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Early View

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Short-acting β_2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study

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Summary:

Findings from SABINA III, which included 8351 patients from 24 countries, indicate that across treatment steps and clinical care settings, high SABA prescriptions were associated with higher rates of severe exacerbations and poorer asthma control.

Abstract

Background: To gain a global perspective on short-acting β_2-agonist (SABA) prescriptions and associated asthma-related clinical outcomes in patients with asthma, we assessed primary health data across 24 countries in 5 continents.

Methods: SABINA III was a cross-sectional study that employed electronic case report forms at a study visit (in primary or specialist care) to record prescribed medication(s), over-the-counter (OTC) SABA purchase, and clinical outcomes in asthma patients (≥12 years old) during the past 12 months. In patients with ≥1 SABA prescription, associations of SABA with asthma symptom control and severe exacerbations were analysed using multivariable regression models.

Results: Of 8351 patients recruited (n=6872, specialists; n=1440, primary care), 76.5% had moderate-to-severe asthma and 45.4% experienced ≥1 severe exacerbation in the past 12 months. Thirty-eight percent of patients were prescribed ≥3 SABA canisters; 18.0% purchased OTC SABA, of whom 76.8% also received SABA prescriptions. Prescriptions of 3–5, 6–9, 10–12 and ≥13 SABA (vs 1–2) were associated with increasingly lower odds of controlled or partly controlled asthma (odds ratio [95% CI]: 0.64 [0.53–0.78], 0.49 [0.39–0.61], 0.42 [0.34–0.51] and 0.33 [0.25–0.45], respectively; n=4597) and higher severe exacerbation rates (incidence rate ratio [95% CI]: 1.40 [1.24–1.58]; 1.52 [1.33–1.74]; 1.78 [1.57–2.02]; 1.92 [1.61–2.29], respectively; n=4612).

Conclusions: This study indicates an association between high SABA prescriptions and poor clinical outcomes across a broad range of countries, healthcare settings and asthma severities, providing support for initiatives to improve asthma morbidity by reducing SABA over-reliance.

Introduction

Asthma is a common disease worldwide and the most common chronic disease of childhood [1]. In the face of a rising prevalence in a majority of the countries globally [2], the substantial decreases in asthma-related hospitalisations and reduction in asthma deaths by more than one-half, even in countries with relatively poor resources for asthma care [2, 3], are considered to be due largely to the introduction of inhaled corticosteroids (ICS) and other effective controller therapies. However, this decrease in asthma morbidity has stalled in many countries, including in those with provision and access to the most effective controller therapies [3], suggesting the need for additional measures to avoid morbidity and preventable deaths from asthma. A case-based enquiry into factors associated with asthma deaths in the UK identified several potentially modifiable issues, chief among which were the underuse of ICS and an excessive use of short-acting β_2-agonists (SABAs) [4]. Of concern is that almost one-half of asthma deaths in the UK were among patients considered by their physicians to have asthma of mild-to-moderate severity [4]. Studies performed with inhaler dose counters confirm that much of the SABA overuse occurs during asthma worsening as patients seek relief [5]; occasionally, this may delay initiation of more effective treatment to prevent the attack or delay presentation for medical care [6]. It is salient to recognise that two-thirds of asthma deaths occur outside of medical facilities [4].

Research on alternative approaches to symptom-based titration of as-needed SABA has established the value of replacing a SABA with a combination of a low-dose ICS with a rapid-onset long-acting β_2-agonist (LABA) [7] or a SABA as reliever [8, 9]. Single inhaler for maintenance and reliever therapy [7, 10, 11] has been endorsed as the preferred treatment for moderate-to-severe asthma in local guidelines [12, 13] and in the Global Initiative for Asthma (GINA) report [14]. More recently, on the basis of evidence of efficacy and safety observed in randomised controlled trials [15, 16] and in real-life studies [17, 18], GINA now

recommends ICS/formoterol combination inhalers taken only as-needed as sole therapy for patients with mild asthma [14, 19]. If applied widely, this approach has the potential to reduce SABA overuse and ensure that more patients receive doses of anti-inflammatory treatment when symptoms develop, targeting the underlying airway inflammation [20]. However, inclusion of these recommendations into national guidelines and formularies can be challenging as they represent a major shift in treatment approach, and there are important considerations of cost and benefit in every country based on local factors. Information on the current status of SABA use and the potential burden associated is not readily available for many countries outside of Europe. A more current and detailed knowledge of local SABA use and its association with continuing asthma morbidity may assist policymakers and clinicians in assessing the potential benefits of switching to ICS-containing relievers as the standard of care for asthma in these countries [14].

SABA use IN Asthma (SABINA) III forms part of the SABINA group of observational studies [21–25] that seek to assess SABA prescriptions for asthma around the world. In SABINA III, we investigated prescriptions and over-the-counter (OTC) purchases of SABA, other asthma medication prescriptions and associated clinical outcomes among patients with asthma attending primary and specialist care in 24 countries, including several with limited healthcare resources. We employed a standardised methodology that circumvented the need for electronic records and databases.

Methods

Study design

SABINA III was a multi-country, observational, cross-sectional study conducted in 24 countries (figure 1). Retrospective data were obtained from existing medical records, and patient data, including an assessment of current asthma symptom control, were collected

during a study visit and entered real-time on an electronic case report form. Physicians entered data on exacerbation history, comorbidities, and information of medication prescriptions for asthma in the eCRF based on patient medical records. Additionally, physicians were required to enquire and record, at the study visit, whether patients had experienced exacerbations that were not recorded in the medical record. SABA OTC purchase data based on patient recall was obtained directly from the patient at the study visit and entered in the eCRF by the investigator. All site investigators were trained in using the eCRF system. The data collected were checked by monitors and data management teams, who ensured that queries raised (either by the eCRF system or by the monitors) were resolved. The final database was locked and signed off before statistical analyses on the final data was performed. Recruitment occurred from March 2019 to January 2020. We report multi-country–aggregated data; regional and country-specific data will be published separately.

Study population

Purposive sampling of primary and specialist care potential study sites was performed by a national coordinator in each country with the intention of obtaining a sample representative of how patients with asthma were being treated in their country (supplementary table E1). At each site, patients (aged ≥12 years) with a diagnosis of asthma in their medical records, ≥3 prior consultations with their healthcare provider and having medical records containing data for ≥12 months before the study visit were enrolled. Patients with a diagnosis of other chronic respiratory diseases (such as chronic obstructive pulmonary disease) or with an acute respiratory condition were excluded.

Ethics approval

The study was conducted in compliance with the study protocol, the Declaration of Helsinki and local ethics committee approvals, and informed consent was obtained from all patients or their legal guardians.

Statistical analysis

SABA prescriptions in the 12 months before the study visit were categorised as none, 1–2, 3–5, 6–9, 10–12 and ≥13 canisters, and ≥3 SABA canister prescriptions were considered as overuse [18,22].

The level of asthma symptom control was evaluated using the GINA assessment for asthma symptom control [26]. At least partly controlled asthma (partly controlled plus well-controlled asthma) was used as the outcome of clinical relevance. Severe exacerbations in the 12 months before the study visit were defined based on the American Thoracic Society/European Respiratory Society recommendations [27]. For secondary analyses, logistic regression and negative binomial models were used to analyse the associations of SABA prescriptions with at least partly controlled asthma (reference: uncontrolled asthma) and rate of severe exacerbations, respectively. Patients with missing data on covariates and those for whom there was no record of SABA prescriptions during the past year were excluded from secondary analyses. The latter prevented confounding of the results due to use of other relievers (such as low-dose ICS/formoterol or oral or nebulised SABA) in these patients with zero SABA prescriptions. All regression models used complete-case analyses and were adjusted for pre-specified covariates and potential confounders (based on the literature and modelling data from SABINA I [22]). Covariates included age (continuous), sex, body mass index (continuous), education (primary/secondary school, high school or university and/or post-university), healthcare insurance (not reimbursed, partially reimbursed or fully reimbursed), practice type (primary or specialist care), investigator-classified asthma

severity (guided by GINA 2017 treatment steps [26]: steps 1–2, mild asthma; steps 3–5, moderate-to-severe asthma), asthma duration (continuous), number of comorbidities (0, 1–2, 3–4 or ≥5) and smoking status (active, former or never smoker).

All statistical tests were two-sided and at a 5% level of significance and were performed using R statistical software (version 3.6.0).

Results

Study population

Overall, 8462 patients were recruited, and 8351 patients were included in the primary analysis (figure 2): 36.7% from Asia, 21.3% from Africa, 16.6% from the Middle East, 13.1% from Latin America, 7.4% from Russia and 4.8% from Australia (figure 1).

Most patients (n=6872 [82.3%]) were enrolled by specialists (figure 2), and 76.5% were classified by investigators as having moderate-to-severe asthma. The mean age of enrolled patients was 49.4 (standard deviation [SD]: 16.7) years; a majority were female (n=5691 [68.1%]) and had never smoked (n=6747 [80.8%]) (table 1). Over a quarter of the patients (n=2281 [27.3%]) had no healthcare reimbursement. Overall, 45.4% of patients reported ≥1 severe exacerbation within the past 12 months, and 13.1% reported ≥3 severe exacerbations (table 2). Asthma symptom control was assessed as well controlled in 43.3% of patients, partly controlled in 32.2% and uncontrolled in 24.5%.

Asthma treatment

SABA prescriptions

Among all patients, 24.3% were prescribed one or two SABA canisters in the past 12 months, and 38.0%, ≥3 SABA canisters. Prescriptions of ≥3 SABA canisters were reported in 45.8% of patients with mild asthma and 35.6% with moderate-to-severe asthma (figure 3). The

prevalence of ≥3 SABA prescriptions in the past 12 months varied in the 24 countries, ranging from 7.6% in South Korea to 74.9% in South Africa (figure 4).

Prescriptions of SABA as monotherapy were reported in 5.1% of patients, almost exclusively for mild asthma (supplementary table E2). Of these, more than half (53.6%) were prescribed ≥3 SABA canisters, and 29.9%, ≥10 SABA canisters in the past year. Overall, 58.0% of patients on any maintenance therapy were also prescribed SABA (supplementary table E2), of whom 61.7% were prescribed ≥3 and 29.3%, ≥10 SABA canisters.

No SABA prescriptions were reported in 3076 (37.8%) patients and more commonly in those with moderate-to-severe asthma vs mild asthma (41.4 vs 25.9%, figure 3). See supplementary results and tables E3–E5 for additional details.

SABA obtained OTC without prescriptions

Overall, 18.0% of patients reported purchasing SABA OTC (table 3), of whom 48.8% purchased ≥3 canisters. Among patients who purchased SABA OTC (n=1503), 76.8% had also received SABA prescriptions (supplementary figure E1): 69.9% for ≥3 canisters and 35.8% for ≥10 canisters in the past 12 months.

Prescriptions for asthma medications other than SABA

ICS as sole maintenance therapy was prescribed for 17.6% of patients overall, of whom >50% had mild asthma (supplementary table E2). The mean number of ICS canisters prescribed was 8.1 (SD: 8.7), with 51.8% of patients being prescribed ≤6 canisters in the past year (supplementary figure E2).

Most (79.2%) patients were prescribed ICS/LABA, while a total of 264 patients (3.2%) received prescriptions for a biologic agent. The majority of the latter were prescribed omalizumab, although mepolizumab, dupilumab and benralizumab were also prescribed. See supplementary table E6 for additional data on other asthma medication prescriptions.

