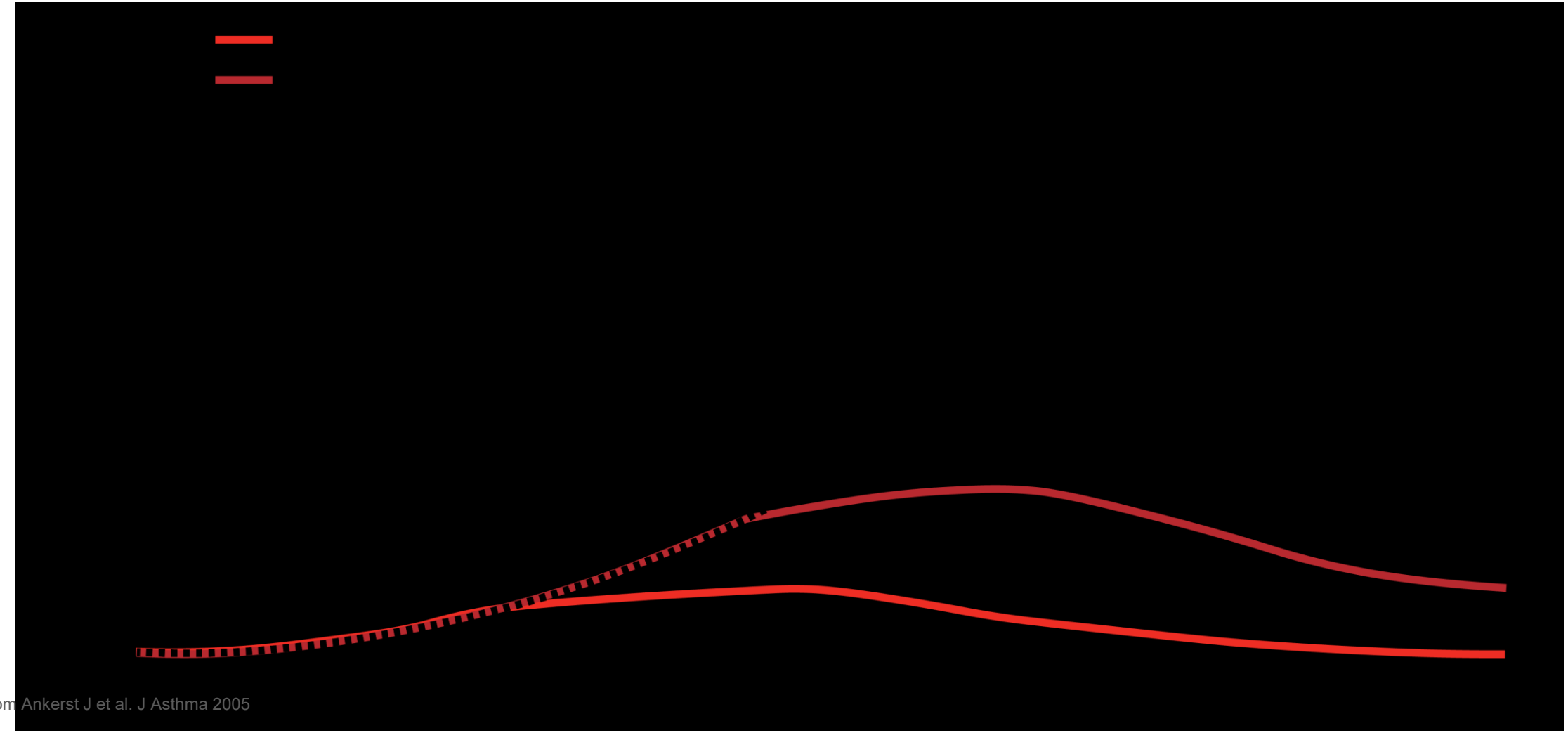
Profile of 425 exacerbations



SABA, short-acting β_2-agonist.

Adapted from Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer CA, O'BYRNE PM, Lofdahl CG, Pauwels RA, Ullman A. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. American journal of respiratory and critical care medicine. 1999 Aug 1;160(2):594-9.

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 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

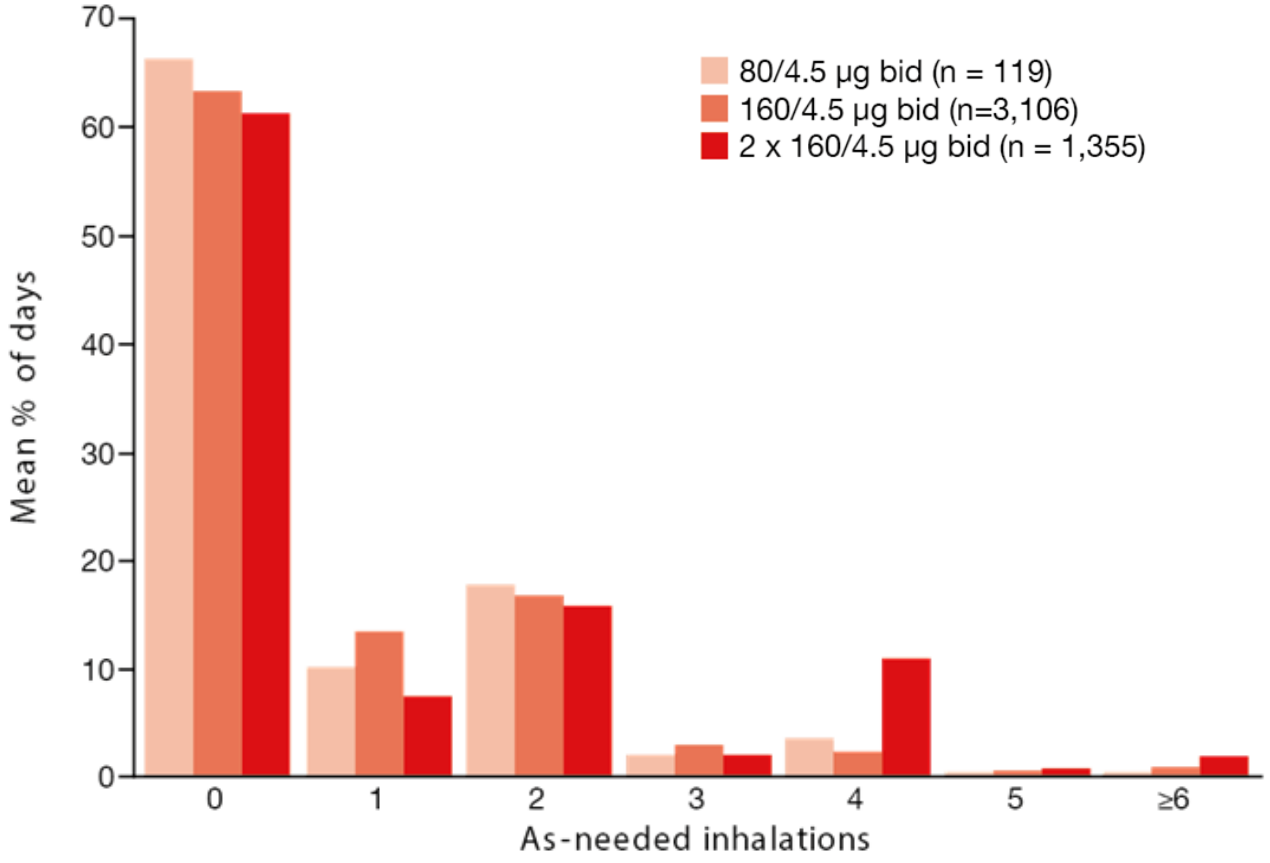


Figure adapted from Stahlberg et al, 2015.

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..

- Patients on the most common regimen used a mean of 2.53 inhalations per day in total,[1] compared with an assumption of 3 inhalations per day (two maintenance, one as-needed) based on previous clinical trials[2–5]
- This reduction suggests mean medication costs with Symbicort® (160/4.5 µg bid plus as-needed) may be 15% lower in real-life practice than previous clinical trials have suggested

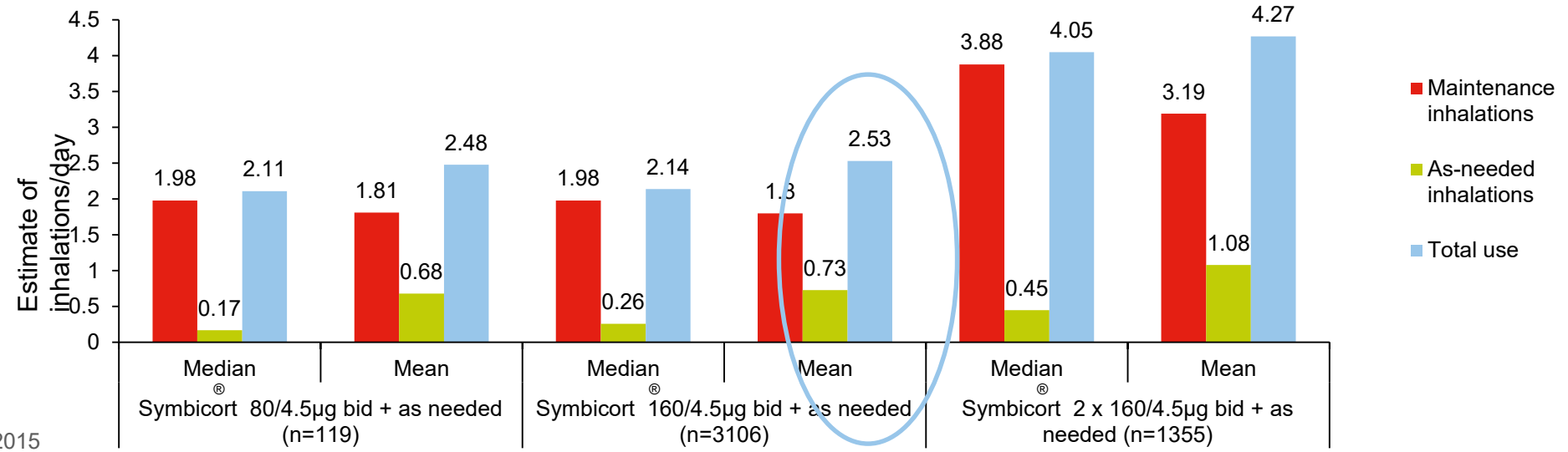


Figure source: Stallberg et al. 2015

*Symbicort® maintenance and reliever therapy

bid, twice per day; RCT, randomised controlled trial

1.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. 2. 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. 3. 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. 4. Bousquet J, Boulet LP. Peters MJ et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med 2007*; **101**: 2437-46. 5. Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *OpinCurr Med Res 004*; **20**: 1403-18

1

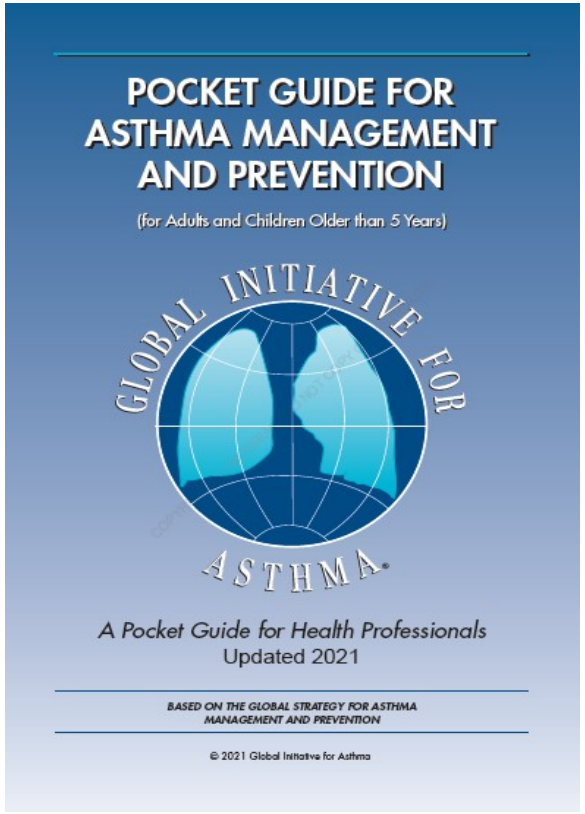
***Track 1*: The reliever is as-needed low dose ICS-formoterol.**
This is the preferred approach recommended by GINA for adults and adolescents. Using low dose ICS-formoterol as reliever reduces the risk of severe exacerbations compared with regimens with SABA as reliever, with similar symptom control.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

