



Review article

Ultra-LABAs for the treatment of asthma

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ABSTRACT

The term ultra-LABA indicates once-daily β_2 -AR agonists (abediterol, indacaterol, olodaterol and vilanterol) that are single enantiomers of the (R)-configuration. All have a near full-agonist profile at human β_2 -AR. They can be prescribed in asthmatics only when associated with an ICS, although further confirmations need to clarify what really these agents add if used in association to ICS and in what asthmatic patients this association may have more value. They are also under development in triple inhalers that include an ultra-LABA, a LAMA and an ICS. The once-daily posology might increase adherence in long-term treatment of asthma but superiority to twice-daily LABAs has not yet been fully demonstrated. In any case, still no ultra-LABA can be recommended as preferred.

1. Introduction

The term ultra-long-acting β_2 -agonists (LABA) was coined in 2005 to indicate once-daily β_2 -adrenoceptor (AR) agonists that were under development for the treatment of asthma and chronic obstructive pulmonary disease (COPD) and to be able to differentiate them from the classic twice-daily LABAs, formoterol and salmeterol [1].

In 2007 Beeh and colleagues published the first study that investigated the effects of an ultra-LABA in asthma [2]. Once-daily indacaterol at doses of 200 and 400 μ g provided sustained 24-h bronchodilation, with a rapid onset of action and a good tolerability and safety profile. It was also documented that indacaterol 200 μ g provided effective 24-h bronchodilation, with a longer duration than salmeterol 50 μ g and a good overall safety profile [3] and the 300 μ g and 600 μ g doses of indacaterol had a similar effect to formoterol in the early post-dose period (up to 4 h) but were more effective at 24 h post-dose, with an increase over placebo in 24-h trough forced expiratory volume in 1 s (FEV₁) almost twice that observed post-formoterol [4].

There was an obvious need to explain why indacaterol was so long lasting [5]. At that time, the two main theories explaining the long duration of effect of different LABAs were the ‘diffusion microkinetic’ theory focused on formoterol and the ‘exosite’ hypothesis focused on salmeterol. It was suggested that in airway smooth muscle, small lipid rafts, the areas of the plasma membranes where β_2 -ARs are held together in close contact with signaling and effectors molecules, might

play a role in long duration of action of indacaterol. Actually, indacaterol has a two-fold higher affinity for lipid raft domains compared with salmeterol, which might contribute to the difference in duration of action between these two drugs.

2. The need for developing ultra-LABAs

Always in 2007, we were invited to write a point of view on ultra-LABAs and we highlighted that it was likely that once-daily administration of a LABA would lead to increased convenience for patients, mainly enhancement of adherence, which would also have resulted in a possible overall improvement of clinical outcomes in patients with asthma [6]. However, the pharmacological characteristics of any new ultra-LABA had to be considered very carefully to understand how it would fit into current treatment strategies and whether it should be used only in combination with other drugs.

At that time, there was concern regarding the safety of use of LABAs that resulted from prospective studies [7]. Nonetheless, inhaled β_2 -agonists remained the most effective bronchodilators available for the fast relief of asthma symptoms and, as such, they were an important component of asthma management [8]. Since a LABA in combination with an inhaled corticosteroid (ICS) continued to be the most effective asthma treatment, it was possible to foresee that once-daily combinations of ultra-LABAs and ICSs would become central in the treatment of asthmatic patients in the next years [8].

Abbreviations: β_2 -AR, β_2 -adrenoceptor; cAMP, cyclic adenosine monophosphate; COPD, chronic obstructive pulmonary disease; FDC, fixed dose combination; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist

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Table 1
Pharmacological characterization of ultra-LABAs compared to salbutamol and traditional LABAs.