Context of care

For mild asthma, primary care physicians (PCPs) tended to prescribe ≥3 SABA canisters as monotherapy more commonly than specialists (60.6% vs 47.3%, respectively) (supplementary table E2). The number of patients prescribed ≥3 SABA canisters on a background of maintenance therapy, by PCPs for patients with mild and moderate-to-severe asthma was also higher (71.8% and 65.9% vs 61.0% and 60.1%, respectively, for PCPs vs specialists) (supplementary table E2).

Association between SABA prescriptions and asthma-related health outcomes

Among patients with ≥1 SABA prescription (supplementary figure E3), higher SABA prescriptions were associated with increasing rates of severe exacerbations (figure 5a and supplementary table E7). Patients prescribed 3–5 SABA canisters (vs 1–2 SABA canisters) had 40% more severe exacerbations (adjusted incidence rate ratio [IRR]: 1.40 [95% confidence interval (CI): 1.24–1.58]), and this increased further with increasing SABA prescriptions (range of adjusted IRRs: 1.40–1.92). Prescription of 3–5 SABA canisters (vs 1–2 SABA canisters) was also associated with a significantly lower odds of having at least partly controlled asthma (adjusted odds ratio [OR]: 0.64 [95% CI: 0.53–0.78]), and this decreased further with increasing SABA prescriptions (range of adjusted ORs: 0.64–0.33) (figure 5b and supplementary table E7). See supplementary table E8 for unadjusted analyses.

Discussion

Our study describing asthma medication prescriptions by PCPs and specialists for patients with mild or moderate-to-severe asthma in 24 countries with a wide global representation confirms high levels of SABA prescriptions, with 38% of patients being prescribed ≥3 SABA canisters in the past 12 months. Use of ≥3 SABA canisters/year is considered undesirable since it indicates over-reliance on SABA for the management of persistent symptoms [28], usually related to the underuse of ICS and other controllers. GINA-defined controlled or partly controlled asthma specifies that SABA reliever use should not be >2 doses/week, which equates to <2 standard SABA canisters/year. In support of this threshold, in our study, even after adjusting for known confounding factors, SABA prescriptions higher than two canisters/year were associated with an increasing rate of severe exacerbations and a lower likelihood of satisfactory symptom control. More than half of the patients with mild asthma receiving SABA alone for as-needed use were prescribed ≥3 canisters, and almost one-third, ≥10 canisters, suggesting that a majority should have been considered for additional maintenance treatment with controllers. Among patients prescribed controller treatment, more than 60% received ≥3, and almost one-third, ≥10 SABA canister prescriptions in the past year, suggesting overuse of SABA instead of optimisation of controller treatments. Although there were differences in prescribing between PCPs and specialists, the pattern of SABA over-reliance was common to both. SABA monotherapy for mild asthma was more commonly prescribed by PCPs and in higher numbers, and SABA prescriptions for moderate-to-severe asthma by both categories of prescriber were similarly high.

In some of the countries surveyed, SABA may be obtained without a prescription, increasing the potential for SABA overuse [29, 30]. Overall, one-fifth of patients in our study reported obtaining SABA in this way, of whom one-half purchased ≥3 canisters in the past year. In most cases (77%), these canisters were in addition to those prescribed by their physician. The

potential for overuse by patients receiving SABA from two sources is suggested by the fact that among such patients, 70% also received prescriptions for ≥3 and 35%, for ≥10 SABA canisters in the past year.

Overall, these findings are similar with what has been observed in SABINA I and II studies in Europe. Across the UK, Germany, Spain, Sweden and Italy [22], SABA prescription/possession of ≥3 SABA canisters/year (33%) was slightly lower than in SABINA III, although differences were observed between countries. SABA overuse ranged from 38% in the UK to 9% in Italy. Subsequently, it was confirmed that in Italy, SABA overuse was higher (>50%) when SABAs dispensed by pharmacists, including those purchased without a prescription were included [25].

The findings in our study confirming the association between SABA prescriptions and poor asthma outcomes contribute to the growing evidence that SABA overuse in asthma needs to be addressed if further reductions in asthma morbidity and mortality are to be achieved. An association between SABA prescription/possession and severe exacerbations [22, 24, 25] and even asthma deaths [24] has been reported in the SABINA I (UK) and II (Sweden and Italy) studies. Similar findings have been observed in other studies of SABA use in asthma [28]—high SABA overuse, which may occur even on symptom-free days [31], being associated with worse asthma control.

The growing concern about the negative effects of SABA use on global efforts to improve asthma outcomes has led to research into alternative treatment options for providing quick relief from asthma symptoms either for occasional symptom relief or, more importantly, when breakthrough symptoms herald an approaching severe exacerbation. Foremost has been examining the potential of ensuring that use of a rapid-onset bronchodilator is always accompanied by use of an ICS to ensure that the underlying airway inflammation is also addressed at these critical times. The single inhaler maintenance and reliever approach was

initially trialled with formoterol, a long-acting bronchodilator with a rapid onset of action like that of SABA, combined with budesonide. Most research has been focussed on this combination, but efficacy has also been shown for the combination of formoterol with beclomethasone [7] and is currently being evaluated for combinations of a SABA with an ICS [8, 9]. The anti-inflammatory reliever approach has been shown to be highly effective in mild asthma [15–18], where it may be used without maintenance dosing, and in moderate-to-severe asthma (with fixed daily dosing of the same combination as maintenance treatment) [7]. Consequently, an anti-inflammatory reliever approach has become the preferred option in both the GINA report and the recently published Updated Report of the National Asthma Education and Prevention Program in the US and in other national guidelines and formularies [13, 19, 32]. The 2019 World Health Organisation Model List of Essential Medicines, which represent "minimum medicine needs for a basic healthcare system" includes budesonide/formoterol for use in asthma [33].

Given the entrenched and time-honoured position of SABA in asthma care spanning more than 50 years, SABINA and similar studies provide potentially useful information about the magnitude of the problem relating to SABA use that may be used to assess the gains that are possible if this alternative reliever strategy were to be introduced globally. The current study is focussed on data from several countries, most of which do not have national databases from which to gauge SABA use. Although not fully representative of asthma care within each country and biased towards specialist services for asthma patients, it provides a snapshot of the situation in a range of countries, including some with limited healthcare insurance or national provision of care. Our findings reveal overuse of SABA by both PCPs and specialists, and although the assessment of asthma control was not as poor as that reported in many cross-sectional surveys [34, 35], most patients were not optimally controlled, asthma attacks remained common and both were associated with SABA use. On the other hand,

37.8% were recorded as having no SABA prescriptions, a proportion similar to that seen in SABINA I in the UK [22]. Although some had obtained SABA OTC, it is likely that many such patients, 89.2% of whom had been prescribed an ICS/LABA combination, may have already been switched to ICS/formoterol as reliever. Unfortunately, the size of this group could not be accurately assessed in our study.

In strategising how to encourage the use of the preferable reliever option, several approaches are needed. First, OTC SABA purchases may need to be better regulated in some countries as part of the education process on reliever use, and limits should be put in place. Entrenched prescribing habits in well-resourced health services, such as automatic repeat prescriptions, may result in high and unnecessary SABA prescriptions [36]. Although easier to enact in developed countries, such a limitation will be difficult in poorer nations where the relatively low cost and accessibility of SABA are relied on for short-term benefit despite the fact that they may help to entrench poor asthma care. In such settings, the bias towards using relievers rather than more costly controller medications is likely to be greater. Access to affordable combination medications should be a key priority as it is likely that in these countries, the single inhaler maintenance and reliever approach will be of greatest benefit in view of its strong effects on reducing asthma worsening and attacks, which pose an avoidable high burden on health services [1, 37]. These approaches will need to be accompanied by national initiatives targeting patients, physicians and other stakeholders such as pharmacists to increase awareness of updated treatment guidelines. Creation of national asthma programmes based on current evidence-based asthma guidelines and tailored to the context of clinical practice and local resources can play a critical role in this endeavour. National or regional asthma programmes have been shown to be more effective than conventional treatment guidelines in improving asthma care [38]. Patient involvement is also crucial and patient advocacy groups can play a significant role in disseminating appropriate treatment

information [39]. Besides these measures, the current move away from SABA as reliever to be replaced by an ICS-containing rapid onset reliever for all treatment steps, as now proposed by GINA, may, in some countries, represent the most significant step toward addressing over-reliance and overuse of SABA. This trend was already evident in our study in the high proportion of patients who received prescriptions for ICS/LABA and no provision for a SABA.

As a limitation, it is recognised that SABA prescriptions may not necessarily reflect actual usage, which is likely to be lower. However, over-prescribing, particularly in poorly resourced settings, may result in medications being passed on to family and friends, increasing the potential for misassessments and haphazard treatment. Secondly, the assignment of asthma severity based on GINA treatment steps appeared to be poorly adhered to by investigators, as evidenced by the large proportion of patients with mild asthma who received a ICS/LABA prescription. It is possible that instead of assigning severity according to the 2017 GINA classification [26], a later version that proposed as-needed ICS/formoterol for mild asthma may have been followed. In our study, the non-random selection of sites with a majority representing specialist care resulted in the enrolment of more patients with moderate-to-severe asthma. In view of this bias, we have avoided comparisons of data obtained from participants enrolled by specialists with those recruited in primary care. However, these data from different contexts and of differing severities of asthma permit broad generalisations. Further, this cross-sectional study does not permit an assessment of a causal link between SABA prescriptions and asthma outcomes and does not discount reverse causality; the results simply represent an association. Our aim to include data from a large number of countries and practices with different methods of recording clinical data necessitated acceptance of limitations in methods of collecting source data, such as reliance on patient recall for some questions and limiting the scope of the questionnaire. For example,

data on comorbidities and the number and type of all maintenance medications was not obtained. Lastly, the basis for an asthma diagnosis in each participant was not requested. However, misdiagnosis is not likely to have had an impact on the main findings of this study.

Our SABINA III findings demonstrating that 38% of patients in 24 countries in 5 continents are over-prescribed SABA (≥3 canisters/year), extend the data from the SABINA studies in Europe [22–25]. Although drivers for SABA prescribing may differ by country, SABA over-prescription results in an unnecessary burden of poor asthma symptom control and severe asthma exacerbations with their attendant risks. These findings support the need for continued efforts to improve asthma care in these countries, particularly relating to the prescribing of SABA and the need to switch to combination medications that provide both quick symptom relief and an anti-inflammatory effect.

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Author contributions

EDB, DBP, AC, RJPvdV and MJHIB designed the study. EDB, DBP, H-CW, AK, PS, AC, RJPvdV and MJHIB contributed to data collection, data analysis, data interpretation and writing. EDB, DBP, AC and MJHIB act as guarantors.

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AstraZeneca funded the study; was involved in the study design, protocol development, study conduct and statistical analysis; and was given the opportunity to review the manuscript before submission. AstraZeneca also funded medical writing support. All authors had full access to all the data, wrote the report and accept responsibility for its publication.