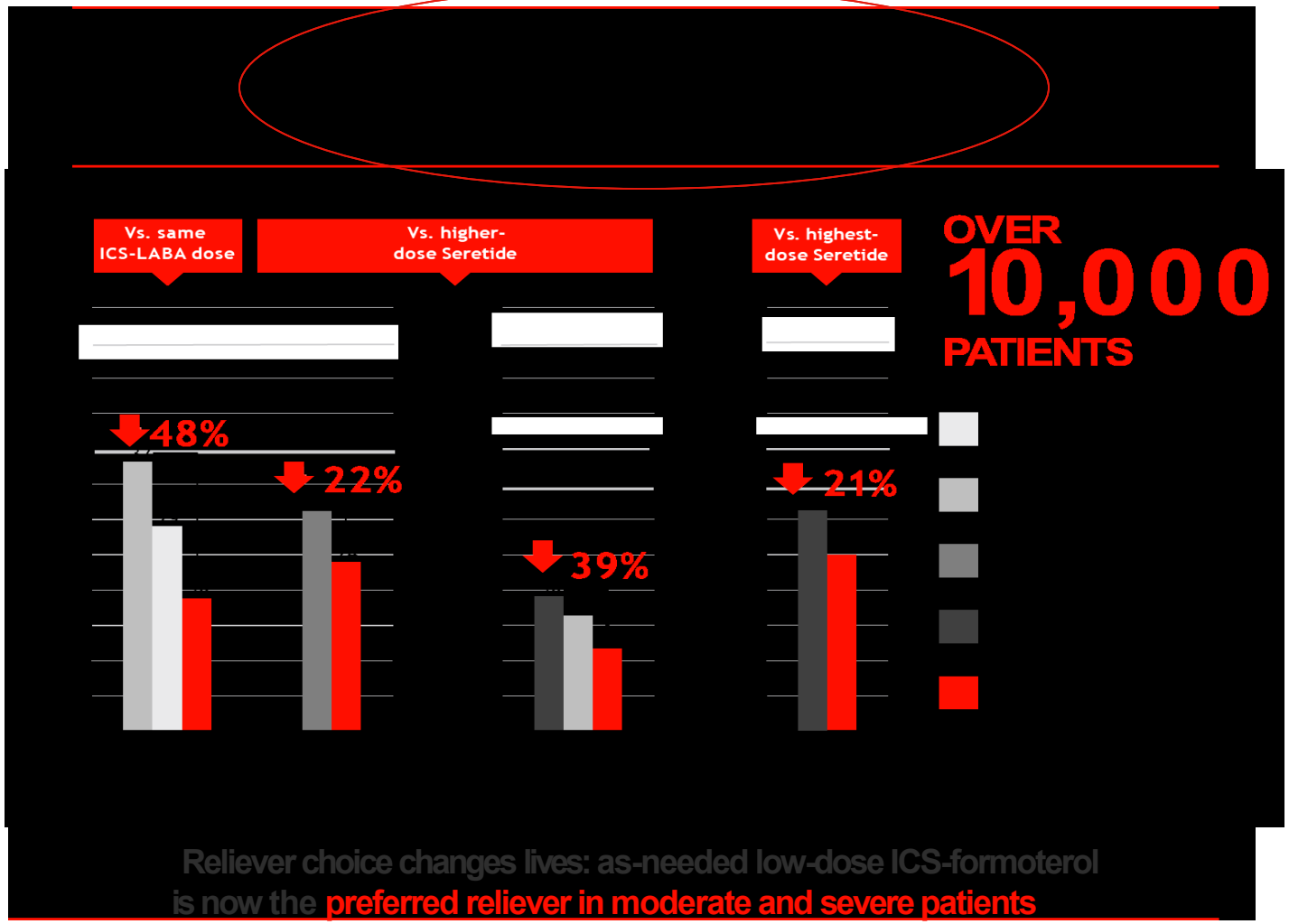
***Track 2*: The reliever is as-needed SABA.** This is an alternative approach when Track 1 is not possible or is not preferred by a patient who has no exacerbations on their current therapy.



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

Disclaimer : (Budesonide/Formoterol is indicated only in management of Moderate to Severe Asthma (GINA Stage 3 to 5) as per label in Jordan , Iraq, Syria ,Sudan & Libya

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



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

. 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.

fewer severe exacerbations**

with Symbicort®* 160/4.5 µg bd + additional inhalations as needed vs salmeterol/fluticasone 50/250 µg bd + SABA as needed[1]

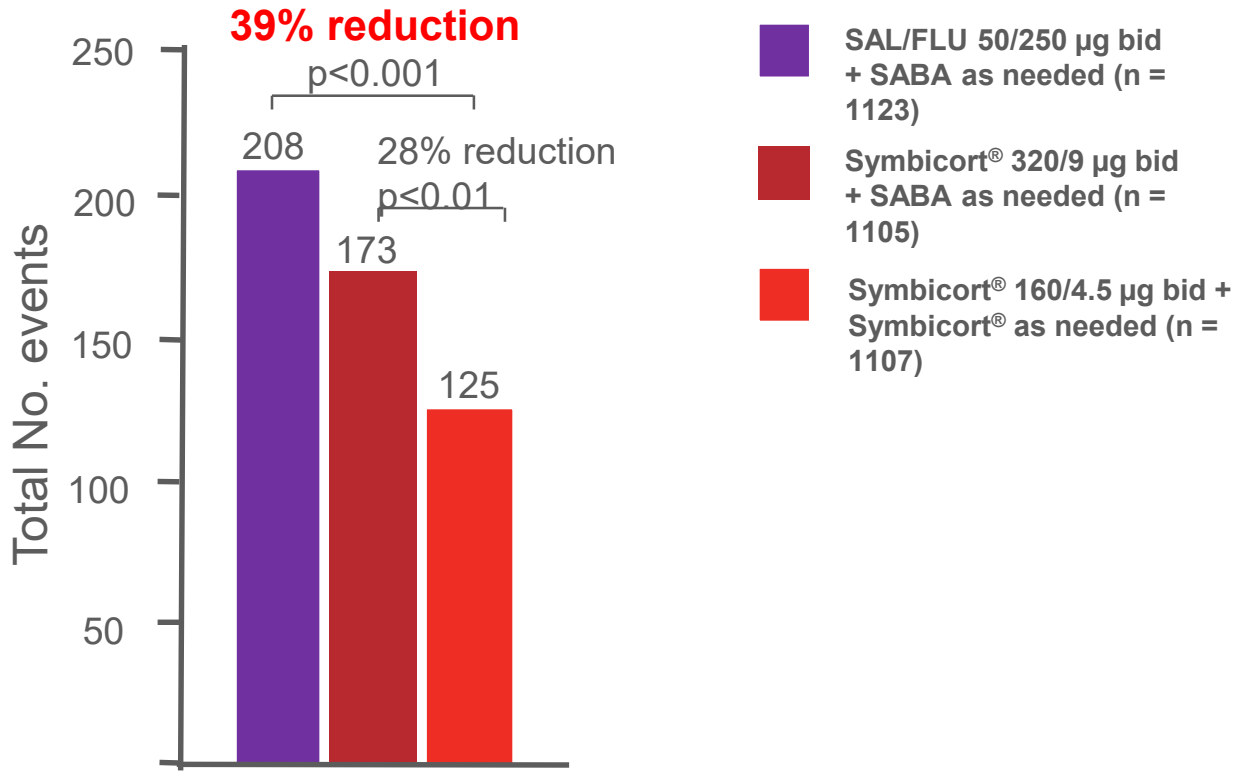
- 19 and 12 events/100 patients/6 months for salmeterol/fluticasone + SABA and Symbicort®*, respectively[1]
- Total number of severe exacerbations = 208 vs 125 for salmeterol/fluticasone + SABA and Symbicort®*, respectively[1]

*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). 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). Rate reduction for severe exacerbations: 0.61; 95% CI 0.49-0.76.[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.

- As well as meeting its primary endpoint (time to first severe exacerbation), in this study, Symbicort®* reduced the number **of severe exacerbations** over 6 months



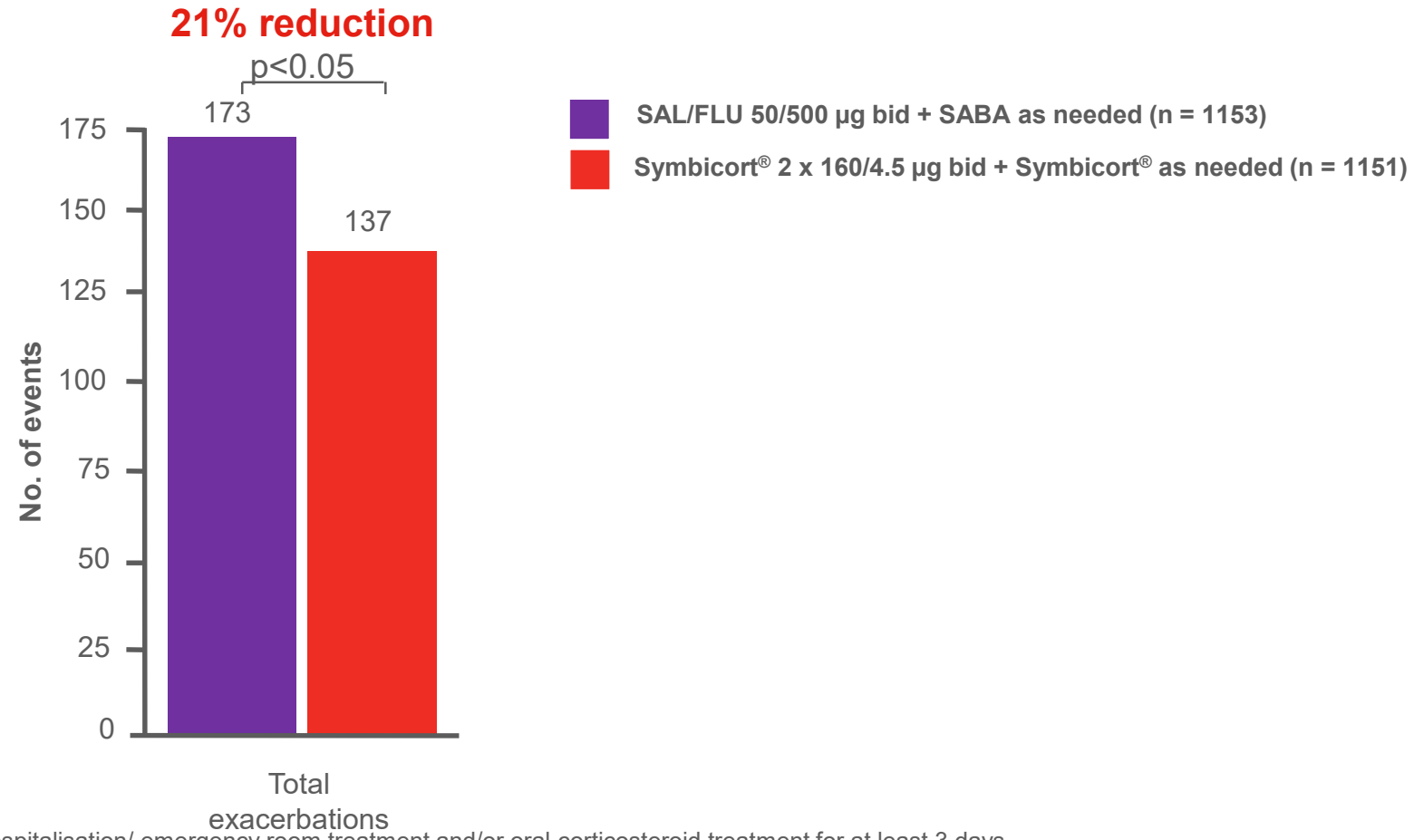
*Symbicort® maintenance and reliever therapy.

Severe exacerbations were defined as exacerbations requiring either **A.** hospitalisation, **B.** emergency room treatment or **C.** treatment with oral steroids

bid, twice per day; 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.

- Although the primary endpoint (time to first **severe exacerbation**) was not met, in this study, Symbicort®* reduced the number of severe exacerbations over 6 months



*Symbicort® maintenance and reliever therapy.

Severe exacerbations were defined as deterioration in asthma leading to hospitalisation/ emergency room treatment and/or oral corticosteroid treatment for at least 3 days

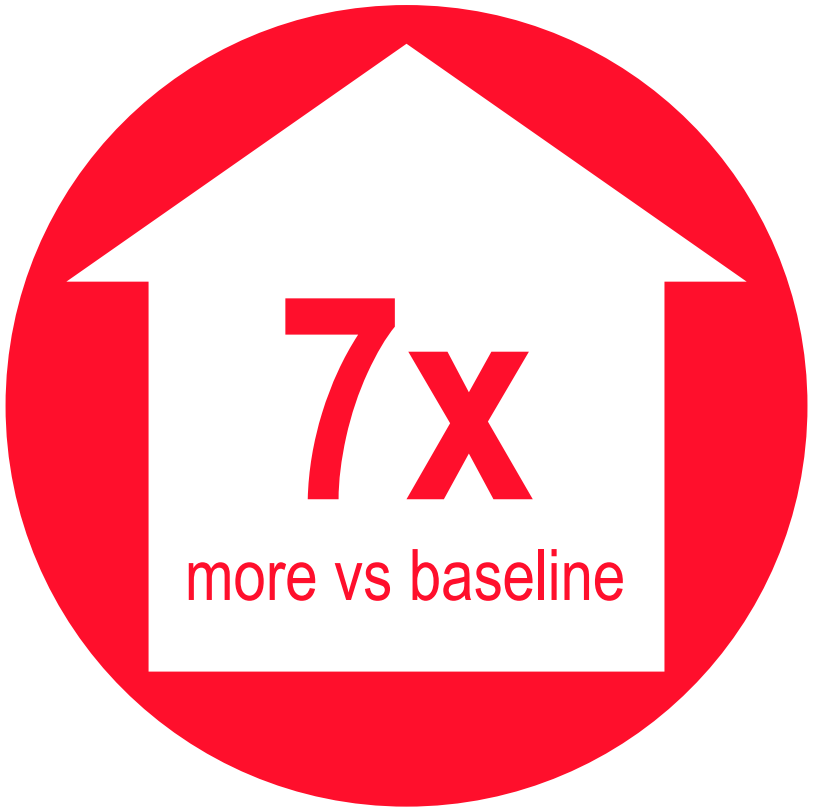
bid, twice per day; SABA, short-acting β_2-agonist; SAL/FLU, salmeterol/fluticasone.

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.

Why Symbicort® Turbuhaler® is different?