β -agonist	pKi		IA (% isoprenaline)	Functional selectivity ratio $\beta_1:\beta_2$	Onset $t_{1/2}$ (min)	Duration of action (min)	Reference
	β_1	β_2					
Salbutamol	5.39 $\pm$ 0.06	6.12 $\pm$ 0.09 6.25 $\pm$ 0.04	47 $\pm$ 1	1:27	11.0 $\pm$ 4.0	14.6 $\pm$ 3.7	[54, 17, 55]
Salmeterol	6.11 $\pm$ 0.09 6.14 $\pm$ 0.02	9.19 $\pm$ 0.12 9.61 $\pm$ 0.03 9.24 $\pm$ 0.08	38 $\pm$ 1 41 $\pm$ 0.01	1:525 1:3,000 1:1,259	19 $\pm$ 5 8.3 $\pm$ 0.8	230 $\pm$ 55 > 720	[54, 53, 17, 56, 55]
Formoterol	6.12 $\pm$ 0.09 6.07 $\pm$ 0.04	7.84 $\pm$ 0.05 8.05 $\pm$ 0.02 8.29 $\pm$ 0.03	90 $\pm$ 1 95 $\pm$ 0.04 100 $\pm$ 3	1:150 1:166 1:13	6 $\pm$ 1 5.8 $\pm$ 0.7	76 $\pm$ 14 35.3 $\pm$ 8.8	[54, 17, 56, 53, 55]
Abediterol	23.1 $\pm$ 5.6	0.2 $\pm$ 0.0	91	1:60 1:116	23 $\pm$ 2.0	> 480	[16, 14, 53]
Indacaterol	6.21 $\pm$ 0.12 154.4 $\pm$ 45.9	7.36 $\pm$ 0.06 7.92 $\pm$ 0.02 18.3 $\pm$ 3.0	73 $\pm$ 1 99 $\pm$ 5 86 $\pm$ 0.02	1:2 1:16 1:4 1:8	14 $\pm$ 1 7.8 $\pm$ 0.7 16 $\pm$ 1.3	449 $\pm$ 62 > 720 318 $\pm$ 54	[54, 53, 17, 55, 16, 14]
Olodaterol	7.33 $\pm$ 0.05 159.0 $\pm$ 29.3	9.14 $\pm$ 0.04 3.5 $\pm$ 0.2	88 $\pm$ 2	1:65 1:32 1:45	9 $\pm$ 0.8	325 $\pm$ 64	[56, 16, 14]
Vilanterol	835.8 $\pm$ 84.2	9.42 $\pm$ 0.02 1.8 $\pm$ 0.4	70 $\pm$ 3	1:2,400 1:243 1: 464	3.1 $\pm$ 0.3 13 $\pm$ 0.8	> 480	[17, 16, 14]

Definition of abbreviations: IA, intrinsic activity; pKi, the negative logarithm to base 10 of the equilibrium dissociation constant of a ligand determined in inhibition studies.

In any case, we were firmly persuaded that ideally, there was a need for a new LABA that is fast acting and has true 24 h duration of action, providing consistent improvements in the symptoms that matter to patients [9]. In our opinion, criteria for a new β_2 -AR agonist had to include longer duration of action (compared with existing LABAs), true 24 h sustained bronchodilator efficacy allowing once-daily dosing, fast onset of action, superior efficacy compared with existing LABAs and favourable safety and tolerability profile.

However, it was also obvious to those who were experts in the field that it should not be overlooked that intrinsic efficacy is a key pharmacologic parameter that differs dramatically among available β -AR agonists [10]. β_2 -AR agonists of high intrinsic efficacy offer advantages over weak agonists in emergency management of asthma though their use is associated with dose-dependent adverse effects.

3. Pharmacological profile of ultra-LABAs

Extensive preclinical studies have investigated the pharmacological profile of ultra-LABAs (Table 1). Studies involving indacaterol have been performed both in vitro and in vivo, and have documented that it offers a quick onset of action and 24 h bronchodilating effect [11]. The onset of action was fast for salbutamol, formoterol, and indacaterol, whereas it was significantly slower for salmeterol. In human lung slices, the duration of action ranking was indacaterol > salmeterol > formoterol > salbutamol. When compared with human lung slices, in the rat lung slices, similar potency, intrinsic efficacy, and onset of action were observed for indacaterol, formoterol, and salmeterol.

Interestingly, comparing indacaterol with isoprenaline, salbutamol, formoterol and salmeterol it was shown that the rate of cyclic adenosine monophosphate (cAMP) generation varies for each agonist and correlates well with intrinsic efficacy [12]. The high-efficacy agonists promote the most rapid rise in cAMP levels and the rate of cAMP

accumulation is influenced by agonist efficacy. This, in combination with lipophilicity, may explain why β_2 -AR agonists demonstrate differences in their onset of action.

