Therapeutic potential for novel ultra long-acting β_2-agonists in the management of COPD: biological and pharmacological aspects

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Chronic obstructive pulmonary disease (COPD) is characterised by progressive airflow limitation. In moderate-to-severe COPD, long-acting bronchodilators are the basis of therapy. Inhaled long-acting β_2-agonists (LABAs) are used for the treatment of COPD. LABAs have been in use since the 1990s enabling persistent bronchodilation for 12 hours; however, sustained bronchodilation is desirable. Compared with twice-daily LABAs, new LABAs with ultra-long duration (ultra-LABAs) could provide improvements in efficacy and compliance with fast onset of action, 24-hour bronchodilation and a good safety profile. Several novel ultra-LABAs showing once-daily delivery profiles are in development. In this article, we discuss these novel agents' properties and clinical trials of their efficacy and safety, including the only licensed ultra-LABA, indacaterol.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by progressive airflow limitation therefore bronchodilator therapy is the cornerstone its symptomatic management. In patients with COPD from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages II to IV, long-acting bronchodilators are the mainstay of therapy [Global Initiative for Chronic Obstructive Lung Disease (GOLD): global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2010), http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf]. Inhaled long-acting β_2-agonists (LABAs), such as formoterol and salmeterol have been used for the treatment of COPD since the late 1990s but they have a limited duration of action (DoA) [1,2]. Novel ultra-long-acting β_2-agonists (ultra-LABAs) with a 24-hour DoA could provide improvements in efficacy, compared with twice-daily LABAs, and the once-daily dosing is an important strategy in improving compliance. In addition, they demonstrate fast onset of action, and a safety profile comparable to current LABAs [3]. A variety of ultra-LABAs are currently undergoing development, one of these, indacaterol, a LABA with a 24-hour duration of bronchodilation and fast onset of action, has recently been made available for clinical use in the management of COPD [4,5]. Other once-daily LABAs include carmoterol, vilanterol trifenatate, olodaterol, LAS100977 and PF-610355 with preliminary results indicate potential for once-daily dosing in clinical management of COPD [6].

The introduction of ultra-LABAs also provides the opportunity to develop combination inhalers of two or more classes of once-daily long-acting bronchodilators, which might be advantageous for patients with COPD through simplification of treatment regimens and improvements in efficacy [3]. Ultra-LABAs used both alone and in combination with long-acting muscarinic antagonists represent a promising advance in the treatment of COPD, and are likely to further improve outcomes for patients [3]. In this article, we describe the biological and pharmacological aspects of ultra-LABAs and their potential clinical use in current and future management of COPD. Also, we discuss the various ultra-LABAs with their important/novel efficacy and safety properties.

Ultra-LABA pharmacodynamic and pharmacokinetic properties

The mechanism of how β_2-agonists interact with β_2-adrenoceptors to produce cyclic adenosine monophosphate (cAMP) and smooth muscle relaxation is summarised in Fig. 1 [3]. There is a wealth

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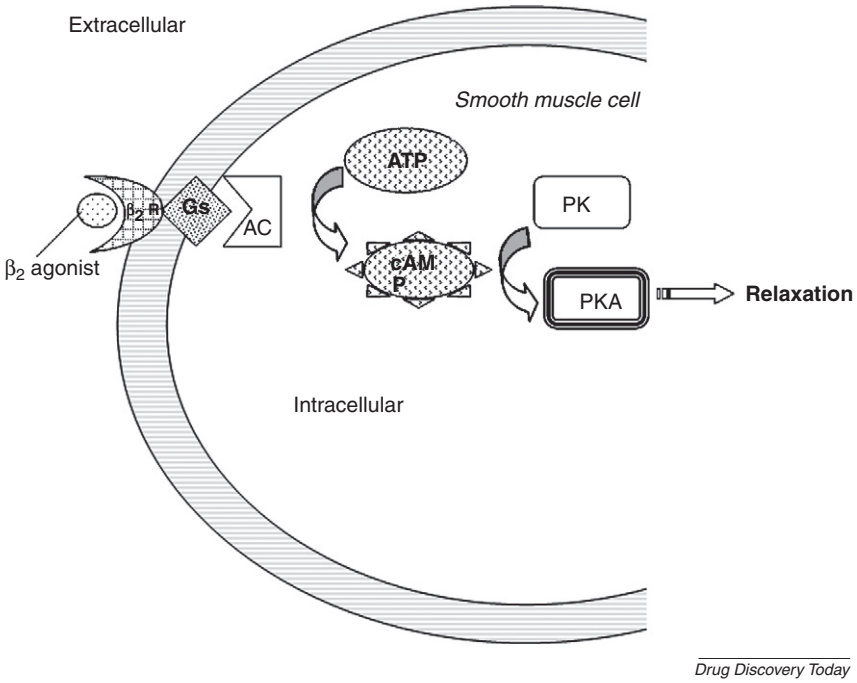

