

INVITED REVIEW

An independent in-depth analysis proposing adjusted Global Initiative on Asthma Step 1–2 treatment suggestions

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Abstract

The Global Initiative on Asthma (GINA) strategy included major changes for the treatment of mild asthma in the 2020 version that are even taken to the next level in 2021, leaving a preferred track with only rescue therapy with inhaled corticosteroid and formoterol (ICS-FORM) for steps 1–2 in 12+ years old. It has been questioned how solid the evidence behind these recommendations is. We decided to independently conduct an in-depth analysis of published evidence based on a comprehensive evaluation of original articles and related appendices and publications, including quality of evidence and risk of bias per article. We first defined the major asthma treatment goals and proceeded to review how these were met in publications referenced in the main asthma guidelines. For patients with GINA (2021) Step 1 characteristics, the analysis supports GINA's decision to avoid SABA monotherapy and to prefer ICS-FORM rescue with an alternative ICS rescue every time a SABA is used for ≥ 12 years, even though evidence is extrapolated from step 2 patients. For 6- to 11-year-olds, we propose to consider ICS-FORM rescue as an alternative, as its use has been approved in this age group, be it not as rescue medication. For patients with GINA 2021 Step 2 characteristics, our proposal slightly differs from GINA 2021. We propose to continue avoiding the separate use of SABA, using ICS rescue whenever a fast-acting bronchodilator is taken (even with ICS maintenance). Also, the superiority of ICS-FORM rescue over classical step 2 treatment is not uniform and year-long experience is lacking. Consequently, for now, both treatment options seem equal: ICS-FORM rescue or ICS maintenance with SABA (+ICS) rescue. For 6- to 11-year-olds, ICS rescue every time a SABA is used has the advantage of lower total ICS dose; as alternative we suggest ICS-FORM rescue. The best treatment option depends on patient characteristics and treatment goals. Recommendations should be reviewed as soon as new evidence becomes available.

Proposal: 1) have always ICS in the rescue medication; 2) no clear superiority of any of the two step 2 options

STEP 1: rescue with ICS-FABA versus SABA			
	12+ years	6-11 years	
Evidence	Extrapolated: high Q step 2 trials ✓ ICS-FABA	Extrapolated: medium Q step 2 trials ✓ ICS-FABA	
Consider	Mono-SABA linked to augmented asthma deaths, lung function decline		
GINA 2021	ICS-FORM Alternative: ICS + SABA	ICS + SABA	
Proposal (differences in red)	Agree	ICS + SABA Alternative: ICS-FORM	

STEP 2: rescue with ICS-FABA versus ICS MAINT + rescue SABA			
	12+ years	6-11 years	
Evidence	High Q step 2-3 trials rescue ICS-FABA = ICS maint + rescue SABA.	Medium Q step 2 trials rescue ICS-FABA = ICS maint + rescue SABA.	
Consider	ICS-FORM equal or less severe exacerbations, slightly more symptoms, lower lung-function, higher FeNO. Long-term effects yet unknown. Availability. Cost.		
GINA 2021	Rescue ICS-FORM Alternative: ICS maint, rescue SABA	ICS maint, rescue SABA	
Proposal (differences in red)	Both 1st options: Rescue ICS-FORM or ICS maint, rescue ICS + SABA	ICS maint, rescue ICS + SABA Alternative rescue only: ICS + SABA or ICS-FORM	

= SABA
 = ICS
 = ICS-FORM

GRAPHICAL ABSTRACT

Proposed step 1 and step 2 treatment recommendations. According to age-group treatment options for GINA, step 1 and step 2 patients are reviewed starting in the first row with level of evidence as of November 2021 and main considerations to be taken into account, followed by GINA 2021 recommendations and, based on the above, our proposal to slightly adjust these in the last row in red.

1 | INTRODUCTION

Since the end of the past millennium, it is common knowledge that asthma is in principle an inflammatory airway disease. Over the past decade it has become clear that there exist several different underlying pathophysiological mechanisms, but even so, with few exceptions, almost all patients with asthma have an inflammatory infiltrate in the airways. In a recent cluster analysis of over 400 asthmatic patients, more than 85% showed type-2 inflammation (allergic or eosinophilic).¹

However, inflammation does not seem to explain the full picture of asthma, and abnormal functioning of the structural cells, such as smooth muscle and epithelial cells and fibroblasts, also forms an integral part of the underlying anomalies. The pendulum swinging from asthma, thought of in the 70–80s as a reversible bronchoconstriction, to asthma thought of as a purely inflammatory disease in the 90s² is now considered to rest somewhere in between these two models.³

These evolving concepts on the pathophysiological mechanisms underlying asthma go hand in hand with the evolution in treatment recommendations, from rescue bronchodilator monotherapy to maintenance treatment with inhaled corticosteroids (ICS), ending up with all kinds of combined treatment of bronchodilators plus ICS. However, rescue medication has been solely with bronchodilators till 2016 when the Global Initiative on Asthma (GINA) proposed the Maintenance and- Rescue Treatment (MART) strategy for step 3 treatment in adolescents and adults, using one and the same ICS-formoterol (ICS-FORM) inhaler for maintenance and rescue medication. The BTS/SIGN and GEMA guidelines followed somewhat later with similar recommendations, as did several other national guidelines.⁴

In this same line of thinking, GINA suggested in 2019 the major change in decades related to mild asthma therapy, recommending the anti-inflammatory rescue⁵: ICS-FORM in one inhaler *pro re nata* (PRN),

Key messages

- New evidence on mild asthma therapy does not favour SABA monotherapy in children and adults.
- As needed treatment containing ICS added to a fast-acting β_2 -agonist (in one or different inhalers) at any treatment step seems to reduce (severe) exacerbations.
- GINA Step 2: for now, PRN ICS-FORM or ICS plus SABA at equipoise with ICS maintenance, both should be first options.

which in 2021 became the preferred step 1 and step 2 treatment option, without any maintenance inhaler.⁶ For patients 12 years and older, the alternative rescue option for step 1 is ICS and a short-acting beta-2 agonist (SABA) in two separate inhalers, vetoing monotherapy with SABA; for step 2, the classical therapy with ICS (low dose) maintenance and SABA rescue became an alternative option.

This last proposal for a change in preferred step 1 and step 2 therapy has mainly been based on a few recent pivotal randomized controlled trials, whose results have been interpreted differently by various groups of specialists leading to diverse conclusions on what to recommend as the preferred treatment. This could jeopardize asthma outcomes as it might obstruct the uniform message we need to deliver to the public. Thus, as an independent team not linked to any of the trials or from industry we decided to conduct an in-depth review of the complete evidence behind these proposed changes of step 1 and step 2 therapy. The objective of this review article is to provide a clear description of the recruited patients and the obtained results in the pivotal trials in the light of what we consider the prime objectives of asthma therapy and eventually propose possible minor adjustments to the treatment options from GINA for mild asthma.

2 | METHODS

We first review the main treatment goals in asthma, then define mild asthma for this study and review its treatment options as recently proposed by several main asthma guidelines,^{6–9} subsequently we describe our search for evidence and article selection for this review, based on the guidelines' articles, and finally the data extraction process.

2.1 | Main treatment goals in asthma

As many different outcome parameters are used in clinical trials on asthma, it was mandatory to clearly define upfront the main treatment goals in asthma. Table 1 depicts the main objectives of asthma therapy defined by our group, which translate into the following tangible treatment objectives, in order of importance:

1. Avoiding severe exacerbations
2. Enhancing symptom control
3. Improving lung function or avoiding lung function decline
4. Keeping systemic CS dose as low as possible and, secondarily, keeping ICS dose as low as possible.
5. Respiratory quality of life.

Surely improved respiratory-related quality of life is also one of the crucial outcome parameters, resulting from the first three above-mentioned items; however, as this has been evaluated with different tools in the various trials, comparison is less straightforward.