Once-daily LABAs (abediterol, indacaterol, olodaterol and vilanterol) are single enantiomers of the (R)-configuration [13]. All have a near full-agonist profile at human β_2 -AR. This seems to be an important pharmacological property, because high-efficacy agonists may cause a greater loss of ARs than low-efficacy agonists but are more tolerant to this, as they have “spare receptors” effect, resulting in a loss in potency but not necessarily any loss of maximal effect and are therefore less sensitive to loss of receptors through desensitization.

A comparison between these four agents documented that abediterol association to human β_2 -ARs was comparable with that obtained for olodaterol, slower than that of vilanterol and faster than that of indacaterol [14]. In the case of β_1 -ARs, abediterol associated faster than the other LABAs tested, while vilanterol association rate was slower than indacaterol and olodaterol. Furthermore, the residence time of abediterol at the β_2 -AR (185.5 min) was between 30 and 64 times longer than that of the other LABAs tested (2.9–6.2 min). All compounds showed a fast dissociation from β_1 -ARs with half-lives between 1.3 and 2.4 min.

The description of the main pharmacological characteristics of these four ultra-LABAs [15] shows that indacaterol has high intrinsic activity at human β_2 -ARs in vitro and is able of inducing rapid onset of action and long-term bronchodilatation (> 24 h); vilanterol has β_2 -ARs selectivity and elicits very long bronchodilatation (> 72 h); olodaterol has high selectivity for β_1 - and β_2 -ARs and induces valuable 24 h bronchodilatation effect; and abediterol is endowed with β_1 - and β_2 -ARs selectivity and high potency of bronchodilation and causes rapid onset and long duration of action.

It is likely that, as is the case for formoterol and salmeterol, even for these new β_2 -AR agonists there are different mechanisms that explain

the very long duration of action [16]. High lipophilicity and consequently high partitioning into the cell membrane is invoked as a key factor that may explain the long duration of indacaterol and vilanterol, whereas their residence time at the human β_2 -AR seems to be insufficient to explain their duration of action. In any case, it is not possible to rule out that vilanterol binds directly to an anchored binding site within the β_2 -AR [17]. The ternary complex, with a dissociation half-life of 18 h, might be a rationale for the 24-h duration of action of olodaterol, but this explanation contrasts with the view that slow receptor dissociation is not a key factor in the duration of action of inhaled once-daily LABAs. A long residence time at the human β_2 -AR, with a much slower dissociation half-life than indacaterol, olodaterol and vilanterol seems to be the most likely explanation for the sustained action of abediterol but also in this case, this explanation contrasts with the view that slow receptor dissociation is not a key factor in the duration of action of inhaled once-daily LABAs. In any case, the high affinity for the β_2 -AR of abediterol and its physicochemical properties may also contribute to the effects observed in asthma and COPD.

3.1. Ultra-LABAs in asthma

The four currently available ultra-LABAs have been studied in asthmatic patients both as monotherapy and in combination with an ICS or as part of a triple therapy including an ICS and a LAMA.

In particular, the effects elicited by ultra-LABAs on the bronchoconstrictor stimulus have been assessed in subjects suffering from asthma because a body of evidence indicates that chronic β_2 -agonist treatment leads to tolerance to its protective effects against a bronchoconstrictor stimulus despite well-maintained bronchodilation [18].

Furthermore, although the association of a LABA with an ICS is still the best approach to treat asthma, there is increasing documentation that long-acting muscarinic antagonists (LAMAs), at least tiotropium that is the only LAMA presently approved for use in asthma, are a highly effective adjunctive therapy in asthma poorly controlled by ICS/LABA combination [19]. Therefore, there is a real interest in developing ICS/LABA/LAMA fixed dose combinations (FDCs) in a single inhaler to be used also for treating asthma. The prospect is that a single inhaler triple therapy will certainly be well accepted by all those patients who are currently taking tiotropium as an add-on to the usual ICS/LABA therapy. In effect, treatment compliance and patient acceptability may improve with single inhaler triple therapy since it can be a bit cumbersome to use separate inhalers. Patients with good compliance have better control of their asthma [20] and this could contribute to successful asthma management. Two ICS/LABA/LAMA FDCs under development include an ultra-LABA (Table 2). The results of some trials are becoming public knowledge.

3.2. Indacaterol

The safety and tolerability of indacaterol 200, 400 and 600 μ g compared with placebo, dosed once daily were assessed over 28 days in patients with asthma [21]. Indacaterol had a favourable therapeutic index. It was well tolerated, and was not associated with any adverse cardiac or metabolic effects, while providing effective 24-h bronchodilation.