FIGURE 1

Biological and pharmacological effects on smooth muscle cells of β2 selective agonists. β_2-Agonists interact with β_2-receptor on the cell membrane; β_2-receptor active a stimulatory protein G, which active adenylcyclase. Adenylcyclase uses ATP to produce cAMP, which successively actives PK into PKA, with the result of muscle relaxation. *Abbreviations*: AC: adenylcyclase; ATP: adenosine triphosphate; β_2R: β_2-receptor; cAMP: cyclic adenosine monophosphate; Gs: stimulatory G protein; PK: inactive protein kinase; PKA: active protein kinase A.

of evidence supporting the role of LABAs in the treatment of stable COPD, including bronchodilation and reduced air trapping resulting in improved lung function and exercise tolerance, in addition to improved quality of life and symptoms, and reduced exacerbations [7]. However, current LABAs need to be improved upon to provide a prolonged relaxant effect which in turn will result in better patient compliance and improved clinical outcomes. An ideal LABA would be one that provides a longer DoA compared with current LABAs (once-daily dosing and 24-hour bronchodilation), fast onset of action, more efficacious to current LABAs, and favourable safety and tolerability profile, the 'ultra-LABA' [6]. Of note, improved patient outcomes have been noted with the use of tiotropium bromide, a once-daily inhaled anti-muscarinic antagonist for the treatment of COPD [5].

With the extended DoA of ultra-LABAs, unlike with short-acting β_2-agonists and LABAs, over a 24-hour period the bronchial tone smoothens leading to prolonged and sustained bronchodilation which might be termed 'pharmacological stenting' [8]. Moreover, it has been proposed that at rest the prolonged bronchodilation of ultra-LABAs not only results in reduced breathlessness, but also lung emptying in tidal respiration resulting in 'pharmacological lung volume reduction' [4]. A variety of these longer half-lives, once-daily dosing β_2-adrenoceptor agonists, ultra-LABAs, are being developed and undergoing trials, including indacaterol, olodaterol, carmoterol, vilanterol trifenatate, LAS100977 and PF-610355. Only indacaterol has been licensed as a once-daily bronchodilator, and hence most of the data are available from its studies, whereas for the other mentioned ultra-LABAs information is limited and often available from conference abstracts. Below we discuss each of the ultra-LABAs. A summary of the data available on these agents has been shown in Table 1.

Indacaterol

Indacaterol is a chirally pure inhaled ultra-LABA that was designed not only on the basis of the *in vitro* evidence of its lipophilicity and rationalisation of its onset and DoA profile, but also because of its potency and intrinsic efficacy [9]. Indacaterol has similar binding affinity at the β_2-adrenoceptor as formoterol but less than salmeterol [10]. However, indacaterol has a mean maximum effect of isoprenaline (E_{max}) of 73% compared with 38% and 47% of salmeterol and salbutamol respectively, albeit lower than formoterol (90%) at the β_2-adrenoceptor. Moreover, indacaterol has minimal activity at the β_1-adrenoceptor (E_{max} 16%), but a full agonist at the β_3-adrenoceptor (E_{max} 113%). *Ex vivo* work on isolated human bronchi reported that the onset of action of indacaterol (7.8 ± 0.7 min) was not significantly different to formoterol (5.8 ± 0.7 min) and salbutamol (11 ± 4.0 min), but significantly faster than salmeterol (19.4 ± 4.3 min). Both indacaterol and salmeterol had >12-hour DoA compared with the shorter times with formoterol (35.3 ± 8.8 min) and salbutamol (14.6 ± 3.7 min) [11]. Similar observations were noted in human precision-cut lung slices [12]. Unlike salmeterol, indacaterol does not antagonise the fast-acting effect of the isoprenaline response [11]. Despite the prolonged efficacy of indacaterol, it does not demonstrate tachyphylaxis *in vitro* [10]. At the molecular level, β_2-adrenergic agonist stimulation induces desensitisation of the β_2-adrenoceptor. Indacaterol, behaves as a near-full agonist, hence it does not induce desensitisation, unlike low-efficacy agonists at

TABLE 1

Summary data on currently available and under evaluation by trials of the ultra-LABAs

