



COMMENTARY

The Changing Asthma Management Landscape and Need for Appropriate SABA Prescription

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Received: October 26, 2022 / Accepted: December 14, 2022 / Published online: January 30, 2023
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ABSTRACT

Short-acting β_2 agonists (SABAs) have been a mainstay of asthma treatment since the 1950s, and have been mainly recommended as-needed for symptom relief alongside daily inhaled corticosteroid (ICS)-based maintenance treatment for the past 30 years. However, patient adherence to regular ICS-based anti-inflammatory maintenance therapy is frequently poor, leading to SABA overuse for symptom relief and associated poor outcomes. At present, there is a

lack of consensus between treatment guidelines on how SABA should be used, and as-needed ICS-formoterol is suggested by some as an alternative reliever therapy. Here, we examine the pharmacology and current use of inhaled SABAs, identify that regular dosing of ICS can encourage appropriate SABA use, and appraise the evidence used to support the changing reliever treatment recommendations. We conclude that SABA continues to play an important role in the asthma management landscape, and give our views on how it should be used in patients with mild–moderate asthma, to complement regular ICS-based maintenance treatment.

Keywords: Asthma; GINA; Guidelines; Recommendations; SABA; Salbutamol; Treatment

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Key Summary Points

Inhaled short-acting β_2 agonist (SABA) reliever therapy, as a complement to regular inhaled corticosteroid (ICS)-based maintenance treatment, plays a well-established role in asthma management

An appraisal of current evidence found that regular ICS with as-needed SABA gives better asthma control and bronchoprotection compared with as-needed ICS-formoterol, even at suboptimal adherence

Regular ICS dosing encourages appropriate SABA use by managing airway inflammation, improving asthma control, and subsequently reducing the need for symptom relief

SABA reliever use is a valuable tool for assessing asthma control, and thereby informing treatment modification decisions

It is our view that treatment recommendations should encourage regular ICS dosing, supported by as-needed SABA use and patient education on the importance of adherence

INTRODUCTION

Asthma has been treated with β agonists for thousands of years, since the first medicines were derived from plants (Fig. 1) [1, 2]. Inhaled short-acting β_2 agonists (SABAs), including salbutamol, were developed in the 1950s and became the primary therapies for all asthma severities [1, 2]. After it was established in the 1990s that asthma is a chronic inflammatory disease, inhaled corticosteroids (ICSs) were identified as the most effective anti-inflammatory treatment [3], and recommendations for SABA use were changed from ‘regular’ to ‘as-needed’ therapy for symptom relief [1, 2]. The

superior efficacy and safety of inhaled versus oral SABAs were also demonstrated in the 1990s [4], leading asthma guidelines to favor inhaled administration [5–9]. A regimen that combines inhaled SABA reliever for use as required with ICS-based regular maintenance therapy was proposed for patients with frequent symptoms to improve asthma control, reduce lung function deterioration, and prevent exacerbations [1, 2].

In 1994, the addition of a long-acting β_2 agonist (LABA) to ICS treatment for poorly controlled asthma was shown to give better clinical outcomes compared to increasing the ICS dose [1, 10]. Inhaled fluticasone propionate (FP) and salmeterol was the first combination ICS and LABA maintenance therapy licensed for use [11]. The early 2000s saw development of regimens with ICS and the fast-onset LABA formoterol (FOR) [2, 12].

Despite treatment advances, current asthma management is often suboptimal [13, 14]. To address this, treatment recommendations are shifting to reflect concerns regarding poor patient adherence to maintenance therapy, over-reliance on SABA, and newly available data on ICS dosing approaches [9, 15, 16]. As some recommendations now propose use of ICS-FOR in place of SABA [9, 15], it is relevant to re-evaluate current evidence for SABA treatment, and to discuss the concerns around its overuse, in order to understand how SABAs should be used appropriately in practice.

In this commentary, we summarize the pharmacology, recommendations for use, and prescription of inhaled SABAs, then present an appraisal of the available evidence around SABA use for asthma symptom relief. We recognize that as-needed ICS-FOR is now being proposed as a reliever therapy, but note that, at present, while as-needed use of ICS-FOR is accepted in some recommendations, including those of the Global Initiative for Asthma (GINA) and the National Asthma Council in Australia [9, 17], it has not been approved by the US Food and Drug Administration, European Medicines Agency, or the majority of scientific societies [5–8, 18–24]. Based on the evidence, we give our views on appropriate SABA use in mild-moderate asthma. This article is based on a review of