2.2 | Avoid asthma deaths

Since 2000, Suissa et al.¹⁰ were able to associate the regular use of low-dose ICS with a decreased risk of death from asthma in a nested case-control study using a population-based cohort in Canada. The investigators went on to demonstrate that the rate of death from asthma decreased by 21% with each additional canister of ICS used in the previous year (adjusted rate ratio, 0.79; 95% confidence interval

[CI], 0.65–0.97). Similar findings were published in Latin-America¹¹ and more recently by Reddel et al.¹² These studies were all conducted in the era when GINA Step 2 asthma treatment was ICS maintenance with SABA as reliever therapy. Whether intermittent ICS rescue has the same beneficial effect on asthma deaths remains to be demonstrated. On the other hand, the overuse of SABA has been linked to an augmented risk of asthma deaths.^{13,14} Concluding, to reduce the risk of asthma deaths in patients with mild asthma, early introduction of ICS and avoiding SABA monotherapy should be pursued.

2.3 | Avoid severe exacerbations and thus loss of lung function on the long term

O'Byrne et al.¹⁵ demonstrated lung function decline is linked to the rate of severe asthma exacerbations, which was later confirmed by Ortega et al.,¹⁶ using the ATS/ERS definition of severe exacerbations (worsening of asthma requiring use of systemic corticosteroids for ≥ 3 days and/or hospitalization and/or emergency department visit). Also, in recent-onset mild persistent asthma, low-dose ICS maintenance therapy was associated with less severe asthma-related events and an improvement in lung function, both in adults^{12,17} and in children.¹⁸ Hence, the importance of severe exacerbation reduction as a goal in asthma therapy. To avoid confusion and misinterpretation, it is imperative to stick to the strict definition of severe exacerbations, as defined by the American Thoracic Society (ATS). Some tend to use the term "exacerbations" and severe exacerbations without distinction, leading to confusion and possibly an erroneous interpretation of results.

2.4 | Control asthma symptoms

The other dimension of asthma therapy goals is here and now: control of symptoms.

These asthma treatment goals are not mutually exclusive, but rather partly linked to one another. Thus, Meltzer et al. demonstrated how exacerbation frequency related to asthma control, as

TABLE 1 Main goals of asthma therapy in order of importance and their impact on selection of asthma treatment recommendations

Goals of asthma management	Associated with	Translated into asthma treatment recommendations
1. Avoid asthma deaths	- Reduction in asthma deaths linked to early ICS introduction - Augmented asthma death rate associated with SABA overuse	- Start ICS early on - Avoid SABA monotherapy at any level
2. Avoid loss of lung function on the long term	Loss of lung function is related to severe asthma exacerbation rate	Aim for a reduction in severe exacerbations
3. Control asthma symptoms	- Symptom control improves asthma-related quality of life - Symptom control reduced exacerbations in moderate–severe, atopic patients	Aim for asthma control
4. Reduce side-effects of medication	Systemic corticosteroids (CS), high-dose inhaled CS	- Avoid need for systemic CS (severe – exacerbations) - Keep ICS dose as low as possible

Abbreviations: CS, corticosteroid; ICS, inhaled corticosteroid; SABA, short-acting beta-2 agonist.

measured with the Asthma Control Questionnaire (ACQ-7); however, mind that the dose-response curve was quite horizontal at low symptom level, and a relation only became clear with more symptoms. Also, this study was retrospective and conducted in patients with moderate-to-severe atopic asthma.¹⁹ The existence of such relationship has not been demonstrated in the patient group our review is about: e.g. patients with mild asthma. The minimal clinically important difference (MCID) for the ACQ is 0.5.

2.5 | Reduce side-effects of medication

The most important side-effects of medication in mild asthma are probably related to the total dose of corticosteroids, both inhaled and systemic on one hand and the adrenergic side-effects (tremor and nervousness) of fast-acting beta-2 agonists on the other. The former seems of special importance in children, while the latter is more frequently observed in adult patients. In all seven trials, there was one asthma-related death as adjudicated by an external independent blinded adjudication committee; this was in the regular budesonide (BUD) group.²⁰

In this review, when comparing the different treatment options, we shall focus on severe asthma exacerbations, symptom control, lung function and corticosteroid dose (total and inhaled). When drawing our conclusions, we shall centre on risk reduction of asthma-related deaths.

2.6 | Definition of mild asthma

For this review, patients with mild asthma are defined as those candidate for GINA 2021 Step 1 or Step 2 therapy. Although mild asthma was used to be considered a mild disease by many, this concept has been questioned lately, once it became clear that a third of all severe exacerbations that arrive at the emergency department were in patients with mild asthma.²¹ Others showed that the ratio of severe exacerbations in mild asthma ranges from 0.12 to 0.77 per patient per year²¹ and even among patients who die from asthma, some were classified as mild asthmatics and treated as such.²² Thus, mild asthma should not be considered a mild disease. Furthermore, a post hoc analysis of a large, multinational trial in patients with recent-onset mild asthma (the START trial), comparing maintenance low-dose budesonide versus placebo, showed that after 3 years there was a reduction in severe asthma-related events and improved lung function in the ICS maintenance group.²³ Also, investigators found there was no difference in the beneficial effect between patients classified at study start as intermittent or persistent, nor between those with 0-1, 1-2 or more than 2 days with symptoms a week during run-in, demonstrating that even patients with non-frequent symptoms fare worse on placebo as compared to low-dose maintenance ICS.¹² However, the problem with patients who have intermittent and mild symptoms is the often poor compliance with maintenance therapy.²⁴

2.7 | Treatment options for mild asthma: GINA Step 1 and Step 2 therapy

As described above, we defined mild asthma pragmatically as those patients who are candidate for GINA 2021 Step 1 or Step 2 therapy. The objective of our review was to compare the outcome of patients with mild asthma receiving:

1. No maintenance, [ICS-FABA rescue] in one or two inhalers*
2. No maintenance, SABA rescue
3. ICS low-dose MAINT plus SABA rescue

*[ICS-FABA rescue] is defined as rescue therapy with ICS and a fast-acting beta-2 agonist (FABA). This can be in two inhalers, giving an ICS every time a patient inhales either salbutamol or terbutaline or in one inhaler containing budesonide-formoterol (BUD-FORM) or beclomethasone-formoterol (BDP-FORM). The second treatment option is only SABA rescue, and the third option [ICS MAINT plus SABA rescue] consists of regular ICS (low dose) and SABA rescue. In this review, we compare the efficacy and safety of 1 against 2 and 1 against 3 for patients with mild asthma.

2.8 | Article selection and information extraction on step 1 and step 2 therapy

We searched three of the highest-quality asthma guidelines, GINA 2021,⁶ BTS/SIGN 2019⁷ and GEMA 5.1,⁸ for references to the articles on which the guideline development groups based their treatment step 1 and step 2 recommendations. We included studies conducted during the last 15 years. We excluded articles that mainly referred to the MART strategy, as this is GINA Step 3 therapy. Only original papers were accepted, including the main articles, the protocol descriptions and the online appendices. Per article two independent researchers extracted a pre-established dataset on study characteristics, baseline characteristic of the subjects and asthma outcomes with the different treatments, especially focusing on our predefined main treatment goals and the three therapeutic options mentioned in previous sections of this manuscript. Moreover, the quality of each article and the risk of bias were evaluated with GRADE and Delphi risk of bias respectively.

3 | RESULTS

See Table S1 for articles on steps 1-2, referenced in the three guidelines. Of these, we selected seven trials for in-depth review, in order of date of publication: BEST 2007,²⁵ TREXA 2011,²⁶ SYGMA 1,²⁷ SYGMA 2,²⁰ Novel START,²⁸ PRACTICAL²⁹ and Sumino 2020.³⁰ We extracted data from the core publications and their online appendices plus some side-publications, e.g. protocol descriptions. A summary of each trial can be found in File S1, Boxes S1-S7.

Characteristics related to the study design and logistics are summarized in Table 2, while Table 3 displays the key inclusion and exclusion criteria and baseline characteristics of the recruited patients. SYGMA 1 and 2 are two large company-sponsored trials with thousands of patients, while the others are smaller. With regard to ICS-FORM rescue versus regular ICS, they were planned as superiority trials, but during the interim analysis it became clear that a much larger study population would have been needed for that goal and it was decided to convert SYGMA 1 and 2 into non-inferiority trials; the BEST trial²⁵ was a non-inferiority trial from the start. The studies included two to four different treatment arms, thus the three treatment options of our special interest, were not studied in all trials. Now, a brief description of each of these seven studies shall be given here below specifically focusing on the key outcome parameters we defined above (severe exacerbation and symptoms reduction, lung function and daily ICS dose), followed by summary tables of outcome variables of all trials together.