Drug name (previous name)	Company	Intrinsic efficacy						Binding affinity to β-adrenoceptors			Selectivity for β_2/β_1	Onset of action	Duration of action
		β_1		β_2		β_3		β_1	β_2	β_3			
		pEC_{50}	IA	pEC_{50}	IA	pEC_{50}	IA						
Indacaterol (QAB149)	Novartis	6.60[a] (±0.24)	16[a] (±2)	8.06[a] (±0.02)	73[a] (±0.13)	6.72[a] (±0.13)	113[a] (±7)	6.21[a] (±0.12)	7.36[a] (±0.06)	5.48[a] (±0.14)	1.46[a]	35 ± 2[b]	>12[b]
Olodaterol (BI 1744)	Boehringer Ingelheim	7.55[c] (±0.08)	52[c] (±8)	9.93[c] (±0.07)	88[c] (±2)	6.57[c] (±0.08)	81[c] (±2)	7.33[c] (±0.05)	9.14[c] (±0.04)	5.26[c] (±0.14)	2.38[c]	3–6[c]	
Vilanterol Trifenatate (GSK642444)	Glaxo Smithkline	6.40[d] (±0.1)		9.40[d] (±0.0)	69 (±5)	6.1[d] (±0.2)					3.0[d]	6.6[d]	
Carmoterol (CHF 4226, TA 2005)	Chiesi			10.19[e] (±0.15)	88.6[e] (±4.1)							28 ± 2[b]	1.6 ± 0.1[b]
LAS100977	Almirall												
PF-610355	Pfizer												6.23[f]

pEC_{50} – based on *in vitro* human β_2-adrenoceptors; binding affinity to β-adrenoceptors – binding affinity of the ultra-LABAs to the three β-adrenoceptors as calculated by their dissociation constants based on *in vitro* human β_2-adrenoceptors; selectivity for β_2 over β_1 expressed as pEC_{50} at β_2-adrenoceptor – pEC_{50} at β_1-adrenoceptor; onset of action (in minutes) – measured at compound concentrations nearest to their IC_{50} (inhibitory concentration time to decay to 50% of maximal response during washout phase) values in guinea pig tracheal strips; duration of action (in hours) – based on *in vitro* guinea pig tracheal strips measured at compound concentrations nearest to their IC_{50} values in guinea pig tracheal strips.
Abbreviations: β_1: β_1-adrenoceptor; β_2: β_2-adrenoceptor; β_3: β_3-adrenoceptor; IA: percentage of isoprenaline-induced maximal response; pEC50: negative logarithm of the molar concentration that produces a cyclic adenosine monophosphate response equal to 50% of its maximal response.

[a] Ref. [10].
[b] Ref. [9].
[c] Ref. [18].
[d] Ref. [28].
[e] Ref. [14].
[f] Ref. [38].

equal occupancy (i.e. they require more receptors to produce a consequent response, thus are more sensitive to a loss of functional receptors). By contrast, high-efficacy agonists, like indacaterol, although loose more receptors, are tolerant to this as they possess 'spare receptors' which might cause a loss in potency but not maximal effect. Indacaterol has no key differences compared with salmeterol in liposome partitioning independent of the lipid composition, however, several minor ones in steady state and kinetic interactions with lipid membranes exist, which have been attributed to the rapid and longer DoA of the former [13]. Salmeterol alters membrane fluidity, unlike indacaterol, which might result in altered functioning of the receptor and hence attenuated intrinsic efficacy. It has been reported that lipid rafts, including calveolae (specialised lipid rafts), on the membrane of smooth muscle cells might be further responsible for better therapeutic effects of indacaterol. Different β_2-agonists have different DoAs due to their diversity in lipophilicity. Indacaterol and formoterol have analogous lipophilicity which renders to rapid cAMP accumulation that is responsible for the pivotal role in β_2-adrenoceptor-induced smooth muscle relaxation [14]. This combined with the higher intrinsic activity of indacaterol might further explain the fast onset and longer DoA.

It was reported through the use of Breezhaler® [Novartis (http://www.novartis.co.uk/index.shtml)], indacaterol, had dose-proportional pharmacokinetics at doses between 150 and 600 μg/day and achieved a steady state at 12 days [15]. It is rapidly absorbed into the systemic circulation with a median T_{max} of 15 min. Furthermore, a single administration of indacaterol at various doses (400–3000 μg/day) in mild or moderate COPD subjects produced minimal decreases in fasting serum potassium and glucose levels, and there were no significant electrocardiogram changes even at doses far in excess of the therapeutic range [16]. Moreover, indacaterol has no ethnic factors that influence its efficacy in patients with COPD [17].

Olodaterol

Olodaterol is an enantiopure, selective and potent inhaled β_2-adrenoceptor agonist with excellent β_2-adrenoceptor selectivity profile. Its intrinsic activity of 88% of isoprenaline makes it a near-full agonist [18]. *In vitro* studies of olodaterol reported that it dose-dependently reversed the constriction induced by different stimuli, such as histamine, acetylcholine (ACh) and electric field stimulation (EFS), with an efficacy not statistically different from the full agonist formoterol in all conditions [18]. This shows the high selectivity of the β_2-adrenoceptor in terms of affinity and potency. Of note, olodaterol had a lower β_1-adrenoceptor agonism, hence it could be interpreted as having an excellent bronchodilatory effect with attenuated cardiovascular consequences. Unlike salmeterol, *in vitro* observations demonstrate that olodaterol possesses moderate propensity to accumulate in the lipid bilayer, suggesting that lipophilicity is probably not the only mechanism of its prolonged action [19]. It has been identified that olodaterol also has a persistent interaction with the β_2-adrenoceptor which is fast, but its dissociation is biphasic. The slow-dissociation component is due to a ternary complex formation (a stabilised complex between the agonist, receptor and G protein), which is an active, functional signalling moiety with a dissociation half-life of 17 hours, to which can be attributed the rationale for its 24-hour action [19].