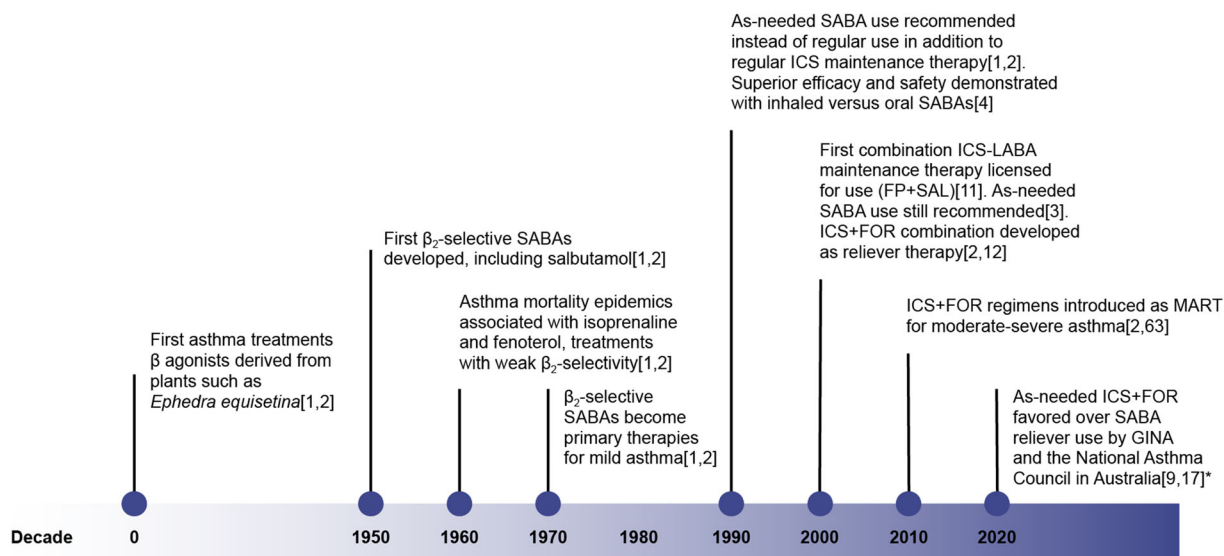


Fig. 1 History of SABA use. *The US Food and Drug Administration, European Medicines Agency and the majority of scientific societies have not approved this indication [5–8, 18–24]. FOR formoterol, FP fluticasone

propionate, *GINA* Global Initiative for Asthma, *ICS* inhaled corticosteroid, *LABA* long-acting β_2 agonist, *MART* maintenance and reliever therapy, *SABA* short-acting β_2 agonist, *SAL* salmeterol

previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

SABA PHARMACOLOGY

B_2 agonists exert their ability to relax airway smooth muscle (ASM) by binding β_2 adrenoreceptors, which are present in high numbers within ASM [25, 26]. Following binding, the canonical signaling pathway generates intracellular cyclic adenosine monophosphate (cAMP), which activates the effectors cAMP-dependent protein kinase A and exchange protein activated by cAMP. These effectors induce the relaxation of the ASM through phosphorylation of key regulatory proteins, down-regulation of Ras homolog family member A (RhoA), and sequestration of intracellular calcium ions [25, 26].

Although the LABA FOR and the SABA salbutamol are both β_2 receptor agonists, differences in the electrochemical shapes of their head groups mean that FOR binds the receptor

with higher affinity than salbutamol, leading to more prolonged signal transduction [27]. Both inhaled salbutamol and FOR have fast onset of action, with some studies showing that salbutamol has a comparable or slightly faster onset of action than FOR [27–30].

A double-blind randomized controlled trial (RCT) has shown no difference between the bronchodilator effect of salbutamol and ICS-FOR in average forced expiratory volume in 1 s (FEV_1) achieved from first dose to a 90-min assessment point [mean ratio 98.4%; 95% confidence interval (CI) 91.6, 105.7; $p = 0.66$] [30]. In a different RCT, focusing on an earlier time-point clinically relevant in terms of acute bronchodilation (2 min), the non-inferiority FEV_1 boundary of -0.06 L for budesonide (BUD)-FOR compared with salbutamol was not met [31]; mean FEV_1 change from baseline 2 min after treatment administration was 0.08 L for BUD-FOR [standard deviation (SD) 0.14, $n = 49$] and 0.17 L for salbutamol (SD 0.18, $n = 48$) [31]. Over the 30 min post-dose, FEV_1 was higher with salbutamol than BUD-FOR (mean difference 0.10 L, $p < 0.001$); however, this was less than the suggested threshold for

the minimum patient perceivable improvement of 0.23 L [32], and the study did not show any differences in perceived breathlessness between the treatments [31]. Another RCT examining effects 1 min after administration showed that salbutamol was significantly more effective at reversing methacholine-induced dyspnea than BUD-FOR (mean change in Borg score – 0.41 for salbutamol vs. BUD-FOR; $p = 0.024$); however, after 3 min, while there was still a numerical difference in favor of salbutamol, while the difference between the treatments was no longer statistically significant [33]. Taken together, the results from these RCTs suggest that patients are not likely to experience better relief with BUD-FOR than salbutamol [30, 31, 33].

SABA SAFETY

Historically, high doses of agents with weaker β_2 -selectivity, isoprenaline and fenoterol, have been associated with mortality epidemics in the 1960s and 1970s [1, 2, 34]. However, since regulatory warnings were issued for these molecules, fewer deaths have been associated with SABA use [35, 36]. In addition, it has been reported that there is no direct association between mortality risk and treatment with the stronger β_2 -selectivity molecule, salbutamol, used appropriately (defined as supporting suitable regular ICS-based maintenance therapy) [35].

While use of SABAs alone does not treat airway inflammation and may cause tachyphylaxis [2, 37–39], ICS treatment reverses desensitization of β_2 receptors caused by β_2 agonist exposure [37–39], and evidence from cell culture studies suggests that therapeutic doses of topical corticosteroids increase β_2 receptor density in human nasal mucosa cells [40]. Therefore, patients with good adherence to regular ICS treatment may be less prone to β_2 agonist tachyphylaxis and more likely to experience maximal benefit from their SABA reliever therapy.