Conflict of interest

EDB is a member of the Science Committee and Board of GINA and reports personal fees from ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, Menarini, Novartis, Orion, Regeneron Pharmaceuticals and Sanofi Genzyme. DBP has board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Regeneron, Sanofi Genzyme, Teva Pharmaceuticals and Thermofisher; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline (GSK), Mylan, Mundipharma, Novartis, Pfizer, Teva and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia,

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Data sharing

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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Figures

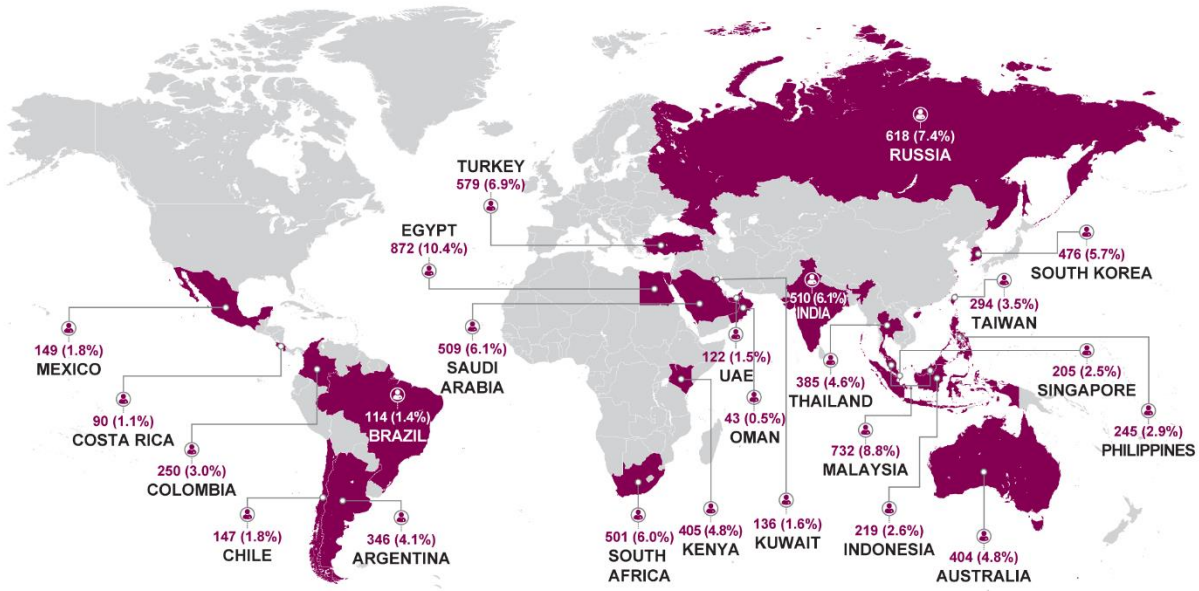


FIGURE 1 Patient enrolment across countries

UAE: United Arab Emirates.

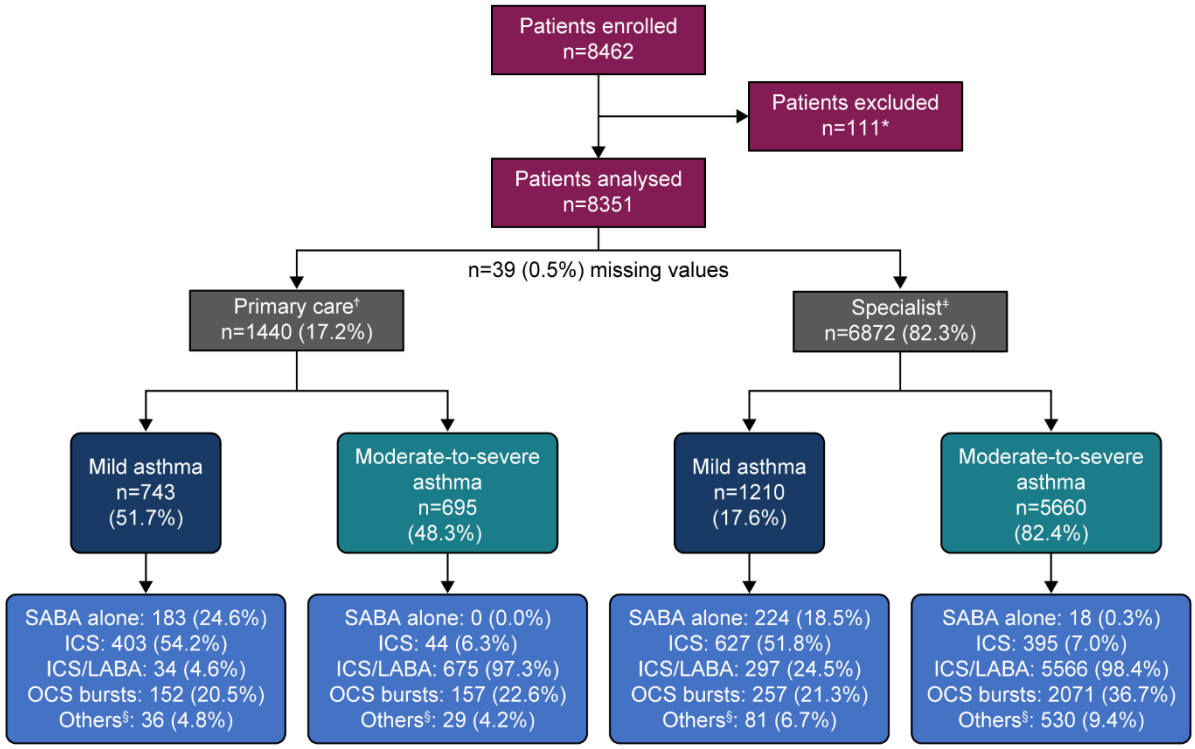


FIGURE 2 Patient population by practice type and asthma severity

*Excluded because the duration of asthma was <12 months.

†Missing severity for primary care: 2.

‡Missing severity for specialist: 2.

§"Others" includes OCS maintenance dosing and OCS prescribed for any reason other than asthma.

Note: Patients could have been prescribed multiple treatments in the past 12 months.

ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; OCS: oral corticosteroid; SABA: short-acting β_2-agonist.

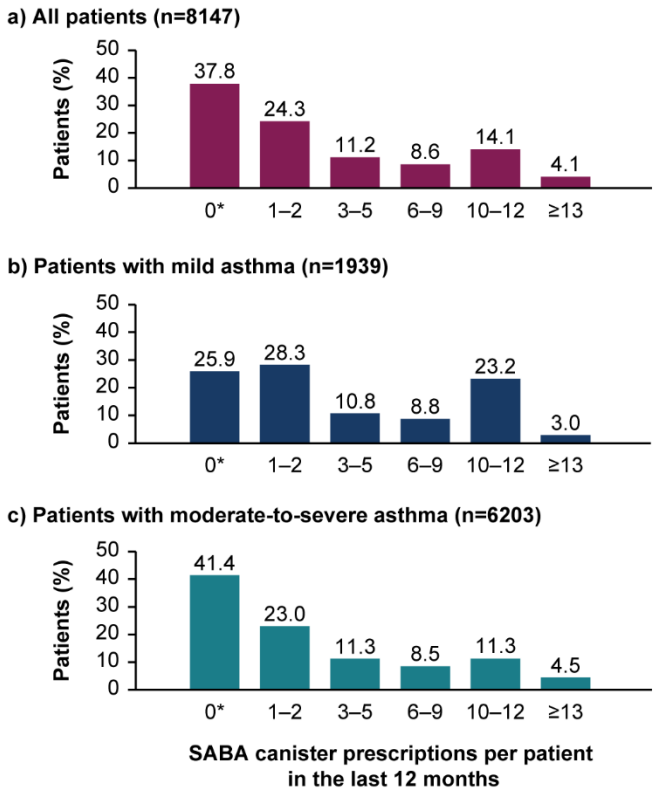


FIGURE 3 SABA prescriptions according to asthma severity

*The category of patients classified as having zero SABA canister prescriptions included patients using non-SABA relievers, non-inhaler forms of SABA and/or SABA purchased OTC.

Missing data for the overall population: n=204; mild asthma: n=19; moderate-to-severe asthma: n=185.

OTC: over the counter; SABA: short-acting β_2-agonist.

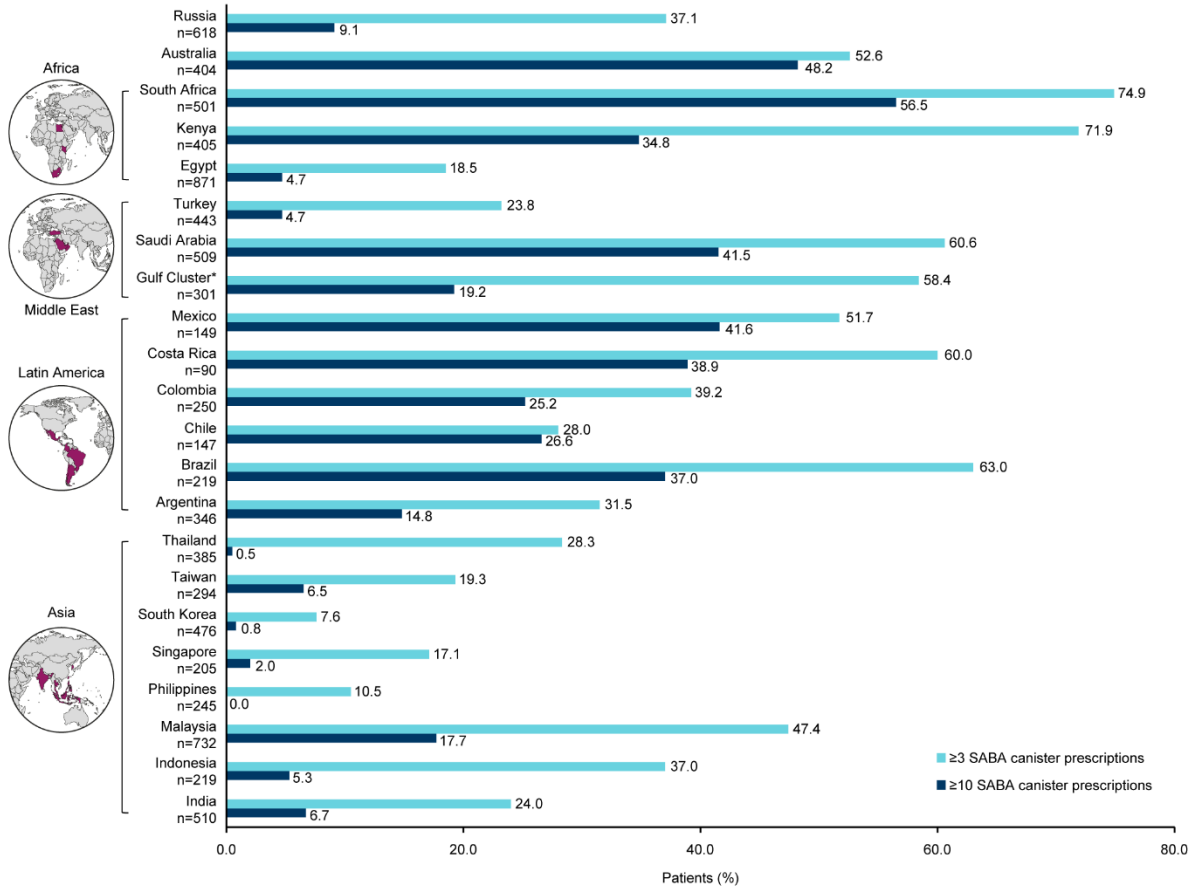


FIGURE 4 SABA prescriptions across the SABINA III countries

*"Gulf cluster" includes United Arab Emirates, Oman and Kuwait.