In vivo studies of bronchoconstriction induced by intravenous ACh in anaesthetised guinea pigs and dogs using olodaterol delivered through a Respimat Soft Mist Inhaler® [Boehringer Ingelheim (http://www.boehringer-ingelheim.co.uk/)] intratracheally reported that time to maximal bronchoprotection after a single inhalation was 3–6 min in guinea pigs and 10 min in dogs [18]. In the same study olodaterol delivered intraduodenally, showed that for a given degree of bronchodilator activity, olodaterol had a greater cardiovascular (as measured by heart rate) and metabolic (as measured by serum potassium, lactate and glucose) safety margin than formoterol [18]. This was maintained at 24 hours, suggesting a sufficient therapeutic window in humans.

Carmoterol

Carmoterol is pure non-catechol β_2-adrenoceptor agonist having structural elements from both formoterol and procaterol. The methoxyphenyl group in carmoterol has been found to be crucial to the β_2-selectivity of the molecule [20]. Carmoterol has 53 times higher affinity for the β_2-adrenoceptors than for β_1-adrenoceptors; demonstrating its high potency and selectivity. Moreover, it has a rapid onset and long DoA both *in vitro* and *in vivo* studies [21,22]. Its protracted action *in vitro* cell cultures is similar to salmeterol and indacaterol, but shorter for formoterol and salbutamol [23]. *In vitro* functional cAMP accumulation studies reported that carmoterol had a rapid comparable intrinsic activity to formoterol and lipophilicity [14]. Furthermore, carmoterol is more potent and has a longer duration of muscle relaxation than formoterol and salmeterol in methacholine-challenged guinea pig tracheal smooth muscle [20,22–24].

Carmoterol has been investigated in healthy volunteers, patients with asthma and patients with COPD, with multiple escalating doses [3,25]; with no significant dose–response effects on serum glucose and potassium levels, or cardiovascular complications. A 41% lung deposition of carmoterol has been demonstrated using the hydrofluroalkane, 134a, propellant (Modulite® Technology – Chiesi) [26]. Moreover, no tolerance to bronchodilatory efficacy has been noted after two weeks of treatment with both carmoterol and salmeterol [27].

Vilanterol trifenatate

Vilanterol, with the acetate salt, is a selective β_2-adrenoceptor agonist in human functional cellular assays. It has a greater selectivity for the β_2-adrenoceptor than formoterol, indacaterol and salbutamol [28]. In electrically induced contraction of superfused guinea pig tracheal strips vilanterol was reported to have a rapid onset and prolonged DoA, and was equipotent with formoterol [negative logarithm of EC_{50} ($pEC_{50} = 8.6$), but more potent than salmeterol ($pEC_{50} = 6.7$) or indacaterol ($pEC_{50} = 7.0$)] [29]. Vilanterol's rapid onset of action and extended DoA was confirmed in preconstricted human tissue [30].

In vivo studies of conscious guinea pigs, bronchoconstriction induced by histamine, nebulised vilanterol was equipotent to salmeterol, and at equivalent doses had a longer DoA than formoterol but similar to salmeterol [29]. Of note, vilanterol's duration increased further in a dose-dependent fashion. Interestingly, vilanterol is a soft ultra-LABA (i.e. it is converted by human liver microsomes/hepatocytes to metabolites that are 1000-fold less

active than the parent compound) [31]. This would suggest that inhaled vilanterol would have little systemic adverse events.

Vilanterol has been clinically assessed in patients with asthma and COPD in numerous studies [3,32–34]. It was found that vilanterol does not only have a rapid and prolonged bronchodilation of over 24 hours, improved FEV_1 five minutes after dosing (clinically and statistically significant) compared with placebo, but also that inhaled vilanterol was safe (no significant changes in cardiovascular parameters, and serum potassium and glucose) and well tolerated.

LAS100977

In vitro investigation of LAS100977, another ultra-LABA, in isolated human bronchi have reported that it not only has the highest specificity for the β_2-adrenoceptor compared with salmeterol, formoterol and indacaterol, but also has similar potency to the latter two and ten times more potent than salmeterol [35]. Furthermore, it has a rapid onset of action (10 min) compared with salmeterol (19 min) and indacaterol (14 min), but more than formoterol (6 min). Besides these properties LAS100977 has longer DoA compared with salmeterol and formoterol, but analogous to indacaterol. In selectivity binding and tissue functional assessments, LAS100977 showed a higher β_2/β_1-selectivity and activity compared with formoterol and indacaterol.