However, it has been documented that the physiological antagonism

of airway narrowing triggered by indacaterol cannot outcompete methacholine-induced bronchoconstriction for long [22]. Indacaterol produced a much lower degree and duration of effect than glycopyrronium. At 1 h, the ultra-LABA improved methacholine tolerance by approximately one-third of that achieved with the long-acting muscarinic antagonist (LAMA) treatment. In addition, most participants returned within one doubling concentration of their baseline PC₂₀ by 24 h. The combination of indacaterol and glycopyrronium significantly decreased slope at 1 and 24 h but not at 48 h.

The combination of mometasone furoate and indacaterol (QMF149) is currently in development for the treatment of inadequately controlled asthma. In a phase II study designed to investigate the impact of QMF149 compared with mometasone furoate on several outcomes, asthma-related death, intubation or hospitalisation in adolescent and adult patients with asthma, and also improvements in lung function, symptom control and rescue medication use, and reductions in risk in time to first exacerbation requiring oral corticosteroids, and in the annual rate of asthma exacerbations requiring oral corticosteroids, were all significantly in favour of treatment with QMF149 [23]. QMF149 was also associated with a numerical, but not significant, reduction in the risk of serious asthma exacerbations. In the QUARTZ study (ClinicalTrials.gov Identifier: NCT02892344), once-daily, low dose QMF149 150/80 μ g met the primary and key secondary endpoints (trough FEV₁ and ACQ-7 score at Week 12, respectively) when compared to once-daily mometasone furoate 200 μ g in both adult and adolescent patients with asthma [24].

The PLATINUM program is the Novartis phase III clinical development program which supports the development of QMF149 and mometasone furoate/indacaterol/glycopyrronium (QVM149) and includes four studies: the QUARTZ study, which compares QMF149 vs mometasone furoate, the PALLADIUM study, which compares QMF149 vs mometasone furoate and salmeterol/fluticasone, the IRIDIUM study which compares QVM149 vs QMF149 and salmeterol/fluticasone, and the ARGON study which compares QVM149 to a combination of salmeterol/fluticasone and tiotropium [24].

Triple therapy with QVM149 80/150/50 μ g delivered by Breezhaler once-daily was superior to the placebo irrespective of administration time of morning or evening, with mean differences in FEV₁ AUC_{0–24h} of 610 mL when administered in the morning and of 615 mL when administered in the evening [25]. In another study, QVM149 Breezhaler 80/150/50 μ g and 160/150/50 μ g once-daily was superior to the comparator, fluticasone propionate/salmeterol 500/50 μ g twice-daily with mean differences in FEV₁ of 159 mL and 172 mL, respectively [26].

3.3. Vilanterol

Single doses of inhaled vilanterol in subjects with asthma were well tolerated with no clinically significant unwanted systemic effects [27]. Vilanterol produced a rapid and prolonged bronchodilation over 24 h supporting the potential for once-daily administration. The vilanterol treatment in asthmatics on an ICS resulted in a statistically significant increase on day 7 in trough FEV₁ and weighted mean 24-h FEV₁ versus placebo [28]. Non-inferiority between once-daily (6.25, 12.5 and 25 μ g) versus twice-daily (6.25 μ g) vilanterol dosing was also shown. Furthermore, regular once-daily treatment with vilanterol was well

Table 2

Key characteristics of combination inhalers with an ultra-LABA currently licensed or under development for the treatment of asthma.

Drug class	Generic name	Dose	Manufacturer	Device
ICS/LABA	Fluticasone furoate/vilanterol	100/25 μ g	GSK	DPI - Ellipta
	Mometasone furoate/indacaterol (QMF149)	160/150 μ g	Novartis	DPI - Breezhaler
ICS/LABA/LAMA	Fluticasone furoate/vilanterol/umeclidinium	100/25/62.5 μ g	GSK	DPI - Ellipta
	Mometasone furoate/indacaterol/glycopyrronium (QVM149)	160/150/50 μ g	Novartis	DPI - Breezhaler

tolerated in asthma patients symptomatic on current ICS therapy and resulted in a prolonged duration of bronchodilation of at least 24 h at doses of 12.5 µg and greater, with a favourable therapeutic ratio at doses of 12.5 µg and 25 µg, with the largest benefit seen at the 25 µg dose [29]. Nonetheless, in adult asthmatic patients uncontrolled on an ICS after 12-week treatment, the improvement in FEV₁ was of 359 ± 42.9 mL with once-daily vilanterol (25 µg), 283 ± 41.9 mL with twice-daily salmeterol and 289 ± 42.9 mL for placebo [30]. The increase in FEV₁ was not statistically significantly different between vilanterol and placebo. Essentially, there was a variable response to inhaled vilanterol in adult patients with persistent symptoms already on an ICS.