3.1 | Results: summary of the trial outcomes

Table 4 summarizes the efficacy and safety outcomes we defined above for patients in the treatment arms of Step 1 GINA treatment: [ICS-FABA rescue] versus SABA rescue, while Table 5 summarizes the same for patients in the treatment arms with Step 2 GINA treatment: [ICS-FABA rescue] versus ICS MAINT plus SABA rescue. Color coding is explained in the table footnotes. In the online repository, a more comprehensive presentation of the outcome variables can be found in Table S2.

In relation to the quality of the trials, GRADE rating can be found just before the summary of the trials in the supplementary file of seven study summaries. All were graded moderate to high in quality of evidence, although some points were scored in the Delphi risk-of-bias evaluation as is shown in Figure 1, especially in the open trials. For detailed risk-of-bias analysis per trial, see File S1, and for detailed GRADE rating, see Table S3, while the final GRADE rating is depicted in the last column of Figure 2.

4 | DISCUSSION

After the clear presentation of complete trial outcomes, as well as the kind of patients recruited and the quality of the trials, we would like to present our conclusions on which treatment we would propose in patients classified as GINA Step 1 or Step 2 with the knowledge available at this moment, along with several considerations we consider of importance in making the individualized treatment decision per patient. To simplify data analysis, we synthesized the main outcomes of the seven trials in Figure 2, comparing both options for step 1 (PRN SABA vs. PRN FABA+ICS) and both options for step 2 (PRN FABA+ICS vs. ICS maintenance) therapy.

4.1 | Patients included in the selected trials: according to the GINA 2021 treatment steps

As the assignment of treatment steps has evolved over the years, GINA recommends to recruit patients into clinical trials not based on treatment steps but rather on the level of control and the medication needed to obtain or maintain control.⁶ In all the here reviewed trials, medication needed to control asthma was described in each of them and an inclusion criterion in most. As such, we were able to assign treatment steps of the median recruited patients (excluding outlayers, as minimum-maximums were not always well described). We concluded that the median patient recruited had GINA 2021 Step 2 characteristics. However, in some trials, a fair amount of probable step 3 patients were enrolled, as the median number of rescue puffs per day was ≥ 0.5 and some trials also recruited patients controlled on medium-dose ICS or ICS (low dose) plus LABA.³⁰ Step 1 patients were rare and no subgroup analysis on these very mild patients was presented in any of the trials.

As for the age of patients and the subanalysis of paediatric age groups, only two trials^{26,30} were included and analysed children separately. Thus, the conclusions on steps 1–2 asthma therapy in children are less solid than in adults and mostly extrapolated.

4.2 | Treatment suggestions for patients with GINA 2021 Step 1 characteristics

Adolescents and adults: our proposal is in line with GINA, see Figure 3.

In our analysis, all evidence for Step 1 therapy options is extrapolated from studies conducted with children and adults with GINA Step 2 (–3) characteristics. In the context of efficacy/effectiveness parameters, Table 3 and Figure 2 show us the superiority of rescue therapy that includes an ICS over rescue with only SABA, be it ICS-FORM in one inhaler^{20,27–29} or be it ICS and SABA in separate inhalers.^{25,26,30} Most evidence in this age group comes from trials using ICS-FORM. ICS-FORM is easier to use as it is one inhaler, however, if cost is an issue, the alternative option of two separate inhalers is also viable. Then, ICS given together with SABA seems to enhance β_2 -agonist-induced bronchodilation in human small airways by increasing cAMP production in airway smooth muscle.³¹ Moreover, the risk of severe exacerbations and even fatal outcome when continuing on only SABA if asthma worsens on the long run has to be weighed in; thus, we recommend against SABA monotherapy.

Children 6–11 years: our first option proposal is in line with GINA; as alternative, we suggest ICS-FORM rescue. Evidence is too scarce to recommend in favour or against the sole use of SABA.

All evidence for this recommendation is extrapolated from one trial with ICS and SABA in two separate inhalers in children with GINA Step 2²⁶ (and from ICS-FORM in older patients in step 2, see above). ICS-FORM has been approved for children 4 years and older,

TABLE 2 Study designs of pivotal trials on ICS rescue reviewed in this manuscript

	PAPI	TREXA	SYGMA 1
Design	DBPC-RCT	DBPC-RCT	DBPC-RCT
Date	2002–2004	2007–2009	2014–2017
Centres	25	5	262
Participants			
Age	18–75 years	5/6 to 18 years	≥12 years
Asthma diagnosis	History of mild persistent asthma with reversibility	History of mild persistent asthma	Symptoms and historical reversibility
Treatment step	2	2	2–3
Inclusion criteria			
Previous treatment	ND	Naive/Low dose ICS/Other	Uncontrolled on SABA “as needed”/ Controlled on low stable dose ICS or LTRA
Symptoms	ND	ND	ND
SABA use	ND	ND	Terbutaline ≥3 days last week of the run-in
Night symptoms	ND	ND	ND
Exacerbations	ND	1–2 previous year	DN
FEV ₁ %	>75%	>80%	Only SABA: ≥60% post-bronchodilator and ≥80% predicted, previous treatment ≥80%
Adherence during baseline	≥80%	ND	Data must be recorded ≥8 days of the last 10 days of the run-in
Exclusion criteria			
OCS	Considered	Considered	Considered
Smoking	Considered	ND	Considered
Life-threatening asthma	Considered	Considered	Considered
Exacerbations	ND	ND	ND
Use medication	≥500 µg/day of beclomethasone	1 in the past 3 months	Change asthma treatment 30 days prior visit 1
Rescue treatment	≥4 puffs/day 2 consecutive days	>2 days/week	≥6 terbutaline per day, for ≥2 days of 14 days of run-in; for ≥3 days of 15–21 days of run-in; for ≥4 days of 22 or more days of run-in
Hospitalization	ND	ND	ND
FEV ₁ %	PEF variation ≥20%	<60% predicted at visit 1	ND
Other	ND	Significant medical illness	Significant medical illness
Concluding step 1, 2 or 3 patients	Step 2	Step 2	Steps 2–3

Abbreviations: FEV₁, forced expiratory volume in 1st second; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LTRA, leukotriene receptor antagonist; ND, not done; PEF, peak expiratory flow; SABA, short-acting β_2 -agonist; yo, years old.

SYGMA 2	NOVEL	PRACTICAL	SUMMINO
DBPC-RCT	Open RCT	Pragmatic/Open RCT	Pragmatic/Open RCT
2014–2017	2016–2017	2016–2017	2015–2016
354	16	15	12
≥12 years	18–75 years	18–75 years	6–17 years
Symptoms and historical reversibility	Self-report of a doctor's diagnosis of asthma	Self-report of a doctor's diagnosis of asthma	Physician- diagnosed asthma
2	2–3	2–3	2–3
Uncontrolled on SABA “as needed”/controlled on low stable dose ICS or LTRA	SABA	SABA/ICS low or medium dose	Low-dose ICS, LTRA, or low-dose ICS plus LABA
ND	ND	GINA 2014 partly controlled or well controlled with treatment, no controller with poor adherence or technique	Asthma Evaluation Questionnaire score up to score 2 in 2 of 3 questions with total score ≤5
Terbutaline ≥3 days last week of the run-in	SABA ≥2 previous 4 weeks but on average ≤2 per day/SABA ≤2 occasions per day previous 4 weeks	SABA ≥2 in the last 4 weeks	ND
ND	ND	≥1 last 4 weeks	ND
ND	Severe/No Severe exacerbations last 12 months	Exacerbation requiring OCS last 52 weeks	ND
Only SABA: ≥60% post-bronchodilator and ≥80% predicted, previous treatment ≥80%	ND	ND	≥80%
	ND	ND	ND
Considered	Considered	Considered	ND
Considered	Considered	Considered	ND
Considered	Considered	Considered	ND
ND	ND	ND	ND
Asthma worsening requiring change in asthma treatment other than SABA	LABA, LTRA, theophylline, anticholinergic agent or cromone last 12 weeks	LABA, LTRA, theophylline, anticholinergic agent or cromone last 12 weeks	Asthma requiring daily combination therapy with medium-to-high dose ICS with LABA
≥6 terbutaline per day, for ≥2 days of 14 days of run-in; for ≥3 days of 15–21 days of run-in; for ≥4 days of 22 or more days of run-in	ND	ND	ND
ND	Hospitalization in previous 12 months	ND	ND
ND	≤50%	ND	ND
Significant medical illness/Randomization SYGMA 1	Significant medical illness	Significant medical illness	Significant medical illness
Step 2	Step 2	Steps 2–3	6–11 yo: Step 2 12–17 yo: Steps 2–3