Aerosolised LAS100977 in an anaesthetised Beagle dog ACh-induced bronchoconstriction model demonstrated a 27-fold more potent inhibition compared with salmeterol [36]. Moreover, LAS100977 had a prolonged anti-bronchoconstrictive effect than salmeterol, and little effect on the heart rate; which would suggest a reduced potential to cardiovascular side effects. In a clinical study of healthy volunteers, inhaled LAS100977 at various doses ranging from 5 to 50 μg, reported an increase in the specific airway conductance (sGAW) and decrease airways resistance at 24 hours after treatment administration compared with placebo [37].

PF-610355

PF-610355 is a selective sulphonamide derived β_2-adrenoceptor agonist. The sulphonamide moiety confers high levels of intrinsic crystallinity and simplifies its solid formation selection [38]. Compared with salmeterol, PF-610355 displays high levels of potency, long DoA for the β_2-adrenoceptor in the airway smooth muscle of *in vitro* guinea pig tracheal assay. In functional cAMP accumulation assessments, PF-610355 was not only potent, but also had greater selectivity for β_2-adrenoceptors compared with salmeterol [38]. Intratracheal administration of PF-610355 in rats has shown that the rate of absorption from the lung into the systemic compartment was significantly slower than salmeterol. Similarly, human microsomal assay investigations have demonstrated that PF-610355 has a lower oral bioavailability due to poor absorption through the gut lumen and high first pass metabolism [38]. Together these two observations would provide evidence for its safety in reducing systemic side effects.

In vivo efficacy assessed in an anaesthetised dog model of bronchoconstriction induced by ACh reported that intratracheally administered PF-610355 was equipotent to formoterol, but more potent than salmeterol and had a longer DoA compared with formoterol and salmeterol [38]. Furthermore, at equipotent doses PF-610355 had greater efficacy, DoA and therapeutic index (as assesses by cardiovascular changes) compared with salmeterol. In a rabbit lung cough model, PF-610355 and salmeterol were inactive [38]. Hence, unlike indacaterol, PF-610355 is unlikely to cause cough in humans.

In healthy subjects a single dose of PF-610355 had an enhanced DoA as measured by sGAW compared with placebo and salmeterol [39]. In patients with asthma, PF-610355 was safe, because there were no significant changes in serum potassium and glucose, no cardiovascular complications and well tolerated in the clinical dose range [40]. Moreover, the plasma pharmacokinetics of inhaled PF-610355 displays sustained stability after single or multiple doses, but is reduced in patients with asthma compared with healthy subjects (i.e. higher concentrations of PF-610355 in patients with asthma compared with healthy volunteers were needed to achieve the same heart rate) [41].

Pharmacological aspects and therapeutic efficacy of ultra-LABAs in COPD

Indacaterol, the first ultra-LABA approved in the EU for the maintenance bronchodilatory treatment of COPD in adults, shows a rapid and 24-hour bronchodilatory action that enables for once-daily administration. Phase II studies provide data that indacaterol has a good cardiovascular safety profile and no antagonism with rescue medications [42–46].

The doses approved for registration were 150 and 300 μg once-daily [39]; moreover in the same study the efficacy of indacaterol at different doses (150–300 and 600 μg) at 24 hours were as good as formoterol 12 μg twice-daily. The efficacy of indacaterol in the maintenance bronchodilator treatment of COPD was assessed in five large randomised double-blind placebo-controlled multicentre studies [47–51] (Table 2). A comparative analysis of these five studies has recently been published [5]. Indacaterol (150 and 300 μg once-daily) significantly improved FEV_1 (130–180 ml and 170–180 ml, respectively) compared with placebo [47–51]. Indacaterol 300 μg once-daily was more effective than tiotropium 18 μg once-daily [48], salmeterol 50 μg twice-daily [50] and formoterol 12 μg twice-daily [49] in improving FEV_1 values versus placebo. COPD exacerbations were significantly reduced by indacaterol versus placebo [48,49] but without differences if compared with formoterol or tiotropium or salbutamol. The percentage of days of poor COPD control was lower in indacaterol group (at doses of 150, 300 and 600 μg) than in placebo group [47,49]. Moreover, the percentage of days with no rescue medications was higher in indacaterol at all tested doses groups than all the active compounds in all studies. In general, indacaterol showed to have greater effects on COPD symptoms than tiotropium, formoterol or salmeterol, although differences between indacaterol and active comparators were not always statistically significant. Significant improvements in health-related quality of life (HR-QOL) were observed with indacaterol versus placebo [49,50]. Once-daily indacaterol was generally well tolerated, with a tolerability profile similar to placebo [47–51]. As might be expected, adverse event incidences appeared higher in the 26-week [48,50] and 52-week [46] trials than in the 12-week [31,47] trials. The most common adverse events were COPD worsening and nasopharyngitis. The occurrence of cough was mild in severity, transient, and tended to decline with the duration of treatment [47–51]. In all treatment groups (including placebo) a reduction of serum potassium levels