Suboptimal ICS use results in inadequate anti-inflammatory treatment, often coupled with increasing use of reliever treatment [16, 40, 41]. Receiving ≥ 3 SABA 200-dose

canisters per year (corresponding to > 1 inhalation per day) without adequate regular ICS maintenance therapy is associated with increased hospitalization and mortality risk, irrespective of asthma severity [9, 14, 42, 43]. High SABA reliever use associated with underuse of ICS treatment remains common: in a study of UK treatment patterns published in 2021, 19.1–24.2% of patients used ≥ 4 SABA inhalers per year, attributable to underuse of maintenance treatment [44]. Excessive SABA use, insufficient uptake of ICS prescriptions, and failures to issue personal asthma action plans identified in an audit of 50 UK practices highlight that more proactive asthma care is needed [45].

The Swedish SABINA II registry study ($n = 365,324$) has reported that higher SABA use is associated with increased exacerbation and mortality risk in the real world, but this does not mean that a causal effect was shown; notably, inappropriate use of SABA was common, as SABA overuse (≥ 3 canisters per year) was reported in 30% of patients, and 28% of the study population took no ICS maintenance therapy [43]. Approximately 85% of patients who overused SABA at baseline had continuous overuse during the observation period, and the proportion of patients not using ICS was more than doubled by the end of the study [43].

It is probable that the poor asthma outcomes seen with increased SABA reliever use result from underlying uncontrolled asthma, often associated with inadequate ICS use, rather than SABA use itself [46]. Conversely, less requirement for SABA appears to correspond with better asthma control: in an Australian pharmacy-based survey of 412 patients, a greater proportion of SABA non-overusers had well-controlled asthma than SABA overusers (48.1% vs. 5.9%, respectively; $p < 0.001$) [47]. In a study demonstrating daily SABA use as a strong predictor of poor future asthma control and severe exacerbations, it was noted that only 21.7% of patients had well-controlled asthma at baseline [48]. These findings suggest that, in many cases, poor asthma control likely precedes and drives SABA overuse and future adverse outcomes.

Overall, it is clear that frequent use of as-needed SABA, without regular ICS-based

Table 1 Advantages and disadvantages of ICS-FOR versus SABA reliever use in mild asthma

As-needed reliever therapy	Advantages	Disadvantages
ICS-FOR	Guaranteed administration of ICS to treat underlying inflammation in patients with poor adherence to maintenance ICS [9, 64]	As-needed ICS use may lead to undertreatment of inflammation and airway remodeling [62] Less symptom control than with SABA [65]
SABA (to complement regular ICS therapy)	Underlying inflammation treated effectively by regular ICS [53–58] Better symptom control than with ICS-FOR [65]	Potential for overreliance on SABA and underuse of ICS in patients with poor adherence [59–61, 80] Potential for less exacerbation control than with ICS-FOR [66]

FOR formoterol, ICS inhaled corticosteroid, SABA short-acting β_2 agonist

maintenance therapy, is not appropriate, and leads to suboptimal asthma management [9]. Poor adherence to ICS treatment likely contributes to worsening of unstable asthma and increases the risk of severe exacerbations [49]. Additionally, secondary analyses of an RCT comparing BUD-FOR maintenance and reliever therapy (MART) versus fixed dose BUD-FOR plus as-needed SABA showed that, for $\geq 90\%$ of the days on which reliever therapy was overused, patients did not obtain medical review within 48 h of overuse, regardless of the ICS-LABA regimen they were prescribed [49]. This indicates that, unfortunately, there is often a lack of action by healthcare providers to address SABA

overuse, when it occurs. In patients regularly taking ICS, high levels of SABA use should be viewed as an indicator of poor asthma control and prompt physicians to review their asthma management [9, 42, 48, 50–52].

ICS REGULAR DOSING: BENEFITS AND CHALLENGES

A major pathophysiology underlying asthma is airway inflammation [53, 54]. Continuous regular use of ICS therapy reduces inflammation, exacerbation risk, and asthma-related mortality across all severities [53–58]. The long-term benefit of daily low-dose ICS has even been shown in patients with mild asthma and intermittent symptoms present ≤ 2 days per week [53].

Unfortunately, many patients do not adhere well to long-term daily ICS-based maintenance therapy [16, 41]. Patients perceive that ICSs do not provide immediate symptom relief and may have concerns about side effects with regular corticosteroid use [41, 57]. Such patients frequently rely on SABA alone for symptom relief, which can lead to increased SABA use and ICS underuse leading to poor asthma outcomes [9, 59–61].

Under-treatment of inflammation causes decline in lung function, worsening of asthma control, increased risk of exacerbation, and airway remodeling [62]. In addition, a population-based cohort study of the Canadian Saskatchewan Health databases showed that the mortality rate ratio for asthma-related death increased from ~ 0.2 with 12 canisters per year to ~ 0.6 with 6 canisters per year and to > 2.25 with no ICS use [56].

Modeling studies suggest that poor ($\leq 50\%$) adherence to regular ICS therapy gives a sub-optimal asthma control benefit-risk profile for BUD and FP, while there is less loss of bronchoprotection with the longer-acting corticosteroid fluticasone furoate [57, 58]. This highlights that the clinical outcomes of poor adherence may vary with the ICS molecule prescribed [57, 58]. Overall, poor adherence to ICS, and thus under-treatment of inflammation, can explain why studies have noted adverse

outcomes with SABA use in the absence of regular ICS therapy [9, 14, 42, 43, 45, 48, 58].