TABLE 3 Methods of the seven studies (study duration, treatment groups, baseline data of patients included)

		PAPI		TREXA		SYGMA 1		SYGMA 2		NOVEL		PRACTICAL		SUMMINO	
Methods	Run in	4 weeks/ 250 µg BDP BID and albuterol rescue		4 weeks/ 40 µg BDP BID, and albuterol rescue		2-4 weeks only terbutaline as-needed		2-4 weeks only terbutaline as-needed		No		No		2-4 weeks transitioned BDP (40 µg, BID for 6- to 11yo and 80µg, BID for 12- to 17-yo, with chamber)	
	Additional treatment permitted if worsening	Oral corticosteroids for severe exacerbation		Albuterol for exercise-induced asthma		Open-label BUD 200 µg BID, 2 to 4 weeks or longer (investigator's decision)		ND		ND		Intranasal corticosteroid		In Regular BDP.- Dosing adjustments by the PCP according to asthma control	
	Adherence to treatment evaluation	Diary cards		Electronic measurements review at each visit.		Inhaler monitor every day		Inhaler monitor every day but access to results only at the end		Electronic inhaler usage monitors access to results only at the end		Electronic inhaler usage monitors access to results only at the end		ND	
	Trial Visits	8		Every 4-8 weeks for 44 weeks		8		6		7		6		6	
	Masking	Yes		Yes		Yes		Yes		No		No		No	
	Treatment duration	24 weeks		44 weeks		52 weeks		52 weeks		52 weeks		52 weeks		12 months	
	Treatment groups	1. Albuterol as needed (ALB)	118	1. Albuterol as needed (ALB)	74	1. Terbutalin as needed (TERB)	1277	Not included		1. Albuterol as needed (ALB)	223	Not included		Not included	

Note: Color codes—Light blue: SABA; dark blue: ICS-FABA rescue; orange ICS maintenance SABA rescue; grey: ICS maintenance, SABA-ICS rescue; brown ICS-SABA maintenance, SABA rescue.

Abbreviations: ALB, albuterol; BDP, beclomethasone dipropionate; BID, twice daily; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1st second; ICS, inhaled corticosteroid; LABA, long acting β_2 -agonist; LTRA, leukotriene receptor antagonist; ND, not done; PCP, primary care physician; PEF, peak expiratory flow; SABA, short acting β_2 -agonist; yo, years old.

			2. BDP/SABA as needed (COMBI BDP)		122	2. BDP/SABA as needed (COMBI BDP)		71	2. BUD/FORM as needed (COMBI BUD)		1277	1. BUD/FORM as needed (COMBI BUD)		2089	2. BUD/FORM as needed (COMBI BUD)		220	1. BUD/FORM as needed (COMBI BUD)		437	1. BDP/SABA as needed (COMBI BDP)		103
			3. BDP bd (Regular BDP)		106	3. BDP bd (Regular BDP)		72	3. BUD bd (Regular BUD)		1282	2. BUD bd (Regular BUD)		2087	3. BUD bd (Regular BUD)		226	3. BUD bd (Regular BUD)		448	2. BDP bd (Regular BDP)		103
						4. BDP bd and BDP/SABA as needed (COMBINED GROUP)		71	Not included			Not included			Not included			Not included			Not included		
			4. BDP/SABA bd and albuterol as needed (REGULAR COMBI)		109	Not included			Not included			Not included			Not included			Not included			Not included		
Baseline	Baseline Demographics and Clinical Characteristic	Primary outcome variable	Morning PEF			Time to first exacerbation that required prednisone			Electronically recorded weeks with well-controlled asthma			Annualized rate of severe asthma exacerbations			Annualized rate of severe exacerbations			Annualized rate of severe exacerbations			Change in ACT/cACT from baseline to 12 months.		
		Age, Mean	36.8-40.6 years			10.4-11.4 years			39-40 years			40.7-41.3 years			34.9-36 years			42.8-43.3 years			10.1-10.3 years		
		Symptoms	Symptoms control	Symptom free days % 47-51.6		Asthma control days during run in: 89.5-94.4			ND			ND			ND			GINA Partly controlled: 48-51%			ACT: 21.1-22.0 cACT 21.6-21.8		

TABLE 3 (Continued)

			Symptom score Daytime.-0.7-1.2 Symptom score Nighttime.-0.7-1.1		ND	ND	ND	GINA Uncontrolled: 27-29%	ND
		ACQ-5 score	ND	ND	1.54±0.97	1.51±0.90	1.1 ± 0.7	1.1-1.2	ND
	Exacerbations	ND		Hospital visits in previous year: 0.2-0.3	754 (19.7)	3257 (78.0)	Severe exacerbation in the previous 12 months 0.91-94.5%	0: 88%	ND
						727 (17.4)	Severe exacerbation in the previous 12 months 1: 5.5-9%	1: 9-10%	Exacerbations in the past 12 mo: 0.7- 0.8
	Treatment	Patient-reported SABA	Puff/day: 0.4-0.5	ND	ND	ND	Mean 3.2-3.8	Mean 4.3-4.9	ND
		Patient-reported use of ICS	Mean daily dose of ICS: 439.7-472.7	Previous year: 72-77%	ND	ND	ND	In the 12 weeks before enrolment 70-71%	ND
	Pulmonary function	On-treatment FEV1	87.2-88.9	100.1-101.5	84.18±14.07	84.3±13.9	89.2-90.3	87.4-87.8%	98.6-99.8
		FeNO	ND	Median 11.2-12.8	ND	ND	37-38	26-30	ND

ALB = albuterol; BDP = beclomethasone dipropionate; BID = twice daily; ND = not done; FeNO = fractional exhaled nitric oxide; FEV₁: Forced expiratory volume in 1st second; ICS = inhaled corticosteroid; LABA = long acting β_2 -agonist; LTRA = leukotriene receptor antagonist; PCP = primary care physician; PEF = peak expiratory flow; SABA = short acting β_2 -agonist; yo = years old
Color codes: Light blue: SABA; dark blue: ICS-FABA rescue; orange ICS maintenance SABA rescue; grey: ICS maintenance, SABA-ICS rescue; brown ICS-SABA maintenance, SABA rescue.

but use of ICS-FORM as rescue is off-label. As such, the first option in this age group is ICS rescue every time a SABA is used. In children, the risk for fatal outcome with only SABA use has not been well established yet; also, some experts prefer to prescribe therapy with the lowest ICS dose as possible. As such here our position related to mono-SABA therapy in very mild asthma is neutral.

4.3 | Treatment suggestions for patients with GINA 2021 Step 2 characteristics (Figure 3, left part)

Adolescents and adults: In line with GINA, we suggest against the sole use of SABA as rescue. We propose to always add an extra ICS puff, every time a SABA is used; to consider both step 2 GINA options as first-line and as alternative for ICS-FORM, we propose ICS rescue every time a SABA is used.

Children 6–11 years: We suggest either ICS maintenance plus [ICS and SABA] rescue or ICS rescue every time a SABA is used (for non-compliant patients, those who wish to be in control or reduce ICS use) as first options; as alternative we suggest ICS-FORM rescue. We do not recommend in favour or against the sole use of SABA rescue when giving regular ICS.

4.3.1 | In patients with good adherence to regular ICS

SYGMA 1 and PRACTICAL best represent the group of compliant patients, with adherence rates of 78.9% and 76% respectively. Under

these circumstances, PRACTICAL was able to show a reduced severe exacerbation rate for ICS-FORM rescue and SYGMA 1 showed non-inferiority of ICS-FORM, concluding that even in highly adherent patients ICS-FORM rescue is at least as good as or better than regular ICS in reducing severe exacerbations. For regular ICS therapy, SYGMA 1 showed an improvement in symptom control and lung function, while in PRACTICAL there was no difference, concluding that regular ICS is at least as good as, or better than, ICS-FORM rescue in controlling symptoms and lung function. Thus, as for efficacy, here both options seem to be at equipoise, as long as patients are strongly adherent.

