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Early View

Research highlights

SABINA: global programme to evaluate prescriptions and clinical outcomes related to short-acting β_2-agonist use in asthma

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Title

SABINA: global programme to evaluate prescriptions and clinical outcomes related to short-acting β_2-agonist use in asthma

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Take home message (254/256 characters including spaces):

As SABA overuse is associated with exacerbations and mortality, GINA no longer recommends SABA only as a preferred reliever in asthma. A consistent pattern of high SABA use from the SABINA programme would indicate a global public health issue.

To the Editor:

Asthma, a chronic inflammatory fluctuating disease with day-to-day variability in lung function and symptoms, is estimated to affect 339 million individuals worldwide [1]. The long-term goals of asthma management are to achieve good control of asthma symptoms and to minimise the risk of asthma-related death, exacerbations, and persistent airflow limitation [2]. As such, treatment with inhaled corticosteroids (ICS) to control the underlying airway inflammation is the cornerstone of asthma management. However, previous global treatment recommendations and several current national treatment guidelines recommend short-acting β_2-agonists (SABAs) for use as-needed for symptom relief across all asthma severities, and as monotherapy treatment for the mildest form of asthma [3, 4]. This, together with patients' natural behaviour to seek immediate symptom relief, may contribute to an emphasis on symptom management rather than treating the causative underlying inflammation [5, 6], potentially leading to SABA over-reliance.

As a result of growing evidence that SABA over-reliance is associated with an increased risk of asthma-related exacerbations and mortality, the Global Initiative for Asthma (GINA) no longer recommends treating adolescents and adults with SABA alone as-needed for symptom relief [7]. Instead, GINA recommends as-needed low-dose ICS-formoterol as the preferred reliever for all GINA treatment steps, eliminating SABA monotherapy in Step 1 [2]. This ensures that patients treat the underlying inflammation, while also experiencing immediate symptom relief given that the long-acting β_2-agonist formoterol component has a fast onset of action [8, 9]. Thus, the recent GINA update places the treatment of inflammation with ICS further at the forefront of asthma management, even in the mildest asthma patients [2, 7].

A global view of SABA prescriptions is needed to understand the public health burden of SABA over-reliance in asthma management. We hypothesise that high SABA use occurs among a significant proportion of mild, moderate and severe asthma patients worldwide. Currently, only few country-specific studies have reported on the burden of SABA overuse using various definitions and study designs [10–12]. The overarching goal of the SABINA (SABA use IN Asthma) programme is to capture the current burden of SABA use on a global scale. To embrace the diversity of different healthcare systems, treatment behaviours, local data availability and structure, we constructed a scientifically robust framework that introduced a flexible method to measure this burden. The SABINA programme therefore aims to describe asthma treatment prescription patterns, the extent of high SABA use, and its impact on asthma-related clinical outcomes through a series of large observational cohort studies using a harmonised approach.

SABINA: design

Due to the diversity in healthcare systems, data availability and robustness across countries, the SABINA programme comprises three main pillars: SABINA I (retrospective observational research database study in one country), SABINA II (retrospective observational database studies in eight countries), and SABINA III (cross-sectional study in 25 countries) (**Figure 1**). All three pillars share a common objective and design principles from a granular core protocol (SABINA I) to ensure scientific alignment. The SABINA II and III protocols are adaptations of the SABINA I protocol, which uses a robust database specifically designed for high quality clinical research, to accommodate country- or region-specific characteristics (e.g. healthcare systems, local guidelines, data availability, and local evidence gaps). Key study characteristics and definitions are captured for each protocol to

maintain an overview of similarities and differences across the SABINA programme to facilitate interpretation of overall results (**Table 1)**.

The core requirements for patient inclusion in all three pillars are 1) age ≥12 years and 2) current asthma diagnosis. Additionally, all studies should describe SABA prescription or dispensing patterns during the 12 months before the index date (date when patient meets all inclusion criteria). The definition of one SABA canister has been harmonised across all SABINA studies based on treatment guidelines and an assumed average of 150 puffs/inhaler. Data are further harmonised by using similar categories across all SABINA pillars (e.g. SABA prescriptions, asthma severity and age). High SABA use has been defined as ≥3 SABA canisters/year, based on the 2016 British Thoracic Society (BTS) guidelines [13] and GINA recommendations in place at the time of study design.