Implementation of adequate, regularly-dosed ICS therapy can encourage appropriate SABA reliever use [61]. A retrospective cohort study of British Columbian administrative health data showed that regular ICS use (ratio of ICS to total asthma medications > 0.5) was strongly associated with lower risk of SABA overuse in the following year, versus irregular ICS use (OR 0.10; 95% CI 0.10, 0.11) [61].

REVIEW OF LITERATURE COMPARING ICS-FOR VERSUS SABA AS RELIEVER MEDICATION, ACCORDING TO ASTHMA SEVERITY

Over the last two decades, low-dose ICS-FOR has been introduced as MART for moderate-severe asthma [2, 9, 12, 63]. More recently, attempts have been made to present ICS-FOR as a useful reliever treatment for mild asthma [2, 9, 12, 63]. The rationale for this approach is to guarantee administration of ICS, or a higher dose of ICS, at the time of an exacerbation, with the LABA FOR being used for symptom relief [9, 64]. There are potential advantages and disadvantages to reliever treatment with as-needed ICS-FOR and SABA (Table 1); however, the evidence for these therapies must be carefully interpreted with regard to the clinical characteristics of the populations studied, and whether regular maintenance treatment was used.

In 2019, GINA recommendations underwent major updates to incorporate emerging data, particularly from the SYGMA studies, on as-needed ICS-FOR use, and shifted to encourage “as-needed low-dose ICS-FOR” in place of SABA reliever in mild and moderate asthma [15, 42, 43, 56, 63, 65–68]. Among the cited studies is a 24-week trial of 303 patients that showed fewer severe asthma exacerbations were experienced with ICS-FOR maintenance therapy plus as-needed ICS-FOR, versus ICS-FOR maintenance therapy plus as-needed SABA (relative rate 0.54; 95% CI 0.36, 0.82; $p = 0.004$), potentially due to increased ICS exposure [63]. Another key reason for the introduction of as-

needed ICS-FOR recommendations was an acceptance that patients with asthma frequently have poor adherence to ICS-based maintenance therapy and, subsequently, an over-reliance on SABA for symptom relief [9, 69].

SYGMA 1 showed that fewer exacerbations and superior asthma control were achieved with as-needed BUD-FOR versus as-needed SABA in GINA Step 2 patients, for whom maintenance ICS is recommended. However, when regular BUD was used with as-needed SABA, as-needed BUD-FOR gave inferior asthma control by comparison, measured by well-controlled asthma weeks and the Asthma Control Questionnaire-5 (ACQ-5), while exacerbation rates were similar [65]. As-needed BUD-FOR gave well-controlled asthma for 34.4% of the electronically recorded weeks, in comparison to 44.4% with regular BUD plus as-needed SABA (OR 0.64; 95% CI 0.57, 0.73) [65]. The SYGMA 2 study, comparing as-needed BUD-FOR versus regular BUD with as-needed SABA, provided a similar pattern of results: there was no difference in exacerbation rates (the primary outcome), while ACQ-5 and lung function favored regular BUD with as-needed SABA [65, 70].

RCTs ensure high levels of treatment adherence. The open-label PRACTICAL trial was designed to allow real-life adherence patterns in patients with mild-moderate asthma; 60% adherence was observed in the regular BUD treatment arm, which is lower than in the SYGMA RCTs [65, 70, 71]. The rate of severe exacerbations was lower with as-needed BUD-FOR than regular BUD plus as-needed SABA in PRACTICAL (relative rate 0.69; 95% CI 0.48, 1.00; $p = 0.049$) [71]. Severe exacerbations were defined as use of systemic corticosteroids for ≥ 3 days because of asthma, or admission to hospital or an emergency department because of asthma requiring systemic corticosteroids [71]. Subgroup analysis indicated that the treatment difference was greater in individuals with lower adherence [71]. Overall, for GINA Step 2 patients, SYGMA and PRACTICAL highlight the benefits of regular ICS treatment combined with SABA on asthma control when levels of adherence are high, but that the benefits of regular ICS treatment are compromised