4.3.2 | In patients with poor adherence to regular ICS

However, in real life a fair number of patients with mild asthma end up being non-adherent, stopping ICS once they “finished” their maintenance inhaler as they feel well or reluctant to use long-term ICS afraid of side-effects. The latter even counts for several physicians. A recent Latin-American study reported 41% poor adherence.³² These patients are prone to mono-SABA use. Also, due to patient empowerment, there is a considerable group among younger patients and parents who prefer taking control of their disease, instead of following doctor's orders.³³ In the PRACTICAL and Sumino trials, patients' and parents' ratings of treatment satisfaction with ICS-FABA rescue was 90%.³⁴ In the trials with low adherence (SYGMA 2, novelSTART and Sumino), the only differences between both options were as follows:

ICS-FORM rescue reported less severe exacerbations in novel-START, while regular ICS enhanced symptom control in two trials and lung function in SYGMA 2. Again, both options seem to be at equipoise.

4.3.3 | Children 6–11 years with mild asthma

For children, evidence of ICS-FABA rescue efficacy comes from two trials, showing non-inferiority compared to regular ICS in both, but the TREXA trial being underpowered in relation to severe exacerbations. It did show improved lung function and reduced FeNO in the regular BDP group, however, none reaching the minimal clinically important difference. And, this enhanced efficacy was accompanied by growth retardation with regular low-dose BDP, see below. Both trials used ICS plus SABA in separate inhalers, thus this is one of our first options for children in step 2. Evidence for efficacy and safety of ICS-FORM rescue in children

is extrapolated from adolescent–adult trials, leaving this as an alternative step 2 option.

4.3.4 | Thoughts about cost of therapy in GINA Step 2 therapy

In relation to costs, it is important to see the whole picture of cost of treatment during months or years of therapy. For acquisition at start, the ICS-FORM inhaler is more expensive than ICS and SABA, both readily available as generics. However, for ICS maintenance with a 120-dose inhaler, a new one should be obtained every 1–2 months, and approximately 1–2 SABA inhalers a year. This as opposed to 0.5 puffs/day with ICS-FORM rescue, making one of these latter inhalers last 240 days (based on the median number of rescue-puffs/day in the seven trials). Then, there are the hidden and indirect costs: severe exacerbations lead to loss of work or school and include short courses of systemic CS that,

TABLE 4 Outcomes SABA PRN vs. ICS FABA PRN

		PAPI	TREXA	SYGMA 1	NOVEL
Exacerbations	Severe exacerbations	COMBI BDP trends better than ALB $p=0.057$	ND	COMBI BUD better than TERB $P<0.001$.	COMBI BUD better than ALB RR 0.40 (0.18 to 0.86).
	Time to the first severe exacerbation	ND	ND	COMBI BUD better than TERB $P<0.001$.	COMBI BUD better than ALB HR 0.38 (0.18–0.82),
	Moderated-to-severe exacerbation	ND	ND	ND	ND
	Time to first moderated-to-severe exacerbation	ND	ND	ND	ND
	Exacerbations	COMBI BDP better than ALB, 0.74 vs 1.63; $p<0.001$	ND	ND	COMBI BUD better than ALB, 0.49 (0.33 to 0.72); $P<0.001$
	Time to the first exacerbation	COMBI BDP better than ALB $P=0.003$	No difference between COMBI BDP vs ALB HR 0.62 (0.37–1.05) $P=0.073$	ND	COMBI BUD better than ALB HR 0.46 (0.29–0.73).
	Mild exacerbation	COMBI BDP trend better than ALB	ND	ND	ND
Asthma symptoms	ACQ-5 score	ND	ND	COMBI BDP trends better than ALB (SNR)	COMBI BUD trends better than ALB -0.15 (-0.24 to -0.06) (SNR)
	Daily Asthma Symptoms	No difference between COMBI BDP vs ALB. -0.28 $p=0.11$	ND	COMBI BUD better than TERB $P<0.001$.	ND
	Night Asthma symptoms	No difference between COMBI BDP vs ALB -0.05 $p=0.77$	ND	ND	ND
	Nocturnal awakenings	COMBI BDP better than ALB -0.10, $p=0.03$	ND	COMBI BUD better than TERB $P<0.001$.	ND
	Symptom-Free Days	No difference between COMBI BDP and ALB +5.69, $p=0.13$	ND	COMBI BUD better than TERB $P=0.003$.	ND
	Asthma Control Days	ND	No difference reported between groups.	No difference between COMBI BUD vs TERB $P=0.552$.	ND
	Asthma symptom control, (electronically recorded weeks with well-controlled asthma)	ND	ND	COMBI BUD better than TERB $P=0.046$. OR 1.14 (1.0–1.30)	ND

Note: Dark blue: ICS-FABA rescue better than SABA, with statistical significance; very light blue: ICS-FABA rescue trends to be better than SABA, without reaching statistical significance; blue: ICS-FABA rescue trends to be worse than SABA, without reaching statistical significance.

Abbreviations: ACQ, asthma control questionnaire; ALB, albuterol; AQLQ, asthma-related quality of life questionnaire; BDP, beclomethasone dipropionate; BID, twice daily; BUD, budesonide; COMBI, combination; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1st second; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LTRA, leukotriene receptor antagonist; ND, not done; OCS, oral corticosteroid; PDNeq, prednisone equivalent units; PEF, peak expiratory flow; SABA, short-acting β_2 -agonist; SNR, statistical significance not reported; TERB, terbutaline; yo, years old.

TABLE 4 (Continued)

	Self-reported, missed school days per year	ND	ND	ND	ND
Pulmonary function test	FEV1	COMBI BDP better than ALB +0.12 p=0.007	COMBI BDP trends better than ALB (SNR)	COMBI BUD better than TERB P <0.001.	No difference reported across the trial groups
	Morning PEF	COMBI BDP better than ALB +9.47 (0.83 to 18.11) p=0.03	No difference reported between groups.	COMBI BUD better than TERB 11.95 (7.89 to 16.00) P <0.001.	ND
	Evening PEF	No difference between COMBI BDP and ALB 7.2, p=0.11	ND	COMBI BUD better than TERB 10.94 (6.99 to 14.90) P <0.001.	ND
	FeNO	ND	No difference between COMBI BDP vs ALB (SNR)	ND	COMBI BUD trends better than ALB difference geometric mean 0.83 (0.75 to 0.91) visit 7. (SNR)
	Methacholine bronchial responsiveness	ND	No difference between groups.	ND	
Rescue medication	Beta-agonist-containing actuations per day	No difference between COMBI BDP vs ALB -0.16 p=0.11	ND	ND	COMBI BUD trends better than ALB. (NRS) BUT: 1 dose of SABA = 2 puffs, 1 dose of BUD-FORM = 1 puff!
	Mean Change from Baseline in Percentage of As-Needed Medication-Free Days	ND	ND	No difference between COMBI BUD vs TERB 0.02 (-1.99 to 2.04) P =0.982.	ND
	Mean Change from Baseline in As-Needed Reliever Usage	ND	ND	No difference between groups (Trend) (SNR)	ND
Glucocorticoid	ICS metered dose (µg)	COMBI BDP 19 milligrams vs ALB 0mg	ND	ND	ND
	% patients with event needing additional glucocorticoids (ICS or OCS for asthma)	ND	ND	COMBI BUD better than TERB HR 0.41 (0.34 to 0.50)P <0.001.	ND

	Days with OCS treatment	ND	ND	No difference between COMBI BUD and Regular BUD (NRS)	ND
	Time to the use of additional glucocorticoids for asthma	ND	ND	COMBI BUD better than TERB HR 0.41 (0.34 to 0.50) P <0.001.	ND
	Total systemic GC exposure; BUD doses, PDNeq BUD doses and total systemic GC exposure	ND	ND	ND	COMBI BUD trends worse than ALB (SNR)
Q of L	AQLQ score	ND	No difference reported between groups.	COMBI BDP trends better than ALB (SNR)	ND
Adverse events	Adverse events	No difference reported between groups. (SNR)	ND	No difference across the trial groups (SNR)	ND
	Discontinuation due to study-specific asthma-related events	ND	ND	COMBI BUD better than TERB P =0.002.	ND
	Linear Growth	ND	No difference between COMBI BDP vs ALB -0.3cm (0.2) p=0.26	ND	ND
	Treatment failures	ND	ND	ND	COMBI BUD better than ALB RR 0.33 (0.17 to 0.63)
Adhe	Adherence to the twice-daily, blinded maintenance regimen	ND	ND	No difference across the trial groups (SNR)	No differences between trial groups. (SNR)

ALB = albuterol; ACQ = asthma control questionnaire; AQLQ = Asthma related quality of life questionnaire; BDP = beclomethasone dipropionate; BID = twice daily; BUD = budesonide; COMBI = combination; FeNO = fractional exhaled nitric oxide; FEV₁: Forced expiratory volume in 1st second; ICS = inhaled corticosteroid; LABA = long acting β_2 -agonist; LTRA = leukotriene receptor antagonist; ND = not done; OCS = oral corticosteroid; PEF = peak expiratory flow; PDNeq = prednisone equivalent units; SABA = short acting β_2 -agonist; yo = years old; SNR = statistical significance not reported; TERB = terbutaline.