Symbicort®
budesonide/formoterol

Symbicort® – Efficacy data: Symptoms and asthma control



Asthma control days

Asthma control days defined as:

- no day-time symptoms
- no night-time symptoms
- no night awakenings caused by asthma
- no as-needed medication use

Symbicort®*: Baseline 5.8% vs Treatment 41.3%

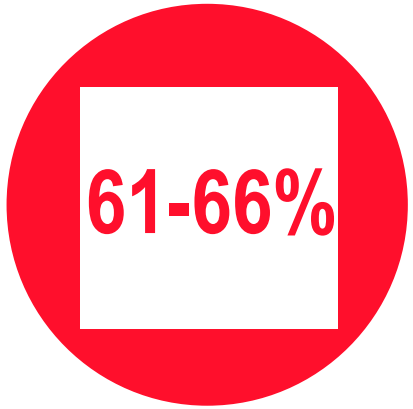
*Symbicort® maintenance and reliever therapy

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 (p=0.0034). 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]

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.

reduction in night-time awakenings vs baseline[1]

Symbicort®*: Baseline 33.7% vs Treatment 14.1%



reliever-free days**[2]

Symbicort®* was associated with a high proportion of reliever-free days in this study involving 4581 patients enrolled from 12 countries[2]

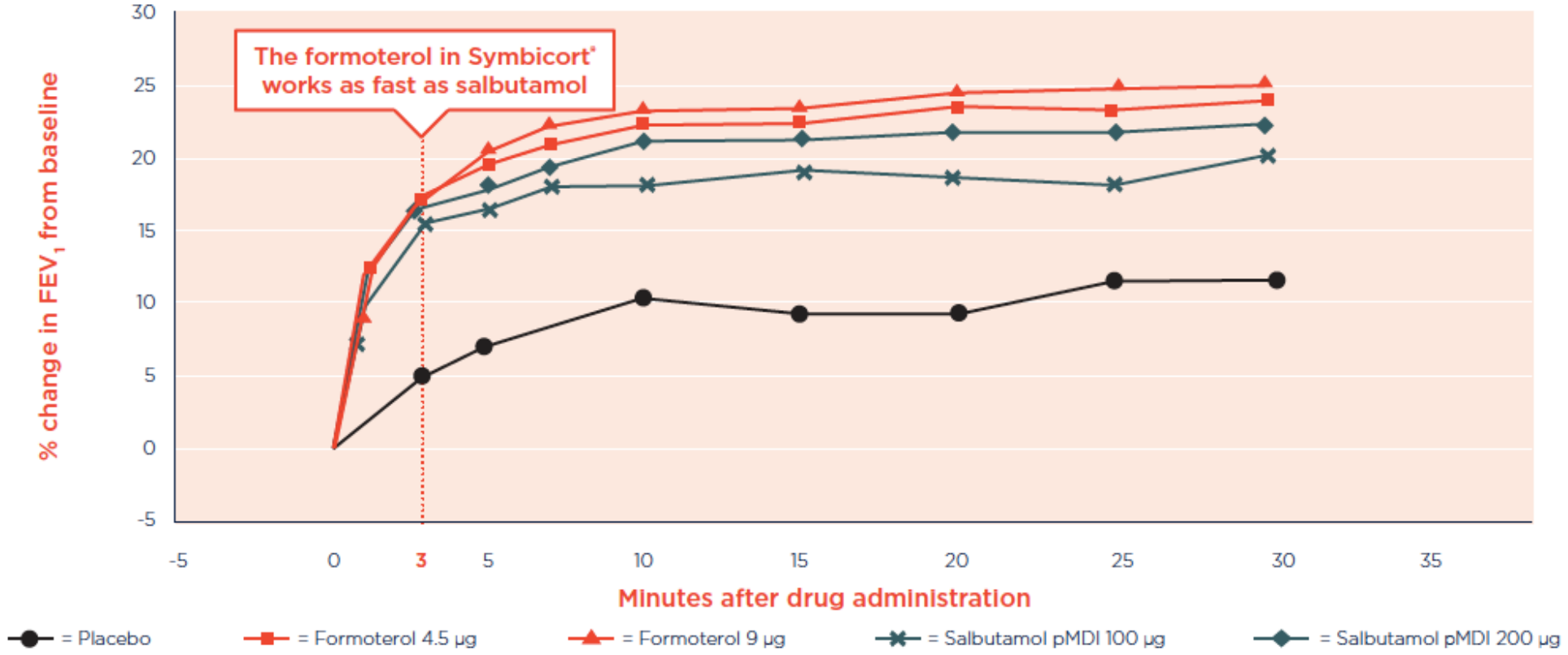
… now also demonstrated in real-life use in clinical practice[2]

*Symbicort® Maintenance and Reliever

Patients in the two lower-dose groups had slightly more reliever-free days[2] **Ref 1: 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 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 (p=0.0034). Study results also showed salmeterol/fluticasone 25/125 µg two inhalations bd + terbutaline as needed has similar results for night-time awakenings: Baseline 31.5% vs Treatment 14.0%. **Ref 2:** 12-month European observational study undertaken to fulfil regulatory commitments, enrolled patients prescribed Symbicort® Maintenance and Reliever and grouped them based on regimen: 80/4.5 µg one inhalation twice daily (bd); 160/4.5 µg one inhalation bd; 160/4.5 µg two inhalations bd (all plus as needed). Primary outcome was met: mean (median) total numbers of Symbicort® inhalations/day were 2.48 (2.11), 2.53 (2.14), and 4.27 (4.05) for 80/4.5 µg bd, 160/4.5 µg bd, and 2 × 160/4.5 µg bd, respectively.

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. ; 2. 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.

- Improvement in FEV_1 is as rapid and effective with formoterol 4.5 or 9 µg as with salbutamol 100 or 200 µg



N = 36

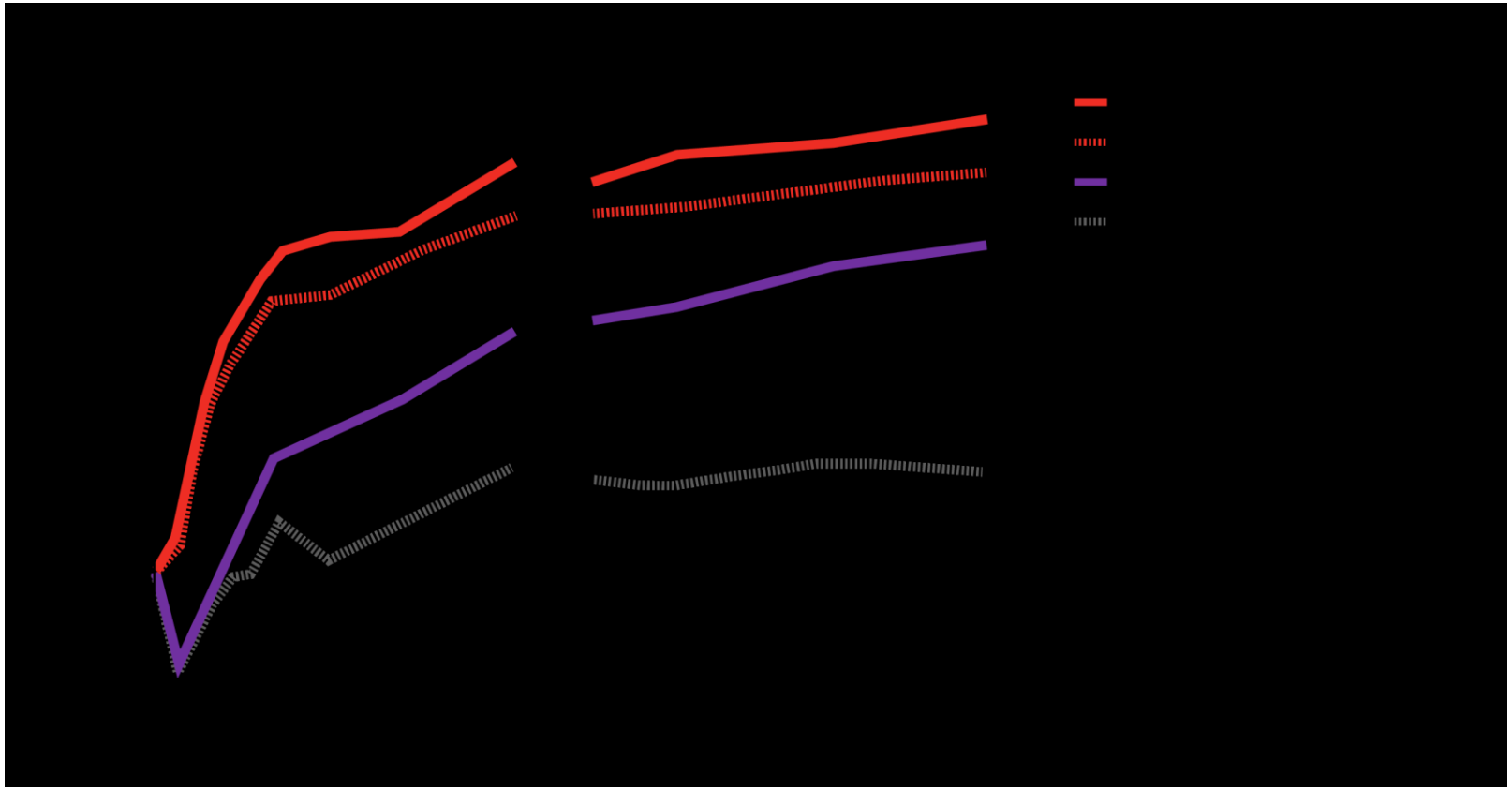
Figure source: Seberová E and Andersson A. 2000

FEV_1, forced expiratory volume in 1 second; pMDI, pressurised metered dose inhaler

Seberová E, Andersson A. Oxis®(formoterol given by Turbuhaler®) showed as rapid an onset of action as salbutamol given by a pMDI. Respiratory medicine. 2000 Jun 1;94(6):607-11..

- Symbicort® showed a faster onset of action than salmeterol/fluticasone (mean FEV_1 at 3 min or average FEV_1 0–15 min, both $p<0.001$) in a double-blind, randomised, placebo-controlled and crossover study

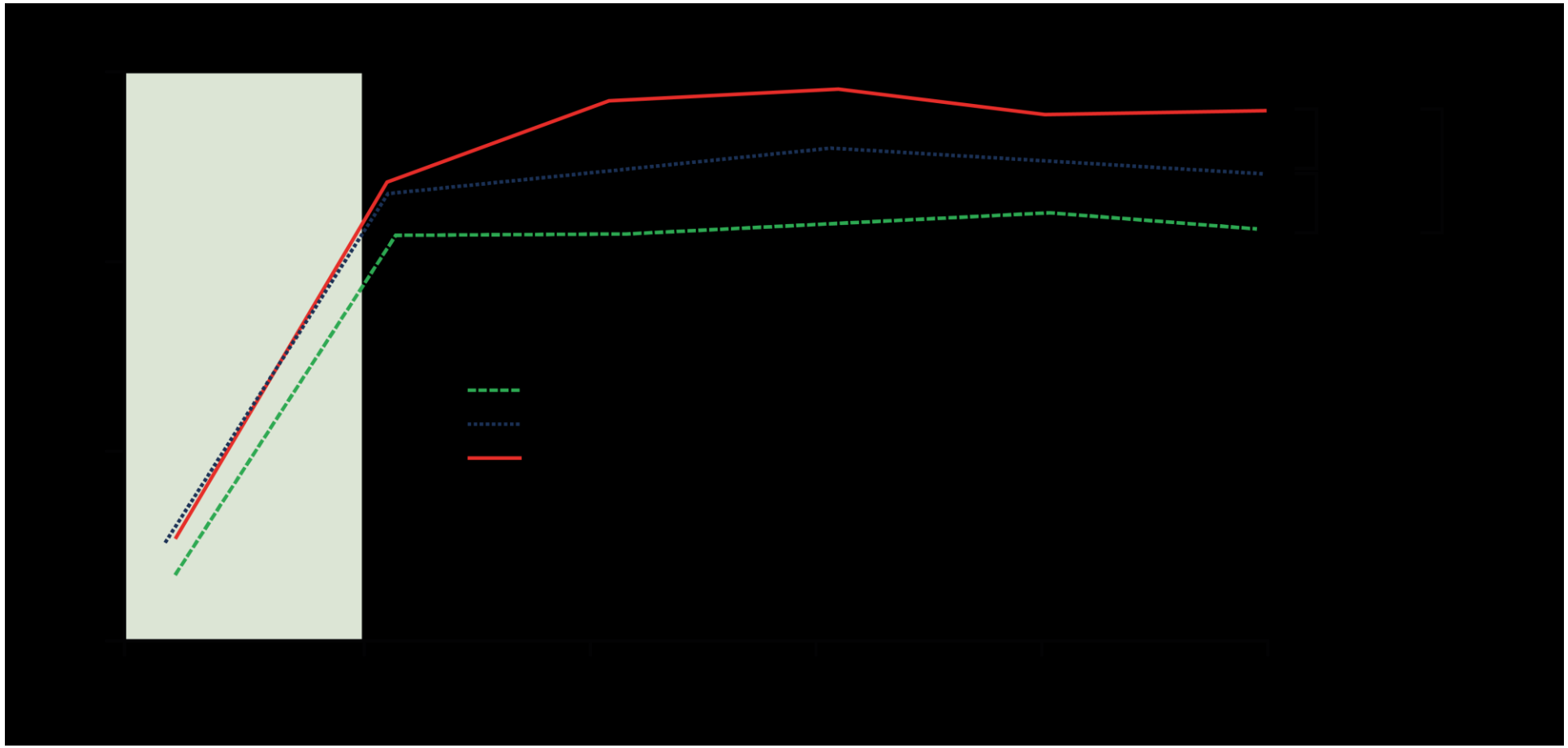
Percent FEV_1 change up to 15 min and 3 hours with Symbicort® (one or two inhalations; 160/4.5 mg) compared with salmeterol/fluticasone (50/250 mg) and placebo



FEV_1, forced expiratory volume in 1 second

Palmqvist M, Arvidsson P, Beckman O, Peterson S, Lötvall J. Onset of bronchodilation of budesonide/formoterol vs. salmeterol/fluticasone in single inhalers. Pulmonary pharmacology & therapeutics. 2001 Jan 1;14(1):29-34.