SABINA I

The SABINA I pillar consists of an open cohort study utilising the Clinical Practice Research Datalink (CPRD) [14] in the United Kingdom (UK) during 2007–2017. Current asthma patients (with an asthma diagnosis code recorded within 3 years before study entry) will be included when they meet the inclusion criteria (**Table 1**) during the study period and will be followed up for as long as possible. Asthma severity is based on the treatment that corresponded with the highest available BTS treatment step (steps 1–5) during the 12-month period before the index date [13]. The most severe patients (BTS step 6) are excluded due to the inability to capture all confounding variables needed to fully understand this population.

Of the included asthma patients, the majority are expected to have primary care records that are linked with secondary care data from the Hospital Episode Statistics and mortality data

from the Office for National Statistics [15]. If there is ≥12 months of medical history available after study entry, these patients will be included in regression analyses for asthma-related exacerbations and healthcare resource utilisation (HCRU). Exacerbations are defined as a short course of oral corticosteroid (OCS) treatment, a hospital admission or emergency room visit linked to an asthma diagnosis code, or death due to asthma. HCRU is defined as asthma-related physician or hospital visits.

SABINA II

A total of eight countries (Canada, France, Germany, Italy, Israel, the Netherlands, Spain, and Sweden) have adapted the SABINA I protocol for local implementation, as part of the SABINA II pillar **(Table 1)**. In doing so, local study designs, definitions, and analyses have evolved depending on data availability, local clinical practice, and treatment guidelines. Data sources vary per country, from primary care records with prescription data (e.g. Netherlands) to healthcare claims or pharmacy databases with dispensing data (e.g. Israel) to national population registries (e.g. Sweden). In some countries (e.g. Sweden), various databases can be linked to obtain further information on outcomes including HCRU or asthma-related mortality.

Current asthma definitions are adapted according to local recording practices, with modification of the comprehensive definitions from SABINA I in some countries. Asthma severity definitions are also adapted in local studies, depending on which guidelines are used (BTS guidelines in the UK, Canadian Thoracic Society guidelines in Canada, GINA guidelines in all other countries). To further allow for harmonisation of results across the SABINA programme, short-course OCS treatment is included as a core component of the asthma-related exacerbation definition in each study. Other components of the exacerbation

definition in SABINA I, such as emergency room visits, hospital admissions, and mortality are adapted into the individual country study designs pending local data availability as described in **Table 1**. HCRU definitions are similar to SABINA I with slight variations, such as asthma-related medical procedures which are included in Spain and in- and outpatient visits in Sweden; however, HCRU is not assessed in the Netherlands. Finally, analyses vary from descriptions of SABA prescription trends to formal testing of associations between SABA prescriptions and asthma-related clinical outcomes or HCRU.

SABINA III

Due to the lack of robust longitudinal electronic medical records in a large part of the world, the third pillar of the SABINA programme is designed to capture clinical information through an electronic clinical report form (eCRF). SABINA III is a multicentre, retrospective, cross-sectional study comprising 25 countries (**Figure 1**). At least 7,500 patients will be enrolled, distributed among study sites selected to ensure a viable sample of patients with physician-diagnosed asthma, from both general practices and specialist clinics in each participating country.

Participation in the SABINA III study will be subject to the receipt of signed informed consent from patients or legal guardians. Asthma medication prescription patterns in the 12 months before the study visit will be described and categorised across all 25 countries. As oral treatments are prevalent in many emerging market countries [1], SABINA III will also describe the prescription patterns of oral asthma therapies, with a focus on OCS. The data will be collected on a centrally designed eCRF, which also records demographics, asthma diagnosis date, disease severity based on GINA 2017 recommendations, comorbidities, smoking status, and GINA Assessment of Asthma Control at the time of the visit. Finally,

data on severe exacerbations leading to either an asthma-related hospitalisation or emergency room visits in the past 12 months will be collected and described for each country.