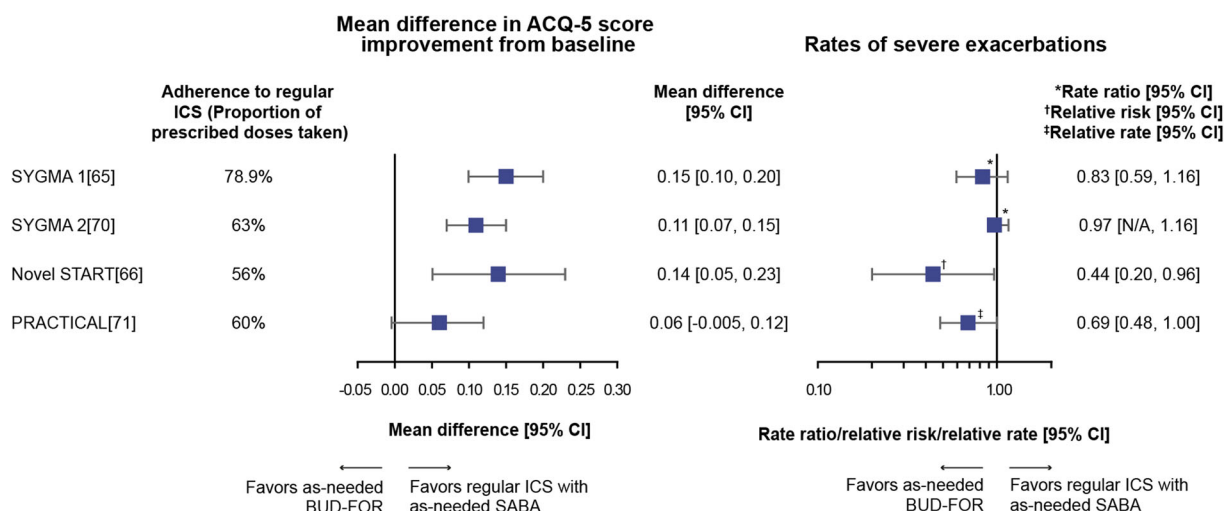


Fig. 2 Graphical overview of asthma control and severe exacerbation data from the SYGMA 1, SYGMA 2, Novel START, and PRACTICAL studies. *SYGMA 2 used an upper one-sided 95% CI for severe exacerbation rate ratio. †, ‡, ‡In all studies, severe exacerbations were defined as worsening asthma leading to systemic corticosteroid use

by poor adherence which could then favor the use of as-needed BUD-FOR instead. It is important to note that these studies do not provide evidence that as-needed ICS-FOR has greater efficacy than as-needed SABA for GINA Step 1, as the SYGMA studies were conducted in GINA step 2 patients, and most of the participants in the PRACTICAL study were using ICS before study entry and/or had partly controlled or uncontrolled asthma.

The open-label Novel START study was conducted in patients with mild asthma, using SABA without ICS prior to study enrollment [66]. At baseline, the mean ACQ-5 score was 1.1, and 45.5% of the population were using SABA more than twice per week [66]. These characteristics indicate that many patients had suboptimal asthma control on SABA treatment alone, and therefore it would be incorrect to classify them as needing GINA Step 1 treatment. The patients were randomized to receive as-needed BUD-FOR, SABA alone, or regular BUD therapy (which was taken at 56% adherence) plus as-needed SABA. The primary endpoint was annualized exacerbation rate; this was lower with as-needed BUD-FOR versus SABA (relative rate 0.49; 95% CI 0.33, 0.72; $p < 0.001$), but

for ≥ 3 days, hospitalization, or an emergency department visit leading to systemic corticosteroid treatment. *ACQ-5* Asthma Control Questionnaire-5, *BUD* budesonide, *CI* confidence interval, *FOR* formoterol, *ICS* inhaled corticosteroid, *SABA* short-acting β_2 agonist

there was no significant difference between as-needed BUD-FOR and regular BUD therapy plus as-needed SABA (relative rate 1.12; 95% CI 0.70, 1.79; $p = 0.65$) [66]. An exacerbation was defined as worsening asthma that resulted in ≥ 1 of the following: an urgent medical consultation; prescription of systemic glucocorticosteroids; or an episode of high β_2 agonist use, defined as > 16 actuations of albuterol or > 8 actuations of BUD-FOR within 24 h [66]. As-needed BUD-FOR only outperformed regular BUD plus as-needed SABA on the secondary endpoint of reducing the risk of severe exacerbations (relative risk, 0.44; 95% CI 0.20–0.96) [66]. On the other hand, regular ICS plus SABA provided better symptom control than as-needed ICS-FOR, with lower ACQ-5 scores observed (mean difference 0.14, 95% CI 0.05, 0.23) [66]. When airway inflammation was measured, the mean fraction of exhaled nitric oxide across all timepoints was significantly higher with as-needed ICS-FOR versus ICS maintenance therapy plus as-needed SABA (ratio of geometric means 1.13; 95% CI 1.02, 1.25; $p < 0.001$) [66, 71]. This is consistent with other evidence suggesting that as-needed use of ICS may result in reduced bronchoprotection, undertreatment

of asthma, and worsening control compared with regular ICS [57, 62].

Overall, the SYGMA RCTs and the open-label PRACTICAL and Novel START studies have focused on study populations comprising either entirely, or at least partly, GINA Step 2 patients [65, 66, 70, 71]. With this in mind, the results showing that as-needed ICS-FOR is superior to SABA alone are expected, as any ICS-based therapy would result in better outcomes compared with SABA monotherapy in this context. The outcomes for as-needed ICS-FOR versus regular ICS with as-needed SABA require careful interpretation. The results indicate that good adherence to regular ICS with as-needed SABA gives better outcomes compared with as-needed ICS-FOR [65, 66, 70, 71]. While suboptimal adherence to regular ICS still gives better asthma control than as-needed ICS-FOR, as-needed ICS-FOR may prevent more severe exacerbations in these patients (summarized in Fig. 2) [65, 66, 70, 71].

VALUE OF RELIEVER USE FOR ASSESSMENT OF ASTHMA CONTROL STATUS

An advantage of SABA reliever therapy is that the frequency of uptake is a helpful and commonly employed measure of asthma control [42, 48, 50–52]. Indeed, the GINA assessment of asthma control considers frequency of SABA reliever use, alongside daytime symptoms, nighttime awakening, and activity limitation due to asthma [9]. It might be possible to use as-needed ICS-FOR uptake as an indicator of asthma control for ICS-FOR regimens, but the relationship between frequency of ICS-FOR use and patient outcomes is not yet well established [9].