TABLE 2

Randomised, double-blind, parallel-group, placebo-controlled, Phase III trials on the efficacy of indacaterol in the maintenance treatment of COPD in adults

Trial name	Pt No.	Ind. dose (μg)	Duration	Versus	Study outcomes	Ref.
INSURE	89	150–300	5-min post-inhalation	Placebo salbutamol 200 μg Fluticasone/salmeterol (500/50 μg)	Ind. 150 μg ΔFEV_1 versus Plac.: 100 ml* Ind. 300 μg ΔFEV_1 versus Plac.: 120 ml* Ind. 150 μg ΔFEV_1 versus Salb: 10 ml Ind. 300 μg ΔFEV_1 versus Salb: 30 ml Ind. 150 μg ΔFEV_1 versus Flut-Salb: 50 ml** Ind. 300 μg ΔFEV_1 versus Flut-Salb: 70 ml*	[45]
INTIME	169	150–300	2 weeks	Placebo tiotropium 18 μg	Ind. 150 μg ΔFEV_1 versus Plac.: 170 ml* Ind. 300 μg ΔFEV_1 versus Plac.: 150 ml* Ind. 150 μg ΔFEV_1 versus Tiot.: 40 ml Ind. 300 μg ΔFEV_1 versus Tiot.: 30 ml	[46]
INDORSE (safety)	450	150–300	26 weeks	Placebo	Ind. 150 μg AEs: 76% (mild–mod) 10.4% (severe) Ind. 300 μg AEs: 77% (mild–mod) 12.3% (severe) Plac. AEs: 68% (mild–mod) 10.5% (severe)	[52]
INLIGHT 1	416	150	12 weeks	Placebo	Ind. ΔFEV_1 versus Plac.: 130 ± 24 ml* Ind. Δ days poor control versus Plac.: −22.5%* Ind. AEs 49.3%/Plac. AEs 46.8%	[47]
INHANCE	416	150–300	26 weeks	Placebo tiotropium 18 μg	Ind. 150–300 μg ΔFEV_1 versus Plac.: 180 ml* Tiot. ΔFEV_1 versus Plac.: 140 ml* Ind. 150/300 μg ΔTDI versus Plac.: 1.00/1.18* Ind. 150/300 μg ΔSGRQ versus Plac.: −3.3/−2.4* Tiot. ΔTDI versus Plac.: 0.87* Tiot. ΔSGRQ versus Plac.: −1.0	[48]
INVOLVE	432	300–600	52 weeks	Placebo formoterol 12 μg	Ind. 300–600 μg ΔFEV_1 versus Plac.: 170 ml* Ind. 300–600 μg ΔFEV_1 versus Form.: 100 ml* Ind. 300–600 μg ΔTDI versus Plac.: >1*	[49]
INLIGHT 2	1.002	150	26 weeks	Placebo salmeterol 50 μg	Ind. ΔFEV_1 versus Plac.: 170 ml* Ind. ΔFEV_1 versus Salm.: 60 ml* Ind. ΔSGRQ versus Plac.* Ind. ΔTDI versus Plac.*	[50]
INSIST	1.123	150	12 weeks	Placebo salmeterol 50 μg	Ind. ΔFEV_1 $AUC_{5m\text{-}11h\ 45m}$ versus Salm.: 57 ml [35–79]* Ind. ΔFEV_1 versus Salm.: 60 ml [37–83]*	[51]

Abbreviations: AEs: adverse events; AUC: area under curve; Ind: indacaterol; Flut: fluticasone; Form: formoterol; Plac.: placebo; Pt No.: patient number in study; Salb: salbutamol; SGRQ: St George's Respiratory Questionnaire; Tiot: tiotropium; TDI: transition dyspnoea index.

* $P < 0.001$.

** $P < 0.05$.

(<3.0 mmol/l) in 0.7% of patients was reported [47–50]. Whereas, a slight increase in corrected QT (QTc) interval values (>60 ms) was reported in a small percentage of patients (<0.7%) [47–51]. Another trial published recently on indacaterol safety not only confirmed the safety, but also reported that there was no tolerance of bronchodilator effect by indacaterol [52].

Olodaterol is a novel ultra-LABA in a late stage of development [3,6]. Preclinical studies suggest a possible once-daily dosing with a fast onset of action [18]. In a clinical Phase II study of patients with COPD, not only was there an observation of an increase in trough FEV_1 compared with placebo at four weeks, but also there were no differences in the FEV_1 profile after the first dose and four weeks of treatment with olodaterol, suggesting the lack of clinical desensitisation [53]. A Phase III study comparing four (2, 5, 10 and 20 μg) doses of olodaterol delivered by Respimat® once-daily compared with placebo in patients with COPD has been completed and results have recently been published [54]. All doses of olodaterol provided greater bronchodilation in FEV_1 compared with placebo in 24 hours, in a dose–response fashion and were well tolerated. Long-term studies are in progress (http://www.clinicaltrials.gov) to supply confirmation if olodaterol administered one daily will provide an efficacious and stable bronchodilation in patients with COPD. No data about comparison with other LABAs or ultra-LABAs are available to date (Table 3).