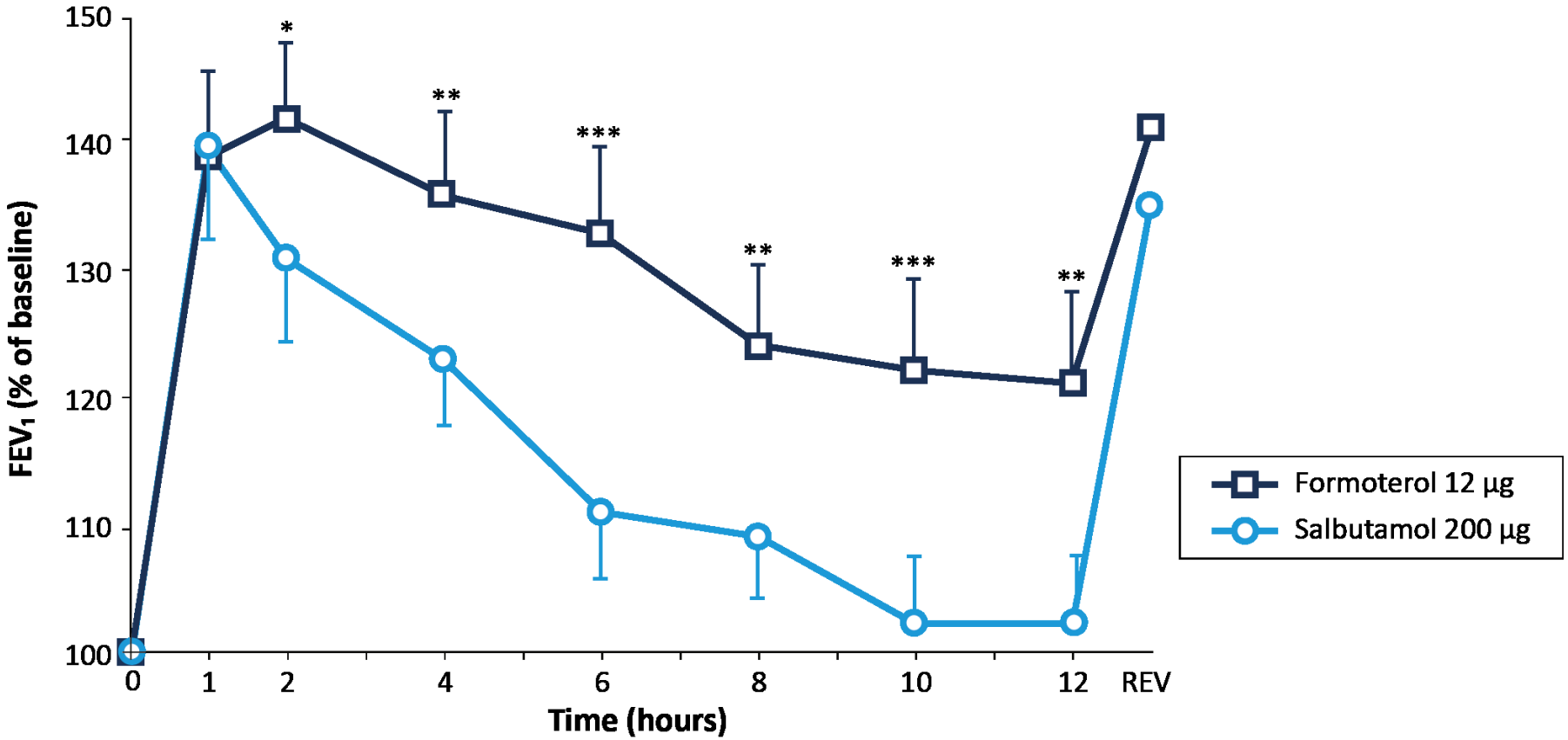
- Increases in FEV_1 occurred in each treatment group during run-in when all patients used budesonide/formoterol maintenance plus SABA, but additional increases in FEV_1 were also seen with as-needed budesonide/formoterol vs formoterol and terbutaline



FEV_1, forced expiratory volume in 1 second; SABA, short-acting β_2-agonist.

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 randomized controlled, double-blind study. The Lancet. 2006 Aug 26;368(9537):744-53.;368:744–753

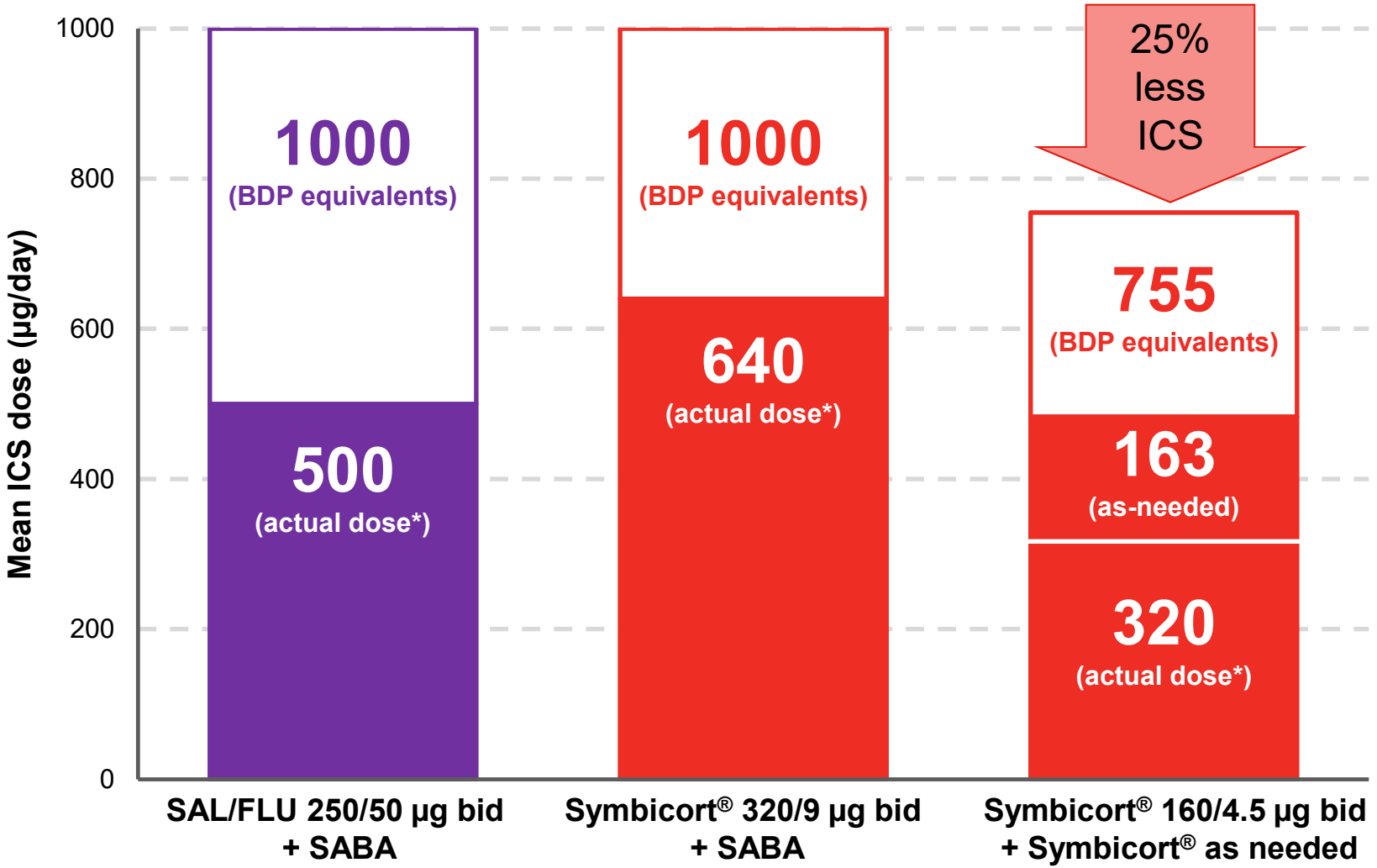
- The formoterol component of Symbicort® provides greater bronchodilation than salbutamol over 12 hours in patients with asthma



*p<0.05; **p<0.01; p<0.001

FEV_1, forced expiratory flow in 1 second; REV, reversibility

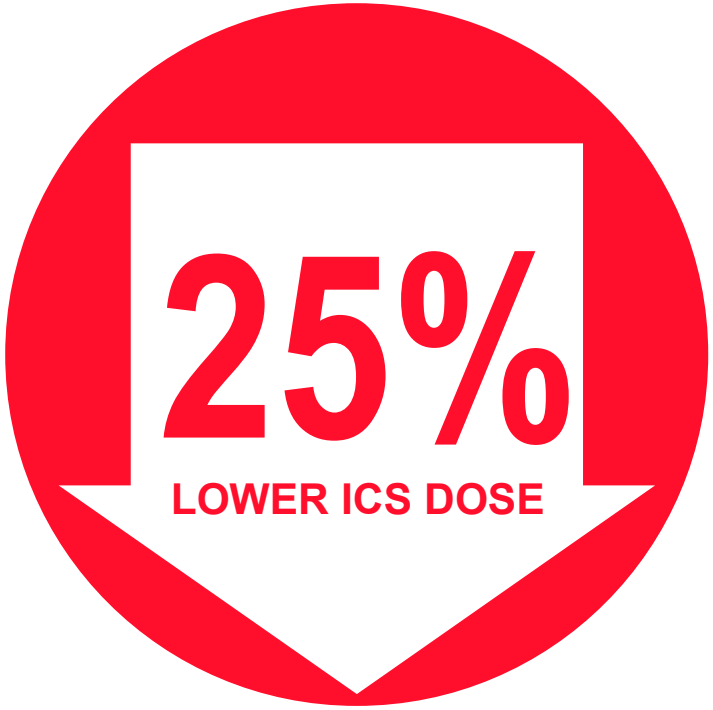
Maesen FP, Smeets JJ, Gubbelmans HL, Zweers PG. Bronchodilator effect of inhaled formoterol vs salbutamol over 12 hours. Chest. 1990 Mar 1;97(3):590-4.



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

lower mean ICS dose†

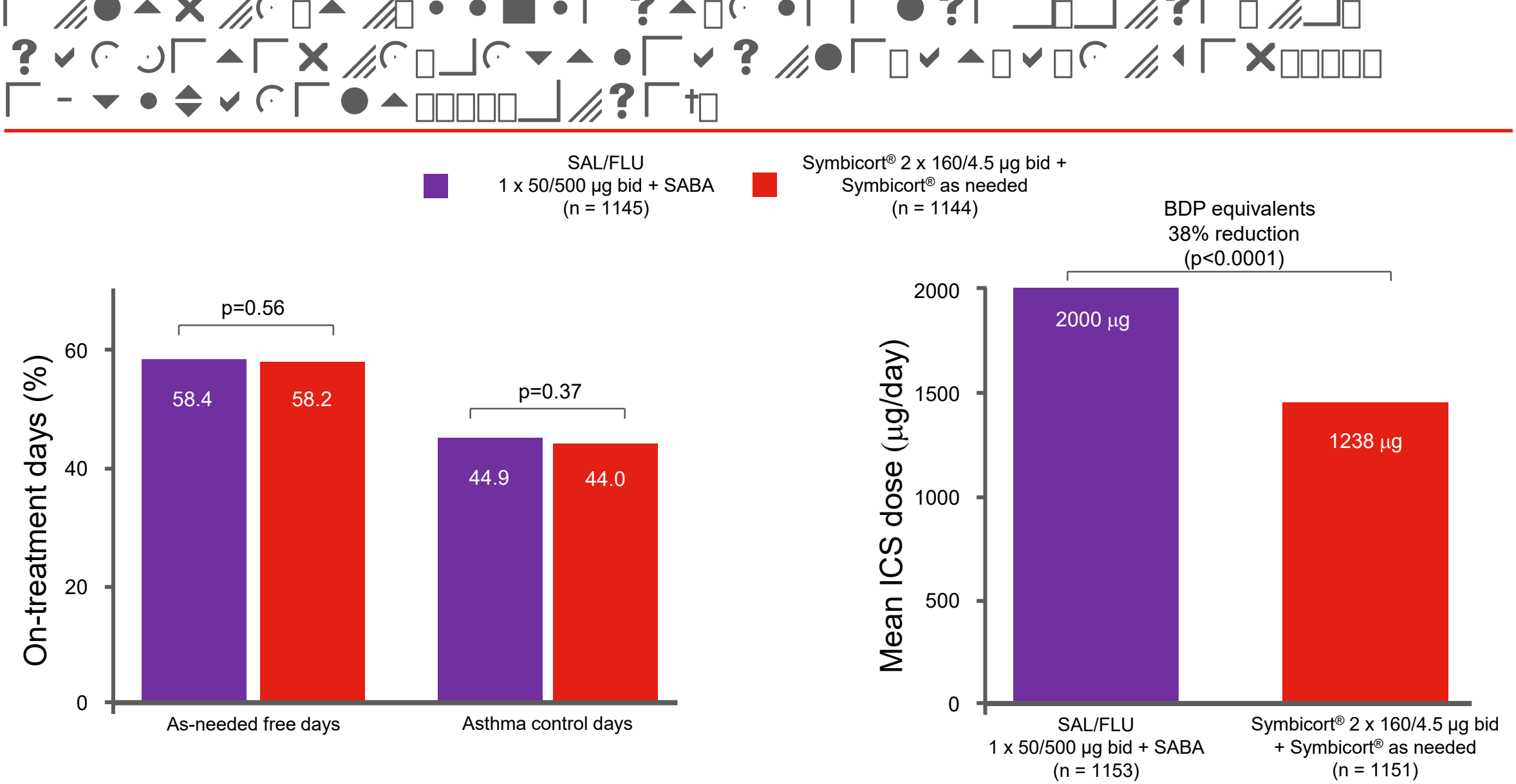
compared with salmeterol/fluticasone 50/250 µg bd + SABA as needed[1]

- 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.