Dark blue: ICS-FABA rescue better than SABA, with statistical significance; Very light blue: ICS-FABA rescue trends to be better than SABA, without reaching statistical significance; blue: ICS-FABA rescue trends to be worse than SABA, without reaching statistical significance.

adding up, augment the risk of osteoporosis, and other long-term side-effects of systemic steroids. Therefore, it seems ICS-FORM is not a more expensive option, although detailed cost-effectiveness studies are needed.

4.3.5 | Frequency of rescue therapy use and risk of severe exacerbations

The mean number of daily rescue puffs used in the SABA groups was around 0.5–0.7, in the ICS-FABA rescue 0.45–0.53 (exemption: 0.9 in the PRACTICAL trial with steps 2–3 patients) and in the regular ICS groups 0.25–0.52. In interpreting these numbers, it has to be taken into account that a SABA dose normally consists of two puffs while an ICS-FORM dose of one.

Some of the investigators wondered if frequent use of rescue therapy might augment the risk of exacerbations. Thus, a post hoc analysis of the SYGMA 1 trial was conducted to study the risk of

severe exacerbation during a 3-week interval after a day of high rescue use of ICS-FORM or SABA. The higher the use of SABA, the higher the frequency of a severe exacerbation. However, augmenting the number of ICS-FORM puffs on 1 day (from 2 to 8), the risk of a severe exacerbation was practically annulled.³⁵

4.3.6 | Efficacy of step 2 treatment options according to status of T2 inflammation

Pavord et al.³⁶ demonstrated that in patients with mild asthma and only rescue SABA at baseline, the reduction in (severe) asthma exacerbations with ICS-FORM did not depend on the presence of T2 inflammation and was seen even in the patients with blood eosinophil count $<0.15/\mu\text{L}$ (28% of all). However, the predefined further analysis of the data of the NovelSTART trial showed that while the reduction in (severe) exacerbations observed in the ICS-FORM rescue group was independent of the presence of T2 biomarkers,

TABLE 5 Outcomes ICS FABA PRN vs. BUD MAINTENANCE AND SABA PRN

		PAPI	TREXA	SYGMA 1	SYGMA 2	NOVEL	PRACTICAL	SUMMINO
Exacerbations	Severe exacerbations	No difference between COMBI BDP vs regular BDP $p=0.099$	ND	No difference reported between COMBI BUD vs Regular BUD	No difference between COMBI BUD vs Regular BUD group. No difference in pretreatment stratified groups	COMBI BUD better than Regular BUD RR 0.44 (0.20–0.96)	COMBI BUD better than Regular BUD RR 0.69 (0.48–1.0) $p=0.049$	ND
	Time to the first severe exacerbation	ND	ND	No difference between COMBI BUD vs Regular BUD $P=0.52$	No difference between COMBI BUD vs Regular BUD 0.96 (95% CI 0.78–1.17)	COMBI BUD better than Regular BUD HR 0.41 (0.19–0.90)	COMBI BUD better than Regular BUD HR 0.60 (0.40–0.91) $p=0.015$	ND
	Moderated-to-severe exacerbation	ND	ND	No difference between COMBI BUD vs Regular BUD	ND	ND	COMBI BUD better than Regular BUD RR 0.70(0.51–0.95) $p=0.024$	ND
	Time to first moderated-to-severe exacerbation	ND	ND	ND	ND	ND	COMBI BUD better than Regular BUD HR 0.59(0.41–0.84) $p=0.004$	ND
	Exacerbations	No difference between COMBI BDP vs REGULAR BDP $p=0.80$	ND	ND	ND	No difference COMBI BUD vs Regular BUD. RR 1.12 (0.70 to 1.79) $P=0.65$	ND	No significant difference COMBI BDP vs Regular BDP $p=0.62$
	Time to the first exacerbation	No difference between COMBI BDP vs REGULAR BDP (SNR)	COMBI BDP trend worse than Regular BDP (NSR)	ND	ND	No difference COMBI BUD vs Regular BUD HR 0.93 (0.55–1.57)	ND	No significant difference COMBI BDP vs Regular BDP $p=0.49$
	Mild exacerbation	COMBI BDP trend worse than Regular BDP 38 VS 29 (SNR)	ND	ND	ND	ND	ND	ND

Note: Dark blue: ICS-FABA rescue better than regular ICS with SABA rescue, with statistical significance; light blue: ICS-FABA rescue trends to be better than regular ICS with SABA rescue, without reaching statistical significance; dark orange: regular ICS with SABA rescue better than ICS-FABA rescue, with statistical significance; light orange: regular ICS with SABA rescue trends to be better than ICS-FABA rescue, without reaching statistical significance.

Abbreviations: ACQ, asthma control questionnaire; ALB, albuterol; AQLQ, asthma-related quality of life questionnaire; BDP, beclomethasone dipropionate; BID, twice daily; BUD, budesonide; COMBI, combination; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1st second; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LTRA, leukotriene receptor antagonist; ND, not done; OCS, oral corticosteroid; PDNeq, prednisone equivalent units; PEF, peak expiratory flow; SABA, short-acting β_2 -agonist; SNR, statistical significance not reported; TERB, terbutaline; yo, years old.

TABLE 5 (Continued)

Symptoms	ACQ-5 score	ND	ND	COMBI BUD trend worse than Regular BUD. In figure. (SNR)	COMBI BUD worse than Regular BUD $p=0.036$. Mean change from baseline $p<0.001$	COMBI BUD trends worse than Regular BUD 0.14 95% CI, 0.05 to 0.23 (SNR)	No difference between COMBI BUD vs Regular BUD 0.06, (−0.005 to 0.12); $p=0.07$	No significant difference between COMBI BDP vs Regular BDP $p=0.10$
	Daily Asthma Symptoms	No difference between COMBI BDP vs Regular BDP +0.03 (−0.38 to 0.32)(SNR). Asthma Symptoms Score (Day)	ND	COMBI BUD worse than Regular BUD $p=0.004$	ND	ND	ND	ND
	Night Asthma symptoms	No difference between COMBI BDP vs Regular BDP +0.01 (−0.35 to 0.37). (SNR) Asthma Symptoms Score (Night)	ND	ND	ND	ND	ND	ND
	Nocturnal awakenings	No difference between COMBI BDP vs Regular BDP 0.02 (−0.11 to 0.07) (SNR)	ND	COMBI BUD worse than Regular BUD $p=0.002$	ND	ND	ND	ND
	Symptom-Free Days	No difference between COMBI BDP vs Regular BDP −2.15 (−9.63 to 5.33) (SNR)	ND	COMBI BUD worse than Regular BUD $p=0.002$	ND	ND	ND	ND
	Asthma Control Days	ND	No difference between COMBI BDP vs Regular BDP	COMBI BUD worse than Regular BUD $p<0.001$.	ND	ND	ND	ND
	Asthma symptom control, (electronically recorded weeks with well-	ND	ND	COMBI BUD trends worse than Regular BUD OR=0.64 (0.57 to 0.73) (SNR)	ND	ND	ND	ND
Pulmonary function test	controlled asthma)							No significant difference between COMBI BDP vs Regular BDP $p=0.84$
	Self-reported, missed school days per year	ND	ND	ND	ND	ND	ND	
	FEV1	COMBI BDP trends better than Regular BDP +0.09 (−0.01 to 0.18) (SNR)	COMBI BDP and ALB worse than Regular BDP and COMBINED group $p=0.024$	COMBI BUD worse than Regular BUD. −9.98 (−14.03 to −5.93) $p=0.001$	COMBI BUD worse than Regular BUD $p=0.003$	No difference reported across the trial groups	No difference between COMBI BUD vs Regular BUD 0.006 L (−0.026 to 0.04) $p=0.69$	No significant difference between COMBI BDP vs Regular BDP $p=0.14$
	Morning PEF	No difference between COMBI BDP and Regular BDP −2.49 (−11.40 to 6.42). (SNR)	No difference reported between groups.	COMBI BUD worse than Regular BUD. −9.98 (−14.03 to −5.93) $p=0.001$	COMBI BUD worse than Regular BUD $p=0.016$	ND	ND	ND
	Evening PEF	No difference between COMBI BDP and Regular BDP −1.91 (−10.94 to 7.13) (SNR)	ND	COMBI BUD worse than Regular BUD −6.23 (−10.18 to −2.29) $p=0.002$	ND	ND	ND	ND
	FENO	ND	COMBI BDP and ALB worse than Regular BDP and COMBINED.	ND	ND	COMBI BUD trend worse than Regular BUD. Ratio of geometric mean 1.13 (1.02 to 1.25) Visit 7.	COMBI BUD worse than Regular BUD 1.13 (1.07–1.21) $p<0.001$	ND
	Methacholine bronchial responsiveness	ND	No difference between groups.	ND	ND	ND	ND	ND
Resc	Beta-agonist-containing	No difference between COMBI BDP and Regular	COMBI BDP trend worse	ND	COMBI BUD trend worse than Regular BUD (SNR)	No difference between COMBI BUD	COMBI BUD trends worse than Regular BUD (SNR)	ND