Vilanterol (in combination with fluticasone furoate) provided significant bronchoprotection against methacholine-induced bronchoconstriction for at least 24 h in patients with mild-to-moderate asthma [31]. However, when combined with fluticasone furoate, it was unable to provide a better long-term protection from exercise-induced bronchoconstriction than fluticasone propionate [32]. Nonetheless, a 21 days combined treatment with vilanterol and fluticasone furoate offered further protection from the early asthmatic response relative to its components, significant protection over vilanterol alone from the late asthmatic responses, and produced sustained protection from hyper-responsiveness 24 h post-dose [33].

A body of evidence supports the use of fluticasone furoate combined with vilanterol, the only approved ICS/ultra-LABA FDC for the treatment of asthma, in patients for whom ICS/LABA therapy is appropriate. Fluticasone furoate/vilanterol FDC is effective and generally well tolerated in patients with persistent asthma and has similar overall efficacy and tolerability to twice-daily fluticasone propionate/salmeterol [34]. In addition, fluticasone furoate/vilanterol FDC reduces the risk of severe asthma exacerbations, and improves asthma control and measures of asthma-related quality of life [34]. In asthma patients with night-time symptoms, night-time awakenings improved faster with fluticasone furoate/vilanterol compared with fluticasone furoate [35].

Intriguingly, the Salford Lung Study on asthma, a randomised, comparative effectiveness study, showed that in patients with a general practitioner's diagnosis of symptomatic asthma and on maintenance inhaler therapy, initiation of a once-daily treatment regimen of combined fluticasone furoate/vilanterol improved asthma control without increasing the risk of serious adverse events when compared with optimized usual care [36]. In a retrospective analysis of prescribing patterns for asthma medication in Japan, the use of once-daily fluticasone furoate/vilanterol was associated with higher medication adherence (as measured by number of prescribed days and proportion of days covered), a lower rate of treatment discontinuation, and similar short-β₂-agonist and oral corticosteroid use, compared with twice-daily fluticasone propionate/salmeterol [37]. In any case, there are only inadequate data indicate that clinical and patient-oriented efficacy/safety outcomes of fluticasone furoate/vilanterol are likely comparable to other available combinations for adults with asthma, although the once-daily dosing, flexibility of dose timing, the design, and ease of use of the device are likely to be viewed favourably by patients compared to other available ICS/LABA combinations delivered with other devices [38]. Therefore, additional larger and long-term comparative studies are needed to determine whether these features translate into greater efficacy, safety, patient preference, or adherence versus other ICS/LABA combinations.

The pivotal phase III CAPTAIN study of once-daily single inhaler triple therapy fluticasone furoate/vilanterol/umeclidinium compared to vilanterol/umeclidinium, in the treatment of patients living with uncontrolled asthma met its primary endpoint, demonstrating a statistically significant 110 mL improvement in lung function (measured by change from baseline in trough FEV₁ at 24 weeks of treatment) for fluticasone furoate/vilanterol/umeclidinium 100/25/62.5 µg compared with vilanterol/umeclidinium 25/100 µg and a statistically significant 92 mL improvement in trough FEV₁ for fluticasone furoate/vilanterol/

umeclidinium 200/25/62.5 µg versus vilanterol/umeclidinium 25/200 µg [39]. The key secondary endpoint was annualised rate of moderate/severe exacerbations for fluticasone furoate/vilanterol/umeclidinium versus vilanterol/umeclidinium and demonstrated a 13% reduction in exacerbations, however this effect was not statistically significant.

3.4. Olodaterol

Several studies have documented that olodaterol monotherapy delivered by Respimat Inhaler once-daily on top of ICS therapy is able to induce an effective 24-h bronchodilation and is safe [40,41]. However, the value of these studies is limited by the fact that they have not been powered to assess the differences between the doses and frequencies of administration tested [42]. Therefore, it is not possible to formulate a solid conclusion on the best dose and/or dose frequency to be used in asthma.