Discussion

SABA does not treat the underlying airway inflammation in asthma [2, 16]. Therefore, GINA no longer recommends treatment with as-needed SABA alone for symptom relief, and low-dose ICS-formoterol is now the preferred reliever for all GINA treatment steps [2]. This recent major change in the recommendations for asthma management requires an extensive re-evaluation of SABA use worldwide. Although designed before the major update by GINA in 2019, the SABINA programme aims to further substantiate the GINA directive by identifying the global public health burden of SABA prescriptions and subsequent impact on asthma-related clinical outcomes.

The flexible design of the SABINA programme allows for studies to be clinically relevant within each respective country, while also facilitating harmonisation of results between countries. For instance, while the outcomes measured are tailored to suit the diverse needs of each country, all SABINA studies have similar objectives related to determining prescription patterns and exacerbations and healthcare resource utilisation related to SABA use. Notably, standardisation of the high SABA use definition enables evaluation at a global level. The collection of both longitudinal and cross-sectional data from various sources provides a large and diverse dataset describing prescription patterns and their clinical impact. In addition, the use of eCRFs for countries lacking robust databases supports the generation of valuable local public health data that otherwise would not have been possible.

A programme of this magnitude cannot, of course, be implemented without limitations. For instance, to collect data across a multitude of countries, the protocols have to be flexible to align to country-specific data availability and definitions (e.g. asthma coding and exacerbations). Although this might lead to some loss of granularity, it enables the insights generated from the SABINA programme to be both applicable for local needs and generalisable for the rest of the world. The use of prescription or dispensing data has inherent limitations in relation to adherence; actual behaviour in relation to medication intake is often not captured through these measures. Moreover, if the SABINA programme shows a consistent pattern of SABA over-prescriptions potentially indicating over-reliance, across the variety of study designs, it is likely to be indicative of a major public health issue as hypothesised.

Quantifying the extent of high SABA use is only part of the solution to improving asthma outcomes. Underlying patient and physician behaviour also need to be better understood to truly effect public health change. Thus, SABINA will also include qualitative research methodologies, such as questionnaires and focus groups aimed at healthcare practitioners and patients, to understand attitudes and actions driving medication usage behaviour. These qualitative methods may also be applied in other countries in the future, similar to the quantitative part of the SABINA programme. Finally, it will also be important to better outline existing incentives and barriers within national healthcare systems and policies, which may impact patient and physician behaviour.

In conclusion, the structured yet flexible SABINA programme will enable the generation of country-specific data on SABA prescription and associated asthma-related clinical outcomes. Additionally, the SABINA programme will provide relevant context to the current global public health burden caused by high SABA use in asthma.

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Conflicts of interest: All authors are employees of AstraZeneca. C. Nan holds shares in AstraZeneca and GlaxoSmithKline. R. van der Valk holds shares in GlaxoSmithKline.

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Figure legend

Figure 1: SABINA (SABA use IN Asthma) programme, including objective and participating countries