TABLE 5 (Continued)

	actuations per day	BDP +0.07 (−0.13 to 0.26) (SNR)	than Regular BDP (NSR)			and Regular BUD (SNR)		
	Mean Change from Baseline in Percentage of As-Needed Medication-Free Days	ND	ND	COMBI BUD worse than Regular BUD −7.15 (−9.16 to −5.14) p<0.001	COMBI BUD worse than Regular BDP p<0.001	ND	ND	ND
	Mean Change from Baseline in As-Needed Reliever Usage	ND	ND	No difference between groups (SNR)	COMBI BUD trend worse than Regular BUD (SNR)	ND	ND	ND
Glucocorticoid treatment	ICS metered dose (µg)	ND	ND	COMBI BUD better than regular BDP (SNR)	COMBI BUD better than regular BDP (SNR)	COMBI BUD trends better than Regular BUD. (SNR)	COMBI BUD better than Regular BUD −126.5 µg per day; 95% CI −171.0 to −81.9; p<0.001	COMBI BDP better than Regular BDP p<0.001
	% patients with event needed additional glucocorticoids (ICS or OCS for asthma)	ND	ND	No difference COMBI BUD vs Regular BUD HR 0.87 (0.70 to 1.07) p=0.175	ND	COMBI BUD trends better than Regular BUD (SNR)	COMBI BUD trends worse than Regular BUD (SNR)	ND
	Days with OCS treatment	ND	ND	No difference between COMBI BUD and Regular BUD (NRS)	No difference between COMBI BUD vs Regular BUD	ND	ND	ND
	Time to the use of additional glucocorticoids for asthma	ND	ND	No difference between COMBI BUD and Regular BUD HR 0.87 (0.70 to 1.07). P=0.175	No difference between COMBI BUD vs Regular BUD	ND	ND	ND
	Total systemic glucocorticoid exposure; budesonide doses, prednisone equivalent	ND	ND	ND	ND	COMBI BUD trends better than Regular BUD (SNR)	ND	ND

this was not the case for the BUD maintenance group where a reduction in exacerbations compared to the SABA rescue group was only demonstrated in the subgroups with blood eosinophil counts $\geq 0.3/\mu\text{l}$.³⁶

4.3.7 | ICS dosing (including ICS maintenance and rescue) related to efficacy and side-effects: growth

The dose in ICS-FABA differs between the seven trials (Figure 2). The only two trials that showed superiority of ICS-FABA in reducing severe exacerbations compared to regular ICS used 160 µg BUD per rescue puff.

Consistently, in all trials, the daily ICS dose with ICS-FABA rescue was lower than with regular ICS treatment, as was the total CS burden (adding-up systemic CS during exacerbations) in those trials where this parameter was reported. In TREXA, 44 weeks of regular BDP resulted in a 1.1 cm (SD 0.3) growth retardation compared to 0.3 cm (SD 0.2) in the BDP-FABA rescue.

Only TREXA included a group with regular BDP plus BDP rescue every time SABA is taken. This group did not differ from the regular BDP plus SABA rescue group in any of the parameters, and growth retardation was exactly the same in both.²⁶ In the light of avoiding at all cost mono-SABA therapy – as justified above – and putting this treatment goal higher than reducing the total ICS dose, for regular

low-dose ICS we would suggest to prescribe ICS rescue every time SABA is used.

4.4 | Limitation of the findings and unmet needs

There are still several unanswered questions, and thus recommendations have to be adjusted as soon as new evidence indicates so. The reduction in severe exacerbation risk with budesonide–formoterol reliever compared with maintenance budesonide was similar in Māori and Pacific adults compared with New Zealand Europeans.³⁷ Even so we consider one of the main limitations of the here presented evidence, the somewhat limiting inclusion criteria, even in the “pragmatic” trials, reducing generalizability of results. Large longitudinal truly pragmatic trials like registries would be of enormous help, just as the International Severe Asthma Registry (ISAR) in severe asthma.

Several unmet needs are as follows:

- No subgroup analysis for adherent patients in the regular ICS groups was conducted to see how their outcomes compare to ICS-FORM rescue.
- During the course of some trials, patients were withdrawn from the trial if they presented exacerbations. Thus, as the end of the trial you end up with better controlled patients. As a consequence,

TABLE 5 (Continued)

Table 5: Outcomes ICS FABa PRN vs BUD MAINTENANCE AND SABA PRN (total 5 pages) 5

	budesonide doses and total systemic glucocorticoid exposure							
QoL	AQLQ score	ND	No difference reported between groups.	COMBI BUD trends worse than Regular BUD. Graphics only, no values (SNR)	COMBI BUD worse than Regular BUD $p < 0.001$	ND	ND	No significant difference COMBI BDP vs Regular BDP
Adverse events	Adverse events	No difference reported between groups. (SNR)	ND	No difference across the trial groups (SNR)	No difference across the trial groups (SNR)	ND	COMBI BUD worse than Regular BUD RR: 1.06 (1.00 to 1.12) $p = 0.05$	No significant difference COMBI BDP vs Regular BDP (SNR)
	Discontinuation due to study-specific asthma-related events	ND	ND	No difference between COMBI BUD vs Regular BUD group $p = 0.526$	COMBI BUD trends better than regular BDP (SNR)	ND	ND	No significant difference COMBI BDP vs Regular BDP
	Linear Growth	ND	COMBI BUD trends better than Regular BDP (SNR)	ND	ND	ND	ND	ND
	Treatment failures	ND	No significance is reported between groups	ND	ND	No difference between COMBI BUD vs Regular BUD RR 0.56 (0.28-1.13)	No difference between COMBI BUD vs Regular BUD RR 0.84 (0.35-2.0) $p = 0.69$	ND
Adhere	Adherence to the twice-daily, blinded maintenance regimen	ND	ND	No difference across the trial groups (SNR)	No difference across the trial groups (SNR)	No difference across the trial groups (SNR)	No difference across the trial groups (SNR)	ND

ALB = albuterol; ACQ = asthma control questionnaire; AQLQ = Asthma related quality of life questionnaire; BDP = beclomethasone dipropionate; BID = twice daily; ND = not done. BUD = budesonide; COMBI = combination; FeNO = fractional exhaled nitric oxide; FEV₁: Forced expiratory volume in 1st second; ICS = inhaled corticosteroid; LABA = long acting β_2 -agonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid; PEF = peak expiratory flow; PDNeq = prednisone equivalent units; SABA = short acting β_2 -agonist; yo = years old; SNR = statistical significance not reported; TERB = terbutaline

Dark blue: ICS-FABA rescue better than regular ICS with SABA rescue, with statistical significance; light blue: ICS-FABA rescue trends to be better than regular ICS with SABA rescue, without reaching statistical significance; Dark orange: regular ICS with SABA rescue better than ICS-FABA rescue, with statistical significance; light orange: regular ICS with SABA rescue trends to be better than ICS-FABA rescue, without reaching statistical significance;

when looking at some parameters of all patients at the end of the trial, some treatment-groups could be favored as the worst patients already dropped out of that group, so only the best patients are left over improving the 'mean score' for that treatment group at the end of the trial.