Carmoterol is a highly selective β_2-adrenoceptor agonist, with particular affinity binding to tracheal adrenoceptors [20,55]. In patients with COPD, Phase II studies have demonstrated a long duration of bronchodilation with 4 μg of carmoterol with an improvement of FEV_1, which is better than salmeterol 50 μg twice-daily [56,57]. No significant adverse events were observed in electrocardiogram, blood pressure, serum potassium or glucose levels in patients treated with carmoterol. Likewise there was no tolerance to the bronchodilatatory effects after two weeks of treatment [25,27]. However, up-to-date and more detailed reports of longer-term treatment are not available on carmoterol treatment in patients with COPD.

Vilanterol trifenatate is a new selective β_2-adrenoceptor agonist, showing a greater selectivity for β_2-adrenoreceptor and potency than indacaterol and salbutamol [30]. Safety and pharmacodynamic and kinetic properties were tested on patients with COPD

TABLE 3

Clinical trials assessing therapeutic efficacy of ultra-LABA compounds

Name	Dose	Trial type	Study outcomes	Ref.
Indacaterol	See Table 2	See Table 2	See Table 2	See Table 2
Olodaterol	2, 5, 10, and 20 μg	Phase III COPD versus placebo	Olod. 2 μg ΔFEV_1 versus Plac.: 70 ml* Olod. 10 μg ΔFEV_1 versus Plac.: 119 ml*	[54]
Vilanterol trifenetate	25, 50, and 100 μg	Phase II COPD versus placebo	Vilan. 25 μg ΔFEV_1 versus Plac.: 190 ml Vilan. 50 μg ΔFEV_1 versus Plac.: 206 ml Vilan. 100 μg ΔFEV_1 versus Plac.: 210 ml	[34]
Carmoterol	2–4 μg	Phase II COPD versus placebo salmeterol 50 μg	Carmot. 2 μg ΔFEV_1 versus Plac.: 94 ml Carmot. 4 μg ΔFEV_1 versus Plac.: 112 ml** Salm. ΔFEV_1 versus Plac.: 78 ml	[57]
LAS100977	5, 10, and 25 μg	Phase II asthma versus placebo salmeterol 50 μg	LAS 5 μg ΔFEV_1: 636 ml* versus Plac.-Salm. LAS 10 μg ΔFEV_1: 660 ml* versus Plac.-Salm. LAS 10 μg ΔFEV_1: 689 ml* versus Plac.-Salm.	[58]
PF-610355	108, 368, 736, and 1472 μg	Phase II asthma versus placebo salmeterol 50 μg	PF 108 μg ΔFEV_1 versus Plac.: 61 ml PF 368 μg ΔFEV_1 versus Plac.: 240 ml PF 736 μg ΔFEV_1 versus Plac.: 344 ml* PF 1472 μg ΔFEV_1 versus Plac.: 395 ml*	[59]

Carmot.: carmoterol; Olod.: olodaterol; LAS: LAS100977; PF: PF-610355; Salm.: salmeterol; Vilan.: vilanterol.
* $P \leq 0.001$.
** $P \leq 0.05$.

[32,33]. In a Phase II clinical trial it has been tested at different doses (25, 50 and 100 μg) producing rapid bronchodilation maintained over 24 hours, but not associated with any unwanted clinical systemic adverse effects [34]. There are no studies in the literature assessing the long-term efficacy and tolerability of vilanterol.

LAS100977 is a novel ultra-LABA with high β_2/β_1 selectivity, with a promising reduced potential for cardiac adverse effects in men [35]. In a Phase II study enrolling mild-to-moderate persistent patients with asthma, three different doses of LAS100977 (5, 10 and 25 μg), were tested compared with salmeterol or placebo. The study reported not only a rapid and sustained significant improvement of lung function parameters after LAS100977 compared with placebo and salmeterol, but also that all three doses of LAS100977 were safe and well tolerated with only minor side effects (tremor and headaches with the two higher doses) [58]. To date, no studies have yet been published regarding the use of LAS100977 in patients with COPD.

PF-610355, a new selective β_2-adrenoceptor agonist sulphonamide derived, has been tested in a preliminary trial on patients with asthmatic showing at different doses (368, 736 and 1472 μg) a better increase of FEV_1 values compared with salmeterol 50 μg [59]. To date, no data are available on the use of PF-610355 in patients with COPD.