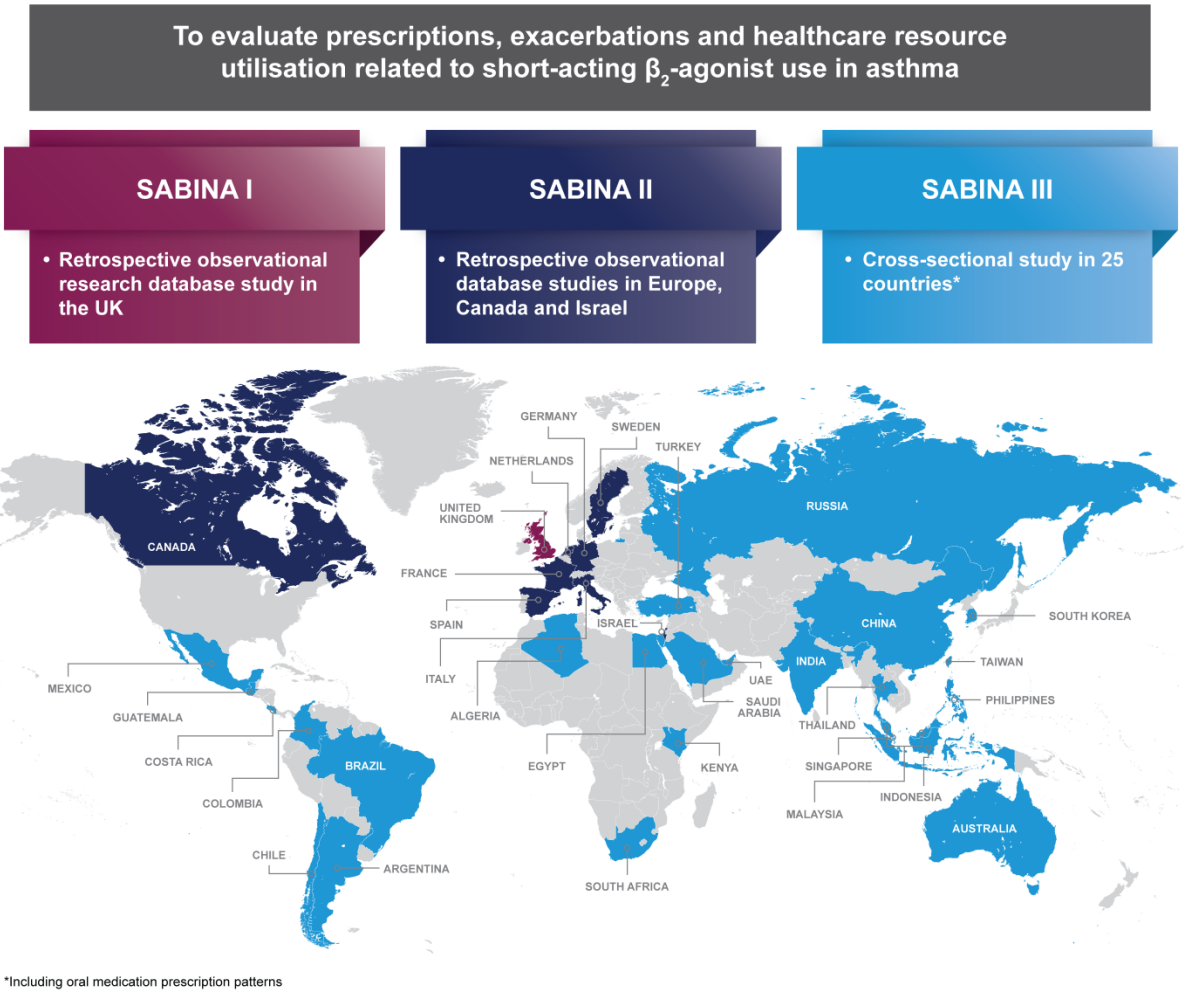

Table 1: Key parameters across the SABINA (SABA use IN Asthma) programme.