SABA: short-acting β_2-agonist; SABINA: SABA use IN Asthma.

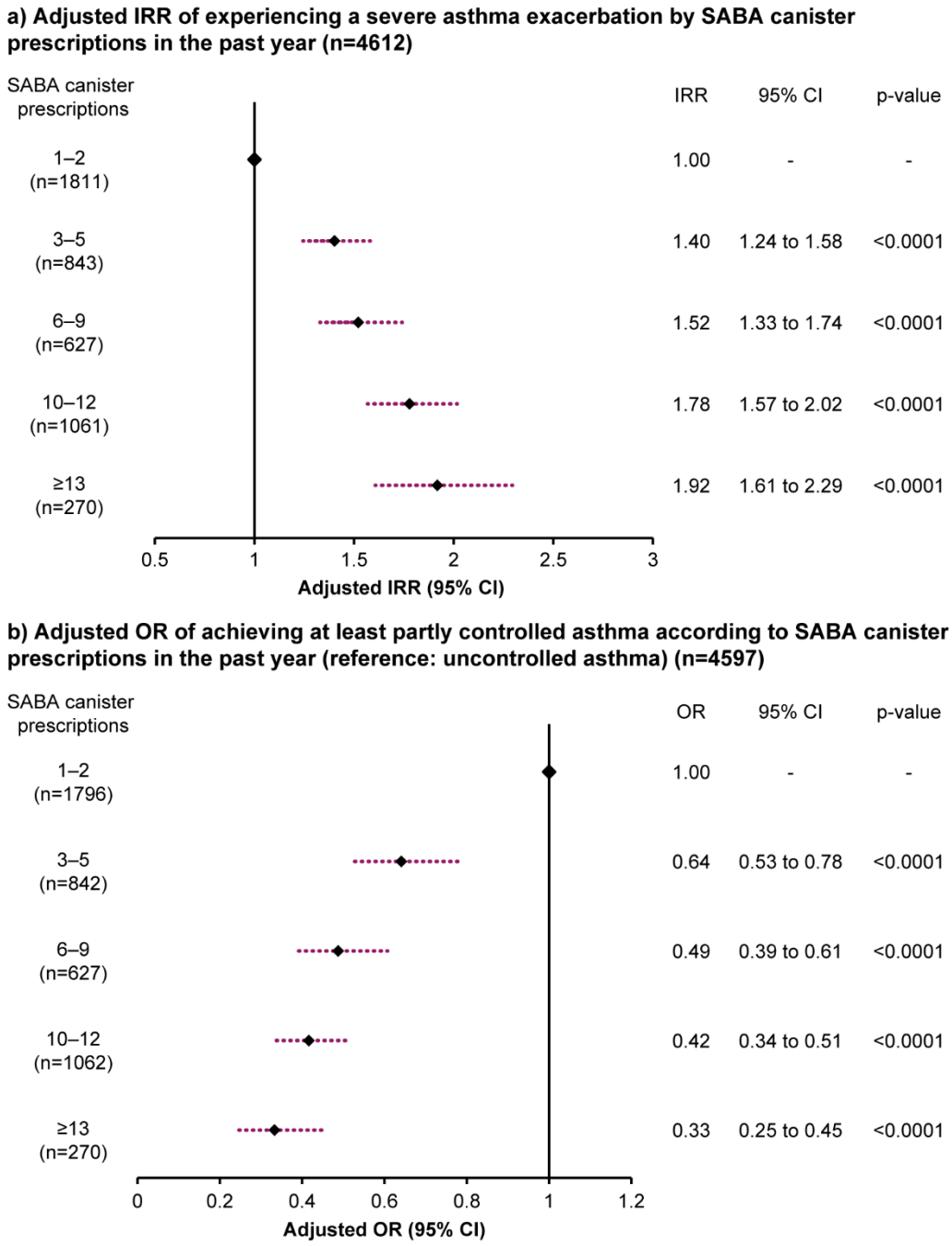


FIGURE 5 Association of SABA prescriptions with severe exacerbations in the past 12 months and the level of asthma symptom control

Based on the covariable significance in the models, IRRs are corrected by country, age, sex, BMI, smoking history, GINA step and education level. ORs are corrected by country, age, sex, BMI, asthma duration, smoking history, comorbidity, GINA step and education level.

BMI: body mass index; CI: confidence interval; GINA: Global Initiative for Asthma; IRR: incidence rate ratio; OR: odds ratio; SABA: short-acting β_2-agonist.

Tables

TABLE 1 Sociodemographics and disease characteristics presented by asthma severity and practice type

	All (n=8351)	**Primary care (n=1440)**			**Specialists (n=6872)**		
		Investigator-classified mild asthma (n=743)	**Investigator-classified moderate-to-severe asthma (n=695)**	**All (n=1440)**	**Investigator-classified mild asthma (n=1210)**	**Investigator-classified moderate-to-severe asthma (n=5660)**	**All (n=6872)**
Age (years)							
Mean (SD)	49.4 (16.7)	45.8 (16.8)	50.2 (16.4)	47.9 (16.7)	44.7 (18.0)	50.8 (16.2)	49.7 (16.7)
Median (IQR)	51.0 (37.0–62.0)	47.0 (34.0–58.0)	51.0 (38.0–62.0)	49.0 (36.0–60.0)	44.0 (31.0–59.0)	52.0 (39.0–63.0)	51.0 (38.0–62.0)
Sex, n (%)							
Female	5691 (68.1)	535 (72.0)	452 (65.0)	988 (68.6)	779 (64.4)	3895 (68.8)	4676 (68.0)
BMI (kg/m^2)							

	All (n=8351)	Primary care (n=1440)			Specialists (n=6872)		
		Investigator-classified mild asthma (n=743)	Investigator-classified moderate-to-severe asthma (n=695)	All (n=1440)	Investigator-classified mild asthma (n=1210)	Investigator-classified moderate-to-severe asthma (n=5660)	All (n=6872)
Mean (SD)	27.8 (6.19)	27.7 (6.44)	28.1 (6.55)	27.9 (6.49)	27.2 (6.46)	27.9 (6.05)	27.8 (6.13)
BMI groups (kg/m^2), n (%)							
<18.5	256 (3.1)	32 (4.3)	15 (2.2)	47 (3.3)	61 (5.0)	148 (2.6)	209 (3.0)
≥18.5 to 24.9	2619 (31.4)	241 (32.4)	232 (33.4)	474 (32.9)	402 (33.2)	1734 (30.6)	2136 (31.1)
≥25.0 to 29.9	2954 (35.4)	247 (33.2)	230 (33.1)	477 (33.1)	430 (35.5)	2031 (35.9)	2463 (35.8)
≥30.0	2522 (30.2)	223 (30.0)	218 (31.4)	442 (30.7)	317 (26.2)	1747 (30.9)	2064 (30.0)
Education level, n (%)							
Primary or secondary school	2877 (34.5)	346 (46.6)	187 (26.9)	533 (37.0)	393 (32.5)	1937 (34.2)	2330 (33.9)

	All (n=8351)	Primary care (n=1440)			Specialists (n=6872)		
		Investigator-classified mild asthma (n=743)	Investigator-classified moderate-to-severe asthma (n=695)	All (n=1440)	Investigator-classified mild asthma (n=1210)	Investigator-classified moderate-to-severe asthma (n=5660)	All (n=6872)
High school	2013 (24.1)	166 (22.3)	151 (21.7)	318 (22.1)	373 (30.8)	1312 (23.2)	1685 (24.5)
University and/or post-university	2792 (33.4)	203 (27.3)	297 (42.7)	501 (34.8)	392 (32.4)	1887 (33.3)	2281 (33.2)
Not established	668 (8.0)	28 (3.8)	60 (8.6)	88 (6.1)	52 (4.3)	523 (9.2)	575 (8.4)
Missing data	1	0	0	0	0	1	1
Healthcare/medication funding, n (%)							
Not reimbursed	2281 (27.3)	320 (43.1)	191 (27.5)	511 (35.5)	444 (36.7)	1317 (23.3)	1762 (25.6)
Partially reimbursed	1851 (22.2)	152 (20.5)	196 (28.2)	348 (24.2)	241 (19.9)	1253 (22.1)	1494 (21.7)
Fully reimbursed	3940 (47.2)	258 (34.7)	281 (40.4)	539 (37.4)	507 (41.9)	2871 (50.7)	3379 (49.2)

	All (n=8351)	Primary care (n=1440)			Specialists (n=6872)		
		Investigator-classified mild asthma (n=743)	Investigator-classified moderate-to-severe asthma (n=695)	All (n=1440)	Investigator-classified mild asthma (n=1210)	Investigator-classified moderate-to-severe asthma (n=5660)	All (n=6872)
Not specified	276 (3.3)	13 (1.7)	27 (3.9)	42 (2.9)	18 (1.5)	216 (3.8)	234 (3.4)
Missing data	3	0	0	0	0	3	3
Smoking status history, n (%)							
Active smoker	497 (6.0)	27 (3.6)	63 (9.1)	91 (6.3)	81 (6.7)	322 (5.7)	403 (5.9)
Former smoker	1105 (13.2)	97 (13.1)	119 (17.1)	216 (15.0)	146 (12.1)	741 (13.1)	887 (12.9)
Never smoker	6747 (80.8)	619 (83.3)	513 (73.8)	1133 (78.7)	983 (81.2)	4595 (81.2)	5580 (81.2)
Missing values	2	0	0	0	0	2	2
Asthma duration (years)							
Mean (SD)	14.9 (14.31)	17.9 (14.78)	16.5 (13.91)	17.2 (14.37)	13.9 (13.50)	14.6 (14.43)	14.4 (14.27)

	All (n=8351)	Primary care (n=1440)			Specialists (n=6872)		
		Investigator-classified mild asthma (n=743)	Investigator-classified moderate-to-severe asthma (n=695)	All (n=1440)	Investigator-classified mild asthma (n=1210)	Investigator-classified moderate-to-severe asthma (n=5660)	All (n=6872)
Median (IQR)	10.0 (4.0–21.0)	13.0 (7.0–25.5)	13.0 (6.0–22.0)	13.0 (6.0–24.0)	9.5 (4.0–20.0)	10.0 (4.0–20.0)	10.0 (4.0–20.0)
GINA treatment step, n (%)							
Step 1	714 (8.5)	316 (42.5)	0 (0)	316 (21.9)	396 (32.7)	0 (0)	396 (5.8)
Step 2	1244 (14.9)	427 (57.5)	0 (0)	427 (29.7)	814 (67.3)	0 (0)	814 (11.8)
Step 3	2279 (27.3)	0 (0)	371 (53.4)	371(25.8)	0 (0)	1900 (33.6)	1900 (27.6)
Step 4	2872 (34.4)	0 (0)	261 (37.6)	261 (18.2)	0 (0)	2595 (45.8)	2595 (37.8)
Step 5	1237 (14.8)	0 (0)	63 (9.1)	63 (4.4)	0 (0)	1165 (20.6)	1165 (17.0)
Missing data	5	0	0	2	0	0	2

	All (n=8351)	Primary care (n=1440)			Specialists (n=6872)		
		Investigator-classified mild asthma (n=743)	Investigator-classified moderate-to-severe asthma (n=695)	All (n=1440)	Investigator-classified mild asthma (n=1210)	Investigator-classified moderate-to-severe asthma (n=5660)	All (n=6872)
Comorbidities, n (%)							
None	2962 (35.5)	328 (44.1)	264 (38.0)	593 (41.2)	535 (44.2)	1822 (32.2)	2358 (34.3)
1–2	3900 (46.7)	319 (42.9)	276 (39.7)	596 (41.4)	512 (42.3)	2773 (49.0)	3286 (47.8)
3–4	1228 (14.7)	89 (12.0)	126 (18.1)	215 (14.9)	136 (11.2)	870 (15.4)	1006 (14.6)
≥5	261 (3.1)	7 (0.9)	29 (4.2)	36 (2.5)	27 (2.2)	195 (3.4)	222 (3.2)

BMI: body mass index; GINA: Global Initiative for Asthma; IQR: interquartile range; SD: standard deviation.