DIFFERENCES BETWEEN TREATMENT GUIDELINES AND PHYSICIAN ATTITUDES TO RELIEVER TREATMENT

Global and national guidelines for SABA use vary (Table 2) [5–9, 20–24]. Notably, GINA

recommendations now favor reliever treatment with as-needed low-dose ICS-FOR for mild asthma (Steps 1 and 2) and ICS-FOR maintenance therapy is accepted as the Track 1 treatment for moderate–severe asthma (GINA Step 3 and beyond) [9]. Many other asthma guidelines advocate for regular ICS-based maintenance treatment complemented with as-needed SABA [5–9, 20–24]. These disparities may lead to confusion on best practice among healthcare professionals.

The APPaRENT 1 study showed that the ICS-based treatment approaches used by most physicians for asthma Steps 1 and 2 involve regularly-dosed ICS and as-needed SABA reliever (21.2%; 156/736), while 13.0% (96/736) were prescribed as-needed ICS-FOR [72]. This could be explained by the finding that more physicians prioritize symptom control than exacerbation risk in patients with mild asthma [287/736 (9.0%) vs. 85/736 (11.5%), respectively] [72], since the SYGMA 1 study showed inferior symptom control with as-needed ICS-FOR versus regularly dosed ICS [65, 72], and a retrospective matched cohort study demonstrated better symptom control with once-daily fluticasone furoate-vilanterol versus twice-daily BUD-FOR [73]. Importantly, patients receiving ICS-FOR MART remain susceptible to SABA overuse; the APPaRENT studies reported that 85.4% (479/561) of physicians prescribed SABA in addition to MART (APPaRENT 1) [72], with the same incorrect use of MART reported by 85% (521/616) of patients (APPaRENT 2) [74].

AUTHORS VIEWPOINT

Appropriate Regular ICS-Based Maintenance Therapy is Key to Optimize Asthma Management

Since 2019, the GINA strategy has proposed two treatment tracks for adults and adolescents (Table 3) [9]. However, based on the strong evidence that regular ICS can manage the inflammation underlying asthma, improve asthma control, and subsequently reduce the need for SABA to relieve symptoms, we feel that treatment recommendations should not

Table 2 Summary of adult asthma treatment recommendations by various guidelines

		Canada [20]	France [21]	GINA [9]	Japan [7]	Korea [8]
Year updated		2021	2021	2022	2020	2016
STEP 1	PREF	M: None	M: None	M: None	M: Low-dose ICS/LTRA	M: None
		R: As-needed SABA/ BUD + FOR	R: As-needed SABA/ICS + FOR	R: As-needed low-dose ICS + FOR	theophylline R: SABA	R: As-needed SABA
	ALT		M: Low-dose ICS R: As-needed SABA	M: Low-dose ICS whenever SABA taken R: As-needed SABA		M: Low-dose ICS R: As-needed SABA
	STEP 2	PREF	M: ICS R: As-needed SABA/ BUD + FOR	M: Low-dose ICS/as-needed ICS + FOR R: As-needed SABA/ICS + FOR	M: Low/medium-dose ICS/ ICS + LABA/LAMA/ LTRA/theophylline	M: Low-dose ICS R: As-needed SABA
	ALT		M: LTRA R: As-needed SABA/ BUD + FOR	M: Low-dose ICS/low-dose ICS whenever SABA taken/LTRA R: As-needed SABA	R: SABA	M: LTRA / low-dose theophylline R: As-needed SABA
	STEP 3	PREF	M: ICS + LABA R: As-needed SABA/ BUD + FOR	M: Low-dose ICS + LABA R: As-needed SABA/ICS + FOR	M: Low-dose ICS + FOR R: As-needed low-dose ICS + FOR	M: Medium/high-dose ICS/ ICS + LABA/LAMA/ LTRA/theophylline/anti-IL- 4 α Ab
	ALT		M: Medium-dose ICS/low-dose ICS + LTRA/low-dose ICS + theophylline R: As-needed SABA	M: Low-dose ICS + LABA R: As-needed SABA	R: SABA	M: Medium/high-dose ICS/low-dose ICS + LTRA (or + theophylline) R: As-needed SABA/low-dose ICS + FOR
	STEP 4	PREF	M: ICS + LTRA and/or tiotropium R: As-needed SABA/ BUD + FOR	M: Medium-dose ICS + LABA R: As-needed SABA/ICS + FOR	M: Medium-dose ICS/ ICS + LABA/LAMA/ LTRA/theophylline/anti-IL- 4 α Ab/anti-IgG Ab/anti-IgE Ab/ anti-IL-5 α /oral corticosteroid/bronchial thermoplasty R: SABA	M: High-dose ICS/ ICS + LABA/LAMA/ LTRA/theophylline/anti-IL- 4 α Ab/anti-IgG Ab/anti-IgE Ab/ anti-IL-5 α /oral corticosteroid/bronchial thermoplasty R: SABA
	ALT		M: High-dose ICS/high-dose ICS + LTRA/high-dose ICS + theophylline R: As-needed SABA	M: Medium/high-dose ICS + LABA R: As-needed SABA		