- The Sumino trial is in Afro-American children, generalizability of the results is not clear.
- Patients are used to take (and physicians to prescribe) two puffs of their SABA rescue inhaler whenever they feel the need, however, with ICS-FORM, the dose is one puff,^{20,27,29} not two. Yet another issue that should be taught clearly when opting for ICS-FORM as rescue.
- Does long-term (years) ICS-FORM rescue maintain lung function just as low-dose ICS maintenance did in the START trial?
- What does long-term (years) rescue with an inhaler that contains a long-acting beta agonist, FORM, do to lung function, especially in children?
- With regular ICS: Is the preferred rescue option only SABA or 200 BUDeq rescue every time a SABA dose is inhaled?

- National registries of risk factors of asthma deaths should now also include a patient group with ICS-FABA rescue use only.

5 | CONCLUSIONS

Taking all these considerations into account for GINA 2021 Step 1 patients, the preferred treatment would be ICS-FORM in adolescents/adults and ICS+SABA in separate inhalers in 6- to 11-year-olds. For treatment in patients with GINA 2021 Step 2 characteristics, we suggest to keep both as first-line options: ICS-FABA as needed or the classical step 2 regular low-dose ICS, but here as rescue therapy ICS rescue every time SABA is inhaled. If selecting the first option, step 1 and step 2 treatment become the same. Thus, some discuss about eliminating step 1 altogether.

For the final treatment decision, it is important to have both options and select according to patient characteristics (age, adherent or not, comfortable with long-term maintenance therapy or not), patient's expectations and treatment goals (reduce severe exacerbations,

control symptoms, reduce total ICS dose) and patient's (and physician's) fears of long-term ICS therapy and cost, to mention some. Whichever option is selected, patient education on the correct use

of the treatment schedule and a revision during follow-up visits are mandatory to succeed. This could be of specific importance in the light of a reduction in clinic visits of asthma patients seen lately in the light

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias*)	Selective reporting (reporting bias)	Other bias
Papi 2007	●	●	●	●	●	●	●
Martinez 2011	●	●	●	●	●	●	●
O'Byrne 2018	●	●	●	●	●	●	●
Bateman 2018	●	●	●	●	●	●	●
Beasley 2019	●	●	●	●	●	●	●
Hardy 2019	●	●	●	●	●	●	●
Sumino 2020	●	●	●	●	●	●	●

FIGURE 1 Delphi risk-of-bias assessment of the individual trials on the newly proposed GINA Steps 1–2 therapy included in this review

Study, age	Patients step	ICS-FABA as-needed vs SABA as-needed			ICS-FABA as-needed vs ICS MAINT + PRN SABA			Dose rescue ICS per puff*	Adherence	GRADE rating
		Severe Exacerb.	Sympt	LFT & FeNO	Severe exacerb	Sympt	LFT & FeNO			
BEST, 18+y	Step 2			PEF			PEF	200 µg*	NR	3
TREXA, 6–18 years	Step 2						FEV ₁ and***	80 µg		3
Sigma 1, 12+ years	Step 2–3							160 µg	78.9%	4
Sigma 2, 12+ years	Step 2	xxxx	xxxx	xxxx				160 µg	62.8%	4
NovelSTART, 18+ years	Step 2–3			**			***	160 µg	56%	3
PRACTICAL, 18+ years	Step 2–3	xxxx	xxxx	xxxx			***	160 µg	76%	4
Sumino, 6–17 years	Step 2 (6–11y)	xxxx	xxxx	xxxx				80 µg HFA	60%	2
	Step 2–3 (12–17y)	xxxx	xxxx	xxxx				80 µg HFA		3

Color coding: **blue** = in favor of ICS-FABA; **orange** = in favor of ICS MAINT, **green** = no statistically significant difference

FIGURE 2 Summary table of main asthma therapy goals as met by the trials on the newly proposed GINA Steps 1–2 therapy included in this review. FABA, fast-acting beta-2 agonist; ICS, inhaled corticosteroid; MAINT, maintenance; NR, not reported; PEF, peak expiratory flow; PRN, *pro re nata*; SABA, short-acting beta-2 agonist. *Expressed as dose delivered to the patient, generally equal to 80% of the metered dose (e.g. BDP 250 µg = 200 µg delivered dose). **FeNO ratio of geometric mean: more reduced in BUD-FORM rescue versus SALB rescue. *** FeNO is a measure of eosinophilic inflammation of the lungs. The ratio of the geometric mean of all absolute FeNO values in a patient: was more reduced in the BUD maintenance group when compared with the BUD-FORM rescue group. And more reduced in the BDP maintenance group versus BDP-SABA rescue only. However, if we analyze FeNO value-change from start to finish of the trial there was no difference between groups

Proposal: 1) have always ICS in the rescue medication; 2) no clear superiority of any of the two									
STEP 1: rescue with ICS-FABA versus SABA					STEP 2: rescue with ICS-FABA versus ICS MAINT + rescue SABA				
	12+ years		6-11 years			12+ years		6-11 years	
GINA 2021	ICS-FORM Alternative: ICS + SABA		ICS + SABA	 	GINA 2021	Rescue ICS-FORM Alternative: ICS maint, rescue SABA		ICS maint, rescue SABA	 
Proposal (differences in red)	Agree		ICS + SABA Alternative: ICS-FORM	 	Proposal (differences in red)	Both 1 st options: Rescue ICS-FORM or ICS maint, rescue ICS + SABA		ICS maint, rescue ICS + SABA Alternative rescue only: ICS + SABA or ICS-FORM	 

 = SABA
  = ICS
  = ICS-FORM

FIGURE 3 Proposed minimal changes to step 1 and step 2 asthma therapy, as compared to GINA 2021. The two principals are as follows: (1) have always ICS in the rescue medication; and (2) no clear superiority of any of the two step 2 options in patients 12 years and older. FABA, fast-acting beta-2 agonist; FORM, formoterol; ICS, inhaled corticosteroid; MAINT, maintenance; SABA, short-acting beta-2 agonist

of the COVID-19 pandemics, as a recent survey documented {Eguiluz-Gracia}.³⁸ Peer education, as used in the Sumino trial, or even online peer education could be an excellent opportunity.

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CONFLICT OF INTEREST

Dr. Larenas-Linnemann reports personal fees from Allakos, Amstrong, Astrazeneca, DBV Technologies, Grunenthal, GSK, Mylan/Viatris, Menarini, MSD, Novartis, Pfizer, Sanofi, Siegfried, UCB, Carnot and Bayer and grants from Sanofi, Astrazeneca, Novartis, Circassia, GSK and the Purina institute outside the submitted work. Dr. Navarrete-Rodríguez has nothing to disclose. All other co-authors declare absence of conflict of interest.

AUTHOR CONTRIBUTIONS

DL-L: concept, design, literature search, table development (simple tables [3 + GRADE]), interpret results, writing draft (whole text). EMN-R: literature search, table development (Comprehensive tables [all]), interpret results, writing draft (summary of one

publication). JAL-P: literature search, table development (simple tables [2 + GRADE]), interpret results, writing draft (summary of one publication). RB: table development (simple tables [1 + GRADE]), interpret results, writing draft (summary of one publication). MCC-S: table development (simple tables [1 GRADE]), interpret results. BEDR-N: literature search, table development (simple tables [1 + GRADE]), interpret results, writing draft (summary of one publication). UG-R, LG: table development (simple tables [1 + GRADE]), interpret results, writing draft (summary of one publication). ECL-E: simple tables review, interpret results. All authors contributed to the critically revising of the article, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

ETHICAL STATEMENT

The here presented work has been conducted respecting the most complete ethical standards, and all treatment options and their evidence were evaluated and discussed in depth, until consensus agreement was reached on suggested therapy recommendations.

DATA AVAILABILITY STATEMENT

All data on which the manuscript is based on are presented as tables or added as online repository files.

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SUPPORTING INFORMATION

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