TABLE 2 Asthma-related severe exacerbations and asthma symptom control presented by asthma severity and practice type

	All (n=8351)	**Primary care (n=1440)**			**Specialists (n=6872)**		
		Investigator-classified mild asthma (n=743)	**Investigator-classified moderate-to-severe asthma (n=695)**	**All (n=1440)**	**Investigator-classified mild asthma (n=1210)**	**Investigator-classified moderate-to-severe asthma (n=5660)**	**All (n=6872)**
Number of severe asthma exacerbations in the past year							
Mean (SD)	1.1 (2.09)	1.1 (2.99)	0.9 (1.60)	1.0 (2.42)	0.8 (1.81)	1.1 (2.03)	1.1 (2.00)
Severe asthma exacerbations in the past year by group, n (%)							
0	4555 (54.5)	453 (61.0)	428 (61.6)	882 (61.3)	772 (63.8)	2880 (50.9)	3653 (53.2)
1	1810 (21.7)	129 (17.4)	130 (18.7)	259 (18.0)	206 (17.0)	1338 (23.6)	1544 (22.5)
2	892 (10.7)	59 (7.9)	62 (8.9)	122 (8.5)	109 (9.0)	655 (11.6)	764 (11.1)
3	493 (5.9)	47 (6.3)	32 (4.6)	79 (5.5)	51 (4.2)	362 (6.4)	413 (6.0)
>3	600 (7.2)	55 (7.4)	43 (6.2)	98 (6.8)	72 (6.0)	424 (7.5)	497 (7.2)

	All (n=8351)	Primary care (n=1440)			Specialists (n=6872)		
		Investigator-classified mild asthma (n=743)	Investigator-classified moderate-to-severe asthma (n=695)	All (n=1440)	Investigator-classified mild asthma (n=1210)	Investigator-classified moderate-to-severe asthma (n=5660)	All (n=6872)
Missing data	1	0	0	0	0	1	1
Level of asthma symptom control, n (%)							
Well controlled	3610 (43.3)	318 (42.8)	282 (40.6)	601 (41.7)	608 (50.4)	2388 (42.3)	2996 (43.7)
Partly controlled	2686 (32.2)	244 (32.8)	258 (37.1)	503 (34.9)	361 (29.9)	1805 (32.0)	2167 (31.6)
Uncontrolled	2034 (24.5)	181 (24.4)	155 (22.3)	336 (23.3)	237 (19.7)	1450 (25.7)	1688 (24.6)
Missing data	21	0	0	0	4	17	21

SD: standard deviation.

TABLE 3 Patients who purchased SABA without a prescription (OTC) in the past 12 months

	All **(n=8351)**
Patients who purchased SABA without a prescription in the past 12 months, n (%)	
Yes	1503 (18.0)
No	6512 (78.0)
Unknown	333 (4.0)
Missing data	3
Total	8348 (100.0)
Canisters or inhalers per patient obtained without a prescription, n (%)	
1–2	770 (51.2)
3–5	450 (29.9)
6–9	114 (7.6)
10–12	64 (4.3)
≥13	34 (2.3)
Not applicable*	71 (4.7)

*“Not applicable” could be selected in the eCRF when patients purchased SABA in a different form (e.g., oral or nebulised) without a prescription.

eCRF: electronic case report form; OTC: over the counter; SABA: short-acting β_2-agonist.

Supplementary material

Short-acting β_2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study

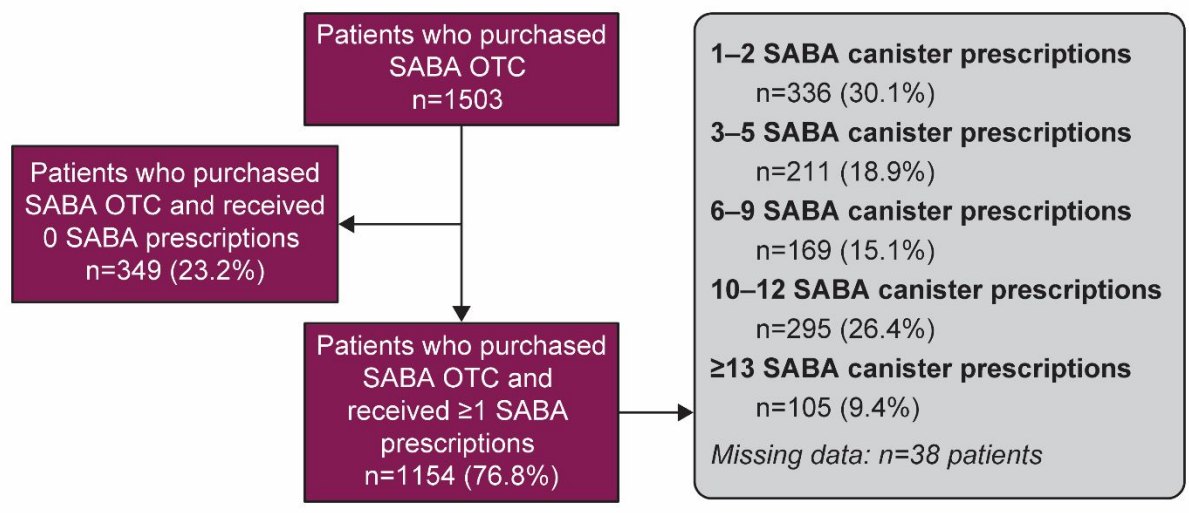
SUPPLEMENTARY RESULTS

Patients without a SABA prescription

Among patients not prescribed a SABA (n=3076), 89.2% had been prescribed ICS/LABA, and 11.4% reported having purchased SABA OTC during the past 12 months (supplementary table E3). A minority (2.3%) had received other treatments that might have been used for symptom relief (supplementary table E3). One or more bursts of oral corticosteroids (OCS) were prescribed for 25.4% of these patients, and 4.2% were prescribed long-term OCS treatment. Patients with no SABA prescriptions (vs those with ≥1 SABA prescriptions) were more likely to be classified at GINA step 3 or higher (82.7% vs 70.3%) (supplementary table E4) and less likely to have experienced ≥1 severe asthma exacerbation in the past year (35.0% vs 50.6%) (supplementary table E5).

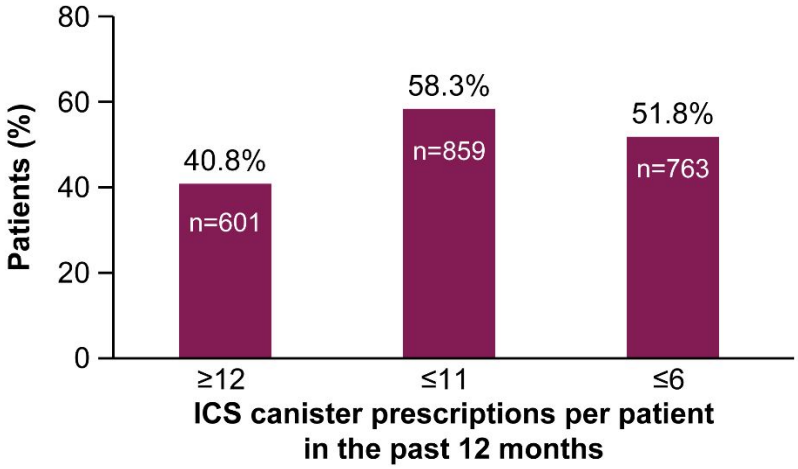
SUPPLEMENTARY FIGURES

SUPPLEMENTARY FIGURE E1 Over-the-counter SABA purchases and prescriptions in patients with asthma



OTC: over the counter; SABA: short-acting β_2-agonist.

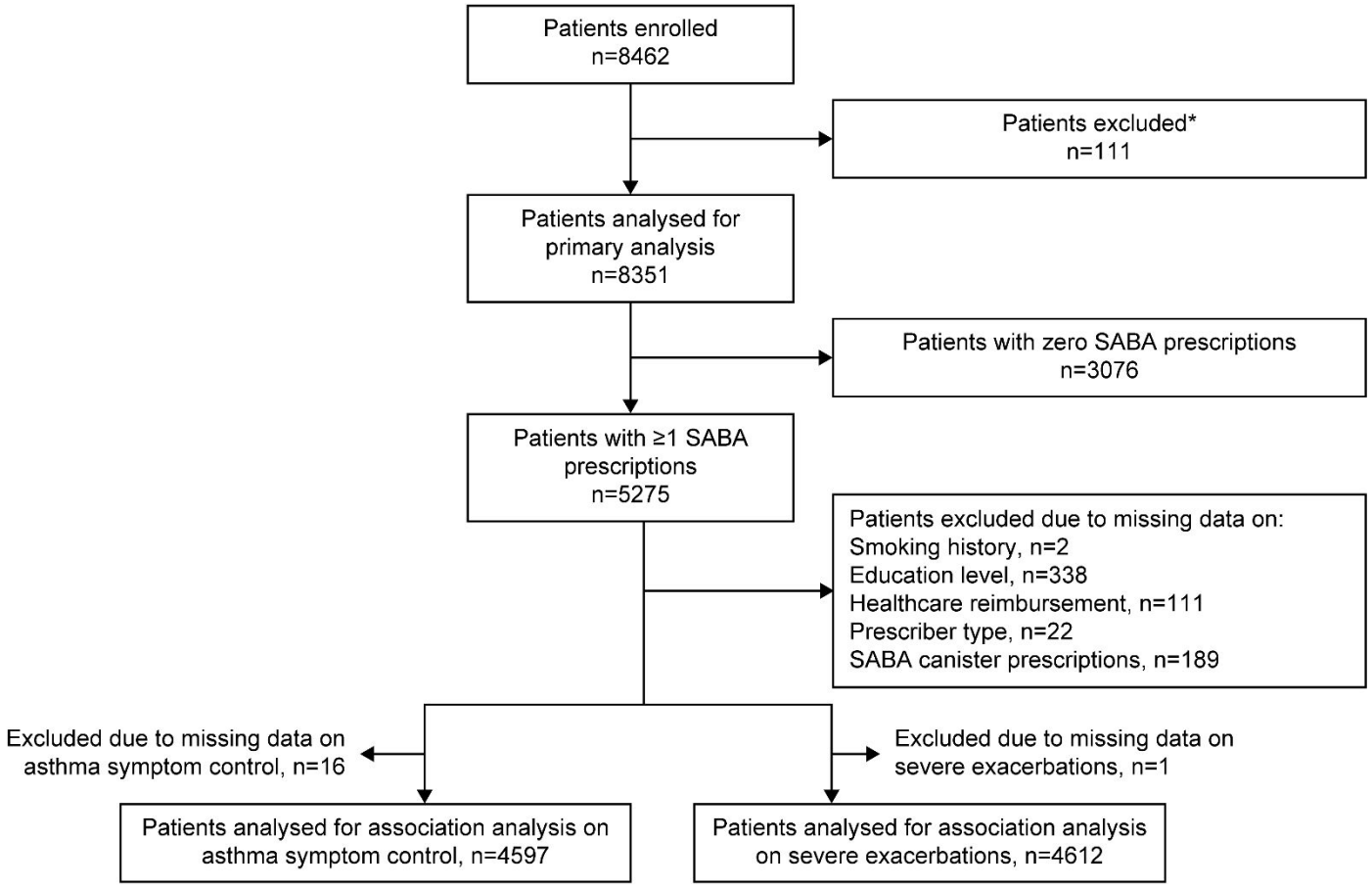
SUPPLEMENTARY FIGURE E2 ICS canisters prescribed in the past year in patients on ICS monotherapy as controller*



*Of the 1473 patients prescribed ICS monotherapy, data on number of canisters prescribed were not available for 13 patients.