Table 2 continued

	NAEPP [5]	Singapore [6]	Spain [22]	Thailand [23]	United Kingdom [24]
Year updated	2020	2020	2021	2021	2019
STEP 1	PREF M: None ALT R: As-needed SABA	M: Low-dose ICS/LTRA with as-needed low-dose ICS + FOR/low-dose ICS whenever SABA taken R: As-needed SABA/as-needed ICS + FOR	M: None R: As-needed SABA/ICS + FOR/ICS + SAL	M: Daily low-dose ICS R: As-needed low-dose ICS + FOR/as-needed SABA	M: Low-dose ICS R: As-needed SABA
STEP 2	PREF M: Low-dose ICS R: As-needed SABA	M: Low-dose ICS/LTRA with as-needed low-dose ICS + FOR/low-dose ICS whenever SABA taken R: As-needed SABA/as-needed ICS + FOR	M: Low-dose ICS R: As-needed SABA/ICS + FOR/ICS + SAL M: LTRA R: As-needed SABA/ICS + FOR/ICS + SAL	M: Daily low-dose ICS + LABA R: As-needed low-dose ICS + FOR/as-needed SABA	M: Low-dose ICS R: As-needed SABA
STEP 3	PREF M: Daily LTRA/cromolyn, nedocromil, zileuton or theophylline R: As-needed SABA M: Daily combination low-dose ICS + FOR R: As-needed ICS-FOR ALT M: Daily medium-dose ICS/low-dose ICS + LABA/low-dose ICS + LAMA/low-dose ICS + LTRA/ ICS + theophylline or zileuton R: As-needed SABA	M: Low-dose ICS + LABA/low-dose ICS + LTRA/medium-dose ICS/MART with low-dose ICS + FOR R: As-needed SABA/as-needed ICS + FOR	M: Low-dose ICS + LABA R: As-needed SABA/ICS + FOR M: Medium-dose ICS R: As-needed SABA/ICS + FOR	M: Medium-dose ICS + LABA R: As-needed low-dose ICS + FOR/as-needed SABA	M: Add inhaled LABA to low-dose ICS (fixed-dose or MART) R: As-needed SABA (unless using MART)
STEP 4	PREF M: Daily medium-dose ICS + FOR R: Medium-dose ICS + FOR ALT M: Daily medium-dose ICS + LABA or daily medium-dose ICS + LAMA R: As-needed SABA	M: Medium-dose ICS + LABA/medium-dose ICS + LTRA/high-dose ICS (tiotropium can be added)/MART with medium-dose ICS + FOR R: As-needed SABA/as-needed ICS + FOR	M: Medium-dose ICS + LABA R: As-needed SABA/ICS + FOR M: Medium-dose ICS + LTRA/medium-dose ICS + LABA + LAMA R: As-needed SABA/ICS + FOR	M: Medium/high-dose ICS + LABA + xanthines/LTRA/LAMA/biologics/low-dose OCS R: As-needed low-dose ICS + FOR/as-needed SABA	M: Increase ICS to medium-dose or add LTRA R: As-needed SABA

Where + is shown, combination therapy can be used if available

Ab antibody, *ALT* alternative treatment track, *BUD* budesonide, *FOR* formoterol, *GINA* Global Initiative for Asthma, *ICS* inhaled corticosteroid, *IL* interleukin, *IgE/G* immunoglobulin E/G, *LABA* long-acting β_2 agonist, *LAMA* long-acting muscarinic antagonist, *LTRA* leukotriene receptor antagonist, *M* maintenance, *MART* maintenance and reliever therapy, *NAEPP* National Asthma Education and Prevention Program, *OCS* oral corticosteroid, *PREF* preferred treatment track, *R* reliever, *SABA* short-acting β_2 agonist, *SAL* salmeterol

Table 3 Changes in treatment options recommended by GINA in 2018 and post-2019

		GINA 2018 [81]	GINA 2019 [15] and 2020 [82]		GINA 2021 [80] and 2022 [9]
STEP 1	PREF	Maintenance: None	Maintenance: None	Track	Maintenance: None
		Reliever: As-needed SABA	Reliever: As-needed low-dose ICS + FOR	1	Reliever: As-needed low-dose ICS + FOR
	ALT	Maintenance: Low-dose ICS	Maintenance: Daily low-dose ICS whenever SABA taken	Track	Maintenance: Low-dose ICS whenever SABA taken
		Reliever: As-needed SABA	Reliever: As-needed SABA	2	Reliever: As-needed SABA
STEP 2	PREF	Maintenance: Low-dose ICS	Maintenance: Daily low-dose ICS	Track	Maintenance: None
		Reliever: As-needed SABA	Reliever: As-needed low-dose ICS + FOR	1	Reliever: As-needed low-dose ICS + FOR
	ALT	Maintenance: Low-dose ICS + LABA/LTRA	Maintenance: Daily LTRA/ low-dose ICS whenever SABA taken	Track	Maintenance: Low-dose ICS/low-dose ICS whenever SABA taken/LTRA
		Reliever: As-needed SABA	Reliever: As-needed SABA	2	Reliever: As-needed SABA

Where + is shown, combination therapy can be used if available. The recommendations changed in 2019 are highlighted in bold