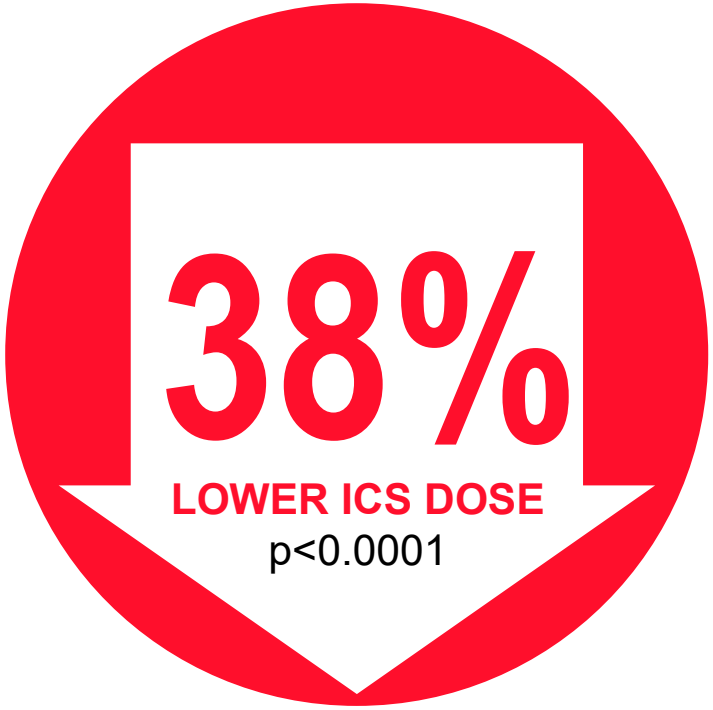
*Symbicort® maintenance and reliever therapy

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

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

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.

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

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, or 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

CFC: chlorofluorocarbon; DPI: dry powder inhaler; HFA: hydrofluoroalkane

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

Why Symbicort® Turbuhaler® is different?

Symbicort®
budesonide/formoterol

Symbicort® – Safety profile

- Data from RCTs in >14,000 patients indicate **no additional safety findings with Symbicort® as-needed on top of maintenance therapy compared to fixed maintenance dosing[1–5]**
- Safety data from the six double-blind RCTs in asthma, where Symbicort®* was used for ≥6 months in adults and adolescents, were assessed[6]
- Data pooling allowed examination of rarer events as well as predictable adverse effects
  - N=14,346
  - Co-primary endpoints: All-cause mortality and asthma-related SAEs
  - Secondary endpoints: Overall and cardiac SAEs, DAEs, asthma-related and cardiac-related DAEs
  - Estimated Mantel-Haenszel relative risks were calculated for Symbicort®* versus comparators

*Symbicort® maintenance and reliever therapy

DAE, discontinuation because of an adverse event; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; RCT, randomised controlled trial; SABA, short-acting β_2-agonist; SAE, serious adverse event

1. Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquert L, Centanni S, Boulet LP, Naya IP, Hultquist C. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Current medical research and opinion. 2004 Sep 1;20(9):1403-18 2. Rabe KF, Pizzichini E, Ställberg B, Romero S, Balanzat AM, Atienza T, Lier PA, Jorup C. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. Chest. 2006 Feb 1;129(2):246-56.; 3. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, Ekström T, Bateman ED. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. American journal of respiratory and critical care medicine. 2005 Jan 15;171(2):129-36 4. 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. 5. 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. 6. Sears MR, Radner F. Safety of budesonide/formoterol maintenance and reliever therapy in asthma trials. Respiratory medicine. 2009 Dec 1;103(12):1960-8.

- There **were no notable differences** between Symbicort®* and alternative fixed dose-treatment in terms of the incidence of β_2-agonist or ICS class-related AEs

Preferred term	Patients reporting ≥1 AE, n (%)	
	Symbicort®* (n = 5,584)	Comparators (n = 8,762)
Dysphonia	61 (1.1)	91 (1.0)
Oral candidiasis	58 (1.0)	69 (0.8)
Tremor	33 (0.6)	67 (0.8)
Palpitations	34 (0.6)	37 (0.4)
Pneumonia†	33 (0.6)	68 (0.8)
Cataract	3 (0.05)	4 (0.05)
Glaucoma	4 (0.07)	3 (0.03)

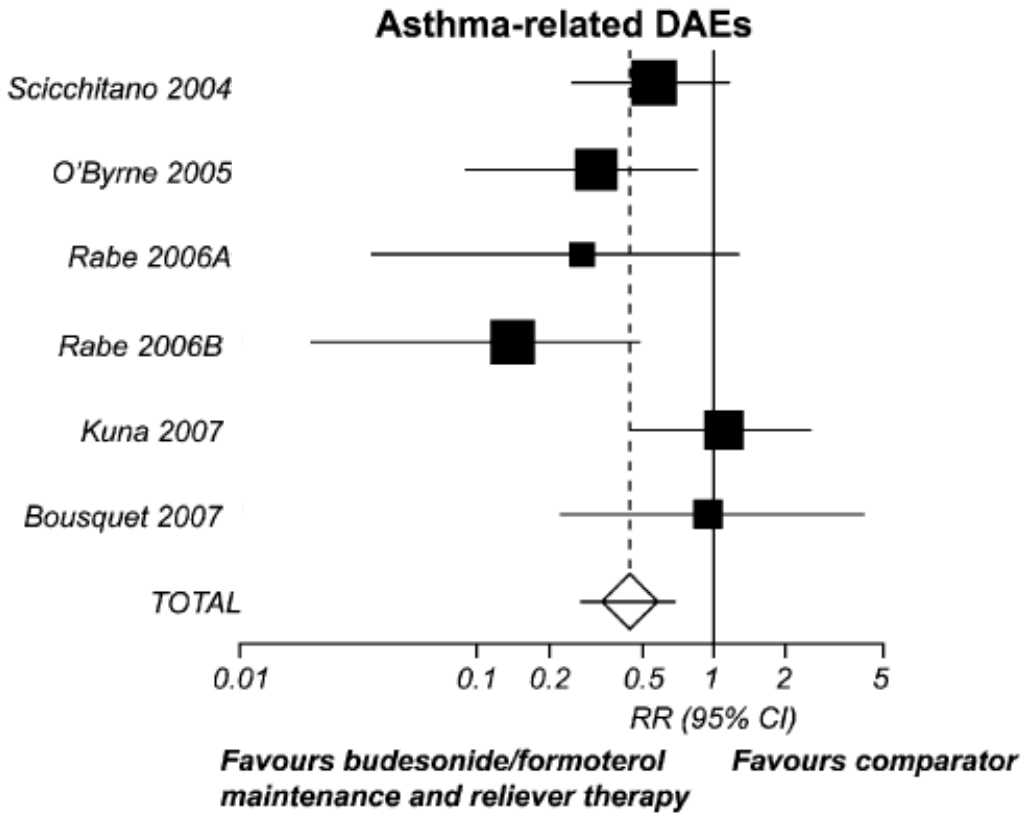
*Symbicort® maintenance and reliever therapy

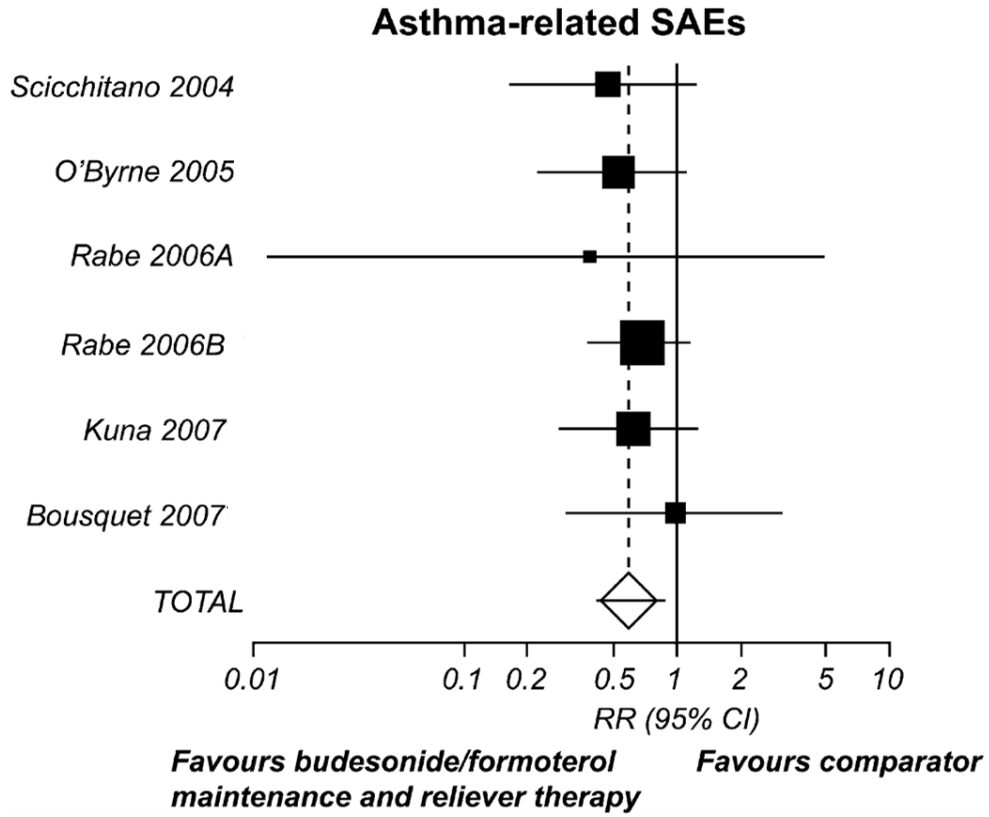
†Pneumonia was included for completeness, due to the current debate on the relationship between ICS use and pneumonia risk in COPD; †as there were multiple arms in some of the clinical trials, the number of patients in the comparator groups exceed those in the Symbicort® maintenance and reliever therapy groups.

AE, adverse event; ICS, inhaled corticosteroid.

Sears MR, Radner F. Safety of budesonide/formoterol maintenance and reliever therapy in asthma trials. Respiratory medicine. 2009 Dec 1;103(12):1960-8.

- Pooled analysis of safety data from six double RCTs found that asthma-related DAEs and SAEs were significantly reduced with Symbicort®* vs comparator therapy



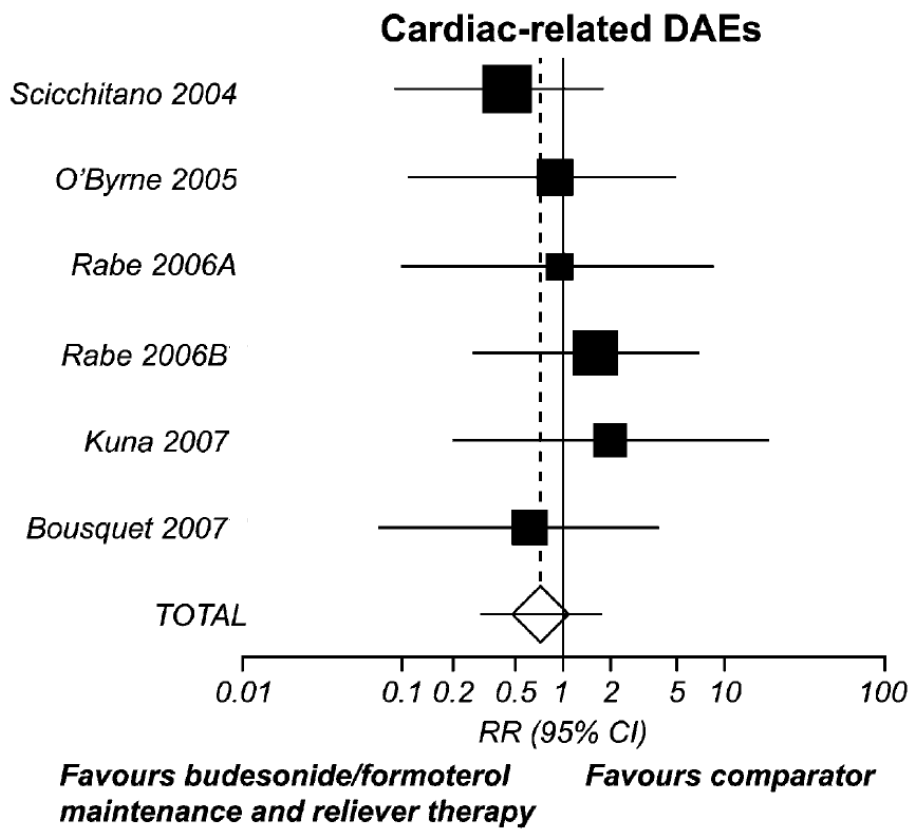


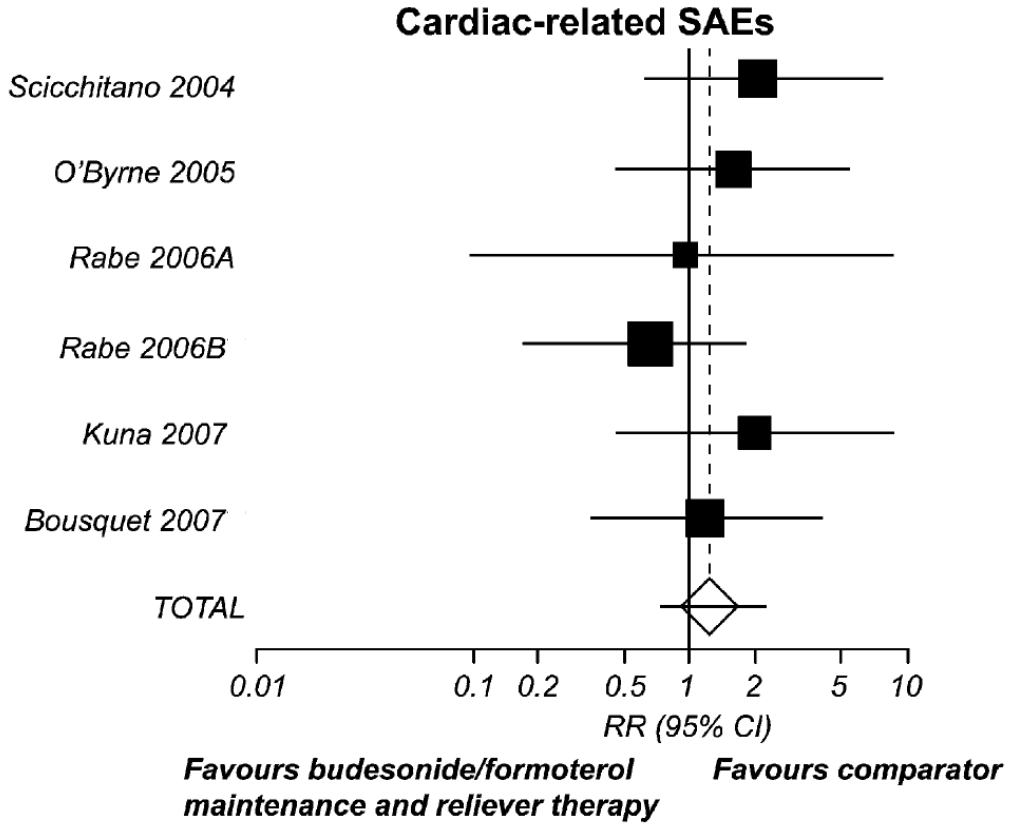
*Symbicort® maintenance and reliever therapy

CI, confidence interval; DAE, discontinuation due to adverse events; FD, fixed dose; RCT, randomised clinical trials; RR, relative risk; SAE, serious adverse event..