ICS: inhaled corticosteroid.

SUPPLEMENTARY FIGURE E3 Patients included in the analyses for secondary objectives



*Excluded because the duration of asthma was <12 months.

SABA: short-acting β_2-agonist.

SUPPLEMENTARY TABLE E1 List of SABINA III sites and investigators

Country	Site #	Investigator	Affiliation
Australia	AUS01	Florian Heraud	Optimum Patient Care Australia
		Lenore Irvine	Optimum Patient Care Australia
		Victoria Carter	Optimum Patient Care Australia
		David Price	Optimum Patient Care Australia
Costa Rica	CRI01	Ted Mitchell Brumley	Laboratorio Función Pulmonar, Centro Médico Momentum Pinares
	CRI02	María Felicia Montero Arias	Hospital Clínica Bíblica, Sede Santa Ana, San José
	CRI03	Carlos Estrada Garzona	Hospital CIMA San José
Egypt	EGY01	Adel Khattab	Ain Shams University
	EGY02	Ahmed Fathy	Chest Consultant Private Clinic
	EGY03	Ahmed Hussien	Chest Consultant Private Clinic
	EGY04	Samah Selim	IM Consultant Private Clinic
	EGY05	Assem el Essawy	Fayoum University
	EGY06	Reem el Korashy	Cairo University
	EGY07	Heba Helmy	Chest Consultant Private Clinic
	EGY08	Ahmed Abd el Hafeez	Cairo University
	EGY09	Ibrahim Khalil	Chest Consultant
	EGY10	Mohamed Hanteera	Tanta University
	EGY11	Yasmine Hamdy	Cairo University
	EGY12	Ashraf Madkour	Ain Shams University
	EGY13	Ashraf Okba	Ain Shams University
	EGY15	Gehan El Assal	Ain Shams University
	EGY16	Abdallah Shafik	IM Consultant Private Clinic
	EGY17	Nabil Fawzy	IM Consultant Private Clinic
	EGY20	Ahmed Elsayed	Chest Consultant Health Insurance
	EGY21	Mostafa Shawki Ahmed	Ain Shams Specialized Hospital
	EGY22	Ahmed El-Halafawy	Cairo University
	EGY25	Tarek Samy Essawy	Chest Consultant Private Clinic
	EGY27	Lamiaa Hassan Shaaban	Assuit University
	EGY28	Mohamed Fawzy Abdelghany Yassin	Assuit University

Country	Site #	Investigator	Affiliation
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	EGY32	Ashraf Ishak Barsom	Chest Consultant
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	EGY34	Tarek Hamdy Hassan Abdel Hameed	Zagazig University
	EGY35	Ibrahim Aly Mohamed Dewedar	Ain Shams University
	EGY36	Ahmed Mohamed Abd el Hady Eldeeb	Chest Consultant
	EGY37	Hesham Salah Eldin Hamdy Mortada	Chest Consultant
	EGY38	Emad Edward Seif	Chest Consultant
	EGY39	Abo Elmatey Elsherif	IM Consultant Private Clinic
	EGY40	Wagdy Abd Elfattah Mohamed	Chest Consultant Private Clinic
	EGY42	Mohamed Eletreby	Mansoura University
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Kenya	KEN01	Lilian Rukwaro	Baraka Medical Centre
	KEN02	Samuel Gathua	Menelik Chest Clinic
	KEN03	Millicent Kamau	Reuben Medical Centre
	KEN04	Jeremiah Chakaya	Fortis Clinic
	KEN05	Musa Mohammed Josephine Nguri	Mama Lucy Kibaki Hospital
	KEN06	Gituma	Mbagathi District Hospital
	KEN07	Lucina Koyio	Kibera South Health Centre
	KEN08		Kibera DO Health Centre
	KEN09		APTC Dispensary
	KEN10		Riruta Health Centre
	KEN11		Algadhir Medical Centre
	KEN12		Eastleigh Health Centre
	KEN13		Kasarani Health Centre
	KEN14	Mogoi	Kayole II Health Centre
	KEN15	Jared Mogaka	Mukuru Kwa Njenga Health Centre
	KEN16	Morris Maina	Embakasi Health Centre
	KEN17	David Ndegwa (CDoH, Kiambu County)	Kiambu L5 Hospital

Country	Site #	Investigator	Affiliation
	KEN18	David Ndegwa (CDoH, Kiambu County)	Gatundu L5 Hospital
	KEN19	David Ndegwa (CDoH, Kiambu County)	Tumutumu Medical Clinic
Korea	KOR01	Yoo-Sook Cho	Asan Medical Center
	KOR02	Sang-Heon Kim	Hanyang University Seoul Hospital
	KOR03	Yoon-Seok Chang	Seoul National University Bundang Hospital
	KOR04	Heung-Woo Park	Seoul National University Hospital
	KOR05	Kwang-Ha Yoo	Konkuk University Medical Center
	KOR06	Sang-Ha Kim	Wonju Severance Christian Hospital
	KOR07	Ji-Yong Moon	Hanyang University Guri Hospital
	KOR08	Hye-Kyoung Park	Pusan National University Hospital
	KOR09	Sang-Pyo Lee	Gachon University Gil Medical Center
	KOR10	An-Soo Jang	Soon Chun Hyang University Hospital Bucheon
	KOR11	Young-Mok Lee	GF Internal Medicine
	KOR12	Jeong-Eun Kim	Soo Internal Medicine Clinic
	KOR13	Yang-Deok Lee	Leeyangdeok Clinic
	KOR14	Hui-Jung Kim	Goodbreath Medical Center
	KOR15	Jeong-Cheol Gwon	Sanbon Yonsei Medical Clinic
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	MEX03	José Carlos Herrera García	Unidad de Investigación y Salud de Puebla, S.C. (UISP), Puebla, Mexico
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	MYS05	Irfhan Ali Hyder Ali	Hospital Pulau Pinang, George Town
	MYS06	Lalitha Pereirasamy	Hospital Seberang Jaya, Permatang Pauh
	MYS07	Azza Omar	Hospital Raja Perempuan Zainab II, Kota Bharu
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	MYS09	Noor Aliza Mohd Tarekh	Hospital Sultanah Aminah, Johor Bahru
	MYS10	Chan Swee Kim	Hospital Umum Sarawak, Kuching
	MYS11	Sri Wahyu Taher	Klinik Kesihatan Simpang Kuala, Alor Setar
	MYS12	Paranthaman Vengadasalam	Klinik Kesihatan Greentown, Ipoh
	MYS13	Norsiah Ali	Klinik Kesihatan Masjid Tanah, Melaka
	MYS14	Nor Azila Mohd Isa	Klinik Kesihatan Nilai, Nilai
	MYS15	Husni Hussain	Klinik Kesihatan Salak, Sepang
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	PHL02	Leilanie A. Nicodemus	FMAB Qualimed
	PHL03	Evangeline L. Parena-Santiago	Batangas Medical Center
	PHL04	Marie ElaineV. Capalla	West Visayas University Hospital
	PHL05	Ronnie Z. Samoro	Healthlink Medical, Surgical, Dental Clinic & Diagnostic Center
	PHL06	Bryna Kimberly Bayate-Jabines	Western Visayas Medical Center
	PHL07	Jessie F. Orcasitas	Metro Davao Medical and Research Center
	PHL08	Miranila Hernandez-Matibag	The Medical City
	PHL09	Ronnel S. Matibag	M&R Santos Clinic
	PHL10	Janet C. Bernardo	Davao Doctors Hospital
Russia	RUS01	Natalia Kostina	Voronezh regional clinical Hospital No 1