Olodaterol had a sustained protection against methacholine-induced bronchoconstriction of at least 32 h [43]. All doses studied were significantly better than placebo at all time points; furthermore, a dose-dependent effect was demonstrated.

3.5. Abediterol

In patients with stable, persistent asthma, once-daily abediterol 2.5–10 µg provided clinically relevant and statistically significant improvements from baseline in bronchodilation compared with placebo over a 7-day treatment period [44]. In addition, it showed a good overall safety and tolerability profile at all doses examined. However, no bronchodilatory dose-response effect was seen at the relatively high doses of abediterol examined.

4. Ultra-LABAs in paediatric asthma patients

Paediatric LABA use is based primarily on data from adults, despite children are not small adults and the magnitude of changes in dose exposure and/or exposure response may not be solely reflected by differences in body weight [45]. Regrettably, very limited data on the pharmacokinetic behaviour of LABAs and almost no data on that of once-daily LABAs are available in the paediatric population. Pharmacokinetic-pharmacodynamic studies in children are needed in order to define well-adjusted, patient-tailored dosing schemes [45].

Vilanterol 25 mg, when dosed once and as repeat doses for 7 days (eight total doses) was well tolerated in paediatric asthma subjects aged 5–11 years [46]. There appears to be no relationship between vilanterol exposure and age or gender. In a large trial children aged 5–11 years with persistent asthma symptoms inadequately controlled on an ICS, vilanterol was safe but failed to show an improvement from baseline in trough FEV₁ for any of the doses (6.25, 12.5 or 25 µg) tested over 4 weeks [47].

The safety and efficacy of vilanterol/fluticasone furoate and QMF149 in children under 12 years of age has not yet been established in the indication for asthma.

5. Conclusion

New ultra-LABAs can be prescribed in asthmatics only when associated with an ICS, although further confirmations need to clarify if they add benefits compared to the classic LABAs when used in association to an ICS and to determine if there is a type of asthmatic patient who can benefit more from their use [15]. The once-daily posology might increase adherence in long-term treatment of asthma but superiority to twice-daily LABAs has not yet been fully demonstrated [48]. However, a recent study that compared asthmatic patients with similar clinical characteristics initiating fluticasone furoate/vilanterol or budesonide/formoterol on measures of adherence, persistence, and the

asthma medication ratio has documented that adherence and treatment persistence were low in both cohorts, but patients initiating once-daily fluticasone furoate/vilanterol were more likely to be adherent, and have an asthma medication ratio greater than or equal to 0.5, and were less likely to discontinue therapy compared with patients initiating twice-daily budesonide/formoterol [49].

No serious adverse effects have been reported in the trials that have explored the safety of ultra-LABAs in patients with asthma, although it has been correctly highlighted that the follow-up periods of these trials were short [49]. Considering the pharmacological profile of these agents, it is not expected for them to have greater adverse cardiovascular effect effects than LABAs due to their high selectivity to β_2 -ARs, but this selectivity may potentially be correlated with a greater loss of ARs [9]. The consequence would be a subsequent reduced sensitivity, known as tachyphylaxis, of airway smooth muscle and inflammatory cells response. It must be emphasized that tachyphylaxis has not been observed with long-term administration of ultra-LABAs. Many studies have shown that there is no loss of efficacy with prolonged administration of these agents since sustained improvements on FEV₁ are consistently observed in those clinical trials that have addressed this issue [50].

Vilanterol, in association with fluticasone furoate, is the only ultra-LABA that has been approved for treatment of asthma. We can hypothesize also the use of free combinations with indacaterol or olodaterol and a long-lasting ICS, but in any case, still no ultra-LABA can be recommended as preferred.

In any case, we do not believe that combinations with an ICS and a ultra-LABA in a single inhaler could be considered suitable for maintenance and reliever therapy (MART) not only because this approach must use a LABA that must be a fast-acting full agonist [51], but also because there is no scientific evidence that ultra-LABAs work as rescue medication, and also there are many factors in addition to scientific evidence that determine prescribing, including regulatory approval, pharmaceutical cost and funding that, whatever the case may be, would delay or deny this possibility of using ultra-LABA/ICS FDCs [52].

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