Sears MR, Radner F. Safety of budesonide/formoterol maintenance and reliever therapy in asthma trials. Respiratory medicine. 2009 Dec 1;103(12):1960-8.

- In the pooled analysis of safety data from six RCTs, Symbicort®* was **not associated with any increased risk of cardiac-related DAEs or SAEs**





*Symbicort® maintenance and reliever therapy.

CI, confidence interval; DAE, discontinuation due to adverse events; RCT, randomised clinical trials; RR, relative risk; SAE, serious adverse event.

Sears MR, Radner F. Safety of budesonide/formoterol maintenance and reliever therapy in asthma trials. Respiratory medicine. 2009 Dec 1;103(12):1960-8.

□●▁▆?•✕✔✔◜▆□▆▁▁▆▆▲?□

Adverse reactions, which have been associated with budesonide or formoterol, are given below, listed by system organ class and frequency. Frequency are defined as: common (≥1/100)

Cardiac disorders	Common	Palpitations
Infections and infestations		Candida infections in the oropharynx
Nervous system disorders		Headache, tremor

Systemic effects of inhaled corticosteroids may occur particularly at high doses prescribed for prolonged periods. These may include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. Treatment with beta2-agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Contraindications and Interactions

Hypersensitivity (allergy) to budesonide, formoterol or lactose (which contains small amounts of milk proteins).

Interactions

The metabolic conversion of budesonide is impeded by substances metabolized by CYP P450 3A4 (e.g. itraconazole, ritonavir). The concomitant administration of these potent inhibitors of CYP P450 3A4 may increase plasma levels of budesonide. The concomitant use of these drugs should be avoided unless the benefit outweighs the increased risk of systemic side effects.

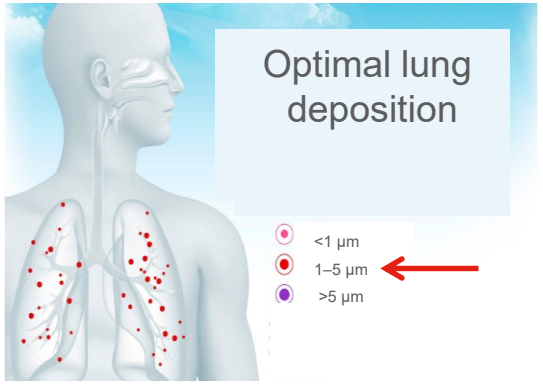
- It is recommended that the **dose is tapered** when the treatment is discontinued and should not **be stopped abruptly**.

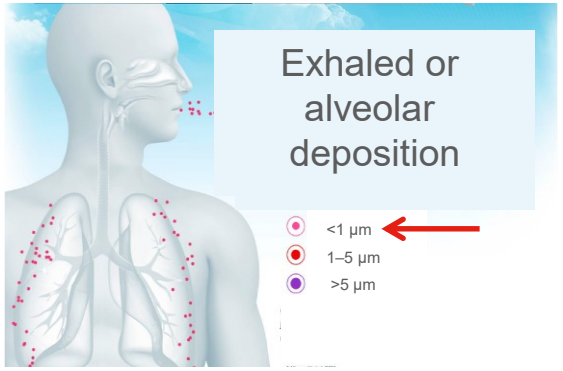
- Symbicort should be administered with caution in patients with **thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure.**

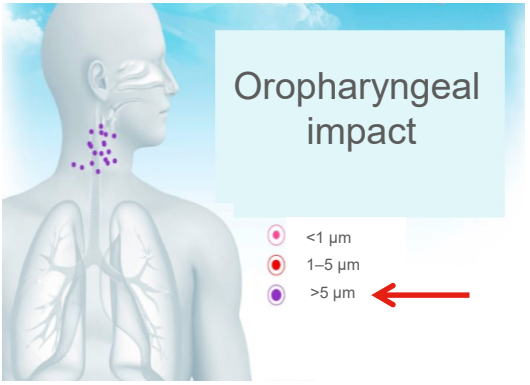
- Potentially serious hypokalaemia may result from high doses of beta2- agonists. Concomitant treatment of beta2-agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the beta2-agonist.

Symbicort® – The role of Turbuhaler®

- **Particles 1–5 µm are optimal** for lung deposition, with those 1–3 µm most likely to be deposited in **central and peripheral airways**[1]
- **Particles <1** µm are most likely to **be exhaled again** but some will **reach the alveoli** and then enter the systemic circulation[1,2]
- **Particles > 5** µm mainly impact on the **oropharynx and are then swallowed**[1,2]
- Oropharyngeal impaction increases at higher inspiratory flow rates[1,2]
- Turbuhaler was the only DPI of 4 tested* that compensated for higher oropharyngeal losses and the shift in deposition to upper airways at higher flow rates[1]
- Turbuhaler delivered **the highest fine particle fraction (FPF) 1–3 µm** of the 4 DPIs tested* as percent of label claim *in vitro*[1]







* Symbicort Turbuhaler, Seretide Diskus, Rolenium Elpenhaler and Foster NEXThaler

1. de Boer AH, Gjaltema D, Hagedoorn P, Frijlink HW. Can 'extrafine'dry powder aerosols improve lung deposition?. European Journal of Pharmaceutics and Biopharmaceutics. 2015 Oct 1;96:143-51.; 96:14351; 2. Demoly P, Hagedoorn P, de Boer AH, Frijlink HW. The clinical relevance of dry powder inhaler performance for drug delivery. Respiratory medicine. 2014 Aug 1;108(8):1195-203.

Good actuation–inhalation coordination		Poor actuation–inhalation coordination	
Inspiratory flow# ⩾30 L·min^{-1}	Inspiratory flow# <30 L·min^{-1}	Inspiratory flow# ⩾30 L·min^{-1}	Inspiratory flow# <30 L·min^{-1}
pMDI BA-pMDI DPI Nebuliser	pMDI Nebuliser	pMDI+spacer BA-pMDI DPI Nebuliser	pMDI+spacer Nebuliser

pMDI: pressurised metered-dose inhaler; BA-pMDI: breath actuated-pMDI; DPI: dry powder inhaler. #: inspiratory flow can be determined from the flow–volume curve generated during spirometry measurements, or by using devices like the IN-Check Dial®. See Appendix for all product/drug manufacturer details. Reproduced and modified from [34].

Chapman KR, Voshaar TH, Virchow JC. Inhaler choice in primary practice. European Respiratory Review. 2005 Dec 1;14(96):117-22.

urbuhaler®: Design and operation

Mouthpiece is specially designed with spiral channels to deaggregate the dose to respirable particles

Inhalation channel transports dosage of drug aggregates to the mouthpiece

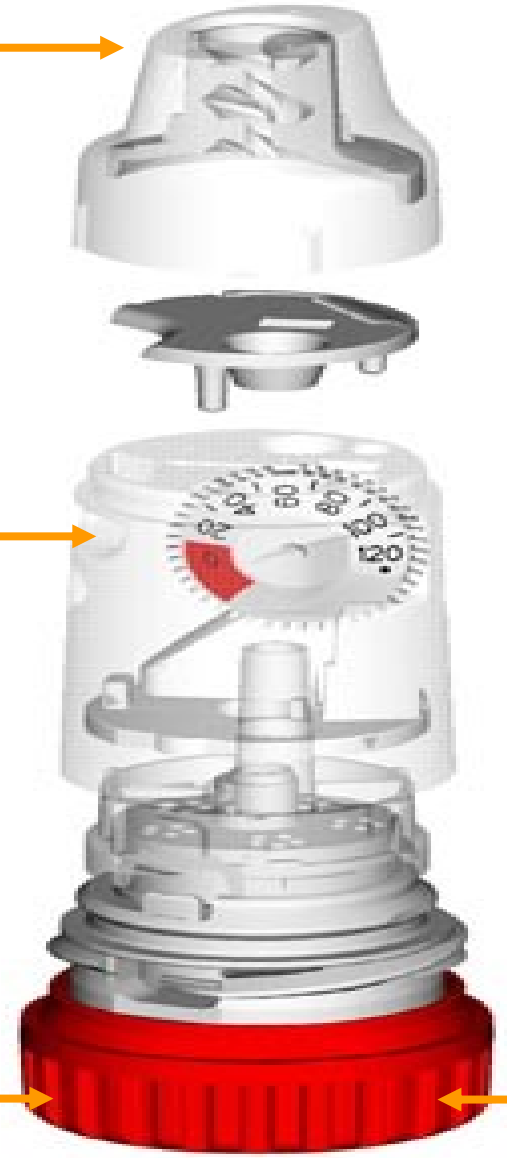
Rotating dosing disc determines the dose of medication for delivery to the inhalation channel

Drug reservoir holds 50,60,100 or 200 doses of medication

Dosing scrapers ensures precise dosing by removing excess amounts of drug

Twist grip loads a single dose when turned completely in one direction and then back again

Symbicort® Turbuhaler® design



Spiral channels

Dose counter

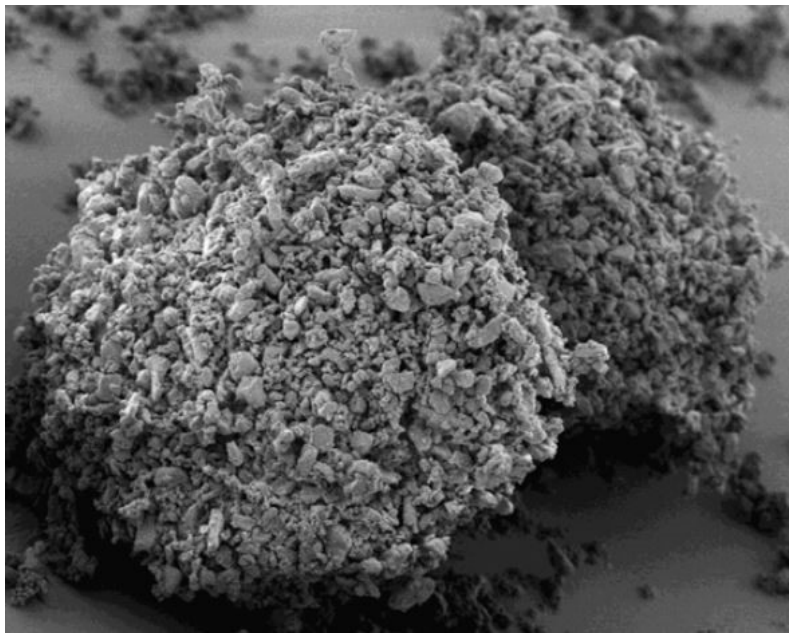
Air inlets

Air inlets

Desiccant store

Turning grip

Each dose is initially in the form of loosely packed powder consisting of spherical particle aggregates of ~5–20 µm[1,2]



Turbulence, generated first in the circulation chamber and then in the helical region and mouthpiece, breaks up the powder aggregate into optimally sized particles for lung deposition[1] (1–5 µm)[3]

1. Milenkovic J, Alexopoulos AH, Kiparissides C. Flow and particle deposition in the Turbuhaler: A CFD simulation. International journal of pharmaceutics. 2013 May 1;448(1):205-13.; 2. Hoppentocht M, Hagedoorn P, Frijlink HW, De Boer AH. Technological and practical challenges of dry powder inhalers and formulations. Advanced drug delivery reviews. 2014 Aug 30;75:18-31.; 3. de Boer AH, Gjaltema D, Hagedoorn P, Frijlink HW. Can 'extrafine'dry powder aerosols improve lung deposition?. European Journal of Pharmaceutics and Biopharmaceutics. 2015 Oct 1;96:143-51.; 96:14351

- Patients of most ages and severity of asthma and COPD have been shown to be able to generate sufficient inspiratory flow (30 L/min) to use a Turbuhaler effectively.[1–4]

  - **Severe COPD[1]**

  Patients with very low lung function (FEV_1 0.7 L/min, PEF 182 L/min) on average generated an inspiratory flow rate of 53 L/min, i.e. well above the required 30 L/min. All 100 patients generated above 28 L/min, which is sufficient for effective drug delivery.