Country	Site #	Investigator	Affiliation
	RUS02	Amyrzhan Kulbaisov	Orenburg Regional Clinical Hospital No 2
	RUS03	Dmitry Tikhanov	Pokrovskaya Hospital, St. Petersburg
	RUS04	Elena Vankova	Clinical Hospital No 2, Kazan
	RUS05	Marina Boldina	City Hospital №28, Pulmonology Consultant Center, Nizhny Novgorod
	RUS06	Irina Costrova	Amur State Medical Academy, Blagoveschensk
	RUS07	Irina Zaykova-Khelimskaya	Railway Clinical Hospital at Khabarovsk-1 Station
	RUS08	Ekaterina Kochegarova	Far East Scientific Center of Breath Physiology and Pathology, Blagoveschensk
	RUS09	Igor Leshchenko	Ural State Medical University, Medical Union "Novaya bolnitsa", Ekaterinburg
	RUS10	Galina Ignatova	South Ural State Medical University Chelyabinsk
	RUS11	Sergey Avdeev	First Moscow State Medical University, Moscow
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	UAE02	Noorah Bawady	Al Badaa PHC, DHA-Dubai, UAE
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Country	Site #	Investigator	Affiliation
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	UAE12	Naim Hazzouri	Al Muhasinah MOH PHC, Dubai, UAE
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	KWT01	Mohamed Negm	Al Adan Hospital, Kuwait
	KWT02	Khaled Hegazy	Sabah El Salem PHC, Kuwait
	KWT03	Mohamed Samir	Rumaitheya PHC, Kuwait
	KWT04	Khaled Khudadah	Ahmadi Hospital, Kuwait
Oman	OMN01	Nasser Al Busaidi	Royal Hospital, Muscat – Sultanate of Oman
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		Joana Diesca	Study Coordinator, Specialized Medical Center
	SAU02	Tarek Dihan	Principal Investigator, King Fahad Specialist Hospital Dammam
		Lamees Gain	Study Coordinator, King Fahad Specialist Hospital Dammam
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Country	Site #	Investigator	Affiliation
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		Hajar Alhayyan	Sub Investigator, King Abdulaziz Medical City - Riyadh
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	ZAF04	Essack Mitha	Newgate Centre, Newtown, Johannesburg, GP
	ZAF05	Ismail Abdullah	Melomed Gatesville Hospital, Gatesville, Cape Town
	ZAF06	Ismail Aboobaker Abdullah	St. Augustine's Hospital Berea, Durban
	ZAF07	Jeevren Reddy	26 Daffodil Street, Stanger, 4450 Kwa-Zulu Natal
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	ZAF12	Michael van der Linden	Ethekwini Hospital & Heart Centre, Newlands East, KZN
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	ARG02	Altieri, Hector Hugo	Centro Integral de Medicina Respiratoria (CIMER), Tucumán
	ARG03	Goffredo, Hernán Diego	Htal Regional Dr Victor Sanguinetti, Comodoro Rivadavia, Chubut
	ARG04	Grilli, Monica	Hospital Español de Mendoza, Mendoza
	ARG05	Zunino, Sergio Daniel	Hospital Italiano de Bs As, CABA
	ARG06	Silva, Damian	Centro de Estudios Neumonológicos Tandil, Buenos Aires
	ARG07	Solis, Marco Antonio	Sanatorio Güemes, CABA
	ARG08	Emery, Nicholas	Hospital Británico, CABA
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Country	Site #	Investigator	Affiliation
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	COL02	Jaller Raad, Rodolfo Antonio	Centro de Investigación Médico Asistencial S.A.S.
	COL03	Reynales, Humberto	Centro de Atención e Investigación Médica - CAIMED
	COL054	Pedrozo-Pupo, John Carlos	Previcare Ltda. Instituto para Cuidado Respiratorio (Respire)
	COL06	Baños Álvarez, Iván de Jesús	Centro de Rehabilitación Pulmonar Integral S.A.S.
	COL07	Eastmond Mahecha, James Junior	Healthy Medical Center S.A.S.
	COL08	Pacheco Gallego, Manuel Conrado	Universidad Tecnológica de Pereira Universidad Visión de las Américas Respiremos Centro de Neumología y Endoscopia Respiratoria
Thailand	THA01	Theerakorn Theerakittikul	Maharaj Nakhon Chiang Mai Hospital, Chiang Mai
	THA04	Anuchit Niyompattama	Maharaj Nakhon Ratchasima Hospital, Nakhon Ratchasima
	THA05	Narongwit Nakwan	Hatyai Hospital, Songkla
Turkey	TUR01	Nejat Altıntaş	Tekirdag Namık Kemal University Faculty of Medicine, Tekirdağ
	TUR02	İsmet Bulut	Sureyyapasa Chest Diseases and Thoracic Surgery Training Hospital, İstanbul
	TUR03	Tülin çağatay	Istanbul University, Istanbul Faculty of Medicine (ÇAPA)
	TUR04	Bilün Gemicioğlu	Istanbul University Cerrahpasa Faculty of Medicine
	TUR05	Özgür İnce	Samsun Medicana International Hospital, Samsun
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Country	Site #	Investigator	Affiliation
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	TUR19	Emel Ceylan	Adnan Menderes University Faculty of Medicine, Aydın
	TUR20	Aykut Çilli	Akdeniz University Faculty of Medicine, Antalya
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	TUR22	Can Sevinç	Dokuz Eylul University Faculty of Medicine, İzmir
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	IND03	Manoj Singh	Apollo Hospital, Gandhinagar, Gujarat
	IND04	Mahesh P.A.	JSS Medical College, Mysuru, Karnataka

Country	Site #	Investigator	Affiliation
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	IND06	Pramod Jhawar	Jhawar Chest, Allergy, Asthma & Bronchoscopy, Sleep Study Centre Indore
	IND08	Sudhir Kumar	Ramkrishna Hospital, Patna
	IND09	Aruna Kumari Badam	Apollo Hospitals Jubilee Hills, Hyderabad
	IND10	Giriyanna Gowda	Allergy and Asthma Clinic, 4D Diagnostics and Polyclinic, Bangalore
	IND11	Manav Manchanda	Asian Institute of Medical Sciences Faridabad, Haryana
	IND12	Manisha Mendiratta	Sarvodaya Hospital & Research Center, Faridabad-121006
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	TWN04	Chou-Chin Lan	Division of Pulmonary Medicine, Taipei Tzu Chi Hospital, New Taipei City
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	TWN06	Jiunn-Min Shieh	Department of Pulmonary Medicine, Chi Mei Medical Center, Tainan
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Country	Site #	Investigator	Affiliation
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	SGP03	Lim Hui Fang	National University Hospital
	SGP03	Geraldine Wong	National University Hospital
	SGP04	Joanne Khor Huiyi	National University Polyclinic
	SGP05	David Tan Hsien Yung	National University Polyclinic
	SGP05	Tan Wee Hian	National University Polyclinic
Indonesia	IDN01	Djajalaksana, Susanthy	Saiful Anwar Hospital - Malang
	IDN01.1	Djajalaksana, Susanthy	Saiful Anwar Hospital – Lawang Hospital - Malang
	IDN01.2	Djajalaksana, Susanthy	Saiful Anwar Hospital – Puskesmas Kendal Kerep - Malang
	IDN01.3	Djajalaksana, Susanthy	Saiful Anwar Hospital - Lavalette Hospital - Malang
	IDN02	Amin, Muhammad	Airlangga University Hospital - Surabaya
	IDN03	Wiyono, Wiwien Heru	Persahabatan National Respiratory Referral Hospital - Jakarta
	IDN04	Tarigan, Amira Permatasari	University of Sumatera Utara Hospital – Medan
	IDN04.2	Tarigan, Amira Permatasari	University of Sumatera Utara Hospital - Aviati Jamin Ginting Clinic - Medan
	IDN05	Susanti, Febrina	Budhi Asih Hospital – Jakarta
	IDN05.1	Susanti, Febrina	Budhi Asih Hospital - Puskesmas Kecamatan Cawang - Jakarta
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Country	Site #	Investigator	Affiliation
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	BRA10	Waldo Mattos	Nossa Senhora da Conceição Hospital

SABINA: SABA use IN Asthma.

TABLE E2 SABA and ICS medication prescriptions in the past 12 months

	All (n=8351)	Primary care (n=1440)			Specialists (n=6872)		
		Investigator-classified mild asthma (n=743)	Investigator-classified moderate-to-severe asthma (n=695)	All (n=1440)	Investigator-classified mild asthma (n=1210)	Investigator-classified moderate-to-severe asthma (n=5660)	All (n=6872)
Patients prescribed SABA monotherapy, n (%)							
Yes	428 (5.1)	183 (24.6)	0 (0)	183 (12.7)	224 (18.5)	18 (0.3)	242 (3.5)
No	7923 (94.9)	560 (75.4)	695 (100.0)	1257 (87.3)	986 (81.5)	5642 (99.7)	6630 (96.5)
Number of canisters or inhalers per patient prescribed in the past year							
Number of patients	422	180	0	180	222	17	239
Mean (SD)	5.8 (5.6)	7.2 (6.1)	-	7.2 (6.1)	4.6 (5.0)	5.5 (3.6)	4.7 (4.9)
SABA canisters or inhalers per patient prescribed in the past year, n (%)							
1–2	196 (46.4)	71 (39.4)	0 (0)	71 (39.4)	117 (52.7)	6 (35.3)	123 (51.5)
3–5	56 (13.3)	15 (8.3)	0 (0)	15 (8.3)	40 (18.0)	1 (5.9)	41 (17.2)
6–9	44 (10.4)	13 (7.2)	0 (0)	13 (7.2)	23 (10.4)	7 (41.2)	30 (12.6)
10–12	107 (25.4)	69 (38.3)	0 (0)	69 (38.3)	35 (15.8)	3 (17.6)	38 (15.9)
≥13	19 (4.5)	12 (6.7)	0 (0)	12 (6.7)	7 (3.2)	0 (0)	7 (2.9)
Missing data	6	3	0	3	2	1	3
Total	422 (100.0)	180 (100.0)	0 (0)	180 (100.0)	222 (100.0)	17 (100.0)	239 (100.0)
Patients prescribed SABA in addition to maintenance therapy, n (%)							
Yes	4847 (58.0)	402 (54.1)	386 (55.5)	788 (54.7)	644 (53.2)	3395 (60.0)	4039 (58.8)
No	3504 (42.0)	341 (45.9)	309 (44.5)	652 (45.3)	566 (46.8)	2265 (40.0)	2833 (41.2)

	All (n=8351)	Primary care (n=1440)			Specialists (n=6872)		
Number of canisters or inhalers per patient prescribed in the past year							
Number of patients	4649	401	355	756	631	3244	3875
Mean (SD)	6.5 (8.6)	6.7 (4.7)	8.1 (14.1)	7.4 (10.3)	6.7 (6.0)	6.2 (8.5)	6.3 (8.1)
Missing data, n (%)	198 (4.1)	1 (0.2)	31 (8.0)	32 (4.1)	13 (2.0)	151 (4.4)	164 (4.1)
SABA canisters or inhalers per patient prescribed in the past year, n (%)							
1–2	1780 (38.3)	113 (28.2)	121 (34.1)	234 (31)	246 (39)	1295 (39.9)	1541 (39.8)
3–5	856 (18.4)	71 (17.7)	45 (12.7)	116 (15.3)	83 (13.2)	653 (20.1)	736 (19.0)
6–9	653 (14.0)	76 (19.0)	41 (11.5)	117 (15.5)	59 (9.4)	473 (14.6)	532 (13.7)
10–12	1041 (22.4)	124 (30.9)	132 (37.2)	256 (33.9)	221 (35.0)	561 (17.3)	782 (20.2)
≥13	319 (6.9)	17 (4.2)	16 (4.5)	33 (4.4)	22 (3.5)	262 (8.1)	284 (7.3)
Missing data	198	1	31	32	13	151	164
Total	4649 (100.0)	401 (100.0)	355 (100.0)	756 (100.0)	631 (100.0)	3244 (100.0)	3875 (100.0)
Patients prescribed ICS monotherapy,* n (%)							
Yes	1473 (17.6)	403 (54.2)	44 (6.3)	447 (31.0)	627 (51.8)	395 (7.0)	1022 (14.9)
No	6878 (82.4)	340 (45.8)	651 (93.7)	993 (69.0)	583 (48.2)	5265 (93.0)	5850 (85.1)
Daily ICS dose prescribed (patients [%])							
Low dose	556 (38.3)	132 (32.9)	10 (25.6)	142 (32.3)	309 (49.8)	104 (26.7)	413 (40.9)
Medium dose	689 (47.4)	231 (57.6)	27 (69.2)	258 (58.6)	263 (42.4)	167 (42.9)	430 (42.6)
High dose	208 (14.3)	38 (9.5)	2 (5.1)	40 (9.1)	48 (7.7)	118 (30.3)	166 (16.5)
Missing values	20	2	5	7	7	6	13
Total	1453 (100.0)	401 (100.0)	39 (100.0)	440 (100.0)	620 (100.0)	389 (100.0)	1009 (100.0)
ICS canisters or inhalers per patient prescribed in the past 12 months							
Number of patients	1460	402	39	441	625	390	1015
Mean (SD)	8.1 (8.7)	7.5 (7.2)	4.8 (4.1)	7.2 (7.0)	8.3 (10.1)	8.6 (8.0)	8.4 (9.3)

	All (n=8351)	Primary care (n=1440)			Specialists (n=6872)		
Missing values, n (%)	13 (0.9)	1 (0.2)	5 (12.8)	6 (1.4)	2 (0.3)	5 (1.3)	7 (0.7)

*ICS monotherapy – ICS alone as controller treatment.