	SABINA I	**SABINA II**								**SABINA III**
		Canada	**France**	**Germany**	**Israel**	**Italy**	**Netherlands**	**Sweden**	**Spain**	
Primary objectives	Determine pattern and trend of SABA and ICS prescriptions	Describe patient demographics and clinical characteristics by asthma severity; Determine prescription patterns of SABA and ICS and identify SABA-ICS balance by asthma severity	Describe healthcare resource burden (HCRU and costs, sick leave, patient-related outcomes, comorbidities) among patients with asthma	Assess potential high use of SABA (and associated ICS use) stratified by asthma severity	Describe asthma prevalence, patient characteristics and treatment patterns; Define and validate criteria for identification and classification of patients with asthma	Describe patient demographics and clinical characteristics by asthma severity; Determine prescription patterns of SABA and ICS and identify SABA-ICS balance by asthma severity	Describe medication use in patients with asthma; Describe how medication use is related to exacerbation risk and level of asthma control	Describe SABA use in patients with asthma by evaluation of demographic and clinical determinants of SABA overuse; Investigate the associations between SABA overuse, exacerbation risk, all-cause mortality, and respiratory-related death	Describe patient demographics and clinical characteristics by asthma severity; Determine prescription patterns of SABA and ICS and identify SABA-ICS balance by asthma severity	Describe pattern and trend of SABA prescriptions across countries
Data source	Primary care records (CPRD), linked with secondary care (HES) and mortality (ONS) data	Alberta, Saskatchewan, Manitoba administrative healthcare databases	CONSTANCES cohort linked with SNDS: randomly selected, nationally representative population cohort linked with national healthcare insurance database	IMS® Disease Analyzer: electronic medical records form primary physician and pulmonologist panels	Maccabi Healthcare Services: administrative database with consultation, prescription, dispensing, hospitalisation, laboratory and medical procedures data	IQVIA databases: electronic medical records from primary care (Longitudinal Patient Database) and secondary care (Patient Analyzer) physicians	NIVEL primary care database: electronic medical records, including laboratory data	Nationwide longitudinal cohort study (HERA): linked data from national patient, pharmacy dispensing and mortality registries	BIG-PAC: electronic medical records from primary and specialised healthcare	Primary data collection from physicians and patients in an eCRF: retrospective medical record extraction and patient interviews in 25 countries

Study period	2007–2017	2016–2018	2016	2013–2018	2017–2018	2015–2018	2016	2006–2016	2017–2018	2019
Age	≥12 years	≥12 years	18–69 years	≥12 years	≥12 years (data available from ≥6 years for local needs)	≥12 years	≥12 years	12–45 years	≥12 years	≥12 years
Asthma definition	Asthma diagnosis code within 3 years of index date	Asthma diagnosis code within 3 years of index date	Self-reported asthma symptoms AND physician diagnosis at cohort entry	Asthma diagnosis code during study period	Asthma diagnosis code AND respiratory system drug dispensation	Asthma diagnosis code 1 year prior to index date	Asthma diagnosis code in medical history AND ≥2 asthma medication prescriptions during study period	≥2 collections for a chronic obstructive lung disease medication within 12 months	Asthma diagnosis code AND ≥2 healthcare uses within study period	Asthma diagnosis recorded any time in medical records
Asthma treatment steps	2016 BTS guidelines [13]	2012 CTS guidelines	2018 GINA recommendations	2018 GINA recommendations	2018 GINA recommendations	2018 GINA recommendations	2018 GINA recommendations	2018 GINA recommendations	2018 GINA recommendations	2017 GINA recommendations
Key secondary outcomes:										
Asthma-related exacerbation Defined by:										
Short-course OCS	Yes	Yes			Yes	Yes	Yes (≥20mg per day)	Yes	Yes	Yes
Increase of maintenance therapy									Yes (dose increase for 3 days)	
Asthma-related antibiotic prescription						Yes				
Emergency room visit	Yes	Yes						Yes	Yes + systemic corticosteroids	Yes
Hospital admission	Yes	Yes				Yes		Yes	Yes	Yes
Asthma-related death	Yes	Yes								

Asthma-related HCRU Defined by:										
Primary care physician visit	Yes	Yes	Yes		Yes	Yes			Yes	
Specialist physician visit			Yes		Yes				Yes	
Hospital visit (out-patient)	Yes	Yes						Yes	Yes	
Hospital admission (in-patient)			Yes	Yes	Yes			Yes	Yes	
Emergency room visit					Yes				Yes	
Medical procedures									Yes	
Medication prescriptions			Yes (including OCS)	Yes (including OCS)	Yes				Yes	

BTS, British Thoracic Society; CPRD, Clinical Practice Research Datalink; CTS, Canadian Thoracic Society; eCRF, electronic case report form; GINA, Global Initiative for Asthma; HCRU, healthcare resource utilisation; HES, Hospital Episode Statistics; ICS, inhaled corticosteroids; OCS, oral corticosteroids; ONS, Office for National Statistics; SABA, short-acting β_2-agonist; SNDS, Système National des Données de Santé.