Clinical impact of ultra-LABAs on COPD management

Current therapeutic guidelines for COPD recommend regular treatment with long-acting inhaled bronchodilators [Global Initiative for Chronic Obstructive Lung Disease (GOLD): global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2010), http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf]. New ultra-LABAs represent an advance in currently available LABAs and an alternative to existing once-daily bronchodilators for the treatment of COPD. A variety of novel LABAs with once-daily profiles are in development. Indacaterol, is a novel inhaled, once-daily ultra-LABA, recently approved and available in Europe for the maintenance treatment of airflow obstruction in adult patients with COPD [48,49]. Indacaterol has a 24-hour bronchodilatory effect, which enables for once-daily administration. The onset of bronchodilation after inhalation of indacaterol is fast, with significant improvements versus placebo where bronchodilation is seen in five minutes after inhalation [5]. In five large ($n = 3389$ included patients) double-blind, placebo-controlled, randomised multicentre Phase III trials [51–57] (the studies: INHANCE, INVOLVE, INLIGHT, INLIGHT-2, and INSIST), patients with COPD who received indacaterol 150, 300 or 600 μg once-daily had a significantly higher mean trough FEV_1 than placebo after at least 12 weeks. Trough FEV_1 differences between patients treated with indacaterol and placebo were 130–180 ml and exceeded the clinically relevant threshold of 120 ml in all five trials. Furthermore, patients with COPD treated with indacaterol had significantly higher mean trough FEV_1 values after 12 weeks than patients who received formoterol, salmeterol or open-label tiotropium [48–51]. COPD exacerbations and symptoms, and HR-QoL was significantly improved in the indacaterol group versus placebo in some studies. Indacaterol was generally well tolerated by adults with moderate-to-severe COPD [5]. It could be hypothesised that a longer duration of bronchodilation with an ultra-LABA might be associated with superior and more consistent efficacy over a range of endpoints than is achieved with a twice-daily LABA. Furthermore, compared with complicated or multiple treatment regimens, simplified (once-daily) treatment regimens represent a significant convenience benefit and increase the likelihood of compliance with treatment as does fast onset of action and a favourable safety profile. Together, these benefits could lead to improved overall clinical outcomes in patients with COPD and might help compliance with the GOLD guidelines [3]. The introduction of ultra-LABAs is likely to further improve outcomes for patients when used in combination with a LAMA, as reported with the combination of currently available LABAs and LAMAs [60]. To confirm this, a Phase III study is

underway to assess the efficacy and safety of indacaterol (150 μg once-daily) combined with tiotropium (18 μg) versus tiotropium (18 μg) treatment alone in patients with COPD [Efficacy and Safety of Indacaterol Plus Tiotropium Versus Tiotropium Alone in Patients With Chronic Obstructive Pulmonary Disease (INTRUST1), http://clinicaltrials.gov/ct2/show/NCT00846586]. The current opinion is that it will be advantageous to develop inhalers containing combinations of two or more classes of once-daily long-acting bronchodilator drugs, in an attempt to simplify treatment regimens as much as possible. Ultra-LABA/LAMA combinations are in development, including QVA149 (indacaterol and NVA237 glycopyrrolate) [61] and vilanterol trifenatate/GSK573719 (ClinicalTrials.gov: 2010, http://www.clinicaltrials.gov). These findings lend support to the concept that combining different classes of drugs with different mechanisms, such as ultra-LABAs and once-daily LAMAs and ICS will further improve efficacy, and represent an important step towards the goal of optimal control for patients with COPD. To assess possible anti-inflammatory effects of LABA, future clinical studies with these drugs should also incorporate inflammatory outcomes [62,63].

Concluding remarks

There is limited evidence that some pharmacological agents might help slow COPD progression. Guidelines for the pharmacological treatment of COPD recommend a stepwise approach, with additional medications at each stage of the disease. Inhaled bronchodilators are central to the treatment of stable COPD. Short-acting bronchodilators (SABAs), such as salbutamol (β_2-adrenoceptor agonist) and ipratropium, are recommended for use, as needed, by patients with mild COPD. Regular use of long-acting bronchodilators is recommended for moderate and more severe COPD. Those recommended include the β_2-adrenoceptor agonists, salmeterol and formoterol, which require twice-daily administration, and the anti-cholinergic tiotropium, which is taken once-daily. Long-acting bronchodilators are fundamental to the management of COPD, hence new ultra-LABAs have the potential to improve outcomes for patients with COPD, both alone (providing an alternative to the only once-daily muscarinic antagonist bronchodilator currently available) or in combination. There is promising data for indacaterol, the only licensed ultra-LABA, but other ultra-LABAs are in different stages of clinical development in COPD. These agents might improve the management of COPD in terms of their efficacy, safety and most importantly optimal patient compliance due to their once-daily administration.

Conflict of interest

JB Morjaria has received honoraria for speaking and financial support to attend meetings from Chiesi, Pfizer, MSD, Boehringer Ingelheim and GSK. Mario Malerba has received honoraria for speaking and financial support to attend meetings from Chiesi, Pfizer, Boehringer Ingelheim, Astra Zeneca and Novartis.

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