ICS: inhaled corticosteroid; SABA: short-acting β_2-agonist; SD: standard deviation.

SUPPLEMENTARY TABLE E3 Asthma treatments in patients with 0 SABA prescriptions (n=3076)

Asthma treatments	**Patients with 0 SABA canister prescriptions, n=3076**	
	Number of patients, n (%)	**Missing values**
SABA OTC	349 (11.4)	3
ICS monotherapy prescriptions	219 (7.1)	0
ICS/LABA combination prescriptions	2743 (89.2)	1
OCS short-course prescriptions	780 (25.4)	5
OCS long-term prescriptions	129 (4.2)	4
Other treatments	70 (2.3)	-
Nebulised SABA	16	-
Oral SABA	2	-
LTRAs	10	-
Nebulised SAMA/SABA	2	-
Theophylline	1	-
Others*	39	-
No other medication/other medication not specified	44 (1.4)	-

***Others included various combinations of LTRA, LAMAs, biologics, antibiotics, anti-allergic medication, nebulised SABA/SAMA and OCS.

ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid; OTC: over the counter; SABA: short-acting β_2-agonist; SAMA: short-acting muscarinic antagonist.

SUPPLEMENTARY TABLE E4 Demographics and disease characteristics of patients with 0 vs ≥1 SABA prescription (secondary analysis dataset)

	All patients (n=8351)	Patients with 0 SABA prescriptions (n=2642)*	Patients with ≥1 SABA prescription (n=4597)
Age (years)			
n	8351	2642	4597
Mean (range)	49.4 (12.0–95.0)	48.9 (12.0–95.0)	49.1 (12.0–93.0)
Sex, n (%)			
Female	5691 (68.1)	1714 (64.9)	3199 (69.6)
BMI (kg/m^2)			
Mean (SD)	27.8 (6.19)	27.3 (6.0)	28.1 (6.3)
Education level, n (%)			
Primary or secondary school	2877 (34.5)	887 (33.6)	1806 (39.3)
High school	2013 (24.1)	686 (26.0)	1208 (26.3)
University and/or post-university	2792 (33.4)	1069 (40.5)	1583 (34.4)
Not established	668 (8.0)	0 (0.0)	0 (0.0)
Missing data	1	0	0
Healthcare insurance/medication funding, n (%)			
Not reimbursed	2281 (27.3)	864 (32.7)	1258 (27.4)
Partially reimbursed	1851 (22.2)	637 (24.1)	985 (21.4)
Fully reimbursed	3940 (47.2)	1141 (43.2)	2354 (51.2)
Missing data	3	0	0
Smoking status history, n (%)			
Active smoker	497 (6.0)	154 (5.8)	255 (5.5)
Former smoker	1105 (13.2)	348 (13.2)	608 (13.2)
Never smoker	6747 (80.8)	2140 (81)	3734 (81.2)
Missing data	2	0	0
Comorbidities, n (%)			
None	2962 (35.5)	1027 (38.9)	1587 (34.5)
1–2	3900 (46.7)	1216 (46)	2170 (47.2)
3–4	1228 (14.7)	329 (12.5)	700 (15.2)
≥5	261 (3.1)	70 (2.6)	140 (3.0)
Asthma duration (years)			
Mean (SD)	14.9 (14.3)	12.2 (13.5)	17.1 (14.9)
Median (min, max)	10.0 (1.0, 85.0)	7.0 (1.0, 83.0)	12.0 (1.0, 85.0)
GINA classification, n (%)			
Step 1	714 (8.5)	226 (8.6)	438 (9.5)
Step 2	1244 (14.9)	230 (8.7)	929 (20.2)
Step 3	2279 (27.3)	917 (34.7)	1038 (22.6)
Step 4	2872 (34.4)	970 (36.7)	1518 (33)

	All patients (n=8351)	Patients with 0 SABA prescriptions (n=2642)*	Patients with ≥1 SABA prescription (n=4597)
Step 5	1237 (14.8)	299 (11.3)	674 (14.7)
Missing data	5	0	0

*Among the 7239 patients in the secondary analysis population (excluding patients with various modelling parameters missing), 2646 patients had 0 SABA prescriptions.
BMI: body mass index; GINA: Global Initiative for Asthma; max: maximum; min: minimum; SABA: short-acting β_2-agonist; SD: standard deviation.

SUPPLEMENTARY TABLE E5 Severe asthma exacerbations in patients with 0 vs ≥1 SABA prescription (secondary analysis dataset)

	All patients (n=8351)	**Patients with 0 SABA prescriptions (n=2642)***	**Patients with ≥1 SABA prescription (n=4597)**
Number of severe asthma exacerbations in the last year			
Mean (SD)	1.1 (2.09)	0.8 (1.8)	1.2 (2.3)
Severe asthma exacerbations in the last year by groups, n (%)			
0 exacerbations	4555 (54.5)	1716 (65.0)	2271 (49.4)
1 exacerbation	1810 (21.7)	486 (18.4)	1088 (23.7)
2 exacerbations	892 (10.7)	200 (7.6)	555 (12.1)
3 exacerbations	493 (5.9)	117 (4.4)	297 (6.5)
>3 exacerbations	600 (7.2)	123 (4.7)	385 (8.4)
Missing data	1	0	1

*Among the 7239 patients in the secondary analysis population (excluding patients with various modelling parameters missing), 2646 patients had 0 SABA prescriptions.
SABA: short-acting β_2-agonist; SD: standard deviation.

SUPPLEMENTARY TABLE E6 Other asthma treatments prescribed in the past 12 months

	All (n=8351)	Primary care (n=1440)			Specialists (n=6872)		
		Investigator-classified mild asthma (n=743)	Investigator-classified moderate-to-severe asthma (n=695)	All (n=1440)	Investigator-classified mild asthma (n=1210)	Investigator-classified moderate-to-severe asthma (n=5660)	All (n=6872)
Patients prescribed ICS/LABA combination, n (%)							
Yes	6610 (79.2)	34 (4.6)	675 (97.3)	711 (49.4)	297 (24.5)	5566 (98.4)	5865 (85.4)
No	1735 (20.8)	709 (95.4)	19 (2.7)	728 (50.6)	913 (75.5)	89 (1.6)	1002 (14.6)
Missing values	6	0	1	1	0	5	5
Total	8345 (100.0)	743 (100.0)	694 (100.0)	1439 (100.0)	1210 (100.0)	5655 (100.0)	6867 (100.0)
Prescribed daily ICS dose in combination (patients [%])							
Low dose	2066 (31.4)	26 (78.8)	324 (48.2)	350 (49.5)	170 (58.4)	1538 (27.8)	1710 (29.3)
Medium dose	3214 (48.9)	5 (15.2)	279 (41.5)	286 (40.5)	106 (36.4)	2804 (50.6)	2910 (49.9)
High dose	1292 (19.7)	2 (6.1)	69 (10.3)	71 (10.0)	15 (5.2)	1197 (21.6)	1212 (20.8)
Missing values	38	1	3	4	6	27	33
Total	6572 (100.0)	33 (100.0)	672 (100.0)	707 (100.0)	291 (100.0)	5539 (100.0)	5832 (100.0)
Patients prescribed OCS burst/short course, n (%)							
Yes	2654 (31.8)	152 (20.5)	157 (22.6)	309 (21.5)	257 (21.3)	2071 (36.7)	2329 (34.0)
No	5683 (68.2)	590 (79.5)	537 (77.4)	1129 (78.5)	951 (78.7)	3579 (63.3)	4531 (66.0)
Missing values	14	1	1	2	2	10	12
Total	8337 (100.0)	742 (100.0)	694 (100.0)	1438 (100.0)	1208 (100.0)	5650 (100.0)	6860 (100.0)

	All (n=8351)	Primary care (n=1440)			Specialists (n=6872)		
Patients prescribed OCS maintenance treatment, n (%)							
Yes	482 (5.8)	28 (3.8)	13 (1.9)	41 (2.8)	51 (4.2)	387 (6.8)	438 (6.4)
No	7858 (94.2)	715 (96.2)	681 (98.1)	1398 (97.2)	1157 (95.8)	5266 (93.2)	6424 (93.6)
Missing values	11	0	1	1	2	7	10
Total	8340 (100.0)	743 (100.0)	694 (100.0)	1439 (100.0)	1208 (100.0)	5653 (100.0)	6862 (100.0)
Patients prescribed antibiotics (for asthma), n (%)							
Yes	1656 (20.0)	64 (8.7)	92 (13.3)	157 (11.0)	149 (12.4)	1346 (24.1)	1495 (22.0)
No	6606 (80.0)	672 (91.3)	600 (86.7)	1273 (89.0)	1050 (87.6)	4246 (75.9)	5298 (78.0)
Missing values	89	7	3	10	11	68	79
Total	8262 (100.0)	736 (100.0)	692 (100.0)	1430 (100.0)	1199 (100.0)	5592 (100.0)	6793 (100.0)

ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; OCS: oral corticosteroid.

SUPPLEMENTARY TABLE E7 Severe exacerbations and level of asthma symptom control across SABA canister prescription categories

	SABA canister prescriptions in the past 12 months					
	1–2 canisters	**3–5 canisters**	**6–9 canisters**	**10–12 canisters**	**≥13 canisters**	**Total**
Patients with severe exacerbations in the past 12 months, n (%)						
0 severe exacerbations	1071 (59.1)	342 (40.6)	269 (42.9)	501 (47.2)	88 (32.6)	2271 (49.2)
1 severe exacerbation	378 (20.9)	249 (29.5)	165 (26.3)	255 (24.0)	41 (15.2)	1088 (23.6)
2 severe exacerbations	163 (9.0)	127 (15.1)	91 (14.5)	134 (12.6)	44 (16.3)	559 (12.1)
≥3 severe exacerbations	199 (11.0)	125 (14.8)	102 (16.3)	171 (16.1)	97 (35.9)	694 (15.0)
Total	1811	843	627	1061	270	4612
Level of asthma symptom control, n (%)						
Patients with uncontrolled asthma	382 (21.3)	252 (29.9)	208 (33.2)	396 (37.3)	131 (48.5)	1369 (29.8)
Patients with at least partly controlled asthma	1414 (78.7)	590 (70.1)	419 (66.8)	666 (62.7)	139 (51.5)	3228 (70.2)
Total	1796	842	627	1062	270	4597

SABA: short-acting β_2-agonist.

SUPPLEMENTARY TABLE E8 Unadjusted analysis: association of SABA prescriptions with severe exacerbations in the past 12 months and level of asthma symptom control

SABA canister prescriptions in the past 12 months	Rate of severe exacerbations			Odds of at least partly controlled asthma		
	IRR	95% CI	p-value	OR	95% CI	p-value
1–2 canisters	*Reference*			*Reference*		
3–5 canisters	1.40	1.23–1.58	<0.0001	0.63	0.53–0.76	<0.0001
6–9 canisters	1.45	1.27–1.67	<0.0001	0.54	0.45–0.67	<0.0001
10–12 canisters	1.56	1.39–1.75	<0.0001	0.45	0.38–0.54	<0.0001
≥13 canisters	2.71	2.27–3.25	<0.0001	0.29	0.22–0.37	<0.0001

CI: confidence interval; IRR: incidence rate ratio; OR: odds ratio; SABA: short-acting β_2-agonist.