  - **Children with asthma[2]**

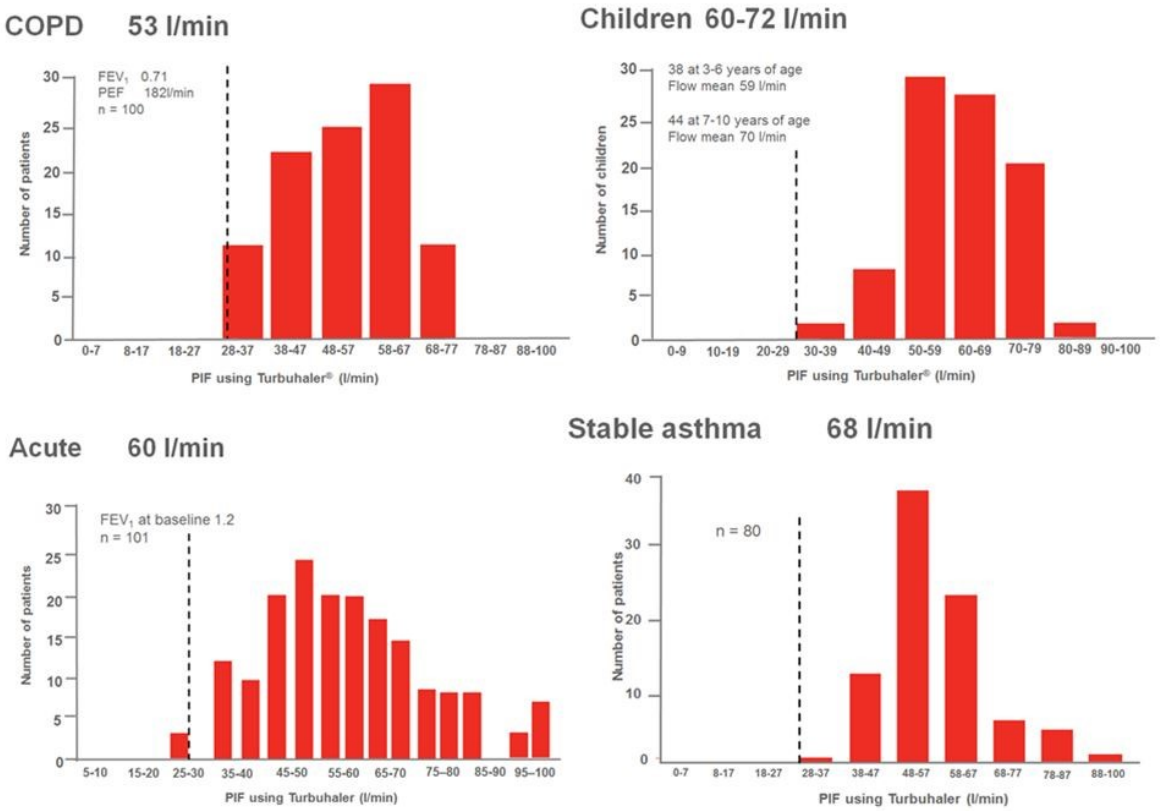
  Children aged 3-6 yrs generated an average 60 L/min and 7-10 year olds generated an average of 70 L/min. All 82 children with asthma generated above the recommended 30 L/min.

  - **Patients with acute asthma[3]**

  Acute asthma patients generated an average 60 L/min PIF through Turbuhaler. Only two of the 99 patients generated below 30 L/min (both 26 L/min, which is still adequate).

  - **Patients with asthma[4]**

  Able to generate at least 40 L/min PIF in a study at their homes

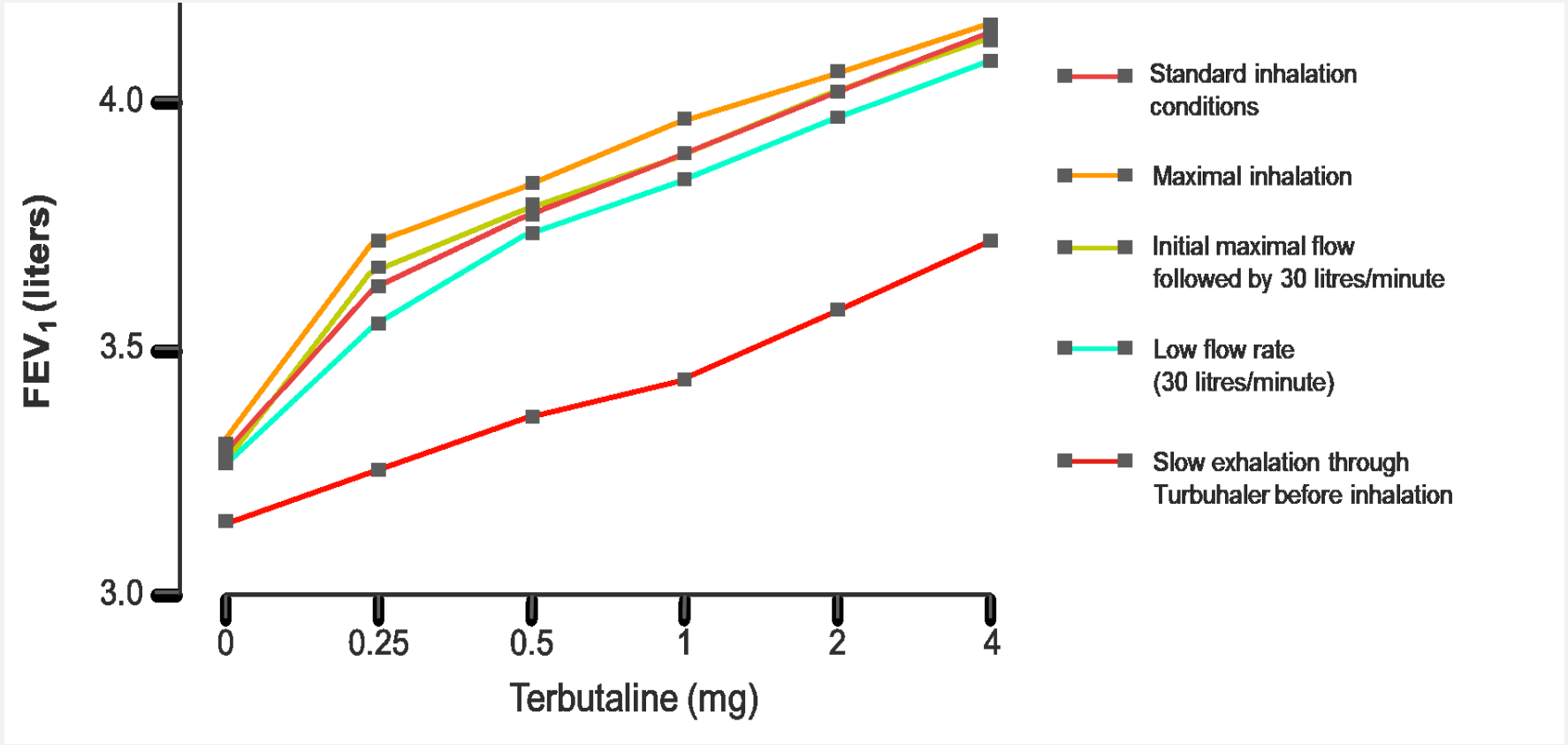


Figures adapted from references stated
Study population details on Notes page

1. budesonide/formoterol; 2. terbutaline; 3. empty Turbuhaler; 4. budesonide Turbuhaler M2 may have been used in these studies. Current Turbuhaler is M3

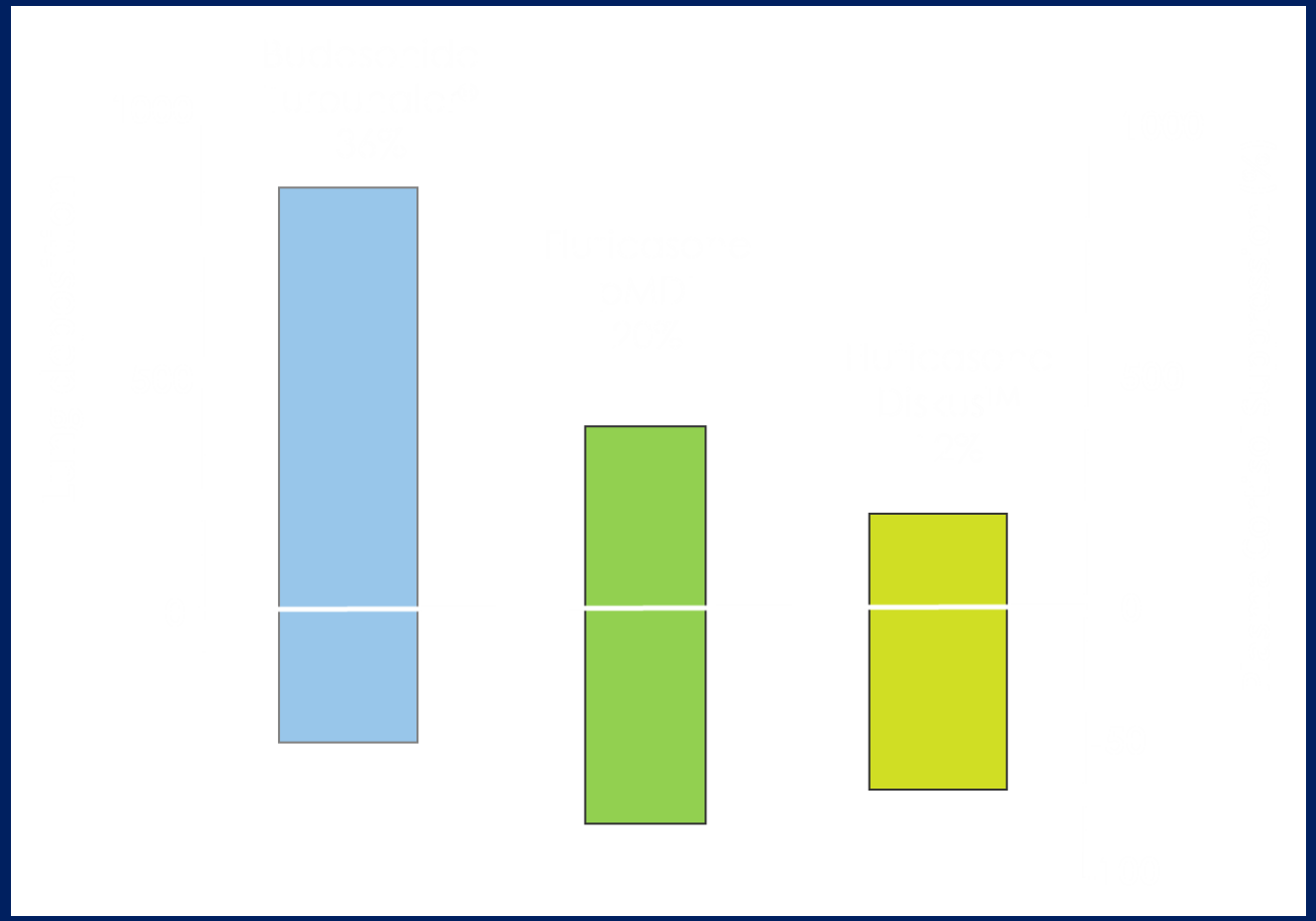
L/min: litres/minute, PIF: peak inspiratory flow

1. Dewar MH, Jamieson A, McLean A, Crompton GK. Peak inspiratory flow through Turbuhaler® in chronic obstructive airways disease. Respiratory medicine. 1999 May 1;93(5):342-4.; 2. Ståhl E, Ribeiro LB, Sandahl G. Dose response to inhaled terbutaline powder and peak inspiratory flow through Turbuhaler® in children with mild to moderate asthma. Pediatric pulmonology. 1996 Aug;22(2):106-10. 3. Brown PH, Ning AC, Greening AP, McLean A, Crompton GK. Peak inspiratory flow through Turbuhaler in acute asthma. European Respiratory Journal. 1995 Nov 1;8(11):1940-1.; 4. Meijer RJ, Van der Mark TW, Aalders BJ, Postma DS, Koeter GH. Home assessment of peak inspiratory flow through the Turbohaler in asthmatic patients. Thorax. 1996 Apr 1;51(4):433-4.



Engel T, Scharling B, Skovsted B, Heinig JH. Effects, side effects and plasma concentrations of terbutaline in adult asthmatics after inhaling from a dry powder inhaler device at different inhalation flows and volumes. British journal of clinical pharmacology. 1992 Apr;33(4):439-44.

Turbuhaler ® delivers 2-3 fold of the labeled dose to the lung than Diskus™ or pMDI

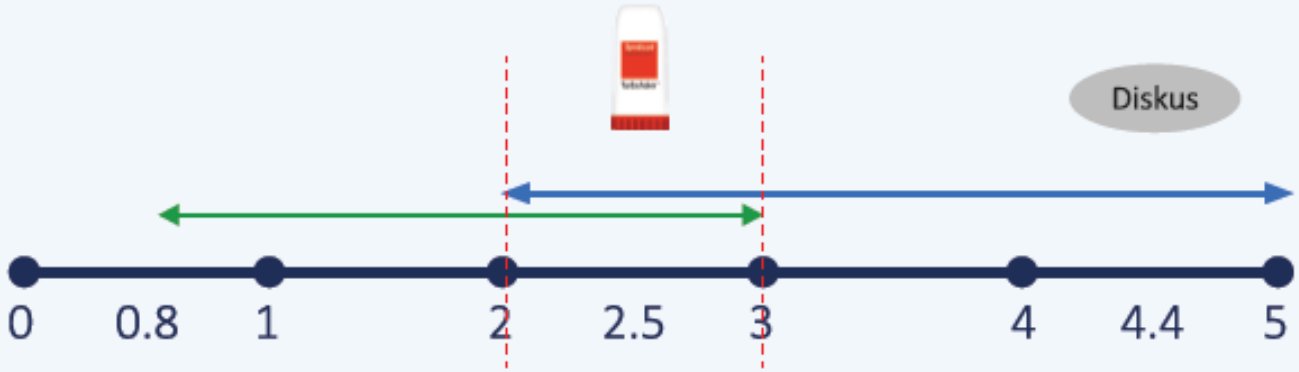


Thorsson L, Edsbäcker S, Källén A, Löfdahl CG. Pharmacokinetics and systemic activity of fluticasone via Diskus® and pMDI, and of budesonide via Turbuhaler®. British journal of clinical pharmacology. 2001 Nov;52(5):529-38.