ALT alternative treatment track, *FOR* formoterol, *GINA* Global Initiative for Asthma, *ICS* inhaled corticosteroids, *LABA* long-acting β_2 agonist, *LTRA* leukotriene receptor antagonist, *PREF* preferred treatment track, *SABA* short-acting β_2 agonist

concede to the challenges of adherence [47, 54, 57, 75]. We also believe, along with others, that recommendations favoring ICS-FOR reliever regimens over as-needed SABA are not based on clear-cut evidence [76–79], as the SYGMA RCTs and supporting open-label studies give rise to complex data that need careful interpretation and understanding [65, 66, 70, 71]. The main contentious points to consider are: (1) these studies mainly focus on GINA Step 2 patients, and have not provided an evidence base to differentiate ICS-FOR and SABA in GINA Step 1 patients; and (2), in GINA Step 2 patients, the SYGMA RCT evidence does not show any superiority of as-needed ICS-FOR over regular ICS treatment plus as-needed SABA, while the latter regimen achieves better asthma control. In support of as-needed ICS-FOR, the open-label studies do show evidence of

superiority of as-needed ICS-FOR over regular ICS plus as-needed SABA for exacerbation endpoints, when adherence is suboptimal [65, 66, 70, 71]. With this complexity, it is reasonable to state that the scientific case for favoring ICS-FOR over regular ICS plus as-needed SABA is far from clear-cut. Indeed, for GINA Step 2, it appears that the best outcomes are achieved by striving to improve regular ICS treatment adherence [65, 66, 70, 71]. It can be argued that, when a patient requires administration of as-needed ICS-FOR, it is because they are symptomatic, and therefore their asthma is uncontrolled; as such, leaving the decision of when to take ICS to the patient may lead to undertreatment [57]. In our view, for appropriate patients, the benefits of regular ICS dosing are sufficient to warrant proactive efforts to improve patient adherence. This might be

achieved through better education of patients about the function of their medications and the need for regular ICS-based treatment to optimize clinical outcomes [9].

SABA Overuse is a Result and Indicator of Poor Asthma Control

We believe SABA overuse is likely the result of chronic poor asthma control rather than its cause. Unfortunately, based on the misinterpretation of some study results, conclusions have instead been drawn that SABA overuse itself might drive loss of asthma control and increase mortality risk [43]. Additionally, several studies currently cited to support the GINA Step 2 recommendations include data from patients who did not receive SABA appropriately (to complement regular ICS-based maintenance treatment), meaning conclusions about the efficacy and safety of SABA monotherapy have been extended to recommendations for patients who should not receive SABA alone [9, 43, 65, 66].

SABAs represent an important tool for measuring the success of asthma management [9]. In our opinion, results from the key studies cited by GINA to support a shift away from SABA use only further highlight the need to monitor frequency of SABA uptake and to use this assessment as a measure for asthma control [42, 43, 56, 67, 68]. Increases in SABA use should prompt investigations into the clinical measures of control, asthma management plan, adherence, and inhaler technique of the patient [9].

Conclusions

Inhaled SABA reliever use to complement ICS-based maintenance treatment is well-established in asthma management, and we believe it remains a useful tool to assess asthma control, inform treatment modification decisions, and individualize management of acute symptoms [1, 2]. We are not alone in our opinion that the evidence base does not yet fully endorse use of ICS-FOR regimens, and, at present, there is no robust or clear-cut evidence showing that as-

needed ICS-FOR has greater efficacy than as-needed SABA for mild asthma (GINA Step 1), or that ICS-FOR has greater efficacy overall than regular ICS plus as-needed SABA for GINA Step 2, because the SYGMA RCTs and the open-label PRACTICAL and Novel START studies showed a pattern of better asthma control with regular ICS plus as-needed SABA, while the benefit of as-needed ICS-FOR on exacerbations was only evident in patients with poor adherence [65, 66, 70, 71]. Furthermore, the inclusion of mixed populations of patients with different asthma severities makes the results of these studies difficult to disentangle [65, 66, 70, 71].

More data are needed to align expert opinions on asthma treatment and to support the development of globally aligned recommendations [76, 78]. Based on the evidence, we believe that patients with asthma who have regular symptoms need regular treatment, which means regular use of ICS-based maintenance therapy to treat the underlying pathophysiology of asthma [53, 54]. The benefits of regular ICS dosing are clear, so our view is that treatment recommendations should not risk suboptimal treatment (which leads to reduced asthma control) by conceding to the challenges of poor adherence [47, 54, 57, 75]. Instead, better adherence might be achieved through proactive efforts to improve patient education [9]. Appropriate SABA use is to complement regular ICS (as an infrequent reliever), and, in exchange, regular ICS supports appropriate SABA use by managing underlying inflammation to minimize symptoms [3, 53–58, 60, 61].

ACKNOWLEDGEMENTS

Funding. This study, along with the Rapid Service and Open Access Fees for publication were funded by GSK.

Medical Writing and Editorial Assistance. Bhumi Aggarwal and Sourabh Fulmali, of GSK, assisted development of the manuscript through facilitation of author meetings and provision of requested references. Editorial support (in the form of writing assistance,

including preparation of the draft manuscript under the direction and guidance of the authors, incorporating authors' comments for each draft, assembling tables and figures, grammatical editing and referencing) was provided by Phoebe Hobbs of Fishawack Communications Ltd, UK, and was funded by GSK.

Author Contributions. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. All authors participated in drafting the manuscript or revising it critically for important intellectual content and gave final approval of the version to be published.

Disclosures. CD has received funding for travel or speaker fees from ALK, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Esteve, Ferrer, GSK, Menarini, Novartis, Stallergenes, Takeda, and Pfizer, and declares no specific conflicts of interest to report regarding this paper. DS has received sponsorship to attend international meetings, honoraria for lecturing or attending advisory boards and research grants from various pharmaceutical companies including Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, Epiendo, Genentech, GSK, Glenmark, Gossamerbio, Kinaset, Menarini, Novartis, Pulmatrix, Sanofi, Synairgen, Teva, Theravance, and Verona.

Compliance with Ethics Guidelines. This article is based on a review of previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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