The choice of inhaler is as important as the choice of drug[1]

The Aerosol Consensus Statement:
Reported that aerosols with mass median aerodynamic diameters (MMADs) of 2-5 µm are optimal for delivery to the airways, whereas aerosols with MMADs of 0.8-3.0 µm are suitable for drug delivery to the parenchyma[2]

- The particle size of FBC Turbuhaler inspired at a flow rate of 60 L/min was **2.4** µm for budesonide and **2.5** µm for formoterol , respectively [3]
- The particle size of SFC Diskus inspired at a flow rate of 60 L/min was **4.4** µm for both salmeterol and fluticasone [4]



suitable for drug delivery to the parenchyma

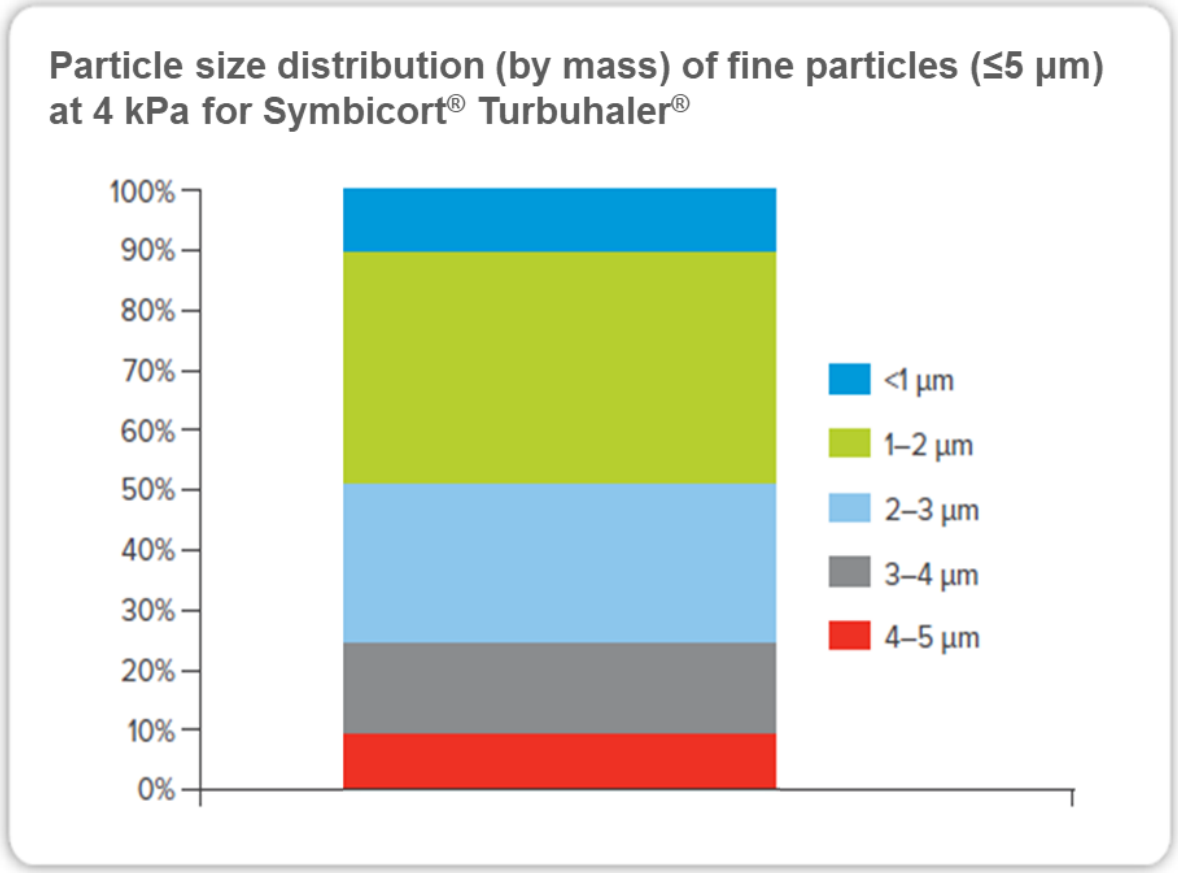
optimal for delivery to the airways

1. Ninane V, Brusselle GG, Louis R, Dupont L, Liistro G, De Backer W, Schlesser M, Vincken W. Usage of inhalation devices in asthma and chronic obstructive pulmonary disease: a Delphi consensus statement. Expert opinion on drug delivery. 2014 Mar 1;11(3):313-23.; 2. American College of Chest Physicians. Aerosol consensus statement. Consensus conference on aerosol delivery. Chest1991;100:1106-9; 3. Tarsin W, Assi KH, Chrystyn H. In-vitro intra- and inter inhaler flow rate-dependent dosage emission from a combination of budesonide and formoterol in a dry powder inhaler. J Aerosol Med2004;17:25-32; 4. Hojo M, Iikura M, Hirashima J, Suzuki M, Sugiyama H. A comparison of long-term anti-inflammatory effect of two ICS/LABA combination inhalers; fix-dosed maintenance therapy with budesonide/formoterol and salmeterol/fluticasone. Allergology International. 2014;63(1):103-11.

- Granlund et al demonstrated that Symbicort® Turbuhaler® delivered approximately 50% of the labelled dose as fine particles of both drugs, whereas Seretide® Diskus® delivered approximately 20% of the labelled dose as fine particles of both drugs.

- This indicates that Symbicort® Turbuhaler® delivers a higher proportion of the labelled dose to the target area in the lungs (Granlund KM et al, European Respiratory Journal, 2000).

- In addition, it was observed that **50%** of the FPF mass for Symbicort® Turbuhaler® had a size ≤2 µm.



50% of the mass of particles have a size ≤2 µm.

Granlund KM. An in-vitro comparison of budesonide/formoterol and fluticasone/salmeterol in dry powder inhalers. Eur Respir J. 2000;16(311):455S.

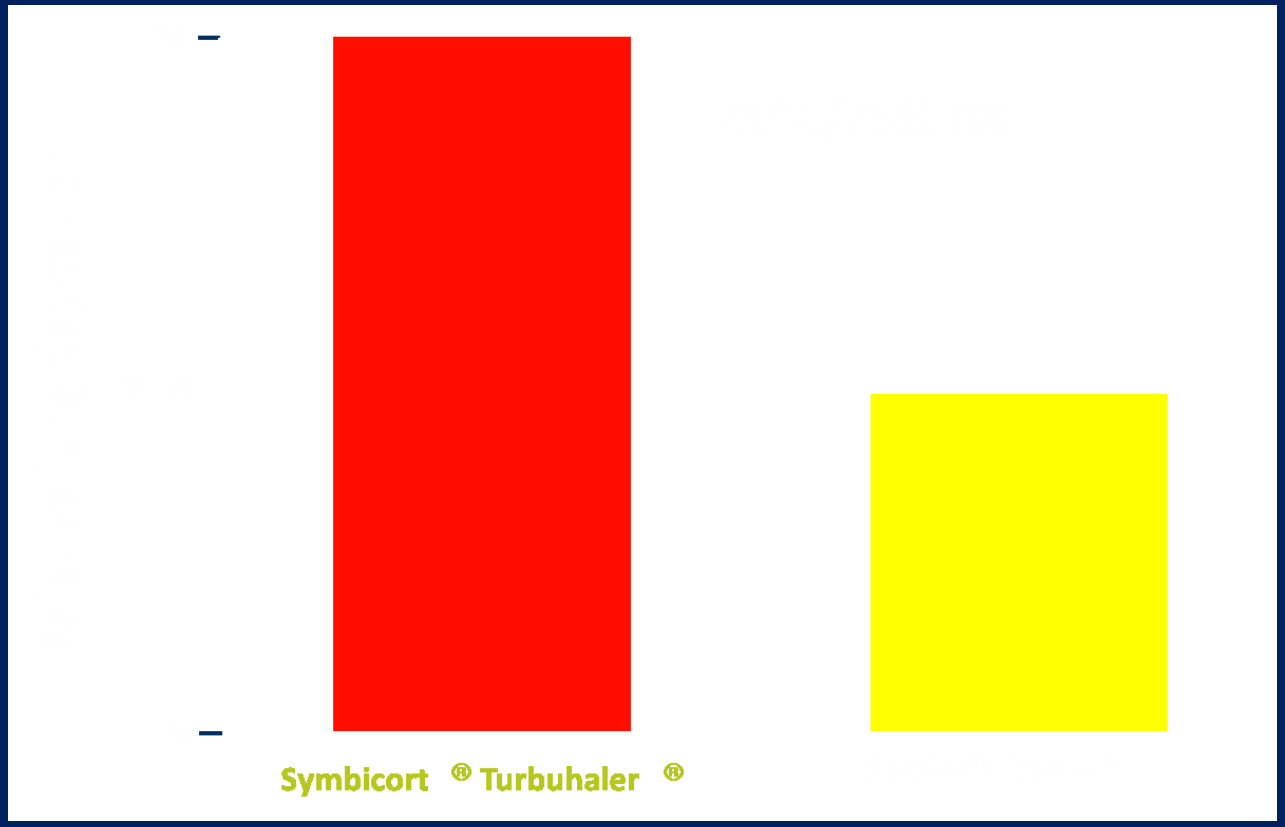
- The conditions dry powder inhaler (DPI) are **stored in may affect their aerosol characteristics** and the resulting lung deposition[1]
- In particular, inhalers **are sensitive to humidity**, particularly at **high room temperatures**[1]
- Most patients are **unaware** of this and store their DPI in humid locations, such as their **bathroom cupboard, when not in use**[2]
- Different manufacturers adopt different approaches to protect against humidity and prolong shelf-life[1]
  - Sealed humidity resistant packs – these only protect until the patient opens the pack
  - Individual doses sealed in laminated foil – again, protection ends when the foil is opened

- The Turbuhaler contains a desiccant within the inhaler body and has a tightly fitting cover to keep out moisture when not in use[1]

1. Janson C, Lööf T, Telg G, Stratelis G, Nilsson F. Difference in resistance to humidity between commonly used dry powder inhalers: an in vitro study. NPJ primary care respiratory medicine. 2016 Nov 17;26:16053.; 2. Lærum BN, Telg G, Stratelis G. Need of education for dry powder inhaler storage and retention–a patient-reported survey. Multidisciplinary respiratory medicine. 2016 Dec;11(1):21..

Effect of storage conditions on lung deposition

Storage under hot and humid conditions significantly reduced lung deposition from salmet/flutica™ Diskus™, but had no effect on drug delivery from Symbicort Turbuhaler.



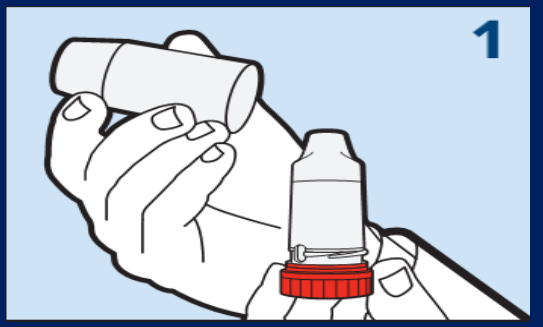
Borgström L, Asking L, Lipniunas P. An in vivo and in vitro comparison of two powder inhalers following storage at hot/humid conditions. Journal of aerosol medicine. 2005 Sep 1;18(3):304-10.

Symbicort Turbuhaler , simple as 1,2,3[1,2]

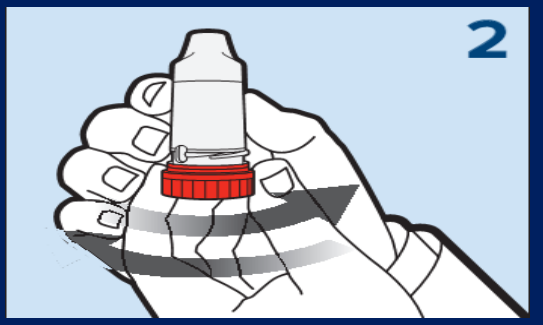
Symbicort Turbuhaler needs only:

3 Simple & Easy steps[1,2]

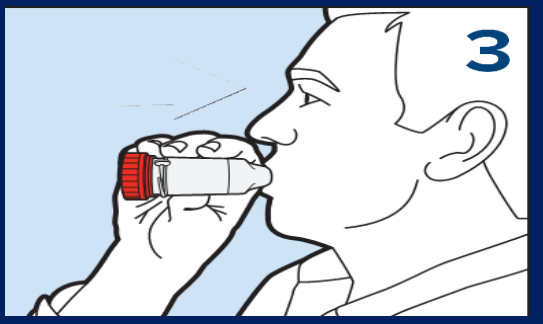
Open the Cap



Twist in both directions until you hear the Click sound



Inhale deeply



1. Louis, R. Le medicament du mois. L'association budesonide 160 micrograms/formoterol 4.5 micrograms (Symbicort TH). Revue Médicale de Liège 2002; 57(11): 741-4. 2. Symbicort Prescribing Information, last reviewed 2017

THANK YOU

AstraZeneca

AstraZeneca Near East, Sweifieh, BLDG 19
Abdelraheem Al-Haj Mohammad street
P.O.Box 17788 Zip Code 11195 Amman-Jordan
Tel: +96265827580